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REVIEW ARTICLE

Hyperlipidemia and associated risk factors: synthetic drugs or medicinal plants? An important question

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Abstract

Hyperlipidemia is a major health issue in industrialized and developing countries that is associated with other complications like angina due to atherosclerosis, diabetes mellitus, strokes, heart attacks, peripheral arterial diseases, obesity, renal failure, liver dysfunction, Cushing's syndrome and glycogen storage disease. Hyperlipidemia is being treated with different classes of synthetic drugs having different mechanisms of action and also differ significantly in the magnitude and type of lipid reduction. The poor efficacy and unwanted side effects of these synthetic drugs has created the need of finding new compounds for the treatment of hyperlipidemia. Herbal drugs are considered to possess minimum or no side effects as compared to synthetic compounds. Furthermore, there is an increasing demand from patients to have drugs from natural products. An increased interest in the research of traditional remedies has put medicinal plants in the mainstream. At present, many studies have their focus to find the plants having antihyperlipidemic activity which in turn, will be useful to reduce the risk of hyperlipidemia. Active ingredients of plants have huge potential to cope with the problem of hyperlipidemia with minimum side effects, thus there is huge demand of these plant based drugs. Herbal drugs can prove to be an excellent strategy for the treatment of hyperlipidemia. Many herbal medicines have already occupied their space as an alternative to synthetic drugs for the treatment of hyperlipidemia. The purpose of this review is to highlight the importance of hyperlipidemia and associated risk factors with their treatment regarding synthetic drugs. Special emphasis has been given to the potential of medicinal plants related to their efficacy against hyperlipidemia.

Keywords

Hyperlipidemia
CVDs
Hypercholesterolemia
Synthetic drugs
Medicinal plants

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Introduction

Hyperlipidemia has become a major health issue due to its high prevalence and association with ischaemic stroke, ischaemic heart diseases and overall mortality. It develops due to abnormal plasma lipid transport and lipid metabolism or dysfunction in the degeneration and synthesis of plasma lipoproteins because of elevated levels of blood fat (Mungall et al., 2003). Additionally, hyperlipidemia causes elevation in the levels of total cholesterol (TC), triglycerides (TGs) and low density lipoproteins (LDL) while decreases the level of high density lipoproteins (HDL) (Mansoor et al., 2009). It is a major factor that contributes towards

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the progression and development of cardiovascular complications like strokes, heart attacks, peripheral arterial diseases and angina due to atherosclerosis (Kahn & Shechter, 1990).

Cardiovascular diseases (CVDs) are the cause of huge number of mortalities in industrialized and developing countries because they are the main risk factor for oxidative stress and metabolic disorders (Rader & FitzGerald, 1998). CVDs are mostly caused by hypercholesterolemia which is associated with diabetes mellitus (DM), hypertension and obesity (Who, 1994). According to World Health Organization (WHO), approximately 150 million people in the world are facing the problem of DM and this number is expected to be double in the year 2025 (Eliza et al., 2009). Hyperglycemia is associated with DM due to the alteration in the levels of liver enzymes, lipid metabolism and glucose (Jain et al., 2011). There are chances of development of atherogenesis in the patients of DM having lipid abnormalities (Otamere et al., 2011). The process of atherogenesis is multifactorial that involves modification in the oxidation of LDL through many pathological events leading to atherosclerosis (Berliner & Heinecke, 1996).

As hyperlipidemia is associated with many other risk factors, the present review has been planned to discuss the (i) complications associated with hyperlipidemia (ii) commercially available synthetic drugs with their mode of action and side effects and (iii) potential of natural products from medicinal plants against these complications.

Diseases associated with hyperlipidemia

Diabetes mellitus: The type-I diabetes patients under normal condition of glycemia, are mostly not hyperlipidemic because increased transportation of free fatty acids (FFAs) towards liver from adipose tissues causes hypertriglyceridemia and ketoacidosis. The increased plasma levels of LDL and TGs with reduced HDL are associated with type-II diabetes. The fat metabolism is mainly effected with elevated levels of insulin and resistance linked with type-II diabetes (Vinik et al 1993). The patients with genetic defects in lipid metabolism have high levels of TGs. The increased levels of LDL in plasma do not indicate DM but may be due to lipoprotein abnormality in the underlying tissue or nephropathy development (Bennett et al., 1995).

Obesity: Hyperlipidemia is often linked with obesity and other lipid metabolic disorders including high adipocyte mass and reduced insulin sensitivity. The large number of FFAs are transported from enlarged adipocytes to the liver where re-esterification occurs and are converted into TGs. These TGs form very low-density lipoproteins (VLDL) and release into circulation. The obesity is mainly associated with low level of HDL but an inverse relation is present in weight loss (Ahmed et al., 2009). The accumulation of abdominal fat and changes in lipid metabolism are present in different conditions like hypertriglyceridemia, low HDL and high LDL. When TG rich VLDL are released in large amount, they result in hypertriglyceridemia, obesity and insulin resistance. The FFAs are also important and their high hepatic update lead to the stimulation and secretion of apoB-100 resulting in hypertriglyceridemia (Marsh, 2003). The VLDL come in contact with lipoprotein lipase (LPL) in peripheral circulation and convert these TGs to VLDL for synthesis of FFAs. These FFAs are utilized by adipose tissues and muscles for energy and remaining particles are consumed by liver to prepare LDL. Large number of LDL is a prominent feature of dyslipidemia and are associated with hypertension and insulin resistance (Austin et al., 1990). The risk of myocardial infarction and coronary artery diseases is increased in the presence of small dense LDL (Austin, 1988).

Atherosclerosis: The relation between atherosclerosis and cholesterol is known for a long time. Metabolic diseases and diabetes are often related to hypertriglyceridemia and lead to atherosclerosis. A close relationship is present between atherosclerosis and hypertriglyceridemia. Two mechanisms are involved that increase the chances of atherosclerosis including endothelial dysfunction and concentration of lipoproteins. The lipoprotein concentration has direct effects by increased oxidative susceptibility (Galeano et al., 1998) and decreased clearance by LDL receptors through liver (Slyper, 1994). An inverse relationship is present between LDL and HDL which functions as a marker for atherogenic TG particles accumulation and insulin resistance (Ross, 1993). This LDL has an important role in macrophages cytokine release for smooth muscle growth and antibody production which results in immune changes. The factors including proliferation of smooth muscles, accumulation of platelets and foam cells lead to the formation of a plaque for atherosclerosis (Ibrahim et al., 2013).

Liver disorders: Liver is a principal organ for lipoprotein clearance and synthesis and its diseases can affect the level of lipoproteins in plasma. Various factors including infections, alcohol and drugs cause hepatitis and lead to increased level of VLDL and hyperlipidemia. The decrease in plasma concentration of TGs and cholesterol due to liver failure results in low lipoprotein synthesis. Hypercholesteremia can be associated with cholestasis and which is a condition in where the excretion of cholesterol via bile is blocked. The cholesterol in free from is combined with polysaccharides in plasma and deposited under skin to produce lesions (Assy et al., 2000).

Renal disorders: The abnormalities in lipoprotein transportation are mainly associated with proteinuria

especially in renal failure cases. The patients have high levels of cholesterol in proteinuria and these changes are developed due to several mechanisms. The high level of LDL is mainly developed due to stimulation caused by protein loss through urinary tract. Proteinuria results into hypoalbumenia and that causes an increased level of 3-Hydroxy-3-Methylglutaryl Coenzyme A (HMG-CoA) reductase leading to hypocholesteremia (Vaziri et al., 2003). The loss of this enzyme through urinary tract leads to low level of HDL and poor maturation of HDL-3 to HDL-2 (Vaziri et al., 2001). The increased level of TGs is mainly present due to incomplete clearance of VLDL and chylomicrons. Renal failure associated with proteinuria is mainly found due to low enzyme activity (Vaziri et al., 2003). All these mechanisms are mainly responsible for lipoprotein metabolism abnormalities in nephrotic problems and renal failure, making these lipoproteins a dominant atherogenic factor. The unusual serum levels of lipids lead to progressive renal failure and may bind with extracellular matrix (Abrass, 2004), where reactive oxygen species like H_2S and superoxide anions are produced due to their oxidation (Chait & Heinecke, 1994).

Reduced activity of endothelial vasodilators like prostacyclin, nitric oxide and increased level of endothelial vasoconstrictors like angiotensin-II have significant renal vascular and pathophysiological effects. These oxidized lipids are engulfed by macrophages and form foam cells and cytokines from these macrophages, recruiting large number of macrophages at lesion site to influence the proliferation of smooth muscle of vessels, endothelial cell functioning and deposition of lipids. The glomerular cells show characteristics similar to cells of atherosclerotic wall (Wheeler & Chana, 1992).

Thyroid diseases: Hypothyroidism is a disease mainly linked with high plasma levels of LDL and it may occur due to slow clearance. Low level of LDL is mainly present in hyperthyroid patients and lipoprotein metabolism imbalance is mainly associated with improper functioning of thyroid. Plasma levels of LDL and HDL are high in hypothyroidism but are low in hyperthyroidism (Heimberg et al., 1985). The chylomicrons clearance is also reduced in hypothyroidism (Weintraub et al., 1999). When number of LDL receptors on hepatocytes are changed, this may affect the LDL plasma level and clearance (Soutar & Knight, 1990). A thyroid responsive element is present in the promoter of LDL receptor gene and this gene expression is mainly regulated by T_3 hormone (Bakker et al., 1998). Changes in the activity of enzymes like hepatic lipase and cholesterol ester transfer protein results in an alteration of HDL cholesterol metabolism and plasma levels (Tall 1993). The activity of enzymes is low in hypothyroidism and high in hyperthyroidism which is mainly associated with plasma level of HDL cholesterol (Tan, 1998). The degree of these changes are mainly linked with severity and period of thyroid dysfunction (Tanis et al., 1996).

Cushing's syndrome: The elevated levels of glucocorticoids are associated with high levels of VLDL and hypertriglyceridemia. In Cushing disease, patients have elevated plasma levels of LDL cholesterol and a similarity exists between Cushing's syndrome hyperlipidemia and metabolic syndrome dyslipidemia. In this disease, VLDL and LDL are found in high levels along with low level of HDL that leads to an increase in TGs and cholesterol (Friedman et al., 1996).

Glycogen storage disease: The glycogen storage disease is one of the sources of secondary hyperlipidemia like von Gierke's disease. This disease mainly occurs as a result of mutation in glucose-6-phosphate and it stimulates the release of FFAs from adipose tissues regardless of hepatic glucose. Formation of hepatic fatty acids causes fat accumulation in the liver. The hyperlipidemia due to this disease is very severe but can be treated with treatment (Ibrahim et al., 2013).

Synthetic drugs with their mechanism of action and side effects: Hyperlipidemia is being treated with different classes of synthetic drugs available in the commercial market. These drugs have different mechanisms of action and also differ significantly in the magnitude and type of lipid reduction. Scientific community is in continuous search for finding different ways to treat the cardiovascular diseases. The drugs like bile acid sequestrants, fibrates and statins, etc. are commonly used for lipid lowering actions but the patients suffer from many side effects. Following are some of the commonly used drugs from different groups with their mechanism of action and side effects.

Statins: Drugs in the class statins have structural similarity with HMG-CoA, which is a cholesterol precursor. They help in the regulation of last step in the cholesterol synthesis, thus statins are the competitive inhibitors of HMG-CoA reductase (Horton et al., 2002). The examples of drugs from this class are atorvastatin and simvastatin @ 80 mg/day and rosuvastatin @ 40 mg/day (Hunninghake et al., 2004). These drugs possess the side effects of hepatitis, myopathy, hypothyroidism, renal insufficiency, sleep disturbance, loss of concentration and headache (Ibrahim et al., 2013).

Niacin (Nicotinic Acid): Niacin reduces the VLDL secretion and synthesis of hepatic TGs by inhibiting the mobilization of FFAs in peripheral tissues. This group also plays an important role in the inhibition of VLDL conversion into LDL (Jin et al., 1999). Crystalline niacin tablets (NIASPAN) are the example of this group of antihyperlipidemic drugs. Many side effects have been reported from this group of drugs including

hepatotoxicity, dyspepsia and flushing (Ibrahim et al., 2013). Furthermore, prostaglandin-mediated purities have been found on the face and upper trunk with skin rashes (Stern et al., 1991).

Bile acid sequestrants: Resins do not bind the cholesterol but bile acids in the intestine, bile acid sequestrants bind the bile acids which are negatively charged because these acids are highly positively charged. They are not absorbed because of having larger size. Excretion of bound bile acids can be observed in the stool. Thus, cholesterol is converted into bile acid at an increasing rate in the liver due to interruption in enterohepatic circulation of bile acids. There is also increase in the hepatic synthesis of cholesterol, which leads to an increase in the concentration of serum TGs, drug effect is limited on the concentration of LDL cholesterol and VLDL circulation is increased into the circulation (Ibrahim et al., 2013). The examples of Cholestyramine @ 8-12 g and Colestipol @ 10-15 g can be quoted for bile acid sequestrants. These drugs have been reported to possess the side effects of disturbing the absorption (Farmer & Gotto, 1994), dyspepsia and bloating (Davidson et al., 1999).

Ezitemibe: Rapid glucuronidation of Ezitemibe occurs in intestines that leads to enterohepatic circulation immediately after glucuronidation. Repeated drug delivery occurs by the mechanism of cessation of cholesterol absorption into enterocytes from intestinal lumen. The parent drug is not as effective as the glucuronide of Ezetimibe because it is localized at the brush borders of intestines. Recirculation of both the glucuronide and Ezetimibe occurs for their delivery back to the intestines at the site of action, thus their effect is increased (Sudhop, 2002). The example of this class is Ezitemibe 10 mg that has side effects like diarrhea, arthralgia, pain in extremities and infection in upper respiratory tract.

Fibric acid derivatives: These drugs have been characterized to regulate the transcription of genes by an interaction with Peroxisome Proliferator Activated Receptors (PPARs) (Kersten et al., 2000). Binding of fibrates to PPARs results in its primary expression in the brown adipose and liver. Clofibrate and related drugs have some resemblance with short chain fatty acids that result in an increased fatty acid oxidation both in muscles and liver with a decrease in the secretion of TG rich lipoproteins. Increased fatty acid oxidation is related to an increase in the uptake of fatty acids and LPL activity. This group contains many drugs that include (i) LOFIBRA 200 mg and TRICOR 140 mg, (ii) Fenofibrate (LOFIBRA) 67, 134 and 200 mg, (iii) Fenofibrate (TRICOR) 145 mg and (iv) Gemfibrozil 600 mg. Like other groups of hypolipidemic drugs, this group also has some side effects. Five percent patients have been reported to possess gastrointestinal disturbances. Bezafibrate, fenofibrate and clofibrate displace the oral anticoagulants from their binding sites. Furthermore, rash, hair loss, urticaria, myalgia, impotence, headache and anaemia are some other complications related to this group of drugs (Ibrahim et al., 2013).

The poor efficacy and unwanted side effects of these synthetic drugs has created the need of finding new compounds for the treatment of hyperlipidemia. Herbal drugs are considered to possess minimum or no side effects as compared to synthetic compounds. Furthermore, there is an increasing demand from patients to have drugs from natural products. Thus, the present focus of experts is to find the ways of treating and reducing the risk of cardiovascular diseases through the use of medicinal plants.

Medicinal Plants as antihyperlipidemic agents: Plant based medicines are relatively safe, eco-friendly, bio-friendly and cost effective. An increased interest in the research of traditional remedies has put medicinal plants in the mainstream. According to WHO, 21000 plant species are used for medicinal purpose and food around the globe. It was indicated in another survey of WHO that 80% of the world population is dependent upon plants for their primary health care (Seth & Sharma, 2004). From ancient times, medicinal plants are being used for the treatment of diabetes in developing countries, while documentation of many plants with lipid lowering effects, has also been done from the start of this century (Kritchevsky, 1995). At present, many studies have their focus to find the plants having hypolipidemic activity which in turn, will be useful to reduce the risk of cardiovascular diseases (Koriem, 2014). Few herbs have been identified to have potential effect against cardiovascular diseases. Thus, it has been suggested that the best prescription against a severe atherosclerosis is any plant-based diet that is rich in legumes, fruit and vegetables and having low saturated fat (Schauer & Fernie, 2006).

The plants have an additional advantage over the synthetic drugs that they possess many active ingredients with different mechanisms of action in order to act as antihyperlipidemic agents. Thus, medicinal plants with antihyperlipidemic property from different families have been discussed below in detail.

Some medicinal plants with antihyperlipidemic potential Family Amaryllidaceae

***Allium sativum* (Garlic):** Numerous therapeutic effects of *Allium (A.) sativum* consumption have been reported *in vitro* and *in vivo*, such as antioxidant, anti-atherosclerotic, anti-diabetic, anti-carcinogenic and immunomodulator. *A. sativum* contains allinase enzyme and sulphur containing compounds which are reported to have cardioprotective and antihypertensive effects (Bhandari, 2012). Lipid lowering effect of herbal mixture containing *A. sativum* in hyperlipidemic adult

albino mice caused decreased TGs, total lipids (TL) and low density lipoproteins-cholesterol (LDL-c) and increased high density lipoproteins-cholesterol (HDL-c) (Javed et al., 2014). Lipid lowering mechanism of action may be based on its antioxidant activity and/or enhanced lipid metabolism (Bhandari, 2012). Other experimental studies have shown that *A. sativum* has anti-atherosclerotic effects owing to the plant's ability to inhibit cholesterol biosynthesis.

Family Rosaceae

***Malus domestica* (Apple):** Hypocholesterolemic effects may be shown by dietary procyanidins of *Malus (M.) domestica* through inhibiting intestinal absorption via reduced micellar solubility of cholesterol (Leontowicz et al., 2003). It was suggested in a study that unripe *M. domestica* having dietary purified procyanidins can reduce the cholesterol in serum and liver by combining the inhibition of intestinal cholesterol absorption and catabolism of hepatic cholesterol. It was further reported that flavonoids of *M. domestica* possess lipid-lowering and anti-inflammatory properties (Sunagawa et al., 2013). The major flavonols in apple peel were found to be quercetin-rich diets, which lessened hyperlipidemia at dose rates of 19 to 35 mg/kg/day after 4 weeks of treatment in obese rats (Wein et al., 2010).

Family Zingiberaceae

***Zingiber officinale* (Ginger):** Use of *Zingiber (Z.) officinale* in cookeries as flavoring agent and spice is very common in the whole world and has reputation of medicinal properties against rheumatism, dropsy, neuralgia, digestive disorders and diabetes (Afzal et al., 2001). Ethanolic extract of *Z. officinale* showed significant antihypercholesterolemic activity in cholesterol-fed rabbits (Bhandari, 2012). Sharma & Shukla (1977) suggested that *Z. officinale* juice possesses a significant effect to lower down the blood glucose level in diabetic and non-diabetic animals. Hypocholesteremic, hypoglycemic and hypolipidemic activities of aqueous extract of *Z. officinale* were further proved in another study on streptozotocin (STZ)-induced diabetic rats. These rats were injected intraperitoneally for seven weeks at daily equivalent dose of 500 mg/kg (Al-Amin et al., 2006).

***Curcuma longa* (Haldi, Turmeric):** Use of *Curcuma (C.) longa* as food component, condiment, drug, cosmetic, flavoring agent and dyestuff is very common. The essential oil of *C. longa* has been reported to have many medicinal properties. The results of a study suggested that *C. longa* oil has an ability to restore the catabolism of TGs, although partially, by suppressing the increased liver concentration of TGs. Other therapeutic uses of *C. longa* oil are the management of hyperlipidaemia and inhibition of lipid peroxidation which ultimately prevents from atherogenic CVDs (Ling et al., 2012).

Family Asteraceae

***Vernonia amygdalina* (Bitter leaf):** Leaves of *Vernonia (V.) amygdalina* are effective antioxidants because they possess such bio-active compounds which have strong electron/hydrogen-donating activity (Atangwho et al., 2013). The methanolic extract of *V. amygdalina* leaves caused a reduction in cholesterol, plasma cholesterol and TGs levels while an increase in the levels of plasma HDL-c in rats. These rats were fed on high cholesterol diets at dose rate of 100 and 200 mg/kg (Adaramoye et al., 2010). In another study, administration of aqueous extract of *V. amygdalina* leaves significantly reduced TGs and suppressed free radical induced oxidative damage in STZ-induced diabetic rats (Nwanjo, 2005).

Family Cucurbitaceae

***Lagenaria siceraria* (Bottle gourd):** Bottle gourd has bottle-shaped fruits and is very famous for the treatment of many ailments and symptoms of atherosclerotic impasse and hyperlipidemia in many parts of India. An experiment was designed in which methanolic extract of fruits of *Lagenaria (L.) siceraria* was administered to rats fed with high fat diet for 30 days at dose rates of 100, 200 and 300 mg/kg p/o. Significant reduction was shown by this extract in the levels of lipids, LDL-c, TGs, total cholesterol (TC), very low-density lipoprotein cholesterol (VLDL-c), while there was an increase in the level of HDL-c (Ghule et al., 2009). Later studies concluded that ethanolic extract of *L. siceraria* fruit had cardioprotective properties to exhibit antihyperlipidemic activity against Triton-X-induced hyperlipidemia in animal experiments (Mohale et al., 2008).

Family Fabaceae

***Arachis hypogea* (Peanut):** The effect of aqueous extract of *Arachis (A.) hypogaea* was checked in normal and alloxan-induced diabetic rats where it reduced the level of blood glucose from 102.60 mg/dl to 88.79 mg/dl and 189.0 mg/dl to 107.55 mg/dl respectively. Furthermore, this extract had significant effect on the reduction of serum TGs, TC and LDL-c in normal and alloxan-induced diabetic rats. The possible mechanism of action may be explained as stimulated secretion of insulin or increase in peripheral utilization of glucose that resulted in hypoglycemic action (Bilbis et al., 2002).

***Glycine max* (Soya bean):** Complex carbohydrate and dietary fiber contents in *Glycine (G.) max* contribute to low glycemic index which is beneficial to reduce the risk of development of diabetes (Salmerón, 1997). Soybean protein administration reduced cholesterol, TGs and LDL levels in healthy persons as well as in diabetic patients (Azadbakht et al., 2003). Furthermore, they reduced the risk of CVDs by lowering blood pressure, blood cholesterol and TGs (McVeigh et al., 2006). Administration of *G. max* seeds @ 20% of daily

food resulted in a significant reduction in levels of TGs, LDL-c, TL and glucose concentration in allaxon-induced diabetic albino rats (Amer, 2012).

Family Acoraceae

***Acorus calamus* (Sweet flag):** Ethyl acetate fraction of *Acorus (A.) calamus* leaves has been reported to have antidiabetic effects by increasing insulin activity (Wu et al., 2009). The alcoholic extract of *A. calamus* containing saponins, prevented the cholesterol absorption and interfered with its enterohepatic circulation and also increased its fecal excretion (Parab & Mengi, 2002). The proposed mechanism of hypoglycemic action of *A. calamus* could be potentiation of plasma insulin by releasing it from the bound form or its pancreatic secretion from existing beta cells (Prisilla et al., 2012).

Family Apiaceae

***Trachyspermum ammi* (Ajowain, Carom):** *Trachyspermum (T.) ammi* is being cultivated in many countries like India, Pakistan, Afghanistan, Europe and Egypt. Seed powder of *T. ammi* @ 2 g/kg reduced TGs, TL, TC and LDL-c up to 53, 49, 71 and 63% respectively and produced hypoglycemic action. However, 62% increase was observed in HDL-c in albino rabbits at the same dose rate. The mechanism of action of *T. ammi* involved in lipid alteration could be its cholestatic effect in the liver by enhanced catabolism or removal of lipoproteins. Furthermore, it could inhibit HMG-CoA reductase and/or inhibiting the lysosomal lipid hydrolytic enzymes secreted by the liver (Javed et al., 2009). In another study, anti-hyperlipidemic activity of methanolic extract of *T. ammi* caused lipid lowering action by decreased TC, LDL-c, TGs and TL (Kumari & Prameela, 1992).

***Carum carvi* (Caraway):** A study conducted on alloxan-induced diabetic rats to check the effect of *Carum (C.) carvi* oil which resulted in alteration of hyperglycemic condition to normal (Ene et al., 2007). The possible mechanism of antihyperglycemic action of *C. carvi* was proposed to stimulate the utilization of glucose by peripheral tissues particularly the adipose and muscle tissues and to inhibit the production of hepatic glucose. In another study, the effect of aqueous extract of *C. carvi* was checked for 2 weeks through oral administration and it was found that the extract significantly decreased the level of blood glucose in STZ diabetic rats. Furthermore, oral administration of *C. carvi* had hypolipidemic and hyporglycemic activities at the dose rate of 1g/kg body weight daily in diabetic rats (Eddouks et al., 2003).

Family Myrtaceae

***Eugenia jambolana* (Jamun):** *Eugenia (E.) jambolana* is well known Indian medicinal plant with diverse phytochemicals like flavonoids, anthocyanines, terpenes, aliphatic acids, phenolics and phytosterols which contribute to its medicinal properties (Yadav et al., 2014). Ethanolic extract of *E. jambolana* was tested to check its anti-diabetic activity on diabetic rabbits and it significantly reduced the peak level of sugar within 2 h time due to the potential of its flavonoids as reported by many researchers (Sharma et al., 2003). The STZ diabetic female albino Wistar rats were fed with *E. jambolana* seed powder at doses 250, 500 and 1000 mg/kg for 15 days resulted in control of diabetes (Sridhar et al., 2005). The hypolipidemic and hypoglycaemic effect of ethanolic extract obtained from seeds of *E. jambolana* (100 mg/kg body weight) was investigated in alloxan-induced diabetic rabbits and it exhibited significant hypolipidaemic effect (Sharma et al., 2003).

Family Lauraceae

***Cinnamomum zeylanicum* (Cinnamon):** The use of aromatic bark of *Cinnamomum (C.) zeylanicum* is very common for its digestive, antispasmodic, antiseptic and particularly hypoglycemic properties in traditional Chinese and Ayurvedic medicines. A study was conducted on cinnamaldehyde (active constituent of *C. zeylanicum*) and it resulted in a dose dependent improvement to control the hyperglycemia and hyperlipidemia in STZ-induced diabetic rats (Kim et al., 2006). Further research on *C. zeylanicum* oil showed good results in STZ-induced diabetic rats where a significant reduction in the level of blood glucose was observed after 3 weeks of treatment (Al-Logmani & Zari, 2011).

Family Lamiaceae

***Ajuga iva* (Bugleweed):** Literature has indicated that flavonoids are the major constituent of the *Ajuga (A.) iva* aqueous extract and they provide protection against diabetes by the reduction of oxidative stress and preserving the integrity of pancreatic b-cells (Fan et al., 2012). A continuous intravenous infusion of a lyophilised aqueous extract of *A. iva* L. at dose rate of 4.2 µg/100 g body weight, exerted hypolipidemic and hypoglycemic effects in STZ-induced diabetic rats. The mechanism of action of the hypoglycemic and hypolipidemic activity appeared to involve insulin sensitization or an insulin-like effect (El-Hilaly et al., 2006).

***Ocimum basilicum* (Basil):** The aqueous extract of the whole plant of *Ocimum (O.) basilicum* was investigated to check its hypolipidemic and hypoglycemic effects at the rate of 20 mg/kg in normal and STZ diabetic rats. It was concluded that the extract did not change the concentration of basal plasma insulin and had significant hypolipidemic and hypoglycemic properties. It was proposed that the aqueous extract of *O. basilicum* may act via inhibition of production of hepatic glucose (Eddouks et al., 2003) through stimulated utilization of glucose by peripheral tissues or improved *in vivo* insulin action. It was further investigated in an experiment that *in vitro* hypoglycemic activity of *O.*

basilicum aqueous extract possessed antioxidant activity possibly through α-glucosidase and α-amylase inhibition, offering anti-hyperglycemic activity (Zeggwagh et al., 2007).

Family Moraceae

***Ficus racemosa* (Fig tree, Goolar fig):** *Ficus (F.) racemosa* has high tannin contents and is widely used in Ayurvedic medicine in India with reports of anti-cancer, gastro-protective, anti-inflammatory and free radical scavenging effects (Khan & Sultana, 2005). Oral administration of tannin fraction from bark extract of *F. racemosa* @ 100 and 200 mg/kg body weight to rats, decreased blood glucose, TC, TGs, LDL and significantly restored the insulin, HDL and the activity of antioxidant enzymes. This ultimately restored the antioxidant status of organs to almost normal levels (Velayutham et al., 2012).

***Morus alba* (White mulberry):** Water extract of *Morus (M.) alba* fruit contains anthocyanins which inhibited LDL oxidation, scavenged free radicals, beneficial activities on blood lipids and atherosclerosis (Du et al., 2008). Freeze-dried powder of *M. alba* fruit was administered to rats fed on high fat diet and it significantly reduced the levels of TC, serum LDL-c, serum and liver TGs and atherogenic index, while serum HDL-c was significantly increased. Additionally, it improved the antioxidant status of blood and liver and reduced the lipid peroxidation (Yang et al., 2010). A study was planned to evaluate the hypoglycemic activity of root bark of Egyptian *M. alba* root bark (MRBF-3). Seventy percent alcoholic extract with flavonoids rich fraction was administered orally to STZ-induced diabetic rats @ 200, 400 and 600 mg /kg/day. The results indicated a significant reduction in the amount of glucose and lipid peroxidation while significant increase in the insulin level (Singab et al., 2005).

Family Poaceae

***Pennisetum glacum* (Pear millet, Bajra):** Bran of *Pennisetum (P.) glaucum* is considered to be a good source of dietary fiber and these dietary fibers have been reported to increase excretion of fecal bile acids, resulting a fall in serum cholesterol (Carr et al., 2003). Moreover, the potency of *P. glaucum* for stimulating fecal bile acid secretion in albino rats may safely be assumed, at least, as a part of mechanisms for its antihyperlipidemic efficacy. *P. glaucum* bran at dose rate of 2, 4 and 6 g/kg body weight showed lipid lowering efficacy in hyperlipidemic rats at post-treatment days 30, 45 and 60. At the level of 6 g/kg, it was able to produce a significant increase in HDL-c (47%) and fall in other lipid profile parameters i.e. TL (41%), TGs (48%), TC (39%) and LDL- c (55%) (Javed et al., 2012).

***Cymbopogon citratus* (Lemongrass):** Various studies have shown that *Cymbopogon (C.) citratus* is used in herbal medicine worldwide for a wide range of applications, including antibacterial, antifungal, antiprotozoal, anti-carcinogenic, anti-inflammatory, antioxidant, cardioprotective, antitussive, antiseptic and anti-rheumatic activities (Gazola et al., 2004). Aqueous and ethanolic extracts of *C. citratus* were orally administered to Wistar albino rats for 30 days and they showed hypoglycemic properties and did not exert oxidative damage (Ademuyiwa et al., 2015). Another study indicated that the aqueous extract of fresh leaves of *C. citratus* reduced the levels of TGs, TC, LDL-c and VLDL-c, while increase in the level of HDL-c when administered orally to Wistar rats for 42 days. Treatment with essential oil of *C. citratus* at the dose rate of 100 mg/kg/day reduced the cholesterol level after 21 days, as previously described both in rats (Adeneye & Agbaje, 2007) and humans (Elson et al., 1989).

Family Capparaceae

***Capparis spinosa* (Caper bush):** *Capparis (C.) spinosa* fruits and flower buds are used as food by diabetic patients due to a belief that they have hypoglycemic and hypolipidemic actions (Afifi-Yazar et al., 2011). It was observed in a study that *C. spinose* caused significant reduction in the levels of TGs, glycosylated hemoglobin and fasting blood glucose in diabetic patients (Fallah Huseini et al., 2013). Repeated oral administration of aqueous extract of *C. spinose* @ 20 mg/kg lowered the lipid profile in normal and severe hyperglycemic rats (Eddouks et al., 2005). The mechanism of action of cholesterol lowering effect of *C. spinosa* may be due to decreased intestinal cholesterol absorption by binding with bile acids and increasing their excretion (Tsai, 1978).

Family Malvaceae

***Hibiscus sabdariffa* (Kerkrade, Rose mallow):** Antihyperlipidemic and antioxidant properties of aqueous extract of *Hibiscus (H.) sabdariffa* leaves have been reported in many investigations (Chen et al., 2013). Alcoholic calyx and leaf extracts of *H. sabdariffa* @ 200 and 500 mg/kg/day decreased the level of TC while LDL-c was consistently reduced regardless of dose and duration of administration (Gosain et al., 2010). An experiment was performed on ethanolic extracts of *H. sabdariffa* calyxes in diabetic animal models and the results showed that it reduced the levels of TC, TGs and LDL-c @ 100 and 200 mg/kg/day. This proved that different extracts of *H. sabdariffa* can be used to treat the patients of hyperlipidemia (Lee et al., 2009).

Family Chenopodiaceae

***Salicornia herbacea* (Pickle weed):** *Salicornia (S.) herbacea* is an annual succulent shrub that grows in salt marshes along the southern and western seashores of Korean peninsula. Many studies and experiments were conducted to find anti-hyperlipidaemic and/or anti-

diabetic agents from indigenous plants of Korea and it was found that 50% ethanolic extract of *S. herbacea* showed anti-hyperlipidemic and hypoglycemic properties in ICR mice. Furthermore, the same extract also possessed potential to protect from type-II diabetes and needs to be checked for future studies (Park et al., 2006).

Family Apocynaceae

***Ichnocarpus frutescens* (Black creeper):** *Ichnocarpus (I.) frutescens* is found all over India and is rich in flavonoids and polyphenols. Kedar and Chakrabarti (1982) proved that polyphenolic extract of *I. frutescens* leaves showed hypolipidemic properties and increased the level of HDL-c at dose rate of 300 mg/kg. Kumarappan & Mandal (2007) also used the same extract of *I. frutescens* leaves in alloxan-induced diabetic rats and observed that the extract showed antihyperlipidaemic effect by reducing the levels of fasting blood glucose. Barik et al. (2008) designed similar kind of study but they used aqueous extract of *I. frutescens* roots and orally administered in STZ-nicotinamide induced type-II diabetic rats at doses 250 and 500 mg/kg. The results indicated that serum glucose level was decreased in diabetic rats while there was increase in the glucose tolerance and ultimately resulted in antidiabetic effect.

Family Rubiaceae

***Anthocephalus cadamba* (Kadam):** *Anthocephalus (A.) cadamba* is widely distributed throughout India, Nepal, Bangladesh, Sri Lanka, Myanmar, Papua New Guinea, Philippines and Indonesia (Sahu et al., 2000). Antioxidant and hypoglycemic properties of *A. cadamba* were studied in alloxan-induced diabetic rats by using hydroethanolic extract of flowering tops at dose rate of 200 and 400 mg/kg. The results established that the extract protected the brain and liver from oxidative damage by diabetes and possessed hypoglycemic effect (Alam et al., 2011). Methanolic root extract of *A. cadamba* was administered orally at two different doses (200 and 400 mg/kg) for 28 days. Various parameters including blood glucose concentration, serum lipids, glycosylated haemoglobin and liver glycogen indicated that the extract possessed antihyperglycemic activity (Acharyya et al., 2013).

Family Sapindaceae

***Sapindus emarginatus* (Soapberries, Soapnuts):** Based on high saponin contents in *Sapindus (S.) emarginatus*, methanolic extract of its pericarps was selected to check antihyperlipidemic activity against Triton induced hyperlipidaemic rats. This extract was administered at dose rates of 100 and 200mg/kg p/o. The results showed a significant decrease in the levels of phospholipid, serum cholesterol, TGs, LDL and VLDL while a significant increase was observed in serum HDL level (Jeyabalan & Palayan, 2009). Ethanolic extract of *S. emarginatus* exhibited hypoglycemic activity, suggesting that its action may be due to high content of alkaloids, flavonoids, terpenoids and saponins present in this extract (Alarcon-Aguilar et al., 2005). After treatment with ethanolic extract, the level of urea and creatinine decreased significantly as compared to the mean level of diabetic group. This further suggested the potential utility of this plant in diabetes-associated complications (Jeyabalan & Palayan, 2009).

Family capparidaceae

***Capparis decidua* (Kair, Karir):** *Capparis (C.) decidua* is a xerophytic shrub which is widely distributed in Asian countries including the western parts of Pakistan and India (Hayat et al., 2008). Alkaloid rich fraction of *C. decidua* was investigated and it was found that it improved the lipid profile by affecting the metabolism of cholesterol, showing its hypolipidemic nature (Subash Babu et al., 2007). Cholesterol lowering effect of this extract could be due to enzyme HMG-CoA that participates in the biosynthesis of de novo cholesterol. This fraction was further confirmed by the analysis of hematological parameters and it proved to be safe for diabetic patients without any significant toxic effects. The same fraction of *C. decidua* was administered to STZ-induced diabetic mice and it resulted in significant reduction in the levels of TGs, TC and blood glucose (Sharma et al., 2010).

Family Solanaceae

***Withania somnifera* (Indian ginseng, Winter cherry):** *Withania (W.) somnifera* is used traditionally for the treatment of numerous ailments including hepatic, cardiovascular, immunological, neurological and metabolic disorders such as diabetes (Mishra et al., 2000). Oral administration of *W. somnifera* root powder, significantly lowered blood glucose in diabetic patients (Andallu & Radhika, 2000). In another study, leaf and root extracts of *W. somnifera* were tested where they increased the uptake of glucose in adipocytes and myotubes dose dependently, with the leaf extract more active as compared to the root extract (Gorelick et al., 2015).

Family Papilionaceae

***Erythrina indica* (Coral tree, Flame tree):** The fresh juice from the bark of *Erythrina (E.) indica* is used by many tribes for the treatment of diabetes (Nadkarni, 1996). Chloroform, ethyl acetate and petroleum ether fractions of ethanolic extract of *E. indica* at the dose rate of 150mg/kg p/o, reduced the levels of TGs, TC, LDL and VLDL-c and increased the HDL level in rats (Kamalraj & Aanandhi, 2012). A study was designed with the objective to investigate the alcoholic and aqueous extracts of stem bark of *E. indica* for hypoglycaemic effects in diabetic and normal rats. The results suggested that both extracts possessed hypoglycaemic activity in normal as well as in diabetic

rats. The possible mechanism of action could be an anti-hyperglycaemic activity of *E. indica* due to free radical scavenging which enhanced the beta cell regeneration against alloxan-induced free radicals (Kumar et al., 2011).

Family Ulvaceae

***Ulva pertusa* (Sea lettuce):** The green alga, *Ulva (U.) pertusa*, is an important food source in various parts of the world and used as a drug in traditional Chinese medicine for hyperlipidaemia, sunstroke and urinary diseases. It was reported that polysaccharide extracted from *U. pertusa* exhibited the hypolipidemic actions. Moreover, its degradation into lower molecular weight fractions without changing the structure and chemical composition, modified the effects on lipid metabolism. Furthermore, ulvan fed mice were observed to have antihyperlipidemic actions due to significant increase in the bile acid excretion (Qi et al., 2012).

***Ulva lactuca*:** Treatment of hypercholesterolemic rats with *U. lactuca* polysaccharide extract induced marked significant decrease in serum TL, TC, TGs and LDL-c concentrations and improved high significant level of HDL-c. This may be due to the ability of extract to hasten the decomposition of free radical species generated during cholesterol administration (Godard et al., 2009). Sulfated polysaccharides from *U. lactuca* were extracted in hot water and precipitated by ethanol, were orally administered to rats fed on a hypercholesterolemic diet for 21 days. They caused significant reduction in serum TGs, TC, TL, LDL-c and VLDL-c levels, whereas, HDL-c concentration was markedly increased (Hassan et al., 2011).

Recommendations: The primary strategy to avoid hyperlipidemia is the dietary intervention because diet plays a pivotal role in the management of hyperlipidemia by reducing cholesterol levels and ultimately decreasing the risk of CVDs and mortality. The foods low in dietary cholesterol and saturated fat, are considered to be the best antihyperlipidemic components providing adequate energy for growth and maintenance of weight. Furthermore, there are some additional recommendations that include: (i) Use of foods rich in anti-oxidants as dark orange, citrus fruit, berries, melons, leafy green vegetables and whole grains instead of supplements. (ii) Intake of dietary fibers should be increased because soluble fiber can result in the reduction of LDL. Soluble fiber is abundantly found in the vegetables, fruits, whole grains, cereals, oats and legumes. (iii) Omega-3-fatty acids consumption should be encouraged because they are associated with cardio protective effects that lower TGs. (iv) Fatty acid composition must be balanced in the diet by monounsaturated and polyunsaturated fatty acids that can lower the level of LDL. (v) Intake of total fat in a low to moderate manner should be encouraged while dietary cholesterol should be discouraged. (vi) Intake of saturated fat, hydrogenated fats and oils, commercial bakery products, hydrogenated peanut butter, animal products with high fat and commercial fried food should be discouraged.

Conclusion and future prospect: Hyperlipidemia is very important disease in developing countries and the treatment with synthetic drugs causes huge monetary expenditure and many side effects. Reducing the risk of CVDs or cerebrovascular diseases or heart diseases is the main purpose of the treatment of hyperlipidemia. Synthetic drugs used against hyperlipidemia possess many side effects including abnormal liver functions, gastric irritation, diarrhea, nausea, vomiting, dry skin and hyperuricemia. Usefulness of active ingredients of plants has a long traditional history and are particularly appealing to the people who question about the safety of synthetic drugs. Luckily, the active ingredients of plants have huge potential to cope with the problem of hyperlipidemia with minimum side effects, thus there is huge demand of these plant based drugs. So, the focus of future research should be based on the plants having lipid-lowering effects to develop phytomedicine against cardiac diseases. Herbal drugs can prove to be an excellent strategy for the treatment of hyperlipidemia. Many herbal medicines have already occupied their space as an alternative to synthetic drugs for the treatment of hyperlipidemia. All the plants discussed in this review, have shown significant antihyperlipidemic effects, thus, it is the need of time to identify and isolate active compounds from these plants. In addition to this, further phytochemical studies are needed regarding the preparation of standardized dose and dose regimen to develop new areas that can be helpful in their improved action against hyperlipidemia.

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