



## A Review of antihyperlipidemic effect of synthetic phenolic compounds

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### ABSTRACT

It is seen that most of the deaths are occurring due to diseases of cardiovascular system. There is a significant impact of lifestyle changes on the quality of health. Utilization of food highly rich with saturated fat and having low fiber content is one of the factors of disarray in energy balance. It is now evinced that hyperlipidemia is depicted as a major risk factor for the premature development of atherosclerosis and its cardiovascular complications. The prevalence of obesity has doubled in the past 25 years; today, two-thirds of adults are overweight in the United State [1].

### 1. Introduction

It is seen that most of the deaths are occurring due to diseases of cardiovascular system. There is a significant impact of lifestyle changes on the quality of health. Utilization of food highly rich with saturated fat and having low fiber content is one of the factors of disarray in energy balance. It is now evinced that hyperlipidemia is depicted as a major risk factor for the premature development of atherosclerosis and its cardiovascular complications. The prevalence of obesity has doubled in the past 25 years; today, two-thirds of adults are overweight in the United State [1].

Hyperlipidemia is a disorder characterized by the increase in blood low-density lipoprotein (LDL), total cholesterol (TC) and triglycerides (TG). More than 3 million people have this genetic disorder in the United States and Europe. This condition is an indicator of both coronary artery disease and atherosclerosis and is the main cause of cardiovascular disease worldwide. An accepted mean of treating the patients with hyperlipoproteinemia and atherosclerosis is lowering the serum triglycerides (TG) and increasing high-density lipoproteins (HDL) [2].

#### 1.1 Pathophysiology

Cholesterol is composed of three lipoproteins (LDL, HDL and VLDL). High level of LDL results in the deposition of lipid on the wall of arteries causing reduction in blood flow due to formation of plaque on inside wall of arteries which causes narrowing and stiffening of arteries. Pathophysiology of hyperlipidemia can be categorized into primary and secondary hyperlipidaemia [3].

Primary hyperlipidemia involves the idiopathic hyperchylomicronemia defect in the lipid metabolism caused by a defect in lipoprotein lipase activity or due to absence of surface apoprotein C II. Primary hyperlipidemia can occur either due to over production or impaired removal of lipoproteins, it has genetic effect. Primary hyperlipidaemia is due to single gene defect. It is familial and called as monogenic or genetic or poly gene defect which is a multiple genetic defect. Primary hyperlipidemia can be further categorized in to different types

- (i) Type I familial hyperchylomicronemia,
- (ii) Type IIA familial 2 hypercholesterolemia,
- (iii) Type IIB familial combined(mixed) hyperlipidemia,
- (iv) Type III familial dysbetalipoproteinemia,
- (v) Type IV familial hypertriglyceridemia,
- (vi) Type V familial mixed hypertriglyceridemia

Secondary hyperlipidemia is associated with other diseases like diabetes, myxoedema, chronic alcoholism, with use of drugs like corticosteroids, oral contraceptives and beta-blockers. Secondary hyperlipidemia is either due to the defect in lipoprotein or its receptor caused by other diseases like diabetes mellitus, hypothyroidism, chronic renal failure, obesity, alcohol, etc. these factors worsen the condition of the person having primary hyperlipidemia. There are four types of secondary hyperlipidemia (i) Hypercholesterolemia, (ii) Hypertriglyceridemia, (iii) Hypocholesterolemia and (iv) Low HDL [4].

#### 1.2 Etiology/ Risk factors

Gender, age, family history, diet, weight and physical activity are some of the

major factors involved in the development of hyperlipidemia.

Hypertriglyceridemia can be caused by either increased synthesis or inadequate removal of triglycerides or both. We hoped to obtain compounds which would increase lipoprotein lipase (LPL) activity, an important enzyme in the removal of triglycerides, because such compounds should enhance triglyceride catabolism via the enzyme's catalytic action and lower the plasma triglyceride levels. In addition, since a precursor product relationship appears to exist between triglyceride-rich lipoproteins and HDL levels, compounds that increase LPL activity are expected to increase the level of HDL [5].

#### 1.3 Prevalence

According to Global health observatory (GBO) data globally, a third of ischemic heart disease is attributable to high cholesterol. Overall, raised cholesterol is estimated to cause 2.6 million deaths (4.5% of total) and 29.7 million disability adjusted life years (DALYS), or 2.0% of total DALYS. 3

The prevalence of elevated total cholesterol was highest in the WHO Region of Europe (54% for both sexes), followed by the WHO Region of the Americas (48% for both sexes). The WHO African Region and the WHO South East Asian Region showed the lowest percentages (22.6% for AFR and 29.0% for SEAR).

#### 1.4 Treatment options for hyperlipidemia currently in use

##### 1.4.1. Diagnostic tests

Cholesterol levels can be measured and monitored using a blood test which primarily measures the total cholesterol and the three components of cholesterol, HDL (good cholesterol), LDL (bad cholesterol) and triglycerides. Other aspects as lifestyle, family history, personal history, dietary habits, weight, blood pressure, smoking/drinking habits, stress, and other tests, such as blood tests, ECG, and heart scans can be used for diagnostic purposes.

##### 1.4.2. Medications

Currently there are number of medication options to treat hyperlipidemia, but while using medicines physicians also recommend changing life style of patients. So to treat hyperlipidemia is not effective without using life style changing strategy.

Changing life style is essential for patients with high low- density proteins and they should try to make some changes in their routine habits. They can get a better and healthy life by reducing total and saturated fat in the diet, losing weight (if overweight or obese), performing aerobic exercise, and eating a diet rich in fruits and vegetables. It is usually effective within 6-12 months of practicing [6].

If we talk about medication used for treating hyperlipidemia, there are a lot of options which have been using now a day. Statins are the great option to reduce risk of coronary heart disease heart attack, stroke plaque rupture, and death and to lower triglycerides and slightly raise HDL cholesterol levels. Ezetimibe impairs the body's ability to absorb cholesterol from food as well as cholesterol that the body produces internally. Bile acid sequestrants bind to bile acids in the intestine, reducing the amount of cholesterol absorbed from foods. Nicotinic acid (Niacin) is a vitamin used for many people who are 4 unresponsive to statins and having high lipoproteins. Fibrates used for people with raised triglyceride and cholesterol levels and cannot be used for

kidney impaired patients. By changing lifestyle we cannot just treat hyperlipidemia but also can prevent disease to strike. Prevention of hyperlipidemia involves adhering to a "heart healthy" diet, regular exercise habits, no smoking, and maintenance of a healthy weight. By reducing intake of saturated fat, Trans fats, and cholesterol. The diet should consist of a colorful array of whole fruits and vegetables, be high in fiber, and whole grains. Fast foods, high carbohydrate foods, and any foods that do not offer good nutritional value should be restricted or eliminated [7].

#### 1.4.3. Nutritional supplements

Fish oil — eating a diet that includes one to two servings of oily fish can decrease triglyceride levels and risk of death from coronary heart disease [8]. Soy protein — A diet high in soy protein can slightly lower levels of total cholesterol, LDL, and triglycerides, and raise levels of HDL cholesterol [9] Plant stanols and sterols — they may act by blocking the absorption of cholesterol in the intestine thus lower cholesterol level but increase risk of coronary heart disease. Garlic — Garlic is not recommended to lower cholesterol because placebo inactive pill can improve LDL level more than garlic extracts [10].

#### 1.5 Phenolic compounds

Phenolic compounds have been shown to offer protection against atherosclerosis and metabolic disorders like hyperlipidemia, hyperglycemia, and hypercholesterolemia. Phenolic acids and flavonoids have pharmacological properties such as antioxidant, antihypertensive, antimutagenic, antithrombotic, anti-inflammatory, anti-HIV-1, and anticancer [11]. Many reports have indicated that phenolic compounds efficiently induce apoptosis in 3T3-L1 adipocytes.

These compounds provide protection via a range of mechanisms including lowering the concentration of plasma non-HDL cholesterol, reducing serum lipid oxidation, lowering vascular resistance and altering cellular inflammatory signaling pathways [12]. 5 Phenolic compounds have an anti-obesity effect through suppression of dyslipidemia, hepatosteatosis, and oxidative stress.

#### 2. Literature review

Sharma, S. et al., in 2015 undertaken a study to investigate the antihyperlipidemic effect of marketed formulations of terminalia arjuna against Triton WR-1339 induced hyperlipidemia in rats at 200 and 400 mg/kg dose which inhibited the elevation of serum cholesterol and triglyceride levels in hyperlipidemic rats. Marketed formulations also significantly decreased HMG-CoA reductase activity at the dose of 200mg/kg and 400mg/kg. Orally administration showed good antihyperlipidemic activity in Triton WR-1339 induced hyperlipidemic rats [13].

Kooti, et al., in 2014 conducted a study to investigate the effects of hydro-alcoholic extract of celery on lipid profile of rats fed a high fat diet. 24 Wistar rats were randomly allocated into four groups. The control group received saline with high-fat diet and treatment groups received hydro alcoholic extract at doses of 100 and 200 mg/kg/BW with high fat diet by giving over a 30-day period. Afterwards, the serum levels of lipids (TG, cholesterol, LDL, HDL, and VLDL) were determined. Hydro-alcoholic extract of celery significantly decreased cholesterol and LDL in treatment groups compared with control group. Probably celery consumption due to the antioxidant properties leads to appropriate changes in serum lipid profiles and reduces them [14].

Akdım, et al., in 2010 conducted a randomized, double controlled study to examine the efficacy and safety of mipomersen, an antisense inhibitor of apolipoprotein B, on familial hypercholesterolemia. A total of 44 patients were enrolled and were separated into 4 cohorts, with doses ranging from 50-300mg (4:1 active treatment by placebo ratio). Efficacy and safety profile was evaluated. Mipomersen produced significant reduction in LDL cholesterol and other atherogenic Apolipoprotein B containing lipoproteins. LDL was reduced by 21% from baseline in 200mg/week dose group ( $p < 0.05$ ) and 34% from baseline in 300mg/week dose group ( $p < 0.01$ ), with a concomitant reduction in Apolipoprotein B of 23% ( $p < 0.15$ ) and 33% ( $p < 0.01$ ), respectively. Injection site reactions were the most common adverse events. In 7 conclusion, mipomersen, when added to conventional lipid-lowering therapy has an incremental LDL cholesterol lowering effect [15].

Rachh, et al., in 2010 conducted a study on the Effect of *Gymnema sylvestre* R. Br. Leaf extract on hyperlipidemic rats. High cholesterol diet was given to rats for seven days in standard rat chow diet, which induced hyperlipidemia. Then hydroalcoholic extract of *Gymnema sylvestre* R. Br. leaves (200 mg kg<sup>-1</sup> b.wt.) was orally administered once a day to rats, that resulted in

decreased serum cholesterol, LDL, VLDL and increased HDL. This concluded that extract of *Gymnema sylvestre* R. Br. Leaf contained phenolic compounds that resulted in antihyperlipidemic activity [16].

Mokale, et al., in 2010 conducted a study in which a novel series of aminotriazole compounds possessing phenoxy acetic acid moiety were synthesized & evaluated for hypolipidemic activity by using high fat diet induced hyperlipidemia in Sprague-Dawley rats [17].

Hsu, et al., in 2009 conducted a study on the antiobesity effects of rutin (R) and o-coumaric acid (oCA) were investigated. Wistar rats were divided into normal and obese groups, and obese rats were pre-fed a high-fat diet (HFD) containing 40% beef tallow for 4 weeks. Then, R and oCA were given as a supplement to obese rats at doses of 50 and 100 mg/kg, respectively, for a period of 8 weeks. The results showed that body fats were significantly decreased in different tissues as compared to those in the HFD group. Serum lipid profiles, insulin, leptin, Hepatic triacylglycerol and cholesterol levels were significantly decreased in the HFD+ R (high dose, HD) and HFD+oCA (HD) groups as compared to those in the HFD group. Moreover, the consumption of R and oCA reduced oxidative stress and glutathione disulfide (GSSG) content, and enhanced the levels of glutathione (GSH), GSH peroxidase (GPx), GSH reductase (GRd), and GSH S-transferase (GST) in the hepatic tissue of rats with HFD-induced obesity. These results demonstrate that intake of R and oCA can be beneficial for the suppression of high-fat-diet-induced dyslipidemia, hepatosteatosis, and oxidative stress in rats [18]. Idrees, et al., in 2009 conducted a study in which a series of 2-(naphthalen-2-yloxy)propionic acid derivatives were prepared and their hypolipidemic activity were evaluated in the high cholesterol diet (HCD) fed hyperlipidemic rat model. Interestingly, the S-alkylated mercaptotriazole 8b and the 1,3,4-oxadiazole 9 produced striking reduction of serum levels of total cholesterol (TC), triglycerides (TGs) and low-density lipoproteins (LDLs) and elevation of serum high-density lipoproteins (HDLs) being more active than the reference gemfibrozil. In addition, the 1,2,4-triazole 7a, the hydroxypyrazolone 10 and the pyrazolone derivative 11 exhibited good hypolipidemic activity on different lipid parameters [19].

Sashidhara, et al., in 2009 conducted a study on novel derivatives 7-methylaminomethylene-8-oxo-7, 8-dihydroquinoline-5-carbaldehyde 2, which were evaluated in vitro for their antioxidant and in vivo for their antidyplipidemic and post-heparin lipolytic activities. Compound 6 was found to be most active antidyplipidemic and antioxidative agent in this series, respectively, and thus represent a new class of promising lead [20]. Reddy, et al., in 2009 conducted a study on novel derivatives (2-13) which were synthesized from the naturally occurring lupeol (1) and screened for their antihyperglycemic activity (2-11) and antidyplipidemic activity (2-4 and 12-13). The derivative 4 lowered the blood glucose levels by 18.2% and 25.0% at 5 h and 24 h, respectively, in sucrose challenged streptozotocin induced diabetic rats (STZ-S) model at the dose of 100 mg/kg body weight. The compound 4 also significantly lowered 40% ( $P < 0.001$ ) in triglycerides, 30% ( $P < 0.05$ ) in glycerol, 24% ( $P < 0.05$ ) in cholesterol quantity and also improved the HDL-cholesterol by 5% in dyslipidemic hamster model at the dose of 50 mg/kg [21].

Zhu, et al., in 2008 conducted a study on antioxidant and hyperlipidemic activity of resveratrol was determined in cholesterol fed diet rats. Three groups (Control, Res30 and Res70) were made randomly each containing thirty two male Sprague-Dawley (SD) rats and fed a hyperlipidemic diet for 4 weeks. Resveratrol was suspended in 0.3% carboxymethyl cellulose (CMC) solution and given to rats of the Res30 and 9 Res70 groups once a day for 4 weeks by oral intubation at a dose of 30 and 70 mg/kg body weight, respectively. The control group received 0.3% CMC solution alone. Resveratrol significantly lowered serum lipid, hepatic cholesterol (TC) and triglyceride (TG) levels compared to the control. Bile acids excretion, overall potential of the antioxidant system was significantly enhanced by resveratrol. Plasma and hepatic thiobarbituric acid reactive substances (TBARS) levels were lowered while serum superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) activities were increased in the cholesterol-fed rats. It shows that resveratrol maintains an antioxidant efficacy as well as its anti-hyperlipidemic effect [22].

Jang, et al., in 2008 conducted a study to evaluate the effect of gallic acid (GA), linoleic acid (LA), mixture of GA and LA (MGL), and chemically synthesized gallic acid-linoleic acid ester (octadeca-9,12-dienyl-3,4,5-trihydroxybenzoate, GLE) on the ability to ameliorate hyperlipidemia in C57BL/6 mice fed a high-fat diet (HFD). GLE, GA, LA, and MGL were mixed with HFD. This results in decreased average body weight, liver weight, plasma lipids such as TG and LDL and increased HDL. Adipose histology

showed that the supplementation of synthetic GLE from gallic acid and linoleic acid ester as compared to other treatment groups may have more potential hypolipidemic effect on mice fed high-fat diet [23].

Fki, et al., in 2007 conducted a study in which the hypocholesterolemic effects of hydroxytyrosol and OMW extract in rats fed a cholesterol-rich diet were tested. A cholesterol-rich diet was given to Wistar rats for 16 weeks. Serum lipid levels, as well as thiobarbituric acid reactive substances (TBARS) and superoxide dismutase and catalase activities in liver were examined. This diet induced hypocholesterolemia that results in elevated serum total cholesterol and LDL-C. Administration of a low-dose (2.5 mg/kg of body weight) of hydroxytyrosol and a high-dose (10 mg/kg of body weight) of OMW extract significantly lowered the serum levels of TC and LDL-C while increasing the serum levels of high-density lipoprotein cholesterol (HDL-C). In addition, OMW phenolics increased CAT and SOD activities in liver. Results suggested that the hypocholesterolemic effect of hydroxytyrosol and OMW extract might be due to their abilities to lower serum TC and LDL-C levels as well as slowing the lipid peroxidation process and enhancing antioxidant enzyme activity [24].

Kumarappan, et al., in 2007 conducted a study to evaluate the anti-diabetic and antihyperlipidemic effects polyphenolic extract (PPE) of *I. frutescens* leaves in alloxan induced diabetic rats. Alloxan was given to induce diabetes in rats and then PPE of *I. frutescens* leaf was given which resulted in reduction of fasting blood sugar. Administration of PPE (300 mg/kg body weight for 21 days) also showed significant decrease in hepatic HMG-CoA reductase activity, inhibition of ADP-induced platelet aggregation and correction of hyperlipidemic indicators (TC, TGs, VLDL, HDL and LDL). Oral administration of polyphenolic extract (100 mg/kg) significantly enhanced the release of lipoprotein lipase enzyme significantly. Results revealed the therapeutic potential of polyphenolic extract against diabetes, hyperlipidemia and atherosclerosis and associated risks [25].

Odbayar, et al., in 2005 conducted a study to compare the physiological activities of some phenolic compounds affecting hepatic fatty acid syntheses in mice were compared. Experimental diet containing 1% quercetin dihydrate, rutin, or ferulic acid or a control diet free of phenolic compounds were fed to male ICR mice for 15 days. Quercetin lowered the serum cholesterol, serum triglycerides and phospholipid levels in mice, although the difference was not significant. Rutin and ferulic acid did not affect these parameters. Quercetin significantly reduced the activity and mRNA levels of various enzymes involved in hepatic fatty acid synthesis. Rutin reduced a few of the parameters for lipogenesis, but ferulic acid did not affect any of the parameters. It was suggested that a reduction in hepatic lipogenesis is the mechanism underlying the hypolipidemic effect of quercetin [26].

El-Beshbishy, et al., in 2006 conducted a study on hypolipidemic and antioxidant effect of *Morus alba*, its 70% alcohol extract was fractionated over cellulose and then eluted with water to obtain MRBF1, with 50% methanol for MRBF 2 and with 100% methanol for MRBF 3. For the first time from Egyptian plant, 4 compounds namely mulberoside A, 5,7,2V-trihydroxyflavanone-4V-O-h-d-glucoside and albanols A and 11 B were isolated from MRBF 2 on continuous chromatographic purification of fractions of extract. Atherosclerosis was induced experimentally on feeding diet enriched in cholesterol (2% by weight) and coconut oil (25% by weight) in rats for 21 days. To evaluate the hypocholesterolemia activity, hypercholesteremic rats were administered with MRBF 1, MRBF 2 and MRBF 3 in a dose of 500mg/kg/day for 15 days. Plasma total cholesterol, LDL-C, VLDL-C, LDL/HDL ratio and triglycerides, as well as plasma and liver lipid peroxides and glutathione-S-transferase enzyme levels, serum paraoxonase enzyme level, LDL oxidation, LDL aggregation and LDL retention, were measured. Plasma and liver glutathione-S-transferase enzyme levels were unaffected in all studied groups. The results showed that the administration of (MRBF-2 and/or MRBF-3) fractions resulted in lessening of atherosclerotic state. Administration of MRBF-3 significantly retained plasma and liver peroxides towards their normal levels, and also, produced significant increase in resistance towards major atherogenic modifications; LDL oxidation by 44%, LDL aggregation by 30% and LDL retention by 33%. So it was concluded that intake of MRB 2 and MRBF 3 acts as potent hypercholesteremic nutrient and powerful antioxidant through inhibition of LDL atherogenic modifications and lipid peroxides [27].

Figarola, et al., in 2005 examined the effects of two new AGE/ALE inhibitors, LR-9 and LR-74, on the prevention of early renal disease and dyslipidemia in streptozotocin (STZ)-induced diabetic rats. Diabetic rats were treated with either LR-9 or LR-74 for 32 weeks. Progression of renal disease was evaluated by measurements of urinary albumin and plasma creatinine concentrations.

AGE/ALE levels in kidneys were determined by immunohistochemistry. Plasma lipids and their lipid hydroperoxide concentrations were also determined. Treatment of either LR-9 or LR-74 significantly inhibited the increase in albuminuria, plasma creatinine, hyperlipidemia, and plasma lipid peroxidation in diabetic rats without any effects on hyperglycemia. These results suggest that both LR compounds can inhibit the progression of renal disease and also prevent dyslipidemia in experimental diabetes [28]. 12 Refaie, et al., in 2005 conducted a study the effects of 4 (3H) quinazolinone and 2 halogenated derivatives (6, 8-dibromo-2-methyl-4 (3H) quinazolinone and 6-iodo-2-methyl-4(3H) quinazolinone) at a sublethal dose level (2 mg/Kg) on cholesterol metabolism were investigated on rats. Bezafibrate, was used as reference compound for data comparison. Treatment of rats with single and combined hypercholesterolemia with quinazolinone compounds gave rise to highly significant reductions in serum total cholesterol and cholesterol ester levels, whereas serum triacylglycerol level was significantly reduced only after treatment with halogen-substituted quinazolinones in single hyper-cholesterolemia, compared to the control group. Results obtained from this study suggest that the antihyperlipidemic effect of quinazolinone compounds was brought about by inhibition of dietary cholesterol absorption and / or intestinal ACAT activity [29].

KIM, et al., in 2005 performed an activity on the effects of amla on low-density lipoprotein (LDL) oxidation and cholesterol levels in rats. SunAmla and ethyl acetate (EtOAc) extract of amla significantly inhibited thiobarbituric acid (TBA)-reactive substance level in the Cu<sup>2+</sup>-induced LDL oxidation and the effects were stronger than those of probucol. In addition, the administration of SunAmla (at a dose of 20 or 40mg/kg body weight/d) or EtOAc extract of amla (at a dose of 10 or 20mg/kg body weight/d) for 20 d to rats fed 1% cholesterol diet significantly reduced total, free and LDL-cholesterol levels in a dose-dependent manner, and EtOAc extract of amla exhibited more potent serum cholesterol-lowering effect than SunAmla in the same amount. These results suggested that amla may be effective for hypercholesterolemia and prevention of atherosclerosis [30].

Ohmori, et al., in 2003 conducted a study in which it is observed that a newly synthesized benzoic acid derivative methoxybenzoic acid (S-2E), had the capacity to inhibit the biosynthesis of both sterol and fatty acids. In this study the mechanism by which S-2E lowers blood cholesterol and triglyceride levels was reported. Active metabolites of S-2E inhibited both HMG-CoA reductase and acetyl-CoA carboxylase at  $K_i=18.11 \mu\text{M}$  and  $K_i=69.2 \mu\text{M}$ , respectively. Indeed, S-2E (3–30 mg/kg) given orally suppressed the secretion rate of VLDL-cholesterol and triglyceride in Triton 13 WR-1339-injected rats. Furthermore, S-2E lowered the blood total cholesterol and triglyceride levels simultaneously in Zucker fatty rats. It was reported that S-2E may be useful in the treatment of familial hypercholesterolemia and mixed hyperlipidemia [31].

Raederstorff, et al., in 2003 conducted a study on Catechins, compounds derived from green tea, which have been shown to reduce plasma cholesterol levels and the rate of cholesterol absorption. Wistar rats were fed a diet high in cholesterol and fat containing none, 0.25% (0.2 g/day/kg BW), 0.5% (0.4 g/day/kg/BW) or 1.0% (0.7 g/day/kg BW) of EGCG. After 4 weeks of treatment, total cholesterol and low density lipoprotein plasma levels were significantly reduced in the group fed 1% EGCG when compared to the no treatment group. This study provides evidence suggesting that the cholesterol-lowering effect of green tea is mainly elicited by EGCG, abundant catechins contained in green tea. It is suggested that one of the underlying mechanisms by which EGCG affects lipid metabolism is by interfering with the micellar solubilization of cholesterol in the digestive tract, which then in turn decreased cholesterol absorption [32].

Yeh, et al., in 2001 conducted a randomized, double-blind, placebo-controlled intervention study, which showed that aged garlic extract (AGE) supplementation was effective in lowering plasma concentration of total cholesterol by 7% and LDL cholesterol by 10% in hypercholesterolemic men compared with subjects consuming a placebo. Supplementation of AGE in animal diets similarly reduced plasma concentrations of total cholesterol and triacylglycerol by 15 and 30%, respectively. In subsequent experiments using cultured rat hepatocytes, 44–87% inhibition of cholesterol synthesis by the water-extractable fraction, methanol-extractable fraction and petroleum ether-extractable fraction of fresh garlic and Kyolic (liquid form of AGE), were seen. Water soluble and lipid soluble compounds of garlic were used. Activity of water soluble compounds against hyperlipidemia were more than that of lipid soluble compounds. The results studies indicate that the cholesterol-lowering effects of garlic extract, such as AGE, stem in part from inhibition of hepatic cholesterol synthesis by water-soluble sulfur compounds [33]. 14 Poplawski, et al., in 2000 conducted a study in which

a series of  $\alpha$ -asarone isomers was synthesized and investigated for their hypolipidemic and antiplatelet activity. Some compounds are more potent in their hypolipidemic activity like compound 3 that elevated the HDL cholesterol level by 56% and lowering the LDL cholesterol level by 46.8% in rats after 7 days of administration. In the pulmonary thromboembolic in vivo test in mice, two compounds ( $\alpha$ -asarone (6) and compound 4) produced significant antithrombotic effects at 100 mg/kg, namely 44% and 52% protection against lung microembolia, respectively.  $\alpha$ -Asarone derivatives form a new group of potential hypolipidemic and/or antithrombotic agents [34]

Cuchel, et al., in 1997 conducted a study to evaluate the effect of lovastatin, HMG-CoA reductase activity, on the kinetics of de novo cholesterol synthesis and apolipoprotein B in VLDL, IDL and LDL was investigated in five male patients with combined hyperlipidemia. Patients were instructed to follow step 2 diets and were treated with lovastatin and placebo in randomly assigned order for 6-week periods. Deuterium oxide was given orally at the end of each experimental period and de novo cholesterol synthesis was expressed as fractional synthesis rate (C-FSR) and production rate (C-PR). Treatment with lovastatin in these patients had no significant effect on the FCR of apoB-100 in VLDL, IDL, or LDL, but resulted in a significant decrease in the PR of apoB-100 in IDL and LDL. Comparing the kinetic data of these patients with those of 10 normolipidemic control subjects indicated that lovastatin treatment normalized apoB-100 IDL and LDL PR. The results suggested that the declines in plasma lipid levels observed after treatment of combined hyperlipidemic patients with lovastatin are attributable to reductions in the C-FSR and C-PR of de novo cholesterol synthesis and the PR of apoB-100 containing lipoproteins. The decline in de novo cholesterol synthesis may have contributed to the decline in the PR observed [35].

Kurogi, et al., in 1996 conducted a study on rats for hypolipidemic effect of novel compound NO-1886, 4-[[diethoxyphosphoryl]methyl]-N-(4-bromo-2-cyanophenyl)benzamide, Derivatives bearing a 4-[[diethoxyphosphoryl]methyl]phenyl group at the 2-position were found to lower 15 triglyceride and total cholesterol levels. In accord with the decrease in log P\*, quinazolines and 4(3H)-quinazolinones showed good hypolipidemic activity and absorption. When the quinazolinone ring system is substituted at positions 6 and 7 with methoxy groups, increased hypolipidemic activity was observed. The highest hypolipidemic activity was observed when the 3-position was substituted by a methyl or benzyl group [36].

Nawrocki, et al., in 1995 conducted a 6-week, double-blind clinical trial which evaluated lipid parameter responses to different dosages of atorvastatin in patients with primary hypercholesterolemia. Atorvastatin was a new HMG-CoA reductase inhibitor under development. After completing an 8-week placebo-baseline dietary phase, 81 patients were randomly assigned to receive placebo or 2.5, 5, 10, 20, 40, or 80 mg atorvastatin once daily for 6 weeks. Plasma LDL cholesterol reductions from baseline were dose related, with 25% to 61% reduction from the minimum dose to the maximum dose of 80 mg atorvastatin once a day. Plasma total cholesterol and apo B reductions were also dose related. Previously, reductions in LDL cholesterol of the magnitude observed in this study have been seen only with combination drug therapy. In this study, atorvastatin was well tolerated by hyperlipidemic patients, had an acceptable safety profile, and provided greater reduction in cholesterol than other previously reported HMG-CoA reductase inhibitors [37].

Jahroomi, et al., in 1993 conducted a study by orally administration of ErOAc pterocarpus marsupium heartwood and its flavonoid constituents in rats with induced hyperlipidemia by diet as well as triton. Extract was administered for 14 consecutive days that effectively reduce serum TG, TC, LDL and VLDL but no significant effect on HDL [38].

Moussavi, et al., in 1989 conducted a study on a series of compounds derived from 7-acyl-(2H)-1, 4-benzoxazin-3-(4H)-and evaluated for lipid lowering actions in animal models. Their hypocholesterolemic and hypotriglyceridemic activities were tested in normolipemic and in cholesterol-induced hyperlipidemic mice, rats and Syrian hamsters. Two key enzymatic activities (ACAT, HMG CoA Reductase) of the most active compound were also determined [39]. 16

Malinow, et al., in 1986 conducted a study in which Synthetic saponin and sterol compounds were administered orally to warm-blooded animals, which inhibit the absorption of cholesterol and are useful in the treatment of hypercholesterolemia [40].

Witiak, et al., conducted a study to check antihyperlipidemic effect of

chroman and chromone compounds on triton fed hyperlipidemic rats in comparison with phenyl and phenoxy analogs. The results show that chromones induce antihyperlipidemic effect in different manner as compared to chromans and colifibrate [41].

Schurr, et al., in 1972 described a screening test for hypolipidemic agents in which compounds are administered orally to fasted rats after a single intravenous injection of 225 mg Triton WR-1339/kg and serum cholesterol and triglycerides are measured 43 hr post-Triton. Conditions for the screen were established by studying interrelationships between serum cholesterol, triglycerides and Triton levels during the post-Triton period and the effects of Triton dose, route of administration and fasting on serum lipid levels and drug hypocholesterolemic activity. The test detects compounds which inhibit lipid biosynthesis or stimulate lipid catabolism. Several drugs with different mechanisms of action which are hypolipidemic in man, including nicotinic acid, D-thyroxine, triparanol, nafoxidine HCl and clofibrate are active in this system. Results with standard hypolipidemic agents are reproducible and conform well to performance levels of the screen predicted from statistical analysis [42].

## Conclusion

In the present study antihyperlipidemic activity was performed in high fat diet induced hyperlipidemic mice models. It was indicated that there is insignificant difference in the average body weight, liver weight and plasma lipid profile of the phenolic test compound 1, test compound 2 and test compound 3 as compared with the standard drug (Atorvastatin in this study). Although the antihyperlipidemic activity of these phenolic compounds is not strong but literature showed that phenolic compounds show cardiac potential so that these compounds should be evaluated for their cardiovascular potential like cyclooxygenase inhibition, antithrombotic and vasodilator activity.

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