Online Available at www.thepharmaresearch.info

THE PHARMA RESEARCH, A JOURNAL

The Pharma Research (T. Ph. Res.), (2010), 4; 169-176.
Published on- 15 Dec 2010

Original Article

ISSN 0975-8216

COMBATING DYSLIPIDEMIA: SOME ALTERNATIVE APPROACHES

Lubhan Singh*, Sagarika Majhi, V.K.Sharma, Kamal Dua#, Rajeev Kumar

Affiliated to:
*D.J. College of Pharmacy, Niwari Road, Modinagar, U.P.-201204
International Medical University, Kuala Lumpur, Malaysia- 57000
For Email Click Here

ABSTRACT

Nutritional and dietary therapy, weight loss, exercise, and scientifically proven nutritional supplementation should be used initially in appropriately selected patients to manage dyslipidemia. Pharmacologic therapy should be administered in those cases that are at high or very high risk for CHD or who do not respond to nondrug therapy. For patients with no or one risk factor for heart disease (LDL cholesterol goal of <160 mg/dL), therapeutic lifestyle changes that include a diet low in saturated fat, low in cholesterol, and high in fiber and daily physical activity may be enough to satisfy lipid goals. Patients with moderate risk (LDL cholesterol goal of <130 mg/dL) may not necessarily require statin therapy, depending on the severity of risk factors. Many patients prefer nondrug therapies for many reasons including adverse effects of antilipid drugs, contraindications or allergic reactions to drugs, perceptions of adverse effects of drugs, or personal preference for natural or alternative therapies.

Keywords: **Combating Dyslipidemia, Cardio-Vascular Diseases**

INTRODUCTION

Cardiovascular disease is the number one cause of morbidity and mortality in the world, with coronary heart disease (CHD) and myocardial infarction (MI) being the leading causes of death. The 5 major risk factors for CHD—hypertension, dyslipidemia, diabetes mellitus, smoking and obesity —account for 80% of the risk for CHD. Interventions, both pharmacologic and nonpharmacologic, can improve all of these risk factors and decrease the incidence of cardiovascular disease (CVD) and its consequences such as MI, angina, congestive heart failure, and stroke. A more aggressive integrative approach to the management of dyslipidemia is recommended to improve CHD outcomes, minimize adverse effects, and reduce health care costs.[1-3]

Nutrition and Exercise:

Optimal nutrition and proper aerobic and resistance exercise form the cornerstone for the management of dyslipidemia. Changes in weight and body composition with loss of total body and visceral fat can have dramatic changes in serum lipid levels that are similar to many pharmacologic therapies.

Nutrition - Dietary therapy focusing on CV risk reduction incorporates whole foods rather than food components. Dietary studies suggest 3 strategies for the promotion of CV health:

- The substitution of nonhydrogenated unsaturated fats for saturated and trans-fats.
- Increasing dietary consumptions of ω-3 Fatty acids from marine and plant sources.
- Increase consumption of low glycemic fruits and vegetables, nuts, and whole grains and reduce refined grain products.

These 3 components are the essentials of the modern Mediterranean diet. The Portfolio diet, designed to lower LDL, consists of foods high in viscous fiber, soy protein, plant sterols, and nuts. These foods are known to reduce cholesterol. Numerous studies confirm that replacement of saturated fat with polyunsaturated FAs (PUFAs) decrease LDL (Low density lipoproteins) and total cholesterol (TC).[4-5]

Exercise - A preponderance of evidence suggests regular moderate exercise prevents development and progression of atherosclerosis and benefits dyslipidemia and reduces vascular symptoms in patients with documented CVD. The mechanism of benefits is derived from maintenance of body weight, blood pressure control, insulin resistance, and dyslipidemia management, all of which promote endothelial stabilization and vascular health.[6]

When the goal of exercise is weight maintenance, the amount of moderate exercise is 60 to 90 minutes daily or 40 to 60 minutes of physical activity daily. In older adults (65 years and older), the use of metabolic equivalents is difficult because of physical limitations, comorbidities, obesity, and lower functional capacity. Several articles suggest that greater amounts of physical activity produce more metabolic and CV benefit, suggesting more is better.[7]

Clinical Recommendations on Nutrition and Exercise:

1. Optimal daily dietary consumption of at least 10 servings of fruits and vegetables (4 servings of fruits and 6 servings of vegetables), whole grains, mixed soluble and insoluble fibers, low saturated fat, high monounsaturated FA (MUFA) and PUFA, and no trans-fat. In addition, the diet should include moderate to high protein (1.5-1.8 g/kg) and low refined carbohydrate intake.
2. Exercise 60 minutes daily with aerobic and resistance training.
3. Achieve ideal body weight, body mass index, waist circumference, and body composition (body fat). Ideal body fat for women is less than 22% and for men, it is 16%.

Nutritional (Dietary) Supplements:

Tocotrienols and Lipids- The tocotrienols are natural derivatives of vitamin E that demonstrate significant reductions in LDL and total cholesterol in humans. The γ andδ isomers as well as the desmethylated derivatives have the most potent lipidlowering effects with reductions in LDL of 8% to 27%. The tocotrienols reduce formation and increase the degradation of HMG-CoA reductase and increase LDL receptors. Tocotrienols are more effective in reducing LDL and total cholesterol if the concentrations of tocotrienols are high and the tocopherols concentration is low. Tocotrienols provide significant lipid-lowering effects in experimental animals. Most prospective studies have demonstrated significant lipid-lowering effects of tocotrienols in humans.[8-9]

Pantethine - Pantethine is a naturally occurring disulfide compound, which is a derivative of pantothenic acid and a precursor of coenzyme A (CoA). Human studies have shown significant improvement in lipid profiles with pantethine in dyslipidemic patients. Total cholesterol, TGs (Triglycerides) and LDL are reduced and HDL (High density lipoproteins) is increased without any known adverse effects. Pantethine increases arterial cholesteryl esterase activity in cholesterol-fed rats, which enhances the removal of

arterial cholesterol esters and reduces fatty streak formation, lipid deposition, endothelial dysfunction and intimal thickening in the aorta and coronary arteries. Pantethine also reduces oxidation of LDL, which is the most atherogenic form of LDL.[10-11]

ω-3 Fatty Acids - Long-chain ω-3 PUFAs may influence CV risk factors using several mechanisms. These include altering eicosanoid biosynthesis in a manner which affects signalling (Fig 1.), altering membrane fluidity in a manner which influences enzymatic reactions and receptor binding, and directly activating transcription factors in a manner which regulate tens to hundreds of critical genes affecting everything from hyperlipidemia to inflammation. The ω-3 FAs, DHA, and EPA are effective lipid-lowering agents. In doses of 4 g/d, DHA and EPA will reduce TGs up to 45%, VLDL by up to 50% with little change in HDL. In addition, they offer significant reductions in CHD events; improve endothelial dysfunction; improve the AA/EPA ratio; and reduce body fat, body weight, and serum glucose.[12-14]

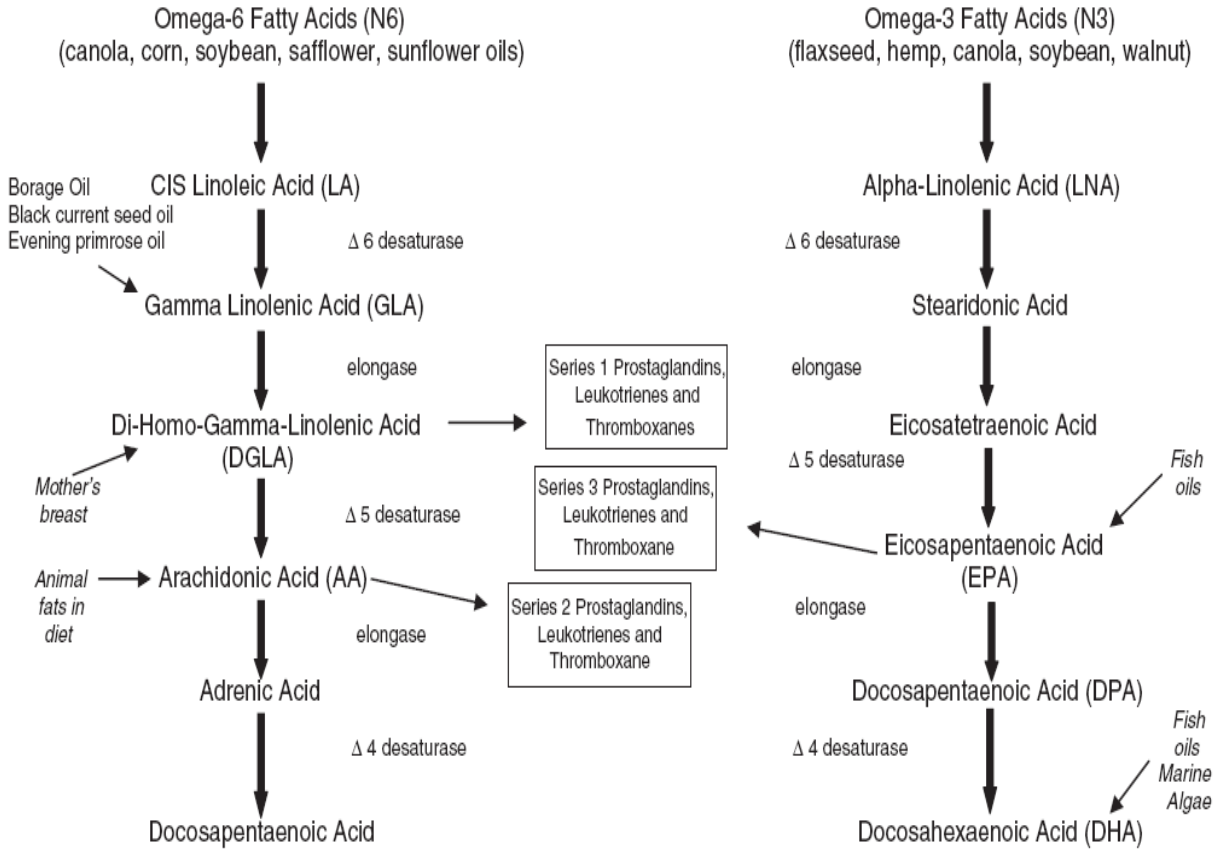

Fig 1. Essential fatty acid pathway

Guggulipid - Guggulipid (Gugule) has been widely used as a medicinal agent in traditional Ayurvedic Indian medicine for more than 2 millennia to treat a variety of ailments including obesity and hyperlipidemia. The active ingredient of this resin extract of the gugule or mukul myrrh tree (Commiphora mukul) is widely considered to be guggulsterone. This plant sterol has been found to be an antagonist ligand for the farnesoid X receptor (FXR) and leads to a reduced expression of bile acid activated genes. Early studies in 1966 by

Satyavati found guggul gum lowered cholesterol and prevented diet-induced atherosclerosis in rabbits.241 Based on early human studies, guggulipid was approved for use as a lipid-altering drug in India in 1987 with at least 10 studies reported; however, most have been non–placebo controlled trials uniformly conducted in the Asian/Indian population.[15-16]

Soy - Replacement of ingested animal protein with vegetable derived protein has been associated with the reduced risk of CVD and a reduction of serum cholesterol levels.244 The beneficial effects of soy protein have been recognized in animals for a century now with evidence of less hypercholesterolemia and atherosclerosis development in laboratory animals given soy protein instead of animal protein. Indeed, in 1999, based on clinical studies demonstrating that a minimum of 25 g of soy protein per day was beneficial in lowering total cholesterol.[17]

Fenugreek - Fenugreek seeds of the Trigonella foenum-graecum plant have been used in Egyptian folk medicine and also as a spice and common dietary adjunct contributing to the taste and flavor of foods. Oil of Fenugreek has a maple like flavor and reportedly urine coloration and odor may occur. In addition to use as a laxative, antipyretic and anti-inflammatory agent, Fenugreek is reported to be beneficial as a traditional plant-based treatment of DM (diabetes mellitus) with additional lipid-modifying effects. In rats fed mucilage fiber of galactomannam isolated from Fenugreek seeds, a reduction in both cholesterol and TG levels was reported, which led to reduced synthesis and secretion of apolipoprotein B–containing VLDL lipoproteins. This suggests a hypolipidemic effect of dietary fiber with glucomannan and a reduction of hepatic VLDL(very low density lipoproteins) production.[18]

Niacin (Nicotinic Acid) - nicotinic acid and its amide form, nicotinamide both are precursors of nicotinamide adenine dinucleotide, the intracellular deficiency of which causes pellagra. In much larger doses, nicotinic acid, but not nicotinamide, modifies the lipid profile. Nicotinic acid was also the first lipid-lowering medication shown to reduce CV events. There are many over-the-counter preparations of niacin, which can be divided into 3 categories: immediate release (marketed as "immediate-release," "crystalline," or "plain" niacin), sustained release (marketed as "sustained-release," "controlled-release," or "time-released" niacin) and no flush (marketed as "no-flush," "zero-flush," or "flush-free" niacin).[19]

Red Yeast Rice - Monascus purpureus rice, popularly known as red yeast rice, is described as the fermented product of rice on which red yeast (M purpureus) has been grown. Although red yeast rice has been used both as a food preservative and for its medicinal properties in China. A strain of Monascus yeast naturally produced a substance that inhibits cholesterol synthesis, named monacolin K (also known as mevinolin or lovastatin), as well as a family of 8 monacolinrelated substances with the ability to inhibit 3-HMG-CoA reductase. In addition to the inhibitors of HMG-CoA reductase, red yeast rice has been found to contain sterols (β-sitosterol, campesterol, stigmasterol, and sapogenin), isoflavones, and isoflavone glycosides and MUFA.[20-21]

Policosanol - Policosanol is the commonly used name for a mixture of long-chain aliphatic alcohols originally derived from purified sugarcane wax. The purported ability of this drug to lower cholesterol without significant side effects has made it one of the fastest growing over-the-counter supplements in the United States. The underlying mechanism of action of policosanol to lower cholesterol has not been definitively elucidated but is proposed to include inhibition of cholesterol synthesis by down-regulating the cellular expression of HMG-CoA reductase.[22-23]

Ginseng - Several varieties of ginseng exist; however, most clinical studies have used either Panax ginseng (commonly known as Asian, Chinese, Korean, or Radix ginseng) or Panax quinquefolius (commonly known as American ginseng). These varieties contain ginsenosides, a diverse group of saponins (or glycosides) that are thought to be the main active components of ginseng. Many studies have been published which reported lipid altering effects of ginseng, at highly variable doses, over periods ranging from 7 days to 3 months.[24-25]

Green Tea - Green tea and its active ingredient, reduce cholesterol levels and atherosclerosis in experimental animal models, and its consumption is associated with reductions in CVD in study populations by lowering fasting and postprandial serum cholesterol. The mechanisms by which green tea may reduce the incidence of CVD include reduction gastrointestinal absorption of cholesterol, up-regulating the hepatic LDL receptor, stimulation of the Fatty acid synthase gene expression in the nucleus, stimulation of cell energy expenditure in the mitochondria, and reducing LDL oxidation.[26]

Plant Sterols - Plant sterols and stanols (phytosterols) are natural fatty substances found in all plants, a class of phytonutrients that have proven benefit in lowering total cholesterol and LDL with variable effects on HDL. The sterols are β- sitosterol, campesterol, stigmasterol (4-desmethyl sterols of the cholestane series) and the stanols, which are saturated sterols. They are similar in structure to cholesterol but are bound to plant fiber, which makes them difficult to absorb. The mechanism of action of phytosterols and phytostanols is to reduce intestinal absorption of cholesterol via competition with incorporation into the micelle. The phytosterols and phytostanols share the same mechanisms of absorption with the cholesterol molecule and influence the cholesterol metabolism inside the enterocytes. They prevent cholesterol absorption from the gut lumen and slow the esterification rate of phytosterols and phytostanols inside the enterocytes.[27-28]

Probiotics and Lipids - Both animal and human studies have documented a modest but significant reduction in serum lipids with long term consumption of oral probiotics.The mechanisms of probiotics in reducing lipids include coprecipitation with bile salts, deconjugation to bile salts, incorporation of cholesterol into the cellularmembrane, and microbial assimilation of cholesterol.[29-30]

Dietary Fiber and Lipids - Dietary fiber is a collective term for a variety of plant substances that are resistant to digestion by human gastrointestinal enzymes. Dietary fibers are classified into 2 major groups depending on their solubility in water.In humans, the structural or matrix fibers such as lignins, cellulose, and some hemicelluloses are insoluble, whereas the natural gel-forming fibers such as the pectins, gums, mucilages, and the hemicelluloses are soluble. The mechanism by which fiber lowers cholesterol including binding of bile acids or cholesterols during the intra luminal formation of micelles; up-regulation of LDL hepatic receptors; increase clearance of LDL; inhibition of hepatic FA synthesis by products of fermentation such as short-chain FAs such as acetate, butyrate, and propionate; changes in intestinal motility; reduced absorption of macronutrients; improved insulin sensitivity; and increased satiety with lower overall energy intake.[31]

Curcumin and Lipids - Curcumin is a natural polyphenolic compound and the most active component of tumeric (Curcuma longa) that demonstrates improvement in serum lipids in experimental animal studies, Curcumin increases the LDL receptor mRNA 7-fold; only slightly increases HMG-CoA reductase and farnesyl diphosphate synthatase; down-regulates PPAR and FA binding protein 1; and increases the activity of hepatic cholesterol-7a-hydroxylase, which increases the rate of cholesterol

catabolism Liver X receptor (LXR) α expression.[32-33]

Sesame - Sesame oil has been demonstrated to have lipid lowering effects on animals and in a few human studies. Sesame oil (Sesame indicum) is rich in both MUFA and PUFA (47% oleic acid and 39% linoleic acid). It also contains lignans such as sesamin and sesamolin and several antioxidant compounds such as sesaminol. Sesamin reduced serum lipid levels in rodents with a concomitant increase in FA oxidation. Sesamin affects the PPAR-α–mediated transcriptional events which modulate lipoprotein metabolism and inflammation and the lignans complex cholesterol from the gut and prevent cholesterol absorption.[34]

Conclusion: Non- pharmacological treatment of dyslipidemia is optimal nutrition, diet, and ideal bodyweight combined with an aerobic and resistance exercise program in all patients. Depending on degree of CV risk, nutritional supplements or drug therapy is the next step. In the high- and very high-risk patients, pharmacologic agents are needed and should be used in conjunction with diet, nutrition, exercise, weight loss, and scientifically proven nutritional supplements. Clinical studies support the ability to reduce serum cholesterol, LDL, and TGs with the combination of diet, lifestyle modifications, and nutritional supplements in most patients. These products offer an alternative to statins in patients who cannot take statins (active liver disease) or whose statin dosage must be restricted because of potential drug interactions or diseases (renal disease).

References:

1. National Center for Health Statistics, American Heart Association: Facts about cardiovascular disease. Circulation 85:A103, 1992
2. Sacks FM, Pfeffer MA, Moye LA, et al: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 335:1001-1009, 1996
3. Burr ML, Fehily AM, Gilbert JF, et al: Effects of changes in fat,fish, and fibre intakes on death and myocardial reinfarction: Diet And Reinfarction Trial (DART). Lancet 2:757-761, 1989
4. Pi-Sunyer X, Blackburn G, Brancati FL, et al: Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. Diabetes Care 30:1374-1383, 2007
5. Yancy Jr WS, Olsen MK, Guyton JR, et al: A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. Ann Intern Med 140:769-777, 2004
6. Maron BJ, Chaitman BR, Ackerman MJ, et al: Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. Circulation 109:2807-2816, 2004
7. Slentz CA, Duscha BD, Johnson JL, et al: Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE—a randomized controlled study. Arch Intern Med 164:31-39, 2004
8. Qureshi AA, Pearce BC, Nor RM, et al: Dietary alpha-tocopherol attenuates the impact of gamma-tocotrienol on 3-hydroxy-3- methylglutaryl coenzyme A reductase activity in chickens. J Nutr 126:389-394, 1996
9. O'Byrne D, Grundy S, Packer L, et al: Studies of LDL oxidation following alpha-, gamma-, or delta-tocotrienyl acetate supplementation of hypercholesterolemic humans. Free Radic Biol Med 29:834-845, 2000
10. McRae MP: Treatment of hyperlipoproteinemia with pantethine: a review and analysis of efficacy and tolerability. Nutr Res 25:319-333, 2005

11. Tomikawa M, Nakayasu T, Tawara K, et al: Effect of pantethine on lipoprotein profiles and HDL subfractions in experimentally hypercholesterolemic rabbits. Atherosclerosis 41:267-277, 1982
12. IsoH,KobayashiM, Ishihara J, etal: Intakeof fishandn3fattyacidsand risk of coronary heart disease among Japanese: the Japan PublicHealth Center-Based (JPHC) Study Cohort I. Circulation 113:195-202, 2006
13. Kromhout D, Feskens EJ, Bowles CH: The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. Int J Epidemiol 24:340-345, 1995
14. Lucas M, Harris WS: Risks and benefits of fish intake. JAMA 297:585, 2007
15. Satyavati GV: Gum guggal (Commiphora mukul)—the success story of an ancient insight leading to a modern discovery. Indian J Med Res 87:327-335, 1988
16. Nityanand S, Srivastava JS, Asthana OP: Clinical trials with gugulipid A new hypolipidaemic agent. J Assoc Physicians India 37:323-328, 1989
17. Terpstra AH, Hermus RJ, West CE: The role of dietary protein in cholesterol metabolism. World Rev Nutr Diet 42:1-55, 1983
18. Sharma RD, Raghuram TC, Rao NS: Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. Eur J Clin Nutr 44:301-306, 1990
19. Altschul R, Hoffer A, Stephen JD: Influence of nicotinic acid on serum cholesterol in man. Arch Biochem Biophys 54:558-559, 1955
20. Endo A, Monacolin K: A new hypocholesterolemic agent produced by a Monascus species. J Antibiot (Tokyo) 32:852-854, 1979
21. Ma J, Li Y, Ye Q, et al: Constituents of red yeast rice, a traditional Chinese food and medicine. J Agric Food Chem48:5220-5225, 2000
22. Wang YW, Jones PJ, Pischel I, et al: Effects of policosanols and phytosterols on lipid levels and cholesterol biosynthesis in hamsters. Lipids 38:165-170, 2003
23. Murphy KJ, Saint DA, Howe PR: Lack of effect of sugar cane and sunflower seed policosanols on plasma cholesterol in rabbits. Asia Pac J Clin Nutr 13(Suppl):S69, 2004
24. Kim SH, Park KS: Effects of Panax ginseng extract on lipid metabolism in humans. Pharmacol Res 48:511-513, 2003
25. Punnonen R, Lukola A: The effect of ginseng on serum total cholesterol, HDL-cholesterol and triglyceride levels in postmenopausal women. Asia Oceania J Obstet Gynaecol 10:399-401, 1984
26. Koo SI, Noh SK: Green tea as inhibitor of the intestinal absorption of lipids: potential mechanism for its lipid-lowering effect. J Nutr Biochem 18:179-183, 200
27. Acuff RV, Cai DJ, Dong ZP, et al: The lipid lowering effect of plant sterol ester capsules in hypercholesterolemic subjects. Lipids Health Dis 6:11, 2007
28. Moruisi KG, Oosthuizen W, Opperman AM: Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis. J Am Coll Nutr 25:41-48, 2006
29. Simons LA, Amansec SG, Conway P: Effect of Lactobacillus fermentum on serum lipids in subjects with elevated serum cholesterol. Nutr Metab Cardiovasc Dis 16:531-535, 2006
30. Fabian E, Elmadfa I: Influence of daily consumption of probiotic and conventional yoghurt on the plasma lipid profile in young healthy women. Ann Nutr Met:387-393, 2006
31. Brown L, Rosner B, Willett WW, et al: Cholesterol-lowering effects of dietary fiber: a meta-analysis. Am J Clin Nutr 69:30-42, 1999
32. Soni KB, Kuttan R: Effect of oral curcumin administration on serum peroxides and cholesterol levels in human volunteers.

Indian J Physiol Pharmacol 36:273-275, 1992

33. Wang S, Chen B, Sun C: Regulation effect of curcumin on blood lipids and antioxidation in hyperlipidemia rats. Wei Sheng Yan Jiu 29:240-242, 2000
34. Sankar D, Rao MR, Sambandam G, et al: A pilot study of open label sesame oil in hypertensive diabetics. J Med Food 9:408-412, 2006