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• Review

Efficacy of polyphenolic ingredients of Chinese herbs in treating dyslipidemia of metabolic syndromes

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ABSTRACT: There is an increasing interest and popularity of Chinese herbal medicine worldwide, which is accompanied by increasing concerns about its effectiveness and potential toxicity. Several ingredients, such as polyphenolic compounds berberine, flavonoids, and curcumin, have been studied extensively by using various animal models. Effectiveness of treatment and amelioration of metabolic syndromes, including insulin resistance and dyslipidemia, has been demonstrated. This review summarizes the major checkpoints and contributing factors in regulation of exogenous and endogenous lipid metabolism, with particular emphasis centered on triglyceride-rich and cholesterol-rich lipoproteins. Available experimental evidence demonstrating the lipid-lowering effect of berberine, flavonoids and curcumin in cell culture and animal models is compiled, and the strengths and shortcomings of experimental designs in these studies are discussed.

KEYWORDS: drugs, Chinese herbal; metabolic syndromes; dyslipidemias; reviews

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1 Introduction

The last 2-3 decades have witnessed a surge of metabolic syndrome worldwide, characterized by central obesity, hypertension, fasting hyperglycemia and diabetic dyslipidemia. Although the pathophysiology of metabolic syndrome is complex and the etiology remains incompletely understood, the symptoms are often associated with insulin/leptin resistance. The hallmark of diabetic dyslipidemia is the reduced plasma concentrations of high-density lipoproteins (HDL) and a concomitant elevation in the plasma concentrations of triglyceride (TG)-rich lipoproteins (TRLs), notably very-low-density lipoprotein-1 ($VLDL_1$) originating from the liver. Abnormal overproduction of hepatic $VLDL_1$ is the predominant contributor to dyslipidemia of metabolic syndrome, which is a consequence of nutrient overabundance within the liver. Various therapeutic strategies have been developed in an attempt to curtail overproduction of $VLDL_1$, such as down-regulating apolipoprotein (Apo) B synthesis[1] and inhibiting microsomal triglyceride-transfer protein (MTP)[2]. In addition, a variety of effective polyphenolic ingredients derived from Chinese herbal medicine, such as berberine, curcumin and flavonoids, have been shown to possess hypolipidemic effect in treating dyslipidemia of metabolic syndrome in humans and animal models. Great

efforts have been made to discover the molecular targets of these compounds, as well as their mode of action. The present review summarizes current understanding of the efficacy of several naturally occurring compounds extracted from medicinal herbs, with emphasis centered on cellular and molecular mechanisms in regulating metabolism of plasma lipoproteins.

2 Plasma lipoproteins

Plasma lipoproteins are microemulsions composed of a core of neutral lipids that is surrounded by a monolayer of amphipathic phospholipids. The surface of lipoproteins is embedded with cholesterol and various proteins termed apolipoproteins. Most of the apolipoproteins are composed of amphipathic α-helices, allowing them to associate with the phospholipid monolayer and render lipoproteins soluble in aqueous solutions. The core of neutral lipids consists mainly of TG and cholesteryl ester (CE). Conventionally, plasma lipoproteins are separated by density gradient ultracentrifugation on the basis of respective buoyancy, hence are named as very-low-, low-, and high-density lipoproteins, respectively. However, classification of plasma lipoproteins according to buoyancy does not specify the lipid or protein constituents of lipoproteins. Thus clinically, plasma lipoproteins are often defined, based on lipid composition, as TG-rich or cholesterol-rich lipoproteins.

2.1 TRLs

Plasma TRLs are synthesized predominantly in the liver and intestine in the form of VLDL and chylomicrons, respectively. Synthesis of TRLs requires the large and extremely hydrophobic ApoB, which is encoded by the *ApoB* gene that transcribed into two different mRNAs encoding the full-length ApoB-100 (4 536 amino acid) in the liver and the C-terminally truncated ApoB-48 (representing the *N*-terminal 48% of ApoB-100) in the intestine. Each VLDL and chylomicron contains a single copy of ApoB-100 and ApoB-48. In addition to ApoB-100 and ApoB-48, VLDL and chylomicron also contain other small apolipoproteins, such as ApoE and ApoC. Formation of TRLs requires the activity of MTP, a microsome-resident protein that catalyzes the mobilization of neutral lipids (TG and CE) utilized for VLDL assembly and secretion[3]. Deficiency of MTP causes familial abetalipoproteinemia in humans, a recessive autosomal disorder characterized by near absence of plasma ApoB-containing lipoproteins in homozygotes. Chemical inhibitors of MTP (*e.g.*, lomitapide) have been developed as a therapeutic means in treating severe hypertriglyceridemia[4].

Formation of VLDL is facilitated by ApoE and ApoC3 in the liver[5], and expression of ApoC3 is especially important for the production of TG-rich $VLDL_1$ under lipid-rich conditions[6]. Antisense oligo approaches against ApoB (*e.g.*, mipomersen) or ApoC3 expression have been developed for the treatment of hypertriglyceridemia[7,8]. It remains to be determined whether long-term inactivating MTP, ApoB, or ApoC3 would result in hepatosteatosis in humans.

2.2 Cholesterol-rich lipoproteins

The main cholesterol-rich lipoproteins in the circulation are low-density lipoproteins (LDL), formed primarily during circulation as the hydrolysis product of VLDL. Hydrolysis of VLDL, accompanied by the conversion of VLDL into LDL, is catalyzed by the activity of lipoprotein lipase (LPL) and hepatic lipase (HL). Unlike that of plasma TRLs, the concentration of plasma LDL is determined primarily by the rate of catabolism rather than synthesis. The most well-characterized protein factor that governs the rate of LDL catabolism is LDL receptor (LDLR), a type I membrane protein that regulates the clearance of plasma LDL via a process termed receptor-mediated endocytosis[9]. The ligands of LDLR are ApoB-100, which is associated with LDL particles, and ApoE, which is associated with chylomicron remnants. Loss-of-function mutations within LDLR are the cause of familial hypercholesterolemia, an autosomal co-dominant disorder characterized by elevated plasma cholesterol, mainly LDL-cholesterol. The LDLR is expressed ubiquitously in all cell types in humans. The expression of LDLR is regulated mainly at transcriptional level by the transcription factor sterol-regulatory element binding protein-2a (SREBP-2a), which is activated under sterol-deprived conditions[10]. Inhibition of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase (HMGR), a rate-limiting enzyme in the *de novo* cholesterol synthetic pathway, could effectively up-regulate LDLR expression, which results in cholesterol-lowering in the plasma. The main effict of some statin drugs (the HMGR inhibitors) is thought to be achieved by the up-regulation of LDLR.

The expression of LDLR is also regulated at the post-translational level by its interaction with proprotein convertase subtilisin/kexin type 9 (PCSK9), which targets LDLR to lysosome for degradation and prevents LDLR recycling to the plasma membrane[11]. Loss-of-function mutations associated with PCSK9 are associated with markedly decreased plasma LDL concentrations, presumably because of the improved stability of LDLR[12]. Antibodies against PCSK9 have been developed as a therapeutic strategy in effectively treating hypercholesterolemia in humans[13].

The other type of cholesterol-rich lipoproteins in the plasma is HDL, which is an ensemble of varied entities heterogeneous in structure and composition. The apolipoproteins associated with HDL are composed of amphipathic α-helices with relatively low affinity towards lipid surface, thus allowing them to exchange between different lipoprotein particles.