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Invited Review

Regulation of PCSK9 by nutraceuticals

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Abbreviations:
ALA, alpha-linolenic acid
ApoB, apolipoprotein B
ApoER2, apolipoprotein E receptor2
APMF, aqueous extract of PM fruit;
ASCVD, atherosclerotic cardiovascular disease
COMIT, canola oil multicenter intervention trial
CGN, cerebellar granule neurons
DHA, docosahexaenoic acid
DPA, Docosapentaenoic acid
EPA, eicosapentaenoic acid
ER, endoplasmic reticulum
EGF-A, epidermal growth factor-like repeat A
FH, familial hypercholesterolemia
GK, glucokinase
HeFH, heterozygous familial hypercholesterolemia
HNF1, hepatocyte nuclear factor1
HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A
LPS, lipopolysaccharide
LDL, low-density lipoprotein
LDL-C

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ABSTRACT

PCSK9 (proprotein convertase subtilisin kexin type 9) is a liver secretory enzyme that regulates plasma low-density lipoprotein (LDL) cholesterol (LDL-C) levels through modulation of LDL receptor (LDLR) density on the surface of hepatocytes. Inhibition of PCSK9 using monoclonal antibodies can efficiently lower plasma LDL-C, non-high-density lipoprotein cholesterol and lipoprotein (a). PCSK9 inhibition is also an effective adjunct to statin therapy; however, the cost-effectiveness of currently available PCSK9 inhibitors is under question. Nutraceuticals offer a safe and cost-effective option for PCSK9 inhibition. Several nutraceuticals have been reported to modulate PCSK9 levels and exert LDL-lowering activity. Mechanistically, those nutraceuticals that inhibit PCSK9 through a SREBP (sterol-responsive element binding protein)-independent pathway can be more effective in lowering plasma LDL-C levels compared with those inhibiting PCSK9 through the SREBP pathway. The present review aims to collect available data on the nutraceuticals with PCSK9-inhibitory effect and the underlying mechanisms.

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Contents

1. PCSK9: biogenesis and physiological function

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key regulator of cholesterol homeostasis that controls low-density lipoprotein (LDL) receptor (LDLR) density on the surface of hepatocytes. PCSK9 is a soluble member of the mammalian proprotein convertase family of serine proteases [1], which is synthesized and secreted mainly by the liver, and in lower extent by other tissues such as the kidney, the small intestine, the central nervous system, the pancreas, the colon epithelium and the vascular smooth muscle cells [2–6]. *PCSK9* gene, located in chromosome 1p33–34.3 close to the third genetic locus associated with familial hypercholesterolemia (FH) [2], encodes an inactive glycoprotein (i.e. pre-PCSK9) with 692 amino acids comprising a signal sequence followed by a subtilisin-like catalytic domain and a C-terminal domain [7–9]. Once the signal peptide is cleaved from pre-PCSK9 in the endoplasmic reticulum (ER), pro-PCSK9 (the soluble zymogen) is formed and then converted to mature secretory PCSK9 through autocatalytic cleavage of the prodomain in the Golgi apparatus [10,11]. After PCSK9 maturation, prodomain stays noncovalently bound to the active site of the catalytic domain, obstructing further enzymatic activity of PCSK9, but serving as a chaperone [12,13]. While the catalytic domain of mature PCSK9 binds to the extracellular epidermal growth factor-like repeat A (EGF-A) domain of LDLR, the C-terminal domain of PCSK9 is required to bind with cell surface proteins such as annexin A2 [14]. The best known function of PCSK9 is the post-translational regulation of LDLR in hepatocytes [15], representing the major route for LDL cholesterol (LDL-C) clearance from the blood circulation [16,17]. Mechanistically, PCSK9 binds to the extracellular EGF-A domain of the hepatic LDLR and promotes lysosomal degradation of LDLRs through two independent intra- and extra-cellular ways. In the relatively faster mode, the intracellular pathway, PCSK9 binds to the EGF-A domain of the newly formed LDLR in the *trans*-Golgi network, where the PCSK9-LDLR complex is targeted to the lysosome [18]. In the extracellular pathway, the secreted PCSK9 circulates in the bloodstream and binds to the EGF-A domain of the LDLR on the surface of hepatocytes, and escorts it into the lysosome compartment through clathrin-mediated endocytosis [19]. Given that normal trafficking of the LDLR back to the cell surface is dependent on the EGF-A domain [20–22], binding of PCSK9 to this domain inhibits recycling of the LDLR to the cell surface and enhances lysosomal degradation of LDLR [23,24]. Consequently, there are not many LDLR remaining to clear LDL-C from the bloodstream when plasma PCSK9 levels are elevated as a result of gain-of-function mutations. Conversely, when there is low or no PCSK9 in the circulation as a result of loss-of function mutations, there will be more intact LDLR which in turn trap more LDL-C from the bloodstream [25].

2. PCSK9: transcriptional regulation

It is known that the proximal promoters of either *PCSK9* or *LDLR* genes contain a functional sterol regulatory element (SRE) that is targeted by sterol-responsive element binding proteins (SREBPs) in response to alterations in intracellular levels of cholesterol [26]. Sterol-dependent regulation of both *PCSK9* and *LDLR* genes have been found to be mediated by SREBP-2 transcription factor [27,28]. Specifically, SREBP-2 is able to upregulate the expression of both PCSK9 and LDLR in states of intracellular cholesterol depletion. Beside the SRE region, promoter region of *PCSK9* also involves a hepatocyte nuclear factor1 (HNF1) response site that binds predominantly to HNF1a, an essential transcription factor for basal expression of *PCSK9* [26]. HNF1a is also involved in SREBP-2-induced maximal *PCSK9* gene expression in response to intracellular cholesterol depletion in HepG2 cells [29]. Site-directed mutagenesis studies have indicated that the HNF1 regulatory site works cooperatively with the SRE and mutations of *HNF1* may reduce the sensitivity of the promoter to sterols and also transcriptional regulatory activity of SREBP-2 on the *PCSK9* promoter [29]. Expression of *PCSK9* is found to be abundant in the liver, possibly due to the rich content of HNF1a transcription factor in the hepatic tissue [29]. Considering the fact that *PCSK9* expression can also be regulated by HNF1 in an LDLR-independent manner, HNF1 inhibition may be an alternative strategy for specific reduction of circulating PCSK9 levels.

3. Statin therapy and PCSK9

Statins, the mainstay of pharmacotherapy for dyslipidemia, indirectly increase the expression of both *PCSK9* and *LDLR* through activation or nuclear translocation of SREBP-2 (Fig. 1) [27]. Statins act mainly through inhibiting 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase which is the rate-limiting enzyme in the cholesterol biosynthesis pathway [30]. Statin-mediated HMG-CoA inhibition is paralleled by simultaneous intracellular cholesterol depletion. Mechanistically, intracellular cholesterol depletion activates the transcription factor SREBP-2 that can induce *LDLR* gene expression and improve hepatic uptake