Soy constituents: modes of action in low-density lipoprotein management

Jan H van Ee

Reviewed here are the modes of action of soy components used as ingredients in foods, which can lower plasma levels of low-density lipoprotein (LDL) and cholesterol, which are markers for the risk for atherosclerosis. Soy ingredients act via more than one mode of action including the following: LDL absorption suppression, cholesterol efflux stimulation, LDL resorption stimulation, LDL oxidation prevention, LDL particle size increase, cholesterol synthesis reduction, and bile secretion increase. Individual genetics, lifestyle, and nutrition habits alter LDL management and a better understanding of the various modes of actions of soy ingredients may facilitate the composition of effective ingredient cocktails. The optimization of food components offers further alternatives to LDL management to augment drug therapy for patients who are unable to reach their target LDL cholesterol levels or who are suffering from side effects or drug insensitivity.

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INTRODUCTION

Many papers have been published about the relationship between soy ingredients and health endpoints, particularly as they relate to serum cholesterol and triglyceride level modulation; in several cases, conflicting results have been noted regarding the efficacy of these ingredients. There is much less published about the potential modes of action of these ingredients with respect to understanding their physiological effects, their potential synergistic interplay, and their possible value in maintaining desirable levels of specific health indicators. One of these indicators is the plasma level of low-density lipoprotein (LDL) cholesterol, which plays a major role in the early stages of atherosclerosis. This process starts with entrapping of (oxidized) LDL cholesterol in the intima, just below the arterial endothelium. After LDL cholesterol oxidation, monocytes are attracted into the intima and then differentiate into macrophages, which ingest oxidized LDL and subsequently differentiate into foam cells. These foam cells join with lymphocytes, platelets, and smooth muscle cells to build up a plaque, which narrows the lumen of the blood vessel and causes restricted blood flow. If plaque rupture occurs, blood clotting and blocking of the blood flow may also occur, which results in ischemic stroke/heart attack.

This paper analyzes the potential modes of action of different soy ingredients in LDL/heart-health management based on animal models and human studies. The paper further reveals the rationale for combining specific, well-known ingredients, like soy sterols, proteins, fatty acids, fibers, and vitamin E, for effective maintenance of low levels of non-oxidized plasma LDL cholesterol. Based on the fundamental differences in their modes of action, many known soy ingredients may potentially act synergistically in maintaining/obtaining low levels of plasma LDL cholesterol and future application of currently rather unknown soy ingredients, such a sphingolipids, lignans, and tocotrienols, showing again different modes of action, may allow for additional modulator choices.

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**SOYBEAN CONSTITUENTS**

Depending on the variety and environmental growing conditions, soy (*Glycine max*) beans are comprised of approximately 18% oil, 15% fibers/insoluble carbohydrates, 15% soluble carbohydrates, and 38% protein. Moreover, soybeans contain several minor constituents such as the following: lecithins (0.5%), sterols (0.3%), isoflavones (0.1%), tocopherols (0.02%), and very low levels of tocotrienols, sphingolipids, and lignans. The oil consists of 6% stearic acid, 9% palmitic acid, 26% oleic acid, 50% linoleic acid, and 7% linolenic acid. The majority of the total soy protein components comprises glycinin (~40%) and β-conglycinin (~27%). Glycinin consists of two subunits (A and B), comprising approximately 22% and 18% of the total soy protein and having molecular weights of 35 kD and 23 kD, respectively. β-conglycinin consists of three subunits (α′, α, and β), comprising approximately 6%, 11%, and 10% of total soy protein and having molecular weights of 70 kD, 68 kD, and 52 kD, respectively. Soy lecithins are a class of natural phospholipids that consists predominantly of phosphatidylcholine, phosphatidylinositol, and phosphatidylethanolamine. Soy sterols form a group of natural phytonutrients with structural similarity to cholesterol; the most abundant soy sterol is beta-sitosterol (60–65%) and the remainder is led mainly by campesterol. Soy isoflavones consist of a family of natural phytonutrients, similar in structure to human estrogens, with the most abundant isoflavones being genistein, daidzein, and glycitein. These isoflavones may be glycosylated and further conjugated with malonate or acetate on the sugars. Soy tocopherols (~200 mg/kg seeds) form part of a group of natural tocochromanols of which γ-tocopherol is the most predominant (~125 mg/kg seeds); it also contains R,R,R,−α-tocopherol (vitamin E), which is most readily retained / is most effective in the human body.1,2

**LOW-DENSITY LIPOPROTEIN**

Serum lipoproteins have been classified as high-density lipoprotein (HDL, diameter ±15 nm), LDL (diameter ±25 nm), or very-low-density lipoprotein (VLDL, diameter >30 nm). HDL particles contain approximately 45% protein (including the apoA protein), 15% cholesterol, and 40% mainly unsaturated triglycerides/fatty acids. LDL particles contain approximately 20% protein (including the apoB protein), 40% cholesterol, 40% mainly saturated triglycerides/fatty acids, and low quantities of fat-soluble antioxidants like vitamin E. Since LDL particles are involved in the transportation of cholesterol and triglycerides for use by cells throughout the body via the bloodstream, elevated levels of plasma LDL are associated with atherosclerosis. Increased levels of LDL frequently result from high triglyceride intake and consequently high concentrations in the liver, where this is matched by in situ cholesterol synthesis and increased packaging into VLDL particles, the precursors of LDL. Also, there is evidence that smaller-sized LDL particles correlate with much faster artery clogging progression than do larger-sized LDL particles.3 This most probably relates to the diameter of the pores in the endothelium (~26 nm), which permits easier penetration by smaller-sized LDL particles, allowing oxidation by free radicals in the endothelium/intima space4 generating oxidized LDL cholesterol, which is considered to be the most atherogenic.5 HDL particles function by carrying cholesterol away from the arteries back to the liver, either via cholesterol transfer from LDL (mediated by cholestereryl ester transfer protein) or by resorption of cholesterol from arterial plaque.6

**PHYTOSTEROLS**

Naturally occurring plant phytosterols differ from cholesterol only in the structure of their side chains; sterols differ from stanols in being unsaturated versus saturated at the C5-C6 double bond in their B ring.7,8 The most abundant plant sterols are sitosterol (see Figure 1A), campesterol, and stigmasterol,9 which are present in vegetable oils (soy), cereals, fruits, and vegetables; stanols are mainly present in oil seeds (soy) and wood pulp but are also in corn, wheat, rye, and rice.10 Due to their low presence in nature, stanols are usually manufactured from sterols by hydrogenation7 resulting in sitostanol, campestanol, and stigmastanol. Despite their structural similarities, the small differences between cholesterol and plant phytosterols/stanols play an important role in the discriminative uptake of cholesterol from the gut, with the latter being easily absorbed and plant phytosterols/stanols being poorly absorbed.10 As a consequence, phytosterols are present only at very low levels in the bloodstream and are considered nonatherogenic.7,11 In fact, dietary use of 2–3 g/day of sterols,7,12,13 stanols,7,14 or their ester derivatives,15,16 generate dose-dependent,7 significant plasma LDL cholesterol lowering (up to minus 10–15% from base level), in both animals and humans. Efficacies of orally administered sterols, stanols, and their esters in reducing human plasma LDL cholesterol are shown to be virtually identical,14,17–19 suggesting the unsaturated bond is irrelevant to their efficacy.20 Experiments with different fatty acids, esterified to the stanol moiety showed comparable LDL cholesterol-lowering capacity,19 indicating the irrelevance of the fatty acids. This is consistent with the finding of Miettinen et al.21 that 90% of the stanols recovered from ileostomy bags were unesterified, suggesting efficient lipolysis of the esters in the small intestine.20 The mechanism underlying the capability of plant sterols/stanols to
reduce plasma LDL cholesterol levels relates to their structural similarity to cholesterol. This enables them to compete with cholesterol for incorporation into micelles, which are translocated over the brush border membrane, from the gut into the plasma, via intestinal cholesterol transporters, known as NPC1L1 and SR-BI.\textsuperscript{12,18,22–24} Next, free sterols/stanols are assumed to be taken up by enterocytes directly and to prevent cholesterol from being esterified by blocking the ACAT system and subsequent transport to the mesenteric lymph. Free sterols/stanols are hypothesized to stimulate the ABC-ATP binding cassette mediated enterocytic cholesterol transfer back to the intestinal lumen for excretion from the body.\textsuperscript{25–28} Consequently, sterols/stanols will significantly downregulate the cholesterol influx and stimulate the efflux over the brush border membrane.\textsuperscript{8,28} The net effect is greater than the increased LDL receptor expression level and the de novo synthesis of cholesterol in the liver to counteract the lower absorption from the gut.\textsuperscript{12,28}

**PROTEINS**

As compared to plant sterols and stanols, vegetable proteins and, specifically, soy proteins replacing animal

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**Figure 1** Chemical structures of some soy constituents. A, beta sitosterol; B, phosphatidylcholine; C, alpha tocopherol; D, glycosylceramide; E, ceramide; F, isolariciresinol; G, pinoresinol; H, delta tocotrienol.
proteins, are reported to reduce elevated cholesterol levels in both animals and hyperlipidemic humans, only modestly, i.e., by about 5%, but still significantly, due to their synergistic efficacy. Support for the effects of soy proteins, per se, rather than potentially copurified constituents such as isoflavones, may be found in experiments and clinical data from Sirtori and Lovati. From these and studies by Baum et al., it may also be concluded that soy proteins are able to reduce plasma LDL levels by stimulating the activity of the LDL receptor apparatus in the liver. Model studies in human HepC2 cells with purified soy protein fractions and their subunits clearly demonstrate that the α′ subunits of soy β-conglycinin (7S globulin) are able to upregulate LDL receptor activity and its mRNA levels, being approximately 10 times more effective than the entire soy protein complex. Research conducted by Cho et al. with Hep T9A4 cells incubated with enzymatically hydrolyzed soy proteins, confirmed the hypothesis of soy peptide mediated stimulation of LDL receptor transcription. Experiments with two different synthetic peptides, each homologous to an amino acid sequence present in the α′ subunit, but absent in the β subunit, showed the peptide with the sequence LRVPAGTTFYVVNPNDENLRMIA has a significant capacity to upregulate LDL, while another, QDKESQEQPRHRKKNK, has virtually none. This clearly indicates that only part of the α′ subunit is important for the upregulation of LDL receptor activity, e.g., lowering plasma LDL levels. Next, the finding by Castiglioni et al. that soy β-conglycinin fed to rabbits is able to significantly delay LDL cholesterol oxidation and that it interacts with thioredoxin suggests that this subunit is able to activate redox proteins involved in the protection of LDL cholesterol from oxidation. The antioxidant role of soy protein and soy β-conglycinin-derived peptides (LLPHH, HPLH, PLHH) was further demonstrated by Takenaka and Chen, respectively. The role for soy proteins in lowering the in vivo oxidation of LDL cholesterol in humans was demonstrated by Scheiber and Jenkins. All in all, there is experimental data supporting the hypothesis that specific bioactive small peptides, generated by digestion/hydrolysis of soy protein, can be absorbed from the intestinal tract into the bloodstream and these subsequently have an upregulation effect on the liver LDL receptor machinery, resulting in lowering of the plasma LDL levels and/or preventing LDL cholesterol from (rapidly) being oxidized. In addition, indirect evidence for a role of soy protein in LDL management may be found in experiments by Duranti et al. with the α′ subunit of soy β-conglycinin, showing a significant decrease in plasma triglycerides in rats fed a cholesterol-rich diet. This effect might be due to decreased lipid synthesis and/or increased lipid degradation, which is in agreement with mechanisms described earlier.

Although the data are rather limited and may not be relevant to normo- and mildly hypercholesterolemic individuals, a totally different mechanism of soy protein mediation in LDL management may reside in positively influencing the LDL particle size. From experiments by Desroches et al. studying the effect of soy proteins on the size distribution of LDL particles under strictly controlled conditions in hypercholesterolemic men and women, it was concluded that soy proteins (50 g/day versus animal protein) induced a significant decrease (~10%) in small-size (<25.5 nm) LDL particles and a significant increase (+15%) in larger-size (>26.0 nm) particles. Soy proteins also decreased the cholesterol content of small LDL particles (~12%) versus an increased level in large LDL particles (+14%). Since smaller-sized LDL particles are reported to be most atherogenic, it may be concluded that soy proteins may shift LDL particle size distribution to a less atherogenic pattern.

### ISOFLAVONES

Although isoflavones, particularly genistein, have been shown to act as antioxidants, most studies carried out to demonstrate the involvement of isoflavones in the prevention of LDL cholesterol oxidation are quite confusing. Preliminary data from early studies suggest an LDL antioxidant effect, whereas later studies revealed no LDL antioxidant activity at all. Therefore, it may be concluded that isoflavones most probably do not play a major role in antioxidative plasma LDL management; rather, their antioxidant characteristics might be more important in protecting the body from oxidative cell/DNA damage. Additionally, studies measuring direct isoflavone-related lowering of LDL cholesterol levels have been ambiguous at best, but in rodents, the lowering effect is more consistent, suggesting an interspecies effect.

### FATTY ACIDS

As described in the first section of this article, soybean oil comprises 15% saturated fatty acids, consisting of 6% stearic acid (C18 = 0) and 9% palmitic acid (C16 = 0), and 83% unsaturated fatty acids, consisting of 26% oleic acid (C18 = 1), 50% linoleic acid (C18 = 2), and 7% linolenic acid (C18 = 3). Consumption of saturated fatty acids and, notably, fatty acids with 12–16-carbon chain length, leads to increased levels of plasma cholesterol, with the exception of stearic acid (C18 = 0), which has virtually no effect on plasma LDL cholesterol concentrations. This increase of plasma cholesterol from saturated fats is due to elevated levels of plasma LDL, which enables large quantities of cholesterol esters, rich in saturated fatty acids, to be absorbed from the bloodstream and transported to the liver. On the other hand, the intake of unsaturated fatty acids, particularly the polyunsaturated (PUFA) fatty acids (C18 = 2 and C18 = 3), has been shown to reduce plasma cholesterol concentrations, with the exception of linolenic acid (C18 = 3), which may actually increase plasma cholesterol levels. The combination of saturated and unsaturated fatty acids in soybean oil appears to have a synergistic effect on plasma cholesterol levels, with the reduction of cholesterol being greater than the sum of the effects of the individual fatty acids.
acids, to be accommodated. Intake of unsaturated fatty acids causes the opposite effect, i.e., a lowering of plasma cholesterol levels, with reductions of up to 14%.71,73–75 This decrease of plasma cholesterol is due to the preference of unsaturated fatty acid to partition into HDL particles, which carry the plasma cholesterol back to the liver for degradation. The fundamental mechanisms underlying the LDL-level increase by saturated fatty acids relate to stimulation of cholesterol synthesis in the liver and to downregulation of the hepatic LDL receptor activity.76,77 Unsaturated fatty acids act by upregulating the activity of these receptors77,78 and by reducing the level of LDL and/or increasing the LDL particle size.79,80 Also, unsaturated fatty acids (notably monounsaturates, having only one double bond), are more resistant to lipid peroxidation,81 thus preventing LDL cholesterol from being oxidized82,83 and making them less atherogenic. Partially hydrogenated soybean oil, manufactured for specific food applications, may contain significant percentages of trans fatty acids, notably elaidic acid (C18 = 1, trans 9), which have been shown to increase plasma LDL and to lower plasma HDL levels quite drastically.76,84,85 Their capability to decrease the LDL particle size is what makes them more atherogenic relative to their saturated counterparts.86

**LECITHIN**

Several studies indicate that lecithin significantly reduces LDL cholesterol levels and increases HDL cholesterol levels in hyperlipidemic animals87,88 and hyperlipidemic humans.89–91 but this could not be demonstrated to the same extent in normolipidemics.89,91 Also, it may be concluded that the hypolipidemic efficacy of lecithin may vary by its composition, e.g., content of unsaturated fatty acids and type of phospholipids;87,92,93 thus, it is hypothesized that soy lecithin, as compared to egg lecithin, is quite effective due to its linoleic acid and phosphatidylcholine content94 (Figure 1B). The linoleic constituent is reported to play an important role in enhancing HDL formation,95 its resorption by the liver, and consequent secretion of bile lipids from the body.96,97 Adequate supply of phosphatidylcholine might be involved in the reduction of LDL plasma cholesterol levels via inhibition of its intestinal absorption, which may be abolished by sufficient phospholipase activity.94 Therefore, reduction of plasma LDL cholesterol by soy lecithin is assumed to relate to reduction of cholesterol uptake from the digestive tract. The increase of HDL is presumably linked to the action of the enzyme lecithin:cholesterol acyltransferase, which transfers an unsaturated fatty acid moiety from lecithin onto cholesteryl esters in HDL, being subsequently degraded in the liver.

**FIBERS**

Based on their simulated intestinal solubility, dietary fibers are usually classified as insoluble/poorly fermentable fibers, comprising celluloses, hemicelluloses, and lignins, or soluble/highly fermentable fibers, comprising pectins, β glucans, galactomannans, and gums.98,99 According to studies in cholesterol-fed rats (60 g/kg body weight/day), dietary soluble viscous fibers may have a significant effect on plasma LDL cholesterol levels, with some types such as rice and wheat bran increasing LDL cholesterol levels and others such as corn bran, oat bran, and soy fibers, significantly decreasing LDL cholesterol levels (minus 10–20%), while leaving the HDL cholesterol concentration untouched.100

In hypercholesterolemic men and hyperlipidemic postmenopausal women (high soy-fiber diet), essentially the same phenomenon could be demonstrated.101,102 Apparently, differences in fiber composition strongly dictate the hypo- or hypercholesterolemic influences on the plasma LDL cholesterol concentrations, with high β glucan levels being quite beneficial.103,104 This could be further substantiated by Jenkins et al. for β-glucan (3 g/day) and psyllium (8 g/day), although the effects were only modest, i.e., <3%.105 Moreover, Andon and Anderson, in their review of the literature on oat fibers over the last 10 years, concluded that the intake of oats may confer health benefits that extend beyond total and LDL cholesterol reduction.106 Finally, according to the National Cholesterol Education Program 2008, there is ample evidence that 5–20 grams of soluble viscous fiber per day reduces plasma LDL cholesterol levels by approximately 5%.

The underlying mechanism might be quite complex, since it has been reported that viscous soluble fibers may decrease the digestion and assimilation of proteins/peptides in the small intestine,107 which may regulate plasma LDL levels (see paragraph on proteins). Next, it may relate to the finding that fiber polysaccharides strongly inhibit pancreatic lipase, affecting the absorption of lipids,108 and subsequently influence plasma LDL cholesterol levels. Last but not least, dietary fibers may contribute to the lowering of LDL cholesterol levels either directly or indirectly. In the direct mode, they surround/lock-in intestinal cholesterol, as is the case with soy fibers.109 Indirectly, they operate through stimulation of bile acids excreted from the body, which stimulates bile acid synthesis from cholesterol, thus reducing the levels of circulating cholesterol, as reported for oat fibers.110–112 More importantly, soluble viscous fiber behaves in the gut as a gel-like substance, which blocks the absorption/transfer of fats and cholesterol into the bloodstream simply by entrapment.113,114 As a result, some fibers such
as oat and psyllium fibers produce lower concentrations of small-sized LDL particles in the blood, thus contributing to a cardioprotective effect.115,116

**VITAMIN E**

Vitamin E is a generic term for a group of tocopherols, comprising all isomeric forms of α-, β-, γ-, and δ-tocopherols and α-, β-, γ-, and δ-tocotrienols, which have beneficial effects in radical scavenging in lipophylic environments.1 Although tocotrienols and γ tocopherol possesses higher radical scavenging activity than α-tocopherol in vitro,117,118 the R,R,R-α-tocopherol (Figure 1C) is the most significant biologically, because of its high uptake and retention in the body.119,120 The other tocopherols are either not retained or are retained at very low levels in body tissue.121 The reason for this resides in the α-tocopherol transfer protein (TTP), which selectively enriches VLDL in hepatocytes with R,R,R-α-tocopherol119,121 from remnants of chylomicrons which contain all different forms of vitamin E.120,121 As a consequence, R,R,R-α-tocopherol accounts for about 90% of the body’s total tocopherols, although the dietary intake of γ-tocopherol is usually much greater.122 About 50% of the total plasma α-tocopherol is found in LDL particles while about 25% is in VLDL and 25% in HDL particles.123 The biological role of α-tocopherol in LDL management is to antagonize LDL cholesterol oxidation to prevent it from becoming more atherogenic.124–126 Basically, this prevention by α-tocopherol relates to its relatively high abundance of LDL particles (6–8 molecules per LDL particle)124 and its effectiveness in scavenging lipid peroxyl radicals, which is several orders of magnitude higher than for the lipid itself. The formed tocopheroxyl radical further reacts with a second lipid peroxyl radical, thus being able to extinguish two lipid peroxidation chains and forming a non-radical tocopheryl quinone, which is degraded and secreted from the body.122 Next, α-tocopherol has been reported to decrease the expression of the scavenger receptors SR-A and CD36,125 which play an important role in the formation of foam cells in the early stage of atherosclerosis. Moreover, α-tocopherol (at high doses) induces anti-inflammatory effects by interfering with the release of cytokines, by preventing the attraction of monocytes into the endothelial intima, and by inhibiting various inflammatory enzyme systems, which also contribute to cardioprotective benefits.125,128

**SPHINGOLIPIDS**

Sphingolipids form a large group of structural, plasma membrane lipids found in all eukaryotes, comprising free sphingoid base, ceramides, sphingophospholipids, and glycosphingolipids. Soybeans, which are considered to be a rich source,129 contain two classes of sphingolipids – glycosylceramide (predominantly) and ceramide130 (Figure 1D,E) at a glycosylceramide content of approximately 20 mg/100 g beans.131 Dietary sphingolipids may be converted into bioactive metabolites, which have been shown in animal studies to significantly reduce plasma cholesterol and hepatic triglyceride levels.132 In mice containing the human ApoE3Leiden gene, giving them a lipoprotein profile comparable to that of humans, 1% phytosphingosine added to the diet, generated a dose-dependent 75% reduction (observed after 9 weeks) of the plasma cholesterol, mostly due to reductions of the plasma VLDL and LDL levels.133–135 Preliminary experiments in overweight humans showed an approximate 10% reduction of total cholesterol and an approximate 13% reduction of LDL cholesterol.135,136 The underlying mechanism was demonstrated to be decreased intestinal cholesterol absorption, which is comparable to the mode of action of phytosterol.134–136 However, sphingolipids also increase cholesterol excretion quite effectively, i.e., up to 60% reduced hepatic cholesterol levels,134,135 making sphingolipids, overall, much more effective than phytosterols/stanols, thus avoiding potentially nonbeneficial high dosages.

**LIGNANS**

Soy lignans (−2 mg/100 g of beans, effective dose −100 mg/day) comprise isolariciresinol (29%; Figure 1F), pinoresinol (21%; Figure 1G), syringaresinol (18%), secoisolariciresinol (16%), lariciresinol (14%), and matairesinol (1%), which are dietary precursors of the mammalian lignans enterolactone and enterodiol.137,138 With respect to plasma LDL control, there is substantial data indicating that lignans, as a class, act as effective antioxidants in preventing LDL cholesterol from being oxidized, rendering them less atherogenic.139–142 This finding was substantiated by Kangas et al.,140 who demonstrated that 7 hydroxy-matairesinol (from Picea abies) is incorporated into isolated LDL fractions to protect LDL cholesterol from being oxidized. Surprisingly, the LDL oxidation inhibition efficiency of hydroxyl-matairesinol is approximately 50% of that of vitamin E, whereas its peroxyl radical scavenging ratio is 4:1 versus 2:1 for vitamin E, indicating a less effective/different mode of action. Next, lignans are able to dose-dependently reduce plasma LDL levels in both animals (minus 14%) and humans (minus 24%).143,144 which might be the result of upregulation of the LDL receptor activity145 and/or downregulation of the hepatic lipoprotein synthesis, leading to lower serum LDL levels.146
TOCOTRIENOLS

Soy tocotrienols have the same aromatic chromanol head (α, β, γ, and δ) as soy tocopherols, but they differ in their tail by having a farnesyl side chain bearing three unsaturated bonds instead of a fully saturated phytyl chain. Predominantly Qureshi et al. and only a few other groups have reported that tocotrienols (150–200 mg/day) are beneficial in reducing the serum LDL cholesterol levels in both animals147,148 and humans149–151 in the order δ > γ > α > β; δ-tocotrienols (see Figure 1H) are reported to be approximately 30 times more effective than β-tocotrienols.151 LDL levels were reduced, dose-dependently, by 65% in chickens and rats152,153 and by 25–40% in hyperlipidemic humans;154,155 however, in healthy individuals, virtually no effect was observed.156 Other attempts to demonstrate the benefits of tocotrienols in LDL management failed157–159 which leaves the question of efficacy open at this time. According to Parker et al.,160 a putative (dual) mode of action of tocotrienols may reside in their ability to post-transcriptionally stimulate the conversion of liver farnesyl (precursor to cholesterol) into farnesol, which enhances proteolytic breakdown of HMG-(hydroxyl-methyl-glutaryl)-CoA reductase, an essential enzyme in the cholesterol biosynthetic pathway. Since this is quite different from the mode of action of pharmaceutical statin preparations, which block HMG-CoA-reductase by competitive inhibition,161 tocotrienol action may be additive to the effect of this LDL cholesterol-lowering drug.

CONCLUSION

In regard to inter-individual variations in cholesterol levels, it should be noted that about 50% of all variations are genetically determined, with family-related hypercholesterolemia occurring in every 1 of 300 people.162 Within this group, almost 50% show genetic variation in the LDL-receptor gene, leading to elevated plasma LDL levels.163 Next to that, mutations in many other genes independently influence LDL and HDL cholesterol concentrations,164 with new genes and variations being discovered frequently.165 Based on this, it is reasonable to assume that phenotypically homogeneous hypercholesterolemic target groups, will be quite heterogeneous genotypically, which might very well explain why the outcomes of studies on the cholesterol-reducing effects of food ingredients are sometimes conflicting. Moreover, differences in individual lifestyles (e.g., physical exercise), nutrition habits, and specific gut floras also contribute to significant heterogeneity in target groups, which leads to debatable efficacies of the ingredients tested. Apparently, this efficacy in LDL management is strongly dependent on a wide variety of sites and levels of control. Therefore, food ingredients might be beneficial for managing proper LDL levels, provided that their mode of action is not being hampered by sites/levels that are being blocked by genetic, lifestyle variations, or nutrition habits. Understanding the differences in the modes of action of various soy ingredients might allow for the composition of rather effective ingredient cocktails, covering various modes of action, and thus broadening and increasing the chances of overcoming genetic, lifestyle, and nutrition barriers. Such cocktails could result in effective LDL management, not only in terms of plasma LDL levels, but more importantly, in terms of LDL-mediated causation, i.e., particle size, microcomposition, and cholesterol oxidation status.

From the data reviewed in the previous sections, it may be concluded, that in terms of LDL management, most, if not all, soy ingredients may act via different modes of action and most ingredients act via more than one different mechanisms (Table 1). These comprise the following: suppression of LDL absorption from the gut (sterols/stanols, fibers, sphingolipids), stimulation of the efflux of cholesterol over the brush border membrane

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</table>

Key: 0, unaffected; +, increased; –, decreased.
back to the intestinal lumen (sterols/stanols), stimulation of LDL resorption from the plasma (protein, lignans, unsaturated fatty acids), prevention from oxidation (lignans, vitamin E, proteins), increase of LDL particle size (protein, fibers, unsaturated fatty acids), reduction of cholesterol synthesis (tocotrienols), and increase of bile secretion (lecithin, sphingolipids, fibers), which form the basis of synergism in LDL management, as has been demonstrated for proteins, fibers, and lecithins by Hoie et al., 163-165 proteins and sterols by Lin et al., 34 or for fibers, proteins, and sterols by Jenkins et al. 167 The differences in modes of action also form the basis for synergism between soy ingredients and LDL-managing drugs, like statin, as exemplified by combinations of sterols and statin,168 fatty acids and statin,170 and fibers and statin;171,172 this opens up the possibility of creating a (cost-) effective von adjunctive therapy for patients who are not able to reach their target LDL cholesterol levels with atin therapy alone.169 Last but not least, by cleverly exploiting the different modes of action of soy ingredients, pharmacotherapy may be surpassed completely for patients who suffer from side effects or who exhibit insensitivity to drug treatments.173,174 From the promising data obtained with other, currently rather poorly examined, soy ingredients, such as lignans, tocotrienols, and sphingolipids, it may be expected that novel and effective ingredient cocktails will be developed in the near future to further optimize non-pharmacological LDL management. Also, based on the positive results obtained with traditional soy foods like tofu, soy milk, and tempeh, the application of new concepts, like whole (soy) bean powder, might lead to interesting results, since these powders contain all soy ingredients, including the ones not yet identified, in their natural proportions and interrelationships.

As mentioned earlier, with respect to the efficacy of individual (new) soy ingredients, it might very well be that a modest response is a reflection of the high number of variations of/in LDL regulatory genes present in the target groups 163-165 rather than of a low specific efficacy toward the genetically unmodified regulatory genes. This phenomenon obviously hampers efficient screening for new LDL-beneficial ingredients, but it also clearly indicates the possible need for their development and application in more individualized nutritional approaches to managing appropriate LDL levels.

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