JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY
REVIEW

J. Agric. Food Chem. 2010, 58, 8119–8133 8119
DOI:10.1021/jf100901b

Non-isoflavone Phytochemicals in Soy and Their Health Effects

Jie Kang, Thomas M. Badger, Martin J. J. Ronis, and Xianli Wu*

USDA Arkansas Children's Nutrition Center, University of Arkansas for Medical Sciences, 15 Children's Way, Little Rock, Arkansas 72202

Epidemiological and clinical studies have linked consumption of soy foods with low incidences of a number of chronic diseases, such as cardiovascular diseases, cancer, and osteoporosis. Over the past decades, enormous research efforts have been made to identify bioactive components in soy. Isoflavones and soy protein have been suggested as the major bioactive components in soy and have received considerable attention. However, there are hundreds of phytochemical components in soybeans and soy-based foods. In recent years, accumulating evidence has suggested that the isoflavones or soy proteins stripped of phytochemicals only reflect certain aspects of health effects associated with soy consumption. Other phytochemicals, either alone or in combination with isoflavones or soy protein, may be involved in the health effects of soy. This review attempts to summarize major non-isoflavone phytochemicals in soy, as well as their bioavailability and health effects. In addition, a brief discussion of components formed during food processing is also included.

KEYWORDS: Soy; soyasaponins; phytosterol; lignan; phytic acid; bioavailability; health effects

1. INTRODUCTION

Soy is one of the most researched foods. Epidemiological studies suggest that soy consumption is associated, at least in part, with lower incidences of a number of chronic diseases (*1*−*4*). Soy-based foods have been consumed in Asian countries such as China and Japan for many centuries. The lower rates of several chronic diseases in Asia, including cardiovascular diseases and certain types of cancer, have been partly attributed to consumption of large quantities of soy foods (*5*, *6*).

In the past few decades, extensive efforts have been made toward identifying bioactive components in soy that are responsible for the health benefits. Isoflavones and soy proteins are the two major groups of components that have received the most attention (*7*−*10*). Isoflavones belong to a broad group of plant-derived compounds that have structural and functional similarities to estrogens, and this has led to the term phytoestrogens (*11*, *12*). The analysis, bioavailability, and health effects of isoflavones have been extensively studied and frequently reviewed (*11*, *13*−*20*). Consumption of isoflavones has been suggested to have multiple beneficial effects on heart disease (*21*−*23*), certain types of cancer (*24*−*26*), bone functions (*27*−*30*), and prevention of obesity (*31*, *32*). The studies of hypolipidemic effects of soy protein started in the 1960s (*33*), but did not gain much attention until the classic meta-analysis published by Anderson et al. in 1995 (*1*). In 1999, the U.S. Food and Drug Administration approved the use, on food labels and in food labeling, of health claims on the association between soy protein and reduced risk of coronary heart disease (CHD) (*34*). Most recently, soy protein was also shown to have other beneficial effects, related to obesity and renal functions (*35*, *36*).

*Author to whom correspondence should be addressed [e-mail wuxianli@uams.edu; phone (501) 364-2813; fax (501) 364-3161].

Accumulating evidence has suggested that the isoflavones or soy protein only reflected certain aspects of health effects associated with soy consumption. For example, using primate models of atherosclerosis, the intact soy protein has been shown to be effective in lowering cholesterol compared to alcohol-extracted soy protein (*37*). However, adding semipurified soy isoflavones to a casein diet had no effect on plasma cholesterol level in these animals (*38*). In another study, the effects of soy protein isolate (SPI) on CYP3A1 expression were suggested to be primarily due to phytochemical components of SPI other than isoflavones (*39*). These studies indicated that other components in soy protein, either alone or in combination with isoflavones or soy protein, may be bioactive. Studies have shown that non-isoflavone compounds, such as soyasaponins, phytic acid, or plant sterols, display a wide range of bioactivities, including anticancer, antioxidative, and antiviral, cardiovascular protective effects, and hepatoprotective actions (*40*).

Whereas numerous studies support the positive effects of consuming soy, potential concerns regarding the safety of soy consumption, especially as related to soy isoflavones, have surfaced within the past decade, adding confusion for consumers (*41*−*44*). One big source of the confusion is the lack of chemical composition information of the study products. Not all soy products are created equal, and different products differ remarkably in both macro- and microconstituents. Accurate interpretation of the variety of studies relies on the knowledge of chemical composition of specific soy foods (*41*). In reference to phytochemicals in soy, phytochemicals other than isoflavones (non-isoflavone phytochemicals) are rarely reviewed. This review attempts to bridge this gap with a summary of non-isoflavone phytochemicals in soy and soy products, their bioavailability, and potential health effects.

Published on Web 06/25/2010

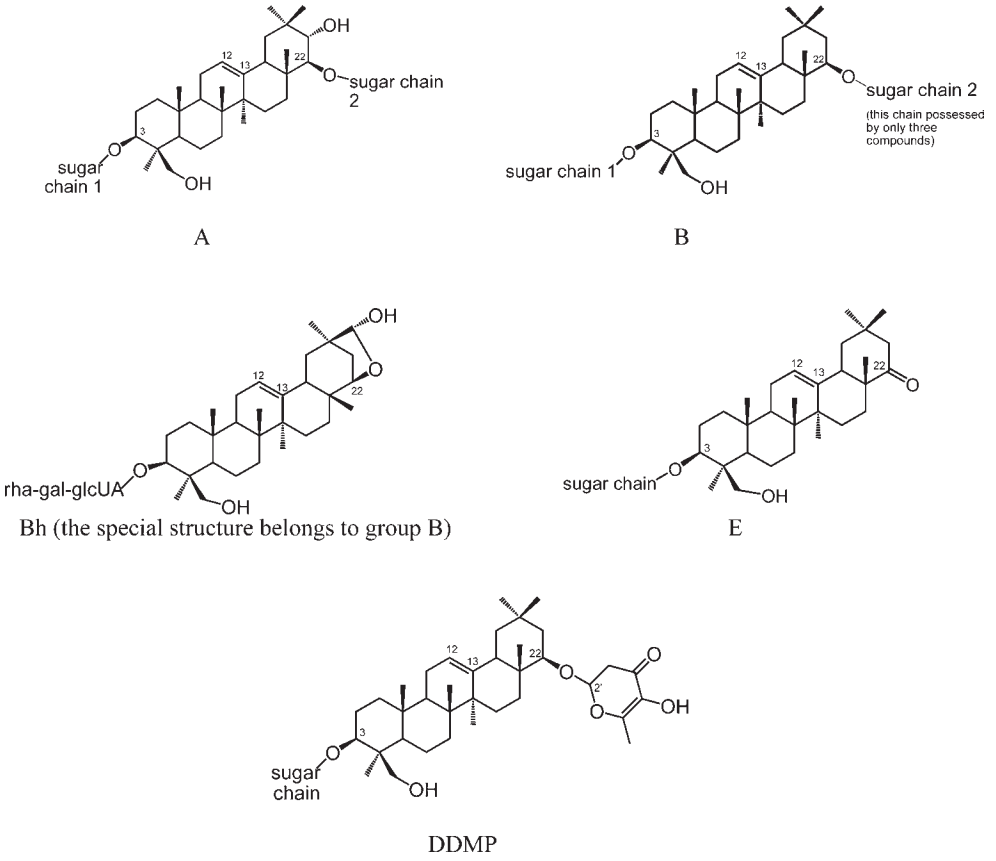


Figure 1. Chemical structures of group A, B, Bh, E, and DDMP soyasaponins in soy.

2. NATURAL NON-ISOFLAVONE CONSTITUENTS IN SOY

In this section, we focus on the phytochemicals that naturally exist in soybean. Composition and contents of phytochemicals in soybean vary depending on the variety and growing environment. In general, the contents of major phytochemicals in soybean are phytic acid (1.0−2.2%) (*45*), sterols (0.23−0.46%) (*46*), saponins (0.17−6.16%) (*47*), isoflavones (0.1−0.3%) (*48*), and lignans (0.02%) (*49*). The first objective is to summarize the structural characterizations of major non-isoflavone phytochemicals in soybean.

Dietary components, when taken orally, must be bioavailable in some form to exert biological effects. A prerequisite for investigating bioactivities of a given food component is to understand if, how, and to what extent it is absorbed, metabolized, and excreted. Bioavailability differs greatly from one component to another on the basis of their chemical structures. It is also influenced by an individual's metabolism, food-processing methods, and interaction with bile acids (*50*). As a second objective of this section, bioavailabilities of major non-isoflavone phytochemicals are briefly summarized.

Last but not the least, potential health effects of major non-isoflavone phytochemicals are summarized. For many years, studies of the health effects of soybean primarily focused on isoflavones or protein isolates. However, other phytochemicals in soy, such as soyasaponins, phytosterols, lignans, phytic acid, and oligosaccharides, have also been found to exert biological activities. These may contribute to overall health effects observed with soy consumption.

2.1. Soyasaponins and Soyasapogenols. *2.1.1. Chemical Characteristics of Soyasaponins and Soyasapogenols.* Saponins are sterol or triterpene glycosides, which occur in a wide variety of plants. Soy-based foods are primary dietary sources of saponins (*51*). Chemical studies of saponins in soy trace back to the 1930s (*52*,*53*). From the 1980s to 1990s, a number of papers, especially those published by Japanese researchers, significantly enriched our knowledge about the chemical structures and diversity of these types of compounds in soy (*54*−*62*).

Saponins in soy are often referred to soyasaponins. They differ from each other by the types of aglycones and the position where the sugar chain is attached. Generally, saponins are classified into four major groups, on the basis of their aglycone structures: groups A, B, E, and DDMP. Group A saponins have a hydroxyl group at the C-21 position, and group B saponins have a hydrogen atom at the same position. Group E saponins differ from groups A and B by having a carbonyl group at C-22. Group B saponins may contain a 2,3-dihydro-2,5-dihydroxy-6-methyl-4*H*-pyran-4-one (DDMP) moiety at the C-22 position and are denoted DDMP saponins (*63*) (**Figure 1**) . DDMP soyasaponins and the acetylated soyasaponins of group A are sometimes considered to be the genuine forms of group A and B in soybeans. Group E soyasaponins are also considered to be phyto-oxidation products of group B soyasaponins (*59*, *64*, *65*). All four groups of soysaponins are glycosides of oleanan triterpene aglycones known as soyasapogenols. The oleanan aglycone contains one or more hydroxyl groups, and carboxylic groups and double bonds may also be present. The sugar moieties are generally attached at the C-3 position and sometimes at the C-22 postion of the aglycones. Group A soysaponins have two sugar chains, separately attached to C-3 and C-22 positions of soyasapogenol A, except for A3 (**16**), which has only one sugar chain at C-3 (**Table 1**). The C-3 sugar chain consists of two or three sugar residues, starting with a glucoronyl residue (glcUA) (*64*). The C-22 side chain consists of two sugar residues, starting with an anarabinosyl and ending with a xylosyl or glycosyl residue (*55*, *60*, *62*, *66*) (**Figure 1**). Group B soysaponins have one

Table 1. Structures and Molecular Formulas of Group A Soyasaponins

no.	name	C-3 sugar chain	C-22 sugar chain	molecular formula	ref
1	Aa (acetyl A_4)	glc(1→2)gal(1→2)glcUA(1→3)	2,3,4-tri-*O*-acetyl-xyl(1→3)ara(1→22)	$C_{64}H_{100}O_{31}$	*62*
2	Ab (acetyl A_1)	glc(1→2)gal(1→2)glcUA(1→3)	2,3,4,6-tetra-*O*-acetyl-glc(1→3)ara(1→22)	$C_{67}H_{104}O_{33}$	*61*
3	Ac	rha(1→2)gal(1→2)glcUA(1→3)	2,3,4,6-tetra-*O*-acetyl-glc(1→3)ara(1→22)	$C_{67}H_{104}O_{32}$	*60*
4	Ad	glc(1→2)ara(1→2)glcUA(1→3)	2,3,4,6-tetra-*O*-acetyl-glc(1→3)ara(1→22)	$C_{66}H_{102}O_{32}$	*60*
5	Ae (acetyl A_5)	gal(1→2)glcUA(1→3)	2,3,4-tri-*O*-acetyl-xyl(1→3)ara(1→22)	$C_{58}H_{90}O_{26}$	*62*
6	Af (acetyl A_2)	gal(1→2)glcUA(1→3)	2,3,4,6-tetra-*O*-acetyl-glc(1→3)ara(1→22)	$C_{61}H_{94}O_{28}$	*61*
7	Ag (acetyl A_6)	ara(1→2)glcUA(1→3)	2,3,4-tri-*O*-acetyl-xyl(1→3)ara(1→22)	$C_{57}H_{88}O_{25}$	*62*
8	Ah (acetyl A_3)	ara(1→2)glcUA(1→3)	2,3,4,6-tetra-*O*-acetyl-glc(1→3)ara(1→22)	$C_{60}H_{92}O_{27}$	*61*
9	Ax	glc(1→2)ara(1→2)glcUA(1→3)	2,3,4-tri-*O*-acetyl-xyl(1→3)ara(1→22)	$C_{63}H_{98}O_{30}$	*66*
10	A_1	glc(1→2)gal(1→2)glcUA(1→3)	glc(1→3)ara(1→22)	$C_{59}H_{96}O_{29}$	*61*
11	A_2	gal(1→2)glcUA(1→3)	glc(1→3)ara(1→22)	$C_{53}H_{86}O_{24}$	*61*
12	A_3	ara(1→2)glcUA(1→3)	glc(1→3)ara(1→22)	$C_{52}H_{84}O_{23}$	*61*
13	A_4	glc(1→2)gal(1→2)glcUA(1→3)	xyl(1→3)ara(1→22)	$C_{58}H_{94}O_{28}$	*61*
14	A_5	gal(1→2)glcUA(1→3)	xyl(1→3)ara(1→22)	$C_{52}H_{84}O_{23}$	*61*
15	A_6	ara(1→2)glcUA(1→3)	xyl(1→3)ara(1→22)	$C_{51}H_{82}O_{22}$	*61*
16	A3	rha(1→2)gal(1→2)glcUA(1→3)		$C_{48}H_{78}O_{19}$	*55*

Table 2. Structures and Molecular Formulas of Group B Soyasaponins

no.	name	C-3 sugar chain	C-22 sugar chain	molecular formula	ref
17	soyasaponin Ba or V	glc(1→2)gal(1→2)glcUA(1→3)		$C_{48}H_{78}O_{19}$	*61*
18	soyasaponin Bb or I	rha(1→2)gal(1→2)glcUA(1→3)		$C_{48}H_{78}O_{18}$	*56*
19	soyasaponin Bc or II	rha(1→2)ara(1→2)glcUA(1→3)		$C_{47}H_{76}O_{17}$	*56*
20	soyasaponin Bb′ or III	gal(1→2)glcUA(1→3)		$C_{42}H_{68}O_{14}$	*56*
21	soyasaponin Bc′ or Bx	glc(1→2)ara(1→2)glcUA(1→3)		$C_{47}H_{76}O_{18}$	*66*
22	soyasaponin IV	ara(1→2)glcUA(1→3)		$C_{41}H_{66}O_{13}$	*54*
23	soyasaponin Bh	rha(1→2) gal(1→2)glcUA(1→3)		$C_{48}H_{78}O_{19}$	*69*
24	3-*O*-{α-L-rhamnopyranosyl(1→2)-[β-D-glucopyranosyl-(1→3)-β-D-galactopyranosyl-(1→2)]-β-D-glucuronopyranosyl}-22-*O*-[β-D-glucopyranosyl(1→2)-α-L-arabinopyranosyl]-3β,22β,24-trihydroxyolean-12-ene	rha(1→2)[glc(1→3)gal(1→2)] glcUA(1→3)	glc(1→2)ara(1→22)	$C_{65}H_{106}O_{32}$	*67*
25	3-*O*-[α-L-rhamnopyranosyl(1→2)-β-D-galactopyranosyl(1→2)]- β-D-glucuronopyranosyl-22-*O*-[α-L-rhamnopyranosyl(1→2)-α-L-arabinopyranosyl]-3β, 22β,24-trihydroxyolean-12-ene	rha(1→2)gal(1→2)glcUA(1→3)	rha(1→2)ara(1→22)	$C_{59}H_{96}O_{26}$	*68*
26	3-*O*-[α-L-rhamnopyranosyl(1→2)-β-D-galactopyranosyl(1→2)]- β-D-glucuronopyranosyl-22-*O*-[α-L-rhamnopyranosyl(1→2)-β-D-glucopyranosyl]-3β, 22β,24-trihydroxyolean-12-ene	rha(1→2)gal(1→2)glcUA(1→3)	rha(1→2)glc(1→22)	$C_{60}H_{98}O_{27}$	*68*

Table 3. Structures and Molecular Formulas of Group E Soyasaponins

no.	name	C-3 sugar chain	molecular formula	ref
27	soyasaponin Bd (sandosaponin A)	glc(1→2)gal(1→2)glcUA(1→3)	$C_{48}H_{76}O_{19}$	*60*
28	soyasaponin Be (dehydrosoyasaponin I)	rha(1→2)gal(1→2)glcUA(1→3)	$C_{48}H_{76}O_{18}$	*60*
29	soyasaponin Bf	glc(1→2)ara(1→2)glcUA(1→3)	$C_{47}H_{74}O_{18}$	*66*
30	soyasaponin Bg	rha(1→2)ara-(1→2)glcUA(1→3)	$C_{47}H_{74}O_{17}$	*66*

sugar chain attached to the C-3 position of soyasapogenol B, with three exceptional compounds that have two sugar chains at the C-3 and C-22 positions (**24**−**26**) (*54*, *56*, *66*−*68*) (**Figure 1**). Most recently, a new soyasaponin Bh (**23**) was identified to bear a unique five-membered ring containing a hemiacetal functionality (**Figure 1**) (*69*). Group E soysaponins contain only one sugar chain at the C-3 position. They are considered to be formed by photo-oxidation at C-22 of group B (*60*, *66*) (**Figure 1**). DDMP soyasaponins are categorized under B type soyasaponins by some researchers (*47*). Their structures were characterized as having a DDMP group conjugated to group B at C-22 (*64*, *70*−*72*) (**Figure 1**). Similar to B type soyasaponins, DDMP soyasaponins contain only one sugar chain attached to the C-3 postion. There are about 36 soysaponins identified in soybean. Their structures and the related references are listed in **Tables 1**−**4**.

Soyasapogenols are aglycones of soyasaponins. They can be obtained by acid or alkaline hydrolysis of soyasaponins. Although soyasapogenols do not exist in soybean naturally, they may exist in certain soy products through food processing. Five soyasapogenols, A (**37**), B (**38**), C (**39**), D (**40**), and E (**41**), have been found through hydrolysis of soyasaponins (*56*, *59*, *73*) (**Figure 2**). Among them, soyasapogenol A (**37**) has a hydroxyl group at both the C-21 and C-22 positions and is considered to be a corresponding aglycone to bisdesmoside soyasaponin group A. Soyasapogenol B (**38**) has only one hydroxyl group, at the C-22 postion. It is considered to be an aglycone of both monodesmoside soyasaponin group B and DDMP. Soyasapogenol E (**41**) is regarded as the corresponding aglycone to soyasaponin group E. Soyasapogenols C (**39**) and D (**40**) are considered by some researchers as not genuine aglycones of soyasaponins but as the acid hydrolysis products of soyasapogenol B (**38**) (*74*).

2.1.2. Bioavailability of Soyasaponin. Saponins are generally considered to have low bioavailability. In an early study in the 1960s, soybean saponin-containing diets were given orally to chicks, rats, and mice. Neither soybean saponins nor soyasapongenols were found in the blood or urine of these organisms.

Table 4. Structures and Molecular Formulas of Group DDMP Soyasaponins

no.	name	C-3 sugar chain	C-22 DDMP	molecular formula	ref
31	soyasaponin αg	glc(1→2)gal(1→2)glcUA(1→3)	DDMP(22→2′)	$C_{54}H_{84}O_{22}$	*65*
32	soyasaponin αa	glc(1→2)ara(1→2)glcUA(1→3)	DDMP(22→2′)	$C_{53}H_{82}O_{21}$	*72*
33	soyasaponin βg or VI	rha(1→2)gal(1→2)glcUA(1→3)	DDMP(22→2′)	$C_{54}H_{84}O_{21}$	*65*
34	soyasaponin βa	rha(1→2)ara(1→2)glcUA(1→3)	DDMP(22→2′)	$C_{53}H_{82}O_{20}$	*65*
35	soyasaponin γg	gal(1→2)glcUA(1→3)	DDMP(22→2′)	$C_{48}H_{74}O_{17}$	*65*
36	soyasaponin γa	ara(1→2)glcUA(1→3)	DDMP(22→2′)	$C_{47}H_{72}O_{16}$	*65*

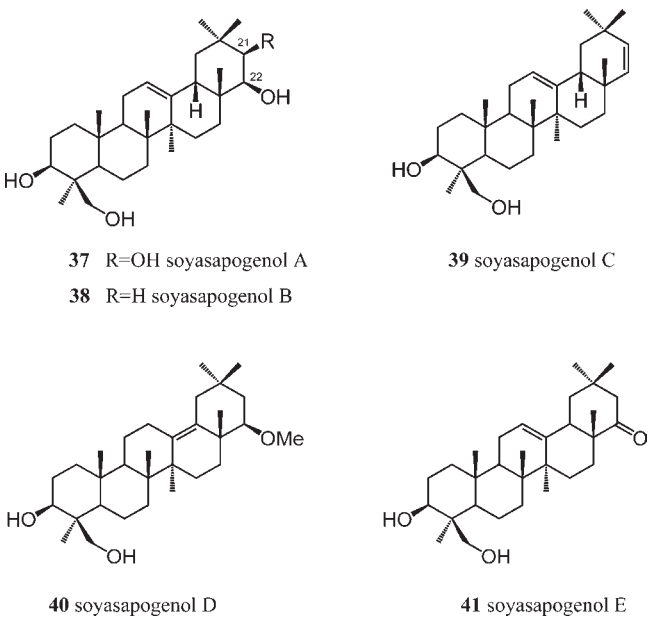


Figure 2. Chemical structures of soyasapogenols A−E (hydrolysis products of soysaponins).

Ingested soybean saponins were hydrolyzed into sapogenins and sugars by cecal microflora (*75*). However, the separation and detection of saponins used in that study were probably not sensitive enough to pick up trace amounts of metabolites. In a human study to evaluate soyasaponin bioavailability (*76*), eight healthy women ingested single doses of concentrated soybean extract containing 434 μmol of group B soyasaponins. Neither soyasaponins nor their metabolites were detected in 24 h urine collection. Soyasapogenol B (**38**), a major metabolite of group B soyasaponins, was found (36.3 ± 10.2 μmol) during five days of fecal collection, but no group B soyasaponins were detected. These results indicated that ingested soyasaponins have low absorbability in human intestinal cells and seem to be metabolized to soyasapogenol B (**38**) by human intestinal microorganisms in vivo and excreted in feces (*76*).

The metabolites of soyasaponin I (**18**) by human fecal bacteria were also investigated in vitro. Fresh feces from 15 healthy women were incubated anaerobically with 10 mmol of soyasaponin I (**18**)/g of feces at 37 °C for 48 h. Two major gut microbial metabolites of soyasaponin I (**18**) were identified as soyasaponin III (**20**) and soyasapogenol B (**38**) by NMR and electrospray ionization MS. Soyasaponin III (**20**) appeared within the first 24 h and disappeared by 48 h. Soyasapogenol B (**38**) seemed to be the final metabolic product during the 48 h anaerobic incubation. Thus, dietary soyasaponins can be metabolized by human gut microorganisms. The sugar moieties of soyasaponins seem to be hydrolyzed sequentially to yield smaller and more hydrophobic metabolites (**Figure 3**) (*77*).

To our knowledge, there is no definitive evidence indicating absorption of soyasaponins or their aglycones in plasma. Physiological activities of saponins may be related to effects in the gastrointestinal (GI) tract through biotransformation. However, there are still huge gaps to be filled to link bioavailability of soyasaponins to their diverse health effects (*47*, *78*).

2.1.3. Health Effects of Soyasaponins and Soyasapogenols. Plant saponins as a whole have been reported to have a wide range of biological activities, which were summarized in a long list in a recent review (*79*). Soyasaponins and soyasapogenols have been reported to display diverse health effects (*80*), including anticancer effects, cardiovascular protective effects, antivirus and hepatoprotective actions, and antioxidant activities (*40*,*47*,*81*,*82*). Their health effects largely depend on their chemical structures (*83*). Because this class of soy compounds is so poorly absorbed, their bioactivity may be caused by indirect actions within the GI tract.

2.1.3.1. Anticarcinogenic Activities. Epidemiological studies have linked soy consumption to lower incidences of various types of cancer (*84*). As a group of major phytochemicals in soy, soyasaponins may be partially responsible (*47*). The evidence for soyasaponins having anticarcinogenic effects in animal models is limited. Nevertheless, soyasaponins and soyasapogenols have been shown to have anticarcinogenic effects in a number of carcinoma cells. Before summarizing the data, we must keep in mind that because soy saponins are poorly absorbed, in vitro studies of these compounds in cell lines may not be able to provide much meaningful indication regarding their in vivo bioactivities.

Most studies related to anticarcinogenic activities of soyasaponins and soyasapogenols have been performed on human colon cancer, liver cancer, or breast cancer cell lines (*85*−*90*). The proposed mechanisms of anticarcinogenic properties of soyasaponins and soyasapogenols include direct cytotoxicity, induction of apoptosis, antiestrogenic activity, inhibition of tumor cell metastasis, antimutagenic activity effect, bile acid binding action, and normalization of carcinogen-induced cell proliferation (**Table 5**) (*91*). From these studies done in different cancer cell lines, we have learned that there are at least three major factors that may affect observed effects from soyasaponins and soyasapogenols. The first factor is the testing materials. Some researchers used crude extracts, whereas others used purified saponins. It is possible that components of the crude extract interact synergistically and thus induce effects not observed with pure saponins. Therefore, investigations with purified saponins are indispensable for matching a result to the molecular action of a specific saponin (*92*). The second factor is the type of cell line. It is clearly shown that different cancer cell lines respond differently to soy saponins. For instance, soyasaponin I (**18**) had no effect on HT-29 colon cell growth (*83*), but it can decrease the migratory ability of B16F10 melanoma cells (*93*). The third factor is the dose. In another study, soyasaponin III (**20**) showed significant growth suppression at the highest concentration tested (50 ppm), and no significant effects at concentrations from 6 to 25 ppm.

2.1.3.2. Cardiovascular Protective Effects. Soyasaponins showed their cardiovascular protective effects through several different mechanisms.

The hypocholesterolemic effects of soy saponins have long been recognized (*94*−*97*). Two mechanisms by which saponins

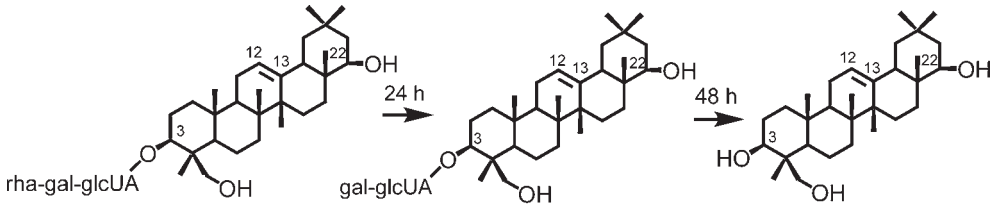


Figure 3. Metabolites of soysaponin I (**18**) by human fecal bacteria.

Table 5. Anticarcinogenic Activities of Soyasaponins and Soyasapogenols

material	cell line	dose	observation	mechanism	ref
total soyasaponins	human HT-1080 fibrosarcoma cell	inhibit metastasis of HT-1080 cells dose-dependently (100−300 μg/mL) after 24 h	inhibit invasion of HT-1080 cells through a Matrigel-coated membrane	suppress MMP-2 and MMP-9 productions and stimulate TIMP-2 secretion	*88*
total soyasaponins	human HT-29 colon cancer cell	decrease HT-29 cell growth in a dose-dependent manner at concentrations of 150, 300, and 600 ppm after 72 h	decrease HT-29 cell growth	suppress inflammatory reposponses; COX-2 and PKC expressions were significantly down-regulated	*89*
total soyasaponins	human HepG2 liver hepatoma cell	inhibit AFB_1-DNA adduct formation in HepG2 liver hepatoma cells by 50.1% at concentration of 30 μg/mL after 48 h	inhibit AFB_1-DNA adduct formation in HepG2 liver cells	induce membrane permeability change	*87*
B-group soyasaponins	human SNB 19 glioblastoma cell	induce SNB 19 glioblastoma cell apoptosis dose-dependently (25−75 μM) after 48 h	induce apoptosis in SNB 19 glioblastoma cells	stimulate cytochrome*c* release and activate caspase cascade	*90*
B-group soyasaponins	human HCT-15 colon cancer cell	suppress HCT-15 colon cancer cell proliferation dose-dependently at concentrations of 25−500 ppm and induce macroautophagy at concentration of 100 ppm after 24 h	suppress HCT-15 colon cancer cell proliferation and induce macroautophagy	delay S-phase cell cycle	*85*
soyasaponin I (**18**)	highly metastatic B16F10 melanoma cell	decrease migratory ability of B16F10 melanoma cell dose-dependently (25−75 μM) after 12 h	decrease migratory ability of cells, enhance cell adhesion to extracellular matrix proteins	inhibit expression of α-2,3-linked sialic acids of B16F10 melanoma cell	*93*
soyasaponin I (**18**)	human MCF-7 breast cancer cell	significantly enhance MCF-7 cells to adhere to the extracellular matrix at 50 μM after 24 h	enhance adhesion of MCF-7 cells to the extracellular matrix proteins	alter MCF-7 breast cancer cell surface α2,3-sialylation pathway	*86*
soyasaponin III (**20**) soyasapogenol B monoglucuronide	human HT-29 colon cancer cell	**20** and soyasapogenol B monoglucuronide show HT-29 colon cancer cell growth suppression at 50 ppm after 72 h	all suppress growth of HT-29 colon cancer cell	cell growth suppression of soyasaponins and soyasapogenols increased with increased lipophilicity	*83*
soyasapogenol A (**37**) soyasapogenol B (**38**)		**37** and **38** show dose-dependent growth suppression from 6 to 50 ppm after 72 h			

can affect cholesterol metabolism were suggested (*98*): (1) Some saponins with particularly defined structural characteristics form insoluble complexes with cholesterol. When this complex-forming process occurs in the gut, it inhibits the intestinal absorption of both endogenous and exogenous cholesterol. (2) Saponins can interfere with the enterohepatic circulation of bile acids by forming mixed micelles. The reabsorption of bile acids from the terminal ileum is effectively blocked (*94*).

In animal models, soyasaponins were found to significantly reduce the serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) concentrations and to increase the high-density lipoprotein cholesterol (HDL-C) levels distinctly in rats (*99*). 24-Methylenecycloartanol (**42**), in combination with soysterol, greatly reduced plasma cholesterol and enhanced cholesterol excretion in rats (*100*). Hamsters fed group B soyasaponins had significantly lowered plasma TC (by 20%), non-HDL-C (by 33%), TG (by 18%), and ratio of TC to HDL-C (by 13%) than those fed casein. Possible mechanisms involved greater excretion of fecal bile acids and neutral sterols (*101*).

The antithrombic action of soyasaponins is evaluated in the model of disseminated intravascular coagulation (DIC) induced by infusion of endotoxin or thrombin in rats. Total soyasaponins prevented the decrease of blood platelets and fibrinogen, and the increase of fibrin degradation products in the DIC induced by infusion of endotoxin or thrombin in rats. In vitro experiments, total soyasaponins, soyasaponins I (**18**), II (**19**), A_1 (**10**), and A_2 (**11**) inhibited the conversion of fibrinogen to fibrin (*102*).

Total soyasaponins decreased elevated blood sugar and lipid peroxidation (LPO) levels and increased the decreased levels of superoxide dismutase (SOD) in diabetic rats caused by streptozocin (*103*).

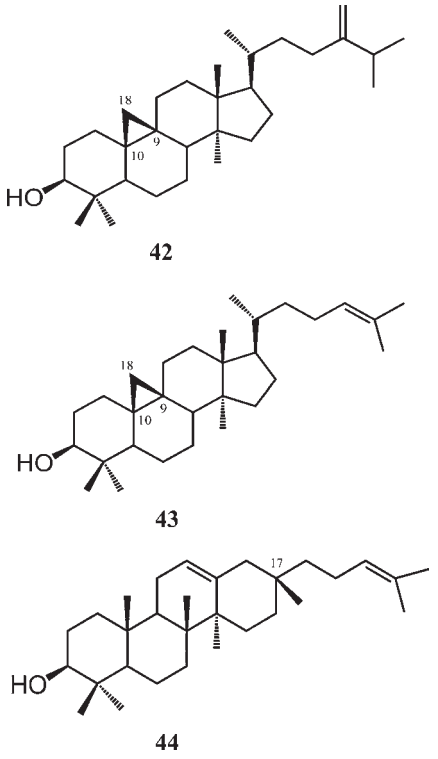


Figure 4. Chemical structures of triterpenes in soy.

In an α-glucosidase inhibitory assay, group B, E, and DDMP soyasaponins were shown to have potent inhibitory activities with IC_{50} values of 10−40 μmol/L (*104*).

2.1.3.3. Antiviral Activities. Soyasapogenols A (**37**), B (**38**), and E (**41**) and soyasaponin I (**18**), a major constituent of group B saponins, completely inhibited HIV-induced cytopathic effects 6 days after infection at concentrations > 0.25 mg/mL, but had no direct effect on HIV reverse transcriptase activity. Soyasaponin I (**18**) also inhibited HIV-induced cell fusion in the MOLT-4 cell system (*105*).

Total soyasaponins showed significant inhibitory effect on the replication of HSV-1 and CoxB3. A soyasaponins cream was used in the treatment of patients suffering from herpes labialis. The treatment was found to be highly effective, with a cure rate of 88.8% for the disease (*106*). Soyasaponin II (**19**) is more potent than soyasaponin I (**18**) as shown by reduction of simplex virus type 1 (HSV-1) production. Soyasaponin II (**19**) was also found to inhibit the replication of human cytomegalovirus and influenza virus. The action is not due to inhibition of virus penetration and protein synthesis, but may involve a virucidal effect (*107*). In a structure−activity relationship study, the activity of soyasapogenol A (**37**) was $< {}^{1}/_{20}$ that of soyasapogenol B (**38**); the hydroxylation at C-21 seemed to reduce anti-HSV-1 activity (*108*).

2.1.3.4. Hepatoprotective Actions. The group B soyasaponins I (**18**), II (**19**), III (**20**), and IV (**22**) all exhibit hepatoprotective actions toward immunologically induced liver injury in primary cultured rat hepatocytes. The action of soyasaponin II (**19**) is almost comparable with that of soyasaponin I (**18**), whereas soyasaponins III (**20**) and IV (**22**) are more effective than soyasaponins I (**18**) and II (**19**). This means that the disaccharide group shows greater action than the trisaccharide group. Furthermore, the soyasaponins having a hexosyl unit show a slightly greater action than those having a pentosyl unit in each disaccharide group or trisaccharide group. Structure−activity relationships suggest that the sugar moiety linked at C-3 may play an important role in hepatoprotective actions of soyasaponins (*109*).

In addition, in in vivo experiments, total soyasaponins inhibit the elevation of transaminases when administered orally to rats with peroxidized corn oil. The liver injury caused by peroxidized salad oil is inhibited by the addition of soyasaponin A_1 (**10**) during peroxidation (*110*).

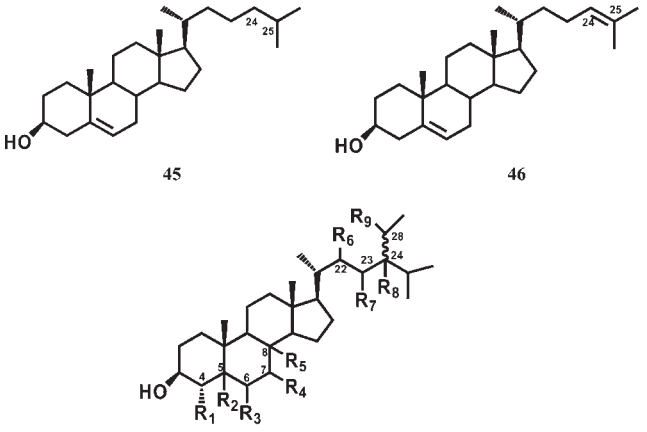
2.1.3.5. Antioxidant Activities. One milligram of DDMP saponin per milliliter scavenges superoxide at a degree equivalent to 17.1 units of SOD/mL by the ESR spin-trapping method. The scavenging superoxide activity of DDMP soyasaponins is caused by the DDMP moiety attached to the triterpene aglycon because soyasaponin I (**18**), which is derived from soyasaponin βg (**33**), but which lacks this group, did not show the scavenging activity (*111*).

2.2. Triterpenes and Sterols. *2.2.1. Chemical Characteristics of Triterpenes and Sterols*. Triterpenes and sterols are found in soybean oil unsaponifiable matter. They are both present in minor quantities.

Three triterpenes have been reported from soy. They are 24-methylenecycloartenol (**42**) (*100*), cycloartenol (**43**) (*100*), and bacchara-12,21-dien-3β-ol (**44**) (**Figure 4**) (*112*), respectively. Compounds **42** and **43** belong to the type of lanostane triterpene. In addition to having basic structural characters of lanostane, they bear an extra triatomic ring in their structures that is formed by cyclization between methyl at C-18 and methine at C-9. Lanostane triterpenes in soy were believed to be the original materials for biosynthesis of soy sterols. Bacchara-12,21-dien-3β-ol (**44**) is a natural occurrence of baccharane-type triterpene, which has an all six-membered tetracyclic skeleton, and its side chain is at the position of C-17. This type of triterpene is extremely rare in nature, and no more than 20 compounds of this type have been separated and identified.

Cholesterol and 13 so-called plant sterols or phytosterols were found in soybean seed or the shoots (*113*) (**Figure 5**). Unlike animals, plant membranes generally contain little or no cholesterol and instead contain several types of phytosterols. Phytosterols are also steroid alcohols, the chemical structures of which are similar to that of cholesterol, but with the presence of one- or two-carbon, saturated or unsaturated, substituents in side chains at C-24 differing from that of cholesterol (**45**) (**Figure 5**) (*46*, *113*). The most abundant phytosterols are sitosterol, compesterol, and stigmasterol (*114*). Phytosterols identified from soy so far include cholesta-5,24-dien-3β-ol (**46**), β-sitosterol (**47**) (*115*), stigmasterin (**48**) (*40*), sitostanol (**49**) (*116*), citrostadienol (**50**) (*115*), isofucosterol (**51**) (*113*), campesterol (**52**) (*117*), 24-epicampesterol (**53**) (*117*), 7-dehydrocampesterol (**54**) (*117*), campestanol (**55**) (*113*), obtusifoliol (**56**) (*113*), 24-methylenelophenol (**57**) (*113*), and 14α-methyl-5α-ergost-8-en-3β-ol (**58**) (*113*). The most abundant soy phytoserol is β-sitosterol (**47**), which was followed by campesterol (**52**) (*114*). These sterols can be divided into four groups on the basis of their backbones. They are cholesterol (**45**), cholesta (**46**), stigmasta (**47**−**51**), and ergosta (**52**−**58**), respectively (**Figure 5**). Compounds **45** and **46** have the same backbone except for the type of bond between C-24 and C-25. The former is a single bond, whereas the latter is a double bond (**Figure 5**). Stigmasta and ergosta also share similar structures with the only difference for stigmasta being that it has one more methyl group at C-28 (**Figure 5**). However, nutritionists prefer to divide the phytosterols into two categories of "Δ^5-sterols", indicating a double bond at position C-5, and "stanols", indicating 5α-reduction of that double bond (*116*). According to the principle, compounds **45**−**48** and **51**−**54** are Δ^5-sterols; **49**−**50** and **55**−**58** are stanols (**Figure 5**).

2.2.2. Bioavailability of Phytosterols. Compared to the absorption of 56.2 ± 12.1% for cholesterol in normal subjects, phytosertols have traditionally been considered as nonabsorbable.



45 46

47 R_1= R_4= R_5= R_6= R_7= R_8= R_9= H, R_2= R_3=$\Delta^{5(6)}$ 24(R)

48 R_1= R_4= R_5= R_8= R_9= H, R_2= R_3=$\Delta^{5(6)}$ R_6= R_7= $\Delta^{22(23)}$ 24(S)

49 R_1= R_2= R_3= R_4= R_5= R_6= R_7= R_8=R_9=H 24(R)

50 R_1= CH_3, R_2= R_3= R_6= R_7= H, R_4= R_5=$\Delta^{7(8)}$ R_8= R_9=$\Delta^{24(28)}$

51 R_1= R_4= R_5= R_6= R_7= H, R_2= R_3=$\Delta^{5(6)}$ R_8= R_9=$\Delta^{24(28)}$

52 R_1= R_4= R_5= R_6= R_7= R_8=R_9=H, R_2= R_3=$\Delta^{5(6)}$ 24(R)

53 R_1= R_4= R_5= R_6= R_7= R_8=R_9=H, R_2= R_3=$\Delta^{5(6)}$ 24(S)

54 R_1= R_6= R_7= R_8=R_9=H, R_2= R_3=$\Delta^{5(6)}$, R_4= R_5=$\Delta^{7(8)}$ 24(R)

55 R_1= R_2= R_3= R_4= R_5= R_6= R_7= R_8=R_9=H 24(R)

56 R_1= CH_3, R_2= R_3= R_4= H, R_5= R_6=$\Delta^{8(9)}$, R_7= CH_3, R_8= R_9=$\Delta^{24(28)}$

57 R_1= CH_3, R_2= R_3= R_6= R_7=H, R_4= R_5= $\Delta^{7(8)}$, R_8= R_9=$\Delta^{24(28)}$

58 R_1= R_2= R_3= R_4= R_8= R_9=H, R_5= R_6= $\Delta^{8(9)}$, R_7= CH_3 24(S)

Figure 5. Chemical structures of sterols in soy.

However, a small but definite absorption does occur. Studies using radioactive sitosterol have reported that the absorption is 0.6−7.5% (*116*). The preferential absorption of cholesterol over phytosterol may be explained partly by the differences in the chemical structures. The addition of a methyl/ethyl group at the C-24 position of the side chain increases the hydrophobicity of phytosterol, thereby reducing their absorption (*118*, *119*).

Bioavailability of phytosterols as a whole group has been extensively studied and frequently reviewed (*119*−*122*). In general, the gastrointestinal absorption of phytosterols in humans is very low. It has been suggested that the extent and rate of phytosterol absorption depend on the side-chain length and the presence of a Δ^5 double bond (*121*). Phytosterols must be incorporated in micellar forms to be absorbed. The sterol-laden micelle interacts with the intestinal brush border membrane, thereby facilitating the uptake of sterols by enterocytes. The precise molecular mechanisms are not yet well-defined, but both cholesterol and phytosterol require the Niemann−Pick C1-like 1 (NPC1L1) protein for their absorption (*123*). NPC1L1 protein is expressed in the small intestine, most likely in the brush border membrane of enterocytes. In addition, two APT-binding cassette (ABC) transporters, ABCG5 and ABCG8, play a role in the absorption of phytosterols and cholesterol into mucosal cells. ABCG5 and ABCG8 form fully active transporters in the enterocytes, and they are responsible for the efflux of absorbed phytosterols and cholesterol back into the intestinal lumen (*124*). Phytosterols are poor substrates for acyl-CoA:cholesterol *O*-acyltransferase (ACAT); therefore, a much smaller part of phytosterols is esterified than of cholesterol (*125*). Unesterified phytosterols and cholesterol are transported back into the intestinal lumen by ABCG5 and ABCG8 (*126*, *127*). Once taken up by the liver through lipoproteins, phytosterols are incorporated into very low density lipoprotein or secreted via the bile. ABCG5 and ABCG8 are also responsible for biliary excretion of phytosterols (*119*).

There are only a few studies designed to specifically look at the different bioavailability of soy Δ^5-sterols and 5α-reduced sterols (stanols). In one study, after a single meal of 600 mg of lecithin-emulsified soy sterols, absorption from 600 mg of Δ^5-sterols given with a standard test breakfast was 0.512 ± 0.038% for sitosterol (**47**) and 1.89 ± 0.27% for campesterol (**52**) in plasma. The absorption from 600 mg of soy stanols was 0.04 ± 0.004% for sitostanol (**47**) and 0.2 ± 0.017% for campestanol (**52**) in plasma. Reduction of the double bond at position 5 decreased absorption by 90%. Plasma $t_{1/2}$ for stanols was significantly shorter than for Δ^5-sterols (*128*).

2.2.3. Health Effects of Phytosterols. Phytosterols (not restricted to soy-based sources), which have long been known to reduce intestinal cholesterol absorption, lead to decreased blood LDL-C levels and lower cardiovascular disease risk. However, other biological activities for phytosterols have also been reported, including anticancer and immune modulatory effects.

2.2.3.1. Phytosterols and Cholesterol Absorption. In the 1950s, phytosterols from soybeans were found to lower serum cholesterol level (*129*). Since then, the cholesterol-lowering effect of phytosterols has been extensively demonstrated in both humans and animals (*130*−*133*). A meta-analysis of 41 trials showed that intake of 2 g/day of stanols or sterols reduced LDL by 10%, with little additional reduction at higher doses (*134*). The U.S. National Cholesterol Education Program has recommended adding 2.0 g/day of phytosterols to the diet of adults to reduce LDL-C and CHD risk (*135*).

Because phytosterols are not systemically absorbed, they are thought to act primarily in the intestinal lumen. As cholesterol analogues phytosterols compete for cholesterol in absorptive micelles, resulting in reduced solubility of cholesterol (*131*). However, recent evidence suggests that the mechanism of action of phytosterols may be more complicated than originally thought (*120*, *132*). As summarized in a most recent review (*120*), because phytosterols/phytostanols do not need to be present in the intestinal lumen simultaneously with cholesterol to inhibit its absorption (*133*), other studies have suggested that phytosterols/phytostanols may exert an unknown molecular action inside enterocytes and hepatocytes. In line with this, injected phytosterols/phytostanols reduced plasma cholesterol levels in hamsters (*136*). To gain insight into the phytosterol/phytostanol influence on circulating cholesterol concentration via mechanisms independent of the luminal incorporation of cholesterol into mixed micelles, the effect of these plant compounds on intestinal LXR-mediated targets involved in sterol absorption has been evaluated. Conclusive studies using ABCA1 and ABCG5/G8-deficient mice demonstrated that the phytosterol-mediated inhibition of intestinal cholesterol absorption is independent of these ATP-binding cassette (ABC) transporters. Other papers have raised questions as to whether phytosterols/phytostanols regulate cholesterol metabolism in intestinal and hepatic cells through independent LXR pathways. A number of studies have proposed a phytosterol/phytostanol action on cholesterol esterification and lipoprotein assembly (ACAT, apoB), cholesterol internalization (NPC1L1, ANXA2), cholesterol synthesis (HMG-CoA reductase, C-24-reductase), and removal of apoB100-containing lipoproteins (LDLr). However, the impact of phytosterol/phytostanol

intake on these physiological processes in vivo remains unclear (*120*).

In one study designed specifically using soybean-derived phytosterols (*137*), it was found that consumption of phytosterol-supplemented ground beef lowered plasma TC and LDL-C concentrations and TC/HDL cholesterol from baseline by 9.3, 14.6, and 9.1%, respectively.

2.2.3.2. Anticancer Effects of Phytosterols. In addition to their cholesterol-lowering actions, mounting evidence suggests that phytosterols possess anticancer effects against a number of different cancers (*138*−*144*). Phytosterols seem to act through multiple mechanisms of action, including inhibition of carcinogen production, cancer-cell growth, angiogenesis, invasion, and metastasis, and through the promotion of apoptosis of cancerous cells. Phytosterol consumption may also increase the activity of antioxidant enzymes and thereby reduce oxidative stress. In addition to altering cell-membrane structure and function, phytosterols probably promote apoptosis by lowering blood cholesterol levels (*139*).

2.2.3.3. Physterols and Immune Function. Several reports have appeared in the literature indicating that phytosterols may have some immunological activity as highlighted in animal models of inflammation or even in vitro and in vivo models of cancer (colorectal and breast cancer). Their direct immune modulatory activity on human lymphocytes has been proven, and the mechanism of action in cancer cells has been elucidated (*145*, *146*).

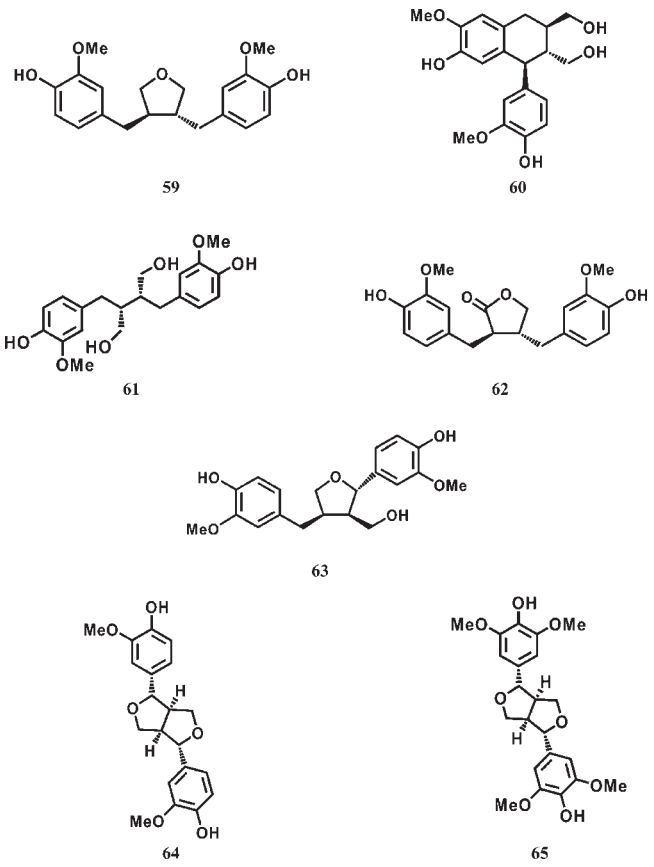


Figure 6. Chemical structures of lignans in soy.

2.3. Lignans. *2.3.1. Chemical Characteristics of Lignans*. Except for isoflavones, lignans are considered to be another main group of phytoestrogens in soy on the basis of their chemical structures. Lignans are defined as dimeric phenylpropanoid (C6−C3) compounds, mostly linked at 8−8′ (**Figure 6**) (*147*, *148*). There were seven lignans identified from soy, namely, anhydrosecoisolariciresinol (**59**), isolariciresinol (**60**), secoisolariciresinol (**61**), matairesinol (**62**), lariciresinol (**63**), pinoresinol (**64**), and syringaresinol (**65**) (**Figure 6**) (*49*, *149*).

2.3.2. Bioavailability of Lignans. Even though there is no study designed specifically for soy lignans, bioavailability of plant lignans in humans has been extensively studied and summarized (*150*). Secoisolariciresinol diglucoside (SDG) and its aglycone secoisolariciresinol (SECO) (**61**) and matairesinol (MAT) (**62**) are by far the most frequently studied dietary lignans. Brifely, plant lignans are metabolized by intestinal bacteria to the enterolignans (also known as mammalian lignans), enterodiol (END) or enterolactone (ENL) (**Figure 7**) (*151*, *152*). END can be further metabolized to ENL. The efficiency of conversion of plant lignan precursors to END and ENL in 24 h incubations with human fecal inocula varied greatly depending on the compound and ranged from 0 to 100% (*151*). Once produced by intestinal bacteria, enterolignans may be efficiently absorbed and conjugated, and the resulting metabolites will be excreted by enterocytes. The major proportion of lignans excreted in urine are conjugated; ENL and END are excreted primarily as monoglucuronides, with small percentages being excreted as monosulfates and free aglycones (*153*).

A number of human studies have shown that dietary intervention with lignan-containing foods leads to an increase in blood levels of enterolignans in nearly all individuals (*150*). For instance, in a study conducted by Kuijsten et al. (*154*), 12 healthy volunteers ingested a single dose of purified SDG (1.31 μmol/kg of body wt). Enterolignans appeared in plasma 8−10 h after ingestion of the purified SDG. END reached its maximum plasma concentration 14.8 ± 5.1 h after the ingestion of SDG, whereas ENL reached its maximum 19.7 ± 6.2 h after ingestion. The mean residence time for END was 20.6 ± 5.9 h and that for ENL was 35.8 ± 10.6 h. Within 3 days, up to 40% of the ingested SDG was excreted as enterolignans via urine, with the majority (58%) as ENL. This study found that at least 40% of the ingested SDG is available for the body. The measured residence time and elimination half-life indicated that enterolignans accumulated in plasma when consumed two or three times a day; thus, steady state plasma concentrations of END and ENL are likely to be achieved because plant lignans are present in many foods and beverages.

2.3.3. Health Effects of Lignans

2.3.3.1. Antioxidant Activity. Pinoresinol (**64**) has been reported frequently as an antioxidant, using thiocyanate antioxidant, Cu^{2+}-induced low-density lipoprotein oxidation, lipid peroxidation in rat liver, DPPH radical, and peroxy radical assays (*155*).

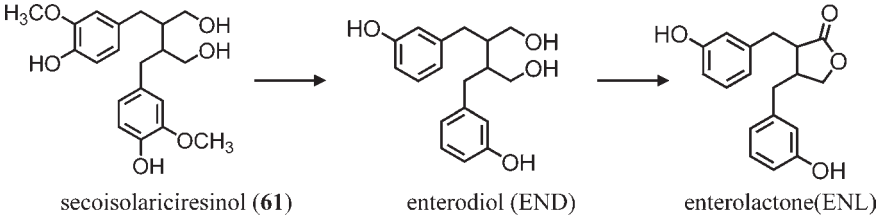
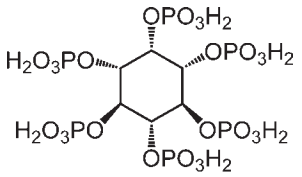


Figure 7. Conversion of secoisolariciresinol (**61**) by human intestinal bacteria.



66

Figure 8. Chemical structure of phytic acid in soy.

Syringaresinol (**65**) has also been demonstrated as antioxidative in Cu^{2+}-induced low-density lipoprotein oxidation and DPPH radical assays (*155*). Lariciresinol (**63**) has a high radical scavenging capacity compared to the well-known antioxidant Trolox. The trapping capacity (mmol of peroxyl radicals scavenged/g of compound) of lariciresinol (**63**) (7.3 mmol/g) is higher than that of Trolox (6.8 mmol/g) (*156*). Secoisolariciresinol (**61**) showed strong antioxidant activity using the DPPH stable radical. The IC_{50} of the compound is 0.017 ± 0.001 mM, which is about 2 times stronger than the standard antioxidant, 2,6-di-(*tert*-butyl)-4-methylphenol (BHT; IC_{50} 0.031 ± 0.001 mM) (*157*). Isolariciresinol (**60**) showed 86.2% inhibition of LPO at 25 μg/mL (*158*).

2.3.3.2. Anticancer Activity. Estrogenic enterolignans, END and ENL, are the major metabolites of lignans in the mammalian gut. Because estrogens were linked to some cancers, especially breast cancer, enterolignans could affect some cancer risk. However, to our knowledge, the estrogenic or antiestrogenic effects of enterolignans in humans are not very clear (*159*). For example, weak estrogenic activity of ENL was demonstrated by Jordan. However, the antiestrogenic activity of ENL was disclosed through depression of estrogen-stimulated rat uterine RNA synthesis (*160*).

The lignan ENL was found to have a biphasic effect on DNA synthesis in human breast cancer MCF-7 cells, showing induction at 10−50 μM and inhibition at high concentration, with an IC_{50} of 82.0 μM (*161*). END and ENL are, respectively, weak and moderate inhibitors of aromatase enzyme activity in a preadipose cell culture system (*160*). For human colon tumor cell lines (LS174T, Caco-2, HCT-15, T-84), at 100 μM concentration, END and ENL significantly reduce the proliferation of all cell lines. ENL was more than twice as effective as END at this concentration (*162*).

2.4. Phytate. *2.4.1. Chemical Characteristics of Phytate*. Phytate, the salt of phytic acid (*myo*-inositol-(1,2,3,4,5,6)hexakisphophate, IP-6, InsP-6) (**Figure 8**), is a naturally occurring polyphosphorylated carbohydrate. It is widely distributed in the plant kingdom. Phytate serves as a storage form of phosphorus and minerals and contains ∼75% of total phosphorus of the kernels (*45*). It is the major source of phosphorus in soy (*81*). Phytate is considered to be a strong chelator of important minerals such as calcium, magnesium, iron, and zinc and can contribute to mineral deficiencies in people. However, recent studies demonstrate that this "antinutrient" effect of IP6 is manifested only when large quantities of IP6 are consumed in combination with an oligoelements-poor diet (*163*).

2.4.2. Bioavailability of Phytate. Under physiological pH (∼6−7), phytic acid is highly charged and shows an extremely high negative charge density. For these reasons, it has been assumed that phytic acid or phytate cannot cross the lipid bilayer of plasma membranes. Nevertheless, recent studies in cell lines, rats, and humans gave some evidence to the gastrointestinal absorption of phytate, even though the mechanisms are not clear (*45*).

In rats, radiolabeled IP6 (*myo*-[inositol-2-^3H(N)]hexakisphosphate) was found to be quickly absorbed from the stomach and distributed throughout the body (*164*). IP6 was found to be rapidly absorbed through the stomach and upper small intestine, became quickly dephosphorylated within the mucosal cells, and was distributed to various organs as inositol and $InsP_1$. Also in rats, a study was conducted to look at the relationship between the oral intake of phytic acid and its urinary excretion (*165*). The results showed that IP6 urinary levels were related to its oral intake. When IP6 was absent from the diet, urinary excretion declined to undetectable levels after 22 days. The addition of increasing amounts of IP6 to the liquid diet caused an increase in its urinary excretion after about 10 days. Adding IP6 in amounts >425 mg/L caused no further increases in urinary excretion. In the follow-up study done by the same group (*166*), IP6 levels in diverse tissues of rats fed diets with different phytic acid contents were determined by GC-MS methodology. When given the diets containing 10 g/kg phytate, the highest IP6 concentrations were found in the brain (5.89×10^{-2} mg/g), whereas the concentrations detected in kidneys (1.96×10^{-3} mg/g), livers (3.11×10^{-3} mg/g), and bones (1.77×10^{-3} mg/g) were similar to each other and 10-fold less than those detected in brain. By comparison of the results of purified diet (IP6 free), the majority of the IP6 found in organs and tissues has a dietary origin and is not a consequence of endogenous synthesis (*167*).

Due to restriction of methodology, studies of the bioavailability of phytic acid in humans are very limited. The pharmacokinetic profile of phytic acid in human subjects showed that given an IP6-poor diet, their basal levels of IP6 found in plasma were 3−5-fold lower than those found in an IP6-normal diet. Therefore, to maintain adequate levels of IP6, people must consume a healthy IP6-rich diet (*163*).

2.4.3. Health Effects of Phytic Acid

2.4.3.1. Anticancer Activities. Phytic acid (**66**) plays an important role in signal transduction, cell proliferation, and differentiation (*168*). Recently, phytic acid (**66**) has received much attention for its role in cancer prevention and control of experimental tumor growth, progression, and metastasis (*169*). A great majority of the studies were done in animals and showed that phytic acid had antineoplastic properties in breast, colon, liver, leukemia, prostate, sarcomas, and skin cancer (*170*, *171*). The results and proposed mechanism of anticarcinogenic activities of IP6 in various cell lines are summarized in **Table 6** (*172*−*175*).

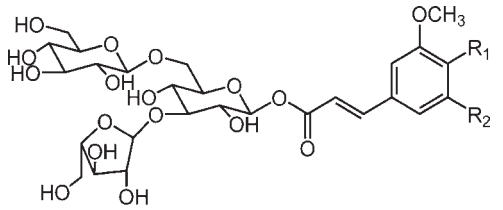
For animal studies, phytic acid can increase blood NK cell activity in DMH-induced colon tumor in rats, suppress rhabdomyosarcoma cell growth in a xenografted nude mice model (*176*), inhibit tumor growth and metastasis in rats (*177*), prolong survival of tumor-bearing mice, and reduce the numbers of pulmonary metastases (*178*). Phytic acid can also inhibit DMBA-induced mouse skin tumor development and the inhibitory effect, probably by modulating proliferation, differentiation, or apoptosis (*179*).

2.4.3.2. Other Health Effects. For a long time IP6 has been recognized as a natural antioxidant. In addition, IP6 possesses other significant benefits for human health, such as the ability to enhance the immune system, prevent pathological calcification and kidney stone formation, lower elevated serum cholesterol, and reduce pathological platelet activity (*169*). IP6 inhibited the replication of HIV-1 in a T cell line as well as that of a freshly isolated strain in peripheral blood mononuclear cells, possibly acting on HIV-1 early replicative stage (*170*).

2.5. Cinnamic Acid Ester Glycosides. *2.5.1. Chemical Characteristics of Cinnamic Acid Ester Glycosides*. Two cinnamic acid ester glycosides were isolated by Hosny et al. from soybean molasses, which is a byproduct of aqueous alcohol soy protein concentrate production (*67*). They were identified as 1-*O*-(*E*)-feruloy[α-L-arabinofuranosyl-(1→3)][β-D-glucopyranosyl(1→6)]-β-D-glucopyranose (**67**) and 1-*O*-(*E*)-3,4,5-trimethoxycinnamoyl-[α-L-arabinofuranosyl(1→3)][glucopyranosyl(1→6)]-β-D-glucopyranose (**68**) (**Figure 9**).

Table 6. Anticarcinogenic Activities of IP

cell line	dose	observation	mechanism	ref
human Caco-2 colon cancer cell	decrease expression of TNF-α and TNFII in a dose-dependent manner (1, 2.5, and 5 mM) after 12 h	decrease expression of TNF-α and TNFII in Caco-2 cells	regulate cytokine production, including TNF-α, to modulate immune response and cell death activation	*168*
human HT-29 colon cancer cell	inhibit proliferation of HT-29 cells at 8 and 13 mmol/L after 12 h	inhibit proliferation of HT-29 cells	affect special cell cycle regulators, reduce overexpression of mutant P53, and prevent PCNA-dependent cellular proliferation	*175*
human MCF-7/Adr MDA-MB 231 and MCF-7 breast cancer cells	MCF-7/Adr, IC_{50} = 1.26 mM MDA-MB 231, IC_{50} = 1.32 mM MCF-7, IC_{50} = 4.18 mM after 96 h	inhibit growth of three breast cancer cells	change cell cycle distribution	*174*
human HepG2 liver hepatoma cell	inhibit growth of HepG2 liver hepatoma cell in a dose-dependent fashion (0.25−5 mM) after 6 days	inhibit growth of HepG2 liver hepatoma cell	modulate cell signal transduction pathways	*176*
human LNCaP prostate cancer cell	inhibit growth of LNCaP prostate cancer cell dose-dependently (0.5−4 mM) after 24 h	inhibit growth of LNCaP prostate cancer cell	inhibit Akt activation, cause CDKI accumulation and induce LNCaP cell cycle arrest	*172*
human DU145 prostate cancer cell	inhibit growth of DU145 prostate cancer cell dose-dependently (0.25−2 mM) after 24 h	inhibit growth of DU145 prostate cancer cell	induce G1 arrest in DU145 cell cycle progression	*173*



67 R_1 = OH, R_2 = H
68 R_1 = OCH_3, R_2 = OCH_3

Figure 9. Chemical structures of cinnamic acid ester glycosides in soy.

3. CONSTITUENTS FORMED DURING PROCESSING

Food processing can dramatically change the compositions and relative contents of the constituents in soy products, and artificial compounds may also occur (*180*). The processing of foods can improve nutrition, quality, and safety; yet, processing can also lead to the formation of antinutritional and toxic compounds. These multifaceted consequences of food processing result from molecular interactions among nutrients and with other food ingredients, both natural and added (*181*).

Some components isolated from soy products such as soy sauce and fermented products do not occur naturally in the soybean, and the types of these compounds vary among different soy products on the basis of processing methods. These compounds may be formed by (1) soybean processing or fermentation, (2) compounds from other ingredients of soy products, and (3) compounds from reaction of components in soybean and/or other ingredients during processing. Even though these compounds are not found naturally in soybean, they do exist widely in various soy products and may contribute to important beneficial or detrimental biological effects associated with soy consumption. Unfortunately, the key role of these compounds is largely ignored.

One group of well-known compounds formed during food processing in soy is Maillard reaction products (*182*, *183*). Maillard reaction is the heat-induced reaction of amino groups of amino acids, peptides, and proteins with carbonyl groups of reducing sugars such as glucose, which results in the concurrent formation of so-called Maillard browning products and acrylamide (*184*). In the past, extensive work has been done on Maillard reaction products in food products including several excellent reviews (*181*, *183*−*186*). Five Maillard reaction products, fructose−lysine (**69**), fructose−alanine (**70**), fructose−valine (**71**), fructose−leucine (**72**), and fructose−isoleucine (**73**) (**Figure 10**), were isolated from soy sauce and miso (*187*, *188*).

Other groups of compounds may also be found in different soy products. Guided by platelet aggregation analysis, two antiplatelet alkaloids, 1-methyl-1,2,3,4-tetrahydro-β-carboline (**74**) and 1-methyl-β-carboline (**75**), were obtained from soy sauce. These two compounds inhibited the maximal aggregation response induced by epinephrine, platelet-activating factor, collagen, adenosine 5′-diphosphate, and thrombin, respectively (*189*). Compound **74** had a much greater inhibitory effect than **75** on platelet aggregation. Three other alkaloids, asperparalines A (**76**), B (**77**), and C (**78**), were found from okara (the insoluble residue of whole soybean) fermented with *Aspergillus japonicus* JV-23 (**Figure 10**) (*190*). Because soybean does not contain alkaloids, these compounds were likely brought into the soy products from other sources.

A series of aromatic compounds were isolated from soy sauce and miso (a traditional Japanese seasoning produced by fermented soybeans) (*191*−*193*). Their structures were identified as 4-hydroxy-2-ethyl-5-methyl-3(2*H*)-furanone (HEMF; **79**), 4-hydroxy-5-ethyl-2-methyl-3(2*H*)-furanone (**80**), 2,5-dimethyl-4-hydroxy-3(2*H*)-furanone (DMHF; **81**), and 3-hydroxy-2-methyl-4*H*-pyran-4-one (maltol; **82**) (**Figure 10**). They are considered to form the base of the sweet aroma of miso. All of these compounds were most likely generated during soy processing and/or fermentation.

Processing may also significantly elevate or reduce certain naturally occurring soybean components. For instance, a remarkable increase in folate content was found after fermentation, 5.2- and 1.7-fold higher than that of the boiled soybeans and soybean seeds, respectively (*194*). Thus, we must be aware that the composition of soybean products may differ substantially from the native soybean.

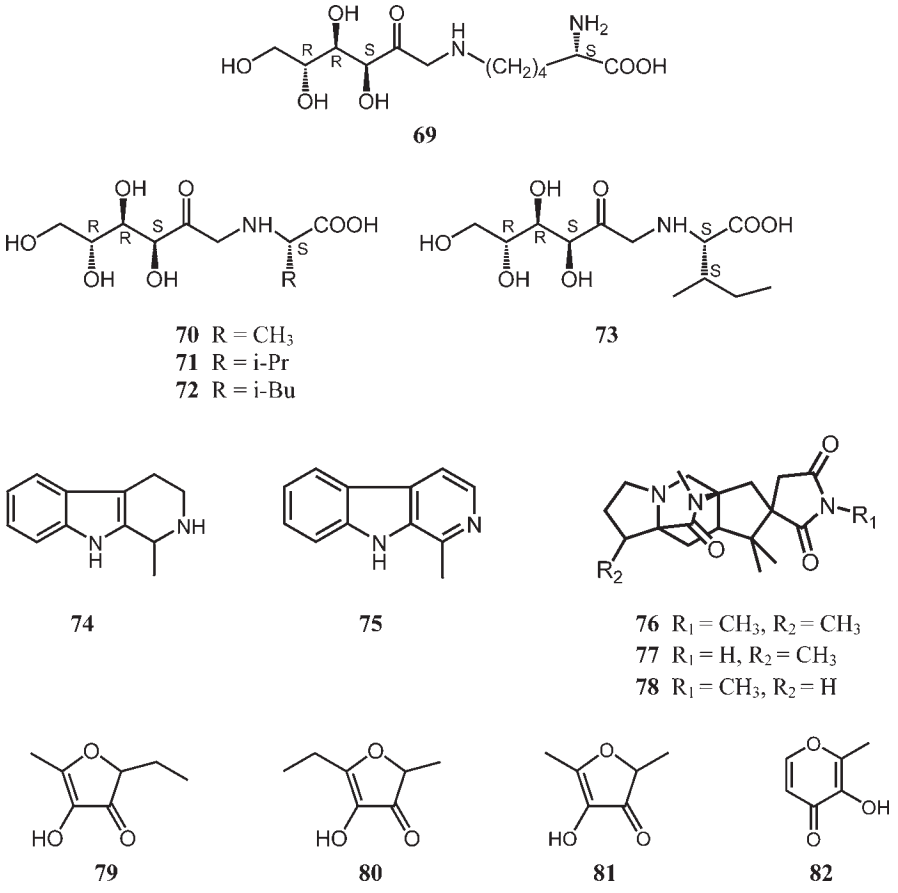


Figure 10. Chemical structures of components in soy products.

4. CONCLUSION

The soybean has been used as a human food source of high-quality protein and other nutrients for hundreds of years and is currently a major source of protein in commercial food products for the beef, pork, and chicken industry. This review summarizes current knowledge about chemical structures, bioavailability, and health effects of non-isoflavone constituents in soy. Clearly, the observed health effects from soy or soy-based foods (other than those attributed to nutrients such as protein) are not solely from the actions of certain individual or types of compounds, but rather due to the mixed effects of different compounds. Additive, synergistic, and/or antagonistic effects of different soy components combine to provide a final effect of soy foods, and these effects may also be altered by phytochemicals from other non-soy foods in a meal. To fully understand the mechanism of health effects of soy, it is important to identify the genuine bioactive compounds in soy.

LITERATURE CITED

(1) Anderson, J. W.; Johnstone, B. M.; Cook-Newell, M. E. Meta-analysis of the effects of soy protein intake on serum lipids. *N. Engl. J. Med.* **1995**, *333*, 276–282.

(2) Boyapati, S. M.; Shu, X. O.; Ruan, Z. X.; Dai, Q.; Cai, Q.; Gao, Y. T.; Zheng, W. Soyfood intake and breast cancer survival: a followup of the Shanghai Breast Cancer Study. *Breast Cancer Res. Treat.* **2005**, *92*, 11–17.

(3) Toyomura, K.; Kono, S. Soybeans, soy foods, isoflavones and risk of colorectal cancer: a review of experimental and epidemiological data. *Asian Pac. J. Cancer Prev.* **2002**, *3*, 125–132.

(4) Zhou, J. R. Soy and the prevention of lifestyle-related diseases. *Clin. Exp. Pharmacol. Physiol.* **2004**, *31* (Suppl. 2), S14–S19.

(5) Wu, A. H.; Ziegler, R. G.; Nomura, A. M.; West, D. W.; Kolonel, L. N.; Horn-Ross, P. L.; Hoover, R. N.; Pike, M. C. Soy intake and risk of breast cancer in Asians and Asian Americans. *Am. J. Clin. Nutr.* **1998**, *68*, 1437S–1443S.

(6) Messina, M. Modern applications for an ancient bean: soybeans and the prevention and treatment of chronic disease. *J. Nutr.* **1995**, *125*, 567S–569S.

(7) Barnes, S.; Boersma, B.; Patel, R.; Kirk, M.; Darley-Usmar, V. M.; Kim, H.; Xu, J. Isoflavonoids and chronic disease: mechanisms of action. *Biofactors* **2000**, *12*, 209–215.

(8) Friedman, M.; Brandon, D. L. Nutritional and health benefits of soy proteins. *J. Agric. Food Chem.* **2001**, *49*, 1069–1086.

(9) Omoni, A. O.; Aluko, R. E. Soybean foods and their benefits: potential mechanisms of action. *Nutr. Rev.* **2005**, *63*, 272–283.

(10) Xiao, C. W. Health effects of soy protein and isoflavones in humans. *J. Nutr.* **2008**, *138*, 1244S–1249S.

(11) Setchell, K. D. Phytoestrogens: the biochemistry, physiology, and implications for human health of soy isoflavones. *Am. J. Clin. Nutr.* **1998**, *68*, 1333S–1346S.

(12) Cabot, W. Phytoestrogens. *J. Am. Acad. Orthop. Surg.* **2003**, *11*, 153–156.

(13) Goldwyn, S.; Lazinsky, A.; Wei, H. Promotion of health by soy isoflavones: efficacy, benefit and safety concerns. *Drug Metab. Drug Interact.* **2000**, *17*, 261–289.

(14) Ren, M. Q.; Kuhn, G.; Wegner, J.; Chen, J. Isoflavones, substances with multi-biological and clinical properties. *Eur. J. Nutr.* **2001**, *40*, 135–146.

(15) Delmonte, P.; Rader, J. I. Analysis of isoflavones in foods and dietary supplements. *J. AOAC Int.* **2006**, *89*, 1138–1146.

(16) Messina, M.; Kucuk, O.; Lampe, J. W. An overview of the health effects of isoflavones with an emphasis on prostate cancer risk and prostate-specific antigen levels. *J. AOAC Int.* **2006**, *89*, 1121–1134.

(17) Vacek, J.; Klejdus, B.; Lojkova, L.; Kuban, V. Current trends in isolation, separation, determination and identification of isoflavones: a review. *J. Sep. Sci.* **2008**, *31*, 2054–2067.

(18) Larkin, T.; Price, W. E.; Astheimer, L. The key importance of soy isoflavone bioavailability to understanding health benefits. *Crit. Rev. Food Sci. Nutr.* **2008**, *48*, 538–552.

(19) Dentith, S.; Lockwood, B. Development of techniques for the analysis of isoflavones in soy foods and nutraceuticals. *Curr. Opin. Clin. Nutr. Metab. Care* **2008**, *11*, 242–247.
(20) Mortensen, A.; Kulling, S. E.; Schwartz, H.; Rowland, I.; Ruefer, C. E.; Rimbach, G.; Cassidy, A.; Magee, P.; Millar, J.; Hall, W. L.; Birkved, F. K.; Sorensen, I. K.; Sontag, G. Analytical and compositional aspects of isoflavones in food and their biological effects. *Mol. Nutr. Food Res.* **2009**, *53*, S266−S309.
(21) Clair, R. S.; Anthony, M. Soy, isoflavones and atherosclerosis. *Handb. Exp. Pharmacol.* **2005**, 301–323.
(22) Clarkson, T. B. Soy, soy phytoestrogens and cardiovascular disease. *J. Nutr.* **2002**, *132*, 566S–569S.
(23) Anthony, M. S.; Clarkson, T. B.; Williams, J. K. Effects of soy isoflavones on atherosclerosis: potential mechanisms. *Am. J. Clin. Nutr.* **1998**, *68*, 1390S–1393S.
(24) Adlercreutz, H. Phyto-oestrogens and cancer. *Lancet Oncol.* **2002**, *3*, 364–373.
(25) Ganry, O. Phytoestrogen and breast cancer prevention. *Eur. J. Cancer Prev.* **2002**, *11*, 519–522.
(26) Sarkar, F. H.; Li, Y. Soy isoflavones and cancer prevention. *Cancer Invest.* **2003**, *21*, 744–757.
(27) Zhang, Y.; Chen, W. F.; Lai, W. P.; Wong, M. S. Soy isoflavones and their bone protective effects. *Inflammopharmacology* **2008**, *16*, 213–215.
(28) Messina, M.; Ho, S.; Alekel, D. L. Skeletal benefits of soy isoflavones: a review of the clinical trial and epidemiologic data. *Curr. Opin. Clin. Nutr. Metab. Care* **2004**, *7*, 649–658.
(29) Setchell, K. D.; Lydeking-Olsen, E. Dietary phytoestrogens and their effect on bone: evidence from in vitro and in vivo, human observational, and dietary intervention studies. *Am. J. Clin. Nutr.* **2003**, *78*, 593S–609S.
(30) Brynin, R. Soy and its isoflavones: a review of their effects on bone density. *Altern. Med. Rev.* **2002**, *7*, 317–327.
(31) Bhathena, S. J.; Velasquez, M. T. Beneficial role of dietary phytoestrogens in obesity and diabetes. *Am. J. Clin. Nutr.* **2002**, *76*, 1191–1201.
(32) Orgaard, A.; Jensen, L. The effects of soy isoflavones on obesity. *Exp. Biol. Med.* (*Maywood*) **2008**, *233*, 1066–1080.
(33) Hodges, R. E.; Krehl, W. A.; Stone, D. B.; Lopez, A. Dietary carbohydrates and low cholesterol diets: effects on serum lipids on man. *Am. J. Clin. Nutr.* **1967**, *20*, 198–208.
(34) U.S. Food and Drug Administration. Food labeling: health claims; soy protein and coronary heart disease. Food and Drug Administration, HHS. Final rule. *Fed. Regist.* **1999**, *64*, 57700−57733
(35) Anderson, J. W. Beneficial effects of soy protein consumption for renal function. *Asia Pac. J. Clin. Nutr.* **2008**, *17* (Suppl. 1), 324–328.
(36) Velasquez, M. T.; Bhathena, S. J. Role of dietary soy protein in obesity. *Int. J. Med. Sci.* **2007**, *4*, 72–82.
(37) Anthony, M. S.; Clarkson, T. B.; Hughes, C. L., Jr.; Morgan, T. M.; Burke, G. L. Soybean isoflavones improve cardiovascular risk factors without affecting the reproductive system of peripubertal rhesus monkeys. *J. Nutr.* **1996**, *126*, 43–50.
(38) Greaves, K. A.; Parks, J. S.; Williams, J. K.; Wagner, J. D. Intact dietary soy protein, but not adding an isoflavone-rich soy extract to casein, improves plasma lipids in ovariectomized cynomolgus monkeys. *J. Nutr.* **1999**, *129*, 1585–1592.
(39) Ronis, M. J.; Chen, Y.; Badeaux, J.; Laurenzana, E.; Badger, T. M. Soy protein isolate induces CYP3A1 and CYP3A2 in prepubertal rats. *Exp. Biol. Med.* **2006**, *231*, 60–69.
(40) Rochfort, S.; Panozzo, J. Phytochemicals for health, the role of pulses. *J. Agric. Food Chem.* **2007**, *55*, 7981–7994.
(41) Erdman, J. W., Jr.; Badger, T. M.; Lampe, J. W.; Setchell, K. D.; Messina, M. Not all soy products are created equal: caution needed in interpretation of research results. *J. Nutr.* **2004**, *134*, 1229S–1233S.
(42) Fitzpatrick, L. A. Soy isoflavones: hope or hype? *Maturitas* **2003**, *44* (Suppl. 1), S21–S29.
(43) Munro, I. C.; Harwood, M.; Hlywka, J. J.; Stephen, A. M.; Doull, J.; Flamm, W. G.; Adlercreutz, H. Soy isoflavones: a safety review. *Nutr. Rev.* **2003**, *61*, 1–33.
(44) Wuttke, W.; Jarry, H.; Seidlova-Wuttke, D. Isoflavones − safe food additives or dangerous drugs? *Ageing Res. Rev.* **2007**, *6*, 150–188.
(45) Schlemmer, U.; Frolich, W.; Prieto, R. M.; Grases, F. Phytate in foods and significance for humans: food sources, intake, processing, bioavailability, protective role and analysis. *Mol. Nutr. Food Res.* **2009**, *53* (Suppl. 2), S330–S375.
(46) Piironen, V.; Lindsay, D. G.; Miettinen, T. A.; Toivo, J.; Lampi, A.-M. Plant sterols: biosynthesis, biological function and their importance to human nutrition. *J. Sci. Food Agric.* **2000**, *80*, 939–966.
(47) Lin, J.; Wang, C. Soybean saponins: chemistry, analysis, and potential of health effects. In *Soybeans as Functional Foods and Ingredients*, 1st ed.; Liu, K., Ed.; AOCS: Columbia, MO, 2004; pp 73−100.
(48) Messina, M. J. Legumes and soybeans: overview of their nutritional profiles and health effects. *Am. J. Clin. Nutr.* **1999**, *70*, 439S–450S.
(49) Penalvo, J. L.; Heinonen, S.-M.; Nurmi, T.; Deyama, T.; Nishibe, S.; Adlercreutz, H. Plant lignans in soy-based health supplements. *J. Agric. Food Chem.* **2004**, *52*, 4133–4138.
(50) Shi, J.; Arunasalam, K.; Yeung, D.; Kakuda, Y.; Mittal, G.; Jiang, Y. Saponins from edible legumes: chemistry, processing, and health benefits. *J. Med. Food* **2004**, *7*, 67–78.
(51) Oakenfull, D. Saponins in food − a review. *Food Chem.* **1981**, *7*, 19–40.
(52) Sumiki, Y. Studies on the saponin of soy bean. I. *Bull. Agric. Chem. Soc. Jpn.* **1929**, *5*, 27–32.
(53) Sumiki, Y. The saponin of soy bean. II. *Bul.l Agric. Chem. Soc. Jpn.* **1930**, *6*, 49–51.
(54) Burrows, J. C.; Price, K. R.; Fenwick, R. G. Soyasaponin IV, an additional monodesmosidic saponin isolated from soyabean. *Phytochemistry* **1987**, *26*, 1214–1215.
(55) Curl, C. L.; Price, K. R.; Fenwick, G. R. Soyasaponin A3, a new monodesmosidic saponin isolated from the seeds of *Glycine max*. *J. Nat. Prod.* **1988**, *51*, 122–124.
(56) Kitagawa, I.; Saito, M.; Taniyama, T.; Yoshikawa, M. Saponin and sapogenol. XXXVIII. Structure of soyasaponin A2, a bisdesmoside of soyasapogenol A, from soybean, the seeds of *Glycine max* Merrill. *Chem. Pharm. Bull.* **1985**, *33*, 598–608.
(57) Kitagawa, I.; Saito, M.; Taniyama, T.; Yoshikawa, M. Saponin and sapogenol. XXXIX. Structure of soyasaponin A1, a bisdesmoside of soyasapogenol A, from soybean, the seeds of *Glycine max* Merrill. *Chem. Pharm. Bull.* **1985**, *33*, 1069–1076.
(58) Kitagawa, I.; Taniyama, T.; Nagahama, Y.; Okubo, K.; Yamauchi, F.; Yoshikawa, M. Saponin and sapogenol. XLII. Structures of acetyl-soyasaponins A1, A2, and A3, astringent partially acetylated bisdesmosides of soyasapogenol A, from American soybean, the seeds of *Glycine max* Merrill. *Chem. Pharm. Bull.* **1988**, *36*, 2819–2828.
(59) Kitagawa, I.; Wang, H. K.; Taniyama, T.; Yoshikawa, M. Saponin and sapogenol. XLI. Reinvestigation of the structures of soyasapogenols A, B, and E, oleanene-sapogenols from soybean. Structures of soyasaponins I, II, and III. *Chem. Pharm. Bull.* **1988**, *36*, 153–161.
(60) Shiraiwa, M.; Harada, K.; Okubo, K. Composition and structure of "group B saponin" in soybean seed. *Agric. Biol. Chem.* **1991**, *55*, 911–917.
(61) Taniyama, T.; Nagahama, Y.; Yoshikawa, M.; Kitagawa, I. Saponin and sapogenol. XLIII. Acetyl-soyasaponins A4, A5, and A6, new astringent bisdesmosides of soyasapogenol A, from Japanese soybean, the seeds of *Glycine max* Merrill. *Chem. Pharm. Bull.* **1988**, *36*, 2829–2839.
(62) Taniyama, T.; Yoshikawa, M.; Kitagawa, I. Saponin and sapogenol. XLIV. Soyasaponin composition in soybeans of various origins and soyasaponin content in various organs of soybean. Structure of soyasaponin V from soybean hypocotyl. *Yakugaku Zasshi* **1988**, *108*, 562–571.
(63) Heng, L.; Vincken, J. P.; Hoppe, K.; van Koningsveld, G. A.; Decroos, K.; Gruppen, H.; van Boekel, M. A. J. S.; Voragen, A. G. J. Stability of pea DDMP saponin and the mechanism of its decomposition. *Food Chem.* **2006**, *99*, 326–334.
(64) Decroos, K.; Vincken, J. P.; Heng, L.; Bakker, R.; Gruppen, H.; Verstraete, W. Simultaneous quantification of differently

glycosylated, acetylated, and 2,3-dihydro-2,5-dihydroxy-6-methyl-4*H*-pyran-4-one-conjugated soyasaponins using reversed-phase high-performance liquid chromatography with evaporative light scattering detection. *J. Chromatogr., A* **2005**, *1072*, 185–193.

(65) Kudou, S.; Tonomura, M.; Tsukamoto, C.; Uchida, T.; Sakabe, T.; Tamura, N.; Okubo, K. Isolation and structural elucidation of DDMP-conjugated soyasaponins as genuine saponins from soybean seeds. *Biosci., Biotechnol., Biochem*. **1993**, *57*, 546–550.

(66) Tsukamoto, C.; Kikuchi, A.; Harada, K.; Kitamura, K.; Okubo, K. Genetic and chemical polymorphisms of saponins in soybean seed. *Phytochemistry* **1993**, *34*, 1351–1356.

(67) Hosny, M.; Rosazza, J. P. N. Novel isoflavone, cinnamic acid, and triterpenoid glycosides in soybean molasses. *J. Nat. Prod*. **1999**, *62*, 853–858.

(68) Hosny, M.; Rosazza, J. P. N. New isoflavone and triterpene glycosides from soybeans. *J. Nat. Prod*. **2002**, *65*, 805–813.

(69) Ali, Z.; Khan, S. I.; Khan, I. A. Soyasaponin Bh, a triterpene saponin containing a unique hemiacetal-functional five-membered ring from *Glycine max* (soybeans). *Planta Med*. **2009**, *75*, 371–374.

(70) Quan, J. S.; Shen, M. H.; Zhang, S. Protective effects of soybean isoflavones and soy saponins on oxidation of lipoproteins. *Shipin Kexue* **2003**, *24*, 121–123.

(71) Kudou, S.; Tonomura, M.; Tsukamoto, C.; Uchida, T.; Sakabe, T.; Tamura, N.; Okubo, K. Isolation and structural elucidation of DDMP-conjugated soyasaponins as genuine saponins from soybean seeds. *Biosci., Biotechnol., Biochem*. **1993**, *57*, 546−550.

(72) Okubo, K. Physiological function of soybean glycosides, especially DDMP saponin. *Daizu Tanpakushitsu Kenkyu* **1993**, *14*, 108–111.

(73) Willner, E. D.; Gestetner, B.; Lavie, D.; Birk, Y.; Bondi, A. Soybean saponins. *J Chem Soc, Suppl*. **1964**, *1*, 5885–5888.

(74) Hu, X. Y.; Wang, X. G. Prospect of soyasaponins (I). The distribution, structure and characteristics. *Chin. Oils Fats* **2001**, *26*, 29–33.

(75) Gestetner, B.; Birk, Y.; Tencer, Y. Soybean saponins. Fate of ingested soybean saponins and the physiological aspect of their hemolytic activity. *J. Agric. Food Chem*. **1968**, *16*, 1031–1035.

(76) Hu, J.; Reddy, M. B.; Hendrich, S.; Murphy, P. A. Soyasaponin I and sapongenol B have limited absorption by Caco-2 intestinal cells and limited bioavailability in women. *J. Nutr*. **2004**, *134*, 1867–1873.

(77) Hu, J.; Zheng, Y. L.; Hyde, W.; Hendrich, S.; Murphy, P. A. Human fecal metabolism of soyasaponin I. *J. Agric. Food Chem*. **2004**, *52*, 2689–2696.

(78) Tsukamoto, C.; Yoshiki, Y. Soy saponin. In *Soy in Health and Disease Prevention*; Sugano, M., Ed.; Taylor and Francis Group: Boca Raton, FL, 2006; pp 155−172.

(79) Guclu-Ustundag, O.; Mazza, G. Saponins: properties, applications and processing. *Crit. Rev. Food Sci. Nutr*. **2007**, *47*, 231–258.

(80) Lee, Y. B.; Lee, H. J.; Kim, C. H.; Lee, S. B.; Sohn, H. S. Soy isoflavones and soyasaponins: characteristics and physiological functions. *Agric. Chem. Biotechnol*. **2005**, *48*, 49–57.

(81) Jiang, H. Y.; Lv, F. J.; Tai, J. Q. Bioactive components of soybean and their function. *Soybean Sci* **2000**, *19*, 160–164.

(82) Lv, F. X.; Lu, Z. X. Research process of bioactive substances in soybean. *Food Sci. Technol*. **2001**, *5*, 69–71.

(83) Gurfinkel, D. M.; Rao, A. V. Soyasaponins: the relationship between chemical structure and colon anticarcinogenic activity. *Nutr. Cancer* **2003**, *47*, 24–33.

(84) Persky, V.; Van Horn, L. Epidemiology of soy and cancer: perspectives and directions. *J. Nutr*. **1995**, *125*, 709S–712S.

(85) Ellington, A. A.; Berhow, M.; Singletary, K. W. Induction of macroautophagy in human colon cancer cells by soybean B-group triterpenoid saponins. *Carcinogenesis* **2005**, *26*, 159–167.

(86) Hsu, C. C.; Lin, T. W.; Chang, W. W.; Wu, C. Y.; Lo, W. H.; Wang, P. H.; Tsai, Y. C. Soyasaponin-I-modified invasive behavior of cancer by changing cell surface sialic acids. *Gynecol. Oncol*. **2005**, *96*, 415–422.

(87) Jun, H. S.; Kim, S. E.; Sung, M. K. Protective effect of soybean saponins and major antioxidants against aflatoxin B1-induced mutagenicity and DNA-adduct formation. *J. Med. Food* **2002**, *5*, 235–240.

(88) Kang, J. H.; Han, I. H.; Sung, M. K.; Yoo, H.; Kim, Y. G.; Kim, J. S.; Kawada, T.; Yu, R. Soybean saponin inhibits tumor cell metastasis by modulating expressions of MMP-2, MMP-9 and TIMP- 2. *Cancer Lett*. **2008**, *261*, 84–92.

(89) Kim, H. Y.; Yu, R.; Kim, J. S.; Kim, Y. K.; Sung, M. K. Antiproliferative crude soy saponin extract modulates the expression of IκBα, protein kinase C, and cyclooxygenase-2 in human colon cancer cells. *Cancer Lett*. **2004**, *210*, 1–6.

(90) Yanamandra, N.; Berhow, M. A.; Konduri, S.; Dinh, D. H.; Olivero, W. C.; Nicolson, G. L.; Rao, J. S. Triterpenoids from *Glycine max* decrease invasiveness and induce caspase-mediated cell death in human SNB19 glioma cells. *Clin. Exp. Metastasis* **2003**, *20*, 375–383.

(91) Rao, A. V.; Sung, M. K. Saponins as anticarcinogens. *J. Nutr*. **1995**, *125*, 717–724.

(92) Bachran, C.; Bachran, S.; Sutherland, M.; Bachran, D.; Fuchs, H. Saponins in tumor therapy. *Mini Rev. Med. Chem*. **2008**, *8*, 575–584.

(93) Chang, W. W.; Yu, C. Y.; Lin, T. W.; Wang, P. H.; Tsai, Y. C. Soyasaponin I decreases the expression of α2,3-linked sialic acid on the cell surface and suppresses the metastatic potential of B16F10 melanoma cells. *Biochem. Biophys. Res. Commun*. **2006**, *341*, 614–619.

(94) Oakenfull, D.; Sidhu, G. S. Could saponins be a useful treatment for hypercholesterolaemia? *Eur. J. Clin. Nutr*. **1990**, *44*, 79–88.

(95) Oakenfull, D. G.; Topping, D. L. Saponins and plasma cholesterol. *Atherosclerosis* **1983**, *48*, 301–303.

(96) Potter, J. D.; Topping, D. L.; Oakenfull, D. Soy, saponins, and plasma cholesterol. *Lancet* **1979**, *1*, 223.

(97) Topping, D. L.; Trimble, R. P.; Illman, R. J.; Potter, J. D.; Oakenfull, D. G. Prevention of dietary hypercholesterolemia in the rat by soy flour high and low in saponins. *Nutr. Rep. Int*. **1980**, *22*, 513–519.

(98) Oakenfull, D. Soy protein, saponins and plasma cholesterol. *J. Nutr*. **2001**, *131*, 2971–2972.

(99) Xiao, J. X.; Peng, G. H.; Zhang, S. H. Prevention effects of soyasaponins on hyperlipidemia mice and its molecular mechanism. *Acta Nutr. Sin*. **2005**, *27*, 147–150.

(100) Kiribuchi, M.; Miura, K.; Tokuda, S.; Kaneda, T. Hypocholesterolemic effect of triterpene alcohols with soysterol on plasma cholesterol in rats. *J. Nutr. Sci. Vitaminol*. **1983**, *29*, 35–43.

(101) Lee, S. O.; Simons, A. L.; Murphy, P. A.; Hendrich, S. Soyasaponins lowered plasma cholesterol and increased fecal bile acids in female golden Syrian hamsters. *Exp. Biol. Med*. **2005**, *230*, 472–478.

(102) Kubo, M.; Matsuda, H.; Tani, T.; Namba, K.; Arichi, S.; Kitagawa, I. Effects of soyasaponin on experimental disseminated intravascular coagulation. I. *Chem. Pharm. Bull*. **1984**, *32*, 1467–1471.

(103) Wang, Y. P.; Wu, J. X.; Zhang, F. L.; Wang, X. R. Effect of soyasaponin and ginsenoside (stem-leave saponin) on SOD and LPO in diabetic rats. *J. Baiqiuen Med. Univ*. **1993**, *19*, 122–123.

(104) Quan, J. S.; Yin, X. Z.; Tanaka, M.; Kanazawa, T. The hypoglycemic effects of soybean hypocotyl extract in diabetic rats and their mechanism. *Acta Nutr. Sin*. **2004**, *26*, 207–210.

(105) Okubo, K.; Kudou, S.; Uchida, T.; Yoshiki, Y.; Yoshikoshi, M.; Tonomura, M. Soybean saponin and isoflavonoids: structure and antiviral activity against human immunodeficiency virus in vitro. *ACS Symp. Ser*. **1994**, *No. 546*, 330–339.

(106) Li, J. B.; Hu, J. S.; Cheng, B. H.; Wang, X. G.; An, Z. Y.; Wei, Y. D. Inhibitory effect of total soyasaponin on virus replication and its clinical application. *Chin. J. Exp. Clin. Virol*. **1995**, *9*, 111–114.

(107) Hayashi, K.; Hayashi, H.; Hiraoka, N.; Ikeshiro, Y. Inhibitory activity of soyasaponin II on virus replication in vitro. *Planta Med*. **1997**, *63*, 102–105.

(108) Ikeda, T.; Yokomizo, K.; Okawa, M.; Tsuchihashi, R.; Kinjo, J.; Nohara, T.; Uyeda, M. Anti-herpes virus type 1 activity of oleanane-type triterpenoids. *Biol. Pharm. Bull*. **2005**, *28*, 1779–1781.

(109) Kinjo, J.; Imagire, M.; Udayama, M.; Arao, T.; Nohara, T. Structure−hepatoprotective relationships study of soyasaponins I−IV having soyasapogenol B as aglycone. *Planta Med*. **1998**, *64*, 233–236.

(110) Ohominami, H.; Okuda, H.; Yoshikawa, M.; Kitagawa, I. Effect of soyasaponins on lipid metabolism. *Wakanyaku Shinpojumu* **1981**, *14*, 157–162.
(111) Yoshiki, Y.; Okubo, K. Active oxygen scavenging activity of DDMP (2,3-dihydro-2,5- dihydroxy-6-methyl-4*H*-pyran-4-one) saponin in soybean seed. *Biosci., Biotechnol., Biochem*. **1995**, *59*, 1556–1557.
(112) Akihisa, T.; Kimura, Y.; Tamura, T. Bacchara-12,21-dien-3β-ol from the seeds of *Glycine max*. *Phytochemistry* **1994**, *37*, 1413–1415.
(113) Marshall, J. A.; Dennis, A. L.; Kumazawa, T.; Haynes, A. M.; Nes, W. D. Soybean sterol composition and utilization by *Phytophthora sojae*. *Phytochemistry* **2001**, *58*, 423–428.
(114) van Ee, J. H. Soy constituents: modes of action in low-density lipoprotein management. *Nutr. Rev*. **2009**, *67*, 222–234.
(115) Garbuzov, A. G.; Medvedev, F. A.; Levachev, M. M. Change in the composition ofsoybean oil sterols after heat treament. *Vopr. Pitan*. **1986**, 67–69.
(116) Ostlund, R. E., Jr. Phytosterols in human nutrition. *Annu. Rev. Nutr*. **2002**, *22*, 533–549.
(117) Kircher, H. W.; Rosenstein, F. U. Purification of campesterol and preparation of 7-dehydro-campesterol, 7-campestenol, and campestanol. *Lipids* **1974**, *9*, 333–337.
(118) Heinemann, T.; Axtmann, G.; von Bergmann, K. Comparison of intestinal absorption of cholesterol with different plant sterols in man. *Eur. J. Clin. Invest*. **1993**, *23*, 827–831.
(119) Brufau, G.; Canela, M. A.; Rafecas, M. Phytosterols: physiologic and metabolic aspects related to cholesterol-lowering properties. *Nutr. Res*. (*N.Y.*) **2008**, *28*, 217–225.
(120) Calpe-Berdiel, L.; Escola-Gil, J. C.; Blanco-Vaca, F. New insights into the molecular actions of plant sterols and stanols in cholesterol metabolism. *Atherosclerosis* **2009**, *203*, 18–31.
(121) de Jong, A.; Plat, J.; Mensink, R. P. Metabolic effects of plant sterols and stanols (review). *J. Nutr. Biochem*. **2003**, *14*, 362–369.
(122) von Bergmann, K.; Sudhop, T.; Lutjohann, D. Cholesterol and plant sterol absorption: recent insights. *Am. J. Cardiol*. **2005**, *96*, 10D–14D.
(123) Altmann, S. W.; Davis, H. R., Jr.; Zhu, L. J.; Yao, X.; Hoos, L. M.; Tetzloff, G.; Iyer, S. P.; Maguire, M.; Golovko, A.; Zeng, M.; Wang, L.; Murgolo, N.; Graziano, M. P. Niemann−Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science* **2004**, *303*, 1201–1204.
(124) Berge, K. E.; Tian, H.; Graf, G. A.; Yu, L.; Grishin, N. V.; Schultz, J.; Kwiterovich, P.; Shan, B.; Barnes, R.; Hobbs, H. H. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* **2000**, *290*, 1771–1775.
(125) Ryan, E. T.; Abraham, K. G.; John, S. P.; Lawrence, L. R. Compared with acyl-CoA:cholesterol *O*-acyltransferase (ACAT) 1 and lecithin:cholesterol acyltransferase, ACAT2 displays the greatest capacity to differentiate cholesterol from sitosterol. *J. Biol. Chem*. **2003**, *278*, 47594–47601.
(126) Yu, L.; Hammer, R. E.; Li-Hawkins, J.; Von Bergmann, K.; Lutjohann, D.; Cohen, J. C.; Hobbs, H. H. Disruption of Abcg5 and Abcg8 in mice reveals their crucial role in biliary cholesterol secretion. *Proc. Natl. Acad. Sci. U.S.A*. **2002**, *99*, 16237–16242.
(127) Yu, L.; Li-Hawkins, J.; Hammer, R. E.; Berge, K. E.; Horton, J. D.; Cohen, J. C.; Hobbs, H. H. Overexpression of ABCG5 and ABCG8 promotes biliary cholesterol secretion and reduces fractional absorption of dietary cholesterol. *J. Clin. Invest*. **2002**, *110*, 671–680.
(128) Ostlund, R. E., Jr.; McGill, J. B.; Zeng, C. M.; Covey, D. F.; Stearns, J.; Stenson, W. F.; Spilburg, C. A. Gastrointestinal absorption and plasma kinetics of soy Δ(5)-phytosterols and phytostanols in humans. *Am. J. Physiol. Endocrinol. Metab*. **2002**, *282*, E911–E916.
(129) Peterson, D. W. Plant sterols and tissue cholesterol levels. *Am. J. Clin. Nutr*. **1958**, *6*, 644–649.
(130) Lin, X.; Ma, L.; Racette, S. B.; Spearie, C. L. A.; Ostlund, R. E., Jr. Phytosterol glycosides reduce cholesterol absorption in humans. *Am. J. Physiol*. **2009**, *296*, G931–G935.
(131) Ostlund, R. E., Jr. Phytosterols, cholesterol absorption and healthy diets. *Lipids* **2007**, *42*, 41–45.
(132) Ostlund, R. E., Jr. Phytosterols and cholesterol metabolism. *Curr. Opin. Lipidol*. **2004**, *15*, 37–41.
(133) Moghadasian, M. H.; Frohlich, J. J. Effects of dietary phytosterols on cholesterol metabolism and atherosclerosis: clinical and experimental evidence. *Am. J. Med*. **1999**, *107*, 588–594.
(134) Katan, M. B.; Grundy, S. M.; Jones, P.; Law, M.; Miettinen, T.; Paoletti, R. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clin. Proc*. **2003**, *78*, 965–978.
(135) Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA, J. Am. Med. Assoc*. **2001**, *285*, 2486−2497.
(136) Vanstone, C. A.; Raeini-Sarjaz, M.; Jones, P. J. Injected phytosterols/stanols suppress plasma cholesterol levels in hamsters. *J. Nutr. Biochem*. **2001**, *12*, 565–574.
(137) Matvienko, O. A.; Lewis, D. S.; Swanson, M.; Arndt, B.; Rainwater, D. L.; Stewart, J.; Alekel, D. L. A single daily dose of soybean phytosterols in ground beef decreases serum total cholesterol and LDL cholesterol in young, mildly hypercholesterolemic men. *Am. J. Clin. Nutr*. **2002**, *76*, 57–64.
(138) Zhao, Y.; Chang, S. K.; Qu, G.; Li, T.; Cui, H. β-Sitosterol inhibits cell growth and induces apoptosis in SGC-7901 human stomach cancer cells. *J. Agric. Food Chem*. **2009**, *57*, 5211–5218.
(139) Woyengo, T. A.; Ramprasath, V. R.; Jones, P. J. Anticancer effects of phytosterols. *Eur. J. Clin. Nutr*. **2009**, *63*, 813–820.
(140) Bradford, P. G.; Awad, A. B. Phytosterols as anticancer compounds. *Mol. Nutr. Food Res*. **2007**, *51*, 161–170.
(141) Awad, A. B.; Williams, H.; Fink, C. S. Phytosterols reduce in vitro metastatic ability of MDA-MB-231 human breast cancer cells. *Nutr. Cancer* **2001**, *40*, 157–164.
(142) Awad, A. B.; Fink, C. S. Phytosterols as anticancer dietary components: evidence and mechanism of action. *J. Nutr*. **2000**, *130*, 2127–2130.
(143) Awad, A. B.; von Holtz, R. L.; Cone, J. P.; Fink, C. S.; Chen, Y. C. β-Sitosterol inhibits growth of HT-29 human colon cancer cells by activating the sphingomyelin cycle. *Anticancer Res*. **1998**, *18*, 471–473.
(144) Philpotts, M. Phytochemicals for cancer prevention. *Lippincott Health Promot. Lett*. **1997**, *2*, 7 and 10.
(145) Bouic, P. J. The role of phytosterols and phytosterolins in immune modulation: a review of the past 10 years. *Curr. Opin. Clin. Nutr. Metab. Care* **2001**, *4*, 471–475.
(146) Bouic, P. J.; Lamprecht, J. H. Plant sterols and sterolins: a review of their immune-modulating properties. *Altern. Med. Rev*. **1999**, *4*, 170–177.
(147) Dixon, R. A. Phytoestrogens. *Annu. Rev. Plant Biol*. **2004**, *55*, 225–261.
(148) Kurzer, M. S.; Xu, X. Dietary phytoestrogens. *Annu. Rev. Nutr*. **1997**, *17*, 353–381.
(149) Mazur, W. M.; Duke, J. A.; Wahala, K.; Rasku, S.; Adlercreutz, H. Isoflavonoids and lignans in legumes: nutritional and health aspects in humans. *J. Nutr. Biochem*. **1998**, *9*, 193–200.
(150) Clavel, T.; Dore, J.; Blaut, M. Bioavailability of lignans in human subjects. *Nutr. Res. Rev*. **2006**, *19*, 187–196.
(151) Heinonen, S.; Nurmi, T.; Liukkonen, K.; Poutanen, K.; Wahala, K.; Deyama, T.; Nishibe, S.; Adlercreutz, H. In vitro metabolism of plant lignans: new precursors of mammalian lignans enterolactone and enterodiol. *J. Agric. Food Chem*. **2001**, *49*, 3178–3186.
(152) Wang, L. Q.; Meselhy, M. R.; Li, Y.; Qin, G. W.; Hattori, M. Human intestinal bacteria capable of transforming secoisolariciresinol diglucoside to mammalian lignans, enterodiol and enterolactone. *Chem. Pharm. Bull*. **2000**, *48*, 1606–1610.
(153) Lampe, J. W.; Atkinson, C.; Hullar, M. A. Assessing exposure to lignans and their metabolites in humans. *J. AOAC Int*. **2006**, *89*, 1174–1181.
(154) Kuijsten, A.; Arts, I. C.; Vree, T. B.; Hollman, P. C. Pharmacokinetics of enterolignans in healthy men and women consuming a single dose of secoisolariciresinol diglucoside. *J. Nutr*. **2005**, *135*, 795–801.

(155) Chin, Y. W.; Chai, H. B.; Keller, W. J.; Kinghorn, A. D. Lignans and other constituents of the fruits of *Euterpe oleracea* (acai) with antioxidant and cytoprotective activities. *J. Agric. Food Chem.* **2008**, *56*, 7759–7764.
(156) Willfor, S. M.; Ahotupa, M. O.; Hemming, J. E.; Reunanen, M. H.; Eklund, P. C.; Sjoholm, R. E.; Eckerman, C. S.; Pohjamo, S. P.; Holmbom, B. R. Antioxidant activity of knotwood extractives and phenolic compounds of selected tree species. *J. Agric. Food Chem.* **2003**, *51*, 7600–7606.
(157) Sutthivaiyakit, S.; Nakorn, N. N.; Kraus, W.; Sutthivaiyakit, P. A novel 29-*nor*-3,4-*seco*-friedelane triterpene and a new guaiane sesquiterpene from the roots of *Phyllanthus oxyphyllus*. *Tetrahedron* **2003**, *59*, 9991–9995.
(158) Mulabagal, V.; Subbaraju, G. V.; Ramani, M. V.; DeWitt, D. L.; Nair, M. G. Lipid peroxidation, cyclooxygenase enzyme and tumor cell proliferation inhibitory lignans from *Justicia* species. *Nat. Prod. Commun.* **2008**, *3*, 1793–1798.
(159) Carreau, C.; Flouriot, G.; Bennetau-Pelissero, C.; Potier, M. Enterodiol and enterolactone, two major diet-derived polyphenol metabolites have different impact on ERα transcriptional activation in human breast cancer cells. *J. Steroid Biochem. Mol. Biol.* **2008**, *110*, 176–185.
(160) Wang, L. Q. Mammalian phytoestrogens: enterodiol and enterolactone. *J. Chromatogr., B: Anal. Technol. Biomed. Life Sci.* **2002**, *777*, 289–309.
(161) Wang, C.; Kurzer, M. S. Phytoestrogen concentration determines effects on DNA synthesis in human breast cancer cells. *Nutr. Cancer* **1997**, *28*, 236–247.
(162) Sung, M. K.; Lautens, M.; Thompson, L. U. Mammalian lignans inhibit the growth of estrogen-independent human colon tumor cells. *Anticancer Res.* **1998**, *18*, 1405–1408.
(163) Grases, F.; Simonet, B. M.; Vucenik, I.; Prieto, R. M.; Costa-Bauza, A.; March, J. G.; Shamsuddin, A. M. Absorption and excretion of orally administered inositol hexaphosphate (IP(6) or phytate) in humans. *Biofactors* **2001**, *15*, 53–61.
(164) Sakamoto, K.; Vucenik, I.; Shamsuddin, A. M. [^{3}H]phytic acid (inositol hexaphosphate) is absorbed and distributed to various tissues in rats. *J. Nutr.* **1993**, *123*, 713–720.
(165) Grases, F.; Simonet, B. M.; March, J. G.; Prieto, R. M. Inositol hexakisphosphate in urine: the relationship between oral intake and urinary excretion. *BJU Int.* **2000**, *85*, 138–142.
(166) Grases, F.; Simonet, B. M.; Prieto, R. M.; March, J. G. Phytate levels in diverse rat tissues: influence of dietary phytate. *Br. J. Nutr.* **2001**, *86*, 225–231.
(167) Grases, F.; Simonet, B. M.; Vucenik, I.; Perello, J.; Prieto, R. M.; Shamsuddin, A. M. Effects of exogenous inositol hexakisphosphate (InsP(6)) on the levels of InsP(6) and of inositol trisphosphate (InsP(3)) in malignant cells, tissues and biological fluids. *Life Sci* **2002**, *71*, 1535–1546.
(168) Cholewa, K.; Parfiniewicz, B.; Bednarek, I.; Swiatkowska, L.; Jezienicka, E.; Kierot, J.; Weglarz, L. The influence of phytic acid on TNF-α and its receptors genes' expression in colon cancer Caco-2 cells. *Acta Pol. Pharm.* **2008**, *65*, 75–79.
(169) Vucenik, I.; Shamsuddin, A. M. Protection against cancer by dietary IP6 and inositol. *Nutr. Cancer* **2006**, *55*, 109–125.
(170) Otake, T.; Mori, H.; Morimoto, M.; Miyano, K.; Ueba, N.; Oishi, I.; Kunita, N.; Kurimura, T. Anti-HIV-1 activity of *myo*-inositol hexaphosphoric acid (IP6) and *myo*-inositol hexasulfate (IS6). *Anticancer Res.* **1999**, *19*, 3723–3726.
(171) Fox, C. H.; Eberl, M. Phytic acid (IP6), novel broad spectrum anti-neoplastic agent: a systematic review. *Complementary Ther. Med.* **2002**, *10*, 229–234.
(172) Agarwal, C.; Dhanalakshmi, S.; Singh, R. P.; Agarwal, R. Inositol hexaphosphate inhibits growth and induces G1 arrest and apoptotic death of androgen-dependent human prostate carcinoma LNCaP cells. *Neoplasia* **2004**, *6*, 646–659.
(173) Singh, R. P.; Agarwal, C.; Agarwal, R. Inositol hexaphosphate inhibits growth, and induces G1 arrest and apoptotic death of prostate carcinoma DU145 cells: modulation of CDKI-CDK-cyclin and pRb-related protein-E2F complexes. *Carcinogenesis* **2003**, *24*, 555–563.
(174) Tantivejkul, K.; Vucenik, I.; Eiseman, J.; Shamsuddin, A. M. Inositol hexaphosphate (IP6) enhances the anti-proliferative effects of adriamycin and tamoxifen in breast cancer. *Breast Cancer Res. Treat.* **2003**, *79*, 301–312.
(175) Tian, Y.; Song, Y. Effects of inositol hexaphosphate on proliferation of HT-29 human colon carcinoma cell line. *World J. Gastroenterol.* **2006**, *12*, 4137–4142.
(176) Vucenik, I.; Kalebic, T.; Tantivejkul, K.; Shamsuddin, A. M. Novel anticancer function of inositol hexaphosphate: inhibition of human rhabdomyosarcoma in vitro and in vivo. *Anticancer Res.* **1998**, *18*, 1377–1384.
(177) Zhang, Z.; Song, Y.; Wang, X. L. Inositol hexaphosphate-induced enhancement of natural killer cell activity correlates with suppression of colon carcinogenesis in rats. *World J. Gastroenterol.* **2005**, *11*, 5044–5046.
(178) Vucenik, I.; Tomazic, V. J.; Fabian, D.; Shamsuddin, A. M. Antitumor activity of phytic acid (inositol hexaphosphate) in murine transplanted and metastatic fibrosarcoma, a pilot study. *Cancer Lett.* **1992**, *65*, 9–13.
(179) Gupta, K. P.; Singh, J.; Bharathi, R. Suppression of DMBA-induced mouse skin tumor development by inositol hexaphosphate and its mode of action. *Nutr. Cancer* **2003**, *46*, 66–72.
(180) Anderson, R. L.; Wolf, W. J. Compositional changes in trypsin inhibitors, phytic acid, saponins and isoflavones related to soybean processing. *J. Nutr.* **1995**, *125*, 581S–588S.
(181) Friedman, M. Nutritional consequences of food processing. *Forum Nutr.* **2003**, *56*, 350–352.
(182) Molnar-Perl, I.; Pinter-Szakacs, M. Monitoring of Maillard reactions in soy products. *Z. Lebensm. Unters. Forsch.* **1986**, *183*, 18–25.
(183) Csaky, I.; Fekete, S. Soybean: feed quality and safety. Part 1: biologically active components. A review. *Acta Vet. Hung.* **2004**, *52*, 299–313.
(184) Friedman, M. Biological effects of Maillard browning products that may affect acrylamide safety in food: biological effects of Maillard products. *Adv. Exp. Med. Biol.* **2005**, *561*, 135–156.
(185) Silvan, J. M.; van de Lagemaat, J.; Olano, A.; Del Castillo, M. D. Analysis and biological properties of amino acid derivates formed by Maillard reaction in foods. *J. Pharm. Biomed. Anal.* **2006**, *41*, 1543–1551.
(186) Dyer, D. G.; Blackledge, J. A.; Katz, B. M.; Hull, C. J.; Adkisson, H. D.; Thorpe, S. R.; Lyons, T. J.; Baynes, J. W. The Maillard reaction in vivo. *Z. Ernahrungswiss.* **1991**, *30*, 29–45.
(187) Nunomura, N.; Sasaki, M.; Asao, Y.; Yokotsuka, T. Studies on flavor components in shoyu. II. Isolation and identification of 4-hydroxy-2(or 5)-ethyl-5(or 2)-methyl-3(2*H*)-furanone, as a flavor component in shoyu (soy sauce). *Agric. Biol. Chem.* **1976**, *40*, 491–495.
(188) Hashiba, H. Isolation and identification of Amadori compounds from miso, white wine and sake. *Agric. Biol. Chem.* **1978**, *42*, 1727–1731.
(189) Tsuchiya, H.; Sato, M.; Watanabe, I. Antiplatelet activity of soy sauce as functional seasoning. *J. Agric. Food Chem.* **1999**, *47*, 4167–4174.
(190) Hayashi, H.; Nishimoto, Y.; Akiyama, K.; Nozaki, H. New paralytic alkaloids, asperparalines A, B and C, from *Aspergillus japonicus* JV-23. *Biosci., Biotechnol., Biochem.* **2000**, *64*, 111–115.
(191) Sugawara, E. Relation between the aroma components and palatability of miso. *Nippon Kasei Gakkaishi* **1992**, *43*, 635–642.
(192) Sugawara, E.; Saiga, S.; Kobayashi, A. Relations between aroma components and sensory evaluation of miso. *Nippon Shokuhin Kogyo Gakkaishi* **1992**, *39*, 1098–1104.
(193) Wang, H.; Jenner, A. M.; Lee, C. Y.; Shui, G.; Tang, S. Y.; Whiteman, M.; Wenk, M. R.; Halliwell, B. The identification of antioxidants in dark soy sauce. *Free Radical Res.* **2007**, *41*, 479–488.
(194) Ginting, E.; Arcot, J. High-performance liquid chromatographic determination of naturally occurring folates during tempe preparation. *J. Agric. Food Chem.* **2004**, *52*, 7752–7758.

Received for review March 8, 2010. Revised manuscript received June 15, 2010. Accepted June 15, 2010. Mention of trade names or commercial products in this publication is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the U.S. Department of Agriculture.