Phytochemicals in Soy and Their Health Effects

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1. Introduction

Consumption of soy foods has been associated, at least in part, with lower incidences of a number of chronic diseases indicated by epidemiological studies (1-4). Soy-based foods have been consumed in Asian countries such as China, Japan and Korea 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).

Soy-based food was first introduced on a large scale to the general U.S. population as a source of high quality protein. A significant increase in soy food consumption during the last decade of the 20th century occurred because of the health benefits soy food might offer independent of their nutrient content (7). In the last few decades, extensive efforts have been made towards identifying bioactive components in soy foods that are responsible for the health benefits. Among them, isoflavones and soy proteins are the two major groups of components that have received the most attention (8-11). Isoflavones belong to a broad group of plant-derived compounds that have structural and functional similarities to estrogens, which has led to the term phytoestrogens (12, 13). Indeed, more than half of the soy-related papers are related to isoflavones (7). The analysis, bioavailability and the health effects of isoflavones have been extensively studied and frequently reviewed (12, 14-21). Consumption of isoflavones has been suggested to have multiple beneficial effects in a number of chronic diseases and medical conditions (4, 22, 23). However, accumulating evidence has also suggested that isoflavones only reflected certain aspects of the health effects associated with soy consumption. Other components in soy, such as soyasaponins, phytic acid or plant sterols, display a wide range of bioactivities, including anti-cancer, anti-oxidative, anti-viral, cardiovascular protective effects, and hepatoprotective actions (24).

* 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.
In this chapter, we summarize the structural characterization of major phytochemicals in soybean and soy-based foods. Potential health benefits of these phytochemicals, especially the non-isoflavone phytochemicals and their preventive effects of chronic and lifestyle-related diseases, are also briefly discussed.

2. Phytochemicals in soybean and their health effects

In this section, the structural characterizations of major phytochemicals that naturally exist in soybean are firstly summarized. Composition and contents of phytochemicals in soybean vary dramatically depending on the variety and growing environment. In general, the

![Chemical structures of isoflavones in soy](image)

Fig. 1. The chemical structures of isoflavones in soy.
Phytochemicals in Soy and Their Health Effects

Contents of major phytochemicals from high to low in soybean are: phytic acid (1.0-2.2%) (25), sterols (0.23-0.46%) (26), saponins (0.17-6.16%) (27), isoflavones (0.1-0.3%) (23), and lignans (0.02%) (28). Secondly, the potential health effects of the major phytochemicals are outlined. For many years, the studies of health effects of soybean phytochemicals primarily focused on isoflavones. 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 Isoflavones

2.1.1 Chemical characteristics of isoflavones

Isoflavones have been known to exist in plants for over 100 years. And soy, including the foods derived from this legume, is considered as a richest dietary source of isoflavones (7). Isoflavones (3-phenyl-4H-1-benzopyran-4-one) are a subclass of more ubiquitous flavonoids, while they differs from flavone (2-phenyl-4H-1-benzopyran-4-one) in that the phenyl group (B ring) is connected to position 3 instead of position 2 (Figure 1) (29). Soy mainly contains three isoflavones, namely daidzein (7,4’-dihydroxyisoflavone) (1), genistein (5,7,4’-trihydroxyisoflavone) (2), and glycitein (6-methoxy-7,4’-dihydroxyisoflavone) (3). Genistein and daidzein have been found in relatively high concentrations in soybean and most soy-based foods. In soybean and non-fermented soy foods, they are generally present as one of the following three β-glucoside conjugates: a) the corresponding glucosides: daidzin (daidzein 7-Ο-β-D-glucoside) (4), genistin (genistein 7-Ο-β-D-glucoside) (5) and glycitin (glycitein 7-Ο-β-D-glucoside) (6); b) the corresponding acetylglucosides: 6’-Ο-acetyldaidzin (7), 6’-Ο-acetylgenistin (8), and c) the corresponding malonylglucosides: 6’-Ο-malonyldaidzin (10), 6’-Ο-malonylgenistin (11) and 6’-Ο-malonylglycitin (12) (29). In addition to β-glucoside conjugates, isoflavones conjugated with other sugar moieties, including 6’-Ο-β-D-arabinose-genistin (13) and 6’-Ο-β-D-xylose-genistin (14). Other isoflavones, including 2’,6’-Ο –diacetyloinin (15), and two dihydro-isoflavanones, dihydrodaidzin (16) and dihydrogenistin (17) were reported recently in the last ten years (30, 31).

2.1.2 Health effects of isoflavones

Health effects of isoflavones were initially thought to be related to their estrogenic activity (23). The molecular structures of isoflavones, especially genistein (2), are similar to that of 17β-estradiol (Figure 2). Isoflavones can bind to both α and β isoforms of esterogen receptor (ER), but their binding affinity to ERβ is about 20 times higher than that to ERα (11). However, compared to physiological estrogen such as 17β-estradiol, isoflavones have approximately 100 times weaker affinities (32). Estrogen-like effects have been proposed as one of the major mechanism of action of isoflavone related to their health effects (8). A second mechanism of action of isoflavones, particularly of genistein, was discovered that genistein is a protein tyrosine kinase (PTK) inhibitor (8). Since then, isoflavones have been shown to affect a diverse array of intracellular signaling pathways (7). For instance, genistein and other isoflavones were found to interact with the peroxisome proliferator activated receptors, PPARα/γ. These nuclear receptors are activated by fatty acids (PPARα) and prostaglandins (PPARγ) and serve as transcription factors (32). As polyphenols, isoflavones also have antioxidant activities,
which were proposed as another important mechanism of action of isoflavones. However, 
isoﬂavones are not strong antioxidant may not be able to scavenge oxidants directly. They 
therefore are considered as antioxidants because of their effects on gene expression of enzymes 
that enhance antioxidant defenses (32). In addition to what has been discussed above, several 
other mechanism have been proposed for the activities of isoflavones, including 
stimulation/inhibition of enzyme activities involved in steroid synthesis and metabolism, 
targeting thyroid peroxidase, and inhibiting cancer metastasis (32).

Consumption of isoflavones has been suggested to have multiple beneﬁcial effects in a 
number of chronic diseases and medical conditions, including certain types of cancer (33-
35), heart disease (36-38), bone functions (39-42) and most recently, prevention of obesity 
(43, 44). Many excellent reviews regarding the different aspects of health effects of soy 
isoﬂavone can be found in the literatures, thus, only a brief outline of the health effects of 
isoﬂavones is provided in this chapter.

2.1.2.1 Isoflavones and prevention of cancer

The incidences of breast and prostate cancers are much higher in the United States and 
European countries compared to Asian countries such as Japan and China. One of the major 
differences in diet between these populations is that the Japanese and the Chinese consume a 
traditional diet high in soy products (35). Epidemiological evidence together with preclinical 
data from animal and in vitro studies strongly supported a correlation between soy isoﬂavone 
consumption and protection towards breast and prostate cancers (45-47). However, clinical 
studies assessing soy consumption and risk of breast cancer have yielded inconsistent results. 
In a most recent meta-analysis of prospective studies suggested that soy isoﬂavones intake is 
associated with a signiﬁcantly reduced risk of breast cancer incidence in Asian populations, 
but not in Western populations. Further studies are warranted to conﬁrm the ﬁnding of an 
inverse association of soy consumption with risk of breast cancer recurrence (48).

Except for breast and prostate cancer, isoﬂavones also showed inhibitory effects on other 
hormone-related (e.g. endometrial, ovarian cancer) or hormone-independent cancers (e.g. 
leukemia and lung cancer) (49).

2.1.2.2 Isoflavones and prevention of cardiovascular diseases

A number of cardioprotective beneﬁts have been attributed to dietary isoﬂavones including 
reduction in LDL cholesterol, inhibition of pro-inﬂammatory cytokines, cell adhesion
Phytochemicals in Soy and Their Health Effects

proteins and inducible nitric oxide production, potential reduction in the susceptibility of the LDL particle to oxidation, inhibition of platelet aggregation and an improvement in vascular reactivity (50). There are not randomized trials investigating the action of isoflavones on the incidence of clinical events. A few recent, well-designed studies have suggested an association of the ingestion of isoflavones with a reduction in the atherosclerotic burden, as indicated by the measurement of the intima-media thickness in carotid vessels (51).

2.1.2.3 Isoflavones and bone health

Observational studies have suggested that populations in Asia with a high dietary soy intake have a lower incidence of osteoporosis-related fractures when compared to Western populations. Isoflavones were suggested to prevent bone loss associated with menopause. Though extensive research using animal models has provided convincing data to indicate a significant improvement in bone mass or other end points following feeding with soyabean, results from intervention studies are still controversial (52). Additional research is needed to determine if isoflavones are an effective alternative to hormone replacement therapy for the prevention and treatment of osteoporosis (42).

2.1.2.4 Isoflavones and prevention of obesity

The prevalence of obesity and related diseases has increased rapidly in the Western world. Obesity is a disorder of energy balance and is associated with hyper-insulinemia, insulin resistance, and abnormalities in lipid metabolism, and it is one of the most important risk factors in the development of Type II diabetes, cardiovascular disease, atherosclerosis, and certain cancers (44). In recent years, evidence is emerging that soy isoflavones play a beneficial role in obesity and diabetes. Nutritional intervention studies in animals and humans indicate that consumption of soy isoflavone or soy protein containing isoflavones reduces body weight and fat mass by lowering plasma cholesterol and triglycerides as well as by other mechanisms (43, 44, 53). Though the published results suggest a beneficial effect of soy isoflavone on obesity in human, these results also suggest that the effect may be dependent on whether the isoflavones are consumed in combination with soy protein (44).

2.2 Soyasaponins and soyasapogenols

2.2.1 Chemical characteristics of soyasaponins and soyasapogenols

Saponins are sterol or triterpene glycosides that occur in a wide variety of plants. Soy-based foods are primary dietary sources of saponins (54). Chemical studies of saponins in soy track back to the 1930’s (55, 56). From the 1980’s to 1990’s, a number of papers, especially those published by Japanese researchers, significantly enriched our knowledge about chemical structure and diversity of this type of compounds in soy (57-65).

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: group 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 group A and B by having a carbonyl group at C-22. Group B saponins may contain a DDMP (2,3-dihydro-2,5-dihydroxy-6-methyl-4H-pyran-4-one) moiety at C-22 position, which are
Phytochemicals – Bioactivities and Impact on Health

denoted as DDMP saponins (66) (Figure 3). DDMP soyasaponins and the acetylated soyasaponins of group A are sometimes considered as the genuine forms of groups A and B in soybeans. Group E soyasaponins are also considered to be phyto-oxidation products of group B soyasaponins (62, 67, 68). All four groups of soyasaponins 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 position of the aglycones. Group A soyasaponins have two sugar chains, separately attached to C-3 and C-22 positions of soyasapogenol A, except for A3 (33), which has only one sugar chain at C-3 (Table 1). C-3 sugar chain consists of two or three sugar residues, starting with a glucoronyl residue (glcUA) (67). C-22 side chain consists of two sugar residues, starting with an anarabinosyl, and ending with a xylosyl or glycosyl residue (58, 63, 65, 69) (Figure 3).

Group B soyasaponins have one sugar chain attached to the C-3 position of soyasapogenol B, with three exceptional compounds that have two sugar chains at C-3 and C-22 positions (41-43) (57, 59, 69-71) (Figure 3). Most recently, a new soyasaponin Bh (40) was identified to bear an unique five-membered ring containing a hemiacetal functionality (Figure 3) (72). Group E soyasaponins 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 (63, 69) (Figure 3). DDMP soyasaponins are categorized under B type soyasaponins by some researchers (27). Their structures were characterized as having DDMP group conjugated to group B at C-22 (67, 68, 73, 74) (Figure 3). Similar to B type soyasaponins, DDMP soyasaponins only contain one sugar chain attached to C-3 position. There are about 36 soyasaponins identified in soybean. Their structures and the related references are listed (Tables 1-4).

Table 1. The structures and molecular formulas of group A soyasaponins

<table>
<thead>
<tr>
<th>NO.</th>
<th>name</th>
<th>C-3 sugar chain</th>
<th>C-22 sugar chain</th>
<th>molecular formula</th>
<th>ref</th>
</tr>
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<tbody>
<tr>
<td>18</td>
<td>Aa (acetyl Aa)</td>
<td>gal(1→2)gal(1→2)glcUA(1→3)</td>
<td>2,3,4-tri-O-acetyl-xyr(1→3)ara(1→22)</td>
<td>C_{48}H_{78}O_{19}</td>
<td>58</td>
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<td>19</td>
<td>Ab (acetyl Aa)</td>
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<td>2,3,4,6-tetra-O-acetyl-gl(1→3)ara(1→22)</td>
<td>C_{48}H_{80}O_{20}</td>
<td>61</td>
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<td>20</td>
<td>Ac</td>
<td>rha(1→2)gal(1→2)glcUA(1→3)</td>
<td>2,3,4,6-tetra-O-acetyl-gl(1→3)ara(1→22)</td>
<td>C_{48}H_{82}O_{21}</td>
<td>62</td>
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<tr>
<td>21</td>
<td>Ad</td>
<td>glc(1→2)ara(1→2)glcUA(1→3)</td>
<td>2,3,4,6-tetra-O-acetyl-gl(1→3)ara(1→22)</td>
<td>C_{48}H_{82}O_{22}</td>
<td>63</td>
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<td>22</td>
<td>Ae (acetyl As)</td>
<td>gal(1→2)glcUA(1→3)</td>
<td>2,3,4-tri-O-acetyl-xyr(1→3)ara(1→22)</td>
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<td>65</td>
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<td>23</td>
<td>Af (acetyl Aa)</td>
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<td>68</td>
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<td>2,3,4-tri-O-acetyl-xyr(1→3)ara(1→22)</td>
<td>C_{48}H_{82}O_{29}</td>
<td>69</td>
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<td>27</td>
<td>Aa</td>
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<td>gl(1→3)ara(1→22)</td>
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<td>Aa</td>
<td>ara(1→2)glcUA(1→3)</td>
<td>gl(1→3)ara(1→22)</td>
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<td>Aa</td>
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<td>xyr(1→3)ara(1→22)</td>
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<td>Aa</td>
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<td>64</td>
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<td>32</td>
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<td>ara(1→2)glcUA(1→3)</td>
<td>xyr(1→3)ara(1→22)</td>
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<td>C_{48}H_{82}O_{19}</td>
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<td>NO.</td>
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<td>soyasaponin Ba or V</td>
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<td>C₄₀H₆₅O₁₉</td>
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<td>35</td>
<td>soyasaponin Bb or I</td>
<td>rha(1→2)gal(1→2)glcUA(1→3)</td>
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<td>C₄₆H₆₅O₁₈</td>
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<td>C₄₇H₇₂O₁₇</td>
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<td>37</td>
<td>soyasaponin Bb’or III</td>
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<td>C₄₂H₆₄O₁₄</td>
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<td>38</td>
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<td>glc(1→2)ara(1→2)glcUA(1→3)</td>
<td>C₄₉H₇₈O₉₂</td>
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Table 2. The structures and molecular formulas of group B soyasaponins

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<td>44</td>
<td>soyasaponin Bd (sandosaponin A)</td>
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<td>45</td>
<td>soyasaponin Be (dehydrosoyasaponin I)</td>
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<td>C₄₆H₆₅O₁₈</td>
<td>63</td>
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<td>46</td>
<td>soyasaponin Bf</td>
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<td>47</td>
<td>soyasaponin Bg</td>
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Table 3. The structures and molecular formulas of group E soyasaponins

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<th>C-22 DDMP</th>
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<td>48</td>
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<td>glc(1→2)gal(1→2)glcUA(1→3)</td>
<td>DDMP(22→2')</td>
<td>C₄₅H₆₄O₂₂</td>
<td>68</td>
</tr>
<tr>
<td>49</td>
<td>soyasaponin αa</td>
<td>glc(1→2)ara(1→2)glcUA(1→3)</td>
<td>DDMP(22→2')</td>
<td>C₄₅H₆₄O₂₁</td>
<td>74</td>
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<td>50</td>
<td>soyasaponin βg or VI</td>
<td>rha(1→2)gal(1→2)glcUA(1→3)</td>
<td>DDMP(22→2')</td>
<td>C₄₅H₆₄O₂₁</td>
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<td>51</td>
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<td>DDMP(22→2')</td>
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<td>gal(1→2)glcUA(1→3)</td>
<td>DDMP(22→2')</td>
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<td>53</td>
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<td>ara(1→2)glcUA(1→3)</td>
<td>DDMP(22→2')</td>
<td>C₄₇H₇₂O₁₆</td>
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Fig. 3. The chemical structures of groups A, B, Bh, E and DDMP soyasaponins in soy.
Soyasapogenols are aglycones of soyasaponins. They can be obtained by acid or alkaline hydrolysis of soyasaponins. Though soyasapogenols don’t exist in soy bean naturally, they may exist in certain soy products through food processing. Five soyasapogenols A (54), B (55), C (56), D (57) and E (58) have been found through hydrolysis of soyasaponins (59, 62, 75) (Figure 4). Among them, soyasapogenol A (54) has two hydroxyl groups at C-21 and C-22 position, which is considered as corresponding aglycones to bis-desmoside soyasaponin group A. Soyasapogenol B (55) has only one hydroxyl group at C-22 position. It is considered to be aglycone of both monodesmoside soyasaponin groups B and DDMP. Soyasapogenol E (58) is regarded as the corresponding aglycone to soyasaponin group E. Soyasapogenols C (56) and D (57) are considered by some researchers not to be genuine aglycones of soyasaponins, but as the acid hydrolysis products of soyasapogenol B (55) (76).

Fig. 4. The chemical structures of soyasapogenols A-E (hydrolysis products of soysaponins).

2.2.2 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 with a long list in a recent review (77). Soyasaponins and soyasapogenols have been reported to display diverse health effects (78), including anti-cancer, cardiovascular protective effects, anti-virus, hepatoprotective actions and antioxidant activities (24, 27, 79, 80). Their health effects largely depend on their chemical structures (81). Since this class of soy compounds are so poorly absorbed, their bioactivity maybe caused by indirect actions within the GI tract.
2.2.2.1 Anti-carcinogenic activities

Epidemiological studies have linked soy consumption to lower incidences of various types of cancer (82). As a group of major phytochemicals in soy, soyasaponins may be partially responsible (27). The evidence for soyasaponins having anti-carcinogenic effects in animal models is limited. Nevertheless, soyasaponins and soyasapogenols have been shown to have the anti-carcinogenic effects in a number of carcinoma cell lines. Before summarizing the data, we must keep in mind that since 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 the anti-carcinogenic activities of soyasaponins and soyasapogenols have been performed in human colon cancer, liver cancer or breast cancer cell lines (83-88). The proposed mechanisms of anticarcinogenic properties of soyasaponins and soyasapogenols include direct cytotoxicity, induction of apoptosis, anti-estrogenic activity, inhibition of tumor cell metastasis, anti-mutagenic activity effect, bile acid binding action and normalization of carcinogen-induced cell proliferation (Table 5) (89). From these studies done in different cancer cell lines, we’ve learned that there are at least three major factors that may affect the observed effects of soyasaponins and soyasapogenols. The first factor is the testing materials. Some researchers used crude extracts while others used purified saponins. It is possible that components of the crude extract interact synergistically, thus inducing 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 (90). The second factor is the type of cell lines. It is clearly shown that different cancer cell lines respond differently to soy saponins. For instance, soya-saponin I (35) had no effect on HT-29 colon cell growth (81), but it can decrease the migratory ability of B16F10 melanoma cells (91). The third factor is the dose. In another study, soya-saponin III (37) showed significant growth suppression at the highest concentration tested (50 ppm), and no significant effects from concentrations 6 to 25 ppm.

2.2.2.2 Cardiovascular protective effects

Soyasaponins showed cardiovascular protective effects through several different mechanisms.

The hypocholesterolemic effects of soy saponins have long been recognized (92-95). Two mechanisms by which saponins can affect cholesterol metabolism were suggested (96): 1) Some saponins with particularly defined structural characteristics form insoluble complexes with cholesterol. When this complex-forming process occurs in the gut, it inhibits intestinal absorption of both endogenous and exogenous cholesterol. 2) Saponins can interfere with the entero-hepatic circulation of bile acids by forming mixed micelles. The re-absorption of bile acids from the terminal ileum is effectively blocked (92).

In animal models, soyasaponins were found to significantly reduce serum total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG) concentrations, and to increase high-density lipoprotein-cholesterol (HDL-C) levels in rats (97). 24-Methylenecycloartanol (59), in combination with soysterol greatly reduced plasma cholesterol and enhanced cholesterol excretion in rats (98). Hamsters fed group B soyasaponins had significantly lower plasma TC (by 20%), non-HDL-C (by 33%), TG (by 18%)
<table>
<thead>
<tr>
<th>materials</th>
<th>cell line</th>
<th>dose</th>
<th>observation</th>
<th>mechanism</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total soyasaponins</td>
<td>Human HT-1080 fibrosarcoma cell</td>
<td>100-300 μg/ml</td>
<td>Inhibit the metastasis of HT-1080 cells dose-dependently after 24 h.</td>
<td>Inhibit the invasion of HT-1080 cells through a Matrigel-coated membrane.</td>
<td>86</td>
</tr>
<tr>
<td>Total soyasaponins</td>
<td>Human HT-29 colon cancer cell</td>
<td>150, 300, 600 ppm</td>
<td>Decrease HT-29 cell growth in a dose dependent manner at concentrations of 150, 300, and 600 ppm after 24 h.</td>
<td>Decrease HT-29 cell growth.</td>
<td>87</td>
</tr>
<tr>
<td>Total soyasaponins</td>
<td>Human HepG2 liver hepatoma cell</td>
<td>30 μg/ml</td>
<td>Inhibit AFB1-DNA adduct formation in HepG2 liver hepatoma cells by 50.1% at concentration of 30 μg/ml after 48 h.</td>
<td>Induce apoptosis in HepG2 liver hepatoma cells.</td>
<td>85</td>
</tr>
<tr>
<td>B-group soyasaponins</td>
<td>Human SNB 19 glioblastoma cell</td>
<td>25-75 μM</td>
<td>Induce SNB 19 glioblastoma cell apoptosis dose-dependently after 48 h.</td>
<td>Induce apoptosis in SNB 19 glioblastoma cells.</td>
<td>88</td>
</tr>
<tr>
<td>B-group soyasaponins</td>
<td>Human HCT-15 colon cancer cell</td>
<td>25-500 ppm, 100 ppm</td>
<td>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.</td>
<td>Suppress HCT-15 colon cancer cell proliferation and induce macroautophagy.</td>
<td>83</td>
</tr>
<tr>
<td>Soyasaponin I (35)</td>
<td>Highly metastatic B16F10 melanoma cell</td>
<td>25-75 μM</td>
<td>Decrease migratory ability of B16F10 melanoma cell dose-dependently (25-75 μM) after 12 h.</td>
<td>Decrease the migratory ability of cells, enhance cell adhesion to extracellular matrix proteins.</td>
<td>91</td>
</tr>
<tr>
<td>Soyasaponin I (35)</td>
<td>Human MCF-7 breast cancer cell</td>
<td>50 μM</td>
<td>Significantly enhance MCF-7 cells to adhere the extracellular matrix at 50 μM after 24 h.</td>
<td>Enhance the adhesion of MCF-7 cells to the extracellular matrix proteins.</td>
<td>84</td>
</tr>
<tr>
<td>Soyasaponin III (37)</td>
<td>Human HT-29 colon cancer cell</td>
<td>50 ppm</td>
<td>37 and soyasapogenol B monoglucuronide show HT-29 colon cancer cell growth suppression at 50 ppm after 72 h.</td>
<td>They all suppress the growth of HT-29 colon cancer cell.</td>
<td>81</td>
</tr>
<tr>
<td>Soyasapogenol A (54)</td>
<td></td>
<td></td>
<td>54 and 55 show a dose-dependent growth suppression from 6-50 ppm after 72 h.</td>
<td>Inhibit the expression of α-2,3-linked sialic acids of B16F10 melanoma cell.</td>
<td></td>
</tr>
<tr>
<td>Soyasapogenol B (55)</td>
<td></td>
<td></td>
<td></td>
<td>Alter MCF-7 breast cancer cell surface α2,3-sialylation pathway.</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. The anti-carcinogenic activities of soyasaponins and soyasapogenols
and a lower ratio of total to HDL cholesterol (by 13%) in hamsters fed group B soyasaponins, compared to those fed casein. Possible mechanisms involved greater excretion of fecal bile acids and neutral sterols (99).

The anti-thrombogenic action of soyasaponins was evaluated in a 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 during DIC induced by infusion of endotoxin or thrombin in rats. In vitro experiments, total soyasaponins, soyasaponins I (35), II (36), A1 (27), and A2 (28) inhibited the conversion of fibrinogen to fibrin (100).

Total soyasaponins decreased elevated blood sugar and LPO levels, and reversed the decreased levels of SOD in streptozocin-induced diabetic rats (101). In an α-glucosidase inhibitory assay, groups B, E and DDMP soyasaponins were shown to have potent inhibitory activities with IC50 values of 10-40 μmol/L (102).

2.2.2.3 Anti-viral activities

Soyasapogenols A (54), B (55), E (58), and soyasaponin I (35), a major constituent of group B saponins, completely inhibited HIV-induced cytopathic effects 6 days after infection at concentration greater than 0.25 mg/mL, but had no direct effect on HIV reverse transcriptase activity. Soyasaponin I (35) also inhibited HIV-induced cell fusion in the MOLT-4 cell system (103).

Total soyasaponins showed significant inhibitory effect on the replication of HSV-1 and CoxB3. A soyasaponin 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 (104). Soyasaponin II (36) is more potent than soyasaponin I (35) as shown by a reduction of simplex virus type 1 (HSV-1) production. Soyasaponin II (36) was also found to inhibit the replication of human cytomegalovirus and influenza virus. This action was not due to inhibition of virus penetration and protein synthesis, but may involve a virucidal effect (105). In a structure–activity relationship study, the activity of soyasapogenol A (54) was less than 1/20 of that of soyasapogenol B (55), and the hydroxylation at C-21 seemed to reduce anti-HSV-1 activity (106).

2.2.2.4 Hepatoprotective actions

The group B soyasaponins I (35), II (36), III (37), and IV (38) all exhibit hepato-protective actions towards immunologically induced liver injury in primary cultured rat hepatocytes. The action of soyasaponin II (36) is almost comparable with that of soyasaponin I (35), whereas soyasaponins III (37) and IV (38) are more effective than soyasaponins I (35) and II (36). This suggests that the disaccharide group shows greater action than the trisaccharide group. Furthermore, the soyasaponins having a hexosyl unit shows a slightly greater action than that of the 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 hepato-protective actions of soyasaponins (107).

Also in in vivo experiments, total soyasaponins inhibit the elevation of liver 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 A1 (27) during peroxidation (108).
2.2.2.5 Antioxidant activities

One mg of DDMP saponin/mL scavenges superoxide at a degree equivalent to 17.1 units of superoxide dismutase/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 since soyasaponin I (35), which is derived from soyasaponin βg (50). Lack of this group didn’t show the scavenging activity (109).

2.3 Triterpenes and sterols

2.3.1 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 identified in soy. They are 24-methylenecycloartenol (59) (98), cycloartenol (60) (98) and bacchara-12,21-dien-3β-ol (61) (Figure 5) (110), respectively. Compounds 59 and 60 belong to the type of lanostane triterpene. In addition to having the basic structural characters of lanostane, they bear an extra tri-atomic ring in their structures that are 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 the biosynthesis of soy sterols. Bacchara-12,21-dien-3β-ol (61) is a natural occurring of baccharane-type triterpene which has all six-membered tetracyclic skeleton, and its side chain is at position 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 thirteen so-called plant sterols or phytosterols were found in soybean seed or the shoots (111) (Figure 6). Unlike animals, plant membranes generally contain little or no cholesterol and instead contain several types of phytosterols. Phytosterols are also steroid alcohols, whose chemical structures 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 (62) (26, 111). The most abundant phytosterols are sitosterol, campesterol and stigmasterol (112). Phytosterols identified from soy so far include cholesterol-5,24-dien-3β-ol (63), β-sitosterol (64) (113), stigmasterin (65) (24), sitostanol (66) (114), citrostanol (67) (113), isofucosterol (68) (111), campesterol (69) (115), 24-epicampesterol (70) (115), 7-dehydrocampesterol (71) (115), campestanol (72) (111), obtusifoliol (73) (111), 24-methylenelophenol (74) (111), and 14α-methyl-5α-ergost-8-en-3β-ol (75) (111). The most abundant soy phytosterol is β-sitosterol (64), followed by campesterol (69) (112). These sterols can be divided into four groups based on their backbones, cholesterol (62), cholesta (63), stigmasta (64-68) and ergosta (69-75) (Figure 6). Compounds 62 and 63 have the same backbone except for the type of bond between C-24 and C-25. The former is single bond while the latter is double bond (Figure 6). 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 6). However, nutritionists prefer to divide the phytosterols into two categories of “Δ5-sterols”, indicating a double bond at position C-5, and “stanol”, indicating 5α-reduction of that double bond (114). According to this principle, compounds 62-65 and 68-71 are Δ5-sterols; 66-67 and 72-75 are stanols (Figure 6).
2.3.2 Health effects of phytosterols

Phytosterols (not restricted to soy-based sources) that have long been known to reduce intestinal cholesterol absorption, lead to decreased blood LDL-cholesterol levels and lower cardiovascular disease risk. However, other biological activities for phytosterols have also been reported, including anti-cancer and immune modulatory effects.
Fig. 6. The chemical structures of sterols in soy.
2.3.2.1 Phytosterols and cholesterol absorption

In the 1950's, phytosterols from soybeans were found to lower serum cholesterol level (116). Since then, the cholesterol-lowering effects of phytosterols have been extensively demonstrated in both humans and animals (117-120). A meta-analysis of 41 clinical trials showed that intake of 2 g/d of stanols or sterols reduced low-density lipoprotein (LDL) by 10%, with little additional reduction at higher doses (121). The U.S. National Cholesterol Education Program has recommended adding 2.0 g/day of phytosterols to the diet of adults to reduce LDL cholesterol and coronary heart disease risk (122).

Because phytosterols are not systemically absorbed, they are thought to act primarily in the intestinal lumen. As cholesterol analogs phytosterols compete for cholesterol in absorptive micelles resulting in reduced solubility of cholesterol (118). However, recent evidence suggests that the mechanism of action of phytosterols may be more complicated than originally thought (119, 123). As summarized in a recent review (123), since phytosterols/phytostanols do not need to be present in the intestinal lumen simultaneously with cholesterol to inhibit its absorption (120), 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 (124). To gain insight into the phytosterol/phytostanol affects on circulating cholesterol concentration via mechanisms independent of the luminal incorporation of cholesterol into mixed micelles, the effects of these plant compounds on intestinal LXR-mediated targets involved in sterol absorption have 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 reports 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 internalisation (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 (123).

In one study specifically using soybean-derived phytosterols (125), it was found that consumption of phytosterol-supplemented ground beef lowered plasma TC and LDL-cholesterol concentrations and TC:HDL cholesterol from baseline by 9.3%, 14.6%, and 9.1%, respectively.

2.3.2.2 Anti-cancer effects of phytosterols

In addition to their cholesterol-lowering actions, mounting evidence suggests that phytosterols possess anti-cancer effects against a number of different types of cancers (126-132). 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 (127).
2.3.2.3. Physterols and immune function

Several reports in the literature suggest that phytosterols may have some immunological activity as highlighted in animal models of inflammation or even in *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 (133, 134).

2.4 Lignans

2.4.1 Chemical characteristics of lignans

In addition to isoflavones, lignans are considered another main group of phytoestrogens in soy, based on their chemical structures. Lignans are defined as dimeric phenylpropanoid (C6-C3) compounds, mostly linked at 8-8′ (Figure 7) (135, 136). They are seven lignans identified from soy, namely, anhydrosecoisolariciresinol (76), isolariciresinol (77), secoisolariciresinol (78), matairesinol (79), lariciresinol (80), pinoresinol (81) and syringaresinol (82) (Figure 7) (28, 137).

2.4.2 Health effects of lignans

2.4.2.1 Antioxidant activity

Pinoresinol (81) 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 (138). Syringaresinol (82) has also been demonstrated as antioxidative in Cu$^{2+}$-induced low density lipoprotein oxidation and DPPH radical assays (138). Lariciresinol (80) has a high radical scavenging capacity compared to the well-known antioxidant Trolox. The trapping capacity (mmoles peroxyl radicals scavenged per gram of compound) of lariciresinol (80) (7.3 mmol/g) is higher than that of trolox (6.8 mmol/g) (139). Secoisolariciresinol (78) showed strong antioxidant activity against DPPH with an IC$_{50}$ of 0.017±0.001 mM. It is about two times stronger than the standard antioxidant, 2,6-di-(tert-butyl)-4-methylphenol (BHT), IC$_{50}$ 0.031±0.001 mM (140). Isolariciresinol (77) showed 86.2% inhibition of lipid peroxidation (LPO) at 25 µg/ml (141).

2.4.2.2 Anticancer activity

Estrogenic enterolignans, END or 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. To our knowledge, the estrogenic or anti-estrogenic effects of enterolignans in humans are not very clear (142). For example, while weak estrogenic activity of ENL was demonstrated the anti-estrogenic activity of ENL was disclosed through depression of estrogen-stimulated rat uterine RNA synthesis (143).

The lignan ENL was found to have a bi-phasic effect on DNA synthesis in human breast cancer MCF-7 cells, showing induction at 10-50 µM and inhibition at higher concentrations, with an IC$_{50}$ of 82.0 µM (144). END and ENL are weak and moderate inhibitors of aromatase enzyme activity in a pre-adipose cell culture system (143). In human colon tumor cell
lines (LS174T, Caco-2, HCT-15, T-84), the same concentration of END and ENL (100 µM) significantly reduce the proliferation of all cell lines, though ENL was more than twice as effective as END (145).
2.5 Phytate

2.5.1 Chemical characteristics of phytate

Phytate (83), the salt of phytic acid (myo-inositol-(1,2,3,4,5,6)hexakisphosphate, 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 phosphorous and minerals and contains ~75% of total phosphorous of the kernels (25). It is the major source of phosphorus in soy (79). Phytate is considered as 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 only manifested when large quantities of IP6 are consumed in combination with an oligoelements-poor diet (146).

Fig. 8. The chemical structures of phytic acid in soy.

2.5.2 Health effects of phytic acid

2.5.2.1 Anti-cancer activities

Phytic acid (83) plays an important role in signal transduction, cell proliferation and differentiation (147). Recently phytic acid (83) has received much attention for its role in cancer prevention and control of experimental tumor growth, progression, and metastasis (148). A great majority of the studies were done in animals and showed that phytic acid had anti-neoplastic properties in breast, colon, liver, leukemia, prostate, sarcomas, and skin cancer (149, 150). The results and proposed mechanism of anti-carcinogenic activities of IP6 in various cell lines are summarized in Table 6 (151-154).

In animal studies, phytic acid can increase blood NK cell activity in DMH-induced colon tumors in rats, suppress rhabdomyosarcoma cell growth in a xeno-grafted nude mouse model (155), inhibit tumor growth and metastasis in rats (156), prolong survival of tumor-bearing mice, and reduce the numbers of pulmonary metastases (157). Phytic acid can also inhibit DMBA-induced mouse skin tumor development and this inhibitory effect is likely, by modulating proliferation, differentiation, or apoptosis (158).

2.5.2.2 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
Decrease the expression of TNF-α and TNFII in a dose dependent manner (1, 2.5 and 5 mM) after 12 h.

Human HT-29 colon cancer cell

Inhibit proliferation of HT-29 cells at 8 mmol/L and 13 mmol/L after 12 h.

Human MCF-7/Adr MDA-MB 231 and MCF-7 breast cancer cells

MCF-7/Adr – IC₅₀ 1.26 mM
MDA-MB 231- IC₅₀ 1.32 mM
MCF-7– IC₅₀ 4.18 mM after 96 h.

Inhibit the growth of three breast cancer cells

Human HepG2 liver hepatoma cell

Inhibit the growth of HepG2 liver hepatoma cell in a dose-dependent fashion (0.25-5 mM) after 6 days.

Human LNCaP prostate cancer cell

Inhibit the growth of LNCaP prostate cancer cell dose dependently (0.5-4 mM) after 24 h.

Inhibit the growth of LNCaP prostate cancer cell

Human DU145 prostate cancer cell

Inhibit the growth of DU145 prostate cancer cell dose dependently (0.25-2 mM) after 24 h.

Inhibit the growth of DU145 prostate cancer cell

Table 6. The anti-carcinogenic activities of IP

system, prevent pathological calcification and kidney stone formation, lower elevated serum cholesterol, and to reduce pathological platelet activity (148). IP6 inhibited the replication of HIV-1 in a T cell line and in a freshly isolated strain in peripheral blood mononuclear cells, possibly acting on HIV-1 early replicative stage (149)

Fig. 9. The chemical structures of cinnamic acid ester glycosides in soy.

84. R₁ = OH, R₂ = H
85. R₁ = OCH₃, R₂ = OCH₃
2.6 Cinnamic acid ester glycosides

2.6.1 Chemical characteristics of cinnamic acid ester glycosides

Two cinnamic acid ester glycosides were isolated by Hosny et al from soybean molasses, which is a by-product of aqueous alcohol soy protein concentrate production (70). They were identified as 1-O-(E)-feruloyl[\(\alpha\)-L-arabinofuranosyl(1\(\rightarrow\)3)][\(\beta\)-D-glucopyranosyl(1\(\rightarrow\)6)]\(\beta\)-D-glucopyranose (84) and 1-O-(E)-3,4,5-trimethoxy cinnamoyl[\(\alpha\)-L-arabinofuranosyl(1\(\rightarrow\)3)] [glucopyranosyl(1\(\rightarrow\)6)]\(\beta\)-D-glucopyranose (85) (Figure 9).

3. Constituents formed during processing

Food processing may dramatically change the compositions and relative contents of the constituents in soy products and artificial compounds may also occur (159). The processing of foods can improve nutrition, quality, and safety; though processing could also lead to the formation of anti-nutritional and toxic compounds. These multi-faceted consequences of food processing result from molecular interactions among nutrients and with other food ingredients, both natural and added (160).

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 based upon processing methods. These compounds may be formed by 1) soybean processing or fermentation; 2) compounds from other ingredients of soy products; 3) compounds from reactions 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.

In Japan, soybeans molasses and soy fermented with Bacillus subtilis (natto) are very popular daily foodstuffs (161). Six isoflavones which differ from that isolated from soy were generated by this process. They are glycitein 7-O-\(\beta\)-D-(2\(^\cdot\),4\(^\cdot\),6\(^\cdot\)-O-triacetyl)glucopyranoside (86), 8-(\(\gamma\)-hydroxy-\(\gamma\),\(\gamma\)-dimethylpropyl)genistin (87), 5-hydroxy-8-(\(\gamma\)-hydroxy-\(\gamma\),\(\gamma\)-dimethylpropyl)-3',4'-dimethoxyisoflavone-7-O-\(\beta\)-D-glucopyranoside (88), 6''-O-succinylaidzin (89), 6''-O-succinylgenistin (90), and 6''-O-succinylglycitin (91) (161, 162) (Figure 10).

Another group of well-known compounds formed during food processing in soy is The Maillard reaction products (163, 164). The 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, that results in the concurrent formation of so-called Maillard browning products and acrylamide (165). In the past, extensive work has been done on Maillard reaction products in food products including several excellent reviews (160, 164-167). Five Maillard reaction products, fructose-lysin (92), fructose-alanine (93), fructose-valine (94), fructose-leucine (95) and fructose-isoleucine (96) (Figure 11) were isolated from soy sauce and miso (168, 169).

Other groups of compounds may also be found in different soy products. Guided by platelet aggregation analysis, two anti-platelet alkaloids, 1-methyl-1,2,3,4-tetrahydro-\(\beta\)-carboline (97) and 1-methyl-\(\beta\)-carboline (98), were obtained from soy sauce. These two compounds inhibited the maximal aggregation response induced by epinephrine, platelet-activating...
Fig. 10. The chemical structures of new isoflavones generated during food processing in soy products.

86. glycine 7-O-β-D-(2"A,4"A,β"A-triacetyle)glucopyranoside

87. \( R_1 = \text{H}, R_2 = \text{OH} \quad 8\text{-}(\gamma\text{-hydroxy-\(\gamma\text{-dimethylpropyl})genistin} \)

88. \( R_1 = R_2 = \text{OCH}_3 \quad 5\text{-hydroxy-8\text{-}(\gamma\text{-hydroxy-\(\gamma\text{-dimethylpropyl})-3\text{'}A,4\text{'}\text{-dimethoxyisoflavone-7-O-β-D-glucopyranoside}} \)

89. \( R_1 = R_2 = \text{H}, R_3 = \text{CH}_2\text{CH}_2\text{COOH} \quad 6\text{"A}-\text{succinyl}laidizin \)

90. \( R_1 = \text{OH}, R_2 = \text{H}, R_3 = \text{CH}_2\text{CH}_2\text{COOH} \quad 6\text{"A}-\text{succinylgenistin} \)

91. \( R_1 = \text{H}, R_2 = \text{OCH}_3, R_3 = \text{CH}_2\text{CH}_2\text{COOH} \quad 6\text{"A}-\text{succinylglycitin} \)
Fig. 11. The chemical structures of other components generated during food processing in soy products.

factor, collagen, adenosine 5'-diphosphate, and thrombin, respectively (170). Compound 97 had much greater inhibitory effect than that of 98 on platelet aggregation. Three other alkaloids, asperparalines A (99), B (100) and C (101) were found from okara (the insoluble residue of whole soybean) fermented with Aspergillus japonicus JV-23 (Figure 11) (171). Since 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) (172-174). Their structures were identified as 4-hydroxy-2-ethyl-5-methyl-3(2H)-furanone (HEMF; 102), 4-hydroxy-5-ethyl-2-methyl-3(2H)-furanone (103), 2,5-dimethyl-4-hydroxy-3(2H)-furanone (DMHF; 104) and 3-hydroxy-2-methyl-4H-pyran-4-one (maltol;105) (Figure 11). 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-fold and 1.7-fold higher than that of the boiled soybeans and soybean seeds, respectively (175). Thus, we must be aware that the composition of soybean products may differ substantially from the native soybean.

4. Conclusion

The soy bean 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 chapter summarizes our current knowledge about chemical structures and health effects of the major phytochemicals in soy. Clearly, the observed health effects from soy or soy-based foods (other than those attributed to nutrients like protein) are not solely from the actions of certain individual or types of compounds, but rather are 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 the meal. In order to fully understand the mechanism of health effects of soy, it is important to identify the genuine bioactive compounds in soy.

5. References

Phytochemicals in Soy and Their Health Effects


[110] Akihisa, T.; Kimura, Y.; Tamura, T., Bacchara-12,21-dien-3β-ol from the seeds of *Glycine max* *Phytochemistry* 1994, 37, 1413-1415


Among the thousands of naturally occurring constituents so far identified in plants and exhibiting a long history of safe use, there are none that pose - or reasonably might be expected to pose - a significant risk to human health at current low levels of intake when used as flavoring substances. Due to their natural origin, environmental and genetic factors will influence the chemical composition of the plant essential oils. Factors such as species and subspecies, geographical location, harvest time, plant part used and method of isolation all affect chemical composition of the crude material separated from the plant. The screening of plant extracts and natural products for antioxidative and antimicrobial activity has revealed the potential of higher plants as a source of new agents, to serve the processing of natural products.