Health benefits of soy and soy phytochemicals

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Abstract: Soy is an important commodity and a long-time staple food in eastern Asian countries. Recent research and clinical studies have provided ample evidence for the health benefits of soy and soy foods, which have also contributed to an increase in soy consumption among the Western population. The current mini-review aims to summarize the current knowledge of the health benefits of soy and soy phytochemicals, and their reported effects in preventing (I) cardiovascular disease, (II) obesity-related metabolic syndrome, (III) certain types of cancers, and (IV) other chronic diseases. In addition to the widely reported soy isoflavones, namely, genistein, daidzein, and glycitein, a novel group of soy phytoalexins, glyceollins, have also shown promising biological activities, such as insulinotropic, antiestrogenic, antiproliferative, antioxidation, anti-inflammation, and cholesterol-lowering effects. The elucidation of soy's health benefits is an important part of promoting the consumption of soy as a functional food and the understanding of the mechanism of actions of soy and soy phytochemicals' biological activities will provide further evidence for the optimized use for health promotion.

Keywords: Soy; phytochemicals; glyceollins; health benefit

Introduction

Soy (*Glycine max*) is an important commodity in the world's food supply and economy (1). Soy consumption as a food has a long history in Asian countries, such as China and Korea (2), while the U. S. accounted for more than 30% of world production in 2013 (3). The popularity of soy foods in the west increased significantly after a 1999 decision by the U.S. Food and Drug Administration to allow health claim of soy protein's protective effect against heart disease (4). The U.S. retail soy food industry grew from $1 billion in 1996 to $4.5 billion in 2013 (5). The nutritional/health promoting value of soy and soy food was the major contributing factor for the increasing demand, as 26% of

U.S. consumers indicated that they are interested in soy foods specifically for the reported health benefits (6-8). Therefore, science-based information on health-promoting effects of soy and soy phytochemicals is of great economic and societal importance and can further promote the use of soy and soy phytochemicals.

Health benefits of soy

Protection against cardiovascular disease

Epidemiological studies have long linked soy consumption to a reduced risk for cardiovascular disease, and soy protein, soy-derived isoflavones, and soy sterols have been studied as

the active components contributing to such effects (2,9-12). A recent review identified soy proteins to be partially responsible for the lipid-lowering effects of soy (10). It has also been suggested that isoflavones may act on the vascular tissue to improve circulation (12-14).

Soy's cardiovascular protective effects were reviewed and highlighted in a meta-analysis of 38 controlled clinical trials in human subjects and the correlation between consumption of soy and lipid levels (15). It was concluded that an average consumption of 47 g soy protein/day resulted in significant decreases in total cholesterol (9.3%), LDL cholesterol (12.9%) and triglycerides (10.5%). On the other hand, in a more recent analysis, the Nutrition Committee of American Heart Association found a much smaller decrease in LDL (3%) with 50 g soy protein consumption per day from eight randomized trials and no apparent benefit in 14 other studies (9). The responses appeared to be highly dependent on the cholesterol level of the subjects. The meta-analysis performed by Anderson and colleagues recruited patients who were strongly hyperlipidemic (total cholesterol >250 mg/dL). It was expected that extreme hyperlipidemia would benefit from greater percentage reductions in total and LDL cholesterol. In contrast, the patients with moderate or minor hyperlipidemia recruited in the later studies showed less response to the soy protein.

One proposed mechanism of soy's cardio-protective effects results from the inhibition of LDL oxidation and reduction of the formation of plaque in the arteries. Soy extracts (16,17) and peptides (18,19) have both been shown to reduce the oxidation of LDL cholesterol *in vitro* and *in vivo*. It was also reported that the anthocyanins found in color seed coat of soy displayed potent anti-oxidant properties and could inhibit LDL oxidation (16,20,21). A more recent hypothesis involves the liver's LDL receptors, which may be affected by soy consumption to enhance their uptake of LDL from the serum and consequently lower serum LDL levels (22).

Protection against obesity-related metabolic syndrome

The potential of soy consumption in mitigating obesity and related complications were reported in recent studies (23,24). The exact efficacy is still under investigation. Mechanistically, the estrogen-like structures of soy isoflavones may contribute to similar activities, such as regulating adipogenesis by binding to estrogen receptors, thus decreasing lipoprotein lipase activity, and PPAR may also be involved in the regulation (24). Levels of genistein, a soy isoflavone, ranging from 0.1 to 1.0 μM have been shown to inhibit adipogenesis,

while higher concentrations (25–50 μM) enhanced adipogenesis, showing a biphasic effect (24). However, evidence in animal models and *in vitro* study did not always apply well to human, which made it inconclusive whether consumption of soy will benefit the obese population. Human clinical experiments did not show any decrease in body weight as expected, but improvements in blood lipids (24) or improvements in insulin resistance was observed (25).

Protection against cancer

Soy has also shown potential in reducing the risk of many types of cancer (26-29) and, among which, breast and prostate cancers are of particular interest due to their sensitivity to sex steroid hormones.

Despite the amount of effort from experimental and epidemiological studies, soy products' effect in breast and prostate cancer prevention or therapy is largely unresolved. Epidemiological studies among Asian population had long connected the lower breast cancer incident with consumption of soy products, which was usually attributed to soy isoflavones (30,31). Alongside the modest protective effects, concern has also been expressed that the estrogenic activity of soy isoflavones may lead to adverse effects on progression and recurrence of breast cancer (32). On the other hand, there were some reviews citing a number of human clinical and epidemiological studies indicating no evidence of risk in human (33-35). Preventative effect of soy against prostate cancer have been reviewed previously (36) and clinical trials have also shown soy's therapeutic effect against prostate cancer (37,38), which, again, was challenged by another intervention study that did not support that soy consumption can benefit men with prostate cancer, while not excluding the possibility of soy's effect in preventing prostate cancer (39).

Mechanisms of soy's cancer prevention effects are attributable to the isoflavones. Previous studies suggested that multiple mechanisms of action may be responsible. Isoflavones have been shown to affect the cell cycle, apoptosis, differentiation, proliferation, growth, along with effects on cell signaling (38,40,41). Isoflavones also exhibited antioxidant capacity. They are well-known scavengers for reactive oxygen species, but recent research is suggestive of additional antioxidant activity beyond direct scavenging of radicals. Genistein, in particular, has been shown to activate transcription factors such as estrogen receptor and stimulate gene expression in breast cancer cells (38). By contrast, genistein inhibited androgen responsive gene expression (42). These results indicating that genistein may
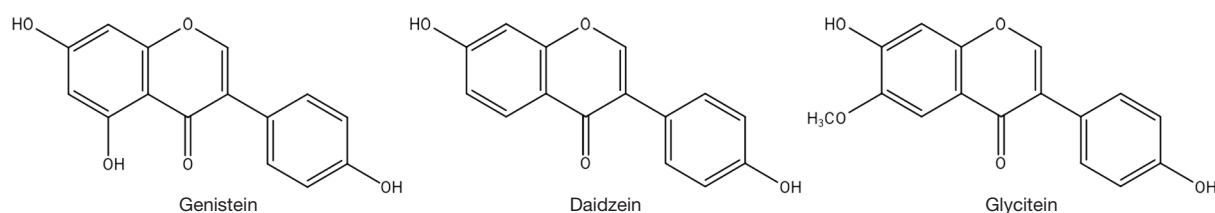
Figure 1 Structure of genistein, daidzein, and glycitein.

have broad ability to impact overall cellular homeostasis through a variety of mechanisms/pathways.

Protection against other chronic diseases

Aside from the diseases mentioned above, soy consumption has also been linked to its effects in other chronic diseases, though not as extensively studied. Diabetes, cognitive function, and immune function are among the list of conditions that can potentially benefit from consumption of soy or soy components (25,43-45). As with the diseases discussed above, it remains unclear whether it is isoflavones, proteins, fiber, or some other component causing the supposed beneficial effects. The complexity of soy components makes it very hard to dissect out the exact active component(s) or compound(s) responsible for any particular bioactivity. Compounds may counteract with each other, or show distinct activities resulting from different concentration or ratio. Thus, the study of each individual component is proven to be necessary and important to gather scientific evidence and knowledge to support soy's health-promoting effects.

Bioactive components of soy

Isoflavones, tocopherols, carotenoids, and phytosterols are the main bioactive components reported in soy (1). Isoflavones are a class of polyphenolics found almost exclusively in legumes, and most prominently in soy. Isoflavones are structurally similar to that of estradiol, which binds weakly to estrogen receptors, eliciting weak estrogenic responses, and earning the title of 'phytoestrogen' (45). Genistein, daidzein, and glycitein are the predominating isoflavones in soy (*Figure 1*) (1). Biological activities of soy isoflavones include prevention against atherosclerosis and other CVD, obesity, osteoporosis, and cancer (24,46-50). Due to its estrogenic effect, genistein has been shown to alter the expression of genes involved in estrogen-

mediated pathways and induce a proliferative response in breast cancer cells at 1–5 μM, while higher concentration (25 μM) of genistein can induce apoptosis and inhibition of proliferation (51). It was also reported that genistein and daidzein affect androgen responsive pathways in prostate cancer cells (52). These findings indicated that the biological activities of soy isoflavones are dose-dependent and involve multiple pathways. Recent research and clinical studies have provided a more comprehensive understanding of the effects and mechanism of actions of the soy isoflavones, however, the exact health outcomes remain elusive and warrant further studies.

Tocopherols are members of the Vitamin E family and can act as antioxidants by scavenging peroxyl radicals (1,53). Carotenoids also possess antioxidant activity, as their highly conjugated structures are extremely vulnerable to oxidation in the presence of light, heat, and oxygen (54). Sterols found in soybean oils are mostly in the non-esterified form. Plant sterols have a structural backbone very similar to that of human cholesterol. The esterified sterols have been shown to reduce serum cholesterol levels when consumed in sufficient quantities (55).

Other soy phytochemicals have not been studied as extensively. Recently, a novel group of soy phytoalexin, the glyceollins, was gathering great interest for their potential biological activities. The chemical and biological properties of glyceollins are reviewed in the following sections.

A novel group of soy phytochemicals: glyceollins

Glyceollins are one of the major groups of phytoalexins in soy. It was first reported in elicited soybean by Zahringer *et al.* in 1977 (56). A number of studies have been conducted to elucidate the biosynthesis of glyceollins in soybean. Banks and Dewick [1983] pointed out that phenylalanine, daidzein, 7,2',4'-trihydroxyisoflavone, 3,9-dihydroxypterocarpan and glycinol are precursors for biosynthesis of glyceollin I, II and III (57). In the
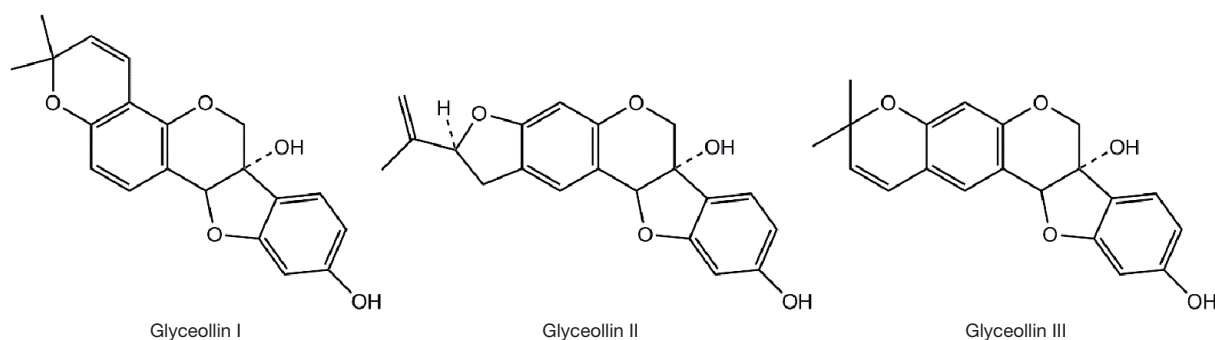
Glyceollin I   Glyceollin II   Glyceollin III

Figure 2 Structure of glyceollins.

following decades, plant scientists had shown interest in glyceollins mainly for its antifungal and antibacterial effects in soybean (58-60), and a number of fungi were identified to be effective elicitors, e.g., *Rhizopus oryzae* (61), *Mucor ramosissimus* (62), *Diaporthe Meridionalis* (63), *Aspergillus sojae* (64). It was determined that glyceollins are in a relatively low amount in unstressed soy (1 to 9 g/g fresh weight of soy, depending on the different parts of soy). While, upon induction, glyceollins concentration can go up to 43 to 955 g/g fresh weight of soy, depending on the different elicitors and parts of soy (65-67). Besides effort in isolating glyceollins from elicited soy, chemical synthesis was also studied. However, due to the time-consuming and multiple steps needed in contiguous ring systems preparation, as well as the maintenance of rigorous stereo-control, only glyceollin I have been synthesized to date with limited preparation capacity (68-71).

Biological activities of soy phytochemical glyceollins

Phytoalexins are inducible chemicals involved in plants' self-defense system (72), which have low molecular weight, possess anti-microbial activities, and are biosynthesized *de novo* in response to stress, including microbial attack, heavy metal salts, or UV radiation (73-75). Aside from the anti-microbial activity, some phytoalexins are also indicated to exhibit chronic disease prevention and health-promoting effects in humans (76).

Glyceollin I, II, and III (*Figure 2*) are the most common isomers isolated from soybean (57). A number of biological activities were reported by previous studies, including antiproliferation (77-79), antiestrogenic (80), antibacterial (81), antinematode (82,83), antifungal activities (84,85), insulinotropic (86) and attenuation of vascular contraction activity in the rat (87).

Insulinotropic effect

Glyceollins' role in improving glucose homeostasis was reported by Park and colleagues (86,88) and they concluded that glyceollins act through regulating glucose utilization in adipocytes and modulating cell function and survival. It was shown that glyceollins could improve insulin-stimulated glucose uptake and decrease triacylglycerol accumulation in 3T3-L1 mouse adipocytes. It was shown that 5 µM glyceollins increased basal glucose uptake by 150%. Additionally, co-incubation of glyceollins and insulin further stimulated maximal glucose uptake above basal levels than that of either stimulus alone. Mechanistically, glucose transporter GLUT4 mRNA and protein expression significantly increased upon exposure of 5 µM glyceollins for 3 h in 3T3-L1 adipocytes (89). In addition, glyceollins slightly improved glucose-stimulated insulin secretion in Min6 pancreatic cells, and they potentiated insulinotropic actions in dysfunction cell. This was associated with decreased cell apoptosis because of the attenuation of endoplasmic reticulum stress. Glyceollins also potentiated GLP-1 secretion to enhance insulinotropic actions in enteroendocrine cells (86). Glyceollins treatment reduced blood glucose levels in diabetic mice and prediabetic rats in oral glucose tolerance testing. The improvement was associated with increased serum insulin levels, hepatic glycogen accumulation, and decreased triglyceride storage. It was proposed that glyceollins improved glucose homeostasis partly by enhancing hepatic insulin sensitivity in type 2 diabetic mice (88,89).

Antiestrogenic and antiproliferative effect

Both estrogenic and antiestrogenic activities have been identified in soy phytochemicals. Daidzein, the precursor

of glyceollins, is known to be weakly estrogenic, while, glyceollins have been shown to be antiestrogenic (80,90). Glyceollins exert greater antagonism toward ER than ER in transiently transfected HEK 293 human embryonic kidney cells. It was also observed that glyceollins' antiestrogenic effect on ER signaling could lead to a marked suppression of 17-estradiol-induced proliferation in MCF-7 cells (80). Among the three glyceollin isomers, it was shown that glyceollin I is the most potent antiestrogenic agent. Glyceollin I could effectively inhibit ERE transcription and endogenous gene expression in MCF-7 cells (78).

The antiestrogenic effect was further tested by Zimmermann *et al.* in athymic mice model and resulted in a 53.4% and 73.1% suppression of MCF-7 and BG-1 xenograft tumor growth, respectively (91). Trefoil factor 1 and progesterone receptor were reported to be affected by glyceollins treatment, and responsible for their breast cancer protective effect (92).

Furthermore, glyceollins were also noticed for their effect in suppressing tumorigenesis in triple-negative breast carcinoma MDA-MB-231 (ER-, PgR- and Her2/neu-) cells. Modest suppression of MDA-MB-231 and MDA-MB-468 cell tumor growth *in vivo* was observed upon glyceollins treatment, and a distinct change in microRNA expression profiles and proteomes in MDA-MB-231 was identified to be responsible for glyceollins' effect. This study indicated that, aside from antiestrogenic effect, glyceollins could also exert antitumor activity in triple-negative breast carcinoma cell systems via alteration of microRNA and proteomic expression profiles (93).

Glyceollins' antiproliferative effect was also studied in the LNCaP human prostate cancer cell. It was shown that glyceollins exerted the growth inhibitory effects through inhibition of G1/S progression and correlated with an up-regulation of CDKN1A and CDKN1B mRNA and protein levels. Furthermore, glyceollins inhibited LNCaP cell growth and cell cycle through a 17--estradiol-mediated event instead of an androgen-mediated event. In addition, glyceollin treatments led to down-regulated mRNA levels for androgen-responsive genes (94).

Antioxidation

Soy extract is known for its antioxidant capacity, and a number of phytochemicals have been identified, among them genistein and daidzein were the focus of previous studies (2,95,96). Structurally, glyceollins (*Figure 2*) are similar to genistein and daidzein (*Figure 1*). Glyceollins

have also been reported for their antioxidant activity. Kim *et al.* reported that glyceollins possess a potent reducing ability, and can inhibit lipid peroxidation, scavenge radicals including singlet oxygen, superoxide anion, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), and 2,2-diphenyl-1-picrylhydrazyl (DPPH). *In vitro* model also indicated glyceollins significantly suppress H_2O_2-induced ROS production in hepa1c1c7 mouse hepatoma cells (64).

Additionally, glyceollins were shown to induce NADPH:quinone reductase in a dose-dependent manner in both Hepa1c1c7 mouse hepatoma and BPRc1 cells. Glyceollins also increased the expression of HO1, -GCL, and GR by promoting nuclear translocation of the Nrf2. Furthermore, glyceollins could upregulate phosphorylation of Akt and antioxidant response element-mediated reporter gene expression, which indicated that glyceollins may induce Nrf2-mediated phase 2 enzyme genes through activation of the PI3K signaling pathway (97).

Anti-inflammation

Anti-inflammatory effect of glyceollins was examined in RAW264.7 mouse macrophage cells. Glyceollins (0.3–3 g/mL) was able to inhibit NO production and iNOS, IL-6 and COX-2 gene expression induced by LPS in RAW264.7 mouse macrophage cells. Mechanistically, glyceollins were shown to suppress the LPS-induced phosphorylation of NF-B p65 and regulate NF-B activity (98).

Cholesterol-lowering effect

Hypercholesterolemia, the increased amounts of cholesterol in the blood, is a major factor contributing to the onset of cardiovascular disease. In a 2013 study, the cholesterol-lowering effect of glyceollins was investigated in a hamster model (99). Fed with a high fat diet containing 250 mg glyceollins per kg diet, significant reductions in plasma VLDL, hepatic cholesterol esters and total lipid content were achieved compared to the control group fed a high fat diet. Consistent with changes in circulating cholesterol, glyceollins supplementation also altered expression of the genes related to cholesterol metabolism in the liver.

Summary

Decades of research and investigation have revealed many aspects of soy and soy foods' health-promoting effects, including protection against cardiovascular diseases,

obesity-related metabolic syndrome, several types of cancers, and other chronic diseases. Soy phytochemicals are an important group of soy components and have been shown to contribute to soy's beneficial effects. Glyceollins, as a novel soy phytochemical, have shown promising biological effects, such as insulinotropic, antiestrogenic, antiproliferative, antioxidative, anti-inflammatory and cholesterol-lowering effects. The understanding of soy phytochemicals' mechanism of action can help and guide the use of soy as a health-promoting food. In addition to the study of biological effects of soy and its phytochemicals, to fully realize the potential of soy, two key factors will also have to be taken into account. Firstly, to target one condition or a specific pathway without taking into consideration of the impact of such effect(s) on other conditions or pathways may not result in the overall improvement of health. The basic research can help accumulate the data and knowledge in an ever-increasing list of effects and mechanism of actions, while the actual health promotion will have to result from a comprehensive understanding and a balance of these effects. Secondly, the era of treating the population as an average is getting to an end. The individual health condition, genetic background, external factors (environmental factors, residing microbiome, and lifestyles, etc.) shall all be accounted for to render the expected benefits effective. Such holistic approach is being made possible by the advance of the life science and medical research and shall guide the future of human health promotion.

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Footnote

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