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Interactions between soy isoflavones and other bioactive compounds: a review of their potentially beneficial health effects

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Abstract We review the recent literature on the protective effects of soy isoflavones and other bioactive components. We review the effect of combinations of three soy isoflavones, daidzein, genistein, and glycitein and examine the interactions of individual soy isoflavones with other compounds such as vitamins, trace elements, chemotherapeutics, and phytoestrogens. We further review the effect of whole isoflavones and other compounds and discuss these effects when assessing the risks associated with various environmental and food compounds.

Keywords Soy isoflavone · Genistein · Daidzein · Glycitein · Health

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Introduction

Soy isoflavones (SIF) are important nutraceutical molecules. The three isoflavones, genistein (GEN), daidzein (DAI), and glycitein (GLY), comprise approximately 50, 40, and 10 % of total isoflavone content, respectively (Murphy et al. 2002; Vacek et al. 2008). Several mechanisms have been proposed for the biological activity of isoflavones since they can function as antioxidants (Foti et al. 2005), antibacterials (Chin et al. 2012), and free radical-scavengers (Lengyel et al. 2013), and can protect tissues against ultraviolet (UV)-induced damage (Iovine et al. 2011). Since isoflavonoids are structurally similar to the human female hormone 17-β-estradiol, they can bind to estrogen receptors (ER) and have estrogen-like activities, suggesting that isoflavonoids exhibit estrogenic action in various tissues (Vitale et al. 2012). In recent years SIF have been studied extensively for their ability to reduce the risk of inflammation and several chronic diseases, like diabetes and cardiovascular disease (CVD).

Numerous studies have investigated the effects of individual natural components on various human diseases and have shown that GEN and DAI were of great biological activity on individual diseases. However, complex mixtures have greater efficacy than their individual components. For example, soy extract inhibits tumor growth better than GEN (Dong et al. 2012), presumably because the various bioactive components in the soy extract have synergistic effects

(Kim et al. 2008). Certainly, when the individual bioactive components of soy extract are separated and tested for their anti-tumor effects independently, their ability to inhibit tumor growth is marginal. Few studies have investigated the combined effects of isoflavones and other dietary antioxidant nutrients.

The aim of this paper is to describe the potential health benefits of interactions between SIF and other bioactive components with an emphasis on articles published in recent years. We summarize and discuss the combinational effects of three SIF, the interaction of individual SIF and other compounds, and the effect among whole isoflavones and other compounds. Future research may focus on investigating the effects of combinations from different categories, with considerable emphasis on elucidating their mechanisms.

Combination of three soy isoflavones

The combination of GEN, DAI, and GLY isoflavones was more effective in inhibiting proliferation and inducing apoptosis of tumor cells than any single compound in human studies, animal studies and cell culture experiments. Isoflavones are known to have anti-inflammatory and anti-tumor activities, due in part to inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity. Here, we also focus on the role of these isoflavones in inflammation and metabolic disorders.

Apoptosis

Although they had no activity individually, a mixture of pure GEN and DAI significantly induced the apoptosis of C4-2B cells (Dong et al. 2013). Low concentrations of a combined mixture of GEN and DAI was protective against UV-induced photodamage, a synergistic effect that was greater than the effect obtained with each isoflavone alone and involved an inhibition of the NF-κB signaling pathway (Iovine et al. 2011). GEN is capable of exhibiting NF-κB-dependent and NF-κB-independent apoptotic control via ROS generation depending on the cell type (Lee and Park 2013). GEN and DAI had different effects on DNA damaged cells (Lepri et al. 2013). Pure GEN promoted increased metastasis to the lymph nodes, but DAI could protect against genistein-induced metastasis (Singh-Gupta et al. 2010). However, a mixture of pure GEN and DAI (at the same concentration as in soymilk) failed to induce significant changes during acute and chronic studies, suggesting an important, uncharacterized role of the soymilk matrix (Rando et al. 2009). More studies are needed to better understand and elucidate all of the pathways mobilized by genistein and daidzein and to fully exploit their pro-apoptotic properties.

Inflammation

Inflammation plays a key role in all of the stages of atherothrombosis, and begins with endothelial dysfunction caused by events such as modified low-density-lipoprotein (LDL) or free radicals (Beavers et al. 2009). There is recent interest in understanding the impact of SIF on the inflammatory process (Rimbach et al. 2008). In animals, isoflavones have been shown to affect adhesion molecules and pro-inflammatory cytokines in vitro and in vivo (Shambayati et al. 2014). GEN is effective in preventing inflammation caused by the Aβ peptide due to its molecular structure (Valles et al. 2010). Substituents at the C-7 and C-40 positions are crucial for the inhibition of tumor necrosis factor (TNF)-induced transcriptional activity of NF-κB (Lee et al. 2010). Similarly, GEN can inhibit cytokine-induced proinflammatory responses in cultured human brain microendothelial cells (Lee and Lee 2008). However, DAI regulates proinflammatory adipokines, thereby improving obesity- related inflammation through peroxisome proliferator activated receptor (PPAR; Sakamoto et al. 2014).

Metabolic disorders

Soy has anti-inflammatory activities that may reduce the risk of CVD (Chacko et al. 2005). SIF have anti-inflammatory properties in cytokine-activated endothelial cells by inhibiting monocyte adhesion. Recent meta-analyses indicate that soy protein directly lowers blood LDL-cholesterol (LDL-C) levels by 3–5 % (Zhan and Ho 2005; Sacks et al. 2006). Equol is an isoflavone metabolite that is produced from DAI. Approximately 30–60 % of humans have the intestinal flora required to produce equol, and equol production may be associated with a reduced risk of chronic diseases (Atkinson et al. 2005). Equol can act as an antioxidant by inhibiting superoxide radical

production and enhancing nitric oxide production, thus modifying LDL oxidation and CHD risk (Hwang et al. 2003). However, Mangano et al. (2013) reported that SIF (either alone or in combination) did not impact serum lipids or inflammatory markers. This approach should not be considered an effective intervention in preventing cardiovascular disease because healthy late postmenopausal women lack the ability to produce equol. A combination of soybean protein and isoflavones could have a positive effect on control of diabetes, although isoflavones alone may not be effective and not all studies show a positive effect. It is unclear which component(s) of the soybeans is biologically active in these studies, and indeed it may be the soluble fiber alone that is beneficial (Chandalia et al. 2000). There are too few studies to reach conclusions on the effects of isoflavones on diabetes or cognitive function.

GEN and DAI have a synergistic effect that is greater than the effect obtained with each isoflavone alone, although they have different effects on apoptosis, inflammation and metabolic disorders. However, consuming a variety of traditional soy foods seems more effective at preventing some diseases than supplementing a normal diet with a pure soy isoflavone mixture.

Combined effects of isoflavones and other compounds

Isoflavone and vitamin

Supplementation with vitamin C (V_C) and isoflavone did not produce a synergistic antioxidant effect (Hutchins et al. 2005). However, a significant reduction in LDL oxidation was reported (Hwang et al. 2000, 2001). DAI can protect LDL from oxidative modification, and its combination with V_C may be superior to the action of the isoflavone alone in vitro (Wang et al. 2010).

Low-dose DAI-induced 17β-estrogen increased ERα expression in young piglet bone cells (De Wilde et al. 2004). Park and Weaver (2012) discussed a possible synergistic effect of SIF, DAI or GEN, and vitamin D (V_D) on bone tissue turnover. They reported that soy phytoestrogens in combination with V_D may synergistically induce osteoblast activation and prevent pre-osteoclast and osteoclast differentiation. Chang et al. (2012) also reported that V_D and DAI have additive effects, especially in regulating both lipid metabolism and bone formation. Rao et al. (2002) demonstrated that genistein and V_D compounds can synergistically inhibit both benign and malignant prostatic epithelial cell growth via cell cycle arrest. The synergistic effects caused a significant increase in V_D receptor protein levels in maturing preadipocytes, and may be effective in reducing bone loss and weight gain after menopause (Lai et al.2011).

Wiegand et al. (2010) reported that GEN did not affect vitamin E (V_E) status in growing rats, no matter the whether it was given as individual substances or in combination with other bioactives. However, supplementation with V_E plus V_C or soy isoflavone may have a protective role in brain dysfunction observed in some menopausal women. The V_E plus V_C or soy isoflavone combinations significantly reversed the effect of ovariectomy on hippocampal Na^+, K^+-ATPase and acetylcholinesterase (AChE) activities in ovariectomized rats (Monteiro et al. 2007).

Isoflavone and minerals

There is growing evidence that nutritional and food factors may play a part in the prevention of the bone loss that occurs with aging (Yamaguchi 2007).

V_D may benefit bone turnover independently of Ca^{2+} absorption and simultaneous administration of V_{D3} and Ca^{2+} could be encouraged for the treatment of postmenopausal osteoporosis in postmenopausal women (Teekachunhatean et al. 2011). A combination of DAI and high Ca^{2+} favorably affects the cortical and trabecular bone in ovariectomized mice, and this effect is mediated by a high Ca^{2+} diet (Fonseca and Ward 2004). However, GEN supplementation could improve the digestibility of crude protein, dry matter and ash and increase levels of Ca^{2+} and P (Sahin et al. 2006). The most effective approach for preventing postmenopausal osteoporosis is hormone (estrogen) replacement therapy, rather than a decrease in Ca^{2+} intake or V_D (Genant et al. 1989).

Zinc (Zn) and GEN have been shown to synergistically enhance bone components (Yamaguchi 2012). Moreover, Swami et al. (2005) reported that GEN could potentiate the antiproliferative actions of V_{D3} in human prostate cancer cells DU145.

GEN synergized with a low dose of arsenic trioxide (ATO; 2.5 mg/kg) to significantly inhibit the growth of hepatocellular carcinoma HepG2 tumors, and

suppress cell proliferation and induce apoptosis in situ with no obvious side effects at a high dose of ATO (5 mg/kg) (Jiang et al. 2010).

Isoflavones and protein

In rats, a hypocholesterolemic effect of a soy diet may involve interactions between the isoflavone and soy protein (Peluso et al. 2000), whereas in cholesterol fed rabbits, attenuation of atherosclerosis by isoflavones does not require the presence of soy protein. Serum albumins are the major soluble protein constituents of the circulatory system and have many physiological functions (Carter et al. 1994). Mandeville et al. (2009) and Bourassa et al. (2010) reported the spectroscopic analysis of bovine serum albumin (BSA) and human serum albumin (HSA) complexes with GEN, respectively, whose constants were $K_{\text{GEN-BSA}} = 1.26(\pm 0.3) \times 10^4$ M^{-1} and $K_{\text{GEN-HSA}} = 2.4\ (\pm 0.40) \times 10^4\ M^{-1}$.

Isoflavones and anti-estrogen administration

Tamoxifen (TAM) is a successful adjuvant therapy for patients with estrogen-dependent breast cancer. Some women who are prescribed TAM may also consume soy products or take a mixture of isoflavone.

Ju et al. (2002) reported that GEN could negate the beneficial effects of TAM. Helferich et al. (2008) also reported that consumption of high-doses of purified forms of phytoestrogens is not recommended for women at high risk of breast cancer, breast cancer patients under TAM therapy, and for breast cancer survivors.

Tanos et al. (2002) disagreed and argued that the synergistic effect of GEN and TAM could play an important role in the prevention of malignant breast disease. Constantinou et al. (2005) also determined that TAM, when combined with soy isoflavone, had a beneficial effect in breast cancer therapy. The most effective diet was the TAM/DAI combination, which was in all aspects more effective while the TAM/GEN combination was less effective than the TAM diet.

Actually, soy is consumed in high quantities in Asia where breast cancer incidence is lower than in Western countries. Thus, a high consumption of soy has been proposed as reducing the risk of developing breast cancer (Miller 1977). Based on epidemiological studies, Magee and Rowland (2012) indicated that soy does not appear to interfere with TAM or anastrozole therapy. Women who are at an increased risk of breast cancer due to polymorphisms in their genes may especially benefit from high soy isoflavone intake. However, there is no clear understanding of how individual SIF affect the risk of developing breast cancer when combined with TAM. We suggest that consumption of a variety of traditional soy foods such as soy flour and tofu should be emphasized. It is also critical to identify the molecular mechanisms by which soy isoflavones exert cancer promotion or inhibition to validate these in human disease and to use them as the molecular markers that could predict isoflavones effects on human breast tumors (Kwon 2014).

Isoflavones and anti-neoplastic effects

GEN at typical physiologic dietary plasma levels may not have a significant effect on the growth of multiform cells but it may enhance the antiproliferative effects of other chemotherapeutic agents. At typical adult dietary plasma levels, GEN can significantly enhance the antiproliferative and cytotoxic action of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, carmustine) in two glioblastoma multiform cell lines, U87 (human) and C6 (rodent) (Khoshyomn et al. 2002).

A novel combination of GEN and cytosine arabinoside (ara-C) could be a promising regimen for the treatment of acute myeloid leukemia (AML) (Shen et al. 2007). GEN also acted synergistically with mitomycin C (MMC) in reducing free radicals and in oxidizing environments (Hartmann and Getoff 2009). Choudhury et al. (2010) examined the synergistic effects of combination of sorafenib (SF) and GEN in human malignant neuroblastoma SK-N-DZ (N-Myc amplified) and SH-SY5Y (N-Myc non-amplified) cell lines, and reported that this combination of drugs could be a potential therapeutic strategy against human malignant neuroblastoma cells having the N-Myc amplification or non-amplification.

Ping et al. (2010) evaluated the synergistic cytotoxicity of taxol (paclitaxel) with GEN in killing hormone-refractory prostate cancer PC-3 cells. Szliszka and Krol (2011) reported that the chemopreventive effects of soy foods on prostate cancer are associated with isoflavone-induced support of TRAIL-mediated apoptotic death.

GEN exhibits anti-cancer effects by inhibiting protein tyrosine kinase that is involved in up-regulation of vascular endothelial growth factor (VEGF). All-trans retinoic acid (ATRA) also up-regulates expression of VEGF. Zhou et al. (2012) demonstrated that genistein effectively enhances the anti-cancer effects of ATRA, particularly by counter-acting the ATRA-induced up-regulation of VEGF.

Isoflavone and antioxidant compounds

SIF significantly inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced oxidative stress, proinflammatory cytokines production and activation of NF-κB. SIF also inhibited the expression of cyclooxygenase 2 (COX-2) and ki-67 (Khan et al. 2012). GEN alone inhibits inflammatory responses through the modulation of monophosphate activated protein kinase (AMPK) and control of COX-2 and this is enhanced in combination with capsaicin (Lai et al. 2011). Moreover, dietary GEN is important not only as a transcriptional regulator of COX-2, but it may also modulate COX-2 enzyme activity to control inflammatory processes (Maldonado-Rojas and Olivero-Verbel 2011).

Verma et al. (1997) showed that curcumin and GEN had synergistic inhibitory effects on the growth of human breast cancer MCF-7 cells induced by endosulfane, DDT, and chlordisdane or 17-beta estradiol.

The estrogenic activity of baicalein and DAI were demonstrated by their strong abilities in stimulating estrogen receptor phosphorylation and transcriptional activation of estrogen responsive element in MCF-7 breast cells (Choi et al. 2013).

Isoflavones and physical activity

The cooperative effects of exercise training and genistein administration on bone mass have been exhibited in ovariectomized (OXV) and androgen deficiency-induced bone loss in mice. The effect of isoflavone intake walking-induced changes in bone and lipid metabolism in postmenopausal women over 24 weeks and showed that the preventive effects of isoflavone on bone loss depended on the individual's intestinal flora for equol production (Wu et al. 2001, 2003, 2006).

Isoflavones and other phytoestrogens

Most phytoestrogens are diphenolic compounds that are structurally similar to natural estrogens, shown to be weak inhibitors of aromatase. Low dose combinations of phytoestrogens substances (GEN, biochanin and DAI) could reduce the activity of aromatase by downregulating its mRNA expression in primary cultures of human granulosa-luteal (GL) cells (Rice et al. 2006). Combining anticancer phytoestrogens (GEN, quercetin and biochanin A) could significantly increase the efficacy of individual components resulting in improved efficacy at physiologically achievable concentrations (Kumar et al. 2011).

Hwang et al. (2001) showed that acerola cherry extract can enhance the antioxidant activity of soy and alfalfa extracts in a variety of LDL oxidation systems. In SV-40 Tag rats, GEN and resveratrol (*trans*-3,5,40-trihydroxystilbene, RES), consumed in the diet, alone and in combination, significantly reduced the most severe grade of poorly differentiated lesions in these transgenic animals compared to a control diet (Harper et al. 2009).

Isoflavone and estrogenic chemicals

Human populations, however, are exposed to mixtures of estrogenic and estrogen-like agents and it is necessary to consider the impact of their combined effects. Le Page et al. (2006) developed a reporter gene assay based on glial cells (U251-MG) transfected with three zebrafish ERs, ethynylestradiol (EE2), estrone (E1), α-zeralenol subtypes, and the brain aromatase promoter linked to luciferase. This system was used to study the combined additive effect of the xenoestrogens and their potential enhancement of estrogenic potency.

There are studies on the interactive effects of bisphenol A (BPA) and GEN in their embryotoxicity using the rat whole-embryo culture (WEC; Xing et al. 2010) and embryonic stem cell test models (Kong et al. 2013). These studies have reported that BPA alone may not have adverse reproductive or developmental effects on human beings. However, BPA and GEN do have synergistic effects at low-doses, which could result in birth defect sand behavioral alterations later in life.

Payne et al. (2000) studied combinations of two, three, and four estrogenic chemicals, o, P′-DDT, GEN, 4-nonylphenol, and 4-n-octylphenol in the yeast estrogen screen. Individual dose–response curves were recorded, and this information was used to successfully predict the combined effects for mixtures with a fixed ratio. They concluded that levels of xenoestrogens may produce significant effects as mixtures. Moreover, they assessed the combined effects of four xenoestrogens on the induction of cell proliferation in MCF-7 cells (Payne et al. 2001). Rajapakse et al. (2002) continued to study the combination of eleven xenoestrogens to affect the actions of β-estradiol by using a yeast reporter gene assay. Their results showed that a combination of sub-NOEC levels of eleven xenoestrogens can also led to a doubling of the effects of E_2.

Summary

Humans are simultaneously exposed to various environmental and food EDs, generally at low levels, and there is a need to consider mixture effects. This paper reviews the combined effect of soy isoflavone and other bioactive components. The combination of three soy isoflavones, DAI, GEN, GLY and their interaction with other compounds, such as vitamins, trace elements, chemotherapeutics, and phytoestrogens are examined. The effect of whole isoflavone and other compounds are discussed. In conclusion, the mixture effects of these combinations from various environmental and food compounds need to be considered in order to maintain human health.

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