

Soy Isoflavones in Integrative Oncology: Increased Efficacy and Decreased Toxicity of Cancer Therapy

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Abstract

Soy consumption in human diet has been linked to decreased incidence of a variety of cancers, suggesting a potential role of soy products in cancer prevention and control. Furthermore, a substantial body of evidence in the literature suggests that soy supplementation may improve the efficacy and prevent the adverse effects of cancer chemotherapy and radiation therapy. Isoflavones constitute the predominant anticancer bioactive compounds in soy. Genistein, which is the most abundant and active isoflavone in soy, has a multitude of effects on cancer cells, including inhibition of NF- κ B activation and DNA methylation, enhancement of histone acetylation, inhibition of cell growth and metastasis, and antiangiogenic, anti-inflammatory, and anti-oxidant effects. Isoflavones are orally bioavailable, easily metabolized, and usually considered safe. In this article, we review in vitro and in vivo evidence as well as the results of clinical and epidemiological studies on the effects of soy isoflavones, with a focus on sensitization of cancer cells to chemotherapy and radiation while at the same time protecting normal cells from the harmful effects of these treatments.

Keywords

prostate cancer, genistein, chemotherapy, radiotherapy

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Introduction

Many studies have been conducted to investigate the interaction of dietary constituents and antineoplastic therapies in both animal models and clinical trials.¹ In particular, soy isoflavones have been suggested to have cancer preventive effects.² Epidemiological studies have shown a significant difference in cancer incidence among different ethnic groups, which could be attributed in part to dietary habits. For example, the incidence of breast cancer and prostate cancer (PCa) are much higher in the United States and Europe where dietary soy intake is low as compared with countries such as China and Japan, where dietary consumption of soy products is much higher. Genistein, a predominant isoflavone in soy, has been shown to inhibit cancer development, growth, and metastasis in animal models. It may act by modulating the genes related to cell cycle control and apoptosis.³

Chemotherapy is a common form of treatment for many types of cancer. Chemotherapeutic drugs are designed to interfere with rapidly dividing cells such as cancer cells. This means that they may also harm normal cells that divide

normally—that is, the cells in the bone marrow, mouth, gastrointestinal tract, nose, nails, vagina, and hair cells, which undergo constant division making them vulnerable to the toxic effects of chemotherapy as well as radiotherapy. Therefore, major research efforts have been aimed at discovering ways of protecting normal proliferating cells from cancer therapy. Many chemotherapeutic agents work by producing free radicals or reactive oxygen species (ROS) which, if not quenched, can damage the cell and its various constituents. However, these species also affect the normal cells. Detoxification of free radicals and ROS is, therefore,

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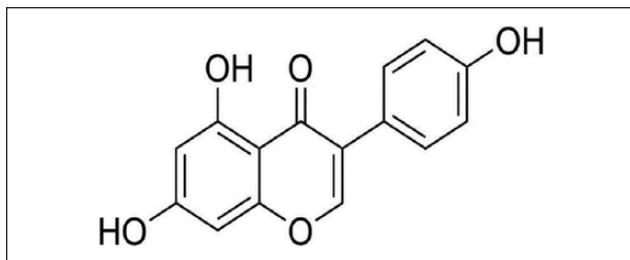


Figure 1. Genistein, 4',5,7-trihydroxyisoflavone.

important and opens up avenues for the use of natural products, most of which have antioxidant properties, useful in the prevention and control of cancer.^{4,6} Inflammation is another hallmark of cancer, and it has been reported in various studies that its inhibition could be beneficial in cancer. In this review, we discuss the effect of soy isoflavones, well known for their antioxidant and anti-inflammatory effects, as potential supplements during conventional cancer therapy, with a special focus on PCa therapy.

Soy Isoflavones: Structure and Metabolism

Isoflavones are polyphenolic plant-derived compounds that have both estrogenic (estrogen agonist) and antiestrogenic (estrogen antagonist) activity. They are the major flavonoids in legumes, particularly soybean, where they are present bound to sugars (glycosides). Soy isoflavones include genistein, daidzein, and glycitein. These compounds are structurally characterized by their 3-phenylchromen-4-one backbone, which consists of 2 benzene rings linked by a heterocyclic pyran ring. In addition to the heterocyclic core, genistein and its related isoflavones are polyphenols (contain several hydroxyl groups attached to core phenyl rings). Genistein, or 4',5,7-trihydroxyisoflavone and daidzein are the most prominent isoflavones in soy products. The structure of genistein is shown in Figure 1. Soybeans and soy products constitute the richest source of isoflavones in human diet.

Genistein can also be synthesized, but humans obtain it from the diet. In soy and soy products, the primary chemical form of genistein exists in the conjugated form known as genistin.⁷ Therefore, people are exposed to genistin far more than genistein when consuming soy and soy products in their diet. Genistein undergoes first-pass metabolism in the liver as well as enterohepatic circulation after absorption from the intestine. The byproducts of isoflavone metabolism may produce different effects on the body.⁸ Studies showed that 90% of genistein in the blood undergoes extensive liver metabolism and exists in either the glucuronidated or sulfated form, whereas only 10% exists in the nonconjugated or free form.⁹

Soy Isoflavones in Cancer Therapy: Effects and Mechanisms

Soy, soybean, or soya bean, is a native East Asian legume, which is widely grown for its edible beans. The beans and its products have been reported to have beneficial effects in cancer, which is largely attributed to the presence of isoflavones.¹⁰⁻¹⁴ In a recent meta-analysis of 30 articles, a clear statistically significant association between soy consumption and decreased PCa risk was reported.¹⁴ Populations in countries like China and Japan, which consume soy foods as part of the regular diet, showed low incidence of PCa. In the analysis of the potential impacts of soy food and isoflavone intake and that of the circulating isoflavones, in both primary and advanced PCa, total soy food ($P < .001$), genistein ($P = .008$), daidzein ($P = .018$), and unfermented soy food ($P < .001$) intakes were found to be significantly associated with decreased risk of PCa. Neither soy food intake, nor circulating isoflavones were associated with advanced PCa risk.¹⁴ The meta-analysis provided a comprehensive updated analysis of previously published data demonstrating that soy foods/isoflavones were associated with reduced PCa risk.

Genistein is one of the most predominant and active flavonoids in soybeans. It can alter a variety of biological processes in estrogen-related malignancies, which include PCa, and has been found to act mainly by altering apoptosis, the cell cycle, and angiogenesis and inhibiting metastasis. The molecular mechanisms of the anticancer and therapeutic effects of genistein has been suggested to involve caspases, B cell lymphoma 2 (Bcl2)-associated X protein, Bcl-2, kinesin-like protein 20A, extracellular signal-regulated kinase 1/2, nuclear transcription factor κ B (NF- κ B), mitogen-activated protein kinase, inhibitor of NF- κ B, Wingless and integration 1 β -catenin, and phosphoinositide 3 kinase/Akt signaling pathways.^{2,15} Its inhibitory effect on NF- κ B is particularly important because the inhibition suppresses inflammation.¹⁶ The NF- κ B and the serine/threonine-specific protein kinase Akt both maintain a homeostatic balance between cell survival and apoptosis. Interestingly, genistein has also been reported to be a potent angiogenesis and metastasis inhibitor, which is promising in cancer prevention, control, and treatment. Genistein also shows synergistic behavior with anticancer drugs, such as doxorubicin, docetaxel, and tamoxifen, suggesting a potential role in combination therapy.¹⁵

In colon cancer in humans, the soy isoflavones, especially genistein, inhibit cell growth and facilitate apoptosis and cell cycle arrest in the G2/M phase.³ The cell cycle arrest in the G2/M phase is accompanied by the activation of ATM/p53, p21 $waf1/cip1$ and GADD45 α as well as downregulation of cdc2 and cdc25A, as demonstrated by quantitative polymerase chain reaction and immunoblotting.³ Interestingly, genistein induced G2/M cell cycle arrest in a p53-dependent manner and suggested the crucial role of the

ATM/p53-p21 cross-regulatory network in mediating the anticarcinogenic effect of genistein. In another study, genistein was found to cooperate with the histone deacetylase inhibitor vorinostat to induce cell death in PCa cells.¹⁷ Recently, this important isoflavonoid has been reported to synergistically increase radiosensitivity of PCa cells. Earlier, the compound was reported to enhance the efficacy of cancer therapy by sensitizing cancer cells to chemotherapy¹⁸⁻²⁰ and also radiotherapy.²¹⁻²⁵ At the same time, the antioxidant²⁶⁻²⁸ and anti-inflammatory²⁹⁻³³ properties of isoflavones add to their beneficial effects in cancer.

Soy isoflavones, mainly genistein, have been reported to have a number of biological effects other than their effects in cancer. These have been summarized in Table 1.

Isoflavones as Potential Candidates in the Prevention and Control of PCa

Epidemiological studies have shown the beneficial effects of soy isoflavones in breast, prostate, and colon cancers in countries such as China and Japan, where the dietary consumption of soy isoflavones is high.³⁴ A recent randomized, double-blind phase 2 clinical study that aimed to investigate the effect of synthetic genistein concentrations and its safety in patients with localized PCa showed that genistein at a dose that can be easily obtained from a diet rich in soy reduced the level of serum prostate-specific antigen (PSA) with no adverse effects of clinical significance.³⁵ A comprehensive meta-analysis on the extent of the possible association between soy-based food consumption and the risk of PCa indicated an inverse relationship between dietary soy isoflavone (genistein and daidzein) consumption and PCa incidence and mortality.³⁶ Nutritionally relevant levels of genistein may modulate the expression of prostate tissue biomarkers associated with cancer prediction and progression.³⁷ In various studies, of all the isoflavones investigated, genistein appears to be the most potent in the prevention and control of cancers, which makes it a promising molecule in PCa.

The use of soy isoflavones has also been considered in combination with other natural products, such as lycopene.³⁸ Dietary intake of lycopene and soy lowers the PCa risk. In vitro studies with lycopene and genistein showed an increase in apoptosis and inhibition of cell growth in androgen-sensitive (LNCaP) and androgen-independent (PC3 and VCaP) PCa cell lines. PSA stabilization has been observed with soy isoflavone intake in PCa patients.¹⁰ Vaishampayan et al³⁸ enrolled 71 patients who had rising PSA levels after failing radical prostatectomy and/or radiation therapy with or without hormone therapy. Participants were randomly assigned to receive a tomato extract capsule containing 15 mg of lycopene alone (n = 38) or together with a capsule containing 40 mg of a soy isoflavone mixture (n = 33) twice daily orally for a maximum of 6 months. There was no decline in

serum PSA in either group qualifying for a partial or complete response. However, 35 of 37 (95%) evaluable patients in the lycopene group and 22 of 33 (67%) evaluable patients in the lycopene plus soy isoflavone group achieved stable disease, described as stabilization in serum PSA level. Data suggested that lycopene and soy isoflavones had activity in PCa patients and may delay progression of both hormone-refractory and hormone-sensitive PCa. However, the effect was not additive. Importantly, a recent phase 2 dose-escalating study in PCa patients examined plasma, prostate, and urine biomarkers of carotenoid and isoflavone exposure and described foundation for tomato-soy juice in future human clinical trials.³⁹ Investigating the efficacy of more compounds of natural origin might be a fruitful area of research in PCa control and treatment. Clinical trials with a mechanistic approach could elucidate potential clinical uses of natural compounds.

Soy Isoflavones in Chemotherapy Toxicity

Chemotherapy often results in the generation of ROS in excess, and thus the oxidative stress, which is evidenced by increased lipid peroxidation and decrease in the levels of total radical-trapping capacity of the tissue and body fluids.⁴⁰⁻⁴² The anthracyclines generate by far the highest levels of oxidative stress. The cytochrome P450 monooxygenase system is the primary site of the generation of ROS during cancer chemotherapy.⁴³ It is important to highlight that the drugs that do not depend on the generation of ROS in their mechanism of action can only mediate their anticancer effects on cancer cells that exhibit unrestricted progression through the cell cycle and have intact apoptotic pathways.⁴⁴ However, oxidative stress can interfere with chemotherapy-induced apoptosis and with cell cycle progression by inhibiting the transition of cells from the G0 to G1 phase, slowing the progression through the S phase by inhibition of DNA synthesis, inhibiting cell cycle progression of the G1 to S phase, and checkpoint arrest. By reducing oxidative stress, antioxidants may counteract the effects of chemotherapy-induced oxidative stress on cell cycle and apoptosis. Thus, antioxidants may enhance the cytotoxicity of antineoplastic drugs.⁵ In contrast, antioxidants might also protect cancer cells against the oxidative damage induced by chemotherapy, which suggests a harmful effect as a result of their use.¹ Antioxidants may decrease chemotherapy-induced damage of normal cells by reducing lipid peroxidation or halting cancer cell proliferation.⁶ In their study, Block et al^{45,46} systematically reviewed randomized controlled clinical trials evaluating the effects of concurrent use of antioxidants in chemotherapy on toxic side effects. The review suggested that antioxidant supplementation may reduce the toxic effects of ROS-generating chemotherapies. Additionally, analysis suggested that concurrent use of supplements and

Table I. Miscellaneous Effects of Soy Isoflavones.

Property	Effect	Reference
Free radical scavenging effect	Protects cells in central nervous system	Wei et al ⁶¹
	Protection against oxidative modification of LDL	Tikkanen et al ⁶²
	Protection of human cortical neuronal HCN1-A and HCN2 cells	Ho et al ⁶³
	Protection of primary cortical neurons from iron-induced free radical reaction and lipid peroxidation	Sonee et al ⁶⁴
	Protection of dopaminergic neurons from lipopolysaccharide-induced injury by inhibiting microglia activation	Wang et al ⁶⁵
	Rescue human amniotic fluid mesenchymal stem cells and Schwann cells from apoptosis by suppressing the macrophage deposits, associated inflammatory cytokines, and fibrin deposits	Pan et al ⁶⁶
	Prevention of endoplasmic reticulum stress-mediated neurotoxicity by inhibiting tau hyperphosphorylation in SH-SY5Y cells	Park et al ⁶⁷
	Alleviation of the endoplasmic reticulum stress-mediated and DNA damage-mediated neurodegeneration caused by homocysteine	Park et al ⁶⁸
Anti-inflammatory	Suppression of lipopolysaccharide-induced inflammation in rat liver	Zhao et al ⁶⁹
Effect on immune system	Immunomodulation	Sakai and Kogiso ⁷⁰
Antiviral	Antiviral properties in vitro and in vivo against a wide range of viruses	Andres et al ⁷¹
Tyrosine kinase inhibitor	Tyrosine kinase inhibition	Akiyama et al ⁷²
Effect on vascular system	Prevention of atherosclerosis and related vascular events	Holzer et al ⁷³
Antihypertensive	Attenuation of hypertension, targeting the kidney to increase renal blood flow, sodium excretion	Martin et al ⁷⁴
Osteopenia	Positive effect in cyclosporin A-induced osteopenia only in sites with high turnover and improvement of the osteoprotective effect of L-arginine	Clementi et al ⁷⁵
Epidermal hyperplasia	Reduction in epidermal hyperplasia caused by topical retinoid treatment	Rittie et al ⁷⁶
Hepatoprotective effect	Effect via suppression of necrosis of hepatocytes and the cellular infiltration in liver parenchyma and prevention of the development of fatty and protein dystrophy in the liver and normalization of the activity of aminotransferases	Saratikov et al ⁷⁷
Drug toxicity	Protection of post-neural tube closure defects of rodents induced by cyclophosphamide	Zhao et al ⁷⁸
	Protection of normal and cancer cells against genotoxic potential of tamoxifen	Wozniak et al ⁷⁹
Radiation injury	Protection against acute radiation injury	Landauer et al ⁸⁰

Abbreviation: LDL, low-density lipoprotein.

chemotherapy might produce better tumor response rates and increased chances of survival, although small sample size and low quality of studies precluded firm conclusions.

Chemotherapeutic drugs are designed to interfere with rapidly dividing cells and kill cancer cells as well as normal cells, such as healthy intestinal mucosal cells, because of their rapid rate of division. Methotrexate (MTX) is one of the common antineoplastic agents that destroys mucosal cells and may result in mucositis, stomatitis, diarrhea, decreased nutrient absorption, translocation of gastrointestinal bacteria, and anorexia.⁴⁷⁻⁴⁹ Various soy products have been shown to provide dramatic protection against MTX

toxicity in animal models.^{48,50-52} Funk and Baker⁵² investigated isolated soybean components in a semipurified diet and showed that they alter MTX toxicity and that soybean meal and soybean concentrate offered the greatest protection, completely alleviating MTX-induced anorexia and diarrhea when included as sole protein source and fed 14 days prior to and 7 days following intraperitoneal MTX injection at 20 mg/kg body weight. In addition, although the rats fed casein-based semipurified diet had necrotic intestine, those fed the soybean-containing complex diet or semipurified diet containing soybean concentrate or soybean isolate showed no signs of necrosis in any part of the

small intestine. In a different study,⁵¹ the same group aimed to determine whether MTX toxicity associated with a casein-based semipurified diet could be ameliorated or prevented by adding fiber or by replacing casein with other protein source. Results of the study showed that addition of amorphous cellulose to semipurified casein-based diet slightly reduced toxicity symptoms. Addition of crystalline cellulose, hemicellulose, and pectin did not lessen toxicity symptoms, whereas replacing casein with soybean concentrate totally alleviated the toxicity symptoms. These findings suggested that it may be possible to develop soybean-based enteral products that would minimize gastrointestinal toxicity experienced by cancer patients undergoing MTX chemotherapy.

Chevreau and Funk-Archuleta,⁵⁰ indicated that soy concentrate was superior in alleviating MTX toxicity compared with commercial enteral products. Rats fed soy concentrate maintained food intake above 90% of preinjection levels, which was greater than all other groups at day 3 and those receiving hydrolyzed or intact casein without fiber on day 4 ($P < .05$). The soy concentrate group also gained more weight when compared with other groups fed hydrolyzed or intact casein without fiber ($P < .05$) and had no diarrhea. The same study showed that crypt necrosis occurred in all groups except those consuming the soy concentrate diet or enteral product containing soy fiber. Funk (52) investigated the ability of a soy-derived antiapoptotic fraction that could inhibit apoptosis in an *in vitro* assay to inhibit MTX-induced gastrointestinal toxicity in rats. Rats fed high doses of the soy-derived antiapoptotic fraction-supplemented diets experienced significantly less weight loss and diarrhea and better food intake ($P < .05$). They also performed mouse embryonic C3H10T1/2 cell apoptosis assay and demonstrated that soy-derived antiapoptotic fraction was a potent inhibitor of apoptosis. It is well known that many chemotherapeutic agents, including MTX, increase the incidence of apoptosis, particularly in the gastrointestinal tract.⁵³ Thus, the studies suggested that the mechanism behind the protection of undesirable gastrointestinal MTX toxicity by soy-derived antiapoptotic fraction was likely to be a result of reduction of apoptotic cell death.

Similarly, despite the beneficial chemotherapeutic effects of bleomycin on cancer cells, cytotoxicity and genotoxicity of bleomycin on normal cells persists as a major problem in chemotherapy. Lee et al¹² demonstrated a number of effects of genistein pretreatment on the toxicity of bleomycin in normal lymphocytes and human leukemia (HL-60) cells. It increased the frequencies of micronuclei in HL-60 cells, decreased the frequencies of micronuclei in human lymphocytes during G0 and G2, increased DNA damage in HL-60 cells, and reduced DNA damage in blood lymphocytes. As a result, dual antagonistic effects of genistein were observed from this study—genistein enhanced the bleomycin-induced cytotoxicity in HL-60 cells, whereas it

protected normal blood lymphocytes. In another study, cisplatin was tested *in vitro* in human lymphocytes for its toxicity. This study showed that cisplatin when combined with genistein considerably reduced the genotoxicity, possibly because of the free radical scavenging activity of genistein.⁵⁴

The results of the *in vitro* and *in vivo* studies supported a novel chemotherapy strategy for treating cancer patients by concurrent administration of chemotherapy with soy isoflavones. Results of a clinical trial conducted by Tacyildiz et al⁵⁵ demonstrated that genistein reduced the adverse effects of chemotherapy in pediatric cancer patients. In this study, 9 cycles of chemotherapy were administered without genistein supplementation, whereas 57 cycles were administered with genistein supplementation. Patients served as their own controls, and the clinical-laboratory data from the first cycle were compared with the data from subsequent cycles. Chemotherapy doses and schedules between first and subsequent cycles remained the same. Genistein levels were 2 to 6 times higher (range = 0.215-0.411 mg/L; median = 0.258 mg/L) during genistein supplementation compared with the no supplementation period (range = 0.058-0.111 mg/L; median = 0.061 mg/L). The results of the study showed that there was less myelosuppression, oral mucositis, infections, and requirement of blood products during the cycles given with genistein supplementation. In addition, 3 children receiving genistein during abdominal radiotherapy experienced less pain and no diarrhea, which is a common side effect of abdominal radiation. Studies with soy products and chemotherapy toxicities are summarized in Table 2.

Bioavailability of Isoflavonoids

Pharmacokinetic studies in healthy adults compared plasma kinetics of pure daidzein, genistein, and their β -glycosides administered as a single-bolus dose to 19 healthy women.⁵⁶ Results demonstrated differences in the pharmacokinetics of isoflavone glycosides compared with their respective β -glycosides. Even though all isoflavones were efficiently absorbed from the intestine, there were striking differences in the fate of aglycones and β -glycosides. Mean times to attain peak plasma concentrations, t_{max} for the aglycones genistein and daidzein were 5.2 and 6.6 hours, respectively, whereas for the corresponding glycosides, it was delayed to 9.3 and 9.0 hours, respectively, which was consistent with the residence time needed for hydrolytic cleavage of the glycoside moiety. The apparent volume of distribution of isoflavones confirmed extensive tissue distribution. In this study, the plasma genistein concentration was consistently higher than that of daidzein when equal amounts of the 2 isoflavones were administered, and this was accounted for by more extensive distribution of daidzein (236 L) compared with genistein (161 L). The systemic bioavailability of genistein (mean area under

Table 2. Studies With Soy Products and Chemotherapy Toxicities.

Agents	Toxicities	Treatment	Results	Reference
Methotrexate	Gastrointestinal toxicity	34 SD rats; groups; control group (casein), casein + soy fraction (0.164% of diet) group, casein + soy fraction (0.493% of diet), casein + soy fraction (1.643% of diet)	Improved food intake $P < .05$, weight gain $P < .05$, decreasing incidence of diarrhea $P < .05$	Funk-Archuleta et al ⁴⁸
Bleomycin	Cytotoxicity and genotoxicity	Human blood lymphocytes obtained from healthy women and human leukemia cell line HL-60 cells (KCLB 10240) pretreated with genistein followed by bleomycin	Enhanced bleomycin-induced cytotoxicity in human leukemia (HL-60) while protecting normal blood lymphocytes	Lee et al ¹²
Cisplatin	Genotoxicity	Human lymphocyte culture of 2 healthy donors treated with cisplatin only and in combination with genistein and gingerol separately in the presence of a metabolic activation system	Reduced genotoxicity because of the free radical scavenging activity of genistein	Beg et al ⁵⁴
Various combination chemotherapy regimens + radiotherapy	Various toxicities	8 Pediatric patients with cancer (served as their own controls); 9 cycles of chemotherapy without soy isoflavone, 57 cycles of chemotherapy with soy isoflavones; chemotherapy doses and schedules same	Genistein levels were 2 to 6 times higher (range = 0.215-0.411 mg/L; median = 0.258 mg/L) during genistein supplementation compared with the no supplementation period (range = 0.058-0.111 mg/L; median = 0.061 mg/L); genistein supplementation: less myelosuppression (shorter duration of neutropenia), oral mucositis, infections (shorter duration of antibiotic use), blood product requirements; no diarrhea during abdominal radiotherapy	Tacyildiz et al ⁵⁵
Etoposide	Alopecia	10 SD rats; etoposide injected daily in 11-day-old SD rats at 1.2 mg/kg ip for 3 days, 5 days before the first injection of etoposide, soymetide-4 orally for 8 days concomitantly with indomethacin, AH23848B, pyrilamine, cimetidine, and PDTC	Oral administration soymetide-4: suppression of alopecia induced by etoposide in neonatal rat models	Tsuruki et al ⁸¹
Methotrexate	Gastrointestinal toxicities	Rats; 5 enteral products containing casein or soy isolate in various forms to 10 rats for 7 days before injection and 7 days after injection of MTX (20 mg/kg)	Soy concentrate diet consumption; maintained food intake above 90% of preinjection levels, which was greater than all other groups at day 3 and those receiving hydrolyzed or intact casein without fiber on day 4 ($P < .05$), no diarrhea, weight gain when compared with other groups fed hydrolyzed or intact casein without fiber ($P < .05$), crypt necrosis (in intestine) occurred in all groups except those consuming the soy concentrate diet	Chevreau and Funk-Archuleta ⁵⁰

(continued)

Table 2. (continued)

Agents	Toxicities	Treatment	Results	Reference
Methotrexate	Gastrointestinal toxicities	Male SD rats; 5 different experiments; products tested: soybean meal, soybean concentrate, soybean isolate and soybean fiber; 14 days prior to and 7 days following intraperitoneal MTX injection	Soybean meal and soybean concentrate offered the greatest protection, completely alleviating MTX-induced anorexia and diarrhea; soybean concentrate and soybean isolate prevented the necrosis (in the small intestine of MTX-injected animals) observed in animals fed the casein-based semipurified diet	Funk and Baker ⁵¹
Methotrexate	Gastrointestinal toxicities	Male SD rats; 6 different experiments; products tested: (1) fiber sources, including crystalline cellulose, amorphous cellulose, hemicellulose, and pectin; (2) protein sources, including casein, soybean concentrate, whey isolate, egg albumen, com gluten meal, and hamburger; in experiments 1 to 4, diets for 14 days before MTX injection, experiments 5 and 6 to evaluate time periods prior to or after MTX dosing on toxicity development	Toxicity was lower when 25% of the protein normally supplied by casein was replaced with soybean concentrate, and no toxicity symptoms were present when 50% or more of the protein was provided by soybean concentrate	Funk and Baker ⁵²
Cisplatin	Nephrotoxicity	Mice; control (n = 10), genistein (10 mg/kg; n = 10), cisplatin (20 mg/kg; n = 10), and cisplatin plus genistein (n = 10)	Genistein; significantly reduced cisplatin-induced renal injury, ameliorated the cisplatin-induced upregulation of ICAM-1 and MCP-1 expression, resulting in decreased infiltration of macrophages into the kidney, significantly reduced cisplatin-induced generation of ROS and NF- κ B activation in HK-2 cells, reduced cisplatin-induced apoptosis in kidney through downregulation of p53 induction	Sung et al ⁸²

Abbreviations: AH23848B, an antagonist of the PGE2 receptor EP4; HK-2, human kidney; HL-60, human leukemia cells; ICAM-1, immunostaining for intercellular adhesion molecule-1; MCP-1, immunostaining for monocyte chemoattractant protein-1; MTX, methotrexate; NF- κ B, nuclear factor- κ B; PDTc, pyrrolidine dithiocarbamate ammonium; ROS, reactive oxygen species; SD, Sprague-Dawley.

the curve [AUC] = 4.54 μ g/[mL h]) was much higher than that of daidzein (mean AUC = 2.94 μ g/[mL h]). Bioavailability was greater when ingested as β -glycosides rather than as aglycones. The pharmacokinetics of methoxylated isoflavones showed distinct differences depending on the position of the methoxyl group in the molecule. Glycitin, found in 2 phytoestrogen supplements, underwent hydrolysis of the β -glycoside moiety and little further biotransformation, leading to high plasma glycitein concentrations. Biochanin A and formononetin, 2 isoflavones found in 1 phytoestrogen supplement, were rapidly and efficiently demethylated, resulting in high plasma genistein and daidzein concentrations typically observed after the ingestion

of soy-containing foods. These differences in pharmacokinetics and metabolism have implications in clinical studies because it cannot be assumed that all isoflavones were comparable in their pharmacokinetics and bioavailability. An analysis of 33 phytoestrogen supplements and extracts revealed considerable differences in the isoflavone content from that claimed by the manufacturers. Plasma concentrations of isoflavones show marked qualitative and quantitative differences depending on the type of supplement ingested.⁵⁶

Various studies, including in vivo studies, have shown that genistein from soy extracts, its free form, and its glycoside genistin are readily bioavailable.¹⁵ Extensive metabolism of

genistein in the intestine, and postabsorption, has been documented both in humans and experimental animals. Among the several metabolites identified in the blood and excreta are dihydrogenistein, dihydrodaidzein, 6'-hydroxy-O-desmethylangolensin, 4-ethylphenol, glucuronide and sulfate conjugates of genistein and its metabolites, and 4-hydroxyphenyl-2-propionic acid. The gut microflora cleaves the C-ring of the isoflavonoid skeleton to give 4-hydroxyphenyl-2-propionic acid and dihydrogenistein.⁵⁷ The metabolism in the gut wall and liver is also known to yield glucuronide and sulfated products.⁵⁸ Few reports suggest that conjugation plays a role in rapid elimination by biliary and urinary excretion.⁸

Adverse Effects of Soy Isoflavones

In an analysis of data from PubMed and EMBASE from 1975 to 2015 (articles selected with the search terms *isoflavone*, *phytoestrogen*, *soy*, *genistin*, and *PCa*), isoflavones are reported not to play an important role in reducing PSA in PCa patients or healthy men, but the intake of various types of phytoestrogens with lower concentrations in the daily diet was reported to produce synergistic effects against PCa. The analysis suggests that the prostate tissue may concentrate isoflavones to potentially anticarcinogenic levels but cautioned that the isoflavones may also act as an agonist in PCa.⁵⁹

Phytoestrogens are structurally and functionally analogous to estrogens. Phytoestrogens and their active metabolites such as equol can remain in food/meat and influence the hormonal balance of the consumers. In animals, intake of phytoestrogens may affect fertility, sexual development, and behavior.⁶⁰

Consumption of soy as dietary supplement may cause mild stomach and intestinal side effects such as constipation, bloating, and nausea and may also cause allergic reactions involving rash, itching, and anaphylaxis in some people.

Conclusion

Chemotherapeutic agents and radiation induce oxidative stress and inflammation, producing side effects in cancer patients. Soy isoflavones, owing to their multiple mechanisms of effects, including the antioxidant and anti-inflammatory effects, may be used as dietary supplements to ameliorate the adverse reactions to anticancer drugs and radiation. At the same time, they may increase the efficacy of cancer chemotherapy and radiation, especially in PCa. The effect of soy isoflavones, particularly genistein, in the prevention and control of PCa has been supported by pre-clinical studies, meta-analyses, and clinical trials, but larger placebo-controlled clinical trials are needed to investigate

the potential use of genistein for amelioration of the adverse effects of anticancer drugs and radiation therapy.

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