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REVIEW

The potential health benefits of the isoflavone glycoside genistin

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Abstract Genistin is a type of isoflavone glycoside and has a broad range of health benefits. It is found in a variety of dietary plants, such as soybean, kudzu (Japanese arrowroot), and other plant-based products. Genistin has been described to have several beneficial health impacts, such as decreasing the risk of osteoporosis and post-menopausal symptoms, as well as anti-cancer, anti-oxidative, cardioprotective, anti-apoptotic, neuroprotective, hepatoprotective, and anti-microbial activities. It may also assist individuals with metabolic syndrome. This review summarizes some of the molecular impacts and prospective roles of genistin in maintaining and treatment of health disorders. The review could help to develop novel genistin medicine with significant health benefits for application in the nutraceutical and pharmaceutical fields.

Keywords Genistin · Isoflavone · Health disorders · Therapeutic activity

Introduction

Flavonoids are a group of phenolic compounds that are widely distributed in the plant kingdom and contain more than 6000 recognized members (Yu et al. 2016). These are also well known for their diverse health benefits. Isoflavones are a large and distinct subclass of flavonoids that includes a class of plant-derived phytoestrogen compounds with estrogenic activity (Messina 2016). The physiological and pharmacological function of isoflavones has been recognized around the globe. Isoflavones are found in large quantities in soybeans, and many types of vegetables, grains, and legumes contain small amounts (Gacek 2014). Isoflavones are found in soybeans as glycosides, which bind to sugar molecules. The fermentation of soybeans or their derivatives allows the isoflavone glycoside to release sugar molecules, resulting in aglycone isoflavone (Fayed 2015). Soy isoflavone glycosides contain genistin, daidzin, and glycitin, and in addition, the aglycones are genistein, daidzein, and glycitein (Islam et al. 2014). Growing interest has been shown in dietary isoflavones due to their likely contribution to the health benefits of legume-rich diets. Genistin (4′, 5, 7-Trihydroxyisoflavone 7-glucoside) is an important isoflavone compound commonly available in agriculturally important legumes plants that are native to East Asia, Southeast Asia, and some Pacific islands (Lee et al. 2011; Wang et al. 2019). Examples include soy, kudzu, lentils, peanut, green peas, chickpeas, and alfalfa which presented in Table 1. It has a wide range of pharmacological and bio-ecological roles as a standardized compound or crude extract. The biological constituent of genistin help to alleviate numerous health conditions such as cancers (Phromnoi et al. 2009; Hamdy et al. 2012; Zhu et al. 2018), heart diseases (Ho et al. 2002; Ko et al. 2009; Gu et al. 2016), neuronal diseases (Zhao et al. 2002; Nakazawa and Ohno 2003; Bhatt et al. 2018), hepatic diseases (Zhao et al. 2006; Kim et al. 2015; Chao et al. 2019), oxidative disorders (Chung et al. 2006; Quan et al. 2009), microbial diseases (Greiner et al. 2001; Chin et al. 2012), metabolic diseases (obesity) (Kojima et al. 2002; Choi et al.

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Table 1 Sources of genistin and standardized methods

Sources	Standardized methods	References
Glycine max (Soybean)	LC–MS, GC–MS, NMR, HPLC, and HSCCC	Du et al. (2001), Ho et al. (2002), Duke et al. (2003), Rostagno et al. (2003), Klejdus et al. (2005a, b), Setchell et al. (2005), Sepehr et al. (2006), Yang et al. (2006), Lee et al. (2007), Tsai et al. (2007), Carrara et al. (2009), Caligiani et al. (2010) and Maggioni et al. (2013)
Pueraria lobata (Kudzu)	CC, TLC, and HPLC	Boue et al. (2003), Cherdshewasart et al. (2007), Sun et al. (2008), Yuan et al. (2009), Zhang et al. (2009), Li et al. (2010), Zhao et al. (2011), Jin et al. (2012) and Mun and Mun (2015)
Fructus Sophorae	LC–MS/MS	Chang et al. (2012)
Spanish pulses	LC	Delgado-Zamarreno et al. (2012)
Secale cereale, Dactylis glomerata, and *Pinus silvestris*	HPLC	Hellstrom and Muntzing (2012)
Stephania venosa	HPLC	Gomuttapong et al. (2012)
Pyrococcus furiosus	HTC	Yeom et al. (2012)
Glycine max (Soy drink)	CZE–ESI–MS	Bustamante-Rangel et al. (2012)
Glycine max *Prunus amygdalus*	HPLC	Park et al. (2012)
Trifolium pratense	HPLC	Kasparova et al. (2012)
Flemingia macrophylla	HPLC	Wang et al. (2012)
Glycine soja	HPLC	Zhou et al. (2011)
Moghania philippinensis	HPLC	Meng et al. (2011)
Huangqi Gegen decoction	HPLC	Wang et al. (2010)
Pueraria candollei	HPLC	Pongkitwitoon et al. (2010)
Radix Puerariae	HPLC	Chen et al. (2010)
Glycine max (Black soybean)	HPLC	Hu et al. (2010)
Glycine max (Germinated soybeans)	HPLC	Shi et al. (2010)
Pueraria mirifica	HPLC	Cherdshewasart and Sriwatcharakul (2007) and Cherdshewasart et al. (2007)
Graptopetalum paraguayense	HPLC	Kao et al. (2010)
Flos perariae (Gehua)	RPLC	Zhang et al. (2010)
Thermotoga maritima	HPLC	Xue et al. (2009)
Pistacia vera	HPLC	Ballistreri et al. (2009)
Millettia nitida	NMR	Cheng et al. (2009)
Radix puerariae, Pueraria lobata, and *Pueraria thomsonii*	HPLC–DAD	Christopoulos et al. (1991)
Black soybeans and black soybean koji	HPLC	Chiou and Cheng (2001) and Huang and Chou 2009)
Sophora japonica	NMR, HPLC, CE-ED	Chu et al. (2005), Kim and Yun-Choi (2008) and Tang et al. (2008)
Trifolium pratense, *Iresine herbstii,* and *Ononis spinosa*	HPLC	Klejdus et al. (2007)
Semen sojae	HPLC	Qu et al. (2007)
Radix Puerariae	HPLC	Sibao et al. (2007)
Pueraria montana	HPLC	Kirakosyan et al. (2006)
Pueraria thunbergiana	HPLC	Son et al. (2019)
Tofu (soy milk)	HPLC	Grun et al. (2001)
Kudzu root	HPLC	Boue et al. (2003)
Pterospartum tridentatum	HPLC	Vitor et al. (2004)
Huaijiao pill	HPLC	Bian et al. (2005)
Arabidopsis thaliana	HPLC–MS	Lapcik et al. (2006)

HPLC high-performance liquid chromatography, *NMR* nuclear magnetic resonance, *LC–MS* liquid chromatography-mass spectrometry, *GC* gas chromatography, *CZE–ESI–MS/MS* CZE-electrospray ionization-tandem mass spectrometry, *TLC* thin-layer Chromatography, *CZE-ESI–MS* capillary zone electrophoresis coupled with electrospray ionization mass spectrometry, *CE-ED* capillary electrophoresis with electrochemical detection

2007b), and osteoporosis (Li et al. 2005; Wong and Rabie 2010). The different pharmacological effects of genistin are therefore summarized by its basic and molecular mechanism of action (Table 2). Genistin has become more important as a food additive and a dietary supplement because of its various biological characteristics, such as antioxidant activity (Andres et al. 2015). Antioxidants are constituents of natural flavanones that defend cells from oxidative damage caused by free radicals generated by oxidation in normal metabolism (Akanda et al. 2019). Like genistein, genistin is a phytoestrogen, which includes 17-μs-estradiol and is structurally comparable to natural and synthetic estrogens (Zaheer and Humayoun Akhtar 2017). Phytoestrogens play a significant role in the prevention of cancer, heart disease and osteoporosis (Mishra et al. 2003). According to the literature, genistin is a biologically active and well-defined isoflavone, and the latest evidence supports their beneficial impacts. In this review, we discuss the biological effects of standardized or natural genistin compounds on human health and the progression of new related remedies.

Basic pharmacokinetics of genistin

Pharmacokinetics is devoted to determining the fate of drugs given to a living organism, including the method of absorption, distribution, metabolism, and excretion (Rizk et al. 2017). A drug's pharmacokinetics depends on variables related to the patient and the chemical properties of the drug. Some patient-related factors may predict pharmacokinetic parameters in populations, such as age, sex, renal function, and genetic structure (Benedetti et al. 2009). Genistin is rapidly absorbed after oral intake and is metabolized by the gut microflora (Setchell et al. 2005). Before absorption into the systemic circulation, most genistein is conjugated with glucuronic acid and excreted in the bile to enter intestinal enterocytes and hepatic circulation. Therefore, the bioavailability of genistin is very limited and less than that of genistein. Genistin excreted from the body with a terminal half-life of 7–8 h (Setchell et al. 2005). Genistin is easily transformed into its aglycone form when ingested along with the diet and hydrolyzed by removing genistein from the covalently bound water. Genistin is the form of the compound that is produced in the intestine and is responsible for the biological processes of isoflavones. It was later discovered that enzymes in the small intestine and liver of humans are also capable of converting isoflavone (Szeja et al. 2017). In fact, hydrolysis starts very rapidly in the digestive system after the ingestion of genistin. The transformation begins in the mouth and then continues in the small intestine. After intestinal absorption, circulating genistin is primarily eliminated by the kidneys through urinary excretion (Krizova et al. 2019). Figure 1 shows the schematic diagram of genistin pharmacokinetics.

The general health benefits of genistin

Anti-cancer effects

Cancer is one of the leading causes of death worldwide and is responsible for more than 8 million deaths per year (Arnold et al. 2017). Cancers have been treated with a variety of medicines, including chemotherapy, hormone therapy, radiation, surgery, immunotherapy, and targeted therapy (Siegel et al. 2016). Although there are different therapeutic modalities available, it is crucial to define the most efficient therapy. It has been suggested that isoflavones reduce the risk of cancers caused by hormones mediated breast cancer and colon cancer. A number of investigations have consistently demonstrated that genistin has anticancer functions. Soy isoflavones are structurally comparable to endogenous estrogens, and the suggestion was made to help safeguard against hormone-dependent cancers. Soybean contains the genistin compound (Fukutake et al. 1996). An in vitro study of the human invasive breast carcinoma MDA-MB-231 cells revealed that genistin inhibited the concentration-dependent activity of matrix metalloproteinase-3 (MMP-3) and cell invasion (Phromnoi et al. 2009). Combination therapies of genistein plus genistin, genistein plus beta-sitosterol, and beta-sitosterol plus genistin inhibit the invasion and migration of breast cancer cells and have shown anti-cancer activity through the regulation of the phosphatidylinositol-3-kinase/mammalian target of rapamycin (PI3K/Akt/mTOR) pathways (Zhu et al. 2018). Another in vivo study using a rat model found that 12-dimethylbenz (a) anthracene (DMBA)-induced breast cancer and elevated markers of tumorigenicity, endocrine derangement, and oxidative stress. However, 3 months of treatment with genistin (1200 mg/kg diet) improved the levels of antioxidant defense with high-potential chemopreventive activity (Hamdy et al. 2012). A mixture of genistin and ipriflavone is also efficient in suppressing methyl nitrosourea-induced mammary tumorigenesis (Hooshmand et al. 2008). Moreover, genistin inhibited the proliferation of human ovarian cancer SK-OV-3 cells by interrupting the cell cycle in either the Gap 1 (G1) or G2/M phase and inducing apoptosis (Choi et al. 2007a). Genistin has shown protective effects against ultra-violate (UV)-induced pBR322 DNA damage and markedly decreased the vitality of M14 cells (Russo et al. 2006). Furthermore, it reduced the proliferation of SCC-9 human oral squamous carcinoma cells (Browning et al. 2005). Genistin treatment decreased the final weights of bladder tumors by 56% through the induction of tumor cell apoptosis and the reduction of angiogenesis of 253J B-V tumors in an orthotopic

Table 2 The health-promoting effects of genistin and the basic mechanism of action

Health disorders	Dose and disease models	The basic mechanism of action	References
Anti-cancer	Treatment of genistin with EC_{50} 72.82 ± 2.66 µM and 127.82 ± 4.70 µM in MCF-7 and MDA-MB-231 cells respectively	Reduced invasion and migration of MDA-MB-231 cells and PI3K/Akt/mTOR pathway regulation	Zhu et al. (2018)
	1 to 100 µM of genistin for 24 and 48 h in ovarian cancer cells (SK-OV-3)	By interrupting the cycle of cells in both phases G1 and G2/M and inducing apoptosis	Choi et al. (2007a)
	253 J B-V tumors in an orthotopic tumor model	Down-regulation of expression of NF-kB in tumor tissues and decrease of insulin-like growth factor-I (IGF-1) levels	Singh et al. (2006)
	Estrogen-stimulated gene expression of the uteri in ovariectomized mice model	Through decreased the levels of estradiol-17 beta (E2)-induced mRNAs expressions of c-jun, IL-1, and TNF-α	Lian et al. (2004)
Anti-osteoporosis	5.9% genistin used in an ovariectomized rat model	By decreasing the total and high-density lipoprotein (HDL) cholesterols and triglyceride level	Hidaka et al. (2003)
	Genistin 1×10^{-8}, 5×10^{-7}, 1×10^{-6}, 5×10^{-6} mol/L in primary mouse bone MSC and osteoblasts	Modulation of mesenchymal stem cells (MSCs) differentiation and inhibition of osteoblast adipocyte transdifferentiation	Li et al. (2005)
	In New Zealand White rabbits	By increasing the development of new bone	Wong and Rabie (2010)
Cardioprotective	20, 40, and 60 mg/kg body weight of genistin in the rat model of myocardial ischemia–reperfusion injury	Ameliorate the IL-6, IL-8, IL-10, and TNF-α levels via the suppression of the P2X7/NF-κB pathways	Gu et al. (2016)
	100 µM of genistin in vascular smooth muscle cells	Genistin directly inhibited the Kv current and regardless of protein tyrosine kinase (PTK) inhibition	Ko et al. (2009)
	Genistin 3.5 × 10–2 g/L in isolated rat carotid arteries	Causes concentration-dependent vascular relaxation	Ho et al. (2002)
Neuroprotective	Genistin 62.38 µg/mL in vitro and nutraceutical that contain genistin (0.5 g/200 g) and (1 g/200 g) in Alzheimer's disease model of male albino Wistar rats	By increasing the activity of AChE and by reducing both the activity of glutathione and catalase	Bhatt et al. (2018)
	Genistin (100 M)	Through non-genomic processes, human neuronal acetylcholine receptors blocked	Nakazawa and Ohno (2003)
	Treatment of genistin (10, 100 and 1000 ng/mL) in neuron culture cells	By reduced the LDH release	Zhao et al. (2002)
Antioxidative	Genistin 0.1 mM (MTs gene) and 0.025, 0.05, and 0.1 mM (G6PD gene) in HepG2 cells	Up-regulated antioxidant genes (MTs) such as MT1A, MT2A, MT1E, and MT1X, and G6PD through MTF-1 induction	Chung et al. (2006)
	Genistin (IC_{50} 1.3–9.3 µM) in primary cultured rat cortical microglia	Through the inhibition of LPS-induced NO production	Yuan et al. (2009)
	Genistin (42%) as compared to the control	Potent peroxynitrite scavengers, preventing the nitration of tyrosine	Lai and Yen (2002)
Anti-apoptotic	Concentrations of genistin 5–50 µM for 24 h in RGC-5 cells	By reducing p42 and p90RSK phosphorylation and caspase activation and ROS generation	Ondricek et al. (2012)
Anti-obesity	In Sprague Dawley rats	By considerably inhibiting the activity of pancreatic lipase	Choi et al. (2007b)
	8 mg genistin/d/100 g body weight for 12 days	Through lipid synthesis suppression	Kojima et al. (2002)

Table 2 (continued)

Health disorders	Dose and disease models	The basic mechanism of action	References
Hepatoprotective	50% *Graptopetalum paraguayense* extracts contained genistin 0.25 g/100 g BW	Through ameliorating serum aspartate transaminase (AST), alanine aminotransferase (ALT), LDH, glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GPx), and vitamin C, E	Chao et al. (2019)
	Genistin in 3.2 or 32 mg/kg daily doses in male rats for 3 days	Suppressing LPS-induced TNF-α, IL-1β, and IL-6 in both the liver and the sera	Zhao et al. (2006)
	Genistin treatment in HepG2 cells and in the rat liver	Through decreasing the ROS that related to downregulation of NADPH oxidase 4 (NOX4) and the up-regulation of SOD, CAT, and GST level	Kim et al. (2015)
Miscellaneous	Soybean seeds and soybean seed coats with hypocotyls extraxt contain isoflavones eg. genistin (200, 400, 800, and 1600 μg/mL) in U-937 cells	By the activation of receptors activated by PPAR	Carrara et al. (2009)
	Isoflavones contain genistin (5 mg) in mice orally for 4 days	A significant reduction of TNF-α in serum level	Hasumuma et al. (2007)
	Genistin (100 μM) in inactivated macrophage	Downregulation of LPS-induced COX-2 expression and mPGES-1 expression	Hamalainen et al. (2011)
	Genistin flavonoid 13.9, 20.1 and 26.8 μM in RAW264.7 cells	Through altering of LPS-induced NO production	Kim et al. (2005)

tumor model in mice (Singh et al. 2006). It also inhibited the proliferation of liver and colon carcinomas and myosarcoma cells in a study in vitro (Bayazit 2004). Dietary supplements of genistin with soy phytochemical concentrate (SPC) containing diet significantly inhibited the tumor growth by 57% and associated with reduced tumor angiogenesis and enhanced tumor cell apoptosis in LNCaP human prostate tumor in mice (Zhou et al. 2002). Genistin isolated from a PCC70 soybean fraction demonstrated a broad variety of growth suppression of HT-29 human colon cancer cells (Plewa et al. 2001). Soybean isoflavone containing genistin markedly inhibited the expression of the estrogen-stimulated gene in the mouse uteri and may stop endometrial carcinogenesis related to estrogen (Lian et al. 2004). Another study showed that 0.1% dietary supplements of genistin for 40 weeks produced anti-cancer effects in the early stages of prostate cancer progression induced by 10 biweekly subcutaneous injections of 3,2′-dimethyl-4-aminobiphenyl (DMAB) in male F344 rats (Kato et al. 2000). The basic mechanism of anti-cancer effects of genistin presented in Fig. 2.

Anti-osteoporosis and post-menopausal symptoms effects

There is a direct correlation between the lack of estrogen in the periods of perimenopause and menopause and the development of osteoporosis (Ji and Yu 2015). In aged women, the key reason for osteoporosis is the deterioration of the estrogen hormone in the body. The estrogen deficiency that accompanies menopause plays the main role in osteoporosis in women, which may result in debilitating fractures (Kelly et al. 2019). Isoflavones are structurally comparable to estrogen, bind to estrogen receptors, and influence estrogen-mediated gene products (Kuiper et al. 1998). Soy isoflavones have been extensively investigated in maintaining bone substance for its effects on bone health and in combating osteoporosis by improving bone strength in postmenopausal females (Lanou 2011). Osteoporosis is a chronic disorder of the bones that reduces bone density and bone quality, which leads to decreased bone strength and increased risk of bone fracture (Nih Consensus Development Panel on Osteoporosis Prevention and Therapy 2001). Several studies have reviewed the impacts on osteoporosis and menopausal symptoms of soy isoflavone or supplements and phytoestrogens. Soybean product fujiflavone P40 and *Sophora japonica,* which containing genistin, act as an anti-osteoporotic agent in the ovariectomized rat model (Hidaka et al. 2003; Abdallah et al. 2014). Another study has shown that bone loss in ovariectomized rats was substantially prevented by 4 weeks of oral administration of genistin (50 mg/kg/day) (Uesugi et al. 2001). Moreover, 50 days of treatment with a combination of genistin-rich isoflavones and fructooligosaccharides in the diet revealed a greater effect in preventing a bone loss

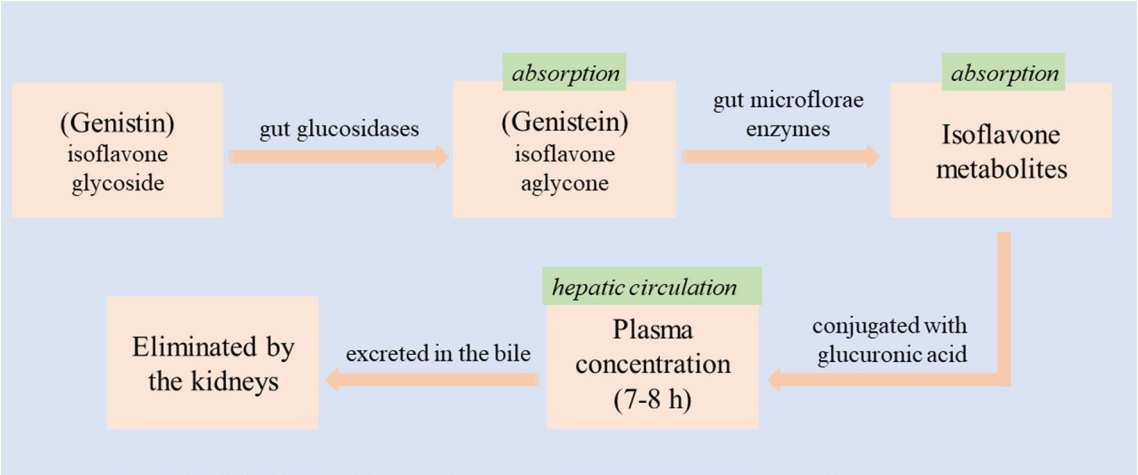

Fig. 1 Pharmacokinetics of genistin. Genistin is rapidly absorbed after oral intake and is metabolized by the gut microflora. Then, it conjugated with glucuronic acid and excreted in the bile to enter intestinal enterocytes and hepatic circulation. The maximum plasma concentrations are reported at approximately 7–8 h for genistin and aglycone. After intestinal absorption, circulating genistin is primarily eliminated by the kidneys through urinary excretion

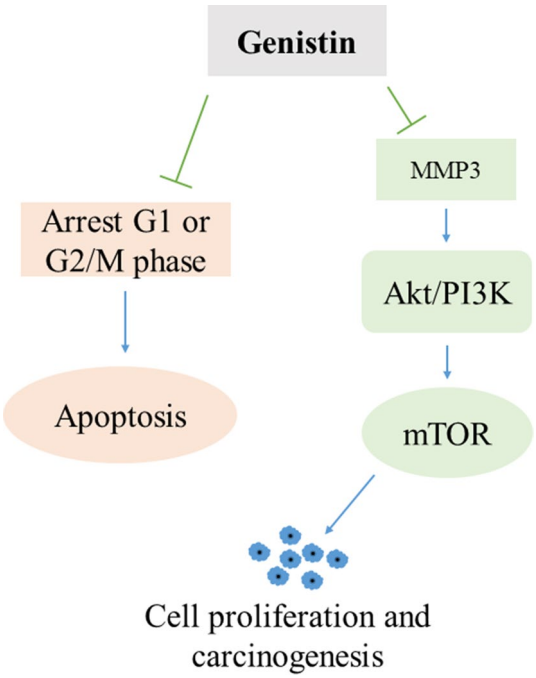

Fig. 2 Mechanism of anti-cancer effects of genistin. Genistin inhibited the invasion and migration of cancer cells through the regulation of the PI3K/Akt/mTOR pathways. Moreover, inhibited the proliferation of cancer cells by interrupting the cell cycle in either the Gap 1 (G1) or G2/M phase and inducing apoptosis

than only a genistin-rich isoflavone diet in Sprague–Dawley (SD) rats (Hooshmand et al. 2010). Genistin stimulates the proliferation of osteoblasts and bone marrow stromal cells, and it also helps in preventing the development of osteonecrosis (Li et al. 2005). Permanent cessation of menstruation resulting in the loss of ovarian follicle growth is known as menopause (Spinelli 2004). The common postmenopausal symptoms are sleeplessness, sexual dysfunction, depression, osteoporosis, urogenital atrophy, and hot flashes (Dalal and Agarwal 2015). Hormone therapy with estrogen alone or combined with progestogen is generally favored for the treatment of postmenopausal symptoms. One study revealed that pollen extract containing genistin could be used as a non-estrogenic substitute for hormone therapy in women with menopausal symptoms (Hellstrom and Muntzing 2012). Another study showed that isoflavone-containing genistin supplements ameliorate menopausal symptoms, perhaps through lipid metabolism alteration or by antiestrogen action (Reiter et al. 2009). Moreover, 12 weeks of treatment with isoflavones containing genistin significantly decreased menopause symptom scores with marked improvement in urogenital symptoms compared to a placebo in surgically menopausal women (Mittal et al. 2011). The basic mechanism of anti-osteoporosis effects of genistin presented in Fig. 3.

Cardioprotective effects

Phytoestrogens have gained considerable attention in the sense of cardiovascular disease risk factors because of their potential role (Sacks et al. 2006). Cardiovascular diseases are heart and blood disorders that include coronary heart disease, ischemic stroke, myocardial infarction, rheumatic heart disease, and other conditions that are the world's leading cause of death and are a significant obstacle to sustainable human development (Clark 2013). Epidemiological data show that many of the key risk variables associated with cardiac diseases are of environmental and biological origin

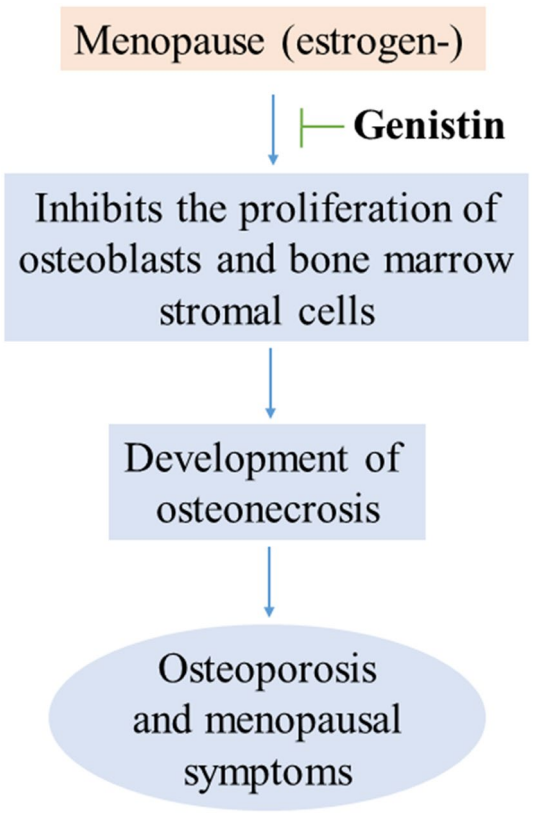

Fig. 3 Mechanism of anti-osteoporosis effects of genistin. Genistin stimulates the proliferation of osteoblasts and bone marrow stromal cells, and it also helps in preventing the development of osteonecrosis

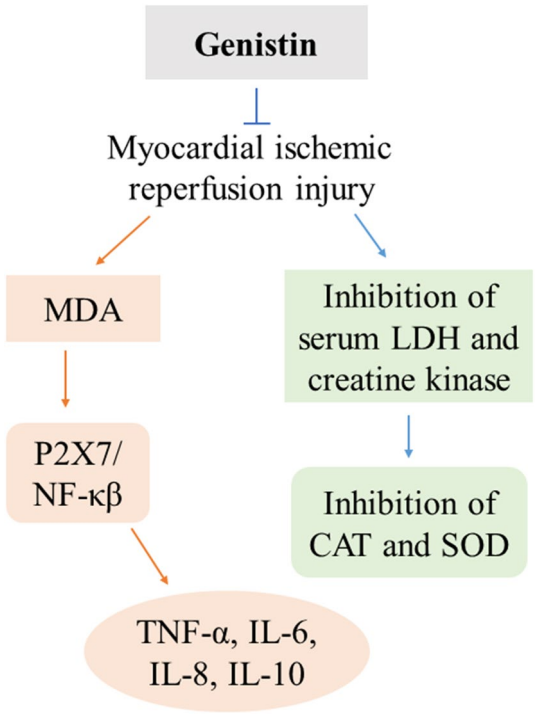

Fig. 4 Mechanism of cardioprotective effects of genistin. Genistin ameliorates the proinflammatory cytokines IL-6, IL-8, IL-10, and TNF-α levels through blocking of P2X7/NF-kβ pathways. In addition, genistin decreased creatine kinase and LDH levels in coronary flow. Also, it enhanced the CAT, and SOD activities

(Greiser et al. 2005). Clinical complications associated with cardiac disease are mostly defined by acute occlusion of blood clotting and may lead to myocardial infarction. Genistin pretreatment has been shown to have protective effects in myocardial ischemia/reperfusion injuries in rats through antioxidant and anti-inflammatory activities by improving mitochondrial morphology and oxidation systems. Furthermore, suppression of interleukin (IL-6, IL-8, IL-10), and tumor necrosis factor-alpha (TNF-α) cytokine levels through the P2X7/nuclear factor-kappa B (NF-κB) pathways (Gu et al. 2016). It has also been found that the amplitude of the voltage-dependent K + (Kv) current was inhibited by genistin in freshly isolated coronary arterial smooth muscle cells from rabbits (Ko et al. 2009). Also, genistin treatment helps to a relaxation of rat carotid artery rings (Ho et al. 2002). The basic mechanism of the cardioprotective effects of genistin presented in Fig. 4.

Neuroprotective effects

There have been various studies on the impact soy isoflavones have on neurological dysfunction. Neurological disorders are diseases of the brain, spine, and nerves. The most common neurological diseases include epilepsy, Parkinson's disease, stroke, brain tumor, dementia, and Alzheimer's disease (Ishwarya and Narendhirakannan 2016). Alzheimer's disease is a neurodegenerative abnormality defined by the presence of amyloid plaques in the form of the fibrillary protein (Serrano-Pozo et al. 2011; Bhatt et al. 2017). Soy estrogens play an important role to improve brain health. Estradiol also plays the main role in the neurobiology of aging because endocrine and neural senescence overlap in time and are mechanistically intertwined in complex feedback loops (Morrison et al. 2006). Genistin reversed colchicine-induced behavioral and neurochemical changes in rats via effective antioxidant activity. Moreover, genistin treatment moderately increased the acetylcholinesterase (AChE) activity and in contrast reduced both glutathione and catalase activity. This suggests that it could have beneficial impacts on cognitive defects related to Alzheimer's disease (Bhatt et al. 2018). Genistin blocks the recombinant human neuronal nicotinic receptor, which can result in neuronal regulation by continuously influencing the function of acetylcholine receptors or channels (Nakazawa and Ohno 2003). A new in-vitro study showed that genistin has a modest degree of neuroprotective efficacy through the reduction

of glutamate-induced lactate dehydrogenase (LDH) levels (Zhao et al. 2002).

Anti-oxidative effects

Oxidative stress leading to cell death and causing a variety of illnesses, including cancer, heart disease, cataracts and congestive disorders (Liu et al. 2018). Genistin shows antioxidant properties by scavenging and decreasing the activities of free radicals (Jung et al. 2002; Wang et al. 2012). Malondialdehyde (MDA) is considered an important biomarker of oxidative damage to lipids. High levels of MDA in plasma indicate increased lipid peroxidation. Genistin has the ability to reduce MDA in the plasma (Bebrevska et al. 2010). The activation of microglial cells is associated with neurodegeneration and control of alcoholic toxicities (Crews et al. 2006), resulting in the delivery of nitric oxide (NO) and numerous proinflammatory cytokines (Kreutzberg 1996). Genistin substantially decreases release of LPS-induced NO in cortical microglia of primary cultured rats (Yuan et al. 2009). Lipid peroxidation is implicated in a number of diseases. Lipid peroxidation can cause cellular dysfunction and tissue injury by changing the structure and function of vital membrane proteins (Ramana et al. 2017). One study showed that genistin significantly reduces the lipid peroxide levels in liver plasma in Goto-Kakizaki (GK) rat (Quan et al. 2009). Indirectly, Genistin can display antioxidant properties by triggering antioxidative proteins. One of the most effective antioxidative proteins is metallothionein (MT), which can prevent oxidative stress and protect cells in vitro (Abel and de Ruiter 1989; Lazo et al. 1995). Genistin induces MT expression via the activity of metal regulatory transcription factor 1 (MTF-1) (Chung et al. 2006). The effective oxidant peroxynitrite is formed by the reaction of NO and superoxide and can induce oxidation of low-density lipoproteins (LDL). This leads to an increase in the risk of different diseases like atherosclerosis. Genistin can effectively scavenge peroxynitrite, leading to a reduced risk of cardiovascular diseases and chronic inflammatory diseases (Lai and Yen 2002). Another study showed that genistin treatment has a protective effect against hydrogen peroxide (H_2O_2)-induced oxidative injury in cultured human endothelial cells (Vitor et al. 2004).

Anti-apoptosis effects

Apoptosis is a physiological process that eliminates damaged cells in multi-cellular organisms and allows ordinary cell renovation by preserving ordinary growth and homeostasis of tissue (Green and Kroemer 2005). Cancer and many other disorders such as neuronal degeneration and diabetes occur through imbalances and aberrant mechanisms in the apoptotic pathway (Indran et al. 2011). Apoptosis also serves as a protective mechanism, as in the case of immune reactions or cells suffering from diseases or harmful agents (Norbury and Hickson 2001). In an in vitro study, genistin treatment rescued iodoacetic acid-induced cell death and reduced caspase activation, reactive oxygen species (ROS) production, and the phosphorylation of p42 and p90RSK in retinal ganglion cells (RGC-5) (Ondricek et al. 2012).

Anti-obesity/hypolipidemic effects

Excess body adiposity is a major nutritional disorder caused by an imbalance between energy intake and uptake (Loos and Rankinen 2005). Obesity has many adverse effects, such as diabetes, cancer, heart disease, and hypertension (MacDougald and Lane 1995; Cowherd et al. 1999). The intestine cannot absorb alimentary lipids directly unless triglycerides are hydrolyzed into fatty acids and 2-monoacylglycerol by the action of the pancreatic lipase enzyme. Genistin can be used as an effective treatment for obesity because it inhibits pancreatic lipase enzyme activity, which encourages more dietary lipid excretion without absorption and also suppresses adipocyte differentiation (Choi et al. 2007b). Enormous proteins are excreted through the urine due to glomerulonephritis, resulting in hypoalbuminemia (Cameron 1990), as well as secondary hyperlipidemia, which is initiated by increased lipid and lipoprotein synthesis by the liver (Appel and Appel 1990). Genistin can reduce hyperlipidemia by suppressing hepatic lipid synthesis (Kojima et al. 2002). The basic mechanism of anti-obesity/hypolipidemic effects of genistin presented in Fig. 5.

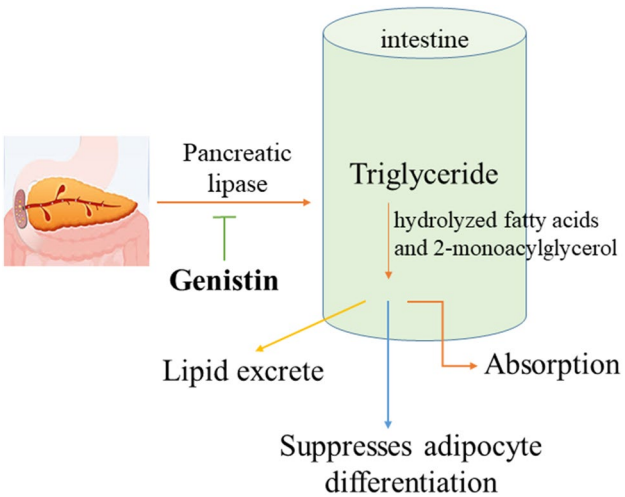

Fig. 5 Mechanism of anti-obesity/hypolipidemic effects of genistin. Genistin inhibited pancreatic lipase enzyme activity, which encourages more dietary lipid excretion without absorption and also suppresses adipocyte differentiation through the triglycerides hydrolyzed into fatty acids and 2-monoacylglycerol

Hepatoprotective effects

The liver is a vital organ in multiple essential activities, such as digestive and excretory functions, nutrient preservation, and toxic chemical neutralization. The liver can experience a number of abnormalities, including hepatic steatosis, fatty liver, hepatitis, fibrosis, hepatocarcinoma, and cirrhosis (Zhang et al. 2018). Toxic substances such as alcohol, xenobiotics, mycotoxin and lipopolysaccharides (LPS) are the major causes of live injury (Ingawale et al. 2014). Liver injury mediated by alcohol + carbon tetrachloride (CCl_4) can be eliminated by complementary and alternative treatment with genistin (Chao et al. 2019). Genistin can also guard against LPS-induced acute hepatic inflammation by suppressing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Zhao et al. 2006). Moreover, genistin can protect against oxidative stress in the liver induced by tert-butyl hydroperoxide by regulating ROS-related enzymes (Kim et al. 2015). The basic mechanism of hepatoprotective effects of genistin presented in Fig. 6.

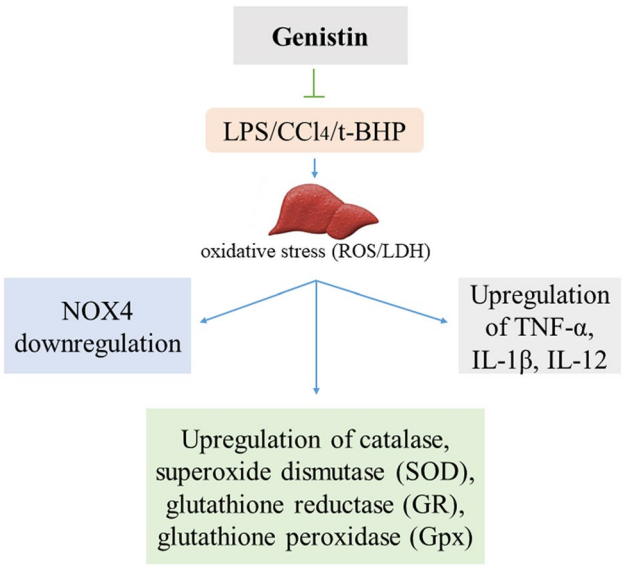

Fig. 6 Mechanism of hepatoprotective effects of genistin. Genistin suppressed the oxidative stress-mediated pro-inflammatory cytokines TNF-α, IL-1β, and IL-12 levels. Moreover, genistin can protect against oxidative stress in the liver via regulation of ROS-related enzymes such as NOX4, SOD, GR, and GPx levels

Anti-microbial effects

Resistance to antimicrobials has become a growing concern worldwide (Cushnie and Lamb 2005). Genistin-based flavonoids have antimicrobial activity (Panche et al. 2016). Flavonoids work through the inhibition of cytoplasmic membrane function, nucleic acid synthesis, and energy metabolism (Cushnie and Lamb 2005). Soybean fermentation broth (SFB) of genistin has reported effective antibacterial activity in vitro against *Salmonella typhimurium, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris,* and *Staphylococcus aureus.* It also has potent elimination effects on vancomycin-resistant *Enterococcus faecalis* in SD rats and the BALB/c mice (Chin et al. 2012). Genistein was supplied through the soy glycoside, genistin, which acts as an effective immune modulator that enhances the elimination of systemic serum viruses and their growth of the bodies in pigs challenged with the porcine reproductive and respiratory syndrome virus (PRRSV) (Greiner et al. 2001).

Miscellaneous

An in vitro study of activated macrophages showed that genistin-containing isoflavones have anti-inflammatory effects (Hamalainen et al. 2011). Another in vivo study on mice showed that isoflavones containing genistin reduced the LPS-induced TNF-α in the serum (Hasumuma et al. 2007). Moreover, genistin inhibited LPS-induced NO production and inducible NO synthase (iNOS) expression in RAW264.7 cells (Kim et al. 2005). Perinatal exposure of male rats to dietary genistin influenced Leydig cell differentiation and played a significant part in the function of the testis (Sherrill et al. 2010). An in vivo study on rabbits showed that intravitreal injection of 40 µg of genistin can efficiently decrease traumatic proliferative vitreoretinopathy (You and Jiang 2010). Moreover, Pueraria isoflavonoids containing genistin show antipyretic, analgesic, and muscle-relaxant activities in an LPS-induced mouse model (Yasuda et al. 2005). Treatment with a kudzu root extract containing genistin reduced alcohol intake and alcohol withdrawal symptoms in an alcohol-preferring rat model (Benlhabib et al. 2004).

Summary and future research directions

Genistin is an isoflavone with a multitude of health benefits. Several experimental studies have highlighted that genistin has a significant protective impact on specific disease conditions of particular target organs. This concise review may assist in comprehending the health advantages of plant-containing genistin and help to develop this isoflavone as a promising therapeutic agent for the prevention and treatment of health disorders. Nevertheless, more standardization and documentation are needed for clinical trial data of soy isoflavones like genistin in order to further validate the claims of health benefits.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Abdallah HM, Al-Abd AM, Asaad GF, Abdel-Naim AB, El-halawany AM (2014) Isolation of antiosteoporotic compounds from seeds of *Sophora japonica*. PLoS ONE 9:e98559. https://doi.org/10.1371/journal.pone.0098559

Abel J, de Ruiter N (1989) Inhibition of hydroxyl-radical-generated DNA degradation by metallothionein. Toxicol Lett 47:191–196. https://doi.org/10.1016/0378-4274(89)90075-1

Akanda MR, Uddin MN, Kim IS, Ahn D, Tae HJ, Park BY (2019) The biological and pharmacological roles of polyphenol flavonoid tilianin. Eur J Pharmacol 842:291–297. https://doi.org/10.1016/j.ejphar.2018.10.044

Andres S, Hansen U, Niemann B, Palavinskas R, Lampen A (2015) Determination of the isoflavone composition and estrogenic activity of commercial dietary supplements based on soy or red clover. Food Funct 6:2017–2025. https://doi.org/10.1039/c5fo00308c

Appel GB, Appel AS (1990) Lipid-lowering agents in proteinuric diseases. Am J Nephrol 10(Suppl 1):110–115. https://doi.org/10.1159/000168204

Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F (2017) Global patterns and trends in colorectal cancer incidence and mortality. Gut 66:683–691. https://doi.org/10.1136/gutjnl-2015-310912

Ballistreri G, Arena E, Fallico B (2009) Influence of ripeness and drying process on the polyphenols and tocopherols of *Pistacia vera* L. Molecules 14:4358–4369. https://doi.org/10.3390/molecules14114358

Bayazit V (2004) Cytotoxic effects of some animal and vegetable extracts and some chemicals on liver and colon carcinoma and myosarcoma. Saudi Med J 25:156–163

Bebrevska L, Foubert K, Hermans N, Chatterjee S, Van Marck E, De Meyer G, Vlietinck A, Pieters L, Apers S (2010) In vivo antioxidative activity of a quantified *Pueraria lobata* root extract. J Ethnopharmacol 127:112–117. https://doi.org/10.1016/j.jep.2009.09.039

Benedetti MS, Whomsley R, Poggesi I, Cawello W, Mathy FX, Delporte ML, Papeleu P, Watelet JB (2009) Drug metabolism and pharmacokinetics. Drug Metab Rev 41:344–390. https://doi.org/10.1080/10837450902891295

Benlhabib E, Baker JI, Keyler DE, Singh AK (2004) Kudzu root extract suppresses voluntary alcohol intake and alcohol withdrawal symptoms in P rats receiving free access to water and alcohol. J Med Food 7:168–179. https://doi.org/10.1089/109662041224210

Bhatt PC, Pandey P, Panda BP, Anwar F, Kumar V (2017) Commentary: L-3-n-butylphthalide rescues hippocampal synaptic failure and attenuates neuropathology in aged APP/PS1 mouse model of Alzheimer's disease. Front Aging Neurosci 9:4. https://doi.org/10.3389/fnagi.2017.00004

Bhatt PC, Pathak S, Kumar V, Panda BP (2018) Attenuation of neurobehavioral and neurochemical abnormalities in animal model of cognitive deficits of Alzheimer's disease by fermented soybean nanonutraceutical. Inflammopharmacology 26:105–118. https://doi.org/10.1007/s10787-017-0381-9

Bian QQ, Yang ZP, Liu JQ, Liu SM (2005) Simultaneous determination of the four effective components in Huaijiao pill by HPLC. Zhongguo Zhong Yao Za Zhi 30:1513–1515

Boue SM, Wiese TE, Nehls S, Burow ME, Elliott S, Carter-Wientjes CH, Shih BY, McLachlan JA, Cleveland TE (2003) Evaluation of the estrogenic effects of legume extracts containing phytoestrogens. J Agric Food Chem 51:2193–2199. https://doi.org/10.1021/jf021114s

Browning AM, Walle UK, Walle T (2005) Flavonoid glycosides inhibit oral cancer cell proliferation–role of cellular uptake and hydrolysis to the aglycones. J Pharm Pharmacol 57:1037–1042. https://doi.org/10.1211/0022357056514

Bustamante-Rangel M, Delgado-Zamarreno MM, Carabias-Martinez R, Dominguez-Alvarez J (2012) Analysis of isoflavones in soy drink by capillary zone electrophoresis coupled with electrospray ionization mass spectrometry. Anal Chim Acta 709:113–119. https://doi.org/10.1016/j.aca.2011.10.015

Caligiani A, Palla G, Maietti A, Cirlini M, Brandolini V (2010) 1H NMR fingerprinting of soybean extracts, with emphasis on identification and quantification of isoflavones. Nutrients 2:280–289. https://doi.org/10.3390/nu2030280

Cameron JS (1990) Proteinuria and progression in human glomerular diseases. Am J Nephrol 10(Suppl 1):81–87. https://doi.org/10.1159/000168199

Carrara VS, Amato AA, Neves FA, Bazotte RB, Mandarino JM, Nakamura CV, Filho BP, Cortez DA (2009) Effects of a methanolic fraction of soybean seeds on the transcriptional activity of peroxisome proliferator-activated receptors (PPAR). Braz J Med Biol Res 42:545–550. https://doi.org/10.1590/s0100-879x2009000600011

Chang L, Ren Y, Cao L, Sun Y, Sun Q, Sheng N, Yuan L, Zhi X, Zhang L (2012) Simultaneous determination and pharmacokinetic study of six flavonoids from *Fructus sophorae* extract in rat plasma by LC-MS/MS. J Chromatogr B Anal Technol Biomed Life Sci 904:59–64. https://doi.org/10.1016/j.jchromb.2012.07.015

Chao WW, Chen SJ, Peng HC, Liao JW, Chou ST (2019) Antioxidant activity of *Graptopetalum paraguayense* E. Walther leaf extract counteracts oxidative stress induced by ethanol and carbon tetrachloride co-induced hepatotoxicity in rats. Antioxidants (Basel). https://doi.org/10.3390/antiox8080251

Chen TR, Chen LA, Wei QK (2010) Evaluation of quality of Radix Puerariae herbal medicine by isoflavonoids. J Pharm Pharmacol 62:644–650. https://doi.org/10.1211/jpp/62.05.0013

Cheng J, Wang J, Liang H, Wang Y, Zhao Y (2009) Constituents of *Millettia nitida* var. hirsutissima. Zhongguo Zhong Yao Za Zhi 34:1921–1926

Cherdshewasart W, Sriwatcharakul S (2007) Major isoflavonoid contents of the 1-year-cultivated phytoestrogen-rich herb, *Pueraria*

mirifica. Biosci Biotechnol Biochem 71:2527–2533. https://doi.org/10.1271/bbb.70316
Cherdshewasart W, Subtang S, Dahlan W (2007) Major isoflavonoid contents of the phytoestrogen rich-herb *Pueraria mirifica* in comparison with *Pueraria lobata*. J Pharm Biomed Anal 43:428–434. https://doi.org/10.1016/j.jpba.2006.07.013
Chin YP, Tsui KC, Chen MC, Wang CY, Yang CY, Lin YL (2012) Bactericidal activity of soymilk fermentation broth by in vitro and animal models. J Med Food 15:520–526. https://doi.org/10.1089/jmf.2011.1918
Chiou RY, Cheng SL (2001) Isoflavone transformation during soybean koji preparation and subsequent miso fermentation supplemented with ethanol and NaCl. J Agric Food Chem 49:3656–3660. https://doi.org/10.1021/jf0015241
Choi EJ, Kim T, Lee MS (2007a) Pro-apoptotic effect and cytotoxicity of genistein and genistin in human ovarian cancer SK-OV-3 cells. Life Sci 80:1403–1408. https://doi.org/10.1016/j.lfs.2006.12.031
Choi I, Kim Y, Park Y, Seog H, Choi H (2007b) Anti-obesity activities of fermented soygerm isoflavones by *Bifidobacterium breve*. BioFactors 29:105–112
Christopoulos DC, Nicolaides AN, Belcaro G, Kalodiki E (1991) Venous hypertensive microangiopathy in relation to clinical severity and effect of elastic compression. J Dermatol Surg Oncol 17:809–813. https://doi.org/10.1111/j.1524-4725.1991.tb03264.x
Chu Q, Fu L, Wu T, Ye J (2005) Simultaneous determination of phytoestrogens in different medicinal parts of *Sophora japonica* L. by capillary electrophoresis with electrochemical detection. Biomed Chromatogr 19:149–154. https://doi.org/10.1002/bmc.431
Chung MJ, Kang AY, Lee KM, Oh E, Jun HJ, Kim SY, Auh JH, Moon TW, Lee SJ, Park KH (2006) Water-soluble genistin glycoside isoflavones up-regulate antioxidant metallothionein expression and scavenge free radicals. J Agric Food Chem 54:3819–3826. https://doi.org/10.1021/jf060510y
Clark H (2013) NCDs: a challenge to sustainable human development. Lancet 381:510–511. https://doi.org/10.1016/S0140-6736(13)60058-6
Cowherd RM, Lyle RE, McGehee RE Jr (1999) Molecular regulation of adipocyte differentiation. Semin Cell Dev Biol 10:3–10
Crews FT, Bechara R, Brown LA, Guidot DM, Mandrekar P, Oak S, Qin L, Szabo G, Wheeler M, Zou J (2006) Cytokines and alcohol. Alcohol Clin Exp Res 30:720–730. https://doi.org/10.1111/j.1530-0277.2006.00084.x
Cushnie TP, Lamb AJ (2005) Antimicrobial activity of flavonoids. Int J Antimicrob Agents 26:343–356
Dalal PK, Agarwal M (2015) Postmenopausal syndrome. Indian J Psychiatry 57:S222–S232. https://doi.org/10.4103/0019-5545.161483
Delgado-Zamarreno MM, Perez-Martin L, Bustamante-Rangel M, Carabias-Martinez R (2012) Pressurized liquid extraction as a sample preparation method for the analysis of isoflavones in pulses. Anal Bioanal Chem 404:361–366. https://doi.org/10.1007/s00216-012-5912-z
Du Q, Lib Z, Ito Y (2001) Preparative separation of isoflavone components in soybeans using high-speed counter-current chromatography. J Chromatogr A 923:271–274. https://doi.org/10.1016/s0021-9673(01)01031-7
Duke SO, Rimando AM, Pace PF, Reddy KN, Smeda RJ (2003) Isoflavone, glyphosate, and aminomethylphosphonic acid levels in seeds of glyphosate-treated, glyphosate-resistant soybean. J Agric Food Chem 51:340–344. https://doi.org/10.1021/jf025908i
Fayed AE (2015) Review article: health benefits of some physiologically active ingredients and their suitability as yoghurt fortifiers. J Food Sci Technol 52:2512–2521. https://doi.org/10.1007/s13197-014-1393-8
Fukutake M, Takahashi M, Ishida K, Kawamura H, Sugimura T, Wakabayashi K (1996) Quantification of genistein and genistin in soybeans and soybean products. Food Chem Toxicol 34:457–461. https://doi.org/10.1016/0278-6915(96)87355-8
Gacek M (2014) Soy and legume seeds as sources of isoflavones: selected individual determinants of their consumption in a group of perimenopausal women. Menopause Rev-Przeglad Menopauzalny 13:27–31. https://doi.org/10.5114/pm.2014.41081
Gomuttapong S, Pewphong R, Choeisiri S, Jaroenporn S, Malaivijitnond S (2012) Testing of the estrogenic activity and toxicity of *Stephania venosa* herb in ovariectomized rats. Toxicol Mech Methods 22:445–457. https://doi.org/10.3109/15376516.2012.668573
Green DR, Kroemer G (2005) Pharmacological manipulation of cell death: clinical applications in sight? J Clin Invest 115:2610–2617. https://doi.org/10.1172/JCI26321
Greiner LL, Stahly TS, Stabel TJ (2001) The effect of dietary soy genistein on pig growth and viral replication during a viral challenge. J Anim Sci 79:1272–1279. https://doi.org/10.2527/2001.7951272x
Greiser KH, Kluttig A, Schumann B, Kors JA, Swenne CA, Kuss O, Werdan K, Haerting J (2005) Cardiovascular disease, risk factors and heart rate variability in the elderly general population: design and objectives of the cardiovascular disease, living and ageing in Halle (CARLA) study. BMC Cardiovasc Disord 5:33. https://doi.org/10.1186/1471-2261-5-33
Grun IU, Adhikari K, Li C, Li Y, Lin B, Zhang J, Fernando LN (2001) Changes in the profile of genistein, daidzein, and their conjugates during thermal processing of tofu. J Agric Food Chem 49:2839–2843. https://doi.org/10.1021/jf010028+
Gu M, Zheng AB, Jin J, Cui Y, Zhang N, Che ZP, Wang Y, Zhan J, Tu WJ (2016) Cardioprotective effects of genistin in rat myocardial ischemia-reperfusion injury studies by regulation of P2X7/NF-kappaB pathway. Evid Based Complement Altern Med 2016:5381290. https://doi.org/10.1155/2016/5381290
Hamalainen M, Nieminen R, Asmawi MZ, Vuorela P, Vapaatalo H, Moilanen E (2011) Effects of flavonoids on prostaglandin E2 production and on COX-2 and mPGES-1 expressions in activated macrophages. Planta Med 77:1504–1511. https://doi.org/10.1055/s-0030-1270762
Hamdy SM, Latif AK, Drees EA, Soliman SM (2012) Prevention of rat breast cancer by genistin and selenium. Toxicol Ind Health 28:746–757. https://doi.org/10.1177/0748233711422732
Hasumuma R, Kawaguchi K, Kikuchi S, Sugiyama T, Kumazawa Y (2007) Effects of isoflavones and soybeans fermented with *Bacillus subtilis* on lipopolysaccharide-induced production of tumor necrosis factor-alpha and fibrinolysis in vivo. Immunopharmacol Immunotoxicol 29:323–333. https://doi.org/10.1080/08923970701513526
Hellstrom AC, Muntzing J (2012) The pollen extract femal—a nonestrogenic alternative to hormone therapy in women with menopausal symptoms. Menopause 19:825–829. https://doi.org/10.1097/gme.0b013e31824017bc
Hidaka S, Okamoto Y, Miyazaki K, Uesugi T (2003) Evaluation of a soybean product fujiflavone P40 as an antiosteoporotic agent in rats. Phytother Res 17:112–119. https://doi.org/10.1002/ptr.1047
Ho HM, Chen R, Huang Y, Chen ZY (2002) Vascular effects of a soy leaves (*Glycine max*) extract and kaempferol glycosides in isolated rat carotid arteries. Planta Med 68:487–491. https://doi.org/10.1055/s-2002-32545
Hooshmand S, Khalil DA, Murillo G, Singletary K, Kamath SK, Arjmandi BH (2008) The combination of genistin and ipriflavone prevents mammary tumorigenesis and modulates lipid profile. Clin Nutr 27:643–648. https://doi.org/10.1016/j.clnu.2008.04.012

Hooshmand S, Juma S, Arjmandi BH (2010) Combination of genistin and fructooligosaccharides prevents bone loss in ovarian hormone deficiency. J Med Food 13:320–325. https://doi.org/10.1089/jmf.2009.0059

Hu Y, Ge C, Yuan W, Zhu R, Zhang W, Du L, Xue J (2010) Characterization of fermented black soybean natto inoculated with *Bacillus natto* during fermentation. J Sci Food Agric 90:1194–1202. https://doi.org/10.1002/jsfa.3947

Huang RY, Chou CC (2009) Stability of isoflavone isomers in steamed black soybeans and black soybean koji stored under different conditions. J Agric Food Chem 57:1927–1932. https://doi.org/10.1021/jf803702x

Indran IR, Tufo G, Pervaiz S, Brenner C (2011) Recent advances in apoptosis, mitochondria and drug resistance in cancer cells. Biochim Biophys Acta 1807:735–745. https://doi.org/10.1016/j.bbabio.2011.03.010

Ingawale DK, Mandlik SK, Naik SR (2014) Models of hepatotoxicity and the underlying cellular, biochemical and immunological mechanism(s): a critical discussion. Environ Toxicol Pharmacol 37:118–133. https://doi.org/10.1016/j.etap.2013.08.015

Ishwarya M, Narendhirakannan RT (2016) The advances in neurobiology. Adv Neurobiol 12:293–306. https://doi.org/10.1007/978-3-319-28383-8_15

Islam MA, Punt A, Spenkelink B, Murk AJ, Rolaf van Leeuwen FX, Rietjens IM (2014) Conversion of major soy isoflavone glucosides and aglycones in in vitro intestinal models. Mol Nutr Food Res 58:503–515. https://doi.org/10.1002/mnfr.201300390

Ji MX, Yu Q (2015) Primary osteoporosis in postmenopausal women. Chronic Dis Transl Med 1:9–13. https://doi.org/10.1016/j.cdtm.2015.02.006

Jin SE, Son YK, Min BS, Jung HA, Choi JS (2012) Anti-inflammatory and antioxidant activities of constituents isolated from *Pueraria lobata* roots. Arch Pharm Res 35:823–837. https://doi.org/10.1007/s12272-012-0508-x

Jung HA, Kim AR, Chung HY, Choi JS (2002) In vitro antioxidant activity of some selected *Prunus* species in Korea. Arch Pharm Res 25:865–872

Kao TK, Ou YC, Raung SL, Chen WY, Yen YJ, Lai CY, Chou ST, Chen CJ (2010) Graptopetalum paraguayense E. Walther leaf extracts protect against brain injury in ischemic rats. Am J Chin Med 38:495–516. https://doi.org/10.1142/S0192415X10008019

Kasparova M, Siatka T, Klimesova V, Dusek J (2012) New synthetic pyridine derivate as potential elicitor in production of isoflavonoids and flavonoids in *Trifolium pratense* L. suspension culture. Sci World J 2012:746412. https://doi.org/10.1100/2012/746412

Kato K, Takahashi S, Cui L, Toda T, Suzuki S, Futakuchi M, Sugiura S, Shirai T (2000) Suppressive effects of dietary genistin and daidzin on rat prostate carcinogenesis. Jpn J Cancer Res 91:786–791. https://doi.org/10.1111/j.1349-7006.2000.tb01014.x

Kelly RR, McDonald LT, Jensen NR, Sidles SJ, LaRue AC (2019) Impacts of psychological stress on osteoporosis: clinical implications and treatment interactions. Front Psychiatry 10:200. https://doi.org/10.3389/fpsyt.2019.00200

Kim JM, Yun-Choi HS (2008) Anti-platelet effects of flavonoids and flavonoid-glycosides from *Sophora japonica*. Arch Pharm Res 31:886–890. https://doi.org/10.1007/s12272-001-1242-1

Kim AR, Cho JY, Zou Y, Choi JS, Chung HY (2005) Flavonoids differentially modulate nitric oxide production pathways in lipopolysaccharide-activated RAW264.7 cells. Arch Pharm Res 28:297–304. https://doi.org/10.1007/bf02977796

Kim EY, Hong KB, Suh HJ, Choi HS (2015) Protective effects of germinated and fermented soybean extract against tert-butyl hydroperoxide-induced hepatotoxicity in HepG2 cells and in rats. Food Funct 6:3512–3521. https://doi.org/10.1039/c5fo00785b

Kirakosyan A, Kaufman PB, Chang SC, Warber S, Bolling S, Vardapetyan H (2006) Regulation of isoflavone production in hydroponically grown *Pueraria montana* (kudzu) by cork pieces, XAD-4, and methyl jasmonate. Plant Cell Rep 25:1387–1391. https://doi.org/10.1007/s00299-006-0198-2

Klejdus B, Mikelova R, Petrlova J, Potesil D, Adam V, Stiborova M, Hodek P, Vacek J, Kizek R, Kuban V (2005a) Determination of isoflavones in soy bits by fast column high-performance liquid chromatography coupled with UV-visible diode-array detection. J Chromatogr A 1084:71–79. https://doi.org/10.1016/j.chroma.2005.05.070

Klejdus B, Mikelova R, Petrlova J, Potesil D, Adam V, Stiborova M, Hodek P, Vacek J, Kizek R, Kuban V (2005b) Evaluation of isoflavone aglycon and glycoside distribution in soy plants and soybeans by fast column high-performance liquid chromatography coupled with a diode-array detector. J Agric Food Chem 53:5848–5852. https://doi.org/10.1021/jf0502754

Klejdus B, Vacek J, Benesova L, Kopecky J, Lapcik O, Kuban V (2007) Rapid-resolution HPLC with spectrometric detection for the determination and identification of isoflavones in soy preparations and plant extracts. Anal Bioanal Chem 389:2277–2285. https://doi.org/10.1007/s00216-007-1606-3

Ko EA, Park WS, Son YK, Kim DH, Kim N, Kim HK, Choi TH, Jung ID, Park YM, Han J (2009) The effect of tyrosine kinase inhibitor genistein on voltage-dependent K+ channels in rabbit coronary arterial smooth muscle cells. Vascul Pharmacol 50:51–56. https://doi.org/10.1016/j.vph.2008.09.004

Kojima T, Uesugi T, Toda T, Miura Y, Yagasaki K (2002) Hypolipidemic action of the soybean isoflavones genistein and genistin in glomerulonephritic rats. Lipids 37:261–265. https://doi.org/10.1007/s11745-002-0889-z

Kreutzberg GW (1996) Microglia: a sensor for pathological events in the CNS. Trends Neurosci 19:312–318

Krizova L, Dadakova K, Kasparovska J, Kasparovsky T (2019) Isoflavones. Molecules. https://doi.org/10.3390/molecules24061076

Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B, Gustafsson JA (1998) Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology 139:4252–4263. https://doi.org/10.1210/endo.139.10.6216

Lai HH, Yen GC (2002) Inhibitory effect of isoflavones on peroxynitrite-mediated low-density lipoprotein oxidation. Biosci Biotechnol Biochem 66:22–28. https://doi.org/10.1271/bbb.66.22

Lanou AJ (2011) Soy foods: are they useful for optimal bone health? Ther Adv Musculoskelet Dis 3:293–300. https://doi.org/10.1177/1759720X11417749

Lapcik O, Honys D, Koblovska R, Mackova Z, Vitkova M, Klejdus B (2006) Isoflavonoids are present in *Arabidopsis thaliana* despite the absence of any homologue to known isoflavonoid synthases. Plant Physiol Biochem 44:106–114. https://doi.org/10.1016/j.plaphy.2005.11.006

Lazo JS, Kondo Y, Dellapiazza D, Michalska AE, Choo KH, Pitt BR (1995) Enhanced sensitivity to oxidative stress in cultured embryonic cells from transgenic mice deficient in metallothionein I and II genes. J Biol Chem 270:5506–5510. https://doi.org/10.1074/jbc.270.10.5506

Lee SJ, Ahn JK, Khanh TD, Chun SC, Kim SL, Ro HM, Song HK, Chung IM (2007) Comparison of isoflavone concentrations in soybean (*Glycine max* (L.) Merrill) sprouts grown under two different light conditions. J Agric Food Chem 55:9415–9421. https://doi.org/10.1021/jf071861v

Lee GA, Crawford GW, Liu L, Sasaki Y, Chen X (2011) Archaeological soybean (*Glycine max*) in East Asia: does size matter? PLoS ONE 6:e26720. https://doi.org/10.1371/journal.pone.0026720

Li XH, Zhang JC, Sui SF, Yang MS (2005) Effect of daidzin, genistin, and glycitin on osteogenic and adipogenic differentiation of bone marrow stromal cells and adipocytic transdifferentiation of

osteoblasts. Acta Pharmacol Sin 26:1081–1086. https://doi.org/10.1111/j.1745-7254.2005.00161.x
Li G, Zhang Q, Wang Y (2010) Chemical constituents from roots of *Pueraria lobata*. Zhongguo Zhong Yao Za Zhi 35:3156–3160
Lian Z, Niwa K, Gao J, Tagami K, Onczi K, Mori H, Tamaya T (2004) Soybean isoflavones inhibit estrogen-stimulated gene expression in mouse uteri. Eur J Gynaecol Oncol 25:311–314
Liu Y, Zhang X, Kelsang N, Tu G, Kong D, Lu J, Zhang Y, Liang H, Tu P, Zhang Q (2018) Structurally diverse cytotoxic dimeric chalcones from *Oxytropis chiliophylla*. J Nat Prod 81:307–315. https://doi.org/10.1021/acs.jnatprod.7b00736
Loos RJ, Rankinen T (2005) Gene-diet interactions on body weight changes. J Am Diet Assoc 105:S29–34. https://doi.org/10.1016/j.jada.2005.02.015
MacDougald OA, Lane MD (1995) Transcriptional regulation of gene expression during adipocyte differentiation. Annu Rev Biochem 64:345–373. https://doi.org/10.1146/annurev.bi.64.070195.002021
Maggioni S, Bagnati R, Pandelova M, Schramm KW, Benfenati E (2013) Genistein and dicarboximide fungicides in infant formulae from the EU market. Food Chem 136:116–119. https://doi.org/10.1016/j.foodchem.2012.07.094
Meng M, Yan L, Song X, Zhang Q, Wang Z (2011) HPLC characteristic fingerprint of *Moghania philippinensis* root. Zhongguo Zhong Yao Za Zhi 36:1202–1206
Messina M (2016) Soy and health update: evaluation of the clinical and epidemiologic literature. Nutrients. https://doi.org/10.3390/nu8120754
Mishra SI, Dickerson V, Najm W (2003) Phytoestrogens and breast cancer prevention: what is the evidence? Am J Obstet Gynecol 188:S66–70. https://doi.org/10.1067/mob.2003.405
Mittal N, Hota D, Dutta P, Bhansali A, Suri V, Aggarwal N, Marwah RK, Chakrabarti A (2011) Evaluation of effect of isoflavone on thyroid economy & autoimmunity in oophorectomised women: a randomised, double-blind, placebo-controlled trial. Indian J Med Res 133:633–640
Morrison JH, Brinton RD, Schmidt PJ, Gore AC (2006) Estrogen, menopause, and the aging brain: how basic neuroscience can inform hormone therapy in women. J Neurosci 26:10332–10348. https://doi.org/10.1523/JNEUROSCI.3369-06.2006
Mun SC, Mun GS (2015) Dynamics of phytoestrogen, isoflavonoids, and its isolation from stems of *Pueraria lobata* (Willd.) Ohwi growing in Democratic People's Republic of Korea. J Food Drug Anal 23:538–544. https://doi.org/10.1016/j.jfda.2015.04.003
Nakazawa K, Ohno Y (2003) Block by phytoestrogens of recombinant human neuronal nicotinic receptors. J Pharmacol Sci 93:118–121
Nih Consensus Development Panel on Osteoporosis Prevention D, Therapy (2001) Osteoporosis prevention, diagnosis, and therapy. JAMA 285:785–795. https://doi.org/10.1001/jama.285.6.785
Norbury CJ, Hickson ID (2001) Cellular responses to DNA damage. Annu Rev Pharmacol Toxicol 41:367–401. https://doi.org/10.1146/annurev.pharmtox.41.1.367
Ondricek AJ, Kashyap AK, Thamake SI, Vishwanatha JK (2012) A comparative study of phytoestrogen action in mitigating apoptosis induced by oxidative stress. In Vivo 26:765–775
Panche AN, Diwan AD, Chandra SR (2016) Flavonoids: an overview. J Nutr Sci 5:e47. https://doi.org/10.1017/jns.2016.41
Park M, Jeong MK, Kim M, Lee J (2012) Modification of isoflavone profiles in a fermented soy food with almond powder. J Food Sci 77:C128–C134. https://doi.org/10.1111/j.1750-3841.2011.02504.x
Phromnoi K, Yodkeeree S, Anuchapreeda S, Limtrakul P (2009) Inhibition of MMP-3 activity and invasion of the MDA-MB-231 human invasive breast carcinoma cell line by bioflavonoids. Acta Pharmacol Sin 30:1169–1176. https://doi.org/10.1038/aps.2009.107
Plewa MJ, Berhow MA, Vaughn SF, Woods EJ, Rundell M, Naschansky K, Bartolini S, Wagner ED (2001) Isolating antigenotoxic components and cancer cell growth suppressors from agricultural by-products. Mutat Res 480–481:109–120. https://doi.org/10.1016/s0027-5107(01)00174-9
Pongkitwitoon B, Sakamoto S, Tanaka H, Tsuchihashi R, Kinjo J, Morimoto S, Putalun W (2010) Enzyme-linked immunosorbent assay for total isoflavonoids in *Pueraria candollei* using anti-puerarin and anti-daidzin polyclonal antibodies. Planta Med 76:831–836. https://doi.org/10.1055/s-0029-1240725
Qu LP, Fan GR, Peng JY, Mi HM (2007) Isolation of six isoflavones from *Semen sojae* praeparatum by preparative HPLC. Fitoterapia 78:200–204. https://doi.org/10.1016/j.fitote.2006.11.002
Quan J, Yin X, Kanazawa T (2009) Effect of soybean hypocotyl extract on lipid peroxidation in GK rats. J Clin Biochem Nutr 44:212–217. https://doi.org/10.3164/jcbn.07-53
Ramana KV, Srivastava S, Singhal SS (2017) Lipid peroxidation products in human health and disease 2016. Oxid Med Cell Longev 2017:2163285. https://doi.org/10.1155/2017/2163285
Reiter E, Beck V, Medjakovic S, Mueller M, Jungbauer A (2009) Comparison of hormonal activity of isoflavone-containing supplements used to treat menopausal complaints. Menopause 16:1049–1060. https://doi.org/10.1097/gme.0b013e31819c146c
Rizk ML, Zou L, Savic RM, Dooley KE (2017) Importance of drug pharmacokinetics at the site of action. Clin Transl Sci 10:133–142. https://doi.org/10.1111/cts.12448
Rostagno MA, Palma M, Barroso CG (2003) Ultrasound-assisted extraction of soy isoflavones. J Chromatogr A 1012:119–128. https://doi.org/10.1016/s0021-9673(03)01184-1
Russo A, Cardile V, Lombardo L, Vanella L, Acquaviva R (2006) Genistin inhibits UV light-induced plasmid DNA damage and cell growth in human melanoma cells. J Nutr Biochem 17:103–108. https://doi.org/10.1016/j.jnutbio.2005.05.011
Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M, American Heart Association Nutrition C (2006) Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee. Circulation 113:1034–1044. https://doi.org/10.1161/CIRCULATIONAHA.106.171052
Sepehr E, Robertson P, Gilani GS, Cooke G, Lau BP (2006) An accurate and reproducible method for the quantitative analysis of isoflavones and their metabolites in rat plasma using liquid chromatography/mass spectrometry combined with photodiode array detection. J AOAC Int 89:1158–1167
Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT (2011) Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 1:a006189. https://doi.org/10.1101/cshperspect.a006189
Setchell KD, Brzezinski A, Brown NM, Desai PB, Melhem M, Meredith T, Zimmer-Nechimias L, Wolfe B, Cohen Y, Blatt Y (2005) Pharmacokinetics of a slow-release formulation of soybean isoflavones in healthy postmenopausal women. J Agric Food Chem 53:1938–1944. https://doi.org/10.1021/jf0488099
Sherrill JD, Sparks M, Dennis J, Mansour M, Kemppainen BW, Bartol FF, Morrison EE, Akingbemi BT (2010) Developmental exposures of male rats to soy isoflavones impact Leydig cell differentiation. Biol Reprod 83:488–501. https://doi.org/10.1095/biolreprod.109.082685
Shi H, Nam PK, Ma Y (2010) Comprehensive profiling of isoflavones, phytosterols, tocopherols, minerals, crude protein, lipid, and sugar during soybean (*Glycine max*) germination. J Agric Food Chem 58:4970–4976. https://doi.org/10.1021/jf100335j

Sibao C, Dajian Y, Shilin C, Hongx X, Chan AS (2007) Seasonal variations in the isoflavonoids of radix Puerariae. Phytochem Anal 18:245–250

Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. CA Cancer J Clin 66:7–30. https://doi.org/10.3322/caac.21332

Singh AV, Franke AA, Blackburn GL, Zhou JR (2006) Soy phytochemicals prevent orthotopic growth and metastasis of bladder cancer in mice by alterations of cancer cell proliferation and apoptosis and tumor angiogenesis. Cancer Res 66:1851–1858. https://doi.org/10.1158/0008-5472.CAN-05-1332

Son E, Yoon JM, An BJ, Lee YM, Cha J, Chi GY, Kim DS (2019) Comparison among activities and isoflavonoids from *Pueraria thunbergiana* aerial parts and root. Molecules. https://doi.org/10.3390/molecules24050912

Spinelli MG (2004) Depression and hormone therapy. Clin Obstet Gynecol 47:428–436. https://doi.org/10.1097/00003081-200406000-00019

Sun YG, Wang SS, Feng JT, Xue XY, Liang XM (2008) Two new isoflavone glycosides from *Pueraria lobata*. J Asian Nat Prod Res 10:729–733. https://doi.org/10.1080/10286020802016198

Szeja W, Grynkiewicz G, Rusin A (2017) Isoflavones, their glycosides and glycoconjugates. Synthesis and biological activity. Curr Org Chem 21:218–235. https://doi.org/10.2174/1385272820666160928120822

Tang YP, Zhu HX, Duan JA (2008) Two new isoflavone triglycosides from the small branches of *Sophora japonica*. J Asian Nat Prod Res 10:65–70. https://doi.org/10.1080/10286020701273858

Tsai HS, Huang LJ, Lai YH, Chang JC, Lee RS, Chiou RY (2007) Solvent effects on extraction and HPLC analysis of soybean isoflavones and variations of isoflavone compositions as affected by crop season. J Agric Food Chem 55:7712–7715. https://doi.org/10.1021/jf071010n

Uesugi T, Toda T, Tsuji K, Ishida H (2001) Comparative study on reduction of bone loss and lipid metabolism abnormality in ovariectomized rats by soy isoflavones, daidzin, genistin, and glycitin. Biol Pharm Bull 24:368–372. https://doi.org/10.1248/bpb.24.368

Vitor RF, Mota-Filipe H, Teixeira G, Borges C, Rodrigues AI, Teixeira A, Paulo A (2004) Flavonoids of an extract of *Pterospartum tridentatum* showing endothelial protection against oxidative injury. J Ethnopharmacol 93:363–370. https://doi.org/10.1016/j.jep.2004.04.003

Wang Z, Li W, Gao Y, Liu J (2010) Simultaneous determination of nine isoflavonoids in Huangqi Gegen decoction by high performance liquid chromatography. Zhongguo Zhong Yao Za Zhi 35:2689–2692

Wang BS, Juang LJ, Yang JJ, Chen LY, Tai HM, Huang MH (2012) Antioxidant and antityrosinase activity of *Flemingia macrophylla* and glycine tomentella roots. Evid Based Complement Alternat Med 2012:431081. https://doi.org/10.1155/2012/431081

Wang DJ, Khan MS, Cui L, Song XY, Zhu H, Ma TY, Li XY, Sun R (2019) A novel method for the highly efficient biotransformation of genistein from genistin using a high-speed counter-current chromatography bioreactor. RSC Adv 9:4892–4899. https://doi.org/10.1039/c8ra10629k

Wong RW, Rabie AB (2010) Effect of genistin on bone formation. Front Biosci (Elite Ed) 2:764–770

Xue Y, Yu J, Song X (2009) Hydrolysis of soy isoflavone glycosides by recombinant beta-glucosidase from hyperthermophile *Thermotoga maritima*. J Ind Microbiol Biotechnol 36:1401–1408. https://doi.org/10.1007/s10295-009-0626-8

Yang X, Deng Z, Wang J, Ding M (2006) Preparation of soybean isoflavone glucosides by reversed-phase high performance liquid chromatography. Se Pu 24:363–366

Yasuda T, Endo M, Kon-no T, Kato T, Mitsuzuka M, Ohsawa K (2005) Antipyretic, analgesic and muscle relaxant activities of pueraria isoflavonoids and their metabolites from Pueraria lobata Ohwi-a traditional Chinese drug. Biol Pharm Bull 28:1224–1228. https://doi.org/10.1248/bpb.28.1224

Yeom SJ, Kim BN, Kim YS, Oh DK (2012) Hydrolysis of isoflavone glycosides by a thermostable beta-glucosidase from *Pyrococcus furiosus*. J Agric Food Chem 60:1535–1541. https://doi.org/10.1021/jf204432g

You J, Jiang D (2010) Effect of genistin on proliferative vitreoretinopathy. Zhong Nan Da Xue Xue Bao Yi Xue Ban 35:749–753. https://doi.org/10.3969/j.issn.1672-7347.2010.07.017

Yu J, Bi X, Yu B, Chen D (2016) Isoflavones: anti-inflammatory benefit and possible caveats. Nutrients. https://doi.org/10.3390/nu8060361

Yuan D, Xie YY, Bai X, Wu X, Yang JY, Wu CF (2009) Inhibitory activity of isoflavones of Pueraria flowers on nitric oxide production from lipopolysaccharide-activated primary rat microglia. J Asian Nat Prod Res 11:471–481. https://doi.org/10.1080/10286020902819822

Zaheer K, Humayoun Akhtar M (2017) An updated review of dietary isoflavones: Nutrition, processing, bioavailability and impacts on human health. Crit Rev Food Sci Nutr 57:1280–1293. https://doi.org/10.1080/10408398.2014.989958

Zhang D, Ren Y, Dai S, Liu W, Li G (2009) Isoflavones from vines of *Pueraria lobata*. Zhongguo Zhong Yao Za Zhi 34:3217–3220

Zhang Z, Li S, Jiang J, Yu P, Liang J, Wang Y (2010) Preventive effects of *Flos perariae* (Gehua) water extract and its active ingredient puerarin in rodent alcoholism models. Chin Med 5:36. https://doi.org/10.1186/1749-8546-5-36

Zhang HY, Wang HL, Zhong GY, Zhu JX (2018) Molecular mechanism and research progress on pharmacology of traditional Chinese medicine in liver injury. Pharm Biol 56:594–611. https://doi.org/10.1080/13880209.2018.1517185

Zhao C, Chan HY, Yuan D, Liang Y, Lau TY, Chau FT (2011) Rapid simultaneous determination of major isoflavones of *Pueraria lobata* and discriminative analysis of its geographical origins by principal component analysis. Phytochem Anal 22:503–508. https://doi.org/10.1002/pca.1308

Zhao L, Chen Q, Diaz Brinton R (2002) Neuroprotective and neurotrophic efficacy of phytoestrogens in cultured hippocampal neurons. Exp Biol Med (Maywood) 227:509–519. https://doi.org/10.1177/153537020222700716

Zhao JH, Arao Y, Sun SJ, Kikuchi A, Kayama F (2006) Oral administration of soy-derived genistin suppresses lipopolysaccharide-induced acute liver inflammation but does not induce thymic atrophy in the rat. Life Sci 78:812–819. https://doi.org/10.1016/j.lfs.2005.05.104

Zhou JR, Yu L, Zhong Y, Nassr RL, Franke AA, Gaston SM, Blackburn GL (2002) Inhibition of orthotopic growth and metastasis of androgen-sensitive human prostate tumors in mice by bioactive soybean components. Prostate 53:143–153. https://doi.org/10.1002/pros.10141

Zhou YY, Luo SH, Yi TS, Li CH, Luo Q, Hua J, Liu Y, Li SH (2011) Secondary metabolites from *Glycine soja* and their growth inhibitory effect against *Spodoptera litura*. J Agric Food Chem 59:6004–6010. https://doi.org/10.1021/jf200821p

Zhu Y, Yao Y, Shi Z, Everaert N, Ren G (2018) Synergistic effect of bioactive anticarcinogens from soybean on anti-proliferative activity in MDA-MB-231 and MCF-7 human breast cancer cells in vitro. Molecules. https://doi.org/10.3390/molecules23071557