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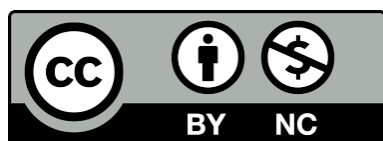
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Plant isoflavones as anticancer agents in nanomedicine

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Abstract: Isoflavones are natural phytoestrogens and belong to a subgroup of flavonoids that can be found mainly in legume plants, especially soybeans (*Glycine max* L.) and the other plants of the Fabaceae family. They have a structure similar to 17 β -estradiol, which allows them to bind estrogen receptors and exhibit estrogenic or antiestrogenic effects. They are found in non-fermented products mainly as glycosides. During the fermentation process, they are converted into bioactive aglycones. Isoflavones are also linked to antioxidant and therapeutic benefits, supporting bone health and cholesterol regulation. Soybean-derived isoflavones, especially genistein, show strong anticancer potential by inhibiting cell growth. Epidemiological studies indicate, that consumption of isoflavones may reduce the risk of some diseases, including breast cancer but these compounds' clinical application is limited due to poor bioavailability, solubility, and stability. Today, integrating traditional medicine and medicinal plants with modern medicine could offer new opportunities for treating various diseases. Nanocarriers such as liposomes, dendrimers, and nanoparticles have been developed to enhance the bioavailability and controlled release of soy isoflavones, enabling their targeted delivery to cancer cells while minimizing off-target effects. In this review, we examine how nanotechnology synergizes with *Glycine max*-derived isoflavones to enhance their bioavailability and biological activity, considering the challenges and limitations of this approach for therapeutic development.

Keywords: Phytoestrogens, nanotechnology, cancer, genistein.

Introduction

Isoflavones are naturally occurring organic compounds related to flavonoids, abundantly present in soybeans and other legumes (Bustamante-Rangel et al., 2018; Rizzo and Baroni, 2018). They are phenolic compounds that contain hydroxyl groups attached to aromatic rings, making them a subclass of flavonoids. Isoflavones, a type of phytoestrogen, share structural similarities with 17 β -estradiol, a human estrogen hormone. Because of these similarities, isoflavones can bind to estrogen receptors in the body and have either estrogenic or anti-estrogenic actions (Kurzer and Xu, 1997; Tham et al., 1998). Isoflavonoids are mostly found in leguminous plants, notably those of the Fabaceae family. Soybeans (*Glycine max*) are the richest sources, accounting for a significant portion of dietary consumption through items including soy flour, soy drinks, miso, and tempeh. Other legumes, such as red and white clover, alfalfa, and beans, contain these chemicals at various levels. In non-fermented soy products, isoflavonoids are largely found as glycosides (conjugated forms), which are transformed into the more physiologically active aglycones during fermentation procedures (Zaheer and Humayoun Akhtar, 2017; Křížová et al., 2019). Trace amounts of isoflavonoids are found in nuts, fruits, and vegetables, but their dietary contribution is minimal compared to soy-derived foods (Bustamante-Rangel et al., 2018). Isoflavonoids have attracted considerable attention for their potential health benefits, including antioxidant, estrogenic, and anti-estrogenic properties, which support their therapeutic applications (Křížová et al., 2019). They are suggested to improve bone density and prevent osteoporosis in postmenopausal women by mimicking estrogen's effects (Ye et al., 2006). Research further suggests that these substances, particularly soy isoflavones, may lower the incidence of hormone-dependent malignancies via pathways involving estrogen receptor signaling and antioxidant activity (Messina et al., 2006a; Messina and Hilakivi-Clarke, 2009). Additionally, these compounds have been associated with improved lipid profiles, including reduced LDL cholesterol and increased HDL cholesterol (Carroll, 1991; Chalvon-Demersay et al., 2017). Furthermore,

these substances have been linked to better lipid profiles, including lower LDL and higher HDL cholesterol (Lethaby et al., 2007).

Nanotechnology, or the manipulation of materials at the nanoscale (1-100 nanometers), has transformed disease treatment, particularly cancer therapy, by allowing for precise, targeted, and efficient drug delivery via nanostructures such as liposomes, dendrimers, and nanoparticles (Nasrollahzadeh et al., 2019; Chehelgerdi et al., 2023). These developments enhance bioavailability, minimize toxicity, and facilitate controlled medication release, leading to significantly improved therapeutic outcomes. Nano-carriers allow for the targeted delivery of larger medication concentrations directly to sick cells, bypassing the constraints of standard therapies. This strategy reduces side effects and adverse responses, simplifies treatment processes, and improves therapeutic success rates (Emeje et al., 2012; Tran et al., 2020).

Breast cancer is the most often diagnosed disease in women and the leading cause of cancer-related death worldwide, with over 2.3 million new cases recorded each year (Sung et al., 2021; Bray et al., 2024). Significant survival inequalities persist despite improvements in targeted medicines, genetic profiling, and early detection. This is especially true in low- and middle-income countries, where timely screening and treatment are often inaccessible. Tumor heterogeneity, medication resistance, significant side effects, and the difficulty of controlling metastatic illness are among the treatment's obstacles (Lei et al., 2021). Age, genetic mutations, hormones, and lifestyle variables are among the risk factors that have been identified (Dumitrescu and Cotarla, 2005). Innovative strategies such as immunotherapy, nanotechnology, and personalized medicine are essential for overcoming these challenges, as they enhance treatment precision, reduce toxicity, and improve outcomes (Han et al., 2019; Li et al., 2021). In this review, we examine the synergy between soy isoflavones and nanotechnology in breast cancer treatment. Although extensive research has evaluated the individual benefits of soy isoflavones and advanced nanotechnology-based drug delivery systems, there remains a notable gap in understanding their combined effects. Specifically,

it is unclear how integrating these natural compounds with nanotechnological strategies may enhance therapeutic efficacy, reduce side effects, and overcome the limitations of traditional therapies.

Application of isoflavones in medicine and human health

Anticancer properties

Isoflavones have antioxidant characteristics, suppress cancer cell growth, and are anti-inflammatory, making them promising cancer preventive medicines (Sohn et al., 2021). These chemicals have been investigated in terms of cancer prevention, including breast, uterine, and prostate cancers (Horn-Ross et al., 2003; Messina et al., 2006a; Messina et al., 2006b; Van der Eecken et al., 2023). Some research has found that in Asian communities with greater soy intake (20-30 g per day), there is an inverse link between soy isoflavone consumption and breast cancer risk. This contrasts with Western populations, where soy consumption is far lower (Xiao, 2008; Dong and Qin, 2011). As a result, soy food consumption in Western countries has increased over the past few decades, driven by the belief in their health benefits, especially their role as functional foods rich in phytochemicals (He and Chen, 2013).

Cardioprotective and anti-atherosclerotic effects

Particularly in communities who consume a lot of soy, such those in Asia, isoflavones have been strongly linked to cardiovascular health. where there are reduced cardiovascular disease rates (Gómez-Zorita et al., 2020). Some studies have shown that genistein, enhances the resistance of low-density lipoprotein cholesterol (LDL-C) to oxidation in vitro, a crucial factor since oxidized LDL-C contributes to atherosclerosis (Setchell and Cassidy, 1999). Furthermore, by raising high-density lipoprotein (HDL) cholesterol and decreasing low-density lipoprotein (LDL) cholesterol, isoflavone consumption improves the blood lipid profile, improves vascular function, and helps prevent atherosclerosis and cardiovascular diseases (Carroll, 1991; Mejia et al., 2019) Beyond lipid regulation, isoflavones promote vascular health by interacting with estrogen receptor β (ER β), stimulating the release of nitric oxide (NO), a

vasodilatory agent. This results in improved endothelial function, blood vessel relaxation, and better circulation (Silva, 2021). Furthermore, isoflavones like equol, a metabolite produced from the isoflavone daidzein by gut microbiota, may play a central role in the cardioprotective effects of soy isoflavones. According to studies, equol has vasodilatory, anti-inflammatory, and antioxidant qualities that help to maintain healthy arteries and prevent atherosclerosis. Its interaction with ER β is the main mechanism by which these effects are mediated (Zhang et al., 2021). In general, these findings highlight the protective effects of soy isoflavones on cardiovascular health and their role in preventing atherosclerosis.

Prevention of osteoporosis

Extensive studies have been conducted on isoflavones' possible function in osteoporosis prevention, particularly among postmenopausal women. Isoflavones bind to estrogen receptor beta (ER β) and operate as selective estrogen receptor modulators, reducing bone loss caused by low estrogen levels during menopause (Morito et al., 2001). Also, isoflavones inhibit osteoclast activity (cells responsible for bone resorption) and promote osteoblast function (cells responsible for bone formation), contributing to the maintenance or increase of bone mineral density (BMD) (Onoe et al., 1997).

Some research show that consuming more soy products, soy protein, or soy isoflavones improves bone resorption or lowers bone mass loss. For example, a meta-analysis of 18 randomized controlled trials conducted between 1995 and 2019 investigated how soy isoflavones affected bone mineral density (BMD) in menopausal women. The study discovered that a daily dose of 106 mg of isoflavones for 6-24 months significantly increased BMD in the lumbar spine, femoral neck, and total hip (Barańska et al., 2022). Also in a similar meta-analysis looked at the effects of soy isoflavone extracts (not soy protein or foods) on bone mineral density (BMD) in menopausal women. Data from 11 randomized controlled trials involving 1,240 women found that taking 82 mg of soy isoflavones daily for 6-12 months increased lumbar spine BMD by 2.38% (Taku et al., 2010).

Hormonal regulation and relief of menopausal symptoms

Phytoestrogens, particularly isoflavones, are used as an alternative to hormone replacement therapy for menopausal symptoms. Because of their structural similarity to estrogen, they can have estrogenic or anti-estrogenic effects, which can help with hot flashes and hormonal imbalances. Modulating estrogen receptors improves overall health (Howes et al., 2006; Lethaby et al., 2007). For instance, a 12-week randomized study examined the effects of a low-fat, vegan diet with daily soybeans on menopausal symptoms in 38

postmenopausal women experiencing hot flashes. The intervention group experienced a 79% reduction in total hot flashes and an 84% decrease in moderate-to-severe hot flashes, compared to 49% and 42% reductions in the control group, respectively (Barnard et al., 2021). Similarly, a meta-analysis analyzed 15 randomized controlled trials involving perimenopausal and postmenopausal women to determine the efficacy of phytoestrogens in relieving menopausal symptoms and discovered that phytoestrogens significantly reduced hot flash frequency when compared to placebo (Chen et al., 2015).

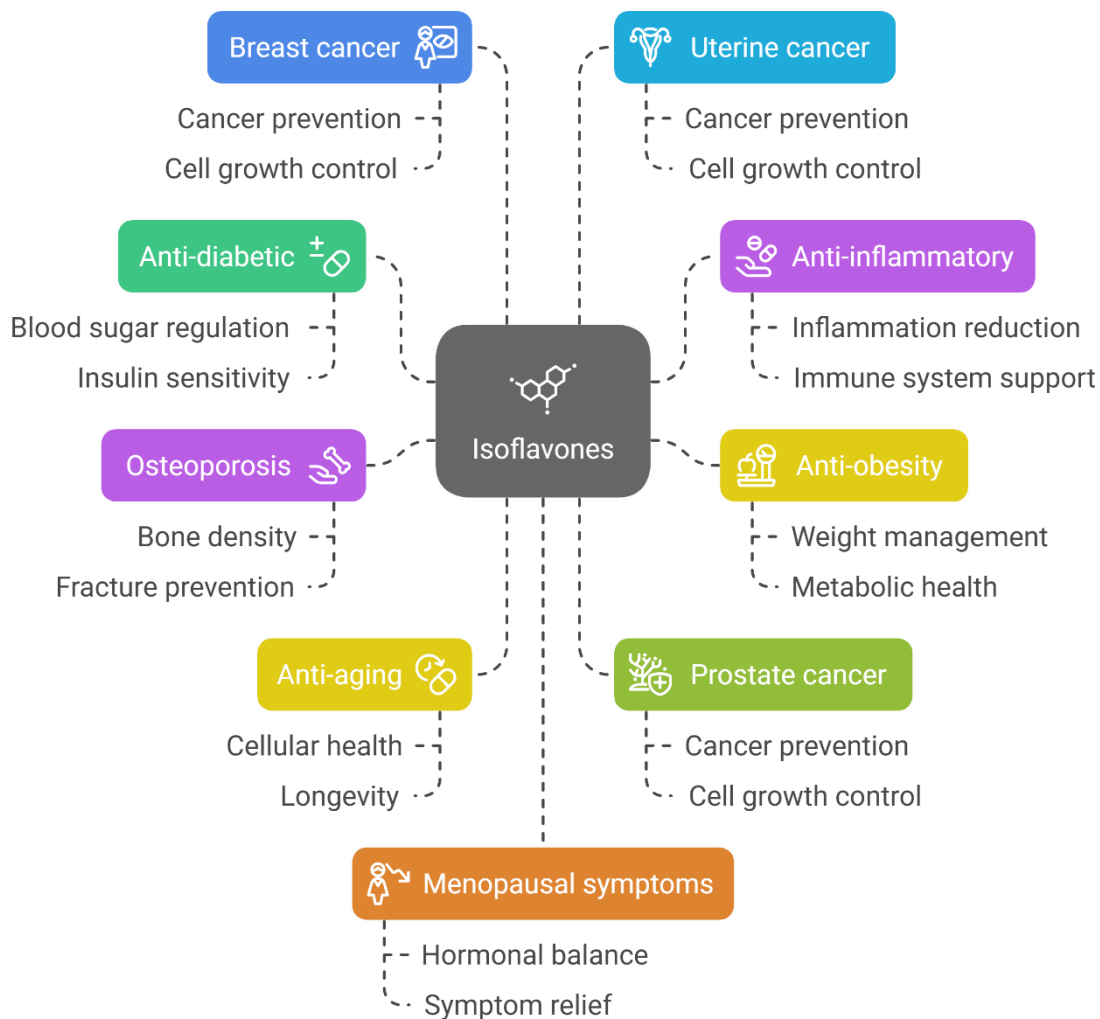


Figure 1. Health benefits and disease-preventive effects of isoflavones in humans.

Antidiabetic effects

Isoflavones, active compounds found in soy, help regulate glucose metabolism and improve insulin sensitivity. According to studies, consuming these compounds can help reduce insulin levels and improve blood sugar control, which is very effective in preventing the onset of type 2 diabetes. Genistein protects pancreatic β -cells from damage and improves insulin secretion. The effect is mediated by the activation of cAMP/PKA signaling pathways, which play a crucial role in maintaining β -cell function and mass. (Gilbert and Liu, 2013). Also, Soy isoflavones may improve lipid and glucose metabolism by acting as antidiabetic PPAR agonists. In obese Zucker rats, a high-isoflavone soy protein diet reduced liver triglyceride and cholesterol levels significantly more than low-isoflavone diets (Mezei et al., 2003). Also Isoflavones' antioxidative properties reduce oxidative stress, which can lead to insulin resistance and β -cell dysfunction (Umeno et al., 2016).

Antioxidant properties

In addition to the advantages listed above, isoflavones scavenge free radicals and help minimize oxidative stress in cells. This antioxidant activity promotes cell health, reduces chronic inflammation, and protects bodily tissues from oxidative damage (Figure 1) (Pietta, 2000; Sohn et al., 2021). Numerous studies have shown that eating soy and its products is particularly effective at reducing oxidative damage (Kim et al., 2021; Wójciak et al., 2024). For example, Genistein, a

powerful soybean isoflavone, effectively reduces reactive oxygen species production while increasing antioxidant enzyme activities, resulting in delayed tumor development and decreased tumor multiplicity in mouse models (Wei et al., 1995).

Isoflavones as bioactive compounds with anticancer potential

Isoflavones, particularly those made from soybeans, are bioactive polyphenols of the flavonoid family that exhibit anticancer activity. Soy isoflavones, including genistein, daidzein, and glycitein, occur in both free (aglycone) and conjugated forms, such as glucosides, malonylglucosides, and acetylglucosides (Figure 2) (Wang and Murphy, 1994b; Sohn et al., 2021). High-performance liquid chromatography analyses reveal that soybeans contain 12 isoflavone isomers, with major forms being genistin, daidzin, and glycitein, along with their malonyl- and acetyl-derivatives (Wang and Murphy, 1994a; b). Isoflavones are produced through the phenylpropanoid pathway, which enables plants to synthesize various secondary metabolites, including lignin, flavone, flavonol, anthocyanin, and tannin. Isoflavones are synthesized from intermediate substrates in the phenylpropanoid pathway, specifically naringenin and liquiritigenin. Naringenin is found in most plants, and it is used to make other phenylpropanoid compounds like flavones, flavonol, and anthocyanin (Figure 3) (Sohn et al., 2021).

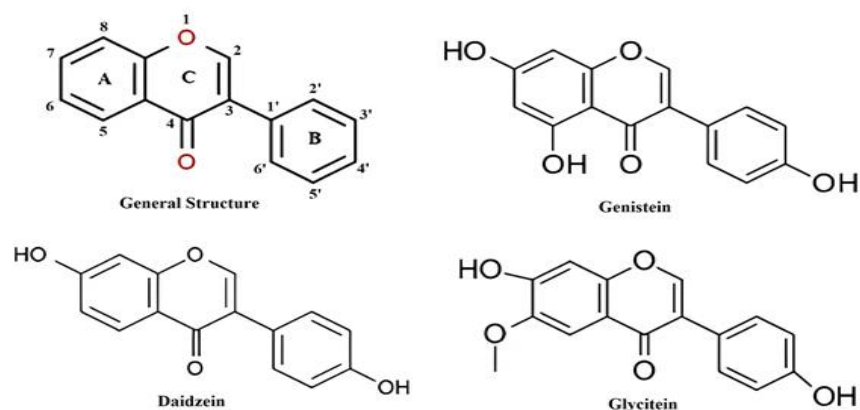


Figure 2. Chemical structure of; Genistein, Daidzein and Glycitein (Sohn et al., 2021).

Soy isoflavones, particularly genistein, have potent anti-proliferative effects in cancer cells by controlling key apoptotic and survival pathways. Pro-apoptotic mechanisms primarily involve mitochondrial-dependent pathways and the activation of caspases such as caspase-3, -7, and -9, which are critical for programmed cell death (Su et al., 2003; Yang et al., 2007; Charalambous et al., 2013). Genistein has been demonstrated to downregulate anti-apoptotic proteins such as Bcl-2 and Bcl-xL while upregulating pro-apoptotic Bax, resulting in cytochrome-c release and apoptosis (Su

et al., 2003; Jin et al., 2010; Sakamoto et al., 2010). Other strategies include generating endoplasmic reticulum stress markers such as DNA damage-inducible transcript 3 (DDIT3) and activating stress response pathways (Obiorah et al., 2014). Genistein's actions are dose-dependent, with low doses regulating survival signals through pathways such as Bax/Bcl-2 and higher doses activating alternative cytotoxic pathways regardless of estrogen receptor (ER) status (Lucki and Sewer, 2011).

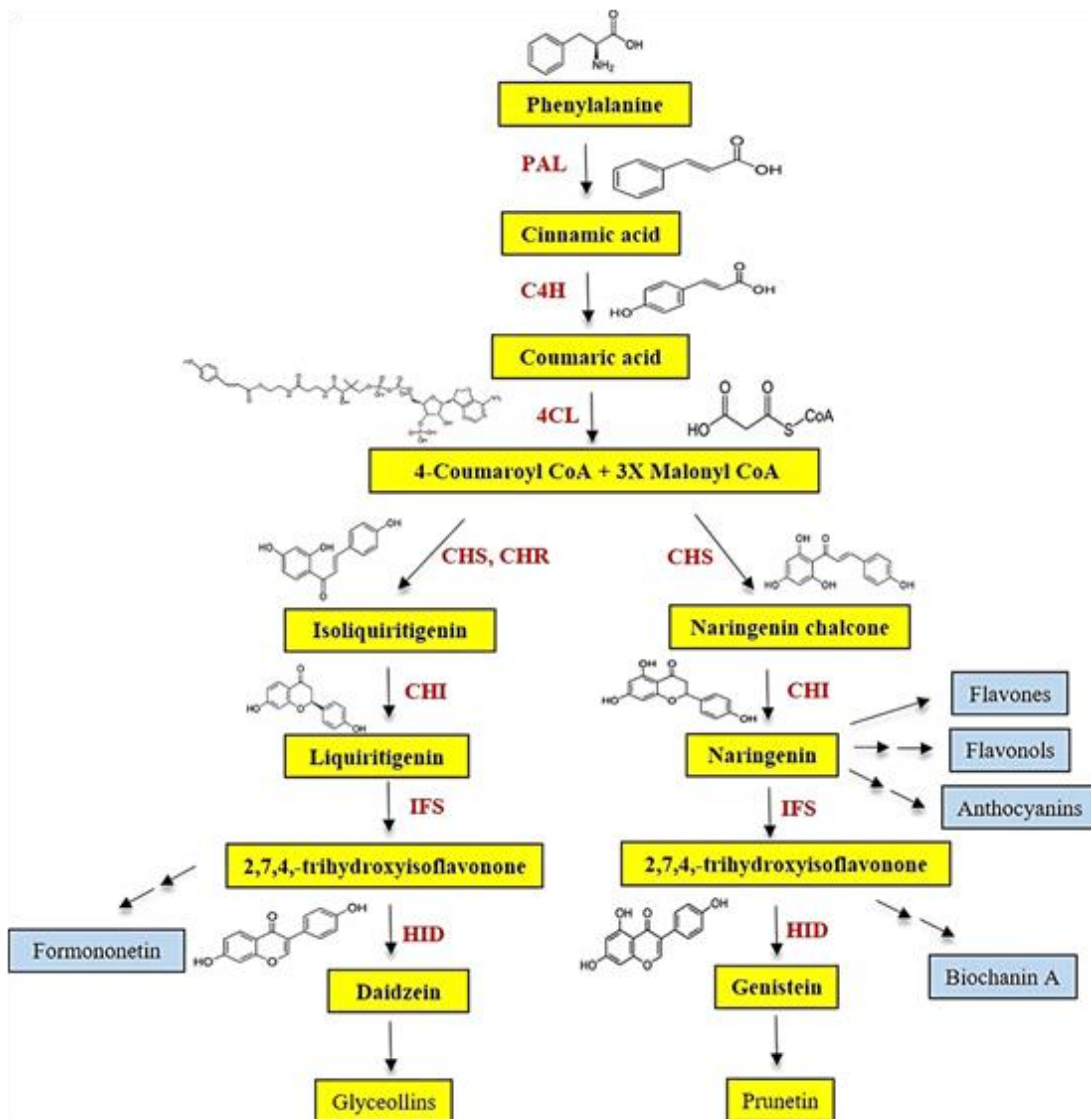


Figure 3. Partial phenylpropanoid pathway for the isoflavone biosynthesis (Sohn et al., 2021).

Genistein suppresses NF- κ B pathway activation, lowering the transcription of genes linked to chemoresistance and survival, especially in aggressive breast cancer subtypes (Pan et al., 2012). Genistein's antimetastatic effects are mediated by angiogenesis inhibition and metastatic marker suppression. Genistein inhibits vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), which are required for angiogenesis and extracellular matrix remodeling. Genistein at high concentrations (>10 μ M) reduces VEGF secretion and chemoinvasion by downregulating pro-angiogenic factors and upregulating inhibitors, such as tissue factor pathway inhibitor-2 (Lee et al., 2007; Hsu et al., 2009). It has also been shown that the PI3K/Akt/mTOR and MAPK/ERK pathways, which are critical for cell survival and metastasis, are targeted by genistein (Li et al., 2008; Ahmad et al., 2013). Thus, while genistein's anti-metastatic effects are promising, further research is essential to elucidate tissue-specific mechanisms and optimize its clinical application.

Researchers have conducted significant research on soy isoflavones, plant-derived chemicals with estrogen-like action, and their function in breast cancer prevention and therapy. Several meta-analyses and observational studies have found that increased soy isoflavone intake is linked to a lower risk of breast cancer, notably in Asian communities where soy consumption is traditionally higher. A meta-analysis of 21 studies (case-control and cohort) indicated a pooled relative risk (RR) of 0.75 for breast cancer associated with soy food consumption, showing a preventive effect, with tofu and miso specifically lowering risk by up to 20% (Qin et al., 2006). A broader meta-analysis of 35 trials found that soy isoflavones were protective for pre- and postmenopausal women in Asian nations, although the benefits were less consistent in Western populations (Chen et al., 2014). Studies conducted in high-soy-consuming Asian populations revealed a clear trend of decreased breast cancer risk with increasing soy isoflavone consumption, with a 29% risk reduction observed at higher intake levels (≥ 20 mg/day) compared to low intake levels (≤ 5 mg/day) (Wu et al., 2008). Similar findings were made by the 300,000-woman China Kadoorie Biobank study, which showed that

moderate soy consumption did not significantly affect the risk of breast cancer, but higher intake levels showed a preventive benefit, reducing the incidence by 3% for every 10 mg/day increase in soy isoflavones (Wei et al., 2020). These findings highlight the preventive effects of soy in Asian dietary patterns, which contrast with the insignificant impact reported in Western cultures where soy intake levels are significantly lower (Brouns, 2002). Further research has looked into the impact of menopausal status and hormone receptor profiles on the soy-breast cancer link. Epidemiological research, like the Shanghai Women's Health Study, discovered that increased soy consumption during adolescence and adulthood was associated with a lower risk of breast cancer, particularly in premenopausal women (Baglia et al., 2016). Stratified analyses revealed that soy isoflavones reduced the risk of estrogen receptor-positive/progesterone receptor-positive (ER+/PR+) breast cancer in postmenopausal women and ER-negative/PR-negative (ER-/PR-) breast cancer in premenopausal women. Also these compound preventive effects were more prominent in breast cancer subtypes determined by hormone receptor status, such as ER+/PR+/HER2- tumors, highlighting the significance of receptor specificity in determining its benefits (Suzuki et al., 2008). These findings emphasize soy isoflavones as a possible dietary component for personalized breast cancer preventive methods.

Innovative nanotechnology advances for enhancing soy isoflavones stability, bioavailability, and delivery systems

Multiple studies have demonstrated innovative methods to enhance the bioavailability and stability of isoflavones through nanotechnology. The selection of these nanoformulation techniques improves biodistribution, pharmacokinetics, bioavailability, and specificity of drug transport to targeted sites (Figure 4) (Sindhu et al., 2021).

Oral bioavailability and nutraceutical enhancement

Nano spray drying has been utilized to produce stable nanoparticles of soy isoflavones with carboxymethyl cellulose, which improves water solubility, bioavailability, and penetration through

biological membranes, with up to 4.5 times the efficiency of the raw material (Del Gaudio et al., 2017). Similarly emulsification-evaporation encapsulation has created small, stable whey protein nanoparticles with high encapsulation efficiency (91.29–92.59%), significantly enhancing antioxidant activity and bioaccessibility (Liu et al., 2022). These findings indicate how nanoparticle-based systems can be used to improve the solubility and bioavailability of isoflavones, which will increase their usefulness in dietary and nutraceutical applications. Encapsulation methods for soy isoflavones using protein-based nanocarriers have demonstrated significant potential in food applications. Isoflavone encapsulation with nanoparticles made from goat milk whey protein and polymerized whey protein has shown high encapsulation efficiencies, improved stability, and better intestinal release during digestion. These systems limit isoflavone

degradation under acidic and hot conditions, hence enhancing bioavailability and transport efficiency (Tian et al., 2020; Liu et al., 2022; Tian et al., 2024). Nanotubes made from α -lactalbumin can deliver soy isoflavones in functional food products, improving dispersibility and texture (Liu et al., 2023). These advancements show the potential of nanoscale systems in adding bioactive compounds like isoflavones into functional foods with increased stability and delivery capabilities.

Dermal delivery systems

Topical delivery systems have shown significant potential for enhancing the use of isoflavones in dermatological applications. Solid-lipid nanoparticles incorporated into a topical gel were found to improve skin deposition and demonstrated excellent safety, showing no irritation (Deshmukh and Amin, 2013).

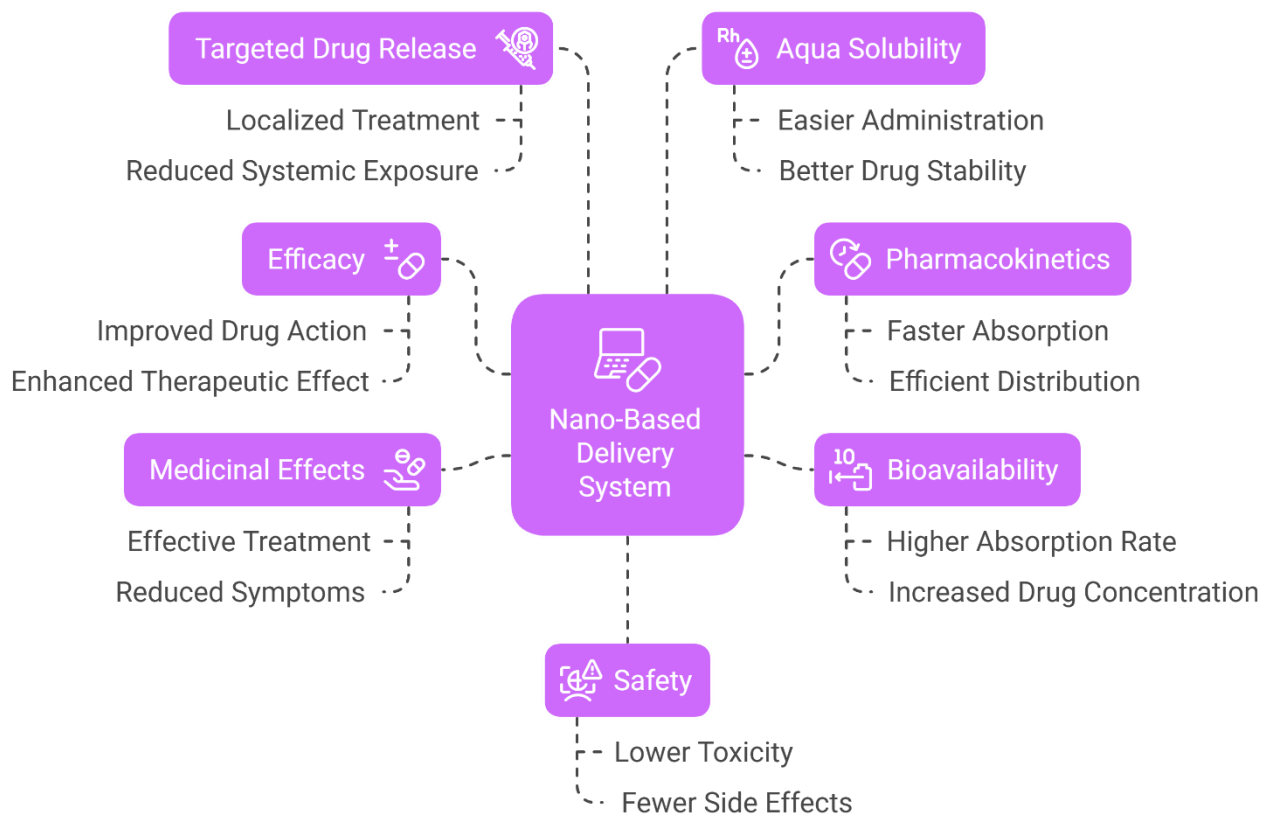


Figure 4. Benefits of nano delivery systems.

Genistein nano-emulsions created through spontaneous emulsification exhibited controlled permeation and efficient retention in the skin (Silva et al., 2009). Also, hydrogels that contain genistein-loaded nano-emulsions have been demonstrated to improve delivery through the skin while displaying desirable rheological properties (de Vargas et al., 2012). Additionally, hydrogels and nano-emulsions that incorporate isoflavones into dermal formulations promote retention within skin layers, ensuring effective delivery for topical applications (Nemitz et al., 2019). With implications in anti-aging and skin health, these results show how well nanocarriers, such as solid-lipid nanoparticles and nano-emulsions, improve cutaneous absorption and stability of isoflavones.

Systemic and multifunctional therapeutic delivery

Nanoencapsulation strategies offer significant advantages for the delivery of soy isoflavones by enhancing their pharmacokinetics and therapeutic efficacy. Slow-release formulations including polymer matrices such as hydroxypropyl-cellulose and ethyl-cellulose lengthen isoflavones residence period in plasma, resulting in a consistent therapeutic effect (Setchell et al., 2005). Similarly, spiral dextrin inclusion complexes and sustained-release microspheres provide controlled release and improved stability, making them ideal for gastrointestinal absorption and systemic effects (Setchell et al., 2005). Similarly, spiral dextrin inclusion complexes and sustained-release microspheres provide controlled release and improved stability, making them ideal for gastrointestinal absorption and systemic effects (Du et al., 2013; Wang et al., 2018).

Furthermore, hydrogel beads made from soybean husk polysaccharides (SHP) have shown effective pH-responsive release, making them appropriate for a variety of applications (Wang et al., 2020). Sustained-release microspheres made of chitosan and sodium alginate sustain steady plasma levels of isoflavones, resulting in increased biological benefits such as anti-aging qualities and antioxidant capacity (Du et al., 2013). These nanoscale systems overcome limitations such as rapid metabolism and low bioavailability, ensuring enhanced functionality. The use of soy isoflavones in multimodal delivery methods indicates their

therapeutic and preventive health benefits. Soy isoflavones integrated into 3D-printed tricalcium phosphate scaffolds inhibit localized malignancies while stimulating bone regeneration, suggesting its potential in post-surgical settings (Sarkar and Bose, 2020). Pharmacokinetic studies show that isoflavones have low toxicity and rapid clearance, making dietary supplements viable for a variety of health benefits, including cancer chemoprevention (Busby et al., 2002). The encapsulation of isoflavones in rice protein nanoparticles demonstrates the compounds' versatility in achieving sustained and targeted release, which is critical for maximizing their therapeutic potential (Mo et al., 2023).

Synergistic role of nano-isoflavones in breast cancer treatment

Soy isoflavones particularly genistein, are potential anti-breast cancer therapeutic agents due to their anti-proliferative and apoptotic activities. Genistein's function in modulating molecular signaling in breast cancer cells, by downregulating estrogen receptor α (ER α) and serum response factor (SRF), has an important role in its inhibitory effects. Genistein has been shown to inhibit cell growth during the G2/M phase. also this compound reduces the proliferative S phase in MCF-7 breast cancer cells, demonstrating its efficacy in preventing cancer development. These effects are partially mediated by estrogen receptor-dependent pathways, highlighting the complexity of the process (Chen et al., 2003). Despite its therapeutic potential, the clinical application of genistein is hampered by its poor bioavailability, solubility, and stability. Nanotechnology-based solutions have addressed these challenges by developing advanced delivery systems. A study explored the formulation of PEGylated silica nanoparticles containing genistein (Gen-PEG-SiHNM), which notably enhanced genistein's dispersion, release profiles, and cytotoxic effectiveness (Figure 5). The nanoparticles are roughly 33 nm in size and have a positive surface charge. Also enhanced genistein's water solubility and enabled pH-dependent drug release and the biological examination revealed that encapsulation increased genistein's antioxidant activity while also activating dual cell death

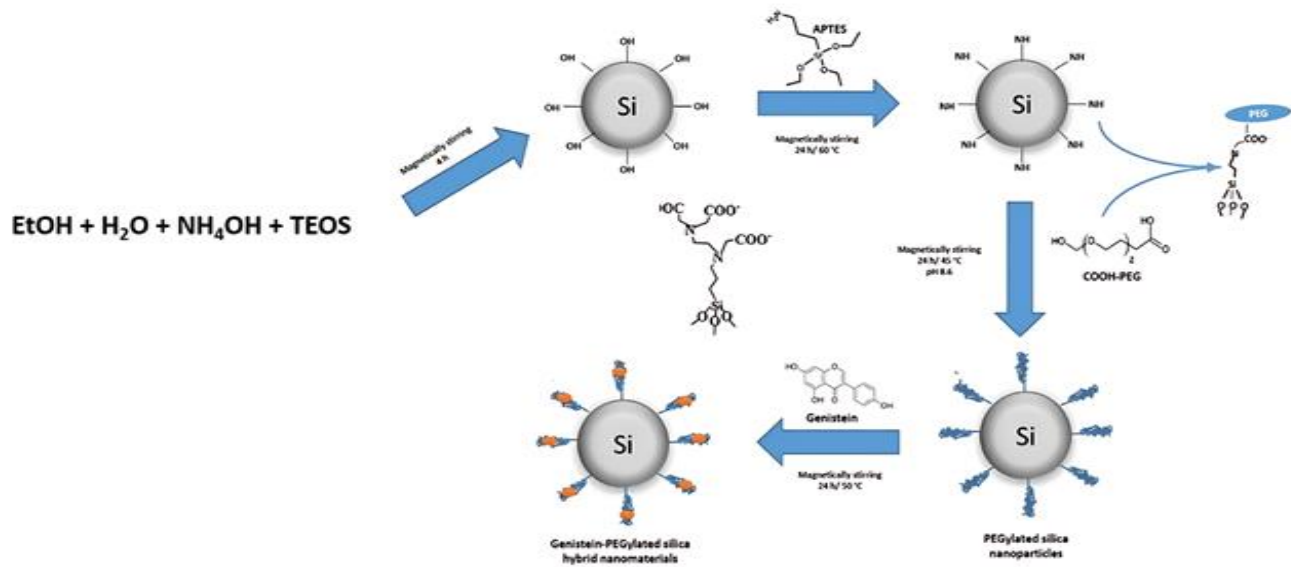


Figure 5. Schematic illustration of the development process for hybrid nanomaterials composed of PEGylated silica nanoparticles and genistein (Pool et al., 2018).

processes, apoptosis, and autophagy. But In contrast, free genistein largely triggered apoptosis, albeit with lower efficiency. This study highlights the potential of Gen-PEG-SiHNM as a more effective, multifunctional therapeutic agent with promising breakthroughs in targeted cancer therapy tactics (Pool et al., 2018; Sindhu et al., 2021). Increased genistein's solubility by more than 350 times compared to free genistein, boosting its therapeutic potential (Figure 6). This study demonstrate GenLip, provides continuous medication release while keeping genistein's antioxidant properties and in breast cancer models these liposomes had robust anticancer effects, with concentration-dependent and time-dependent cytotoxicity and much lower IC50 values than the non-encapsulated drug. Furthermore, GenLip effectively activated P53-independent apoptotic pathways through mitochondrial polarization and caspase-3/7 activation, leading in DNA fragmentation and apoptosis. The liposomal delivery technique significantly reduced off-target effects, increasing the selectivity of genistein's activity on breast cancer cells while sparing healthy cells (Phan et al., 2013b).

Additionally, metallic complexes and bioengineered derivatives of genistein show the

potential to further enhance its therapeutic profile. Copper (II)-genistein complexes, for instance, showed significantly enhanced cytotoxicity and antimetastatic effects, effectively arresting the cancer cell cycle at the G2/M transition and remodeling the actin cytoskeleton to promote cell-cell adhesion and reduced cellular migration and metastasis by suppressing the expression and secretion of metastasis-associated matrix metalloproteinases, further illustrating the promise of nanotechnology-enhanced delivery systems in cancer therapy (Spoerlein et al., 2013).

Challenges and limitations

Despite isoflavones' significant therapeutic potential, poor bioavailability, quick degradation, and difficult extraction procedures prevent soy isoflavones from being used in clinical settings, despite their potential (Amawi et al., 2017). Even though nanotechnology provides ways to improve efficacy and delivery, problems including toxicity, scalability, and regulatory issues still exist and overcoming these mentioned constraints is critical for developing soy isoflavone-based cancer treatments (Gao et al., 2024).

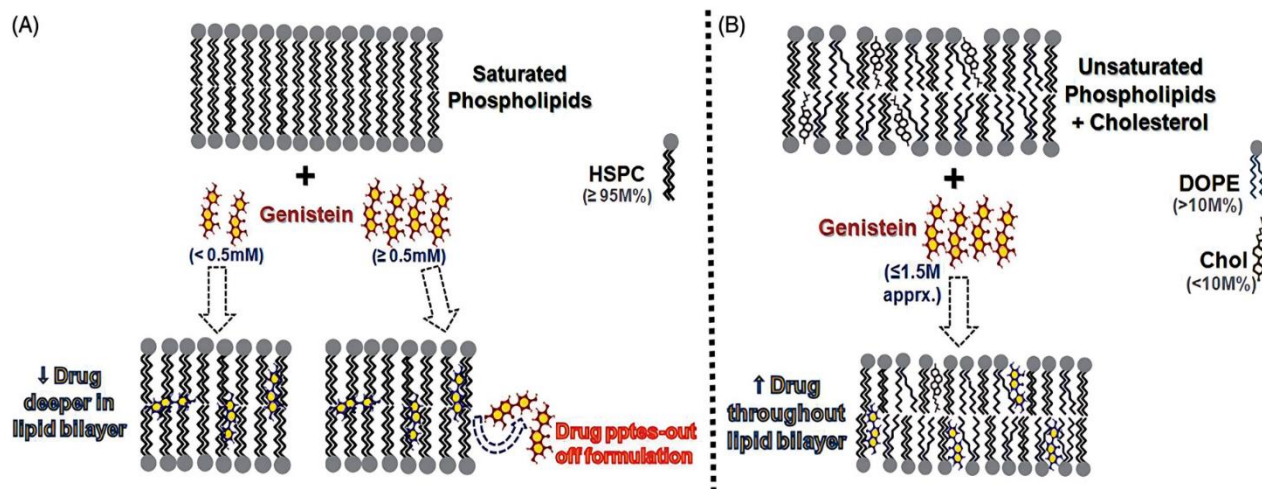


Figure 6. Schematic models illustrating genistein incorporation into liposomal membranes: (A) using rigid, highly saturated lipid components; and (B) employing flexible, unsaturated lipids combined with cholesterol (Phan et al., 2013a).

Intrinsic limitations of soy isoflavones

The use of soy isoflavones such as genistein in cancer treatment has numerous inherent problems. Poor solubility, limited bioavailability, and vulnerability to environmental conditions including temperature and pH restrict their therapeutic potential (Gao and Hu, 2010; Amawi et al., 2017; Gao et al., 2024). Furthermore, their quick breakdown by intestinal microbiota and limited oral absorption result in adverse pharmacokinetics, preventing efficient clinical application (Amawi et al., 2017). Complex techniques for isoflavone extraction, separation, and purification exacerbate the issues, with low yields and high costs limiting scalability. Traditional methods such as Soxhlet, maceration, percolation, and reflux extraction may need several kilograms of plant material to yield less than one gram of isolated chemicals (Hossain and Rahman, 2015; Blicharski and Oniszczuk, 2017). In contrast, modern techniques such as ultrasound-assisted extraction (UAE), microwave-assisted extraction, accelerated solvent extraction, supercritical fluid extraction, and negative pressure cavitation extraction offer more efficient solutions (Blicharski and Oniszczuk, 2017). For example, research found that the UAE produced considerable

extraction efficiencies for target isoflavones after 45 minutes, indicating the possibility of more efficient recovery (Sun et al., 2011). Despite these breakthroughs and novel approaches, commercial-scale extraction is still economically problematic. Furthermore, the structural complexity and unpredictability of these chemicals make them susceptible to changes during manufacture, reducing their efficacy and also these issues demand novel techniques to address constraints in stability, delivery, and bioactivity (Amawi et al., 2017).

Nanotechnology-specific challenges

Nanotechnology offers promising solutions, but it introduces its own set of limitations. Formulating nanocarriers, such as liposomes and other delivery systems, to improve genistein bioavailability and therapeutic efficacy presents technological and financial obstacles. For instance, whereas platelet membrane-coated liposomes increase targeted distribution and stability, their synthesis needs precise optimization and has scaling problems (Gao et al., 2024). Furthermore, toxicological issues and the possible immunogenicity of nanocarriers remain substantial barriers (More et al., 2021; Gao et al., 2024). For instance, both the U.S. Food and Drug Administration (FDA) and European Medicines

Agency (EMA) emphasize the need for a comprehensive characterization of nanomaterials, including an assessment of their physicochemical properties, stability, and potential immunogenicity, and underscore the importance of nonclinical studies to evaluate safety and efficacy. They have created scientific recommendations to address quality, safety, and efficacy while preparing marketing authorization applications for human drugs, including nanomedicines (Hamburg, 2012; Hafner et al., 2014; Sainz et al., 2015). Moreover, cancer cell mechanisms of resistance and the necessity of advanced nanotechnology-based combination therapy hold back clinical translation (More et al., 2021). Addressing these challenge and problems is very impotante to realizing the full potential of soy isoflavones via nanotechnology.

Future directions and prospects

Future research into soy isoflavone nanotechnology should focuses on overcoming challenges such as poor solubility, limited bioavailability, and instability. Genistein, a prominent soy isoflavone, has been demonstrated to have potent anticancer properties, targeting a variety of pathways such as apoptosis, angiogenesis, and metastasis. Nanotechnology is being researched to increase the therapeutic efficacy of genistein. Nanocarriers such as liposomes, nanoparticles, and biomimetic systems show promise in terms of delivery and stability (Spagnuolo et al., 2015). However, these advancements must address concerns such as scalability, production costs, and long-term stability in therapeutic applications. Continued advancements in nanotechnology may lead to the development of formulations capable of overcoming physiological barriers, increasing drug-targeting specificity, and decreasing side effects, especially when used in combination therapy (Spagnuolo et al., 2015; Andreani et al., 2024).

Numerous clinical trials, including "Soy Isoflavones and Breast Cancer Risk Reduction" (NCT00204490, Phase II), "Effects of Soy Compounds on Breast Cancer, Prostate Cancer, and Bone Health" (NCT00200824, Phase II), and "Soy Isoflavones Supplementation in Treating Women at High Risk For or With Breast Cancer" (NCT01219075), have been conducted to examine the effects of isoflavonoids on cancer prevention and treatment.

However clinical translation of soy isoflavones nanotechnology continues in its infancy, with minimal clinical studies completed to date. To close the gap between preclinical success and clinical application, future research should focus on refining nanocarrier design and investigating combination treatments that use soy isoflavones in conjunction with traditional chemotherapeutics (Andreani et al., 2024). Soy isoflavones, after nanotechnology-guided assistance and better understanding of their processes and safety profiles, have wide potential for use as low-cost, non-invasive cancer therapies, particularly concerning drug resistance and therapeutic efficacy. Development on this field requires overcoming the regulatory challenges and establishing standardized, safe preclinical and clinical research protocols (Spagnuolo et al., 2015; Andreani et al., 2024).

Conclusion

Nanotechnology-derived ER α targeting offers new hope for the future of breast cancer treatment by directly linking estrogen receptor modulation with advanced nanocarrier systems. Soy isoflavones, especially genistein, exert their anticancer effects via targeted ER α modulation, but their curative potential has been undermined by poor aqueous solubility, low bioavailability, and instability. New developments such as the synthesis of pH-responsive soybean hull hydrogel beads and liposomal drug delivery systems illustrate a new and groundbreaking approach that not only enhances site-specific targeted drug delivery but also allows for controlled release in various physiological environments. Also, these advanced nanocarriers have greatly enhanced the pharmacokinetics and clinical efficacy of soy isoflavones through delivery into the cellular environment and by initiating mechanisms such as apoptosis, inhibition of angiogenesis, and metastasis prevention. While issues of production scalability, cost, and toxicity remain, recently developed strategies such as modular nanocarrier design and more efficacious extraction processes offer promising means for overcoming these limitations. In the future, greater interdisciplinarity effort will be required to optimize these scalable delivery vehicles and incorporate them into

combination therapies. Such efforts will open new gates for nanotechnology-enhanced treatments that can transform breast cancer management and offer enduring hope for improved therapeutic outcomes.

Supplementary Materials

No supplementary material is available for this article.

Author Contributions

For this review article the Conceptualization, methodology, validation, investigation, resources, data curation and writing—original draft preparation performed by Ali Yousefian. The

writing—review and editing, visualization, supervision, and project administration were performed by Fatemeh Moradian.

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Conflict of Interest Statement

The authors declare no conflict of interest.

References

- Ahmad, A., Biersack, B., Li, Y., Kong, D., Bao, B., Schobert, R., B. Padhye, S., and H. Sarkar, F. (2013). Deregulation of PI3K/Akt/mTOR signaling pathways by isoflavones and its implication in cancer treatment. *Anti-Cancer Agents Med. Chem.* 13(7): 1014-1024.
- Amawi, H., Ashby, C.R., and Tiwari, A.K. (2017). Cancer chemoprevention through dietary flavonoids: what's limiting? *Chin. J. Cancer* 36: 1-13.
- Andreani, T., Cheng, R., Elbadri, K., Ferro, C., Menezes, T., Dos Santos, M.R., Pereira, C.M., and Santos, H.A. (2024). Natural compounds-based nanomedicines for cancer treatment: Future directions and challenges. *Drug Deliv Transl Res* 14(10): 2845-2916.
- Baglia, M.L., Zheng, W., Li, H., Yang, G., Gao, J., Gao, Y.T., and Shu, X.O. (2016). The association of soy food consumption with the risk of subtype of breast cancers defined by hormone receptor and HER2 status. *Int. J. Cancer* 139(4): 742-748.
- Barańska, A., Kanadys, W., Bogdan, M., Stępień, E., Barczyński, B., Kłak, A., Augustynowicz, A., Szajnik, M., and Religioni, U. (2022). The role of soy isoflavones in the prevention of bone loss in postmenopausal women: A systematic review with meta-analysis of randomized controlled trials. *J. Clin. Med.* 11(16): 4676.
- Barnard, N.D., Kahleova, H., Holtz, D.N., Del Aguila, F., Neola, M., Crosby, L.M., and Holubkov, R. (2021). The Women's Study for the Alleviation of Vasomotor Symptoms (WAVS): a randomized, controlled trial of a plant-based diet and whole soybeans for postmenopausal women. *Menopause* 28(10): 1150-1156. doi: 10.1097/gme.0000000000001812.
- Blicharski, T., and Oniszczuk, A. (2017). Extraction methods for the isolation of isoflavonoids from plant material. *Open Chem.* 15(1): 34-45.
- Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R.L., Soerjomataram, I., and Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Cancer J. Clin.* 74(3): 229-263.
- Brouns, F. (2002). Soya isoflavones: a new and promising ingredient for the health foods sector. *Int. Food Res.* 35(2-3): 187-193.
- Busby, M.G., Jeffcoat, A.R., Bloedon, L.T., Koch, M.A., Black, T., Dix, K.J., Heizer, W.D., Thomas, B.F., Hill, J.M., and Crowell, J.A. (2002). Clinical characteristics and pharmacokinetics of purified soy isoflavones: single-dose administration to healthy men. *Am J Clin Nutr* 75(1): 126-136.
- Bustamante-Rangel, M., Delgado-Zamarreño, M.M., Pérez-Martín, L., Rodríguez-Gonzalo, E., and Domínguez-Álvarez, J. (2018). Analysis of Isoflavones in Foods. *Compr. Rev. Food Sci. Food Saf.* 17(2): 391-411. doi: 10.1111/1541-4337.12325.

- Carroll, K.K. (1991). Review of clinical studies on cholesterol-lowering response to soy protein. *J Am Diet Assoc.* 91(7): 820-828.
- Chalvon-Demersay, T., Azzout-Marniche, D., Arfsten, J., Egli, L., Gaudichon, C., Karagounis, L.G., and Tomé, D. (2017). A systematic review of the effects of plant compared with animal protein sources on features of metabolic syndrome. *J Nutr* 147(3): 281-292.
- Charalambous, C., Pitta, C.A., and Constantinou, A.I. (2013). Equol enhances tamoxifen's anti-tumor activity by induction of caspase-mediated apoptosis in MCF-7 breast cancer cells. *BMC cancer* 13: 1-10.
- Chehelgerdi, M., Chehelgerdi, M., Allela, O.Q.B., Pecho, R.D.C., Jayasankar, N., Rao, D.P., Thamaraiyani, T., Vasanthan, M., Viktor, P., and Lakshmaiya, N. (2023). Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. *Mol. Cancer* 22(1): 169.
- Chen, M., Lin, C., and Liu, C. (2015). Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. *Climacteric* 18(2): 260-269.
- Chen, M., Rao, Y., Zheng, Y., Wei, S., Li, Y., Guo, T., and Yin, P. (2014). Association between soy isoflavone intake and breast cancer risk for pre-and post-menopausal women: a meta-analysis of epidemiological studies. *PLoS One* 9(2): e89288.
- Chen, W.-F., Huang, M.-H., Tzang, C.-H., Yang, M., and Wong, M.-S. (2003). Inhibitory actions of genistein in human breast cancer (MCF-7) cells. *Biochim Biophys Acta* 1638(2): 187-196.
- de Vargas, B.A., Bidone, J., Oliveira, L.K., Koester, L.S., Bassani, V.L., and Teixeira, H.F. (2012). Development of topical hydrogels containing genistein-loaded nanoemulsions. *J. Biomed. Nanotechnol.* 8(2): 330-336.
- Del Gaudio, P., Sansone, F., Mencherini, T., De Cicco, F., Russo, P., and Aquino, R.P. (2017). Nanospray drying as a novel tool to improve technological properties of soy isoflavone extracts. *Planta Med.* 83(05): 426-433.
- Deshmukh, K., and Amin, P. (2013). Formulation and evaluation of solid-lipid nanoparticle based 0.1% Soy isoflavone dermal gels. *J Pharm BioSci* 1: 7-18.
- Dong, J.-Y., and Qin, L.-Q. (2011). Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. *Breast Cancer Res. Treat.* 125: 315-323.
- Du, Z., Dou, X., Huang, C., Gao, J., Hu, L., Zhu, J., Qian, Y., Dou, M., and Fan, C. (2013). Preparation, drug releasing property and pharmacodynamics of soy isoflavone-loaded chitosan microspheres. *PLoS One* 8(11): e79698.
- Dumitrescu, R., and Cotarla, I. (2005). Understanding breast cancer risk - where do we stand in 2005? *J Cell Mol Med* 9(1): 208-221.
- Emeje, M.O., Obidike, I.C., Akpabio, E.I., and Ofoefule, S.I. (2012). Nanotechnology in drug delivery. *Rec. Adv. Nov. Drug Carri. System* 1(4): 69-106.
- Gao, R., Lin, P., Yang, W., Fang, Z., Gao, C., Cheng, B., Fang, J., and Yu, W. (2024). Bio-inspired nanodelivery platform: Platelet membrane-cloaked genistein nanosystem for targeted lung cancer therapy. *Int. J. Nanomed.*: 10455-10478.
- Gao, S., and Hu, M. (2010). Bioavailability challenges associated with development of anti-cancer phenolics. *Mini-Rev. Med. Chem.* 10(6): 550-567.
- Gilbert, E.R., and Liu, D. (2013). Anti-diabetic functions of soy isoflavone genistein: mechanisms underlying its effects on pancreatic β -cell function. *Food Funct* 4(2): 200-212. doi: 10.1039/c2fo30199g.
- Gómez-Zorita, S., González-Arceo, M., Fernández-Quintela, A., Eseberri, I., Trepiana, J., and Portillo, M.P. (2020). Scientific evidence supporting the beneficial effects of isoflavones on human health. *J. Nutr.* 12(12): 3853.
- Hafner, A., Lovrić, J., Lakoš, G.P., and Pepić, I. (2014). Nanotherapeutics in the EU: an overview on current state and future directions. *Int. J. Nanomed.* 9: 1005-1023. doi: 10.2147/ijn.S55359.
- Hamburg, M.A. (2012). FDA's approach to regulation of products of nanotechnology. *Science* 336(6079): 299-300.
- Han, H.J., Ekweremadu, C., and Patel, N. (2019). Advanced drug delivery system with nanomaterials for personalised medicine to treat breast cancer. *J. Drug Deliv. Technol.* 52: 1051-1060.

- He, F.-J., and Chen, J.-Q. (2013). Consumption of soybean, soy foods, soy isoflavones and breast cancer incidence: Differences between Chinese women and women in Western countries and possible mechanisms. *Food Sci. Hum. Wellness*. 2(3-4): 146-161.
- Horn-Ross, P.L., John, E.M., Canchola, A.J., Stewart, S.L., and Lee, M.M. (2003). Phytoestrogen intake and endometrial cancer risk. *J Natl Cancer Inst* 95(15): 1158-1164.
- Hossain, M.A., and Rahman, S.M. (2015). Isolation and characterisation of flavonoids from the leaves of medicinal plant *Orthosiphon stamineus*. *Arab. J. Chem.* 8(2): 218-221.
- Howes, L.G., Howes, J.B., and Knight, D.C. (2006). Isoflavone therapy for menopausal flushes: a systematic review and meta-analysis. *Maturitas* 55(3): 203-211.
- Hsu, E.L., Chen, N., Westbrook, A., Wang, F., Zhang, R., Taylor, R.T., and Hankinson, O. (2009). Modulation of CXCR4, CXCL12, and tumor cell invasion potential in vitro by phytochemicals. *J. Oncol.* 2009(1): 491985.
- Jin, S., Zhang, Q., Kang, X., Wang, J., and Zhao, W. (2010). Daidzein induces MCF-7 breast cancer cell apoptosis via the mitochondrial pathway. *Ann. Oncol.* 21(2): 263-268.
- Kim, I.S., Kim, C.H., and Yang, W.S. (2021). Physiologically Active Molecules and Functional Properties of Soybeans in Human Health-A Current Perspective. *Int J Mol Sci* 22(8). doi: 10.3390/ijms22084054.
- Křížová, L., Dadáková, K., Kašparovská, J., and Kašparovský, T. (2019). Isoflavones. *Molecules* 24(6): 1076.
- Kurzer, M.S., and Xu, X. (1997). Dietary phytoestrogens. *Annu. Rev. Nutr.* 17(1): 353-381.
- Lee, W.-Y., Huang, S.-C., Tzeng, C.-C., Chang, T.-L., and Hsu, K.-F. (2007). Alterations of metastasis-related genes identified using an oligonucleotide microarray of genistein-treated HCC1395 breast cancer cells. *Nutrit. Cancer* 58(2): 239-246.
- Lei, S., Zheng, R., Zhang, S., Wang, S., Chen, R., Sun, K., Zeng, H., Zhou, J., and Wei, W. (2021). Global patterns of breast cancer incidence and mortality: A population - based cancer registry data analysis from 2000 to 2020. *Cancer Commun.* 41(11): 1183-1194.
- Lethaby, A., Marjoribanks, J., Kronenberg, F., Roberts, H., Eden, J., and Brown, J. 2007. Phytoestrogens for vasomotor menopausal symptoms. *Cochrane Database Syst Rev* [Online], 17(4).
- Li, Y., Miao, W., He, D., Wang, S., Lou, J., Jiang, Y., and Wang, S. (2021). Recent progress on immunotherapy for breast cancer: tumor microenvironment, nanotechnology and more. *Front. Bioeng. Biotechnol.* 9: 680315.
- Li, Z., Li, J., Mo, B., Hu, C., Liu, H., Qi, H., Wang, X., and Xu, J. (2008). Genistein induces cell apoptosis in MDA-MB-231 breast cancer cells via the mitogen-activated protein kinase pathway. *In Vitro Toxicol.* 22(7): 1749-1753.
- Liu, B., Thum, C., Wang, Q., Feng, C., Li, T., Victorelli, F.D., Li, X., Chang, R., Chen, S., and Gong, Y. (2023). The fortification of encapsulated soy isoflavones and texture modification of soy milk by α -lactalbumin nanotubes. *Food Chem.* 419: 135979.
- Liu, Q., Sun, Y., Cheng, J., and Guo, M. (2022). Development of whey protein nanoparticles as carriers to deliver soy isoflavones. *LWT-Food Sci Technol* 155: 112953.
- Lucki, N.C., and Sewer, M.B. (2011). Genistein stimulates MCF-7 breast cancer cell growth by inducing acid ceramidase (ASAH1) gene expression. *J. Biol. Chem.* 286(22): 19399-19409.
- Mejia, S.B., Messina, M., Li, S.S., Viguiliouk, E., Chiavaroli, L., Khan, T.A., Srichaikul, K., Mirrahimi, A., Sievenpiper, J.L., and Kris-Etherton, P. (2019). A meta-analysis of 46 studies identified by the FDA demonstrates that soy protein decreases circulating LDL and total cholesterol concentrations in adults. *J Nutr* 149(6): 968-981.
- Messina, M., and Hilakivi-Clarke, L. (2009). Early intake appears to be the key to the proposed protective effects of soy intake against breast cancer. *Nutr Cancer* 61(6): 792-798.
- Messina, M., Kucuk, O., and Lampe, J.W. (2006a). An overview of the health effects of isoflavones with an emphasis on prostate cancer risk and prostate-specific antigen levels. *J. AOAC Int.* 89(4): 1121-1134.
- Messina, M., Nagata, C., and Wu, A.H. (2006b). Estimated Asian adult soy protein and isoflavone intakes. *Nutr Cancer* 55(1): 1-12.

- Mezei, O., Banz, W.J., Steger, R.W., Peluso, M.R., Winters, T.A., and Shay, N. (2003). Soy isoflavones exert antidiabetic and hypolipidemic effects through the PPAR pathways in obese Zucker rats and murine RAW 264.7 cells. *J Nutr* 133(5): 1238-1243. doi: 10.1093/jn/133.5.1238.
- Mo, H., Chen, X., Cui, B., Chen, Y., Chen, M., Xu, Z., Wen, L., Cheng, Y., and Jiao, Y. (2023). Formation and characterization of self-assembled rice protein hydrolysate nanoparticles as soy isoflavone delivery systems. *Foods* 12(7): 1523.
- More, M.P., Pardeshi, S.R., Pardeshi, C.V., Sonawane, G.A., Shinde, M.N., Deshmukh, P.K., Naik, J.B., and Kulkarni, A.D. (2021). Recent advances in phytochemical-based Nano-formulation for drug-resistant Cancer. *Med. Drug Discov.* 10: 100082.
- Morito, K., Hirose, T., Kinjo, J., Hirakawa, T., Okawa, M., Nohara, T., Ogawa, S., Inoue, S., Muramatsu, M., and Masamune, Y. (2001). Interaction of phytoestrogens with estrogen receptors α and β . *Biol Pharm Bull* 24(4): 351-356.
- Nasrollahzadeh, M., Sajadi, S.M., Sajjadi, M., and Issaabadi, Z. (2019). "An introduction to nanotechnology," in *Int. Sci. Technol.*: Elsevier), 1-27.
- Nemitz, M.C., von Poser, G.L., and Teixeira, H.F. (2019). In vitro skin permeation/retention of daidzein, genistein and glycitein from a soybean isoflavone rich fraction-loaded nanoemulsions and derived hydrogels. *J. Drug Deliv. Technol.* 51: 63-69.
- Obiorah, I.E., Fan, P., and Jordan, V.C. (2014). Breast cancer cell apoptosis with phytoestrogens is dependent on an estrogen-deprived state. *Cancer Prev. Res.* 7(9): 939-949.
- Onoe, Y., Miyaura, C., Ohta, H., Nozawa, S., and Suda, T. (1997). Expression of estrogen receptor β in rat bone. *Endocrinology* 138(10): 4509-4512.
- Pan, H., Zhou, W., He, W., Liu, X., Ding, Q., Ling, L., Zha, X., and Wang, S. (2012). Genistein inhibits MDA-MB-231 triple-negative breast cancer cell growth by inhibiting NF- κ B activity via the Notch-1 pathway. *Int. J. Mol. Med.* 30(2): 337-343.
- Phan, V., Walters, J., Brownlow, B., and Elbayoumi, T. (2013a). Enhanced cytotoxicity of optimized liposomal genistein via specific induction of apoptosis in breast, ovarian and prostate carcinomas. *J. drug target.* 21(10): 1001-1011.
- Phan, V., Walters, J., Brownlow, B., and Elbayoumi, T. (2013b). Enhanced cytotoxicity of optimized liposomal genistein via specific induction of apoptosis in breast, ovarian and prostate carcinomas. *J. Drug Target.* 21(10): 1001-1011.
- Pietta, P.-G. (2000). Flavonoids as antioxidants. *J. Nat. Prod.* 63(7): 1035-1042.
- Pool, H., Campos-Vega, R., Herrera-Hernández, M.G., García-Solis, P., García-Gasca, T., Sánchez, I.C., Luna-Bárceñas, G., and Vergara-Castañeda, H. (2018). Development of genistein-PEGylated silica hybrid nanomaterials with enhanced antioxidant and antiproliferative properties on HT29 human colon cancer cells. *Am. J. Transl. Res.* 10(8): 2306.
- Qin, L.-Q., Xu, J.-Y., Wang, P.-Y., and Hoshi, K. (2006). Soyfood intake in the prevention of breast cancer risk in women: a meta-analysis of observational epidemiological studies. *J Nutr Sci Vitaminol* 52(6): 428-436.
- Rizzo, G., and Baroni, L. (2018). Soy, soy foods and their role in vegetarian diets. *J. Nutr.* 10(1): 43.
- Sainz, V., Connot, J., Matos, A.I., Peres, C., Zupančič, E., Moura, L., Silva, L.C., Florindo, H.F., and Gaspar, R.S. (2015). Regulatory aspects on nanomedicines. *Biochem. Biophys. Res. Commun.* 468(3): 504-510.
- Sakamoto, T., Horiguchi, H., Oguma, E., and Kayama, F. (2010). Effects of diverse dietary phytoestrogens on cell growth, cell cycle and apoptosis in estrogen-receptor-positive breast cancer cells. *J. Nutr. Biochem.* 21(9): 856-864.
- Sarkar, N., and Bose, S. (2020). Controlled release of soy isoflavones from multifunctional 3D printed bone tissue engineering scaffolds. *Acta Biomater.* 114: 407-420.
- Setchell, K.D., Brzezinski, A., Brown, N.M., Desai, P.B., Melhem, M., Meredith, T., Zimmer-Nechimias, L., Wolfe, B., Cohen, Y., and Blatt, Y. (2005). Pharmacokinetics of a slow-release formulation of soybean isoflavones in healthy postmenopausal women. *J. Agric. Food Chem.* 53(6): 1938-1944.

- Setchell, K.D., and Cassidy, A. (1999). Dietary isoflavones: biological effects and relevance to human health. *J. Nutr.* 129(3): 758S-767S.
- Silva, A., Nunes, B., De Oliveira, M., Koester, L.S., Mayorga, P., Bassani, V.L., and Teixeira, H.F. (2009). Development of topical nanoemulsions containing the isoflavone genistein. *Die Pharmazie-Int. J. Pharm. Sci.* 64(1): 32-35.
- Silva, H. (2021). The vascular effects of isolated isoflavones—A focus on the determinants of blood pressure regulation. *Biology* 10(1): 49.
- Sindhu, R.K., Verma, R., Salgotra, T., Rahman, M.H., Shah, M., Akter, R., Murad, W., Mubin, S., Bibi, P., and Qusti, S. (2021). Impacting the remedial potential of nano delivery-based flavonoids for breast cancer treatment. *Molecules* 26(17): 5163.
- Sohn, S.I., Pandian, S., Oh, Y.J., Kang, H.J., Cho, W.S., and Cho, Y.S. (2021). Metabolic engineering of isoflavones: an updated overview. *Front. Plant Sci.* 12: 670103.
- Spagnuolo, C., Russo, G.L., Orhan, I.E., Habtemariam, S., Daglia, M., Sureda, A., Nabavi, S.F., Devi, K.P., Loizzo, M.R., and Tundis, R. (2015). Genistein and cancer: current status, challenges, and future directions. *Adv Nutr* 6(4): 408-419.
- Spoerlein, C., Mahal, K., Schmidt, H., and Schobert, R. (2013). Effects of chrysin, apigenin, genistein and their homoleptic copper (II) complexes on the growth and metastatic potential of cancer cells. *J. Inorg. Biochem.* 127: 107-115.
- Su, S.-J., Chow, N.-H., Kung, M.-L., Hung, T.-C., and Chang, K.-L. (2003). Effects of soy isoflavones on apoptosis induction and G2-M arrest in human hepatoma cells involvement of caspase-3 activation, Bcl-2 and Bcl-XL downregulation, and Cdc2 kinase activity. *Nutr. Cancer* 45(1): 113-123.
- Sun, Y., Liu, Z., and Wang, J. (2011). Ultrasound-assisted extraction of five isoflavones from *Iris tectorum* Maxim. *Sep. Purif. Technol.* 78(1): 49-54.
- Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., and Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71(3): 209-249.
- Suzuki, T., Matsuo, K., Tsunoda, N., Hirose, K., Hiraki, A., Kawase, T., Yamashita, T., Iwata, H., Tanaka, H., and Tajima, K. (2008). Effect of soybean on breast cancer according to receptor status: a case-control study in Japan. *Int. J. Cancer* 123(7): 1674-1680.
- Taku, K., Melby, M.K., Takebayashi, J., Mizuno, S., Ishimi, Y., Omori, T., and Watanabe, S. (2010). Effect of soy isoflavone extract supplements on bone mineral density in menopausal women: meta-analysis of randomized controlled trials. *Asia Pac. J. Clin. Nutr.* 19(1): 33-42.
- Tham, D.M., Gardner, C.D., and Haskell, W.L. (1998). Potential health benefits of dietary phytoestrogens: a review of the clinical, epidemiological, and mechanistic evidence. *J Clin Endocrinol Metab.* 83(7): 2223-2235.
- Tian, M., Cheng, J., and Guo, M. (2024). Stability, Digestion, and Cellular Transport of Soy Isoflavones Nanoparticles Stabilized by Polymerized Goat Milk Whey Protein. *Antioxidants* 13(5): 567.
- Tian, M., Wang, C., Cheng, J., Wang, H., Jiang, S., and Guo, M. (2020). Preparation and characterization of soy isoflavones nanoparticles using polymerized goat milk whey protein as wall material. *Foods* 9(9): 1198.
- Tran, P., Lee, S.-E., Kim, D.-H., Pyo, Y.-C., and Park, J.-S. (2020). Recent advances of nanotechnology for the delivery of anticancer drugs for breast cancer treatment. *J. Pharm. Investig.* 50: 261-270.
- Umeno, A., Horie, M., Murotomi, K., Nakajima, Y., and Yoshida, Y. (2016). Antioxidative and antidiabetic effects of natural polyphenols and isoflavones. *Molecules* 21(6): 708.
- Van der Eecken, H., Joniau, S., Berghen, C., Rans, K., and De Meerleer, G. (2023). The use of soy isoflavones in the treatment of prostate cancer: a focus on the cellular effects. *Nutrients* 15(23): 4856.
- Wang, H.-J., and Murphy, P.A. (1994a). Isoflavone composition of American and Japanese soybeans in Iowa: effects of variety, crop year, and location. *J. Agric. Food Chem.* 42(8): 1674-1677.
- Wang, H.-j., and Murphy, P.A. (1994b). Isoflavone content in commercial soybean foods. *J. Agric. Food Chem.* 42(8): 1666-1673.

- Wang, P.-P., Luo, Z.-G., and Peng, X.-C. (2018). Encapsulation of vitamin E and soy isoflavone using spiral dextrin: Comparative structural characterization, release kinetics, and antioxidant capacity during simulated gastrointestinal tract. *J. Agric. Food Chem.* 66(40): 10598-10607.
- Wang, S., Shao, G., Yang, J., Liu, J., Wang, J., Zhao, H., Yang, L., Liu, H., Zhu, D., and Li, Y. (2020). The production of gel beads of soybean hull polysaccharides loaded with soy isoflavone and their pH-dependent release. *Food Chem.* 313: 126095.
- Wei, H., Bowen, R., Cai, Q., Barnes, S., and Wang, Y. (1995). Antioxidant and antipromotional effects of the soybean isoflavone genistein. *Proc Soc Exp Biol Med* 208(1): 124-130. doi: 10.3181/00379727-208-43844.
- Wei, Y., Lv, J., Guo, Y., Bian, Z., Gao, M., Du, H., Yang, L., Chen, Y., Zhang, X., and Wang, T. (2020). Soy intake and breast cancer risk: A prospective study of 300,000 Chinese women and a dose-response meta-analysis. *Eur. J. Epidemiol.* 35: 567-578.
- Wójciak, M., Drozdowski, P., Skalska-Kamińska, A., Zagórska-Dziok, M., Ziemlewska, A., Nizioł-Łukaszewska, Z., and Latałska, M. (2024). Protective, anti-inflammatory, and anti-aging effects of soy isoflavones on skin cells: An overview of in vitro and in vivo studies. *Molecules* 29(23). doi: 10.3390/molecules29235790.
- Wu, A.H., Yu, M.C., Tseng, C.-C., and Pike, M.C. (2008). Epidemiology of soy exposures and breast cancer risk. *Br. J. Cancer* 98(1): 9-14.
- Xiao, C.W. (2008). Health effects of soy protein and isoflavones in humans. *J Nutr.* 138(6): 1244S-1249S.
- Yang, S., Zhou, Q., and Yang, X. (2007). Caspase-3 status is a determinant of the differential responses to genistein between MDA-MB-231 and MCF-7 breast cancer cells. *Biochim. Biophys. Acta, Mol. Cell Res.* 1773(6): 903-911.
- Ye, Y.-B., Tang, X.-Y., Verbruggen, M.A., and Su, Y.-X. (2006). Soy isoflavones attenuate bone loss in early postmenopausal Chinese women: a single-blind randomized, placebo-controlled trial. *Eur. J. Nutr.* 45: 327-334.
- Zaheer, K., and Humayoun Akhtar, M. (2017). An updated review of dietary isoflavones: Nutrition, processing, bioavailability and impacts on human health. *Crit Rev Food Sci Nutr* 57(6): 1280-1293.
- Zhang, X., Veliky, C.V., Birru, R.L., Barinas-Mitchell, E., Magnani, J.W., and Sekikawa, A. (2021). Potential protective effects of equol (soy isoflavone metabolite) on coronary heart diseases—from molecular mechanisms to studies in humans. *Nutrients* 13(11): 3739.

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ایزوفلاون‌های گیاهی به عنوان عوامل ضد سرطان در نانوپزشکی

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چکیده: ایزوفلاون‌ها فیتواستروژن‌های طبیعی هستند و به زیرگروهی از فلاونوئیدها تعلق دارند که عمدتاً در گیاهان حبوبات، به ویژه سویا (*Glycine max*) و سایر گیاهان خانواده *Fabaceae* یافت می‌شوند و ساختاری مشابه β -17 استرادیول دارند که به آن‌ها اجازه می‌دهد تا اثرات آنتی استروژنی استروژن و گیرنده‌های استروژن را نشان دهند. آن‌ها در محصولات تخمیر نشده عمدتاً به صورت گلیکوزید یافت می‌شوند. در طی فرآیند تخمیر، آن‌ها به آگلیکون‌های زیست فعال تبدیل می‌شوند. ایزوفلاون‌ها همچنین با مزایای آنتی اکسیدانی و درمانی مرتبط هستند و از سلامت استخوان و تنظیم کلسترول حمایت می‌کنند. ایزوفلاون‌های مشتق شده از سویا، به ویژه جنیستین، با مهار رشد سلولی، پتانسیل ضد سرطانی قوی نشان می‌دهند. مطالعات اپیدمیولوژیک نشان می‌دهد که مصرف ایزوفلاون‌ها ممکن است خطر ابتلا به برخی بیماری‌ها از جمله سرطان سینه را کاهش دهد، اما کاربرد بالینی این ترکیبات به دلیل دسترسی زیستی، حلالیت و پایداری ضعیف محدود است. امروزه تلفیق طب سنتی و گیاهان دارویی با طب نوین می‌تواند فرصت‌های جدیدی را برای درمان بیماری‌های مختلف فراهم نماید. نانوحامل‌هایی مانند لیپوزوم‌ها، دندریمرها و نانوذرات برای افزایش فراهمی زیستی و آزادسازی کنترل‌شده ایزوفلاون‌های سویا ایجاد شده‌اند، و امکان تحویل هدفمند آن‌ها به سلول‌های سرطانی را فراهم می‌کنند و در عین حال اثرات خارج از هدف را به حداقل می‌رسانند. در این مطالعه، چگونگی هم‌افزایی نانوتکنولوژی با ایزوفلاون‌های حاصل از سویا برای افزایش دسترسی زیستی و فعالیت بیولوژیکی آن‌ها بررسی و چالش‌ها و محدودیت‌های این روش در مسیر توسعه کاربردهای درمانی را نیز مورد توجه قرار گرفت.

کلمات کلیدی: فیتواستروژن‌ها، فناوری نانو، سرطان، جنیستین.