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REVIEW

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Natural isoflavonoids in invasive cancer therapy: From bench to bedside

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Cancer is a public health problem worldwide, and one of the crucial steps within tumor progression is the invasion and metastasis of cancer cells, which are directly related to cancer-associated deaths in patients. Recognizing the molecular markers involved in invasion and metastasis is essential to find targeted therapies in cancer. Interestingly, about 50% of the discovered drugs used in chemotherapy have been obtained from natural sources such as plants, including isoflavonoids. Until now, most drugs are used in chemotherapy targeting proliferation and apoptosis-related molecules. Here, we review recent studies about the effect of isoflavonoids on molecular targets and signaling pathways related to invasion and metastasis in cancer cell cultures, in vivo assays, and clinical trials. This review also reports that glycitein, daidzein, and genistein are the isoflavonoids most studied in preclinical and clinical trials and displayed the most anticancer activity targeting invasion-related proteins such as MMP-2 and MMP-9 and also EMT-associated proteins. Therefore, the diversity of isoflavonoids is promising molecules to be used as chemotherapeutic in invasive cancer. In the future, more clinical trials are needed to validate the effectiveness of the various natural isoflavonoids in the treatment of invasive cancer.

KEYWORDS
cancer, invasion, isoflavonoids, metastasis, therapy

1 | INTRODUCTION

Cell invasion and metastasis represent 90% of cancer-associated deaths (Guan, 2015). Cancer conventional therapeutics consists of eradication of the primary tumor by surgery or radiotherapy and systemic chemotherapy (Falzone, Salomone, & Libra, 2018). Furthermore, in metastatic cancer, the administration of chemotherapeutic agents is necessary (Abotaleb et al., 2018). However, despite advances in cancer treatment and high response rates to chemotherapy, these effects are not prolonged. Satisfactory results are short due to the mechanisms of toxicity, chemoresistance, and evasion of the immune system, and cancer continues to be one of the leading causes of death worldwide (Vasan, Baselga, & Hyman, 2019).

Natural products continue to be an essential source of biomolecules with potential therapeutic use in patients with diverse cancer types and have shown resistance to current chemotherapy (Karan et al., 2020). Interestingly, the primary sources of biomolecules in cancer therapeutics have been obtained from microbes and plants found in the environment (Mushtaq, Abbasi, Uzair, & Abbasi, 2018). Currently, around 50% of the drugs used as chemotherapeutics in cancer have been acquired or directly derived from natural products (Newman & Cragg, 2020). Phytochemicals are plant-derived

secondary metabolites that have shown promising potential to either adjuvant or improve efficacy and lessen the side effects of conventional cancer treatments (Choudhari, Mandave, Deshpande, Ranjekar, & Prakash, 2020; Koh, Ho, & Pan, 2019).

Phytochemicals act by promoting cell death, inhibiting cell proliferation and invasion, inducing apoptosis, and stimulating the immune system, making them excellent chemotherapeutic agents (Noriega-Rodríguez et al., 2020; Sánchez-Valdeolívar et al., 2020). Evidence from in vitro, in vivo, and clinical studies suggest that isoflavonoids modulate several signaling pathways involved in cancer development and progression (Rizeq et al., 2020). This review provides information on the scientific research advances of isoflavonoids as invasive cancer therapy agents. The effect of isoflavonoids on tumor invasion and metastasis-related markers is summarized from studies derivates from in vitro, in vivo, and clinical trials. The results suggest that isoflavonoids in the future could be used as alternative or adjuvant therapy in the treatment of invasive and metastatic cancer.

2 | CANCER INVASION AND METASTASIS

Invasion and metastasis of tumor cells are the most significant malignancy feature, which entails the ability to invade surrounding tissue, spread, and colonize distant tissues (Meirson & Samson, 2019). Metastasis is a process of multiple sequential stages whose result is the formation of a secondary from a primary tumor and is the result of the interactions between cancer cells and the tumor microenvironment-related factors, such as the components of the extracellular matrix, the signaling induced by cytokines, interleukins, and growth factors that deregulate cellular signaling pathways and regulation of gene expression (Liskova et al., 2020). Metastatic spread of malignant cells is the responsible hallmark for the most significant number of cancer-related deaths (Meirson & Samson, 2019). Understanding the biological players involved with the metastatic process is crucial to finding therapeutic options for successful interventions (Fares, Fares, Khachfe, Salhab, & Fares, 2020). The metastatic progression of solid tumors is carried out in five main steps: (1) cell migration and local invasion through the basement membrane, (2) infiltration of tumor cells through blood or lymphatic system, (3) survival in circulation, (4) extravasation to secondary tissue, and (5) adaptation to the tumor microenvironment and colonization at secondary tumor sites (Hanahan & Weinberg, 2011). However, the first and perhaps the most crucial step in the metastatic cascade is the invasion of tumor cells (Figure 1) (Haeger, Krause, Wolf, & Friedl, 2014).

Cancer invasion is a process involving the activities of proteolytic enzymes, including matrix metalloproteinases (MMPs) such as MMP-2, MMP-9, and MMP-14, which degrade the extracellular matrix (ECM) proteins, basement membranes, and adhesion molecules (Gerashchenko et al., 2019). Invasion is also associated with the epithelial to mesenchymal transition (EMT), characterized by loss of cell–cell adhesion, changes in cell polarization, actin cytoskeleton remodeling, invadopodia formation, and degradation of the basement membrane underlying the epithelium to enter the bloodstream or lymph nodes and travel to distant organ sites (Gerashchenko et al., 2019; Haeger et al., 2014). During EMT, epithelial markers such as E-cadherin, cytokeratins, and ocludins decrease, whereas the expression of mesenchymal markers such as N-cadherin, vimentin, fibronectin, and secretion of cellular proteases increase (Haeger et al., 2014; Mittal, 2018). The EMT program activation is regulated by several signaling pathways, including the canonical Ras/MAPK, PI3K-Akt-GSKβ-NF-κB, and Wnt/β-catenin pathways (Dongre & Weinberg, 2019). These signaling pathways converge in the activation of the EMT-related transcription factors Snail, Slug, Zeb, and Twist (Olea-Flores et al., 2019). Throughout EMT, changes in the reorganization of the actin cytoskeleton, microtubules, and the intermediate filaments occur, which favors tumor invasion and metastasis (Liu, Lin, Tang, & Wang, 2015). Vimentin is an intermediate filament belonging to mesenchymal cells; it is abundantly expressed in invasive cancer types (Satelli & Li, 2011). Its expression is directly correlated with aggressiveness and poor prognosis, promoting tumor invasion and metastasis (Liu et al., 2015; Meng et al., 2009). Vimentin expression is controlled by Twist, Snail, Zeb1, and Slug transcription factors, which are induced by TGF-β signaling (Francart et al., 2020; Sutoh Yoneyama et al., 2014).

Besides, a substantial correlation between the overexpression or activation of MMPs, cell invasion, and metastasis has been described (Gonzalez-Avila et al., 2019; Juárez-Cruz et al., 2019). MMPs are involved in the proteolytic degradation of the basement membrane and ECM; they play a fundamental role in angiogenesis and metastasis, MMPs expression is induced by growth factors and signaling pathways such as EGF, RTK, PI3K, and NF-κB (Lyu, Xiao, Yin, Yang, & He, 2019; Yang et al., 2020). MMP-14 locally degrades collagen type I, II, and III, as well as gelatin, fibronectin, and laminin, is also recruited during the invadopodia formation and focal contacts, MMP-14 degrade several components of the ECM; additionally, it activates MMP-2 and MMP-9 by cleavage their prodomain. MMP-2 and MMP-9 are also responsible for degrading the main components of the ECM, type IV collagen (Castro-Castro et al., 2016; Stankovic et al., 2010).

Currently, chemotherapy is the conventional treatment applied in invasive cancer therapy (Schirrmacher, 2019; Twelves, Jove, Gombos, & Awada, 2016). However, within its limitations are the toxicity and chemoresistance generated by tumor cells; therefore, finding new treatment alternatives is critical, and natural products appear to have promising potential.

3 | NATURAL PRODUCTS AND CANCER

Natural products have been the basis for discovering new drugs and continue to be an essential source with infinite therapeutic potential for the control of cancer patients, resistant to current treatments (Karan et al., 2020). The primary sources of successful cancer treatment products have been natural compounds derived from microorganisms, marine life forms, and plants (Ratovitski, 2017). Phytochemicals, abundantly present in plants, have shown a positive biological impact on human health, its effect has been reported as

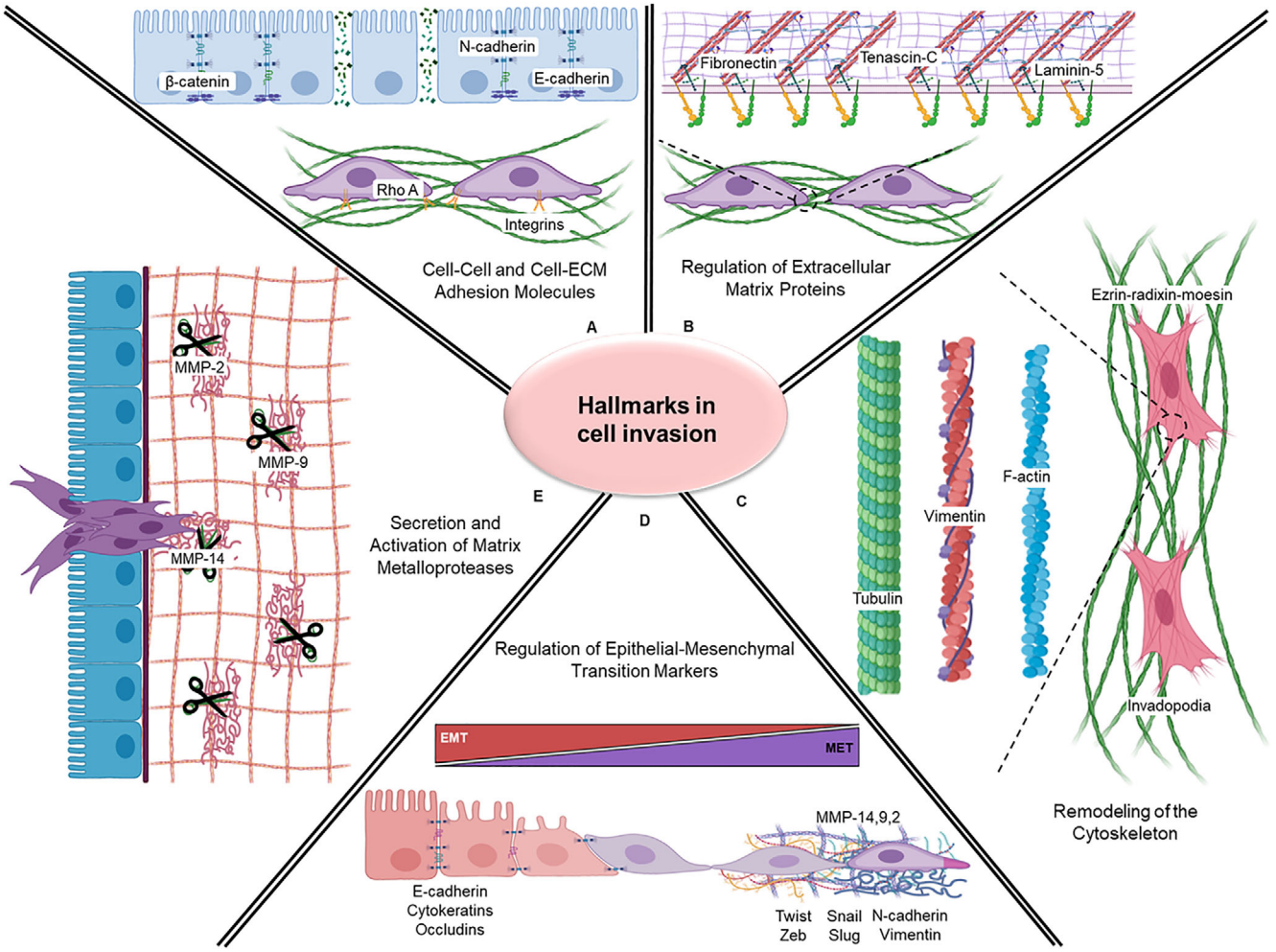

FIGURE 1 Hallmarks in cell invasion: (a) decrease or loss in E-cadherin expression, involved in cell–cell junctions; (b) expression and remodeling of extracellular matrix such as fibronectin, tenascin-C, and laminin5; (c) remodeling of the cytoskeleton; (d) expression of EMT-related markers; and (e) secretion or activation of matrix metalloproteases such as MMP-2, MMP-9, and MMP-14 [Colour figure can be viewed at wileyonlinelibrary.com]

antioxidant, neuroprotective, antiinflammatory, antiinfectious, and anticancer activities (Pérez-Jiménez, Neveu, Vos, & Scalbert, 2010). Among the most effective chemotherapeutic agents of natural origin currently available are the alkaloids vinblastine and vincristine, etoposide, paclitaxel and docetaxel, topotecan, and irinotecan (Demain & Vaishnav, 2011). These phytochemicals regulate the molecular pathways involved in tumor growth and progression; some specific mechanisms include increasing the oxidative state, inhibiting proliferation and the cell cycle progression, inducing apoptosis, and regulating the immune system (Lichota & Gwozdzinski, 2018).

While invasion and metastasis are the most critical steps in carcinogenesis, the strategy to block the cancer cell invasion and metastasis in patients is still limited (Jiang et al., 2015). However, the best approach would be to have a compound that could act in the regulation of adhesion molecules, avoid the degradation of the ECM, block the EMT pathways increasing the levels of epithelial markers, and decreasing the levels of mesenchymal markers (Gerashchenko et al., 2019). In this context, one of the significant challenges for therapeutic accomplishment is the development of chemoresistance in cancer cells against conventional chemotherapeutic agents via modulation of invasion and metastasis markers and also oncogenic signaling pathways (Mansoori, Mohammadi, Davudian, Shirjang, & Baradaran, 2017). Nevertheless, numerous studies have shown that flavonoids could be used for the prevention and treatment of cancer. In nature, polyphenols are generally conjugated with organic acids and sugars, establishing two main categories: flavonoids and non-flavonoids (Abdal Dayem et al., 2016; Avtanski & Poretsky, 2018). In plants, flavonoids are secondary metabolites with antibacterial, antiviral, antioxidant, antitumor, and antiinflammatory activity (Abotaleb et al., 2018). Flavonoids are also the largest subclass of polyphenols; their basic structure includes two benzene rings (A and B) attached to heterocyclic pyran ring (C). Flavonoids are also subdivided into several groups depending on changes in ring C (presence of the 3-hydroxyl group and double bond or 4-oxo group) and modifications in rings A and B and the difference in the number and connection position of the hydroxyl and methoxy groups. According to these chemical

arrangements, flavonoids are also classified into flavanone, flavone, flavanol, flavonol, anthocyanin, and isoflavonoids (Jiang, Doseff, & Grotewold, 2016; Sudhakaran, Sardesai, & Doseff, 2019).

Furthermore, a significant group present in the human diet and several secondary metabolites of a phenolic nature are the isoflavonoids.

4 | ISOFLAVONOIDS

Isoflavonoids or isoflavones are a subgroup of phenolic compounds widely distributed in plants of the Fabaceae family (Křizová, Dadáková, Kašparovská, & Kašparovský, 2019). Structurally, the isoflavonoids possess a B ring attached to position C-3 of ring C (3-phenylchroman skeleton); some examples are genistein (4′,5,7-Trihydroxyisoflavone), daidzein (7,4′-dihydroxyisoflavone), glycitein (7,4′-dihydroxy-6-methoxyisoflavone), biochanin A (5,7-dihydroxy-4′-methoxyisoflavone), and formononetin (7-hydroxy-3-[4-methoxyphenyl]-4H-chromen-4-one) (Al-Maharik, 2019) (Figure 2). The primary sources of isoflavones are legumes from the Fabaceae family, including soybeans (*Glycine max* L.), red clover (*Trifolium pratense* L.), and Chickpea (*Cicer arietinum* L.) (Bilal, Chowdhury, Davidson, & Whitehead, 2014; Křizová et al., 2019).

Isoflavonoids have been found in two chemical forms, aglycones (formononetin and biochanin A) or glycosides (daidzin and genistin). Also, the isoflavone glycosides can be esterified with an acetyl or malonyl group; the presence of hydroxyl and sugar groups increase the solubility of isoflavones in water, while methyl groups, isopentyl units, and other substituents allow isoflavone molecules to be lipophilic (Křizová et al., 2019).

Interestingly, in recent years, various biological activities of isoflavonoids have been reported in the maintenance of human health.

5 | BIOLOGICAL ACTIVITY OF ISOFLAVONOIDS

Isoflavonoids have shown antioxidant effects due to their free radical scavenging capacity by donating hydrogen atoms of the hydroxyl group attached to the benzene ring, thus protecting against oxidative damage and macromolecule damage, reducing low-density lipoproteins (LDL) (Yoon & Park, 2014). Besides, isoflavonoids promote the activation and expression of the antioxidant enzymes catalase (CAT), superoxide dismutase (SOD), and glutathione (GSH), decreasing the activation and expression of hepatic malondialdehyde (MDA) through the regulation of the Nrf2 and PPARγ pathways (Zhang et al., 2013).

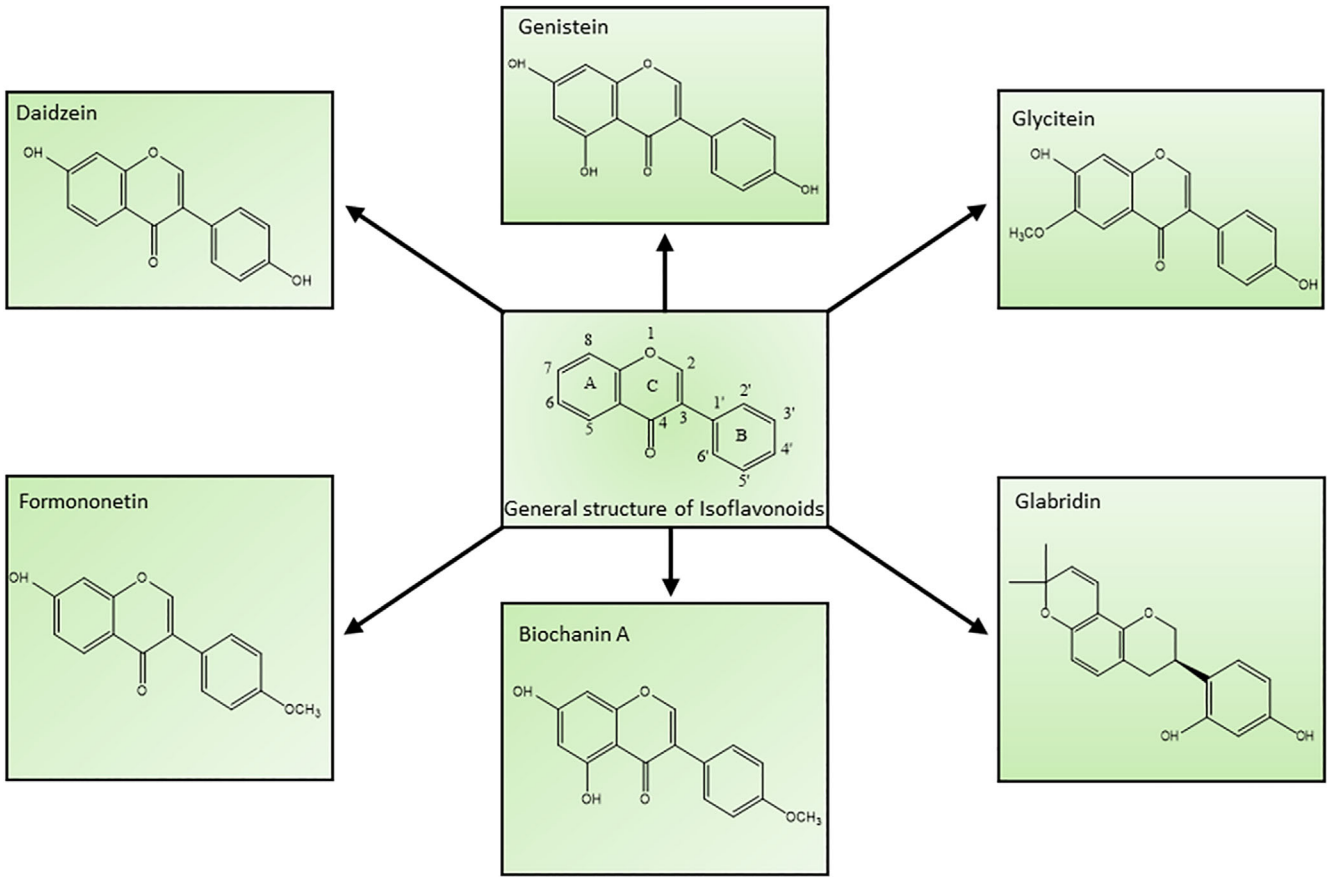

FIGURE 2 Chemical structure of Isoflavonoids including: genistein, daidzein, glycitein, formononetin, biochanin A, and glabridin [Colour figure can be viewed at wileyonlinelibrary.com]

Structurally, isoflavonoids show similarities to estrogens, bind to estrogen receptors with a preferential affinity for ERβ, competing with 17β-estradiol for the receptor's ligand-binding domain, and exhibit estrogenic as well as antiestrogenic activities. The antiestrogenic activity is associated with a lower incidence of estrogen-related cancers such as breast and ovarian cancer, where they have shown antimutagenic, antiproliferative, and antitumor effects (Basu & Maier, 2018; Lepri et al., 2013).

Recent evidence demonstrates the biological effect of isoflavonoid compounds and their potential in developing new drugs to treat invasive cancer (Abdal Dayem et al., 2016). These data are summarized below.

6 | ANTIINVASIVE ACTION OF ISOFLAVONOIDS

Isoflavonoids have shown biological activity as therapeutic agents for the potential treatment of invasive cancer; several studies in vitro, in vivo, and clinical trials show antitumor activity on invasion and metastasis markers, dysregulating different cancer-related signaling pathways (Figure 3).

6.1 | In vitro studies

In numerous in vitro studies, the antiinvasive effect of isoflavonoids has been reported on different cancer cell lines. These findings are summarized below (Table 1).

6.1.1 | Genistein

The most studied isoflavonoid is genistein; its effect has been observed in several cancer cell lines (Table 1). In MDA-MB-435 and MDA-MB-231 breast cancer cells, genistein treatment decreased cell migration and invasion due to decreased osteopontin expression (Khongsti et al., 2021). In PC3 prostate cancer cells, genistein inhibited cell migration by reducing MMP-2 secretion, suggesting that genistein indirectly blocks MMP-2 expression through the p38 MAPK pathway (Shafiee et al., 2020). In HeLa cervical cancer cells, genistein treatment inhibited cell migration and invasion by regulating the FAK-paxillin and MAPK signaling pathways (Chen et al., 2020). In ovarian cancer cells, SKOV-3, A2780CP, and OVCAR-3 that overexpress ERα and ERβ, genistein and daidzein decreased cell migration and invasion by inhibiting activation of the FAK and PI3K/Akt/GSK signaling pathways; these isoflavonoids also increased the expression of p21 and E-cadherin and decreased the expression of vimentin (Chan et al., 2018). Additionally, in B16F10 melanoma cells, genistein inhibited cell migration and invasion by modulation the MAPK and FAK/paxillin pathways, since the treatment decreased expression of p-FAK, p-paxillin, tensin-2, vinculin, and α-actin, also showed a significant effect in the decrease in p-p38, p-ERK, and p-JNK expression (Cui et al., 2017). Genistein also reverses the epithelial-mesenchymal transition in gastric cancer stem cells GCSLC derived from SGC-7901 human gastric cancer cells, the treatment with 7-difluoromethoxyl-5,4′-di-n-octyl genistein decreased N-cadherin and Twist1 expression and increased E-cadherin expression in a FoxM1-dependent pathway (Cao et al., 2016). In another study, genistein inhibited migration in the hepatocellular carcinoma cells HepG2, SMMC-7721, and BEL-7402 by suppressing the EMT program induced by TGF-β. Changes in mRNA and protein levels of mesenchymal markers such as N-cadherin and vimentin and increased expression of epithelial markers as E-cadherin and α-catenin were observed (Dai et al., 2015). Furthermore, in H466 lung cancer cells, genistein reduced cell migration by suppressing FoxM1 activity and decreasing MMP-2 and MMP-9 secretion and activation (Tian et al., 2014). In the hepatocellular carcinoma cells HepG2, Huh-7, and HA22T, genistein decreased 12-O-Tetradecanoylforbol-13-acetate (TPA) -induced invasion and cell migration by suppressing MMP-9 transcriptional expression. This effect is by inhibiting the MAPK, IκB, and PI3K/Akt signaling pathways and regulating the activity of activating protein (AP)-1 and nuclear factor-κB (NF-κB) (Wang et al., 2014). In HeLa cervical cancer cells, genistein inhibited cell migration through the modulation in the secretion of MMP-9 and its inhibitor TIMP-1 (Hussain et al., 2012). In MHCC97-H hepatocellular carcinoma cells, genistein also inhibited invasion, it

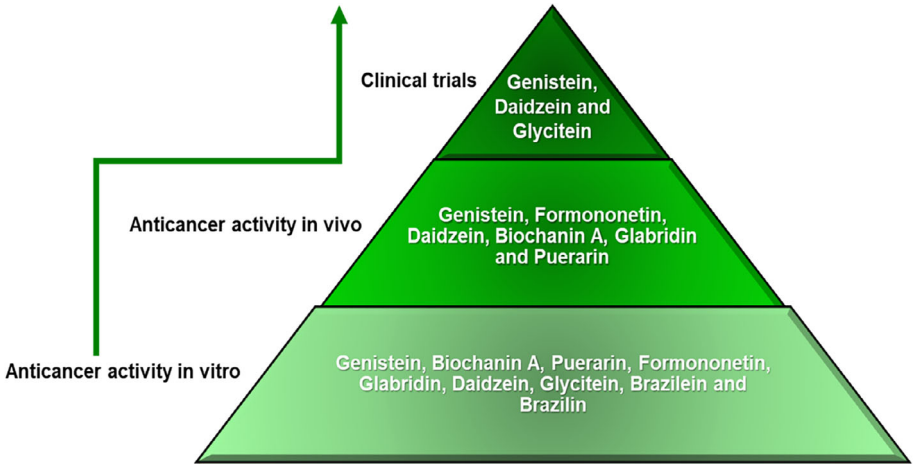

FIGURE 3 Antitumor activity of isoflavonoids in preclininal and clinical trials [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 In vitro effect of isoflavonoids

Isoflavonoid	Model	Concentration/time	Antiinvasive effect	Reference
Genistein	MDA-MB-435 y MDA-MB-231 breast cancer cells	50 μM (72 h)	↓Osteopontin	Khongsti, Das, and Das (2021)
	PC3 prostate cancer cells	50 μM (24 h)	↓MMP-2	Shafiee, Saidijam, Tayebinia, and Khodadadi (2020)
	HeLa cervical cancer cells	100 μM (2 h and 48 h)	↓ FAK-paxillin and MAPK	Chen et al. (2020)
	SKOV-3, A2780CP, and OVCAR-3 ovarian cancer cells	50 μM (48 h)	↓FAK, PI3K/Akt/GSK, vimentin ↑p21, E-cadherin	Chan et al. (2018)
	B16F10 melanoma cells	50 μM (24 h)	↓Tensin-2, vinculin, α-actinin, p38, ERK, JNK	Cui et al. (2017)
	GCSLC gastric cancer stem cells	10 μM (48 h)	↓N-cadherin, Twist ↑E-cadherin	Cao et al. (2016)
	HepG2, SMMC-772,1 and Bel-7402 hepatocellular cancer cells	9 μM (24 h)	↑E-cadherin, α-catenin ↓N-cadherin, vimentin	Dai et al. (2015)
	H466 lung cancer cells	50 μM (48 h)	↓FoxM1, MMP-2, MMP-9	Tian et al. (2014)
	HepG2, Huh-7, and HA22T hepatocellular cancer cells	40 μM (24 h)	↓MMP-9	Wang, Chen, Kao, Liu, and Yeh (2014)
	MHCC97-H hepatocellular carcinoma cells	20 μg/mL (90 min)	↓FAK	Gu, Zhu, Dai, Zhong, and Sun (2009)
	HCC1395 breast cancer cells	50 μM (72 h)	↓MMP-2, MMP-7, CXCL12	Lee, Huang, Tzeng, Chang, and Hsu (2007)
Genistein/Glycitein/ Daidzein	MDA-MB-231 breast cancer cells	50 μM (48 h)	↓MMP-9 ↑TIMP-1	Magee, McGlynn, and Rowland (2004)
Biochanin A	U-87MG and T98 multiforme glioblastoma cells	70 μM (72 h)	↓EGFR, ERK, Akt, MMP-2, MMP-14 ↑p53	Desai et al. (2019)
	Co-culture of the human lung adenocarcinoma cell line A427 and the human monocytic leukemia cell line AML-193	20 μM (24 h)	↓EMT, Snail ↑E-cadherin	Wang, Li, and Chen (2018)
	SK-MEL-28 human malignant melanoma cells	50 μM (48 h)	↓Cell migration and invasion	Xiao, Zheng, Sun, and Yang (2017)
	FaDu pharynx squamous carcinoma cells	25 μM (24 h)	↓MMP-2, MMP-9	Cho et al. (2017)
	HER2-overexpressed SK-BR-3 breast cancer cell	50 μM (72 h)	↓NF-κB, MMP-9, MMP-14	Sehdev, Lai, and Bhushan (2009)
Puerarin	Bel-7,402, Huh7, and L02 hepatocellular carcinoma cells	50 mM (24 h)	↑E-cadherin ↓Vimentin, N-cadherin, Snail, Slug, PTEN	Zhou, Xue, Wang, and Ren (2020)
	T24 and UM-UC-3 bladder cancer cells	50 and 100 μg/mL (24 h)	↓MMP-2, MMP-9	Du, Zhang, and Sun (2020)
	HeLa cervical cancer cells	1–2 mM (48 h)	↓PI3K, Akt, mTOR	Jia, Hu, Yang, and Li (2019)
	T24 and EJ bladder cancer cells	100 μM (48 h)	↓mTOR/p70S6K	Jiang et al. (2017)
	MCF-7 and MDA-MB-231 breast cancer cells	50 μM (24 h)	↓CCR7, CXCR4, MMP-2, MMP-9, ICAM, VCAM, TNF-α, IL-6, NF-κB	Liu, Zhao, Wang, Lin, and Yang (2017)
	A549 lung cancer cells	40 μM (48 h)	↓VEGF, MMP-9, ICAM-1	Kang et al. (2017)

TABLE 1 (Continued)

Isoflavonoid	Model	Concentration/time	Antiinvasive effect	Reference
Formononetin	SGC-7901 and MGC-803 gastric cancer cells	30, 50, and 80 μM (24 h)	↓ miR-542-5p	Wang, Li, Zhao, and Fan (2018)
	SW1116 and HCT116 colon carcinoma cells	200 μM (48 h)	↓MMP-2, MMP-9	Wang, Li, Zhao, and Fan (2018)
	A2780 and SKOV3 ovarian cancer cells	40 μM (48 h)	↓MMP-2, MMP-9	Zhang et al. (2018)
	MDA-MB-231 and T47D breast cancer cells	160 μM (12 h)	↓MMP-2, MMP-9 ↑TIMP-1, TIMP-2	Zhou et al. (2014)
Glabridin	MG63 and HOS human osteosarcoma cell lines	20 mM (24 h)	↓MMP-2, MMP-9	Jie et al. (2019)
	Huh7 and Sk-Hep-1, human hepatoma cell lines	40 μM (24 h)	↓MMP-9	Hsieh, Lin, Yang, Chen, and Chiou (2014)
	Human non-small cell lung cancer A549, MDA-MB-231 breast cancer cells, and HUVEC cells	10 μM (48 h)	↑E-cadherin ↓Vimentin, N-cadherin, Integrin αv, β3	Hsu et al. (2011); Tsai et al. (2011)
Daidzein	MCF10DCIS.com breast cancer cells	30 μM (24 h)	↓MMP-9	Bao et al. (2014)
	MDA-MB-231 breast cancer cells	50 μM (48 h)	↓MMP-2	Magee, Allsopp, Samaletdin, and Rowland (2014)
Glycitein	U87MG human astroglioma cells	50 ng/mL (24 h)	↓MMP-3, MMP-9, NF-κB, AP-1	Lee et al. (2010)
Brazilin	MCF7/HER breast cancer cells	25 μM (24 h)	↓MMP-2, MMP-9	Jenie, Handayani, Susidarti, Udin, and Meiyanto (2018)
Brazilein	MDA-MB-231 breast cancer cells	20 μM (24 h)	↓MMP-9	Hsieh, Tsai, Chu, Chang, and Chang (2013)
	Vascular smooth muscle cells (VSMC)	30 μM (24 h)	↓MMP-9	Guo et al. (2013)

decreased FAK phosphorylation and activation (Gu et al., 2009). While in HCC1395 primary breast cancer cells, genistein inhibited invasion by decreasing the expression of MMP-2, MMP-7, and CXCL12 (Lee et al., 2007). Genistein also significantly decreased the invasive capacity in MDA-MB-231 breast cancer cells, an effect attributed to the decrease in MMP-2 secretion (Magee et al., 2004).

All these data together demonstrate that genistein inhibits MMP-2 and MMP-2 secretion/activation as well as cell migration and invasion in a PI3K-Akt and FAK-paxillin signaling pathways-dependent manner in various cancer cell lines.

6.1.2 | Biochanin A

In the human glioblastoma cell lines U-87 MG and T98 G, biochanin A showed a synergistic effect with the chemotherapeutic agent temozolomide inhibiting the phosphorylation and activation of ERK, Akt, and c-Myc. The treatment also decreased MMP-14 and MMP-2 and promoted the expression of p53 (Desai et al., 2019). Co-culture of the A427 lung adenocarcinoma cell line and the AML-193 monocytic leukemia cell line, biochanin A inhibits invasion in A427 cells and inhibits the production of TNF-α and IL-6, suggesting biochanin A reduces the proinflammatory activity, besides, reduces Snail expression and increases E-cadherin expression, inhibiting thus the EMT process (Wang, Li, & Chen, 2018). In SK-Mel-28 human malignant melanoma cells, Biochanin A inhibits cell migration and invasion through the NF-κB and MAPK signaling pathways (Xiao et al., 2017). Biochanin A also inhibited cell migration and invasion in FaDu human pharynx squamous carcinoma cells, decreasing MMP-2 and MMP-9 secretion, an effect mediated by inhibition in phosphorylation and activation of p38, NF-κB, and Akt signaling pathways (Cho et al., 2017). Biochanin A also inhibited the phosphorylation and activation of ERK1/2 and Akt in SK-BR-3 breast cancer cells that overexpress HER2. It also showed an effect on the inhibition of NF-κB and a decrease in the activity and secretion of MMP-9 and MMP-14, suggesting a blockage in signaling pathways that promote invasion (Sehdev et al., 2009).

Interestingly, these studies report that biochanin A inhibits the expression of MMP-2, MMP-9, MMP-14, and EMT in cancer cell lines. In addition, the signaling pathways by which biochanin A inhibits cell migration and invasion are through ERK, Akt, and NFκB.

6.1.3 | Puerarin

In Bel-7,402, Huh7, and L02 hepatocellular carcinoma cells, puerarin decreased cell migration and invasion; puerarin also controlled the EMT-related genes promoting the expression of E-cadherin and reduce the expression of vimentin, N-cadherin, Snail, and Slug and inhibiting PTEN expression (Zhou et al., 2020). Treatment with

puerarin decreases the migration and invasion of T24 and UM-UC-3 bladder cancer cells, an effect attributed to the decrease in the activation levels of MMP-2 and MMP-9 (Du et al., 2020). Puerarin also inhibited cell migration in HeLa cervical cancer cells by decreasing PI3K, Akt, and mTOR expression (Jia et al., 2019). While in T24 and EJ bladder cancer cells, puerarin inhibited cell invasion and activation of the mTOR/p70S6K signaling pathway (Jiang et al., 2017). In another study, treatment with puerarin significantly inhibited lipopolysaccharide (LPS)-induced cell migration, invasion, and adhesion in MCF-7 and MDA-MB-231 breast cancer cells. An effect due to the decrease in the expression of CCR7, CXCR4, MMP-2, MMP-9, ICAM, and VCAM as well as TNF-α and IL-6, and inhibition in the NF-κB activation suggesting this effect was mediated by phosphorylation of p65 and IκBα (Liu et al., 2017). Furthermore, in A549 lung cancer cells, puerarin inhibited cell migration and invasion due to VEGF expression inhibition, MMP-9, and ICAM-1 (Kang et al., 2017).

Importantly, puerarin inhibits cell migration and invasion in a mTOR/p60S6K pathway-dependent manner in cancer cell lines. It also inhibits the EMT process by decreasing the expression of mesenchymal markers such as Snail, Slug, vimentin, N-cadherin, MMP-2, and MMP-9.

6.1.4 | Formononetin

In SGC-7901 and MGC-803 gastric cancer cells, formononetin treatment inhibited the capacity for cell migration and invasion, suggesting that the effect was due to a decrease in the expression levels of miR-542-5p (Wang & Zhao, 2020). In SW1116 and HCT116 colon carcinoma cells, formononetin suppressed cell growth by dysregulation the expression of cyclin D1 and arrest of the cell cycle in the G0-G1 phase. Formononetin also inhibited the secretion of MMP-2 and MMP-9 by dysregulation the PI3K/Akt signaling pathway and inactivation of the transcription factor STAT3 (Wang, Li, Zhao, & Fan, 2018). Furthermore, in the A2780 and SKOV3 ovarian cancer cell lines, the cell migration and invasion capacity diminished due to the decrease in MMP-2 and MMP-9 expression and dysregulation in ERK phosphorylation (Zhang et al., 2018). In MDA-MB-231 and 4T1 invasive breast cancer cells, formononetin decreased the ability of cell migration and invasion, decreased secretion MMP-2 and MMP-9, and increased expression of the tissue metalloproteinase inhibitors TIMP-1 and TIMP-2, an effect probably due to inhibition of the PI3K/Akt signaling pathway (Zhou et al., 2014).

Importantly, formononetin inhibits cell migration and invasion by downregulation of miR-542-5p. It also inhibits the secretion of MMP-2 and MMP-9 and the expression of the metalloprotease inhibitors TIMP-1 and TIMP-2.

6.1.5 | Glabridin

In MG63 and HOS osteosarcoma cell, glabridin inhibited invasion by decreasing MMP-2 and MMP-9 secretion and by reducing expression of the c-Fos, c-Jun proteins. The formation of the CREB–AP1 (c-Fos–c-Jun) complex was attenuated by inhibiting the phosphorylation and activation of p38 and JNK through the ERK1/2 signaling pathway (Jie et al., 2019). Furthermore, glabridin significantly inhibited cell migration and the invasive capacity of HCC, Huh7, and Sk-Hep-1 human hepatoma cells by inhibiting the ERK1/2/NF-kB/AP-1/c-Fos/c-Jun and JNK1/2/NF-kB/AP-1/c-Fos/c-Jun signaling pathways and consequently reduced the binding of NF-kB and AP-1 to the promoter region of the *MMP9* gene, preventing its transcription (Hsieh et al., 2014). Glabridin also inhibited cell migration and invasion in MDA-MB-231 breast cancer cells, HUVEC human umbilical vein endothelial cells, and A549 lung cancer cells by inhibition of FAK and Src activation and blockage Akt and ERK1/2 signaling pathways, in addition to decreased expression of vimentin and N-cadherin, as well as α5 and β3 integrin (Hsu et al., 2011; Tsai et al., 2011).

6.1.6 | Daidzein

In MCF-10DCIS.com breast cancer cells, daidzein suppressed tumor necrosis factor-α-induced cell migration, as well as MMP-9 activation and invasion by inhibiting Hedgehog/Gli1 signaling (Bao et al., 2014). Daidzein also inhibited invasion in MDA-MB-231 breast cancer cells through the down-regulation of MMP-2 (Magee et al., 2014).

6.1.7 | Glycitein

In U87MG human astroglioma cells, glycitein inhibited cell invasion by preventing activation and secretion of MMP-3 and MMP-9 induced by the tumor promoter PMA, glycitein also inhibited DNA binding and decreased NF-κB and AP-1 transcriptional activity (Lee et al., 2010).

6.1.8 | Brazilein and brazilin

Brazilein and brazilin are the isoflavonoids less studied; the antiinvasive or metastatic effect of these isoflavonoids is shown below. The combination of brazilin with doxorubicin inhibited cell migration in MCF7/HER2 breast cancer cells by decreasing the MMP-2, MMP-9 secretion, and dysregulation of Rac1 decreased in p120 and HER2 expression (Jenie et al., 2018). In MDA-MB-231 breast cancer cells, brazilein inhibited cell migration and invasion by preventing the PI3K/Akt and p38MAPK signaling pathways and inhibiting the transcriptional activity NF-kB and consequently the MMP-9 expression (Hsieh et al., 2013). Finally, brazilin inhibited cell migration, Src phosphorylation, and blocking the ERK1/2 and Akt signaling pathways in VSMC smooth muscle vascular induced by platelet-derived growth factor (PDGF-BB) (Guo et al., 2013).

In conclusion, in several studies using cancer cell lines, isoflavonoids promote a decrease in the expression or activation of invasion-related markers such as MMP-2, MMP-9, and MMP-14. In addition, isoflavonoids inhibit cell migration by inhibiting regulatory

proteins such as FAK and Paxillin, both processes being regulated by signaling pathways such as PI3K-Akt, ERK, and mTOR-p60S6K.

6.2 | In vivo effects

The studies on the in vivo effect of isoflavonoids on invasive cancer markers using animal models are summarized below (Table 2).

6.2.1 | Genistein

In female BALB/c athymic nude mice with MCF-7/ERβ1 and MDA-MB-231/ERβ1 breast tumor cell xenografts, oral administration of genistein suppressed tumor growth in a time and dose-dependent manner, suggesting that the effect was due to arrest of the cell cycle (Jiang et al., 2018). In BALB/c nu/nu female mice, inoculated with HCC-LM3 hepatocellular carcinoma cells, treated with oral genistein showed a significant decrease in tumor size; the effect was inhibiting PCNA expression, HIF-1 α/GLUT1/HK2 (Li et al., 2017). In female Sprague–Dawley rats fed a diet of genistein (genistein for life) and genistein after breast tumor induction using anthracene7,12-dimethylbenz (a) (DMBA), treated with tamoxifen, genistein deficiency reduces de novo tamoxifen resistance. After diagnosis, administration with genistein reduced recurrence risk by decreasing the expression of autophagy-related genes UPR, GRP78, IRE1α, ATF4, and Beclin-1 and proteins linked immunosuppression (TGFβ and Foxp3). Genistein also promotes dysregulation of the cytotoxic T cell marker CD8a in tumors from the genistein group for life and the genistein group post-diagnosis (Zhang et al., 2017). In female BALB/c mice inoculated with S180 mouse sarcoma cells, intraperitoneal, genistein treatment increased radiosensitivity, showing decreased tumor volume and size. The treatment with X-ray in combination with genistein promotes apoptosis by increased Bax expression and decreased Bcl-2 expression (Liu et al., 2016). In nude BALB/c female mice inoculated with MGC-803 gastric cancer cells, daily treatment with genistein for 7 days reduced tumor size and weight relative to control (Huang et al., 2014). In a nude female mice model injected with MCF7 breast cancer cells, genistein injected peritoneally decreased tumor weight and ALDH levels, indicating that the effect was by inhibition in the Hedgehog-Gli1 signaling pathway (Fan et al., 2013). While in a C57BL/6J female mouse model subcutaneous inoculated with the melanoma cell line B164A5, administration of genistein decreased tumor volume and weight as well as metastatic potential (Danciu et al., 2013). In a model of azoxymethane-induced Sprague–Dawley female rat colon cancer, administration of dietary genistein 140 mg/kg from gestation to 13 weeks of age inhibited the development of aberrant colon crypts. Genistein also decreased expression in β-catenin, c-Myc, Wnt5a, and Sfrp2, while lifetime exposure to genistein reduces the incidence and frequency of colon preneoplasia (Zhang, Li, et al., 2013). In BALB/c nu/nu male mice with hepatocellular carcinoma MHCC97-H xenografts, the intraperitoneal administration of genistein for 20 days has been observed inhibited tumor growth and weight and decreased the number of micrometastatic lung foci (Gu et al., 2009). In a model of immunodeficient female mice injected with 253 J BV human bladder cancer cells, treatment with genistein for 2 weeks decreased tumor size, induced apoptosis. It inhibited angiogenesis by decreasing NF-κB expression and increased IκB-α, treatment with dietary genistein also inhibited lung metastasis (Singh et al., 2006). In another study, the nude female mice (ICR-SCID) injected with pancreatic tumor cells COLO 357 and L3.6pl, orally administrated genistein combined with gemcitabine showed a synergistic effect in decreasing tumor weight and inhibition of NF-κB (Banerjee et al., 2005). In mice C57BL/6J treated with a diet enriched with genistein and daidzein (0.3%) for 7 days, the production of IFN-γ after administration of IL-12/IL-18 was decreased, thus modulating the activity of natural killer cells (Mace et al., 2019).

In summary, the administration of genistein in animal models promotes a reduction in tumor size and volume. Interestingly, it also inhibits the number of metastatic tumors in the lung.

6.2.2 | Formononetin

In BALB/c nude mice with SGC-7901 cell xenograft tumors of gastric cancer, intragastric administration with formononetin (30 mg/kg) three times per week decreased tumor size and volume (Wang & Zhao, 2020). In athymic nu/nu female mice with U266 human multiple myeloma xenograft tumors, formononetin intraperitoneally administration inhibited tumor growth and activation of STAT3 and STAT5. It blocked their nuclear translocation by preventing their binding to DNA, suggesting that this effect is correlated with suppression in JAK1, JAK2, and c-Src kinases activation. It is mediated by increased production of reactive oxygen species (ROS) due to the GSH/GSSG imbalance (Kim et al., 2018). In nude BALB/c female mice with HCT116 colorectal carcinoma cell xenograft tumors, formononetin administration significantly reduced tumor growth by inhibiting the PI3K/Akt and STAT3 signaling pathways (Wang, Li, Zhao, & Fan, 2018). Regarding BALB/c nude female mice with CNE1 nasopharyngeal carcinoma cell xenografts, the formononetin treatment at a high or low dose (20 and 10 mg/kg, respectively) administered intraperitoneally every 2 days for 10 days, decreased volume and tumor mass in a dose-dependent manner; formononetin also increased p-JNK1/2, p-p38, Bax, and caspase-3 and decreased p-Akt and Bcl-2 expression (Qi et al., 2016). In BALB/c immunodeficient mice with MDA-MB-231 breast cancer cell xenografts, the treatment with formononetin 100 mg/kg intragastric via decreased tumor volume and weight. Besides, formononetin inhibited the activation of FGF2Rα, PI3K, Akt, STAT3, and the secretion of MMP-2/MMP-9 (Wu et al., 2015). Treatment with formononetin in BALB/c nude female mice with MDA-MB-231-luc breast cancer cells decreased pulmonary metastasis development in a dose and time-dependent manner by inhibiting the PI3K/Akt signaling pathway and decrease in MMP-2 and MMP-9 secretion (Zhou et al., 2014). In a HeLa human cervical tumor cell xenograft model in BALB/c mice, intragastric administration of formononetin at low and high doses (20 and 40 mg/kg, respectively) once daily for

TABLE 2 In vivo effect of isoflavonoids

Isoflavonoid	Model	Dose-time	Effect	Reference
Genistein	In female BALB/c athymic nude mice with MCF-7/ERβ1 and MDA-MB-231/ERβ1 breast tumor cell xenografts	1,000 ppm (30 d)	↓Tumor growth	Jiang, Fan, Cheng, Hu, and Liu (2018)
	Mice BALB/c inoculated with HCC-LM3 hepatocellular carcinoma cells	80 mg/kg (20 d)	↓Tumor size, PCNA, HIF-1 α, GLUT1	Li et al. (2017)
	Female Sprague–Dawley rats	500 ppm (10.9 ± 0.8 weeks)	↓Resistance to tamoxifen, recurrence, *UPR*, *GRP78*, *IRE1α*, *ATF4*, *Beclin-1* genes, TGFβ, FOXP3	Zhang et al. (2017)
	Female BALB/c mice inoculated with S180 mouse sarcoma cells	200 mg/kg (24 h)	↑Radiosensitivity ↓Tumor volume and size	Liu et al. (2016)
	Nude BALB/c mice inoculated with MGC-803 gastric cancer cells	1.5 mg/kg (7 d)	↓Tumor size and weight, BCG2 mRNA	Huang, Wan, Luo, Huang, and Luo (2014)
	Mice inoculated with MCF7 breast cancer cells	50 mg/kg (2 weeks)	↓Tumor weight, ALDH, hedgehog–Gli1 signaling pathway	Fan et al. (2013)
	C57BL/6J mice inoculated with the melanoma cell line B164A5	15 mg/kg (15 d)	↓Tumor volume and weight, and metastatic potential	Danciu, Borcan, Bojin, Zupko, and Dehelean (2013)
	Sprague–Dawley rats with colon cancer	140 mg/kg (13 weeks)	↓Development of aberrant colon crypts, β-Catenin, c-Myc, Wnt5a, Sfrp2	Zhang, Li, Zhou, and Chen (2013)
	BALB/c nu/nu mice with MHCC97-H hepatocellular carcinoma cell xenografts	50 mg/kg (20 d)	↓Tumor growth and weight ↓Number of micrometastatic pulmonary foci	Gu et al. (2009)
	Mice inoculated with human bladder cancer cells 253J BV	0.14% (2 weeks)	↓Tumor size, angiogenesis, lung metastasis, NF-kB ↑IκB-α	Singh, Franke, Blackburn, and Zhou (2006)
	Nude female mice (ICR-SCID) inoculated with COLO 357 and L3.6pl pancreatic tumor cells	1 mg/d (10 d)	↓Tumor weight and NF-kB	Banerjee et al. (2005)
Genistein/ Daidzein	Mice C57BL/6 J	7.246 g/kg (7 d)	↓ IFN-γ production after IL-12/IL-18 treatment	Mace et al. (2019)
Formononetin	BALB/c nude mice with gastric cancer SGC-7901 cell xenograft tumors	(30 mg/kg) three times per week	↓Tumor growth	Wang and Zhao (2020)
	Athymic nu/nu mice with human multiple myeloma xenograft tumors U266	40 mg/kg (3 weeks)	↓Tumor growth and STAT3/5	Kim et al. (2018)
	BALB/c mice with HCT116 colorectal carcinoma cell tumors	15 mg/kg (14 d)	↓Tumor growth, PI3K/Akt and STAT3	Wang, Li, Zhao, and Fan (2018)
	BALB/c mice with CNE1 nasopharyngeal carcinoma cell xenografts	20 mg/kg (10 d)	↓Tumor size, weight ↑p-JNK1/2, p-p38, Bax, caspase-3, p-Ak, Bcl-2	Qi et al. (2016)
	BALB/c mice with MDA-MB-231 breast cancer cell xenografts	100 mg/kg (25 d)	↓Tumor size, weight, FGF2Rα, PI3K, Akt, STAT3, MMP-2, MMP-9	Wu et al. (2015)
	BALB/c mice with MDA-MB-231-Luc breast tumor cell xenografts	20 mg/kg (35 d)	↓Development of metastasis, PI3K/Akt, MMP-2, MMP-9	Zhou et al. (2014)
	BALB/c mice with HeLa human cervical tumor cell xenografts	20 and 40 mg/kg (5 weeks)	↓Tumor weight, volume, pAkt	Jin, Xu, Zhao, Wang, and Cui (2014)
		60 mg/kg (20 d)		Li et al. (2014)

TABLE 2 (Continued)

Isoflavonoid	Model	Dose-time	Effect	Reference
	Nude mice with PC-3 prostate cancer cell xenograft		↓Tumor growth, weight, and Akt/Cyclin D1/CDK4	
	BALB/c nu/nu mice with colon cancer xenografts HCT-116	20 mg/kg (14 d)	↓Tumor size, proliferation, VEGF, MMPs, angiogenesis, invasion	Auyeung, Law, and Ko (2012)
	BALB/c mice with MCF7 breast tumor cell xenografts	60 mg/kg (20 d)	↓Tumor growth, IGF1/IGF1R-PI3K/Akt, and cyclin D1 mRNA	Chen, Zeng, Xin, Huang, and Chen (2011)
Daidzein	Mouse BALB/c inoculated with A549 lung cancer cells	—	↓Tumor size, Ki-67, p65-NF-κB	Guo et al. (2020)
	Nude mice with subcutaneous breast cancer xenografts injected with MCF7 cells and MCF7/ADR cells	5 mg/kg (15 d)	↓Tumor size, weight, ERα, BCRP ↑Bax, p53, p21	Guo et al. (2019)
	Nude mice inoculated with SKVO3 ovarian cancer cells	40 μg/kg (4 weeks)	↓Tumor size and Ki-67 ↑Caspase-3	Hua, Li, Chen, and Liu (2018)
	Nude mice injected with JEG-3 choriocarcinoma cells	20 mg/kg (4 weeks)	↓Xenograft growth, c-Myc, PCNA, p-ERK	Zheng et al. (2017)
	Mice BALB/c nu/nu with PC-3 prostate tumor	0.21 mg/kg (36 d)	↓Tumor size and lymph node metastasis	Singh-Gupta et al. (2010)
Biochanin A	Nude mice with A549 and 95D lung cancer cell xenografts	72 mg/kg (4 weeks)	↓Tumor size ↑Apoptosis	Li et al. (2018)
	Nude athymic female mice with MCF7 breast cancer cell xenografts	15 mg/kg (4 weeks)	↓Tumor volume and size	Moon, Shin, An, and Morris (2008)
	Athymic mice nu/nu with LNCaP prostate cancer cell xenograft	400 μg/mL (10 d)	↓Tumor size, cyclin E ↑p21	Rice et al. (2002)
Glabridin	Female Sprague–Dawley rats with mammary carcinogenesis	1 and 2.5 mg/kg (16 weeks)	↓Tumor volume, size, oxidative stress, and EGFR ↑Restoration of phase I and II antioxidant systems	Zhu et al. (2019)
	BALB/c nude mice with MDA-MB-231 breast cancer cell xenograft	20 mg/kg (6 weeks)	↓Tumor weight, SMAD2, DNMT1, DNMT3a, vimentin	Jiang et al. (2016)
	Male BALB/c nude mice with SK-Hep-1 cell hepatoma xenograft	10 mg/kg (28 d)	↓Tumor formation, MMP-9, ERK1/2, JNK1/2	Hsieh et al. (2014)
Puerarin	Male BALB/c nu/nu mice with xenografts of Bel-7,402 cells and Huh7 hepatocellular carcinoma cells	40 mg/kg (45 d)	↓Tumor weight, size, and metastasis, vimentin, N-cadherin, snail, slug, PTEN ↑E-cadherin	Zhou et al. (2020)
	Nude mice with UM-UC-3 bladder cancer cell xenografts	50 and 100 μg/mL	↓Tumor volume and weight, circular RNA 0020394, and NRBP1 ↑miR-328-3p	Du et al. (2020)
	Male BALB/c mice with colitis-associated colon cancer	4, 6 and 8 mg/kg (21 d)	↓Tumorigenesis, metastasis, TNF-α, IL-17A, N-cadherin, MMP-2, Snai1, Zeb1, Twist1	Deng et al. (2019)
	Mice with A549 lung carcinoma cell xenografts	40 mg/kg (30 d)	↓Tumor volume and size, IL-10, IL-4, TGF-β, MEK/ERK1/2	Kang et al. (2017)
6,8-diprenilgenisteína	BALB/c female mice	2,5 mg/kg (14 d)	↓Lymph node metastasis and VEGFR-2	Bae, Hwang-Bo, Lee, Lee, and Chung (2021)

5 weeks decreased weight and volume of the tumor and inhibited Akt phosphorylation, showing the highest concentration the most significant effect (Jin et al., 2014). In nude mice with PC-3 prostate cancer cell xenograft intraperitoneally administered with formononetin (15, 30, and 60 mg/kg/day) for 20 days, it inhibited tumor growth and weight in a dose-dependent manner. The effect was by inhibition in the activation of the Akt/Cyclin D1/CDK4 pathway (Li et al., 2014). In BALB/c-nu/nu female mice with HCT-116 colon cancer xenografts, 10 days after tumor induction, the treatment with formononetin for 14 days decreased the volume and tumor size and cell proliferation. Formononetin also reduced vascular endothelial growth factor (VEGF) and matrix metalloproteinases expression, suggesting formononetin inhibits angiogenesis and invasion in colon cancer tumor cells (Auyeung et al., 2012). In nude BALB/c mice with MCF7 breast tumor cell xenografts, treatment with formononetin inhibited local tumor growth in a dose-dependent manner, an effect mediated by inhibition in IGF1/IGF1R-PI3K/Akt signaling pathways and decreased expression in cyclin D1 mRNA (Chen et al., 2011).

Interestingly, in the results described in vivo, formononetin decreased the levels of MMP-2, MMP-9 and inhibition of the PI3K-Akt and JAK–STAT signaling pathways. In addition, formononetin decreased tumor size and volume, as well as invasion and metastasis to the lung.

6.2.3 | Daidzein

In BALB/c mice inoculated with A549 lung cancer cells, daidzein decreased tumor size and levels of Ki-67 and p65-NF-κB (Guo et al., 2020). Whereas, in nude mice with subcutaneous breast cancer xenografts injected with MCF7 and MCF7/ADR breast cancer cells, daidzein potentiated the chemotherapeutic effect of topotecan administered gastrointestinally and intraperitoneally every third day for 15 days. It showed a synergistic effect on inhibiting the size and tumor weight, suggesting that daidzein reversed breast cancer resistance to topotecan. Xenograft mice with MCF7 cells treated with topotecan- and daidzein-induced apoptosis through increased Bax, p53, and p21 expression and decreased Bcl2 expression, whereas in MCF7/ADR xenografted mice, the treatment decreased ERα and BCRP expression (Guo et al., 2019). In another study, immunodeficient nude mice inoculated with SKVO3 ovarian cancer cells, daidzein decreased the size of the tumor, suggesting a decrease in the Ki-67 expression and an increase in caspase-3 expression (Hua et al., 2018). Nude mice injected with JEG-3 choriocarcinoma cells, subcutaneous administration of daidzein inhibited xenografts' growth and suppressed c-Myc, PCNA, and p-ERK expression (Zheng et al., 2017). In BALB/c nu/nu nude male mice with PC-3 prostate tumors, the daily treatment with daidzein (0.21 mg/day) for 36 days acted as a radiosensitizer. It showed a synergistic effect with radiotherapy by reducing tumor size and inhibited lymph node metastasis, regulating AP1/Ref-1 (Apurinic/Apyrimidinic Endonuclease 1/Redox Factor-1), NF-κB, and HIF-1α in cells positive for the androgen receptor (AR) (Singh-Gupta et al., 2010).

6.2.4 | Biochanin A

In nude male mice with A549 and 95D lung cancer cell xenografts, treatment with biochanin A during 4 weeks significantly inhibited the tumor size due to cell cycle arrest and apoptosis, decreasing the expression of cyclin A, CDK2, and Bcl-2 and increasing the expression of Bax, Caspase-3, and p21 (Li et al., 2018). In athymic nude male mice with MCF7 breast cancer cell xenografts, treatment with biochanin A inhibited tumor volume and size (Moon et al., 2008). In athymic nu/nu male mice with LNCaP prostate cancer cell xenograft tumors, intraperitoneally treatment with biochanin A 400 μg/mL/day for 10 days, after 3 weeks of tumor implantation, decreased the tumor size, suggesting the effect was due to an increase in p21 and a decrease in cyclin E. However, at 6 weeks, the incidence of tumors was similar between the control group and the treated group, considering that the treatment shows a cytostatic effect, and eventually, the cells recover (Rice et al., 2002).

6.2.5 | Glabridin

In female Sprague–Dawley rats, mammary carcinogenesis by subcutaneous administration of 7,12-dimethylbenz [a] anthracene (DMBA) (25 mg) was induced. Treatment with glabridin once daily for 16 weeks, at a dose of 1, 2.5, and 5 mg/kg, decreased tumor volume and size, as well as oxidative stress by restoring phase I and II antioxidant systems and inhibited EGFR phosphorylation (Zhu et al., 2019). In nude BALB/c mice with MDA-MB-231 breast cancer cell xenograft, treatment with glabridin 20 mg/kg of body weight per day administered for 6 weeks, decreased tumor weight and SMAD2, DNMT1, DNMT3a, and vimentin expression, also decreased methylation of the miR-148a promoter (Jiang, Li, et al., 2016). In male nude BALB/c mice with SK-Hep-1 cell hepatoma xenograft, administration of glabridin 10 mg/kg for 28 days suppressed tumor formation, in addition to decreased levels of MMP-9 and inhibited phosphorylation in ERK1/2 and JNK1/2 (Hsieh et al., 2014).

6.2.6 | Puerarin

Male BALB/c nu/nu mice with Bel-7,402 cell xenografts and Huh7 hepatocellular carcinoma cells, puerarin 40 mg/kg for 45 days decreased the weight, size, number, and diameter of metastatic nodules in the liver also increased E-cadherin expression and reduced vimentin, N-cadherin, Snail, Slug and PTEN expression (Zhou et al., 2020). In nude mice with UUM-UC-3 bladder cancer cell xenografts transfected with puerarin 50 and 100 μg/mL, tumor volume and weight decreased, suggesting that the effect was due to an increase in miR-328-3p and a decrease in levels of circular RNA 0020394 and nuclear receptor 1 binding protein NRBP1 (Du et al., 2020). In male BALB/c mice with colitis-associated colon cancer, intraperitoneally treatment with puerarin 4, 6, 8 mg/kg for 21 days reduced tumorigenesis and metastasis by decreasing the TNF-α, IL-17A, N-cadherin, and

MMP-2 expression as well as a decrease in expression of the transcription factors Snai1, Zeb1, Twist1 (Table 2) (Deng et al., 2019). In contrast, in NOD/SCID mice with A549 lung carcinoma cell xenografts treated with puerarin 40 mg/kg for 30 days, there is a decrease in tumor volume and size, promoting the inhibition of the macrophages polarized to the M2 phenotype and a reduction in the expression of tumorigenesis-related cytokines (IL-10, IL-4, and TGF-β); in addition, puerarin also inhibited the activation of the MEK/ERK1/2 pathway (Kang et al., 2017).

These reports show that in in vivo models, pueranin promotes a decrease in tumor size and volume as well as a reduction in metastatic nodules in the liver. These events are related to the decline of transcription factors related to EMT.

6.3 | 6,8-diprenylgenisteine

In female BALB/c mice with sentinel lymph node from VEGF-A-induced oral cancer, treatment with a natural derivative of genistein (6,8-diprenylgenisteine) at a dose of 2.5 mg/kg every 2 days for 14 days by intraperitoneal injection suppressed lymph node metastasis, suggesting that the effect was by inhibition in VEGFR-2 signaling (Bae et al., 2021).

6.4 | Clinical trials

Isoflavonoids currently under evaluation in phase II and phase III clinical trials in cancer patients must meet the following criteria: randomized, double-blind, placebo-controlled studies (Amawi, Ashby, & Tiwari, 2017; Andrew & Izzo, 2017). Of these, genistein has been evaluated, and the synergistic effect of Genistein/daidzein/glycitein and Genistein/daidzein/equol has been assessed. In Table 3, we summarize the findings found in patients.

6.4.1 | Genistein

In another phase II trial in men with prostate cancer, the administration of genistein for 1 month before radical prostatectomy selectively affected the motility and metastasis-related genes in cancer cells by inhibiting the expression of mitogen-activated protein kinase 4 (MEK4) and MMP-2 (Zhang et al., 2019). In phase II clinical trial, in patients with prostate cancer, the administration of genistein 30 mg, from 3 to 6 weeks before prostatectomy, promoted the PTEN activity and inhibited the MYC activity (Bilir et al., 2017). In phase II clinical trial in 59 patients diagnosed with urothelial bladder cancer, genistein administered orally twice a day (300 or 600 mg/day) for 14 to 30 days before surgery; the treatment was well tolerated, and the administration of genistein inhibited the phosphorylation and activation of EGFR, Akt, and MAPK (Messing et al., 2012). In phase II clinical trial, patients with localized prostate adenocarcinoma in clinical stage T1 or T2, genistein PTI G-4660 150 mg/day for 4 weeks, inhibited the MEK4 kinase activity and decreased the transcriptional level of MMP-2 (Xu et al., 2009).

6.4.2 | Genistein/daidzein/glycitein

Administration of isoflavonoids (55% daidzein, 30% glycitein, and 15% genistein) 80 mg/day for 6 weeks in men with stage T1 or T2 localized prostate cancer reduced the expression of the prostate-specific antigen (PSA). It also decreased the expression of genes involved in the cell cycle, such as *CDC27*, *APAF1*, *CCNB2*, *CCNG2*, *CCNC*, *UBE1*, *CUL2*, *CUL3*, *E2F4*, and *CHEK2* (Hamilton-Reeves et al., 2013). In clinical trials, prostate-specific antigen (PSA) levels decreased in the group of patients with stage T1 or T2 prostate cancer treated with a supplement containing isoflavones (66% daidzein, 24% glycitein, and 10% genistein) 40 mg and curcumin 400 mg for 6 months (Ide et al., 2010).

TABLE 3 Effect of isoflavonoids in clinical trials

Isoflavonoid	Model	Dose-time	Effect	Reference
Genistein	Prostate cancer patients	150 mg/d (1 month)	↓MEK4, MMP-2	Zhang et al. (2019)
	Prostate cancer patients	30 mg/d (3–6 weeks)	↓MYC, PTEN, CD24, HIF-1α	Bilir et al. (2017)
	Patients with urothelial bladder cancer	300 and 600 mg/d (14–30 d)	↓pEGFR, pAkt, pMAPK	Messing et al. (2012)
	Patients with stage T1 or T2 Prostate adenocarcinoma	150 mg/d (4 weeks)	↓MEK4, MMP-2	Xu et al. (2009)
Genistein/ daidzein/ glycitein	Patients with stage T1 or T2 prostate cancer	80 mg/d (6 weeks)	↓PSA, *CDC27*, *APAF1*, *CCNB2*, *CCNG2*, *CCNC*, *UBE1*, *CUL2*, *CUL3*, *E2F4*, *CHEK2*	Hamilton-Reeves et al. (2013)
	Patients with stage T1 or T2 prostate cancer	400 mg/d (6 months)	↓PSA	Ide et al. (2010)
Genistein/daidzein/equol	Prostate cancer patients	47 mg (12 months)	↓PSA	Pendleton et al. (2008)

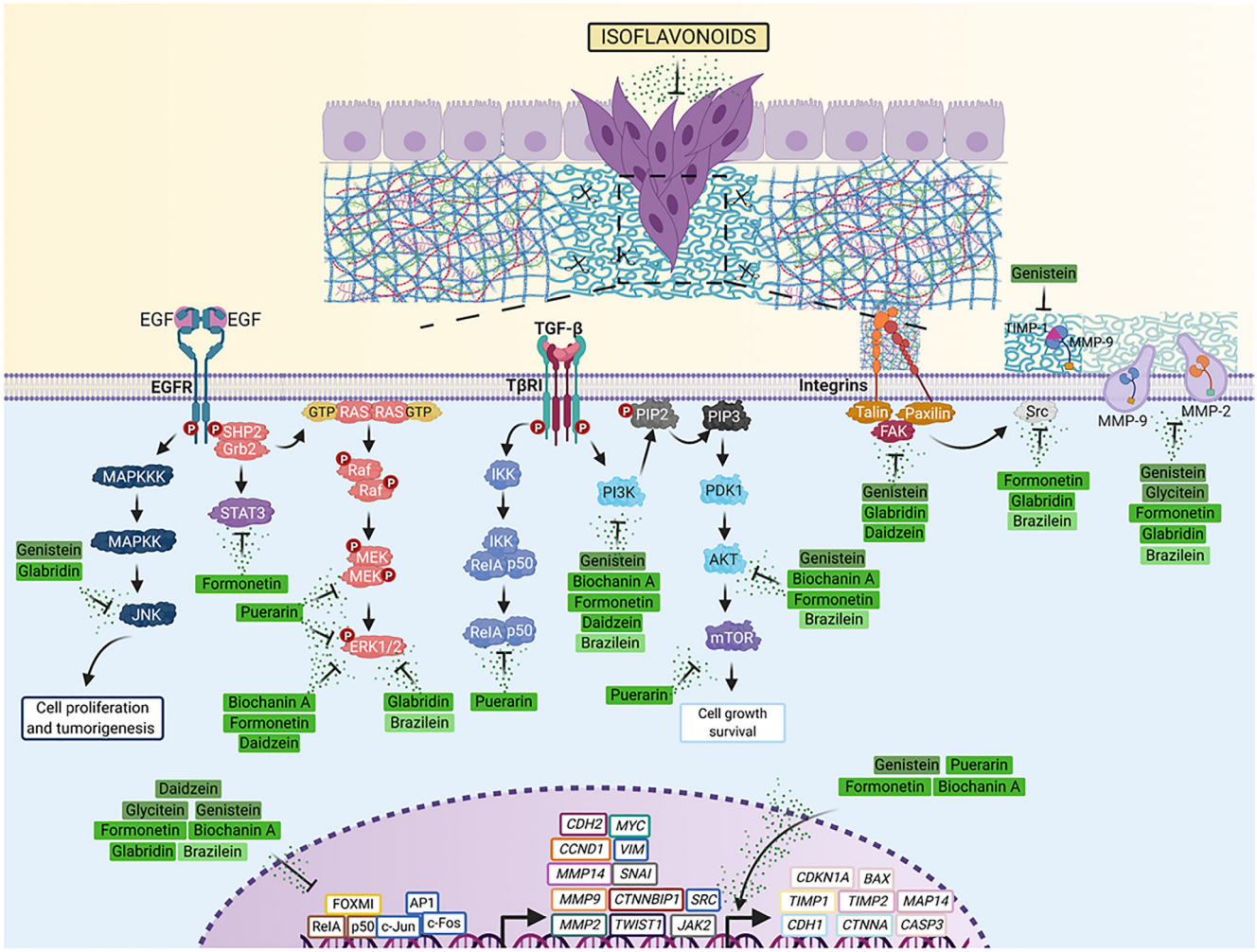

FIGURE 4 Proposed model of the effect of isoflavonoids on molecules related to the process of cell invasion and metastasis. The isoflavonoids biochanin A, formononetin, puerarin, glabridin, genistein, daidzein, glycitein, brazilein and brazilin, block signaling pathways mediated by TGF-β/IRS, EGF/EGFR, FAK/Paxillin, MAPK, IκB, PI3K/Akt ERK, STAT3, FAK, and Src. Downstream these isoflavonoids regulate the expression of transcription factors STAT3, AP1, c-Jun, c-Fos and inhibit the expression of the CDH2, CCND1, MMP14, MMP9, MMP2, MYC, VIM, SNAI, CTNNBIP1, and TWIST1 genes and promote the expression of CDKN1A, CDH1, TIMP1, TIMP2, and CTNNA genes, thus inhibiting the process of tumor invasion and metastasis [Colour figure can be viewed at wileyonlinelibrary.com]

6.4.3 | Genistein/daidzein/equol

While in a phase II study in prostate cancer patients with biochemical recurrence and elevated PSA levels, administration of isoflavonoids (genistein, daidzein, and equol) 47 mg/8 oz for 12 months decrease PSA levels reporting that isoflavonoid administration may have biological activity in men with recurrent prostate cancer (Pendleton et al., 2008).

Even though clinical trial reports indicate the potential of isoflavonoids in the treatment of cancer patients, additional studies are needed to validate their effectiveness without ignoring the limitations regarding the low solubility, bioavailability, and metabolic instability of isoflavonoids. Therefore, alternatives must be found to overcome these challenges.

7 | CONCLUSIONS

Currently, treatment strategies to inhibit cell invasion and metastasis of tumor cells remain limited; chemotherapy is the conventional form applied in the treatment of metastatic cancer; however, within its limitations are high toxicity and chemoresistance, and metastasis remains to be one of the leading causes of cancer deaths. A wide variety of studies supports the biological potential of isoflavonoid compounds on tumor invasion and metastasis. In in vitro assays, these compounds act by interfering with the signaling pathways involved in tumor progression such as NF-κB, PI3K/Akt, or MAPK/ERK. Downstream the isoflavonoids act by repressing genes such as *MMP2*, *MMP9* and *MMP14*, *VIM*, *RAC1*, and *HER2* and promote the expression of epithelial genes such as *CDH1*, *TMP1*, and *TIMP2*. Regarding in vivo assays,

several studies indicate that isoflavonoids decreased tumor volume and size in mice and reported that isoflavonoids act on the signaling pathways described in cancer cell cultures (in vitro assays).

Regarding clinical trials, although there is little evidence of the biological effect of isoflavonoids in humans. Several reports indicate that the effect of isoflavonoids genistein, daidzein, and glycitein are at the level of inhibition of signaling pathways that are related to the proliferation and cell invasion like EGFR, Akt, MAPK, and MMP-2 (Figure 4). Furthermore, there is transcriptional regulation in genes involved in cell invasion and metastasis at the transcriptional level. Considering the findings found in the different study models, these data give us the guideline to consider these isoflavonoids as a pharmacological promise in treating invasive cancer.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

L.C.-S. and N.N.-T. designed, conducted the literature review and wrote the manuscript; M.O.-F., M.D.Z.-E., G.F.-T., M.A.M.-C., A.E.Z.-G. and J.O.-O. conducted the literature review and wrote the manuscript; C.W.-O., and C.O.-P. wrote and revised the manuscript, N.N.-T. developed and designed the research. All authors approved the submitted version.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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