Suppression of Cancer Invasiveness by Dietary Compounds

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Abstract: Tumor invasion and cancer metastasis are interrelated processes involving cell growth, cell adhesion, cell migration and proteolytic degradation of tissue barriers, which are mediated by aberrant intracellular signaling in cancer cells. Natural (green tea polyphenols, soy isoflavones) or dietary compounds (mushroom *G. lucidum*) markedly decreased AP-1 and NF-κB signaling and suppressed invasiveness of cancer cells. This review will summarize alternative approaches for the inhibition of invasive behavior of cancer cells by dietary compounds, which can be considered in adjuvant or combination therapy for the prevention and treatment of cancer metastasis.

Key Words: Cancer invasion, metastasis, green tea, isoflavones, triterpenes, signaling.

INTRODUCTION

Breast, prostate, lung and colorectal cancers account for more than 50% of newly diagnosed cancers every year, and it is estimated that these cancers will be responsible for more than 280,000 cancer deaths in the United States in 2007 [1]. The major reason for such a high mortality from these cancers is the highly invasive behavior of cancer cells, which usually results in cancer progression and metastasis. Therefore, the suppression of cancer invasion will inhibit cancer metastasis and would eventually lead to a decrease in cancer deaths. Although inconclusive, epidemiological studies suggest the importance of different nutritional/natural products in preventing cancer. For example, the low incidence of breast cancers among Asian women has been associated with the high intake of soy products [2], consumption of green tea has been correlated with the prevention of a variety of cancers [3], and an inverse correlation between mushroom intake and the risk of gastric cancer has been described [4]. Because the breast cancer prevention trials with tamoxifen [5], a prostate cancer prevention trial with finasteride [6], and a colon cancer study with celexocib [7] have all demonstrated significant risks/side effects, the use of diet-derived compounds is a more promising strategy to delay or prolong one or more stages of the carcinogenesis process [8].

CARCINOGENESIS AND METASTASIS

Carcinogenesis is a long, overlapping process consisting of multiple stages: initiation, promotion, and progression. The progression stage is characterized by the production of tumor cells with increased proliferative capacity, invasive behavior and metastatic potential [9]. Cancer metastasis results from several interdependent processes, including cell proliferation; angiogenesis; and cell adhesion, migration, and invasion into surrounding tissue [10]. Although these are normal physiological processes, in cancer metastasis they are the consequences of a disrupted intracellular signaling network, which transmits aberrant signals. As recently demonstrated, dietary chemopreventive agents can modulate intracellular signaling pathways and interrupt the carcinogenic process [11]. Therefore, naturally occurring dietary substances can be used as chemopreventive agents to slow, block, or reverse cancer metastasis [3]. Some of the signaling molecules and/or pathways have been identified as constitutively active (by mechanisms involving overexpression of specific molecules or by autocrine/paracrine activation) and therefore are responsible for the aggressive phenotype and metastasis of many cancers, including breast, prostate and colon cancers.

SIGNALING IN INVASIVE CANCERS

The epidermal growth factor (EGF) tyrosine kinase receptor family (EGFR/ErbB1/HER1), ErB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4) exert their biological effects after ligand-dependent or -independent activation, which occurs in about 30% of breast cancers and has been associated with more aggressive forms of breast cancer [12-16]. Increased expressions of EGFR, HER2, HER3, and HER4 have also been described in prostate cancer, and the expression of EGFR and HER2 has been associated with androgen-independent and more aggressive prostate cancers [17-19]. Overexpression of EGFR has been associated with increased cell proliferation and metastasis and decreased survival in colon cancer [20], and up-regulated EGFR signaling has been detected in putative precursors of colon cancer, aberrant crypt foci (ACF) [21]. In addition, HER-2 expression has been suggested as an independent prognostic factor in patients with HER-2-positive colorectal cancers [22]. The activity of the EGF receptor family is mediated through phosphorylation and activation of a variety of signaling molecules, such as phosphatidylinositol-3 kinase (PI3K) and mitogen-activated protein kinase (MAPK), resulting in the stimulation of transcription factors AP-1 and NF-κB [23-39], and finally contributing to tumorigenesis by transactivation of target genes Fig. (**1**).

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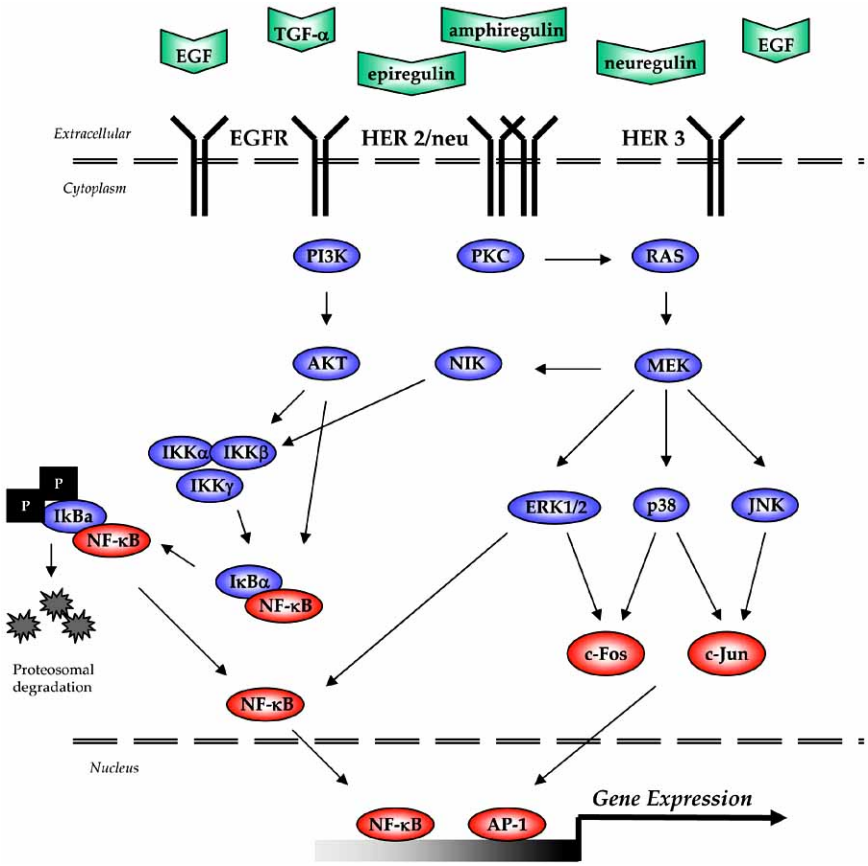


Fig. (1). Intracellular signaling in cancer cells.

In addition to EGF receptor-mediated signaling, NF-κB/AP-1 activation in cancer development, cancer progression and metastasis has also been linked to inflammation [40-42]. Therefore, inflammatory mediators (tumor necrosis factor-α [TNF-α], interleukin-1β [IL-1β] or lipopolysaccharide [LPS]) interact with their specific receptors (TNF-α with TNF receptor, IL-1 with IL-1 receptor, LPS with toll-like receptor [TLR]), resulting in the activation of a variety of kinases and finally leading to the activation of NF-κB [23-26,43-49]. Inflammation mediated through TNF-α and IL-1β also induces the activity of AP-1 through MAP kinases Erk and p38, which control expression of the AP-1 subunit c-Fos, and MAPK c-jun NH_2-terminal kinase (JNK), which controls expression of the AP-1 subunit c-Jun [23,32]. Although NF-κB and AP-1 can be regulated by different mechanisms, they share common intracellular signal transduction pathways [29,30].

In summary, NF-κB and/or AP-1, in addition to controlling the expression of proteins involved in the cancer promotion stages (i.e., cell proliferation and survival) [50-57], also regulate the expression of proteins involved in cancer invasiveness (i.e., cell adhesion, migration and invasion) [58-64] Fig. (**2**).

PROTEOLYTIC ENZYMES

Increased levels of proteolytic enzymes, which are responsible for the degradation of extracellular matrix proteins, have been identified in the serum and tissues of cancer patients, and their expression has been linked to cancer metastasis. Although they demonstrate different specificity (matrix metalloproteinases (MMPs) [65], cysteine proteases [66], and serine proteases [67]) their activity enables invasion and colonization of cancer cells in patients. Serine protease urokinase-type plasminogen activator (uPA) is a protease that cleaves the extracellular matrix and stimulates the conversion of plasminogen to plasmin [68]. Plasmin can mediate invasion of cancer cells directly, by degrading matrix proteins such as collagen IV, fibronectin, and laminin, or indirectly, by activating other matrix metalloproteinases (MMP-2, -3, and -9) or serine protease uPA [69-72]. Furthermore,

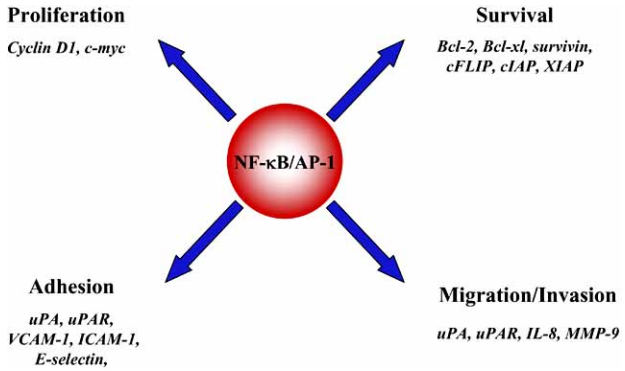


Fig. (2). Proteins involved in cancer invasiveness.

the non-proteolytic activity of uPA contributes to the adhesion and migration of cancer cells. Thus, uPA interacts with uPA receptor (uPAR), which forms the multi-protein complex with integrin receptors and their ligands (e.g. fibronectin, vitronectin) and controls cell adhesion and cell migration [73] Fig. (**3**).

Since uPAR does not contain intracellular domain, the activation of signaling pathways responsible for cytoskeleton reorganization is mediated through the intracellular domains of associated integrins or G-protein–coupled receptors (GPCR) [74,75]. Both uPA and uPAR are overexpressed in different tumors, and the correlation between the levels of uPA in serum and poor prognosis is consistent with the idea that binding of uPA to its receptor contributes to invasion and metastasis of cancer cell [67]. Therefore, uPA and uPAR became logical targets for cancer therapy. Although uPA neutralizing antibodies were originally developed more than 15 years ago [76], other approaches, including urokinase-specific inhibitors, antisense oligonucleotides, small molecules and siRNA targeting uPA and/or uPAR, are being evaluated as possible strategies to inhibit cancer growth, invasion and metastasis [77-86].

Another way to target the formation of uPA-uPAR complex is to reduce the amount of uPA and/or uPAR by down-regulating their expression. Since both uPA and uPAR contain binding sites for NF-κB and AP-1 in their promoter regions [62,63,87], inhibition of these transcription factors will eventually result in the inhibition of uPA-uPAR complex and subsequent suppression of invasive behavior. Therefore, inhibition of PI3K, protein kinase C (PKC), AKT serine-threonine kinase and SYK protein-tyrosine kinase suppresses the activity of NF-κB, which in turn down-regulates expression of uPA and results in the inhibition of migration of breast cancer cells [88-91]. Inhibition of PKC, extracellular signal-regulated protein kinase ERK1/2 and integrin-linked kinase (ILK) suppresses the transcriptional activity of AP-1, leading to the down-regulation of uPA expression and resulting in the inhibition of adhesion, migration and invasion of breast cancer cells [90,92,93]. Collectively, direct or mediated suppression of expression of uPA, by inhibiting the transcription factors controlling the expression of uPA, could have potential therapeutic effects in inhibiting cancer metastasis.

INHIBITORS OF METASTASIS IN FUNCTIONAL NUTRIENTS

A wide variety of fruits, vegetables or nutrient compounds have been suggested as chemoprevention or therapy for cancer *via* the different signaling pathways [94]. Some of these dietary compounds can modulate the signaling pathways responsible for invasive behavior and metastasis of cancer cells.

Green Tea

Green tea, specifically, the dried unfermented leaves from the plant *Camellia sinensis*, is the most globally consumed beverage [3]. Moreover, green tea, and especially its major biologically active compound (-)-epigallocatechin-3-gallate (EGCG) Fig. (**4**), has demonstrated cancer chemopreventative effects in animal cancer models [95,96]. The anti-cancer effects of EGCG can be linked to the modulation of multiple signaling pathways, finally resulting in the down-regulation of expression of proteins involved in the invasiveness of cancer cells (Table **1**). Green tea polyphenols (GTP) containing 50% of EGCG induced cell cycle arrest and suppressed invasive behavior of breast cancer cells by inhibiting AP-1 and NF-κB signaling, resulting in the suppression of secretion of uPA from cancer cells [97]. Therefore, GTP inhibits cell adhesion and cell migration by decreasing uPA, which

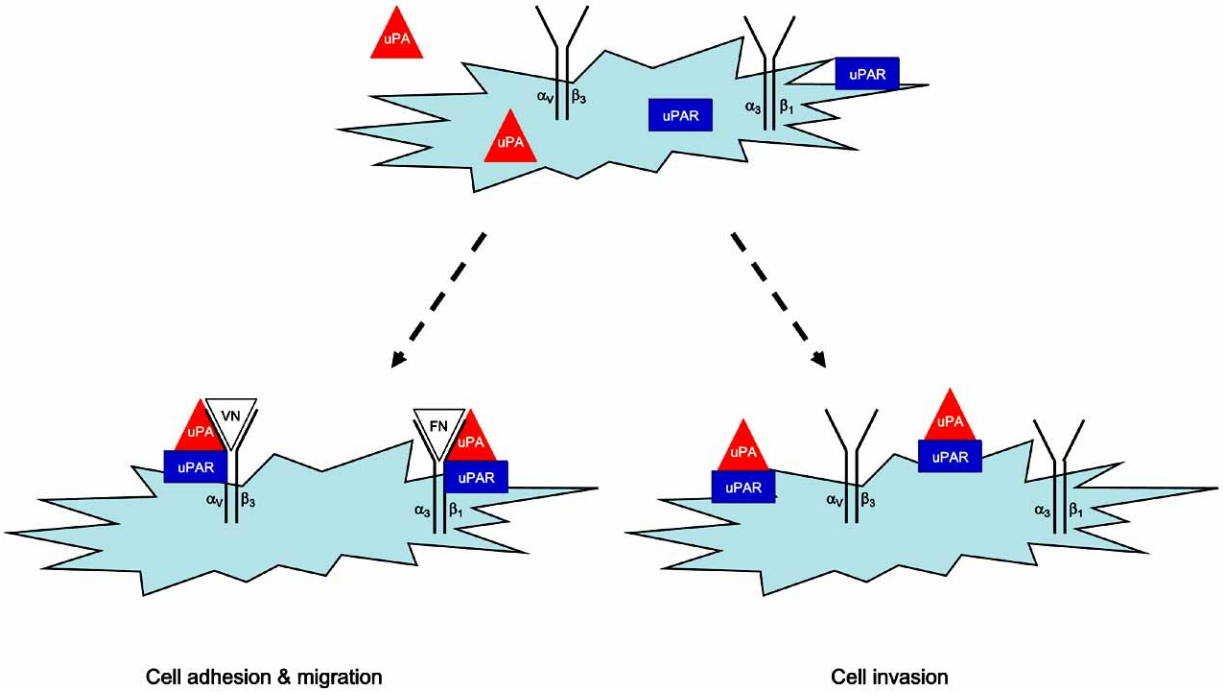


Fig. (3). Role of uPA/uPAR in cancer cell invasiveness.

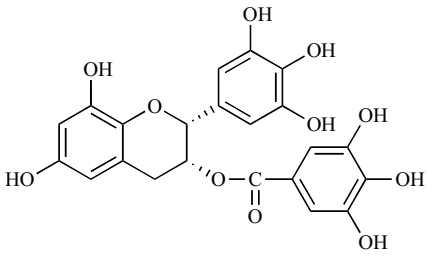


Fig. (4). EGCG.

forms a functionally active receptor complex consisting of uPA, uPAR and the integrin receptor $\alpha_V\beta_3$, which is ligated to vitronectin [74]. Inhibition of uPA secretion by GTP also inhibits the proteolytic activity of uPA, thereby suppressing the invasion of breast cancer cells through matrigel [97].

Reactive oxygen species (ROS)-induced adhesion and invasion of hepatoma cells through the monolayer of mesothelial cells (M-cells) was inhibited by EGCG or tea theaflavins [98]. EGCG significantly suppressed proliferation and the invasive ability of pancreatic carcinoma cells [99], inhibited the adhesion of melanoma cells to laminin [100], and inhibited the growth and invasion of oral carcinoma cells [101]. EGCG directly interacts with the carboxyl-terminal heparin-binding domain of fibronectin (FN), which results in the inhibition of adhesion of lung carcinoma cells to FN [102]. Although some studies have demonstrated that EGCG inhibits the adhesion of different cancer cells, EGCG also

Table 1. Inhibition of Cell Invasiveness by EGCG

Cancer	Cell Line	Mechanism	Function	Ref.
breast	MDA-MB-231	inhibition of NF-κB, and AP-1 activity, inhibition of uPA secretion	inhibition of adhesion, migration and invasion	[97]
		inhibition of HGF receptor, AKT, ERK	inhibition of invasion	[115]
prostate	TRAMP-C1	inhibition of MMP-2 activity	inhibition of invasion	[113]
lung	3LL	interaction between fibronectin and EGCG	inhibition of adhesion	[102]
	95-D	inhibition of NF-κB, MMP-9	inhibition of invasion	[111]
colon	26-L5	?	inhibition of invasion	[122]
melanoma	B16	?	inhibition of adhesion	[100]
ovary	HEY, OVCA 433	inhibition of ET(A)R and ET-1, ERK1/2, p38, uPA, uPAR, MT1-MMP	inhibition of invasion	[116]
sarcoma	HT1080	inhibition of MMP-2 and MMP-9 activity	inhibition of invasion	[107]
liver	AH109A	antioxidant	inhibition of adhesion and invasion	[98]
	SMMC-7721	?	inhibition of migration	[106]
gastric	AGS	inhibition of ERK, JNK, AP-1, MMP-9	inhibition of invasion	[112]
oral	OSC2	induction of apoptosis	inhibition of invasion	[101]
pancreas	PANC-1, MIA PaCa-2, BxPC-3	?, independent of cyclin D1	inhibition of invasion	[99]
brain	DAOY	up-regulation of β1 integrin expression	inhibition of migration by increased cell adhesion	[103]
	U-87	inhibition of MT-MMP1	inhibition of migration	[104]
	SK-N-BE	inhibition of MMP-2 activity	inhibition of invasion	[105]
		inhibition of ERK1/2, MMP-2, MMP-9	inhibition of invasion	[108,109]

stimulated adhesion of medulloblastoma cells to collagen by up-regulating the expression of β1 integrin [103]. Nevertheless, this increase in cell adhesive ability in fact suppressed the invasive behavior of these brain cancer cells [103].

In glioblastoma cells, EGCG inhibited the activity of membrane-type1 matrix metalloproteinase (MT1-MMP) as well as MT1-MMP-dependent pro-MMP2 activation together with the down-regulation of MT1-MMP expression and cell migration [104]. In neuroblastoma cells, the inhibition of MMP-2 activity by EGCG resulted in the suppression of invasion of these cells through matrigel [105]. Proliferation and migration of liver cancer cells was inhibited by EGCG, and the combination of EGCG and ascorbic acid further enhanced this inhibitory effect [106]. Reduction of invasiveness of highly metastatic fibrosarcoma cells through a reconstituted basement membrane matrix or through a monolayer of human umbilical vein endothelial cells (HUVECs) and a gelatin membrane by EGCG was associated with the inhibition of MMP-2 and MMP-9 activity in fibrosarcoma cells [107,108]. As demonstrated in the following study, EGCG inhibited phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2), which suppressed the expression of MMP-2 and MMP-9 and led to the reduction of the enzyme activities of the cancer cells [109]. The inhibition of fibroblast-conditioned medium activation of MMP-2 and MMP-9 in prostate cancer cells by EGCG was also mediated *via* inhibition of phosphorylation of ERK1/2 and p38, and suppression of activation of c-Jun and NF-κB [110]. Nuclear localization of NF-κB as well as MMP-9 expression and invasion was suppressed in lung carcinoma cells treated with EGCG [111]. EGCG also inhibited the phorbol 12–myristate 13-acetate (PMA)-induced invasiveness of gastric cancer cells by inhibiting ERK and c-Jun N-terminal kinase (JNK), resulting in the inhibition of AP-1 and subsequent down-regulation of MMP-9 expression [112]. However, EGCG suppressed invasion of prostate cancer cells through matrigel by inhibiting the secretion of pro-MMP-2 but not MMP-9 [113]. Although one study demonstrated a contradictory effect, where EGCG enhanced the production of pro-MMP-7 *via* the generation of reactive oxygen species and activation of JNK1/2 and c-Jun/c-Fos induction, as well as AP-1 transactivation, this effect was demonstrated only in one colon cancer cell line and not other colon cancer cells [114]. Therefore, because of the heterogeneity of a variety of cancers and signaling pathways involved in growth and metastasis, the specific effect of EGCG could be linked to the particular cancer or particular cancer cell type.

Recent studies demonstrated that EGCG could directly target certain upstream signaling molecules involved in cancer metastasis. EGCG inhibited phosphorylation of the hepatocyte growth factor (HGF) receptor, Met, and inhibited downstream activation of AKT and ERK, which resulted in the suppression of HGF-induced cell motility and invasion of breast cancer cells [115]. Treatment with green tea or EGCG suppressed proliferation and invasion of ovarian carcinoma cells by inhibiting the endothelin (ET) A receptor (ET(A)R)/ET-1 signaling by inhibiting the activation of p38, p42/p44 MAP kinases and PI3 kinase [116]. In addition, EGCG down-regulated ET(A)-R-mediated expression of cyclooxygenase (COX)-1 and COX-2 and prostaglandin E2 (PGE2) production in ovarian carcinoma cells [117].

In addition to have a direct effect of on cancer cells, EGCG also indirectly affects other cells involved in cancer progression and metastasis. For example, adhesion of stromal fibroblasts to collagen was markedly inhibited by EGCG by the down-regulation of expression of integrin $\alpha_2\beta_1$, suggesting that the anti-tumor activity of EGCG can also affect tumor-stroma interaction [118]. Radiation therapy that is widely-used to treat a variety of solid tumors also has various side effects. Ionizing radiation induces the expression of β3 integrin and matrix metalloproteinase (MT1-MMP) in human umbilical endothelial cells, which promotes the cell adhesion, migration and tubulogenesis responsible for tumor neo-vascularization. However, pretreatment of these cells with EGCG prevents the side effects of radiation therapy involved in invasive potential following radiation treatment [119].

Because cell invasiveness is the major factor contributing to the metastasis of cancer, animal experiments have been performed to confirm the anti-invasive activity of green tea polyphenols *in vivo*. Oral infusion of a polyphenolic fraction isolated from green tea (GTP) inhibited prostate cancer development and metastasis in the transgenic adenocarcinoma of mouse prostate (TRAMP) cancer model [120]. Metastasis of mouse mammary carcinoma cells to lungs was inhibited and the survival period of animals was increased after a treatment of EGCG-containing green tea in drinking water [121]. Although EGCG inhibited the invasion of colon cancer cells through matrigel only moderately, the metastasis of colon carcinoma cells to lung was inhibited by 98% [122]. EGCG alone or the combination of EGCG with dacarbazine reduced both primary tumor growth and pulmonary metastases in melanoma-bearing mice [123,124]. Interestingly, the anti-tumor and anti-metastatic effects of green tea and EGCG *in vivo* were linked to the induction of apoptosis in cancer cells [120,121].

Cell invasiveness also plays an important role in the pathogenesis of other diseases. EGCG prevented inflammation-mediated stimuli (TNF-α and IL-1β) induction of adhesion and expression of vascular cell adhesion molecule-1 (VCAM-1) in HUVECs, suggesting the role of tea in preventing atherogenesis [125]. In addition, EGCG reduced migration and tube formation of these endothelial cells by inhibiting both MMP activity and binding of vascular endothelial growth factor (VEGF) to its receptor, resulting in the inhibition of angiogenic differentiation [126,127]. Adhesion, migration and invasion of aortic smooth muscle cells was suppressed by EGCG by mechanisms that include inhibition of NF-κB [128], up-regulation of expression of tissue inhibitor of MMP-2 (TIMP-2) [129] and inhibition of MT1-MMP activity and MMP-2 expression [130,131]. The anti-inflammatory activities of EGCG were demonstrated by the inhibition of adhesion of peripheral blood CD8+ T cells to intracellular adhesion molecule-1 (ICAM-1). Therefore, EGCG down-regulated expression of CD11b on CD8+ T cells, which subsequently inhibited infiltration of these cells into the sites of inflammation [132].

Genistein

Genistein (4',5,7-trihydroxy-isoflavone), Fig. (**5**), is the most prominent soy isoflavone, and its possible anticancer effects have been suggested by epidemiological studies demonstrating the low incidences of certain cancers in Asian countries with diets rich in soy products [133]. As in the case of EGCG, the anti-cancer effects of genistein are linked to the modulation of a variety of signaling pathways involved in the invasive behavior of cancer cells (Table **2**). Genistein inhibited both cell adhesion to vitronectin and cell migration of invasive breast cancer cells by inhibiting the transcriptional activity of AP-1 and NF-κB, resulting in the suppression of uPA secretion from cancer cells [134]. As mentioned above, uPA and its receptor uPAR form complexes with integrins [74]. Therefore, the inhibition of adhesion of mela-

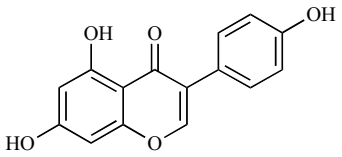


Fig. (5). Genistein.

Table 2. Inhibition of Cell Invasiveness by Genistein

Cancer	Cell Line	Mechanism	Function	Ref.
breast	MDA-MB-231	inhibition of NF-κB and AP-1 activity, inhibition of uPA secretion	inhibition of adhesion, migration and invasion	[134]
		inhibition of MMP-1, -2, -7, -9 and MT1-, MT-2, MT3-MMP	inhibition of invasion	[142]
		inhibition of MMP-9, up-regulation of TIMP-1, PN-II, and alpha 1-AT	inhibition of invasion	[143]
	MDA-MB-468	inhibition of MMP-9, up-regulation of TIMP-1, PN-II, and alpha 1-AT	inhibition of invasion	[143]
	MCF-7	inhibition of MMP-2, -9, and MT3-MMP	inhibition of invasion	[142]
	BT-20	inhibition of integrin expression	inhibition of adhesion	[138]
	F3II	inhibition of uPA secretion	inhibition of migration	[139]
prostate	PC-3, DU-145	inhibition of MMP	inhibition of invasion	[144]
	PC-3, PC-3M,	inhibition of MAPKAPK2, HSP27, p38, MMP-2	inhibition of invasion	[145,146]
lung	H82	inhibition of tyrosine kinase activity	inhibition of adhesion	[136]
colon	26-L5	?	inhibition of invasion	[122]
melanoma	B16	inhibition of tyrosine kinase activity	inhibition of adhesion	[135]
liver	Bel 7402	inhibition of pFAK expression	inhibition of adhesion and invasion	[149]
oral	HSC-3	inhibition of MMP-2 activity	inhibition of invasion	[159]
esophagus	TE-1, T.Tn	inhibition of integrin expression	inhibition of adhesion	[138]
pancreas	AsPC-1, BxPC-3, Capan-2	inhibition of FAK phosphorylation	inhibition of adhesion and invasion	[148]
brain	U87MG	inhibition of MMP-9 activity, inhibition of MT1-MMP and uPAR expression	inhibition of invasion	[147]

noma cells by genistein corresponded to a reduction in the metastatic ability of these cells when pretreated with anti-β1 integrin serum [135]. In addition, TNF-α–stimulated adhesion of small cell lung carcinoma (SCLC) to endothelial cells was also inhibited by genistein through β1 integrin [136]. Inhibition of adhesion of breast and esophageal cancer cells stimulated by heparin-binding EGF-like factor (HB-EGF) by genistein was linked to the down-regulation of expression of β1 integrins [137,138].

Although inhibition of the motility of some breast cancer cells by genistein was linked to the suppression of secretion of uPA but not MMP-2 or MMP-9 [139], in other breast cancer cells, genistein suppressed secretion of uPA, MMP-2, -9, MT1-, MT2-, and MT3-MMP, demonstrating the specificity of the tyrosine kinase pathway in mammary tumor cells [140-142].

Genistein also suppressed constitutive as well as EGF-stimulated invasion of highly metastatic breast cancer cells by down-regulating MMP-9 [143]. Genistein suppressed the invasion of prostate cancer cells through matrigel by inhibiting uPA and MMP production [144], and also inhibited transforming growth factor-β (TGF-β)-mediated induction of MMP-2 and cell invasion by blocking the activation of p38 MAPK [145]. Although TGF-β-mediated phosphorylation of MAP kinase-activated protein kinase 2 (MAPKAPK2) and the 27-kDa heat shock protein (HSP27) was inhibited by genistein, TGF-β-independent activation of the MAPKAPK2-HSP27 pathway, resulting in increased cell invasion, was not suppressed by genistein [146]. Constitutive as well as epidermal growth factor (EGF)-stimulated invasion of glioblastoma cells was suppressed by genistein by inhibiting the enzymatic activity of MMP-9 and down-regulating the expression of MT1-MMP and uPAR [147]. Another inhibitory effect of genistein was demonstrated in pancreatic cancer cells where genistein suppressed cell adhesion and invasion by inhibiting IL-1α-dependent phosphorylation of focal adhesion kinase (FAK) [148]. Inhibition of pFAK resulted in the suppression of invasion of hepatocellular carcinoma cells *in vitro* as well as the inhibition of invasion of these cells into the renal parenchyma in xenotransplanted mice [149].

Genistein suppressed lung metastasis of melanoma cells [150-153] and lung cancer cells [153]. The inhibition of the metastasis of colon carcinoma cells to lung was mediated by the suppression of the invasive behavior of these cells because genistein suppressed the invasion of colon cancer cells through matrigel *in vitro* [122]. Furthermore, genistein suppressed the metastasis of carcinogen-induced accessory sex gland carcinoma cells to lymph nodes [154] and inhibited peritoneal metastasis of azoxymethane-induced intestinal adenocarcinomas [155]. Prevention of metastasis by genistein in an orthotopic model of pancreatic cancer through the induction of apoptosis mediated by the activation of caspase-3 has been reported [156]. Prostate cancer bone metastasis was suppressed by genistein by down-regulating the expression of MMP-9 [157]. Significant reduction of breast cancer metastasis in lungs by genistein has been described in the postsurgical breast cancer model, where after the surgical resection of primary tumors intervention with a genistein-supplemented diet was employed [158].

Although genistein inhibited cell invasion *in vitro* and microvessel density and expression of VEGF in oral squamous cell carcinoma model *in vivo*, genistein treatment did not significantly affect tumor growth and metastasis to the lymph nodes or lungs [159]. Genistein inhibited growth and induced apoptosis of bladder cancer cells by inhibiting NF-κB *in vitro*, and a natural form of genistein, genistin, as well as isoflavone-rich phytochemical concentrate (SPC), inhibited tumor growth by inducing apoptosis and inhibiting angiogenesis *in vivo* [160]. However, only SPC inhibited lung metastasis associated with the down-regulation of NF-κB in tumor tissues and reduction of circulating insulin-like growth factor-I (IGF-I), suggesting that SPC may contain other biologically active compounds with anti-metastatic activity [160]. Alternatively, combining genistein with chemotherapeutic agents such as cisplatin, docetaxel or doxorubicine resulted in significantly greater inhibition of cell growth and induction of apoptosis of cancer cells *in vitro* compared with either agent alone [161]. Genistein combined with gemcitabine inhibited pancreatic cancer *in vivo* [162]. Importantly, genistein combined with cisplatin inactivated NF-κB in pancreatic tumors, resulting in the down-regulation of expression of MMP-9 [163]. Moreover, the combination of genistein and docetaxel inhibited the invasion of prostate cancer cells, and genistein significantly potentiated the anti-metastatic activity of docetaxel in a SCID-human model of prostate cancer bone metastasis [164]. In addition, genistein down-regulated the expression of MMP-9, which was induced by docetaxel treatment [164]. Paradoxically, genistein also demonstrated contradictory effects, where treatment with genistein actually increased prostate cancer cell metastasis to lymph nodes [165]. Nevertheless, the combination of genistein with radiation markedly inhibited primary tumor growth as well as lymph node metastasis [166]. The same effect was recently described in a model of renal cancer, where the treatment of established kidney tumors with genistein stimulated the growth of the primary kidney tumor and increased the incidence of metastasis, whereas the combination of kidney tumor irradiation with genistein significantly inhibited the growth and progression of kidney tumors [167].

Although the majority of studies with genistein alone or combined other treatments demonstrated anti-cancer and anti-metastatic potency against a variety of cancers, some biological effects of genistein can be explained by the presence of additional factors regulating the activity of genistein. For example, the diet used in a particular experiment is crucial for evaluating the chemopreventive activity of tested compounds. As demonstrated by Kim *et al.,* genistein exhibited significant chemopreventive activity against carcinogen-induced breast cancer in one diet, whereas another diet under the same experimental conditions did not show any activity [168].

In addition to their direct effects on cancer cells, chemopreventive/natural agents also modulate the functions of other cells. Genistein demonstrated its anti-angiogenic effects by inhibiting VEGF/bFGF-induced expression of uPA and MMP-1 in endothelial cells (HUVECs) [169]. On the other hand, genistein did not show any effect on the cyclic-strain (corresponding to the hemodynamic forces exerted by blood flow, which initiate angiogenesis) stimulation of mi-

gration and tube formation or expression of uPA and MMP-9 in aortic endothelial cells [170]. In a model of periodontal disease, genistein inhibited uPA production from EGF-stimulated gingival fibroblasts [171]. In a model of idiopathic pulmonary fibrosis (IPF), which is characterized by fibroblast expansion and extracellular matrix accumulation, genistein blocked TGF-β1–dependent up-regulation of MT3-MMP in lung fibroblasts [172].

Ganoderma Lucidum

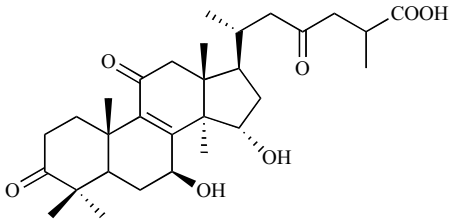
Ganoderma lucidum is an Asian medicinal mushroom that has been used in traditional Chinese medicine to promote good health and to prevent or treat a variety of different diseases including cancer [173]. The anticancer properties of *G. lucidum* have been attributed to either the isolated polysaccharides (β–D-glucans, heteropolysaccharides and glycoproteins), which are responsible for the stimulation of the immune system, or lanostane-type triterpenes (ganoderic acids and their alcohols or aldehydes), which demonstrate activity against cancer cells [173]. *G. lucidum* extract (GLE) containing polysaccharides and triterpenes markedly suppresses the invasiveness of breast cancer cells by inhibiting cell adhesion to the extracellular matrix proteins fibronectin and vitronectin, inhibiting cell migration and inhibiting cell invasion through matrigel (Table **3**) [174]. GLE effects were mediated by inhibiting the transcriptional activity of NF-κB and AP-1, resulting in the down-regulation of expression of uPA and uPAR [175,176]. Mechanistically, GLE inhibits phosphorylation of AKT on Ser^{473} and down-regulates AKT expression, which results in the inhibition of NF-κB in cancer cells [177]. In addition, GLE suppresses oxidative stress-induced cell migration by inhibiting ERK1/2 activity, resulting in the suppression of interleukin-8 (IL-8) from breast cancer cells [178]. Furthermore, the combination of GLE with green tea extract containing 38% of EGCG synergistically inhibited adhesion, migration and invasion of breast cancer cells by down-regulating the expression of uPA [179]. Ethanol and water extracts from *G. lucidum* inhibit carcinogen 4-aminobiphenyl-induced cell migration of bladder cancer cells [180]. Although this effect was associated with increased actin polymerization and increased stress fiber and focal adhesion complex formation, the treatment with *G. lucidum* did not modulate expression of MMP-2 or FAK in bladder cancer cells [180].

In vivo studies demonstrate that an aqueous extract [181], as well as polysaccharides peptide (GLPP) [182] or polysaccharide fraction (Ganopoly) [183] extracted from *G. lucidum,* suppressed the growth of sarcoma-180 tumors in mice. Water-soluble extracts from a cultured medium of *G. lucidum* mycelia prevented the development of azoxymethane- or N.N'-dimethylhydrazine-induced colon tumors in rats and mice, respectively [184-186]. Moreover, lipids extracted from *G. lucidum* suppress the growth of melanoma and sarcoma tumors in mice [187]. Interestingly, the triterpenoid fraction of *G. lucidum* inhibits primary tumor growth in Lewis lung carcinoma (LLC) cells in spleen and significantly reduces metastasis to the liver [188]. Furthermore, triterpenoid fraction suppresses tumor-induced angiogenesis, and the anti-angiogenic compound was identified as the triterpene ganoderic acid F (GA-F) [188]. Another purified triterpene from *G. lucidum*, ganoderic acid T (GA-T), inhibits proliferation of and induces apoptosis in highly metastatic lung cancer cells and suppresses the growth of solid tumors implanted in athymic mice [189]. Interestingly, ganoderic acid X (GA-X) purified from *G. amboinense* suppresses proliferation of and induces apoptosis in hepatoma cells by inhibiting DNA synthesis and activation of ERK and JNK kinases, respectively [190]. Finally, ganoderic acids A (GA-A) and H (GA-H), Fig. (**6**), isolated from *G. lucidum*, suppress colony formation as well as invasive behavior (cell adhesion, migration and invasion) of breast cancer cells by inhibiting AP-1 and NF-κB activity, resulting in the inhibition of uPA secretion [191].

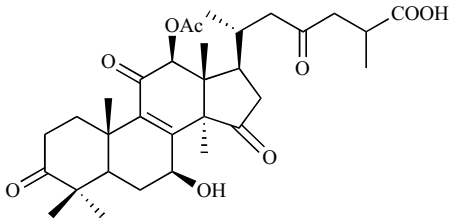
Table 3. Inhibition of Cell Invasiveness by *Ganoderma lucidum*

Cancer	Cell Line	Compound	Mechanism	Function	Ref.
breast	MDA-MB-231	*Ganoderma lucidum* GLE	inhibition of NF-κB and AP-1 activity, inhibition of uPA and uPAR expression, inhibition of uPA secretion	inhibition of adhesion, migration and invasion	[174,175] [176]
		GA-A, GA-H	inhibition of NF-κB and AP-1, inhibition of uPA secretion	inhibition of adhesion, migration and invasion	[191]
	MCF-7	GLE	inhibition of NF-κB, ERK1/2, c-Fos, AP-1, inhibition of IL-8 secretion	inhibition of migration	[178]
prostate	PC-3	*Ganoderma lucidum* GLE	inhibition of NF-κB and AP-1 activity, inhibition of uPA and uPAR expression, inhibition of uPA secretion	inhibition of migration	[175,176]
bladder	HUC-PC MTC-11	GL-W, GL-ET	induction of actin polymerization	inhibition of migration	[180]

Ganoderma lucidum, fruiting bodies or spores; GLE, extract containing 13.5 % polysaccharides and 6 % tritepenes; GA-A, ganoderic acid A; GA-H, ganoderic acid H; GL-W, water extract; GL-ET, ethanol extract.



Ganoderic acid A



Ganoderic acid H

Fig. (6). Biologically active triterpenes.

STRUCTURE-ACTIVITY RELATIONSHIPS

Given the therapeutic or preventive potential of dietary compounds, numerous studies have tried to elucidate the possible structure-activity relationships (SAR) that may be used for the new drug discovery. However, and possibly due to the information being very scattered, the SAR for the dietary compounds is limited to the importance of hydroxyl groups in their general structure [192]. For example, the 3-gallate (containing three hydroxyl groups) and the 5'-hydroxyl group at the trihydroxyphenyl B ring of the green tea catechins (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin-3-gallate (ECG), and (-)-epigallocatechin (EGC), are responsible for inducing apoptosis in cancer cells [193]. In addition, a removal or modification of hydroxyl groups (including methylation, glucuronidation, and sulfate formation) resulted in the reduced biological activities of EGCG [194-198]. In the case of soy isoflavones, genistein (4',5,7-trihydroxy-isoflavone) with three hydroxyl groups demonstrated stronger phytoestrogenic activity then daidzein (4',7-didroxy-isoflavone), which contains two hydroxyl groups [199]. In addition, genistein induced vascular relaxation of the coronary artery, whereas daidzein was less active [200]. Although both genistein and daidzein suppresses migration and adhesion of breast cancer cells, genistein is more potent in inhibiting the transcriptional activity of AP-1 and NF-κB than daidzein [134]. Moreover, glycosylation of these hydroxy-isoflavones resulted in the loss of their activities [134]. A comprehensive review of the SAR of dietary flavonoids was published recently [192]. Finally, hydroxylation of the mushroom triterpenes ganoderic acid H (at position 3) and ganoderic acid A (at positions 7 and 15) could be linked to their potency to inhibit the invasive behavior of cancer cells [191]. Furthermore, other hydroxylated triterpenes isolated from *G. lucidum* were biologically active [189,190, 201-205]. Collectively, the data from many studies with different natural compounds demonstrate the importance of hydroxylation at the particular positions in their structures. However, future SAR studies need to consider what the specific targets of these natural compounds are as well as the molecular mechanisms responsible for their activities.

CONCLUSION

While the anticancer effects of natural products or their biologically active compounds have been described in numerous epidemiological and experimental studies, the understanding of their molecular mechanisms of action have been elucidated only recently. These dietary/natural compounds can be successfully used for adjuvant therapy or combination therapy leading to a decrease in the dosage and the suppression of side effects from chemotherapy. Alternatively, knowledge of the biological functions of these natural products could lead to the development of novel "non-natural" drugs with more pronounced specific effects and enhanced bioavailability.

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