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New Drugs

Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: Phenolic acids, monophenol, polyphenol, and their derivatives

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Abbreviations: Akt, protein kinase B; AP-1, activator protein-1; BDMC, bisdemethoxycurcumin; CDCQ, 3-caffeoyl-4-dihydrocaffeoylquinic acid; CQA, chlorogenic acid; DMC, demethoxycurcumin; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial–mesenchymal transition; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; FGF, fibroblast growth factor; GA, gallic acid; HGF, hepatocyte growth factor; HIF, hypoxia-inducible factors; ICAM, intercellular adhesion molecule; IKK, IκB kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen activated protein kinase; JNK, interleukin-8 kinase; MMP, matrix metalloproteinase; MR-3, 3,5,4’-trimethoxy-trans-stilbene; MT-1 MMP, membrane type-1 MMP; NF-κB, nuclear factor-kappaB; p38/MAPK, p38 mitogen-activated protein kinase; PAI, plasminogen activator inhibitor; PFK, phosphofructokinase; PKC, protein kinase C; PMA, phorbol-12-myristate-13-acetate; ROS, reactive oxygen species; TGFβ, transforming growth factor β; TIMP, tissue inhibitor metalloproteinase protein; TNF, tumor necrosis factor; uPA, urokinase plasminogen activator.

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attention because of their strong antioxidant activity. Shortly afterward, potentially protective effects against oxidative damage diseases (e.g., coronary heart disease, stroke, and cancers) of phenolics in natural food were found. Recently, evidence suggesting phenolic compounds possess an effective inhibitory effect on cancer invasion and metastasis is also increasingly being reported in the scientific literature.

Chemoprevention is defined as the use of natural or synthetic substances to prevent cancer formation or cancer progression. Studies have shown that natural phytochemicals containing phenolic compounds derived from certain plants have the capability to prevent cancer metastasis.7 Phenolic compounds are comprised of a large aggregation of phytochemicals that consist of numerous subgroups defined by their structural characteristics. The literature describing the bioactivity of all phenolic compounds is too vast to summarize in a single article. This review therefore focuses on the in vitro and in vivo data on the anti-invasive and anti-metastatic effects and underlying molecular signaling mechanisms of phenolic acids, monophenol, polyphenol, and their derivatives. The flavonoids, a very large subgroup of phenolics, will therefore not be addressed here.

**Protein targets and molecular pathways for the inhibition of invasion and metastasis**

Metastasis is a complex, multistep process made up of a cascade of interrelated, sequential steps including invasion, migration, adhesion, infiltration, colonization at a distant site, and the subsequent formation of new capillaries.8 To successfully metastasize, invasive tumor cells must overcome three barriers: first, the attachment to basement membrane or extracellular matrices (ECM); second, protease activity must induce local degradation of the matrix; and third, tumor cells must migrate through the modified matrix.9,5 Recently, a new step has been proposed; the creation of a “premetastatic niche” at the target site before the first tumor cells arrive at this distant location. The precise timing of the establishment of the premetastatic niche cannot be determined.10 However, the inhibition of invasion constitutes a new target for chemoprevention between the period of tumor proliferation and the onset of invasion that could prevent the series of events leading to metastasis.11 To identify possible sites to prohibit cells from metastasis, we summarized the regular protein targets and the involved molecular pathways for modulating invasion and metastasis of cancer cells in the following sections.

**Epithelial and mesenchymal markers**

Epithelial–mesenchymal transition (EMT) is a process that converts an epithelial cell to a mesenchymal cell by promoting the loss of cell–cell adhesion and leads to the release of epithelial tumor cells from the surrounding tissue; cell motility is therefore enhanced. Its occurrence during tumor progression was determined to be the major mechanism responsible for mediating the invasive- ness and metastasis of cancer cells.12–14 The characteristics of EMT are the loss of cell polarity, down-regulation of epithelial proteins (e.g., E-cadherin, claudins, occludins, desmoplakin, cytokeratin, and mucin-1), and up-regulation of mesenchymal protein (e.g., fibronectin, vitronectin, fibroblast-specific protein 1 [FSP1], vimentin, smooth-muscle actin, and fibroblast growth factor receptor 2 [FGFR2]).13,15 E-cadherin and N-cadherin are the epithelial- and mesenchymal-specific junction proteins, respectively. The increased expression of E-cadherin and N-cadherin is hence correlated to the suppression and enhancement, respectively, of cell invasion.16,17 The key signaling molecules and pathways involved in the induction of EMT include receptor tyrosine kinase (RTK), the transforming growth factor β (TGFβ) superfamily, WNT, NOTCH, hedgehog pathway18,19 and nuclear factor-kappaB (NF-κB).18 In these EMT-inducing pathways, many transcription factors, such as the snail family (SNA1/snail, SNA2 slug), ZEB family (ZEB1 and 2), Twist1 and 2, and E12/E47, also play a crucial role in the regulation of the EMT transcriptome program.20–25

**Collective tumor cell and single cell migration-related proteins**

To start invading and metastasizing into tissues and vessels, cells must break their adhesions with surrounding tissues and acquire the ability to migrate. Integrins mediate tumor cell attachment to ECM components such as laminin, fibronectin, vitronectin and collagens as well as modulate proteolytic enzymes of intracellular signaling pathways that govern cytoskeletal organization and gene expression.26 When invasion begins, proteases are recruited to the integrins and other adhesion receptors on the cell surface, and the ECM can be remodeled and/or degraded, facilitating this step.27 Hence, integrin signaling is critical for cell invasion and migration, and it can be modulated via focal adhesion kinase (FAK)/Src (a family of proto-oncogenic tyrosine kinases) signaling and the activity of Rho family GTPases.28,29 Afterward, a continuous cycle of actin polymerization and depolymerization causes the extension of cell membrane protrusions leading to the initiation of cell migration, and the cell can begin along with this process.29 Coffin and other actin cytoskeleton regulators are controlled by Rho family GTPases.30,31 In addition, a scaffolding protein called Neural Precursor Cell Expressed, Developmentally Down-regulated 9 (NEDD9) is also amplified in metastatic melanomas32 and forms part of a complex modulating Ras-related C3 botulinum toxin substrate 1 (Rac1) activity and cellular invasion.33 Invasive tumor cells can migrate either as single cells (single cell migration) or in a cluster of cells (collective tumor cell migration). In migration of collective tumor cells, cadherins and other cell–cell adhesion proteins can provide intercellular adhesion.34,35,36 this type of migration in the absence of EMT is mediated by reorganizing the actin cytoskeleton via Ras homolog gene family, member A (RhoA)/Rho-associated protein kinase (ROCK) and ezrin.37 Additionally, many other adhesion and signaling molecules including integrins, CD44, and several Immunoglobulin-domain cell adhesion molecules (IgCAMs) are involved in cell invasion and migration.28,36–38

**ECM and basement membrane degradation-associated proteins**

Degradation of the basement membrane and ECM results in the promotion of cancer cell mobility, invasion, and metastasis.39–41 The degradation is carried out by various proteolytic enzymes, including serine protease, matrix metalloproteinases (MMPs), membrane type-1 MMP (MT-1 MMP), cathepsins, and plasminogen activator. Among these proteases, the expression of MMP-2 and -9 is high in various malignant tumors and is closely related to the ability of these cells to invade and metastasize.42–44 Activation of MMPs is initiated from activation of the urokinase plasminogen activator (uPA) by binding with the urokinase plasminogen activator receptor (uPAR) and, further, specifically cleaves the plasminogen to form the active enzyme plasmin which then activates pro-MMP enzymes. Thus, the uPAR–uPA interaction at the surface of cancer cells is considered highly involved in the invasion and metastasis of cancer cells.45–48 Both plasminogen activator inhibitor (PAI)-1 and -2 are modulators of the interaction of uPA and uPAR in the activation of plasminogen, initiation of signal transduction and induction of cell chemotaxis.49,50 However, the roles of these two inhibitors are essentially different.49 A high level of PAI-2 may be correlated with good prognosis,51 but a high level of PAI-1 in tumors is shown to be correlated with an unfavorable prognosis.52 Additionally, tissue inhibitor metalloproteinase proteins
(TIMPs) are a group of mammalian proteins composed of TIMP-1, -2, -3, and -4 that display a wide-range of sequence homology and structural identity. TIMPs have been reported as natural MMP inhibitors that prevent the degradation of ECM by abolishing the hydrolytic activity of all activated members of the metalloproteinase family, in particular that of MT1-MMP, MMP-2, and -9.53

The transcriptional level of MMP expression is regulated by various transcription factors and mitogen activated protein kinase (MAPK) [e.g., extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (p38/MAPK)] or phosphoinositide-3 kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathways.54–56 The 5’ flanking region of the MMP-9 gene contains several functional regulatory motifs that can bind with several well-characterized transcription factors, including NF-κB (-600), activator protein-1 (AP-1; -533, -79), stimulatory protein-1 (Sp1; -558), or polyoma virus enhancer activator-3 (PEA3; -540).54,57 Through one or more of these binding sites on the specific element-containing target genes, the expression of MMP-9 is regulated by various chemical or physical stimulators, including growth factors [e.g., fibroblast growth factor (FGF)-2, epidermal growth factor (EGF), and hepatocyte growth factor (HGF)], cytokines [e.g., tumor necrosis factor (TNF)-α, oncogenes (e.g., Ras), and phorbol-12-myristate-13-acetate (PMA)].58–62

**Angiogenic activators and inhibitors**

Tumors cannot grow beyond a certain size, generally 1–2 mm³ due to a lack of oxygen and other essential nutrients. Therefore, angiogenesis is a key step for the supplement of nutrients and oxygen to the tumor nodule that leads to the transition of tumors from a dormant state to a malignant one. Tumor cells can break away from an established solid tumor, enter the blood vessel, and be carried to a distant site where they can implant and begin the growth of a secondary tumor. Hence, angiogenesis is absolutely required for metastatic tumor growth. A variety of growth factors, such as FGF, EGF, vascular endothelial growth factor A (VEGFA), and platelet-derived growth factor (PDGF), induce blood vessel growth in tumors and are categorized as angiogenic activators. In contrast, several proteins including thrombospondin 1, angiotatin, endostatin, and tumstatin have the activity to prevent angiogenesis and are classified as angiogenic inhibitors.64,65 Hypoxia-inducible factors (HIF) 1A and 2A are also involved in the induction of an invasive and metastatic phenotype.66,67 HIF1A is degraded by an E3 ubiquitin ligase [von Hippel-Lindau tumor suppressor (VHL)] under normoxic conditions; however, it accumulates due to the increased protein stability during hypoxia. HIF1A regulates numerous target genes, including those genes that are involved in angiogenesis.68 It has been reported that HIF1A induces cell migration through up-regulation of the CXC chemokine receptor 4 (CXCR4)69 and mediates EMT via up-regulation of lysi oxidase (LOX) and the activation of FAK during hypoxia.70 Moreover, HIF1A and hypoxia have also been documented as inducers of several EMT mediators, including Twist, snail, and ZEB1 and 2.71–74

**CXC Chemokine receptor 4 (CXCR4) and its ligand (CXCL12)**

The choice of the site for a secondary tumor is determined by the characteristics of the tumor cell and the nature of the target organ.75–77 Based on several lines of evidence, this proposal has gradually gained acceptance. It has been found that the endothelia of vessels in different tissues express different adhesion molecules and that tumor cells express the corresponding receptors to lead themselves to specific tissue sites.78–80 For example, the expression of CXCR4 on breast tumors enables the cell lines to metastasize toward the tissues that express CXCR4-corresponded ligand, CXCL12 [also called stromal-derived-factor-1 (SDF-1)]. Most of the common locations for breast tumor metastases, including lung, liver, lymph nodes, and bone marrow, are CXCL12-expressing tissues. Furthermore, CXCR4-blocking antibodies impairing lung metastasis have also been revealed in severe combined immunodeficiency (SCID) mouse xenograft experiments.80

**The anti-invasive and/or anti-metastatic activity of phenolic acids, monophenol, polyphenol, and their related derivatives**

Phenolic acids, polyphenol, and monophenol are three subgroups of phenolics, and numerous compounds and related derivatives in these subgroups exhibit inhibitory activities affecting carcinogenesis. A large number of reports on the anti-carcinogenic effects of these compounds in invasion and/or metastasis have focused on the evaluation of curcumin, resveratrol, and their derivatives. Structures of phenolic acids, monophenol, polyphenol, and their derivatives with anti-invasive and/or anti-metastatic activity are shown in Fig. 1, and the underlying molecular mechanisms of these compounds in various types of cancers are summarized in the following sections.

**Curcumin and its derivatives**

Curcumin is a dietary pigment in turmeric (popularly called “curry powder”) and is widely used as a spice and coloring agent in food. Many studies have provided the in vitro and in vivo evidence that demonstrate the potential anti-invasive and/or anti-metastatic activities of curcumin and its derivatives on a variety of cancers. In hepatoma: curcumin inhibited MMP-9 secretion, migration, and invasion of SKHeP181 and CBO140C12 cells82 and the formation of actin stress fibers in CBO140C12 cells were affected by treatment with curcumin.82 In an orthotopic implantation model, daily oral administration of curcumin suppressed intrahepatic metastasis of CBO140C12 cells in a dose-dependent manner.82 Curcumin also suppressed slipping motility and invasive movement of AH109A cells with or without induction by reactive oxygen species (ROS).83 In lung cancer: the suppression of the migration and invasion of A549 cells by curcumin was involved in the mitogen-activated protein kinase kinase kinase (MEKK) 3 and ERK signaling pathway which resulting in the inhibition of MMP-2 and -9 expression.84 Through the suppression of several invasion-related genes, including MMP14, neuronal cell adhesion molecule (NCAM), and integrins α6 and β4, and the activation of JNK, AP-1, Dnaj-like heat shock protein 40 (HJL1), and E-cadherin, curcumin can reduce the cell migration and invasion of CL1-1 cells.85,86

In breast cancer: curcumin exerts a strong anti-invasive effect on estrogen receptor (ER)-negative MDAMB231 cells through the down-regulation of NF-κB/AP-1 dependent MMP-1 and -2 expression, the up-regulation of TIMP-1, and the inhibition of VEGF and b-FGF.87,88 A significantly lower number of lung metastases were observed in an MDAMB231 cell intercardiac injected mouse model treated with curcumin in the diet.89 Narasimhan and Ammanamanchi90 further demonstrated that curcumin can block receptor d’origine nantais (RON) tyrosine kinase-mediated invasion of MDAMB231 and MDAMB468 cells via the regulation of RON and NF-κB expression. Demethoxycurcumin (DMC), one of the active derivatives of curcumin, also showed an inhibitory effect on the adhesion, migration, and invasion of MDAMB231 cells. Upon treatment with DMC, the levels of ECM degradation-associated proteins, including MMP-9, MT1-MMP, uPA, and uPAR, and the expression of intercellular adhesion molecule (ICAM)-1 and CXCR4 as well as the DNA binding activity of NF-κB in MDAMB231 cells were...
Curcumin inhibits the motility and invasion of MDAMB435 cells by directly inhibiting the function of α6β4 integrins and blocking α6β4-dependent Akt activation and expression of a cell motility-promoting factor, ectonucleotide pyrophosphatase/phosphodiesterase (ENPP) 2 (or autotaxin). A paclitaxel (Taxol)-induced invasion of MDAMB435 cells was inhibited by curcumin through the inhibition of IκBα kinase (IKK) activation and the suppression of VEGF, MMP-9, and ICAM-1. In a MDAMB435 cell xenograft model, dietary administration of curcumin significantly decreased the incidence of breast cancer metastasized to lung and suppressed the expression of NF-κB, cyclooxygenase (COX) 2, and MMP-9. A recent in vitro MCF-7 cell and hospital-based case-control study showed that the up-regulation of maspin (a serine protease inhibitor) expression by curcumin might contribute to the inhibition of invasion of breast carcinoma cells.

In prostate cancer: curcumin significantly blocks CC motif ligand 2 (CCL2)-induced adhesion, invasion, and motility in PC-3 cells by suppressing the expression of CCL2, in part through differential regulation of protein kinase C (PKC) and MMP-9 signaling. Treatment with curcumin in vitro and in vivo results in a significant reduction in the expression of MMP-2 and -9 and the invasion/metastasis of DU-145 cells. In laryngeal squamous carcinoma: treatment of HEp2 cells with curcumin reduced the invasive potential and cell viability.

**Fig. 1.** Structures of phenolic acids, monophenol, polyphenol, and their derivatives with anti-invasive and/or anti-metastatic activity.
down-regulated the expressions of MMP-2, MT1-MMP, integrin receptors, and FAK in cells. In colorectal cancer: the chemopreventive and anti-invasive effects of curcumin on neurotensin (NT)-stimulated HCT116 colon cancers may function through the inhibition of NT-induced interleukin (IL)-8 chemokine expression and AP-1 and NF-κB activation. Curcumin also inhibits cell migration of Colo205 cells through the inhibition of NF-κB and the down-regulation of COX-2 and MMP-2 expression. In fibrosarcoma: three active curcumin metabolites, including tetrahydrocurcumin (THC), DMC, and bisdemethoxycurcumin (BDMC), effectively reduced the adhesion and invasion of HT1080 cells and also decreased the levels of MMP-2, -9, uPA, MT1-MMP, and TIMP-2 in cells.

In melanoma: Menon et al. first reported that curcumin inhibits the invasion of B16F10 cells by suppressing MMP-2, thereby inhibiting lung metastasis in an animal model. Another study further demonstrated that curcumin blocks osteopontin (OPN)-induced invasion and migration of B16F10 cells through the suppression of IKK activity and IkBα phosphorylation that leads to reduce the translocation and transcriptional activity of NF-κB. The activity of OPN-induced MT1-MMP and MMP-2 was decreased in both B16F10 cells and animal models. In gastric cancer: curcumin suppressed the expression of human epidermal growth factor receptor (HER) 2 and the activity of p21-activated kinase (PAK) 1, a downstream protein of EGRF, to inhibit the proliferation and invasion of gastric cancer cells. In tongue squamous cell carcinoma: Wang et al. showed that curcumin can suppress the migration and invasion of Tca8113 cells by reducing the activity of MMP-2 and -9. In oral squamous cell carcinoma (OSCC): curcumin down-regulates the expression of uPA, uPAR, MMP-2, and -9. In fibrosarcoma: three active curcumin metabolites, including tetrahydrocurcumin (THC), DMC, and bisdemethoxycurcumin (BDMC), effectively reduced the adhesion and invasion of B16F10 cells and also decreased the levels of MMP-2, -9, uPA, MT1-MMP, and TIMP-2 in cells.

Table 1

The proposed target proteins and mechanisms of curcumin and its derivatives (demethoxycurcumin, bisdemethoxycurcumin, and tetrahydrocurcumin) on the inhibition of cancer invasion/metastasis in vitro and in vivo.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Cell/animal model</th>
<th>Biological effects</th>
<th>Molecular targets</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatoma</td>
<td>SKHeP1/AB109A/CHO140C12</td>
<td>adhesion; migration; invasion; ROS-induced invasion; MMP-9; actin stress fiber</td>
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<td>81–83</td>
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<tr>
<td>Lung cancer</td>
<td>Orthotopic implanted CBO140C12 mice A549/CL1-5</td>
<td>metastasis</td>
<td>–</td>
<td>82</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>MDAMB231/MDAMB468/MCF-7/Taxol-induced MDAMB435/MDAMB435–b4/4</td>
<td>adhesion; migration; invasion;VEGF;MMP-2/-9;MT-1 MMP;uPA/uPAR;ICAM-1;CXCR4;R684 integrin;ENPP2;R0N;VEGF;bFGF</td>
<td>Akt;IKK;NF-κB;AP-1</td>
<td>87–93</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>MDAMB435 xenograft mice</td>
<td>metastasis (to lung);MMP-9;COX-2</td>
<td>–</td>
<td>92</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>MDAMB231/intracardiac injected mice CCL-2-induced PC3/DU-145</td>
<td>metastasis (to lung)</td>
<td>–</td>
<td>88</td>
</tr>
<tr>
<td>Basal-like cancer</td>
<td>HEP2</td>
<td>adhesion; motility; invasion; CII; MMP-2/-9; angiogenesis</td>
<td>–</td>
<td>94–96</td>
</tr>
<tr>
<td>Basal-like cancer</td>
<td>Tca8113</td>
<td>adhesion; invasion; uPA; MMP-2/-9;MT-1 MMP;TIMP-2</td>
<td>–</td>
<td>100,101</td>
</tr>
<tr>
<td>Basal-like cancer</td>
<td>Tca8113</td>
<td>adhesion; invasion; uPA; MMP-2/-9;MT-1 MMP;TIMP-2</td>
<td>–</td>
<td>102–104</td>
</tr>
<tr>
<td>Basal-like cancer</td>
<td>YD-10B OSCC</td>
<td>adhesion; migration; MMP-2/-9;uPA/uPAR</td>
<td>–</td>
<td>107</td>
</tr>
<tr>
<td>Basal-like cancer</td>
<td>PM-A-induced T98G, U87MG, and U373MG/U-87 xenograft mice</td>
<td>migration; invasion;MMP-1/-3/-9/-14;uPA;angiogenesis</td>
<td>–</td>
<td>108–111</td>
</tr>
<tr>
<td>Basal-like cancer</td>
<td>LPA-induced PA-1, OVCAR-3</td>
<td>adhesion; migration; MMP-2/-9; β-catenin</td>
<td>–</td>
<td>112</td>
</tr>
<tr>
<td>Basal-like cancer</td>
<td>LPA-induced PA-1, OVCAR-3</td>
<td>adhesion; migration; MMP-2/-9; β-catenin</td>
<td>–</td>
<td>113</td>
</tr>
</tbody>
</table>

Resveratrol and its derivatives

Resveratrol (3,5,4-trihydroxystilbene), which belongs to the group of stilbenes, is a natural polyphenol originally isolated from white hellebore that is also present in grapes, berries, and peanuts. It is well documented that resveratrol can suppress proliferation and invasion as well as induce apoptosis in a wide variety of tumor cell types. The highly potent inhibitory effects of resveratrol against tumorigenesis suggest that it is an efficient chemopreventive agent for cancer. Compounds that are closely related to resveratrol structurally, such as 3,5,4-trimethoxy-trans-stilbene...
and decreasing focal adhesions (also called cell–matrix adhesions). Resveratrol inhibited MMP-9 expression in SMMC-7721 cells and TNFα-mediated MMP-9 expression in HepG2 cells by down-regulation of the NF-κB signaling pathway. The migratory and invasive abilities of PMA-treated HepG2 and PMA-untreated Hep3B cells were reduced by treatment with resveratrol and its analog, MR-3, through regulation of MMP-2 and -9 and TIMP-1 and -2. Another natural dimethylated analog of resveratrol, pterostiben, can suppress the 12-o-tetradecanoylphorbol-13-acetate (TPA)-induced invasion, migration, and metastasis of HepG2 cells. The TPA-induced expression of MMP-9, VEGF, EGF, and EGRF; signaling of ERK, JNK, p38, PI3K/Akt, and PKC; and transcription factors of NF-κB and AP-1 in HepG2 were all blocked by pterostiben. In lung cancer: administration of resveratrol has a clear anti-metastatic effect; it decreases both the number and the weight of Lewis lung carcinoma (LLC) metastases in animal models via the inhibition of LLC-induced angiogenesis. Resveratrol inhibits the expression of heme oxygenase (HO)-1 and subsequently MMP-9 and -2, which, in part, associated with the HO-1-mediated NF-κB pathway to reduce the migratory and invasive abilities of A549 cells. EGF-induced invasion of A549 cells can be blocked by resveratrol treatment, possibly by suppressing the activation of the ERK and PI3K/Akt signaling pathways, subsequently exerting an inhibitory effect on MMP-2. In contrast, the anti-invasive effects of MR-3 in A549 cells are mediated through the inhibition of JNK and p38 phosphorylation, as well as the reduction of NF-κB and AP-1 protein levels in the nucleus, ultimately leading to the down-regulation of MMP-2 expression.

In breast cancer: resveratrol inhibits the migration of MDAMB231 cells by inducing a rapid global array of filopodia and decreasing focal adhesions (also called cell–matrix adhesions). Resveratrol has also been shown to decrease FAK activity in these cells. Resveratrol and pterostiben both can inhibit heregulin (HRG)-β1-mediated motility and invasion of MCF-7 cells through the down-regulation of MMP-9 expression that is associated with the ERK, p38, and PI3K/Akt signaling pathways. The anti-invasive activity of resveratrol on MCF-7 cells partly originated from the induction of tensin. Resveratrol can inhibit insulin-like growth factor (IGF)-1-mediated cell migration and invasion and MMP-2 expression in MDAMB435 cells through suppression of the PI3K/Akt signaling pathway. Upon incubation with resveratrol, ROS generation and MMP-9 expression in a murine mammary carcinoma cell line 4T1 were decreased, and cell invasion was hence inhibited. In glioblastoma: treatment of glioblastoma cell lines T60, T63, and GBM with resveratrol may suppress the expression of MMP-2 and Secreted Protein Acidic and Rich in Cysteine (SPARC), two major factors in the ECM remodeling that occurs with tumor invasion, suggesting that it may have uses as a therapeutic agent for brain tumor invasion. In melanoma: oral administration of both resveratrol and pterostiben decreased hepatic metastasis in mice with intrasplenically inoculated B16F10 cells, and the anti-metastatic mechanism was related to an inhibition of Vascular Adhesion Molecule 1 (VCAM-1) expression in the hepatic sinusoidal endothelium. In ovarian carcinoma: Qin et al. showed that resveratrol has inhibitory effects on migration and adhesion but has no effect on the invasion capacity of HO-8910PM. LPA-induced migration of OVCAR-3 and CAOV-3 cells under hypoxic condition is efficiently blocked by resveratrol through the inhibition of HIF-1α and VEGF expression, which seems to be associated with both the inactivation of ERK1/2 and 70-kDa S6 protein kinase (p70S6K).

In colon cancer: resveratrol can restrict the migration, adhesion, invasion, and secretion of MMP-9 and -2 in LoVo cells cultured under hypoxic conditions, and it potentially inhibits the expression of VEGF and HIF-1α in colon cancer cells. Suppression of pulmonary metastasis in BALB/c mice challenged with CT26 colorectal adenocarcinoma cells was achieved by oral administration of resveratrol. In fibrosarcoma: resveratrol may exert an antimetastatic effect by inhibiting NF-κB activation and ICAM-1 expression, leading to the suppression of HT1080 fibrosarcoma cell adhesion to ECV304 endothelial cells. In multiple myeloma: resveratrol is an effective in vitro inhibitor of VEGF, MMP-9/-2, and NF-κB, which play a vital role in suppressing the invasion of RPMI8226, U266, and KM3 multiple myeloma cells. In endothelial cell: angiogenesis is the target of anti-neoplastic and chemopreventive therapies. Resveratrol has been found to exhibit an anti-angiogenic profile and has significant vascular-targeting activity. It also inhibits αvβ3 integrin-dependent adhesion of endothelial cells (HUVEC and GM7373) and the recruitment of β3 integrin in focal adhesion contacts.

The proposed target proteins and mechanisms of resveratrol and its derivatives in the inhibition of cancer invasion/metastasis in vitro and in vivo are summarized in Table 2.

Other phenolic acids, monophenol, and polyphenol

Gallic acid (GA)

Gallic acid (3,4,5-trihydroxybenzoic acid), a naturally occurring plant phenolic acid, is a major active component of Chinese gell and has been reported to have anti-invasive and anti-metastatic activities in various cancer cells. In gastric adenocarcinoma: GA has potent inhibitory effects on AGS cell migration by suppressing the expression of MMP-2/-9 and cytoskeletal F-actin. The anti-migratory effect of GA may involve the inhibition of NF-κB activity and multiple proteins related to metastasis and cytoskeletal reorganization signal pathways, including Ras, Cdc42, Rac1, RhoA, RhoB, PI3K, and p38. In Mastocytoma: when treated with GA, DBA/2 mice in which P815 murine mastocytoma cells have been injected intravenously had a decreased number of nodules in the liver, suggesting that GA is an inhibitor of P815 cell metastasis. In Glioma: the suppression of ADAM metalloptedase domain 17 (ADAM17), also called tumor necrosis factor-α-converting enzyme (TACE), and the down-regulation of PI3K/Akt and ERK/MAPK signaling pathways may contribute to a GA-induced decrease of U87 cell invasiveness.

Chlorogenic acid (CGA) and 3-caffeoyl,4-dihydrocaffeoylquinic acid (CDCAQ)

Chlorogenic acid, a family of naturally occurring organic compounds, is one of the phenols found in coffee, Phylllostachys edulis (a bamboo species), and many other plants. The biological activity of CGA is thought to have antivirus, antibacterial, and antifungal effects. It is also an antioxidant and an inhibitor of the tumor-promoting activity of phorbol esters. In hepatoma: CGA was found to have anti-invasive activity in a rat ascite hepatoma cell line, AH1109A and is a strong MMP-9 inhibitor in Hep3B cells. In glioma: the MMP-2 secretion and migration of U-87 cells with or without sphingosine-1-phosphate induction are inhibited by treatment with CGA. In fibrosarcoma: a CGA derivative, CDCAQ, was isolated from Salicornia herbacea and was shown to inhibit PMA-induced MMP-9/-2 secretion and the migration/invasion of HT-1080 cells, which may occur through the inhibition of AP-1 and signaling pathways involving PKCδ, ERK, JNK, and p38.

Caffeic acid (CA) and caffeic acid phenyl ester (CAPE)

Caffeic acid is a widespread phenolic acid that occurs naturally in many agricultural products such as fruits, vegetables,
wine, olive oil, and coffee. CAPE, a CA derivative, was extracted from honey bee propolis and has been synthesized by esterification of CA. In hepatoma; CA was demonstrated to be one of the chemical constituents of coffee that suppresses the invasion of AH109A cells in vitro. Treatment of HepG2 cells with CA and CAPE can suppress PMA-induced MMP-9 expression by inhibiting the binding activity of NF-κB. CAPE exerts its anti-invasive potential through inhibition of MMP-2 and -9 expressions, possibly by targeting NF-κB. In prostate cancer: an effective inhibition of the in vitro invasion of PC3 cells was carried out using CA treatment. In colon cancer; CAPE-treated CT26 cells exhibited not only cell invasion inhibition but also a decrease in MMP-2/9 and VEGF productions. Intraperitoneal injection of CAPE into BALB/c mice reduced the pulmonary metastatic capacity of CT26 cells and decreased the plasma VEGF level. In fibrosarcoma; CAPE inhibited the invasion, motility, and migration of HT1080 cells, and a significant down-regulation of MMP-2/9 and TIMP-2 expression was observed. In endothelial cells: at a low concentration, CAPE can effectively inhibit capillary-like tube formation in HUVEC cultures on Matrigel. This result indicates that CAPE is an antiangiogenic agent.

### Table 2

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Cell/animal model</th>
<th>Biological effects</th>
<th>Molecular targets</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatoma</td>
<td>Hep3B/PMA-induced HepG2/TNFα-mediated HepG2/ROS-stimulatedAH109A/SMMC-7721</td>
<td>[migration; MMP-2/-9; ROS; HGF; VEGF/EGF/EGFR; TIMP-1/-2]</td>
<td>[NFκB; PI3K; PKC; AP-1; NF-kB]</td>
<td>117–122</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>A549/EGF-induced A549/LLC implanted mice and rats</td>
<td>[adhesion; motility; invasion; metastasis; MMP-2/-9; HO-1; angiogenesis; MMP-2/-9; ROS]</td>
<td>[MR-3; PI3K; Akt; AP-1; NF-kB]</td>
<td>123–127</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>MDAMB231/5GF-mediated MDAMB435/MCF7/HRG-j1-mediated MCF7/4T1</td>
<td>[adhesion; migration; invasion; MMP-2/-9; ROS]</td>
<td>[ERK; PI3K/Akt; ERK]</td>
<td>128–133</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>T60/T63/GBM</td>
<td>[filopodia; adhesion to fibronectin; tensin]</td>
<td>[SF3; ERK]</td>
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<tr>
<td>Melanoma</td>
<td>B16MF10 implanted mice</td>
<td>[invasion; migration; invasion; MMP-2/-9; VEGF; TIMP-2]</td>
<td>[PI3K;p38; NF-kb]</td>
<td></td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>H5-8910PM/hyoxia and LPA-induced OVCAR-3,CAOV-3</td>
<td>[adhesion; invasion; MMP-2/-9]</td>
<td>[Akt; ERK]</td>
<td>130</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Hyoxia-induced LoVo/CT26 implanted mice</td>
<td>[adhesion; invasion; MMP-2/-9]</td>
<td>[NF-kb]</td>
<td>115,141</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>HT1080/RPM8226/U266/KM3</td>
<td>[angiogenesis; αvβ3 integrin-dependent adhesion]</td>
<td>[NA]</td>
<td>132,142,143</td>
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<tr>
<td>Multiple myeloma</td>
<td>HUVEC/CM3732</td>
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</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Phenolic/cancer type/Cell model</th>
<th>Biological effects</th>
<th>Molecular targets</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric adenocarcinoma/AGS</td>
<td>[migration; MMP-2/-9; F-actin]</td>
<td>[Cdc42; Ras; Rac1; RhoA; RhoB; PI3K;p38; NF-kb]</td>
<td>144</td>
</tr>
<tr>
<td>Mastocytoma/PB15 implanted mice</td>
<td>[metastasis (to liver)]</td>
<td>[Akt; ERK]</td>
<td>145</td>
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<tr>
<td>Chlorogenic acid/Hepatoma/ACSF</td>
<td>[migration; MMP-9]</td>
<td>[AP-1; PKC6; ERK]</td>
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<td>Colorectal carcinoma/PC3</td>
<td>[invasion; MMP-9]</td>
<td>[NF-kb]</td>
<td>147,155</td>
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<tr>
<td>Colon cancer/CT26/CT26 implanted mice</td>
<td>[migration; invasion; MMP-2/-9; TIMP-2]</td>
<td>[ERK; PI3K/p38; Akt; NF-kb]</td>
<td>158</td>
</tr>
<tr>
<td>Endothelial cell/HUVEC</td>
<td>[angiogenesis]</td>
<td>[ERK; PI3K/p38; Akt; NF-kb]</td>
<td>158</td>
</tr>
<tr>
<td>Carnosol/Endothelial cell/HUVEC</td>
<td>[angiogenesis; αvβ3 integrin-dependent adhesion]</td>
<td>[NA]</td>
<td></td>
</tr>
<tr>
<td>Capsaicin/Melanoma/B16F10</td>
<td>[migration; MMP-9]</td>
<td>[NF-kb]</td>
<td>162</td>
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<tr>
<td>6-Shogaol/HepG2/HeP2B</td>
<td>[migration; invasion; MMP-2/-9; UPA]</td>
<td>[PI3K/Akt/Rac1]</td>
<td>159</td>
</tr>
<tr>
<td>6-Gingerol/Hepatoma/HeP2B/HeP3B</td>
<td>[migration; invasion; MMP-2/-9]</td>
<td>[PI3K/Akt/Rac1]</td>
<td>160</td>
</tr>
<tr>
<td>Breast cancer/MDAMB231</td>
<td>[adhesion; migration; MMP-2/-9; TIMP-1]</td>
<td>[NA]</td>
<td>162</td>
</tr>
<tr>
<td>Melanoma/B16F10 implanted mice</td>
<td>[migration; invasion; MMP-2/-9]</td>
<td>[NA]</td>
<td>163</td>
</tr>
<tr>
<td>Endothelial cell/HUVEC</td>
<td>[angiogenesis]</td>
<td>[NA]</td>
<td>163</td>
</tr>
</tbody>
</table>
Carnosol
Carnosol, a constant constituent of *Rosmarinus officinalis* extracts, is a phenolic diterpene shown to have anticarcinogenic properties. Carnosol inhibited the invasion of highly metastatic mouse melanoma B16F10 cells by reducing MMP-9 expression through suppressing ERK, JNK, p38, and Akt signaling pathways and the inhibition of NF-kB and AP-1 binding activity.\(^{158}\)

Capsaicin
Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is one of the major pungent ingredients found in red pepper that has been reported to possess anti-carcinogenic activity. Capsaicin significantly inhibited the migration of B16F10 melanoma cells without showing obvious cellular cytotoxicity. This effect is correlated with the down-regulation of PI3K/Akt and Rac1 activities.\(^{159}\)

6-Shogaol and 6-gingerol
Shogaols and gingerols are two phenolic substances contained in a volatile oil extracted from ginger (*Zingiber officinale*) root and provide ginger its characteristic odor and flavor. Shogaol is a dehydrated product of the structurally-similar gingerols. Because gingerols are highly concentrated in fresh ginger, shogaols are abundant in dried and thermally treated ginger. Among these two phenolic substances, 6-shogaol [1-(4-hydroxy-3-methoxyphenyl)-4-decen-3-one] is a lipid-soluble organic compound, and 6-gingerol [5-hydroxy-1-(4'-hydroxy-3'-methoxyphenyl)-3-decanone] is an
abundant constituent in ginger. In hepato-both 6-shogaol and 6-
gingerol may exert anti-invasive activity against PMA-treated HepG2 and PMA-untreated Hep3B cells through regulation of MMP-9 and TIMP-1, and 6-shogaol could further regulate uPA activity.160 6-Gingerol also suppresses the ROS-potential invasive capacity of AH109A cells.161 In breast cancer: the adhesion, invasion, motility and activities of MMP-2/-9 in MDAMB231 human breast cancer cell lines inhibited by 6-gingerol treatment have also been shown.162 In melanoma: i.p. administration of 6-gingerol to mice receiving i.v. injections of B16F10 melanoma cells reduced the number of lung metastases.163 In endothelial cells: 6-gingerol inhibits both the VEGF- and bFGF-induced proliferation of human endothelial cells in vitro. It also blocks capillary-like tube formation by endothelial cells in response to VEGF and strongly inhibits sprouting of endothelial cells in the rat aorta and formation of new blood vessel in the mouse cornea in response to VEGF.165

The proposed target proteins and mechanisms of the above-
mentioned compounds on the inhibition of cancer invasion/metast-
asis in vitro and in vivo are summarized in Table 3.

Conclusions

It is obvious that dietary phenolic acids, monophenol, and poly-
phenol possess inhibitory properties against the invasive and metastatic behaviors (e.g., adhesion, migration, and angiogenesis) of a variety of cancer cells in vitro and/or in vivo. This review considers the results of studies on the anti-invasive and anti-metastatic effects and mechanisms of these three subgroups of phenolics. Curcumin, resveratrol, and their related derivatives are the most studied compounds in this area so far, and gallic acid, chlorogenic acid, caffeeic acid, carnosol, capsaicin, 6-shogaol, 6-
gingerol, and their corresponding derivatives are active compo-
nents responsible for the anti-invasive and anti-metastatic actions of dietary vegetables on tumors. The mechanisms underlying the anti-invasion and anti-metastasis properties of these bioactive compounds act through the modulation of the activities of PKC, FAK, and Cdc42; the phosphorylation of Ras, Rac1, ERK, JNK, p38, and tensin in different tumor cells or animal models are presented. The overall signaling pathways and effectual proteins involved in the inhibition of invasion and metastasis of various cancer cells by phenolic acids, monophenol, polyphenol, and their derivatives that we summarized here were represented schematically in Fig. 2. Based on the scientific evidence available, we conclude that daily consumption of natural foods containing adequate phenolics could be beneficial for the prevention of cancer metastasis.

Conflict of interest statement

None declared.

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References


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