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Recent Progress on the Molecular Mechanisms of Anti-invasive and Metastatic Chinese Medicines for Cancer Therapy

Wei Guo, Ning Wang and Yibin Feng

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Abstract

Despite of the recent advances in diagnostic and therapeutic approaches, cancer remains as the leading cause of death worldly with diverse causal factors regarding genes and environment. Invasion and metastasis, as one of the most important hallmarks for cancer, have restrained the successful clinical therapy and are the primary causes of death among cancer patients. So far, most chemotherapeutic drugs are not effective for metastatic cancer due to drug resistance and serious side effects. Therefore, it is urgently essential to develop more effective therapeutic methods. Owing to their diverse biological activities and low toxicity, naturally active compounds derived from Chinese medicines, as a complementary and alternative approach, are reported to promote the therapeutic index and provoked as an excellent source for candidates of anti-metastatic drugs. With the rapid development of molecular biology techniques, the molecular mechanisms of the effects of potential anti-invasive and metastatic Chinese medicines are gradually elucidated. This chapter reviews the potential anti-invasive and metastatic mechanisms of naturally active compounds from Chinese medicines, including suppression of EMT, proteases and cancer-induced angiogenesis, anoikis regulation of circulating tumor cells and regulation of miRNA-mediated gene expression, providing scientific evidence for clinically using Chinese medicines in the field of cancer therapy.

Keywords: Chinese medicines, anti-invasion and metastasis, molecular mechanisms, cancer therapy
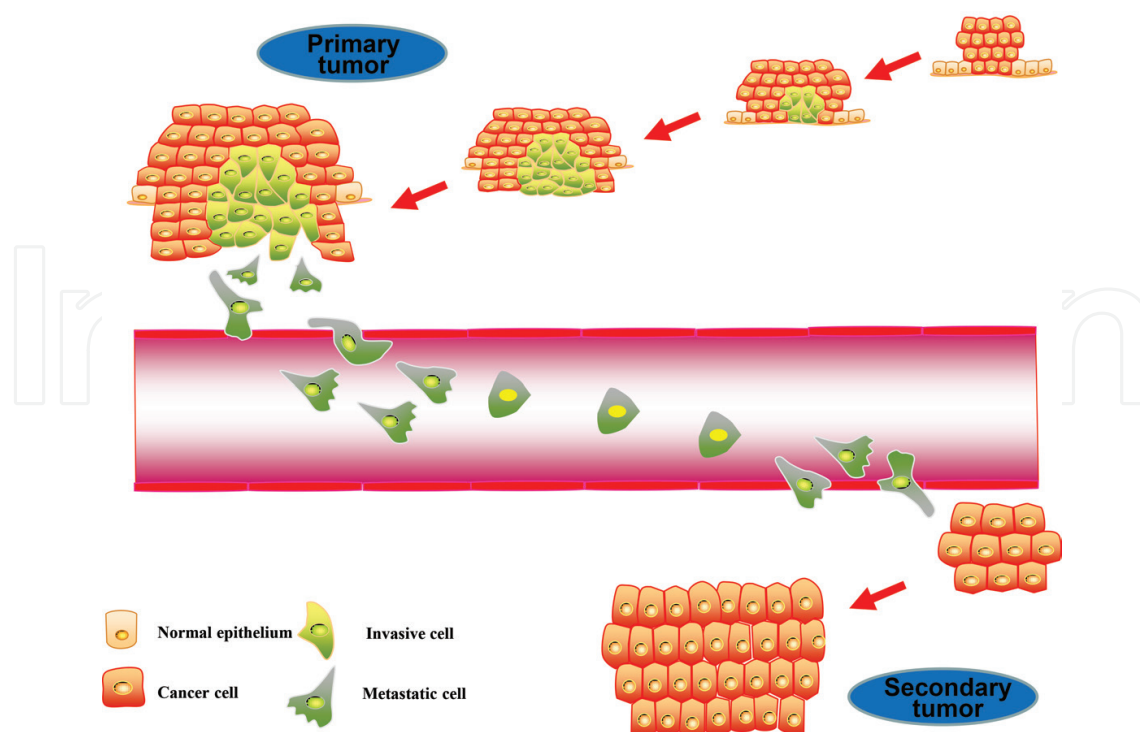
1. Introduction

Despite of all the recent advances in diagnostic and therapeutic approaches, cancer remains the leading cause of death and primary public health hazard all over the world [1, 2]. With diverse causal factors (genetic and environmental, physical, psychological and biochemical factors), cancer has a various disease spectrum to more than a hundred different kinds of malignancies, such as lung cancer, breast cancer, renal carcinoma, hepatocellular carcinoma, and so on [3]. It is a progressive disease with multiple pathological processes covering cancer initiation, development, and metastasis. Cancer is characterized by several key hallmarks [4–6], namely uncontrolled replication ability of abnormal cells, resistance to programmed cell death, invasion into the surrounding extracellular matrix (ECM), sustained capability of angiogenesis, and metastatic spread to other sites.

As one of the most important hallmarks for cancer, metastasis is an intricate process concerning the following six steps (as shown in **Figure 1**): (i) detachment of cancer cells through degrading ECM, (ii) local migration and invasion into the surrounding tissues, (iii) intravasation into blood and/or lymphatic vessel systems, (iv) survival and circulation in the circulatory system, (v) extravasation into the targeted secondary organ site, and (vi) multiplication and formation of a secondary tumor [7–9]. During these steps, the metastatic cancer cells should have special properties to overcome the obstacles, such as the capability of invasion, resistance to anoikis, and angiogenesis. Basically, these steps are regulated by multiple factors, including but not limited to changes of expression of related genes, cytoskeleton remodeling, proteolysis degradation of ECM, and so on [10]. Metastasis is a nonrandom process, and different metastatic cancer types possess their corresponding preferred sites of metastasis. For instance, the preferred sites of breast cancer cells are lung, liver, and bone [11]. Since invasion and metastasis restrain the successful clinical therapy and are the primary causes of death among cancer patients, it has been widely accepted that invasion and metastasis become a highlighted topic of research interests, and active efforts are still needed to understand the underlying molecular mechanisms and develop effective anti-metastatic therapies.

At the present day, there are three conventional therapeutic approaches which are used to treat metastatic cancers, namely surgical resection, chemotherapy, and radiotherapy. Though remain as the main treatment approach for metastatic cancer patients, most chemotherapeutic drugs are not effective for metastatic cancer due to drug resistance and serious side effects. Most chemotherapeutic drugs fail to selectively kill cancer cells without destroying normal cells at the sites of metastasis [12] and thus cause severe toxicity, such as appetite loss, weight loss, insomnia, fatigue, even life threat etc [13, 14]. Although chemotherapeutics significantly leads to regression of the primary tumor, some investigations even report that it may also promote and enhance metastatic formation of a secondary tumor [15, 16]. Besides, metastatic cancers are demonstrated to be largely resistant against chemotherapeutics. Despite that various approaches have been applied to treat metastatic cancers, the clinical outcomes of metastatic cancer treatment are still not at a satisfactory level. Therefore, it is urgently essential to develop more effective therapeutic methods with minimal adverse effects for metastatic cancer treatment.

Figure 1. The process involving in cancer metastasis.

Traditional medicine, such as Chinese medicine, has been shown to exhibit various pharmacological activities and used in treatment of various diseases in Asian countries and regions for a long time [17]. The numerous natural compounds obtained from Chinese medicines chemically range from flavonoids and polyphenols to mineral salts, which have been reported to be an excellent source for anti-cancer agents [18]. Owing to their long-lasting efficacy, diversity in biological activities, and low toxicity, natural active products from Chinese medicines, including single compounds and various extracts, are being developed for treatment of metastatic cancer [19, 20]. In line with such a concept, several natural active products from Chinese medicines have been currently investigated as a complementary and alternative approach, and their anti-metastatic properties have been focused to find newly discovered mechanisms with the hope to promote the therapeutic index of metastatic cancer.

With the rapid development of molecular biology techniques, the molecular mechanisms underlying the effects of potential anti-invasive and metastatic Chinese medicines are gradually elucidated. Understanding of the underlying molecular mechanisms may in turn lead to the discovery of novel anticancer drugs. In summary, this chapter reviews the anti-invasive and metastatic effect of natural active compounds from Chinese medicines and their molecular mechanisms. **Tables 1** and **2** respectively summarized the potential underlying molecular mechanisms of single pure compounds and various extracts from Chinese medicines to suppress cancer invasion and metastasis.

Single pure compound	Cancer type	Study type	Mechanism of actions	Ref. (PMID)
Arctigenin	Breast cancer	In vitro MCF-7 and MDA-MB-231 cells	Suppress MMP-9 and uPA	28035371
	Colorectal cancer	In vitro CT26, MC38, CCD-18Co and SW620 cells and in vivo BALB/c female mice	Induce anoikis via MAPKs signaling, inhibit EMT through increasing E-cadherin and decreasing N-cadherin, vimentin, β-catenin, and Snail and downregulate MMP-2/9	27618887
Astragaloside IV	Breast cancer	In vitro MDA-MB-231 cells and in vivo athymic Balb/c nude mice	Downregulate Vav3 and MMP-2/9	27930970
Berberine	Hepatocellular carcinoma	In vitro MHCC-97L, Bel-7402, SMMC-7721 cells and in vivo nude mice	Downregulate uPA and suppress Id-1 via HIF-1α/VEGF pathway	27092498 25496992
	Nasopharyngeal carcinoma	In vitro HONE1 cells	Suppress Rho GTPases including RhoA, Cdc42, and Rac1	19513545
Notoginsenoside R1	Colorectal cancer	In vitro HCT-116 cells	Reduce MMP-9, integrin-1, E-selectin and ICAM-1 expressions	27840961
Matrine	Prostate cancer	In vitro DU145 and PC-3 and male Balb/c nude mice inoculated subcutaneously with cells	Downregulate MMP-2/9	28000853
Bibenzyl 4,5,4'-trihydroxy-3,3'-dimethoxybibenzyl	Lung cancer	In vitro H292 cells	Suppress EMT markers (vimentin and Snail) and increase the level of E-cadherin and induce anoikis by reduction of activated protein kinase B (p-AKT) and activated extracellular signal-regulated kinase (p-ERK)	24692728
Curcumin	Lung cancer	In vitro H460 cells	Sensitize anoikis by down-regulating Bcl-2	20127174
Imperatorin	Lung cancer	In vitro H23, H292 and A549 cells	Sensitize anoikis by down-regulating Mcl-1 protein and up-regulating Bax	23108812
Artonin E	Lung cancer	In vitro H460, A549 and H292 cells	Sensitize anoikis by down-regulating Mcl-1 protein	23225436

Single pure compound	Cancer type	Study type	Mechanism of actions	Ref. (PMID)
Ecteinascidin 770	Lung cancer	In vitro H23 and H460 cells	Sensitize anoikis by down-regulating Mcl-1 protein and up-regulating Bax	23393342
Renieramycin M	Lung cancer	In vitro H460 cells	Sensitize anoikis by down-regulating survival proteins p-ERK and p-AKT and anti-apoptotic proteins BCL2 and MCL1	27069144
Oroxylin A	Lung cancer	In vitro A549 cells and in vivo nude mice	Sensitize anoikis by inactivating the c-Src/AKT/HK II pathway	23500080
Geraniin	Lung cancer	In vitro A549 cells	Inhibit the TGF-β1-induced EMT	26169124
Genipin	Hepatocellular carcinoma	In vitro HepG2 and MHCC97L cells and in vivo male nude mice	Overexpress TIMP-1 and inhibit MMP-2	23029478
Kukoamine A	Glioblastoma	In vitro C6, U251 and WJ1 cells and in vivo nude mice (BALB/C-nu/nu)	Inhibit EMT and induce anoikis by downregulating expressions of C/EBPβ and 5-LOX	27824118
Gigantol	Lung cancer	In vitro H460 cells	Decrease EMT markers including N-cadherin, vimentin, and Slug	26733180
Moscatilin	Lung cancer	In vitro H460 cells	Inhibit EMT by suppressing mesenchymal cell markers (vimentin, Slug, and Snail) and induce anoikis by survival proteins (ERK and Akt) suppression and Cav-1 down-regulation	26384689
2,3,5- Trimethoxy-4-cresol	Lung cancer	In vitro A549 cells	Suppress Akt, MMP-2 and MMP-9 and increase E-cadherin and TIMP-1	25951809
Deoxyelephantopin	Lung cancer	In vitro A549 cells	Suppress MMP-2, MMP-9, uPA, and uPAR	25686703
Bufalin	Lung cancer	In vitro NCI-H460 cells	Suppress MMP-2, MMP-9, MAPKs, and NF-kB	26446205
Epicatechin-3-gallate	Lung cancer	In vitro A549 cells and in vivo BALB/c nude mice	Inhibit the TGF-β1-induced EMT by up-regulating epithelial marker (E-cadherin) and down-regulating mesenchymal markers (fibronectin and p-FAK)	27224248

Single pure compound	Cancer type	Study type	Mechanism of actions	Ref. (PMID)
Rocaglamide-A	Prostate cancer, breast cancer and cervical cancer	In vitro PC-3, MDA- MB-231, HCT116, HeLa, and 293T cells	Inhibit the activity of Rho GTPases RhoA, Rac1 and Cdc42	27340868
Chamaejasmenin B	Breast cancer	In vitro MDA-MB-231, ZR75-1 and 4T1 cells and in vivo BALB/c mice	Block TGF-beta induced EMT	27374079
Artesunate	Cervical cancer	In vitro CaSki and Hela cells	Inhibit HOTAIR and COX-2 expressions	27736969
Ginsenoside Rd	Breast cancer	In vitro 4T1 cells and in vivo BALB/c mice	Derepress miR-18a-mediated Smad2 expression	27641158
Quercetin	Colorectal cancer	In vitro CT26 and MC38 cells and in vivo BALB/c female mice	Induce apoptosis through the MAPKs pathway, regulate EMT markers including E-, N-cadherin, β-catenin, and snail and regulate MMPs and TIMPs	27823633
Sulforaphane	Lung cancer	In vitro H1299, 95C and 95D cells and in vivo male BALB/c nude mice	Inhibit EMT by silencing miR-616-5p	27890917
Tricetin	Osteosarcoma	In vitro U2OS and HOS cells	Repress MMP-9 via p38 and Akt pathways	27860196
Arsenic trioxide	Chondrosarcoma	In vitro HCS-2/8, OUMS-27, SW1353, and JJ012 cells	Inhibit EMT via the miR-125b/Stat3 axis	27576314
Cucurbitacin B	Breast cancer	In vitro MDA-MB-231 and 4T1 cells	Inhibit angiogenesis via downregulating VEGF/FAK/MMP-9 signaling	27210504
2,3,5,4′-Tetrahydroxystilbene-2-O-β-D-glucoside	Colorectal cancer	In vitro HT-29 cells	Suppress MMP-2 and ICAM-1 via NF-κB pathway	27278328
7,7″-Dimethoxyagastisflavone	Melanoma	In vitro B16F10 cells and in vivo female C57BL/6JNarl mice	Down-regulate the polymerization of F-actin via Cdc42/Rac1 pathway and inhibit lamellipodia formation via suppressing CREB phosphorylation	27487150
Nobiletin	Osteosarcoma	In vitro U2OS and HOS cells	Block ERK and JNK-mediated MMPs expression	27144433

Table 1. Summary on the potential underlying molecular mechanisms of single pure compound from Chinese medicines to suppress cancer invasion and metastasis.

Various extracts	Cancer type	Study type	Mechanism of actions	Ref. (PMID)
Ethanol extract of baked Gardeniae Fructus	Melanoma	In vitro B16F10 and in vivo C57BL/6 mice	Inhibiting the release of pro-angiogenic factors from tumor cells	27779658
Mixture of flavonoids extracted from Korean *Citrus aurantium*	Lung cancer	In vitro A549 cells and in vivo NOD/SCID mice	Induce apoptosis through regulating the apoptosis related protein cleaved caspase-3 and p-p53	No
Bibenzyl compounds isolated from *Dendrobium pulchellum*	Lung cancer	In vitro	Induce anoikis	23472473
Aqueous extract of *Andrographis paniculata*	Esophageal cancer	In vitro EC-109 and KYSE-520 cells	Inhibit anoikis resistance	26885447
Methanol extracts of *Euphorbia humifusa* Willd	Breast cancer	In vitro MDA-MB-231 and in vivo Balb/c mice	Reduce TNFα-induced MMP-9 expression	27776550
Ethanol extract of Lophatheri Herba	Fibrosarcoma, breast cancer, prostate carcinoma and melanoma	In vitro HT1080, MDA-MB231, DU145, B16F10 cells and in vivo C57BL/6J mice and ICR mice	Suppress tumor-induced angiogenesis by decreasing the pro-angiogenic factors	27808120
Coptidis Rhizoma aqueous extract	Hepatocellular carcinoma	In vitro Hep G2 and MHCC97-L cells and in vivo nude mice	Suppress Rho/ROCK signaling pathway and inhibit VEGF secretion	21106616 24363282
Methanol extracts and butanol extracts of *Oldenlandia diffusa*	Breast cancer	In vitro MCF-7 cells	Inhibit PMA-induced MMP-9 and ICAM-1 expressions	27876502
Annona muricata leaf aqueous extract	Breast cancer	In vitro 4 T1 cells and in vivo female BALB/c mice	Induce the apoptosis	27558166
Ethanol extract of *Siegesbeckia orientalis*	Endometrial Cancer	In vitro RL95-2 and HEC-1A	Reverse the TGFβ1-induced EMT	27527140
Polyphenols of *Artemisia annua* L.	Breast cancer	In vitro MDA-MB-231 cells	Suppress EMT by inhibiting MMP-2/-9 and vascular cell adhesion molecule-1	27151203
Gegen Qinlian decoction	Renal carcinoma	In vitro ACHN and Caki-1 cells and in vivo male BALB/c nude mice	Suppress neoangiogenesis via MMP-2 inhibition	25228536

Table 2. Summary on the potential underlying molecular mechanisms of various extracts from Chinese medicines to suppress cancer invasion and metastasis.

2. Suppression of epithelial-mesenchymal transition

Recent studies clearly showed that epithelial-mesenchymal transition (EMT) plays an important role in the metastasis of cancers [21]. As the fundamental step during cancer metastasis, EMT is a complex process during which immotile epithelial cells undergo a morphological transformation into motile mesenchymal-appeared cells, triggering cancer cells to detach from the primary site via the loss of cell-to-cell junctions and thus promoting cell migration [22]. There are

three different subtypes of EMT, and the third subtype of EMT is associated with the invasion and metastasis of cancers [23]. EMT-phenotypic cells can decrease the level of epithelial marker E-cadherin, a junction protein for cell-cell contact. Besides, they can also increase the level of mesenchymal markers, such as N-cadherin, β-catenin, and vimentin, as well as promote transcription factors of EMT switch, such as Slug and Snail [24, 25]. As EMT has been significantly linked to the metastatic behaviors of cancer cells, natural products obtained from Chinese medicines with the ability to suppress EMT are attracting attention for the development of anti-metastasis therapies.

Among potential natural products, geraniin, a polyphenolic component derived from Phyllanthus amarus, has gained considerable attention over the past decade. Previous study has demonstrated that EMT can be induced by transforming growth factor-beta 1 (TGF-β1) and thus stimulates the migration and invasion of lung adenocarcinoma. Geraniin has been shown to inhibit TGF-β1-induced EMT of lung cancer A549 cells in vitro by inducing the epithelial marker E-cadherin and suppressing Snail and mesenchymal marker N-cadherin and vimentin [26]. A compound derived from *Dendrobium ellipsophyllum*, bibenzyl 4,5,4′ -trihydroxy-3,3′-dimethoxybibenzyl was shown to inhibit EMT of lung cancer cells via downregulating EMT markers (vimentin and Snail) and upregulating E-cadherin [27]. Such EMT suppression was also observed in lung cancer cells treated with other single compounds obtained from Chinese medicine, such as moscatilin [28], gigantol [29], and epicatechin-3-gallate [30]. A flavonoid obtained from *Stellera chamaejasme* L., namely chamaejasmenin B, was also reported to block the TGF-β-induced EMT in breast cancer [31]. 5-lipoxygenase (5-LOX) is an enzyme to convert arachidonic acid to leukotrienes [32] and abrogating its expression can inhibit the migration, invasion, and metastasis of cancer cells by suppressing EMT via inactivating E-cadherin and activating snail [33]. CCAAT/enhancer binding protein β (C/EBPβ) was also reported to be related to the migration, invasion, and metastasis of cancer cells by EMT regulation [34]. Kukoamine A, a spermine alkaloid extracted from Cortex lycii radicis, was demonstrated to suppress the migratory and invasive ability of human glioblastoma cell both in vitro and in vivo, and this action was mediated through EMT attenuation via decreasing the levels of 5-LOX and C/EBPβ [35]. Likewise, similar EMT inhibitory effects have also been observed in various extracts from Chinese medicines. *Siegesbeckia orientalis* Linne is a traditionally used Chinese medicinal herb that exhibits various pharmacological activities. Its ethanol extract (SOE) has been reported as a potential anti-metastatic agent by reversing the TGFβ1-induced EMT via ERK1/2, JNK1/2, and Akt pathways [36]. SOE can inhibit the migration and invasion of endometrial cancer RL95-2 and HEC-1A cells in a dose-dependent manner. *Artemisia annua* L. is a traditional medicine which has been applied for treating multiple diseases. The polyphenolic compounds from *Artemisia annua* L. (pKAL) were found to exhibit anti-metastatic property on highly metastatic breast cancer cells MDA-MB-231 [37]. This anti-metastatic property of pKAL was achieved through suppressing EMT by inhibiting MMP-2/-9 and vascular cell adhesion molecule-1 (VCAM-1).

3. Suppression of proteases expression

Matrix metalloproteinases (MMPs) is regarded as primary factors to trigger metastasis [38]. As extracellular zinc-dependent endopeptidases, they can degrade the basement membrane

and ECM and thus play an important role in the migration and invasion of cancers. There are 23 members in MMPs family, among which MMP-2 and MMP-9 are considered to be the key enzymes and play crucial roles in cancer metastasis [39, 40]. The activities of MMPs are finely mediated by tissue inhibitors of metalloproteinases (TIMPs) via their non-covalent binding to the active zinc-binding sites of MMPs [41]. In addition, as a serine-specific protease, uro-kinase-type plasminogen activator (uPA) can also degrade ECM via binding to uPA receptor (uPAR) and activating plasmin [42]. It is well-known that reorganization of the actin cyto-skeleton plays an important role in the migration of cancer cell [43]. This process is mainly regulated by the Rho family GTPases, such as RhoA, Rac1, and Cdc42 via a shuttle between an inactive GDP-bound form and an active GTP-bound form [44, 45]. Since these proteases play an important role in cancer invasion and metastasis via proteolysis, natural products obtained from Chinese medicines with the ability to suppress these proteases are attracting attention for the development of anti-metastasis therapies.

As a phytoestrogen-botanical lignan derived from Arctium lappa, arctigenin was shown to exert its anti-metastatic property through suppressing MMP-9 and uPA of breast cancer cells via inhibiting the upstream signaling pathways including Akt, NF-κB, and MAPK (ERK 1/2 and JNK 1/2), which is dependent to the modulation on estrogen receptor (ER) expression [46]. Such protease regulation was also observed in breast cancer cells treated with astragaloside IV [47]. Notoginsenoside R1 (NGR1) is a primary compound in Panax notoginseng, and its anti-metastatic property has also been revealed [48]. NGR1 can inhibit the migration, invasion, and adhesion of cultured human colorectal cancer cells (HCT-116) via suppressing MMP-9, integrin-1, E-selectin, and ICAM-1 expressions. Such inhibition on colorectal cancer cells was also observed when treated with 2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucoside [49]. As an alkaloid derived from Sophora flavescens, matrine can inhibit the invasion and migration of castration-resistant prostate cancer DU145 and PC3 cells by suppressing MMP-9 and MMP-2 expressions through NF-κB pathway [50]. The phenol derived from Taiwanese edible fungus *Antrodia cinnamomea*, 2,3,5-trimethoxy-4-cresol, was recently described as an effective anti-metastatic agent against lung cancer via suppressing Akt, MMP-2 and MMP-9, and increasing E-cadherin and TIMP-1[51]. Such protease regulation was also observed in lung cancer cells treated with other single compounds derived from Chinese medicine, such as deoxyelephan-topin [52] and bufalin [53]. Genipin, a natural compound obtained from the fruit of Gardenia jasminoides, was reported to exhibit anti-metastatic effect on hepatocellular carcinoma both in cell and animal model. This effect may be related with TIMP-1 overexpression and MMP-2 inhibition of genipin [54]. As an isoquinoline alkaloid isolated from Coptidis rhizome and other medicinal plants, berberine has been shown to exhibit multiple pharmacological actions in treating human diseases, including cancers [55]. Recently, it was reported to inhibit naso-pharyngeal carcinoma cell migration and invasion in vitro through suppressing Rho GTPases including RhoA, Rac1, and Cdc42 [56]. The anti-metastatic ability of Rocaglamide-A was also recently described via inhibiting the activity of Rho GTPases RhoA, Rac1, and Cdc42 [57]. As a dietary flavonoid in Eucalyptus honey and Myrtaceae pollen, tricetin was shown to attenu-ate osteosarcoma cell migration via suppressing MMP-9 via p38 and Akt pathways [58]. Such inhibition on osteosarcoma cells was also observed when treated with nobiletin [59]. The compound obtained from Taxus x media cv. Hicksii, 7,7″-Dimethoxyagastisflavone (DMGF) has been reported to inhibit the invasion and metastasis of melanoma cells in vivo and in vitro

[60]. The mechanism study provided evidence that DMGF can downregulate the polymerization of F-actin via Cdc42/Rac1 pathway and inhibit lamellipodia formation via suppressing cAMP response element-binding protein (CREB) phosphorylation. Likewise, similar protease inhibitory effects have also been observed in various extracts from Chinese medicines. The methanol extracts of *Euphorbia humifusa* Willd was reported to have anti-metastatic effects on breast cancer both in vitro and in vivo via reducing TNFα-induced MMP-9 expression [61]. In addition, the methanol extracts and butanol extracts of *Oldenlandia diffusa* were also shown to block the metastasis of breast cancer via inhibiting PMA-induced MMP-9 and ICAM-1 expressions [62].

4. Suppression of cancer-induced angiogenesis

Angiogenesis is a normal physiological process to sprout new vessels during the development of embryogenesis. To the contrary, pathological angiogenesis is associated with multiple diseases including cancers [63]. Highly malignant tumors can induce angiogenesis to provide sufficient oxygen and nutrients for themselves [64]. Additionally, angiogenesis also provides paths for cancer cells to metastasize distant tissues [65]. In tumor microenvironment, tumor and host cells release pro-angiogenic and anti-angiogenic factors. The pro-angiogenic factors include transforming growth factor (TGF), vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF), epidermal growth factor (EGF), and so on, and there is a fine balance between them. When the balance is skewed to the pro-angiogenic state, tumor shifts from a dormant state to a hyper-vascularized state [66]. Since angiogenesis plays an important role in the metastatic behaviors of cancer cells, natural products obtained from Chinese medicines targeting on tumor-induced angiogenesis have been regarded as promising agents to metastatic cancers.

Berberine has been shown to exhibit a significant inhibition on the migratory and invasive ability of hepatocellular carcinoma cells. Except for downregulation of uPA, berberine also inhibits angiogenesis through suppressing inhibitor of differentiation/DNA binding (Id-1) via HIF-1α/VEGF pathway [67, 68]. Cucurbitacin B (CuB), a plant triterpenoid, obtained from Cucurbitaceae family has been shown to inhibit the metastasis and angiogenesis of breast cancer MDA-MB-231 and 4T1 cells via downregulating VEGF/FAK/MMP-9 signaling [69]. Recently, a study of artesunate, a normal traditional Chinese medicine, has been conducted to investigate the anti-metastatic effects of artesunate on cervical cancer. The results demonstrated that artesunate inhibits cancer cell migration and invasion in vitro through suppressing HOTAIR and COX-2-mediated angiogenesis [70]. Likewise, similar inhibitory effects have also been observed in various extracts from Chinese medicines. The aqueous extract of Coptidis Rhizoma, a traditional Chinese medicinal herb with a long history, was observed to inhibit hepatocellular carcinoma cell migration both in vitro and in vivo through suppressing Rho/ROCK signaling pathway and inhibiting VEGF secretion [71, 72]. Gardeniae Fructus, a fruit obtained from *Gardenia jasminoides* Ellis, has been applied as traditional medicine and possesses various health benefits against multiple diseases. A recent study has shown that the ethanol extract of baked Gardeniae Fructus has an inhibitory effect on the angiogenic

and metastatic ability of melanoma cells both in vitro and in vivo via inhibiting the release of pro-angiogenic factors [73]. Lophatheri Herba, a dried leaf obtained from Lophatherum gracile Brongn, possesses inhibitory effects on the metastasis and angiogenesis of malignant cancer cells at noncytotoxic doses. It has been shown that ethanol extract of Lophatheri Herba (ELH) can inhibit the cancer cell metastasis both in vitro and in vivo through suppressing tumor-induced angiogenesis via decreasing the pro-angiogenic factors [74]. As an ancient Chinese medicine formula, Gegen Qinlian decoction was reported to suppress the neoangiogenesis in xenografted renal carcinoma cell tumor through inhibiting the enzyme activity of MMP-2 [75].

5. Anoikis regulation of circulating tumor cells

Anoikis, known as detachment-induced apoptosis, is a process of programmed cell death [76]. It can block metastasis by eliminating circulating cancer cells. However, in highly metastatic cancer cells, anoikis can be overcome and cancer cells can survive in a circulating condition until reaching a proper secondary site [77]. Anoikis is controlled by Bcl-2 family proteins. The pro-apoptotic proteins, such as Bax and the anti-apoptotic proteins, such as Bcl-2 and Bcl-xL, interact during anoikis [78]. In addition, anti-apoptotic protein myeloid leukemia cell sequence-1 (MCL-1) and caveolin-1 (CAV-1) have also been demonstrated to suppress anoikis [79]. Anoikis has become potential therapeutic target, and discovering new natural products obtained from Chinese medicines targeting anoikis is of great interest [80].

The anti-metastatic study of arctigenin on colorectal cancer has been recently conducted. Arctigenin can induce anoikis via MAPKs signaling, inhibit EMT through increasing E-cadherin and decreasing N-cadherin, vimentin, β-catenin, and Snail, and downregulate MMP-2/9, so that inhibition on the tumor cell migration and invasion both in vitro and in vivo was achieved [81]. Imperatorin, an active furanocoumarin component obtained from the root of *Angelica dahurica*, has been demonstrated to sensitize anoikis by downregulating Mcl-1 protein and upregulating Bax in lung cancer [82]. As a major dietary flavonoid, quercetin was reported to induce apoptosis through the MAPKs pathway, regulate EMT markers including E-, N-cadherin, β-catenin, and snail and modulate MMPs and TIMPs in colorectal cancer [83]. Curcumin, a compound derived from the rhizome of turmeric, was reported to inhibit the migratory and invasive ability of lung cancer cells through sensitizing anoikis, which was associated with downregulation of Bcl-2 [84]. Such anoikis regulation was also observed in lung cancer cells challenged other single compounds obtained from Chinese medicine, such as artonin E [85], ecteinascidin 770 [86], renieramycin M [87], Oroxylin A [88], and so on. In addition, regulation on anoikis was also observed in tumor cells treated with various extracts from Chinese medicines. Annona muricata Linn from Annonaceae family has long been applied to treat different diseases. Recently, its leaf aqueous extract (B1 AMCE) has been reported to exhibit anti-metastatic property in breast cancer [89]. B1 AMCE can significantly suppress the metastasis of 4T1 breast cancer cells in vitro and in vivo via inducing their apoptosis. The aqueous extract of *Andrographis paniculata* was demonstrated to inhibit anoikis resistance in esophageal cancer [89]. The bibenzyl compounds from *Dendrobium pulchellum*

[90] and the mixture of flavonoids extracted from Korean *Citrus aurantium* have been shown to induce apoptosis and inhibit metastasis of lung cancer cells [91].

6. Regulation of miRNA-mediated gene expression

As negative regulators of gene expression, microRNAs (miRNAs) have been shown to modulate multiple biological functions, such as immune response, metabolism, and metastasis [92]. miRNAs mediate the expression of target protein through degrading its mRNA or inhibiting the translation of mRNA via binding to mRNA three prime untranslated region (3′UTR). There is a dual action of miRNAs in cancers, either functioning as cancer promoters or inhibitors. Nearly, all human tumors have the characteristic of miRNAs dysregulation [93]. Since miRNAs play an important role in the metastatic behaviors of cancer cells, developing natural products obtained from Chinese medicines targeting miRNAs may be a promising strategy to treat metastatic cancers.

Recently, the anti-metastatic property of arsenic trioxide (ATO) in chondrosarcoma has been elucidated. It was reported that ATO attenuate the metastasis of chondrosarcoma cells through inhibit miR-125b/Stat3 axis [94]. As a common antioxidant obtained from cruciferous plants, sulforaphane has been reported to inhibit the migratory and invasive ability of lung cancer both in vitro and in vivo. This action is mediated by miR-616-5p [95]. In addition, ginsenoside Rd (Rd), one of the chemical compounds in Panax Notoginseng Saponins, has been investigated for its anti-metastatic property recently. The results showed that Rd treatment inhibited the migratory and invasive ability of breast cancer both in vitro and in vivo via suppressing miR-18a-mediated Smad2 expression [96].

7. Conclusion and future challenges

Accumulating evidence has demonstrated that Chinese medicine is an excellent source for the development of novel therapies for metastatic cancer. As mentioned above, the molecular mechanisms underlying the effects of potential anti-invasive and metastatic Chinese medicines include suppression of EMT (e.g., epithelial and mesenchymal markers), suppression of proteases expression (e.g., MMPs, uPA and Rho GTPases), suppression of cancer-induced angiogenesis (e.g., pro-angiogenic and anti-angiogenic factors), anoikis regulation of circulating tumor cells (e.g., pro-apoptotic and anti-apoptotic proteins), and regulation of miRNA-mediated gene expression (e.g., miR-125b, miR-616-5p and miR-18a). The chapter summarized the potential anti-invasive and metastatic drug candidates, which provided scientific evidence for clinically used Chinese medicines in the field of cancer therapy. Understanding of the underlying molecular mechanisms may in turn lead to discovery and development of novel anticancer drugs. Although these findings show the anti-metastatic potential of Chinese medicines, studies to evaluating the marked efficacies and determining the appropriate therapeutic doses of anti-metastatic Chinese medicines in animal models and clinical trials are still

badly necessary in the future. In addition, the modern techniques such as nanoparticles which may improve the anti-cancer properties via better cellular uptake, enhanced bioavailability, and localization to targeted sites should also be studied in the future.

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