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Perspectives of Plant Natural Products in Inhibition of Cancer Invasion and Metastasis by Regulating Multiple Signaling Pathways

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Abstract

Metastasis is often derived from increased invasion and migration of tumor cells, and is the most frequent cause of cancer-associated death. Either the prophylactic or therapeutic treatment of metastatic cancer remains very challenging today by virtue of the complex histopathology and genetic or epigenetic variations. Medicinal scientists had discovered many potential anti-invasive and anti-metastatic compounds from plant materials. However, data on currently available plant-based compounds inhibiting cancer invasion and metastasis is relatively scanty and no published article has been found with updated information in this unique and important aspect. In the current article, we will review the anti-invasive and anti-metastatic activities of some potential plant compounds with their sources of isolation and mechanistic pathways in different types of cancer cells and xenograft models.

Keywords: Anticancer, anti-invasive, anti-migratory, invasion, metastasis, migration, natural compounds

INTRODUCTION

Cancer is the second leading cause of death in the world, by which about 8 million deaths are reported annually [1-2]. Most of the cancer deaths, accounting nearly 90%, are found in patients with metastasis [3]. Literally, metastasis is a multistep progressive process that includes the unfastening of cells from the primary tumor, the proteolytic degradation of extracellular matrix (ECM), the intravasation of tumor cells into capillary or lymphatic vessels through the basement membrane and the extravasation of tumor cells into different tissues of the body. As a result, cells of the primary tumor invade the distant organs [4]. Proteolytic enzymes that facilitate ECM degradation are suggested to promote metastasis, such as matrix metalloproteinases (MMPs), reversion-inducing cysteine-rich protein with Kazal motif (RECK), tissue inhibitor of metalloproteinases (TIMPs) and extracellular inducer of matrix metalloproteinase (EMMPRIN). The intracellular signaling pathways, for instance, mitogen-activated protein kinase (MAPK), phosphatidylinositide-3 kinase (PI3K), nuclear factor-kappa B (NF-κB) and protein kinase B (Akt), as well as the epithelial-mesenchymal transition (EMT) events are often involved in the metastatic process.

MMPs are a group of calcium-containing zinc-dependent proteolytic enzymes that are associated with cell adhesion, migration and metastasis [5]. MMP-1 to -3, MMP-7 to -21 and MMP-23 to -28 are different classes of MMPs that exhibit various physiological functions. However, MMP-2, MMP-3 and MMP-9 are particularly responsible for the invasive property of metastatic cells. The plasmin-dependent activation of MMPs leads to the breakdown of type IV collagen, which is a major structural component in the basement membrane, consequently facilitates the mobility of cells and enhances tumor invasion, metastasis and angiogenesis [6-7].

RECK is a membrane-bound glycoprotein with an important role in inhibiting invasion and metastasis, as well as MMP activity. In other words, the decreased expression level of RECK promotes cancer metastasis [8-9]. TIMPs are indeed the most important natural inhibitors

regulating the activities of MMPs [10]. A proper balance between the levels of TIMP and MMP is essential to the tight control of ECM modeling and tissue organization. In contrast, an imbalance of the TIMP and MMP levels is found to promote the invasive and metastatic characteristics of various types of cancers [11]. EMMPRIN, also known as CD147 or basigin, is a cell-surface glycoprotein that induces the expression of MMPs in adjacent stromal cells [12]. In fact, EMMPRIN has been shown to directly stimulate proliferation and invasion of cancer cells. The overexpression of EMMPRIN has also been demonstrated to stimulate peritumoral fibroblasts for their release of MMPs, thus generating an ECM-rich microenvironment for tumors as well as metastasis [13]. MAPK and its related signaling cascades, such as extracellular signal regulating kinase (ERK1/2) and c-Jun N-terminal kinase (JNK), are important for the tight modulation of MMPs [14]. The activation of PI3K and PI3K related kinases (PIKK) also contributes to the regulation of cellular growth, differentiation, invasion, migration and metastasis [15]. In this regard, the blockade of the PI3K/Akt pathway often constitutes the antimetastatic and antiangiogenic activities of drugs [16-18]. It is acknowledged that the expression of MMPs is mediated by the MAPK and PI3K/Akt signals as well as the transcriptional activity of NF-κB [19-20] whilst the translocation of NF-κB from the cytoplasm to the nucleus is a common hallmark of metastasis. The inhibition of the MAPK, PI3K/Akt and/or NF-κB signaling cascades is therefore the potential target of anti-metastatic drugs. Tight junctions (TJs) are considered as the junction zippers that provide critical support to cell-cell adhesion and prevent cell migration in epithelial cells [21-22]. TJs also play an important role in the movement of nutrients through the paracellular routes [23]. The disruption of TJs or dysfunction of TJ proteins may lead to an uncontrollable passage of nutrients and growth factors between individual cells. As a result, cellular invasiveness is elevated [24].

Natural compounds are excellent source of anticancer drugs because of their high safety profile, low toxicity and easy availability [25]. A large number of plant-derived compounds

from different classes including flavonoid, isoflavonoid, cannabinoid, chalcone, naphthoquinone, terpenoids, alkaloid, steroid and saponin have been identified to inhibit cancer invasion and metastasis [26]. The anti-metastatic mechanism of many natural compounds is found to be associated with the inhibition of MMPs. This review article summarizes the prime examples of currently available anti-invasive and anti-metastatic compounds isolated from plants and their biological targets and mechanistic pathways.

1. ALKALOIDS

Alkaloids are a group of chemical compounds consisting of a nitrogen-containing heterocyclic ring. A wide variety of plants belonging to the Leguminosae, Loganiaceae, Ranunculaceae, Menispermaceae and Papaveraceae families contain various classes of alkaloids [27]. Many natural alkaloids extracted from plant source exerted potential anticancer and anti-metastatic activities [28]. The anti-invasive and anti-metastatic activities of some representative plant products have been discussed here.

1.1. Evodiamine

Evodiamine ($C_{19}H_{17}N_3O$, MW: 303.36, **Figure 1**) is a quinolone alkaloid extracted from the fruit of *Evodia rutaecarpa*. It is known to possess a spectrum of pharmacological activities including anti-obesity, anti-Alzheimer's disease, antihypertensive, antimicrobial and anticancer activities. Previous studies also reported evodiamine as an effective drug to halt invasion and metastasis of breast, lung and colon cancers [29-31]. Peng and co-workers found that evodiamine remarkably suppressed cell invasion in two kinds of nasopharyngeal carcinoma cells (HONE1 and CNE1); however, only slight effect on cell proliferation was observed [32]. Their evodiamine treatment caused significant reduction specifically on the mRNA and protein levels of MMP-2, but not MMP-9. Such MMP-2 suppression by evodiamine was suggested to be associated with a decreased translocation of NF-κBp65. Although this alkaloidal compound had insignificant effect on the JNK, p38 and Akt

signaling pathways, it notably down-regulated the expression of phosphorylated ERK1/2 (p-ERK1/2), suggesting the partial involvement of the ERK1/2 pathway for its anti-invasive activity. On the contrary, the anti-metastatic effect of evodiamine in human breast cancer was mediated through the downregulation of MMP-9, urokinase plasminogen activator (uPA) and uPA receptor (uPAR) [29]. In general, MAPKs such as JNK, p38 and ERK are renowned regulators for cell survival, apoptosis and migration [33-34]. The abnormal expression of ERK and p38 MAPK is linked to cancer cell migration. The study of You *et al*. suggested that the activation of ERK1/2 was central to the elevated uPA expression in breast cancer cell proliferation and migration [35]. When incubated with evodiamine, MDA-MB-231 breast cancer cells were shown with substantial decreased levels of p-ERK and p-p38 MAPK. Taken together, the anti-metastatic activity of evodiamine in MDA-MB-231 cells may be partially due to the suppression of the ERK and p38 MAPK signaling pathways. Apart from breast cancer cells, similar anti-invasive activities of evodiamine were observed in Lewis lung carcinoma, B16-F10 melanoma and 26-L5 colon carcinoma cells [30-31,36].

1.2. Matrine

Matrine ($C_{15}H_{24}N_2O$, MW: 248.36, **Figure 1**) is a sophora alkaloid, and the active component of *Sophora flavescens* which has been demonstrated with antiviral [37], anti-inflammatory [38] and antifibrotic activities [39]. This alkaloid is frequently used in different regions of China for the treatment of infectious diseases, atherosclerosis, hepatic fibrosis and arrhythmias [40]. It is acknowledged that matrine induced cellular apoptosis in various kinds of cancer cells including gastric, prostate, lung, glioma and cervical cancer cells [41-43]. A recent study reported a concentration-dependent inhibition of migration and invasion in NCI-H1299 non-small cell lung cancer (NSCLC) cells, in which an increased expression of microRNA-133a (miR-133a) was observed while the components of the epidermal growth factor receptor (EGFR)/Akt/MMP-9 pathway were down-regulated [44]. When the cells were treated with anti-miR-133a, the anti-migratory and anti-invasive effects of matrine were

diminished. EGFR, belonging to the ErbB receptor family, and its down-stream regulators Akt and PI3K play a crucial role in the regulation of cell mobility, adhesion, growth and invasion [45-46]. MMP-9 is one of the effectors of Akt, which is overexpressed in many invasive and metastatic cancers due to its role in ECM degradation [47-48]. Matrine caused suppression of the EGFR/Akt/MMP-9 pathway for its anti-invasive and anti-metastatic activities in malignant tumors [44]. The group of Su *et al.* discovered a novel matrine derivative WM130 that provides significant inhibitory effect on cancer invasion and metastasis in Huh-7 hepatocellular carcinoma (HCC) cells and xenograft animals via negatively modulating the expression of MMP-2, p-ERK, p-EGFR and p-Akt, but with an up-regulation of PTEN [49]. Collectively, WM130 inhibited cell proliferation, invasion and migration as well as induced apoptosis in HCC cells by regulating the EGFR/ERK/MMP-2 and PTEN/Akt signaling pathways.

1.3. Sanguinarine

Sanguinarine ($C_{20}H_{14}NO_4$, MW: 332.09, **Figure 1**) is a benzophenanthridine alkaloid available in *Sanguinaria canadensis*, *Chelidonium majus* and *Macleaya cordata* that possesses anti-inflammatory, antimicrobial, antiparasitic, anti-HIV, anti-platelet, anti-angiogenesis and antitumor activities [50]. This alkaloid has drawn much attention of pharmacologists and medicinal chemists because of its safety profile and ability to inhibit tumor cell growth at micromolar concentrations [51]. The anticancer effect of sanguinarine through different pathways have been established in a large number of cancer cell types including breast, colon, prostate, cervical, leukaemia, lymphoma, melanoma, pancreatic, lung, osteosarcoma and human neuroblastoma cells [52-57]. At non-cytotoxic concentrations, sanguinarine decreased the expression of tissue-type plasminogen activator (TPA)-stimulated elevation of MMP-9, COX-2 and prostaglandin E2 (PGE2) in the MCF-7 breast cancer cells [58]. Sanguinarine was found to inhibit the activation of NF-κB and activator protein-1 (AP-1), and the phosphorylation of Akt and ERK while up-regulating the level of heme

oxygenase 1 (HO-1). Upon the silence of HO-1 by siRNA oligos, the inhibitory effect of sanguinarine on MMP-9 and COX-2 was abolished, so as the TPA-induced cell invasion. Taken together, the anti-invasive effect of sanguinarine is mediated through HO-1 in the TPA-induced MCF-7 metastatic cells. Sanguinarine has also been regarded as a novel vascular endothelial growth factor (VEGF) inhibitor for its ability to inhibit VEGF-induced tube formation as well as the secretion of VEGF in human umbilical vein endothelial cells (HUVECs) [59]. Moreover, sanguinarine was shown to suppress VEGF promoter activity in serum starvation and hypoxia, and attenuate the Akt- and p38-dependent VEGF activation, so as the phosphorylation of VE-cadherin. In summary, the anti-angiogenic and anti-invasive activities of sanguinarine in cancer treatment plausibly involve the inhibition of VEGF. Furthermore, a study by Choi *et al*. revealed that the inhibitory effect of sanguinarine on breast cancer cell proliferation, motility and invasiveness was associated with an elevated transepithelial electrical resistance and a modulation of TJs, explicitly claudin-3 and claudin-4, as TJ components were considered as the biological targets of sanguinarine [60].

1.4. Glaucine

Glaucine ($C_{21}H_{25}NO_4$, MW: 355.43, **Figure 1**) is an alkaloidal compound isolated from *Corydalis turtschaninovii* tuber (Papaveraceae) that inhibits the migration and invasion of human breast cancer cells, particularly MCF-7 and MDA-MB-231 cells [61]. The exploration on the underlying mechanism of glaucine revealed that its inhibition on MMP-9 was associated with a suppressed NF-κB expression. Additionally, glaucine reduced the phorbol 12-myristate 13-acetate (PMA)-stimulated degradation of inhibitor of NF-κBα (IκBα) and nuclear translocation of NF-κB. To conclude, the inhibitory effect of glaucine on MMP-9 activity, IκBα degradation and NF-κB activities favors its being a potential therapeutic approach in the treatment of breast cancer.

1.5. Hirsutine

Hirsutine ($C_{22}H_{28}N_2O_3$, MW: 368.48, **Figure 1**) is a bioactive indole alkaloid isolated from

the Uncaria genus which possesses cardioprotective, anti-hypertensive and anti-arrhythmic activities [6263]. Hirsutine is also renowned for its *in vitro* and *in vivo* anti-metastatic activity. In the study of Lou *et al*., hirsutine significantly suppressed the constitutive expression of MMP-2 and MMP-9 and the activation of NF-κB in 4T1 cells; therefore, reducing the invasive and migratory properties of 4T1 cells and preventing breast cancer metastasis in the xenograft mouse model [64].

1.6. α-Tomatine

α-Tomatine ($C_{50}H_{83}NO_{21}$, MW: 1034.19, **Figure 1**) is a natural glycoalkaloid mostly found in immature green tomatoes (*Lycopersicon esculentum*). When tomatoes ripen, the content of glycoalkaloid decreases [65]. The green tomatoes contain as much as 500 mg α-tomatine/kg fresh fruit weight while the red mature tomatoes are left with about 5 mg/kg [66]. Over the past few years, α-tomatine has been extensively investigated for its anticancer effect in numerous cancer cells including colon, breast, prostate, lung, liver cancer, lymphoma and leukemia [67-69]. Synergistic anti-cancer effect has been obtained from the combo treatment of α-tomatine and paclitaxel [70], curcumin [67] or gemcitabine [71]. A previous study from Shieh and colleagues demonstrated that α-tomatine treatment at non-toxic concentrations led to a significant suppression of cell invasion and migration in the NCI-H460 lung cancer cells [72]. In the A549 human lung adenocarcinoma cells, α-tomatine inhibited both mRNA and protein levels of MMP-7 via the inactivation of the focal adhesion kinase (FAK) and PI3K/Akt signaling pathways in addition to an elevated IκBα protein expression, which indicates a reduced NF-κB DNA-binding activity. [73]. However, the anti-invasive and anti-migratory actions of α-tomatine also appeared to be associated with an inhibition of MMP-2 and MMP-9 through regulating the protein kinase C (PKCα)/ERK/NF-κB signaling pathway [74]. In the MCF-7 metastatic breast cancer cells, α-tomatine treatment inhibited the TPA-induced cell invasion and migration, so as the actin cytoskeleton dysarrangement by down-regulating the expression levels of p-ERK1/2, PKCα, p-NF-κB p65 and p-IκBα.

1.7. α-Solanine

α-Solanine ($C_{45}H_{73}NO_{15}$, MW: 868.07, **Figure 1**) is a steroidal glycoalkaloid mainly isolated from Solanaceae species such as nightshade (*Solanum nigrum* Lin) and potato (*Solanum tuberosum* L.) [75]. The anticancer activity of α-solanine in human colon, breast, cervical, liver, lymphoma, and stomach cancer cells was majorly derived from its induction of apoptosis and inhibition of cell proliferation [76]. From the work of Hasanain *et al*., the anti-proliferative activity of α-solanine was shown to be correlated to the reduction of the PI3k and Akt activities and the consequent blockade of their downstream signal transduction pathways such as NF-κB and mammalian target of rapamycin (mTOR) [77]. Under the suppression of the PI3k/Akt signal cascade, α-solanine treatment was also reported with an anti-inflammatory activity on repressing the production of IL-2 and IL-8 [78]. According to Lv *et al.*, α-solanine treatment decreased the expression levels of MMP-2, MMP-9, EMMPRIN, CD44, and eNOS in PANC-1 pancreatic cancer cells in addition to its suppression of VEGF and tube formation in HUVECs [79]. The above studies claimed that the anticancer property of α-solanine was coherent to the attenuated phosphorylation of Akt, mTOR and STAT3. Similarly, Shen and his colleagues reported α-solanine at non-toxic doses considerably promoted the expression of E-cadherin, a principal epithelial marker, RECK, TIMP-1 and TIMP-2 while reducing the expression of mesenchymal marker vimentin, MMP-2, MMP-9 and EMMPRIN [80]. Furthermore, α-solanine was demonstrated to suppress oncogenic miR-21 and stimulate tumor suppressor miR-138 expression. However, dendrosomal solanine (DNS) has been recently suggested to be superior to the original α-solanine in inhibiting breast cancer cell invasion and metastasis *in vitro* and *in vivo* as nil metastasis was observed after DNS treatment (1 mg/kg), but 22% and 67% of metastatic cases were respectively found in α-solanine-treated (1 mg/kg) and control animals [81]. However, DNS at 20 mg/kg caused a decline in white blood cell count. In those DNS-treated mice, expression of Bcl-2 was significantly increased but Bax, MMP-2, MMP-9, mTOR and

Akt were suppressed. Lu *et al*. also reported comparable inhibition of MMP-2 and MMP-9 activities in A2058 melanoma cells by DNS, by which the JNK, PI3K/Akt and NF-κB signaling pathways were down-regulated [82].

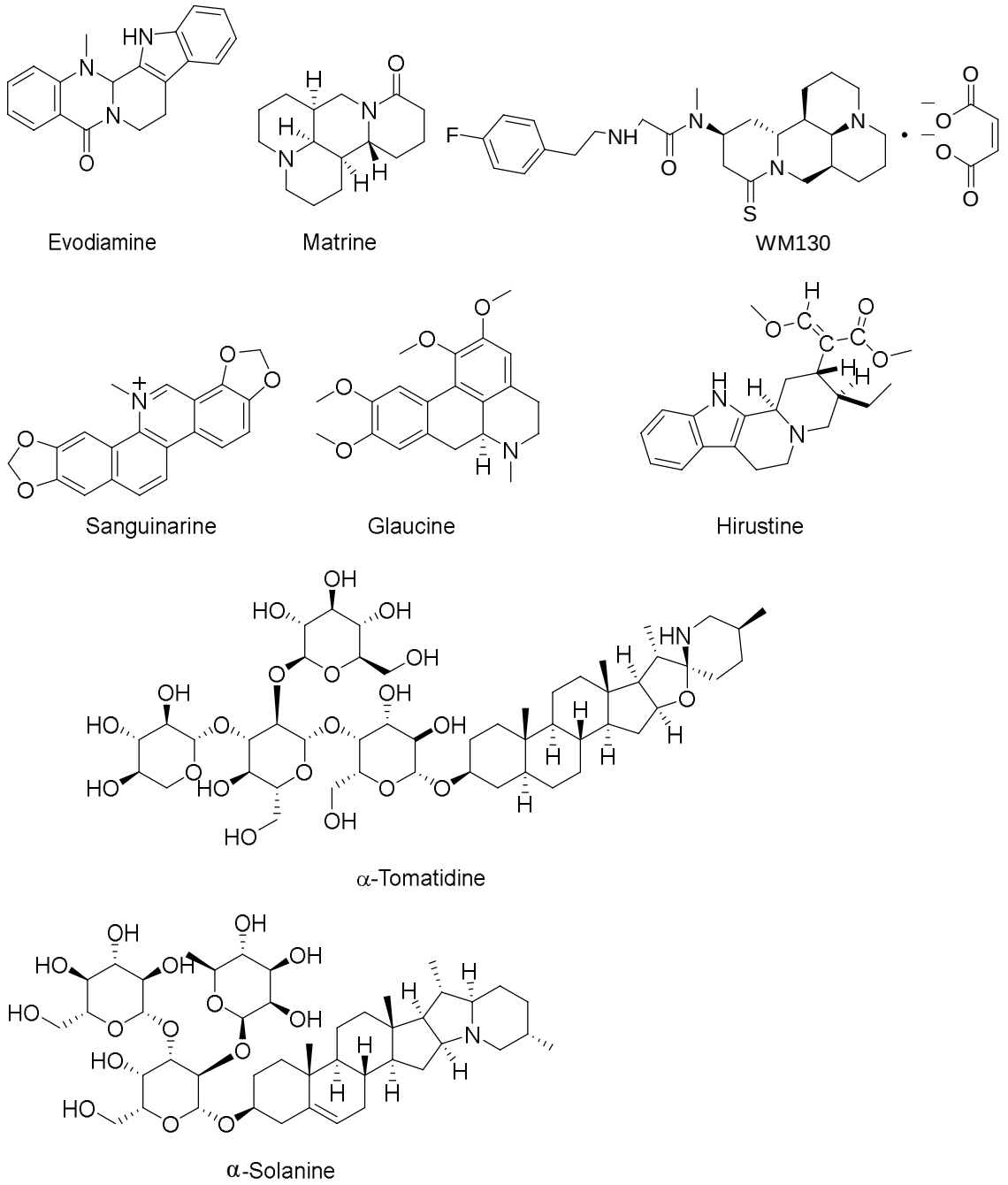


Figure 1. The chemical structures of common alkaloids

2. FLAVONOIDS

Flavonoids are a diverse class of phytocompounds consisting of an aromatic ring fused with a heterocyclic ring which is connected through a linear three-carbon bridge to a second aromatic ring. Depending on their molecular backbone and phenolic group, flavonoids are divided into various subclasses, namely flavone, flavonol, flavanone, flavanonols, flavanols, isoflavones and anthocyanidins [83], which are mainly from the Citrus genus and Rutaceae family. The anti-invasive and anti-metastatic activities of a large number of flavonoids have been identified by *in vitro* and *in vivo* experiments [84-85].

2.1. Wogonin

Wogonin ($C_{16}H_{12}O_5$, MW: 284.27, **Figure 2**) is a bioactive O-methylated flavone compound isolated from *Scutellariae radix* and *Scutellaria baicalensis* that possesses anti-inflammatory, anti-viral and anticancer activities [86-87]. According to numerous literatures, the anticancer effect of this flavonoid is feasibly related to the induction of apoptosis and cell cycle arrest, as well as the inhibition of cell proliferation and angiogenesis [88-91]. Dose-dependent anti-invasive activity of wogonin was observed in the OC2 human oral cancer cells [92] and MDA-MB-231 human breast cancer cells [93] accompanied by the down-regulation of MMP-2, MMP-9 and uPA. Dong *et al*. isolated wogonin from *Scutellaria baicalensis*, which is widely used in traditional Chinese Medicine for the treatment of tumors, and showed dose-dependent inhibitory activity on MMP-2, MMP-9 and p-ERK1/2, but not Akt, in the GBC-SD human gallbladder carcinoma cells [94]. Interestingly, mapsin appears to be a biological target of wogonin as increased mRNA and protein levels of mapsin were obtained after wogonin treatment. Upon the knock-down of mapsin, the inhibitory activity of wogonin on MMP-2, MMP-9 and p-ERK1/2 as well as its anti-invasive activity were almost completely abolished. Collectively, the effect of wogonin on cancer cell proliferation and invasion was plausibly mapsin dependent.

2.2. Naringenin

Naringenin ($C_{15}H_{12}O_5$, MW: 272.26, **Figure 2**) is a bioactive flavanone that is rich in citrus fruits such as oranges (*Citrus sinensis*) and tomatoes (*Lycopersicon esculentum* Mill.). In recent years, this flavanone has attracted substantial interest of researchers due to its anti-inflammatory, antioxidant, antiestrogenic, hypolipidemic, anti-hypertensive and anticancer activities [95]. Lately, the anti-angiogenic effect of naringenin has been demonstrated in HUVECs via its direct inhibition of estrogen-related receptor α (ERRα), which is central to the increased VEGF secretion in angiogenesis [96]. Some early studies documented that the ERRα-modulated endothelial cell migration promoted the arrival of new blood vessels at the cancer site and the subsequent invasion to the nearby tissues during the angiogenic process, thus causing cancer progression and metastasis [97-98]. Yen *et al.* concluded that naringenin inhibited the invasive and metastatic activities of HCC cells by suppressing the MMP-9 activity [99]. However, the naringenin treatment indeed repressed the TPA-induced activation of AP-1 and NF-κB via reducing ERK/JNK phosphorylation, IκB assembly and/or the ERK/PI3K/Akt signaling cascade [100]. Apart from MMP-9, naringenin also inhibited the expression of MMP-2 via suppressing the nuclear translocation of NF-κB, and resulted in a decreased bladder cancer cell migration [101]. Furthermore, naringenin had also been demonstrated to inhibit Akt phosphorylation, which is highly correlated to various human cancer metastases [102-103]. It is generally accepted that cancer cell migration and invasion from the primary site to distant organs or tissues are triggered by EMT events. TGF-β plays important functions in regulating EMT in several malignancies including pancreatic cancer [104]. Targeting the TGF-β signaling pathway may be an effective way to control cancer progression and metastasis. Lou and co-researchers found that significantly decreased levels of mesenchymal markers, namely vimentin, N-cadherin, MMP-2 and MMP-9, led to an inhibition of TGF-β1-induced EMT in the naringenin-treated AsPC-1 and PANC-1 pancreatic cancer cells [105]. Importantly, the expression of Smad3 was also

reduced post naringenin treatment. The above results suggested that the suppressive effect of naringenin on EMT markers was mediated through the TGF-β1/Smad3 signaling pathway.

2.3. Apigenin

Apigenin ($C_{15}H_{10}O_5$, MW: 270.24, **Figure 2**) is a naturally occuring flavonoid in tea and different vegetables, such as onions, parsley, oranges, chamomile, wheat and sprouts [106]. It has been demonstrated to inhibit cell proliferation, motility and angiogenesis, and induce apoptosis in different cell lines including oral, breast, cervical, prostate and colorectal cancer (CRC) cells [107-108]. Some recent studies proposed that the anti-invasive activity of apigenin is plausibly derived from its negative modulation of the Wnt/β-catenin signaling pathway [109]. Concentration-dependent inhibition of CRC cell proliferation, migration and invasion was observed post apigenin treatment in wound healing and transwell invasion assays. Moreover, the lithium chloride-activated canonical Wnt signaling was dose-dependently repressed by apigenin, leading to the suspension of β-catenin nuclear entry, and subsequent abolishment of Wnt signaling molecules. In 2015, Shukla *et al.* propounded apigenin as a specific IκB kinase α (IKKα) inhibitor with a potency in micromolar range [110]. In their study, apigenin inhibited the IKKα kinase activity by interfering the DNA binding of NF-κBp65 in the PC-3 and 22Rv1 human prostate cancer cells. Their *in vivo* investigation further revealed the inhibitory effect of apigenin on prostate tumorigenesis was associated with the suppression of p-IKKα and NF-κBp65 and an elevation of cleaved caspase-3, i.e. an induction of cellular apoptosis. To sum up, apigenin exhibited anti-proliferative and anti-invasive activities via inhibiting IKKα activation and the NF-κB-regulated genes. The anti-proliferative, anti-invasive and anti-migratory effects apigenin were also demonstrated in CRC lines SW480, DLD-1 and LS174T by Chunhua *et al*. [111]. By means of microarray staining, they showed that apigenin increased the expression of mitochondrial transgelin (TAGLN), which is a MMP-9 repressor with an inverse correlation with CRC metastasis. A synergistic effect on reducing Akt Ser473 and Akt

Thr308 phosphorylation was obtained from the combination treatment of apigenin and TAGLN overexpression. To this end, apigenin prevented cancer cell proliferation and migration by increasing TAGLN expression and decreasing MMP-9 and p-Akt. The use of apigenin in MDA-MB-231 breast cancer cells also resulted in a significant restriction of cancer cell proliferation and migration, which was associated with the blockade of the PI3K/Akt pathway and integrin β4 function [112].

2.4. Kaempferol

Kaempferol ($C_{15}H_{10}O_6$, MW: 286.24, **Figure 2**) is a common dietary flavonol found in tea, broccoli, apples, strawberries, beans, citrus fruits and Chinese herbal plants. It is renowned for its antioxidant and anti-inflammatory activities [113]. Besides, this flavonol exhibited anti-migratory and anti-invasive actions on HCCC9810 and QBC939 cholangiocarcinoma cells by reducing the expression of Bcl-2, TIMP-2, MMP-2 and p-Akt while enhancing the levels of Bax, Fas, cleaved caspases-3, -8 and -9 and cleaved PARP [113]. When applied to the xenograft model, kaempferol significantly reduced the tumor size and suppressed the number and volume of metastatic foci without leading to obvious body weight loss of the experimental mice. As reported by Lee *et al.*, the inhibitory effect of kaempferol on migration of MIA PaCa-2, PANC-1 and SNU-213 human pancreatic cancer cells was a result of the down-regulated EGFR-related Src, ERK1/2 and Akt pathways [114]. According to Li *et al.*, Kaempferol reduced the expression levels of MMP-2 and MMP-9 in the MDA-MB-231 human breast carcinoma cells via deactivating the AP-1 and MAPK signaling pathways, and thus resulted in a notable reduction of cell migration and invasion [115]. Similar inhibitory effect of kaempferol was also observed in the B16F10 murine melanoma cells and U-2 osteosarcoma (OS) cells, in which attenuated levels of MMP-2, MMP-9, uPA, ERK, p-38 and JNK as well as suspended PKCα translocation were perceived [116]. Lin *et al.* also demonstrated the anti-metastatic effect of kaempferol in the SCC4 oral cancer cells with a

significant suppression of MMP-2 and TIMP-2, a decreased c-Jun activity as well as a reduced phosphorylation of ERK1/2 [117].

2.5. Genistein

Genistein ($C_{15}H_{10}O_5$, MW: 270.24, **Figure 2**) is an isoflavone extracted from *Glycine max* (L.), *Genista tinctoria* L. and *Nicotiana tabacum* L., and it has been reported with anticancer, antioxidant, anti-inflammatory and cardioprotective activities [118-119]. The anti-invasive activity of genistein in HCC cells was associated with suppressed MMP-9 transcription and inactivation of AP-1 and NF-κB as a consequence of the diminished ERK/JNK phosphorylation and IκB degradation [120]. Additionally, genistein restrained metastatic markers in HCT116, SW620 and HT29 CRC cells by a sufficient suppression of MMP-2 and Fms-Related Tyrosine Kinase 4 (FLT4) [121]. The oral administration of genistein did not significantly reduce the size of the CRC xenograft tumors, but notably hampered metastasis to distant organs in the experimental mice without visible toxicity. When genistein was co-administered with all-trans retinoic acid (ATRA) in lung cancer treatment, a synergetic effect on metastasis restriction was observed [122]. Such combo treatment indeed attenuated the expression levels of mucin 1 (MUC1) and intercellular adhesion molecule-1 (ICAM-1), and thus restrained the metastatic ability of the A549 lung cancer cells. A previous report suggested that genistein potentiated the anticancer and anti-metastatic activities of docetaxel, a mainstay chemotherapeutic agent, during the spread of prostate cancer to the bones by interfering the osteoclastic bone resorption via the osteoprotegerin (OPG)/receptor activator of nuclear factor-κB ligand (RANKL)/MMP-9 signaling pathway. As a result, prostate cancer bone metastasis was remarkably hampered [123]. The use of genistein by Han and colleagues successfully inhibited the invasion and metastasis of PANC-1 pancreatic cancer cells against TGF-β1 stimulation as the expression levels of uPA, vimentin and MMP-2, but not MMP-9, were down-regulated via the Smad4-dependent and -independent pathways [124]. Genistein also inhibited the invasive ability of MCF-7 and MDA-MB-231 breast cancer cells by

tightening the TJs and repressing the expression of claudin-3 and claudin-4 [125]. In targeting the invasiveness of MHCC97-H HCC cells, genistein at concentrations less than 20 μg/ml down-regulated the expression of insulin like growth factor-1 receptor (IGF-1R) and Snail while up-regulating the levels of thrombospondin-1 and E-cadherin [126]. When suppressing the phosphorylation of FAK, genistein significantly reduced the number of pulmonary micrometastatic foci in the xenograft mice. The anti-invasive effect of genistein in TRAMP prostate cancer cells was associated with an induction of kangai-1, which is a prominent suppressor of metastasis [127].

2.6. Isorhamnetin

Isorhamnetin ($C_{16}H_{12}O_7$, MW: 316.27, **Figure 2**) is a naturally occurring O-methylated flavonol isolated from sea buckthorn (*Hippophae rhamnoides* L.) and water dropwort (*Oenanthe javanica*) that has been demonstrated with anti-tuberculosis, anti-inflammatory, anticarcinogenic and antioxidant activities [128]. *In vitro* investigation of isorhamnetin showed inhibition of MDA-MB-231 breast cancer cell migration and invasion, in which the levels of MMP-2 and MMP-9 became minimal [129]. The suppressive effect of isorhamnetin on MMPs was correlated to the decreased phosphorylation of p38 and STAT3, rather than uPA expression or the ERK1/2 or JNK cascades.

2.7. Oroxylin A

Oroxylin A ($C_{16}H_{12}O_5$, MW: 284.267, **Figure 2**) is an O-methylated flavone isolated from *Scutellaria baicalensis* and *Scutellaria radix* that possesses antibacterial, antiviral, anti-inflammatory, anticancer and antithrombotic activities [130-131]. To combat the invasive and migratory properties of MDA-MB-231 breast carcinoma cells, oroxylin A decreased the activity and expression of TIMP-2 and MMPs, explicitly MMP-2 and MMP-9, as well as their inhibitors and upstream regulators [132]. Moreover, oroxylin A treatment was also found to interfere with the PMA-induced translocation of PKCδ, phosphorylation of ERK1/2 and binding activity of AP-1. In counteracting the effect of VEGF on tube formation

and angiogenesis, oroxylin A reduced the phosphorylation of KDR/Flk-1 and the downstream regulators including p38 MAPK and Akt *in vitro* and *in vivo* [133]. In the MDA-MB-435 human breast cancer cells, oroxylin A exhibited anti-metastatic activity by decreasing the secretion of MMP-2 and MMP-9 as well as down-regulating the expression of p-ERK1/2 in a dose-dependent manner [134].

2.8. Myricetin

Myricetin ($C_{15}H_{10}O_8$, MW: 318.24, **Figure 2**) is a ubiquitous flavonoid found in fruits, vegetables, nuts, berries, tea and red wine [135-136]. Considerable numbers of literature have been describing the anticancer effect of myricetin [1137-140], in particular, its anti-migratory effect on the U251 human glioma cells [141]. Myricetin treatment significantly reduced the expression of VEGF, MMP-9. MMP-13 and hypoxia-inducible factor-1α (HIF-1α) via PI3K modulation in the SKH-1 hairless mice [142]. According to Shih *et al.*, myricetin exhibited dose- and time-dependent anti-metastatic activity on the A549 lung cancer cells without displaying notable cytotoxicity. Its inhibitory effect on MMP-2 and uPA activities was well demonstrated in the gelatin and casein zymography assays whereas the immunoblotting results manifested the ERK1/2, c-Fos, c-Jun and NF-κB inhibition [143]. It is worth nothing that the suppressive effect of myricetin on MMP-2, uPA, NF-κB and AP-1 was comparable to the ERK inhibitor (U0126).

2.9. Deguelin

Deguelin ($C_{22}H_{23}O_6$, MW: 394.42, **Figure 2**) is a naturally occurring rotenoid isolated from *Derris trifoliate* and *Mundulea sericea* that shows potent anticancer effect via modulation of signaling pathways inducing apoptosis and cell cycle arrest; hence halts cancer cell proliferation, invasion, metastasis and angiogenesis [144-145]. Deguelin, at low doses, exerted minimal cytotoxicity whilst inhibited the migration and invasion of oral cancer cells by down-regulating IκB phosphorylation, NF-κB transcriptional activity and MMP-2 expression post TNF-α stimulation [146]. On the other hand, treating lung cancer cells with

deguelin down-regulated the expression of Ras-related C3 botulinum toxin substrate 1 (Rac1) and Rho-associated coiled-coil containing protein kinase 1 (Rock1) proteins, which play vital roles in actin cytoskeleton rearrangement and cell motility [147]. *In vitro* and *in vivo* investigations revealed that the inhibition of cell migration and invasion in the U-2 OS human osteosarcoma line by deguelin was associated with down-regulation of TIMP-1, uPA, MMP-1, MMP-2, MMP-9, MMP-13 and VEGF [148]. In addition, Nair *et al.* reported the anti-invasive activity of deguelin in five different cancer cell types was associated with a constant suppression of NF-κB and NF-κB-regulated genes [149].

2.10. Silibinin

The flavonoid compound silibinin ($C_{25}H_{22}O_{10}$, MW: 482.22, **Figure 2**) is the active component of milk thistle (*Silybum marianum*) and is widely known as a hepatoprotective and antioxidant compound. It also exerts pleiotropic anticancer potential in various human malignant tumors including skin, oral, prostate, breast, bladder and colon cancer [150]. Using *in vitro* renal cell carcinoma (RCC) model, Zeng's group claimed that the anti-metastatic effect of silibinin was derived from its induction of autophagy, which was regulated by the adenosine 5'-monophosphate activated protein kinase (AMPK)/mTOR pathway [151]. In the study of another research group, silibinin either alone or in combination with trichostatin A (TSA) or 59-Aza-deoxycytidine (Aza), which are respectively the HDAC and DNMT inhibitors, notably restrained metastatic characteristics in different NSCLC cell lines [152]. Both their results demonstrated that silibinin treatment significantly restored E-cadherin level while reducing the expression of Zeb1, which is a major E-cadherin repressor. The level of E-cadherin was further augmented in the combo treatment with TSA or Aza. As a result, decreased invasion and migration of NSCLC cells were perceived. Taken together, either silibinin alone or in combination with HDAC or DNMT inhibitor may serve as a competent approach to suppress metastatic ability of NSCLC cells at early and advanced stages. In human RCC cell lines ACHN, OS-RC-2 and SW839, silibinin concentration-dependently

suppressed cell migration and invasion via inhibiting the phosphorylation of EGFR and ERK1/2, but not STAT3 or Akt. Moreover, the expression and activity of MMP-9 was accordingly reduced [153]. To this end, the anti-migratory and anti-invasive activities of silibinin in RCC cells appear to be mediated via the blockade of the EGFR/MMP-9 pathway.

Upon the challenge of IL-6, the administration of silibinin led to a considerable down-regulation of MMP-2 in the LoVo colon cancer cells when examined by means of Western blotting, zymography and confocal microscopy [154]. The results from the electrophoretic mobility shift and luciferase assays further revealed that silibinin treatment attenuated the binding of AP-1 to the MMP-2 promoter. Deep *et al.* reported that silibinin prevented migration and invasion of prostate cancer cells by regulating the levels of E-cadherin, β-catenin, Hakai, Snail and Slug as well as p-Akt and p-Src [155]. A significant suppression of uPAR and uPA by silibinin treatment had been reported by another research group [156]. In the ARCaPM prostate cancer cells, Wu *et al.* showed the dose-dependent anti-invasive, anti-motility and anti-migratory activities of silibinin originated from a suppression of vimentin and MMP-2, whereas no effect on the expression of MMP-9 or uPA was found [157]. Similar effect of silibinin on uPA and MMP-2 expression was also observed in the MG-63 osteosarcoma cells as a consequence of the down-regulated FAK and Raf–ERK/c-Jun signaling cascades [158].

2.11. Nobiletin

Nobiletin ($C_{21}H_{22}O_8$, MW: 402.39, **Figure 2**) is an O-methylated flavone isolated from citrus fruit, particularly from the peels of *Citrus sinensis* and *Citrus reticulata*. This compound provides anticancer effect in gastric, glioma, neuroblastoma, lung, breast, colon, ovarian, leukemia and HCC cells [159-165]. Nobiletin has been reported to significantly decrease the cell motility, migration and invasion capabilities of U2OS and HOS osteosarcoma cells in the wound healing and Boyden chamber assays in addition to its suppression on MMP-2 and MMP-9 [166]. The molecular mechanism underlying its anticancer effect was found to be

associated with down-regulations of ERK, JNK, NF-κB, cAMP response element-binding protein (CREB) and specificity protein 1 (SP-1). The co-treatment with ERK and JNK inhibitors made nobiletin more potent in arresting migration and invasion of U2OS cells. Apart from osteosarcoma cells, nobiletin also significantly inhibited the invasion and migration of HepG2 liver cancer cells at non-cytotoxic concentrations. The results of mechanism study indicated that the anti-metastatic activity of nobiletin was correlated to the inhibition of the ERK and PI3K/Akt pathways as well as c-Met function [167]. When MDA-MB-231 breast cancer cells were treated with nobiletin, NF-κB- and MAPK-dependent down-modulation of CXC chemokine receptor-4 (CXCR4) and MMP-9 was observed by Baek *et al*. [168]. On the other hand, Lee *et al.* detected notable down-regulation of MMP-2 and MMP-9 in AGS gastric cancer cells as a consequence of suppressed FAK and PI3K/Akt signaling post nobiletin treatment [169]. Nonetheless, Reduction of NF-κB, Ras, c-Raf, Rac-1, Cdc42 and RhoA by nobiletin had been reported by different research groups.

2.12. Delphinidin

Delphinidin ($C_{15}H_{11}O_7$, MW: 303.24, **Figure 2**) is an anthocyanindin or a plant pigment present in different pigmented fruits and vegetables that exhibits antitumor activities [170-171]. Contemporary data proposed delphinidin treatment can be used to combat ovarian clear cell carcinoma [172]. The molecular mechanism of delphinidin involved a dose-dependent suppression on p-PI3K (Akt and P70S6K) and MAPKs (ERK1/2 and JNK). In MCF-7 breast cancer cells, delphinidin reduced PMA-induced cell invasion and suppressed MMP-9 expression by deactivating NF-κB via MAPK signaling pathways [173]. From the study of Syed *et al.* (2008), the inhibitory effect of delphinidin on immortalized MCF-10A breast cell line appeared stimulatory to the expression of Met receptor and several adaptor proteins such as paxillin, Gab-1 and GRB-2 while inhibitory to the phosphorylation of HGF-mediated tyrosyl, FAK and Src [174]. As far as we know, delphinidin treatment also

exhibited suppressive effect on HGF-induced activation of the Ras-ERK MAPK, PI3K/Akt, STAT3 and NF-κB/p65 pathways in addition to PKCα deactivation.

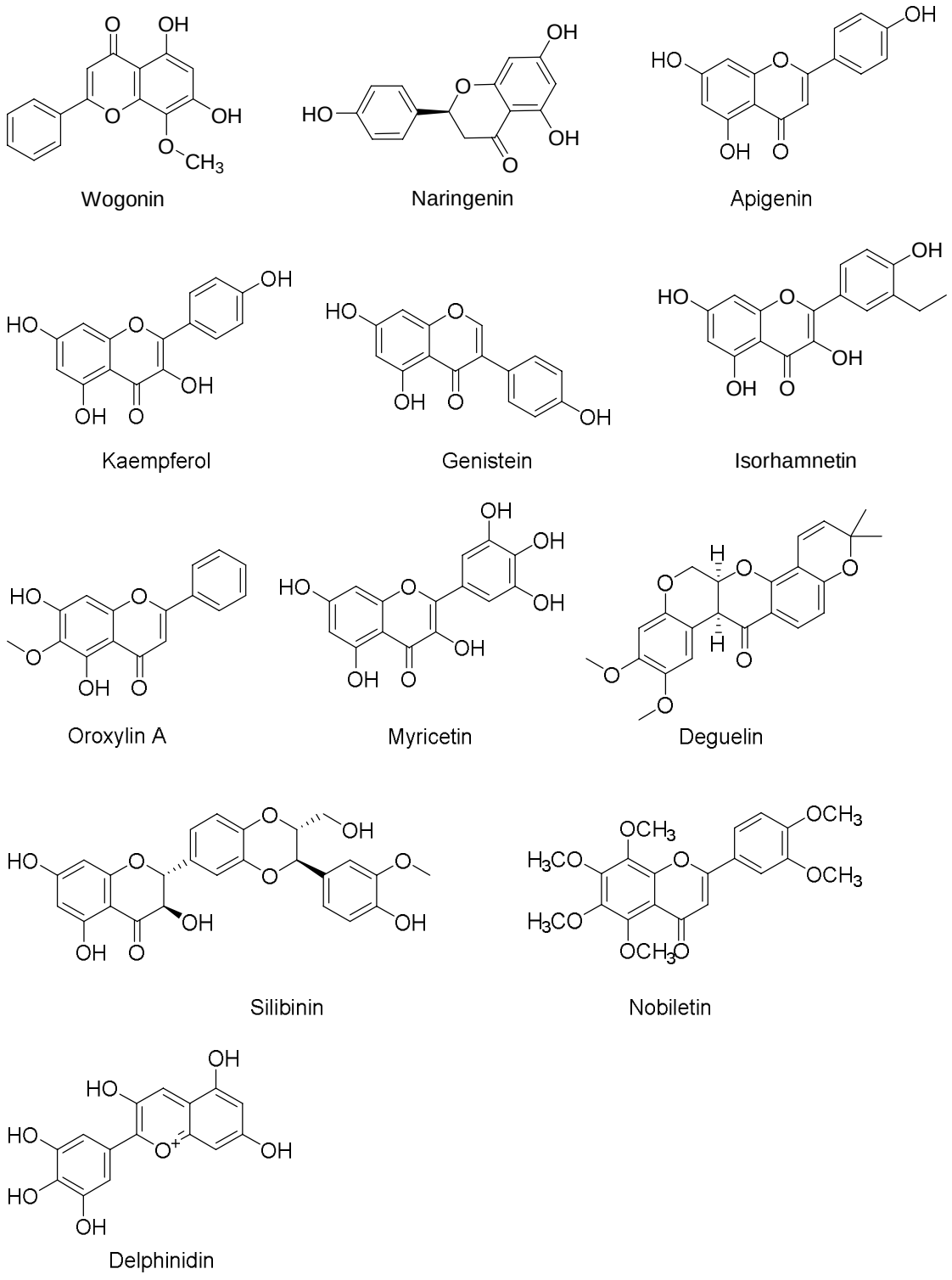


Figure 2. The chemical structures of common flavonoids

3. TERPENES

Terpenes, commonly known as terpenoids, are the largest group of natural compounds since more than 40,000 terpenoids have been identified. Chemically, they consist of isoprene units with a general formula of $(C_5H_8)_n$, where n is the total number of isoprene units [175]. Terpenes can be further subdivided into monoterpenes, sesquiterpenes, diterpenes, sesterterpenes and polyterpenes. A number of previous studies had reported the inhibitory effect of terpenoids on metastasis and angiogenesis [176].

3.1. Sesquiterpene

3.1.1. Aromatic turmerone

Aromatic (ar)-turmerone ($C_{15}H_{20}O$, MW: 216.32, **Figure 3**) is one of the major volatile oils isolated from *Curcuma longa*. The antiproliferative action of this sesquiterpene has been reported effective in P388D1 lymphoblasts, U937 histiocytic lymphoma cells, L-1210 and HL-60 leukemia cells and HCC cells [177-180]. Using MDA-MB-231 breast cancer cells, *Park et al.* demonstrated the inhibitory effect of ar-turmerone on TPA-induced invasion, migration, and colony formation [181]. Although suppressive effect on the expression of TIMP-1, TIMP-2, MMP-2 and COX-1 was obscure, ar-turmerone treatment significantly inhibited the enzymatic activity and expression of MMP-9 and COX-2 at non-cytotoxic concentrations. Such inhibition was plausibly associated with the deactivation of NF-κB and the down-regulation of the PI3K/Akt and ERK1/2 signaling pathways.

3.1.2. α-Bisabolol

α-Bisabolol ($C_{15}H_{26}O$, MW: 222.37, **Figure 3**) is a monocyclic sesquiterpene available in *Matricaria chamomilla* L. that exerts anticancer effect against various kinds of cancer cells, mostly through the induction of apoptosis and autophagy [182-183]. A very recently published paper reported that the anti-proliferative and anti-invasive activities of α-bisabolol in KLM1, KP4, and PANC1 pancreatic cancer cells were the result of up-regulated levels of early growth response 1 (EGR1) and Kisspeptin 1 receptor (KISS1R) [184]. EGR1,

belonging to zinc finger transcription factor family, is a known tumor suppressor gene, and its activation by α-bisabolol was demonstrated effective against pancreatic cancer cell proliferation [185]. However, the effectiveness of α-bisabolol on restraining cellular invasiveness and motility was not profound in the study of Uno *et al.* [184]. On the contrary, α-bisabolol treatment led to a notable elevated level of KISS1, which is commonly considered as a suppressor of metastasis. Thus, it is not surprising that some studies had reported the administration of α-bisabolol inhibited cell migration and invasion in the metastasis of melanoma, gastrointestinal carcinoma and breast carcinoma [186-187]. Pancreatic cancer patients with high levels of KISS1 and its receptor KISS1R were found to survive longer [188]. Thus, the activation of KISS1/KISS1R contributes, at least partially, to the anti-invasive effect of α-bisabolol.

3.2. Triterpene

3.2.1. Celastrol

Celastrol ($C_{29}H_{38}O_4$, MW: 450.62, **Figure 3**) is a triterpene quinone extracted from the roots of "Thunder of God Vine" and *Tripterygium wilfordii* that exerts potent antitumor effect by inhibiting cell proliferation, invasion and angiogenesis, and/or inducing apoptosis or cell cycle arrest in various types of cancer cells including leukemia, lung cancer, gastric cancer, breast cancer, prostate cancer, osteosarcoma, melanoma and glioma cells [189-193]. Celastrol had also been reported with significant anti-metastatic activity in reducing migration and invasion of ECA-109 esophageal cancer cells [194]. Moreover, celastrol was shown to suppress Wnt signaling molecules such as integrins β1, β4 and αV, β-Catenin as well as LRP6 in a concentration-dependent fashion. According to Mi *et al.*, celastrol treatment significantly repressed the TNF-α-induced invasion of MDA-MB-231 human breast cancer cells along with a down-regulation of MMP-9 [195]. In an earlier study, celastrol treatment was also reported to inhibit PMA-induced MCF-7 cell migration and invasion following a suppressed

DNA binding of NF-κB to the MMP-9 promoter, by which the degradation and nuclear translocation of NF-κB was attenuated [196].

3.2.2. Raddeanin A

Raddeanin A ($C_{47}H_{76}O_{16}$, MW: 897.11, **Figure 3**) is a triterpenoid saponin isolated from the traditional Chinese herb *Anemone Raddeana Regel* that exhibited inhibitory effect on the growth of colorectal, liver, lung and hepatic cancer cells [197-200]. This compound significantly suppressed the invasive and migratory potential of BGC-823 human gastric cancer cells [201]. The anti-metastatic activity of Raddeanin A was attributed to the down-regulation of MMP-2, MMP-9, MMP-14 and Rhoc. Further, the up-regulation of the RECK gene may also play a vital role in the raddeanin A-mediated inhibition of invasion and metastasis in gastric cancer cells.

3.2.3. Tubeimoside-1

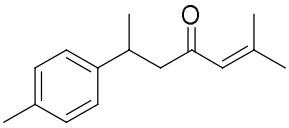
Tubeimoside-1 ($C_{63}H_{98}O_{29}$, MW: 1319.43, **Figure 3**) is a plant-derived triterpenoid saponin extracted from *Bolbostemma paniculatum* [202-203]. This phytocompound showed anticancer activity against a large number of cancer cell lines including prostate, lung, liver, glioma, gastric, hepatocellular, ovarian, cervical, choriocarcinoma and squamous esophageal carcinoma [202-207]. Peng and colleagues suggested the anti-metastatic activity of tubeimoside-1 was associated with the inhibition of NF-κB binding activity and CXCR4 expression in the breast cancer cells [208]. Moreover, the CXCL12-induced invasion was also suppressed by the tubeimoside-1 treatment, so as in the xenograft mice, in which breast cancer metastasis was notably reduced. In another study, tubeimoside-1 exhibited anti-invasive and anti-metastatic activities in CRC cells by suppressing the Wnt/β-catenin signaling pathway [209].

3.2.4. Maslinic acid

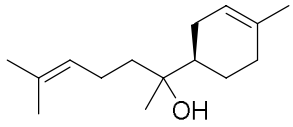
Maslinic acid ($C_{30}H_{48}O_4$, MW: 472.71, **Figure 3**) is a pentacyclic triterpene widely distributed in the skin of olive fruit that exerted anticancer effect on prostate cancer, colon cancer and melanoma cell lines, partly through the induction of apoptosis [210-211]. In the DU145 prostate cancer cells, maslinic acid significantly reduced the secretion of MMP-2, MMP-9, uPA, VEGF, TIMP-1, uPAR and soluble adhesion molecules ICAM and VCAM while increasing the secretion of TIMP-2. As a result, reduced migration and invasion of DU145 cells were observed. Moreover, maslinic acid treatment was also correlated to the decreased expression of HIF-1α, p-Akt and p-ERK [212]. According to Lin *et al.*, maslinic acid inhibited the invasion and migration of OE33 human esophageal squamous cancer cells and SGC-7901 gastric cancer cells by lowering the levels of VEGF and TGF-β1 [213].

3.2.5. Gamma (γ)-tocotrienol

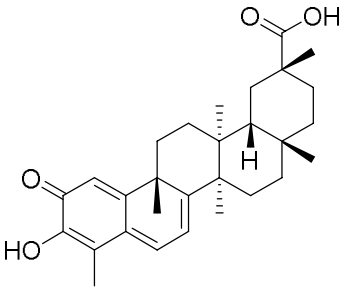
γ-Tocotrienol ($C_{28}H_{42}O_2$, MW: 410.63, **Figure 3**) is a bicyclic monoterpenoid present in cereals and vegetables, and especially plentiful in palm oil and rice bran [214-215]. This monoterpenoid possesses anticancer, antioxidant, anti-inflammatory, cholesterol-lowering, neuro-protective and bone-protective effects [215]. Liu *et al.* showed that the anti-invasive and anti-migratory activities of γ-tocotrienol in the SGC-7901 human gastric adenocarcinoma cells were associated with decreased levels of MMP-2 and MMP-9, but elevated levels of TIMP-1 and TIMP-2 [216]. When incubated with the conditioned medium of SGC-7901 gastric adenocarcinoma cells, tube formation of HUVECs was significantly in the presence of γ-tocotrienol as cyclin D1, CD44, p-VEGFR-2, MMP-9 as well as the canonical Wnt signaling molecules were down-regulated [217].



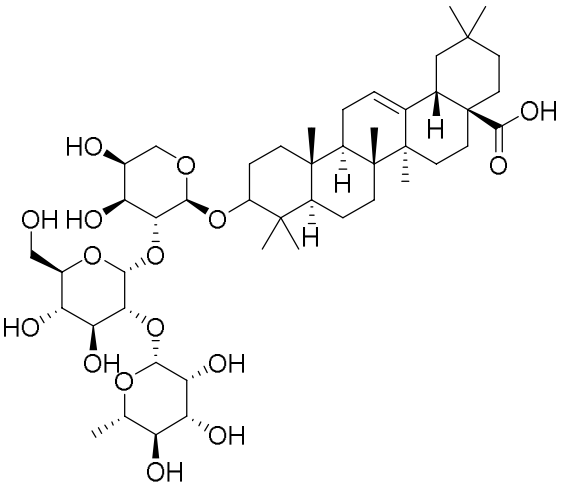
Ar-Turmerone



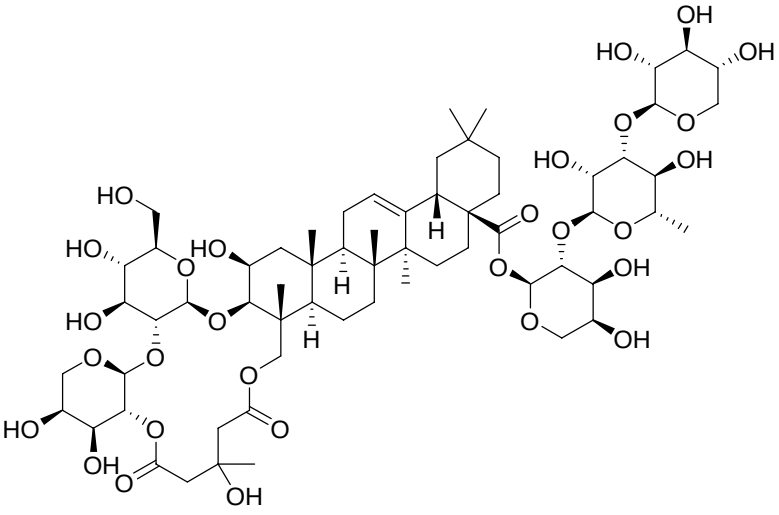
α-Bisabolol



Celastrol



Raddeanin A



Tubeimoside-1

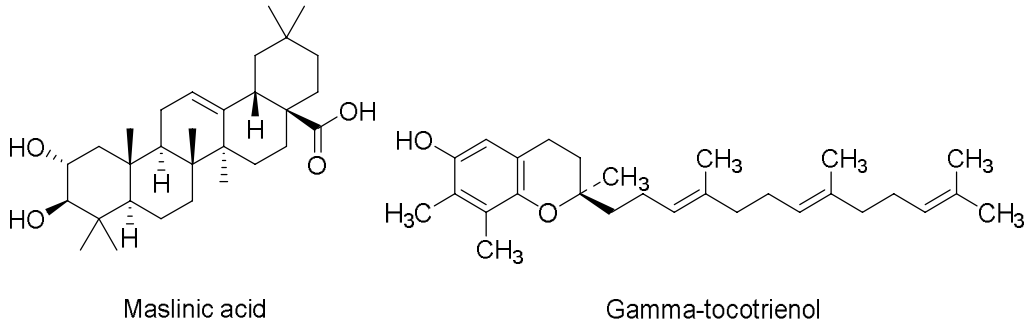


Figure 3. The chemical structures of common triterpenes

4. QUINONES

Quinones-containing natural compounds are one of the largest groups of anticancer drugs. Anthracycline antibiotics are the most commonly used quinone-containing agents for cancer treatment [218]. A large number of quinone derivatives including naphthoquinones, anthraquinones and benzoquinones have been isolated from plant and marine sources that possess remarkable anti-metastatic activity [219-221].

4.1. Emodin

Emodin ($C_{15}H_{10}O_5$, MW: 270.24, **Figure 4**) is an anthraquinone isolated from different traditional medicinal plants such as *Rheum palmatun*, *Radix rhizoma* Rhei, *Polygonum cuspidatum*, *Polygonum multiflorum* and latex of aloe vera leaves [222-223]. Emodin is renowned for its anti-viral, anti-bacterial, anti-inflammatory, hepatoprotective and immunosuppressive activities, and is widely used as a laxative in traditional Chinese medicine [224]. Interestingly, this anthraquinone is effective against pancreatic, lung, ovarian and leukemia cancer cells [225-227]. In the study of Suboj *et al.*, major cell migratory regulators, such as MMP-2, MMP-9 and RhoB, were considerably suppressed in the WiDr colon adenocarcinoma cells upon emodin treatment [228]. This representative anthraquinone has also been reported to strongly decrease cell migration and invasion, metastasis as well as angiogenesis via abating the activation of NF-κB and its down-stream targets MMP-2,

MMP-9 and VEGF while up-regulating cleaved caspase-3 in the SW1990 pancreatic cancer cells, so as the xenograft mice [229].

4.2. Rhein

Rhein ($C_{15}H_8O_6$, MW: 284.22, **Figure 4**) is an anthraquinone, also known as a cassic acid, obtained from rhubarb species, for instance, *Rheum undulatum* and *Rheum palmatum*. This versatile compound is extensively found in a variety of herbal formulations by virtue of its decent medicinal value. In the study of Tsang *et al*., rhein exhibited promising antiproliferative effect against a panel of progressive mammalian carcinoma cells in a manner comparable to other renowned natural compounds, such as curcumin, resveratrol and emodin. It is worth noting that the cytotoxicity of rhein was at least 5 times lower than emodin [230]. As an anticancer compound, rhein suppressed the activation of Akt and NF-κB as well as sonic hedgehog signaling molecules in addition to its attenuation of ECM proteins [231].

4.3. Shikonin

Shikonin ($C_{16}H_{16}O_5$, MW: 288.29, **Figure 4**) is a naphthoquinone derivative extracted from traditional Chinese herbs *Lithospermum erythrorhizon*, *Arnebia euchroma* and *Arnebia guttata* [232], which has antibacterial, anti-HIV, anti-inflammatory and anticancer activities [233]. The anticancer activity of shikonin is mainly attributed to the downregulation of p-ERK, NF-κB, topoisomerase-I, polo-like kinase 1 (PLK1), protein tyrosine kinase (PTK) and proteasome activities, and the upregulation of JNK, PKCα and caspases [234]. The invasiveness of OS cells and the deposition of MMP-13 were concentration-dependently suppressed by the shikonin treatment [235]. Besides MMP-13, Zhang *et al.* reported inhibitory effect of shikonin on MMP-2 and MMP-9 in the U87 and U251 human glioblastoma cells, in which repressed p-PI3K and p-Akt signaling were responsible for its mitigating cell migration and invasion [236]. Similar anti-metastatic activity of shikonin was also found in the PC-3 and DU145 prostate cancer cells. The suppression of MMP-2 and MMP-9 by shikonin was associated with a remarkable regulation of ERK, p38 MAPK, JNK,

Akt and mTOR [237]. In the MDA-MB-231 breast cancer cells, the anti-invasive and anti-migratory effects of shikonin were derived from an inactivation of AP-1 transcription factors [238], which are homodimers and heterodimers formed from members of the c-Jun and c-Fos families [235,239-240].

4.4. Tanshinone IIA

Tanshinone IIA ($C_{19}H_{18}O_3$, MW: 294.35, **Figure 4**) is a quinone constituent of the root of Danshen (*Salvia miltiorrhiza*) that possesses antitumor effect [241-242]. The anti-migratory effect of tanshinone IIA in AGS gastric cancer cells was accompanied with a down-regulation of MMP-2, MMP-7, MMP-9, NF-κB-p65 and COX-2 [243]. Zhang *et al.* described that tanshinone IIA induced apoptosis, inhibited cell proliferation, migration and invasion in the MG-63 osteosarcoma cells [244]. With an attenuation on MMP-2 and MMP-9 expression, promising anti-metastatic activity of tanshinone IIA was also observed in the SW480 CRC cells [245]. Regarding its mechanism of action, this diterpene quinone notably reduced the expression of uPA, MMP-2 and MMP-9 while increasing the levels of TIMP-1 and TIMP-2 levels by interfering the NF-κB signaling pathway.

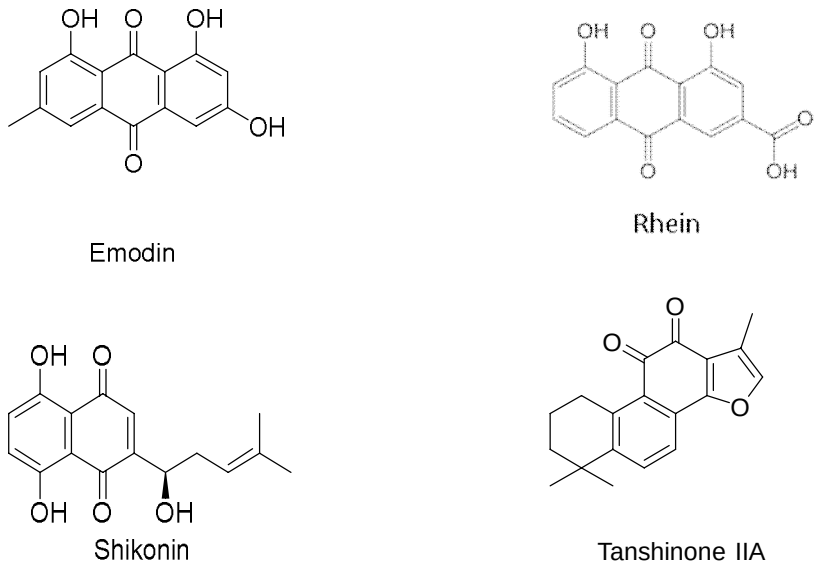


Figure 4. Chemical structures of common quinones

5. PHENOLICS

Phenolics are aromatic compounds consisting of phenolic hydroxyl groups, and they are indeed the secondary metabolites of many plant species serving as defending chemicals. Phenolics are majorly divided into monophenols, biphenols, polyphenols, tannins, lignans, lignins, phenylpropanoids, flavonoids and stilbene according to their chemical structures [83-84]. The inhibitory effect of several polyphenolic compounds, which are also classified as alkaloids and flavonoids have already been discussed in the previous sections of this review article. Henceforth, the following subsections will focus principally on the anti-metastatic activity of those that have not been mentioned.

5.1. Biphenolic and polyphenolic compounds

5.1.1. Curcumin

Curcumin ($C_{21}H_{20}O_6$, MW: 368.38, **Figure 5**) is a hydrophobic phenolic compound found in the rhizome of spice turmeric (*Curcuma longa*) that has potent anticancer activity through its regulation of a variety of pathways and multiple proteins [246]. The IC_{50} value of curcumin differs in different cell lines, due to differences in cell density, ranging from 2 to 40 μg/mL [247]. This biphenol alone or in combination with other therapeutic agent(s) is used as remedies for a wide variety of disorders such as diabetes, obesity, Alzheimer's disease and inflammatory pathologies [248]. Curcumin also serves as a chemotherapeutic compound; its anti-invasive and anti-metastatic activities have been reported by a large number of literatures [249-258]. Chiablaem *et al.* reported that curcumin possessed anti-vasculogenic mimicry (VM) activity, i.e. reducing the ability of dysregulated cells with invasive characteristics to stimulate the generation of microvascular channels in endothelial cells, and suppressed the invasive phenotype of cancer cells via down-regulating the STAT3 and PI3K/Akt signals in the SK-Hep-1 human HCC cells. Upon the anti-VM effect of curcumin, the MMP-9 deposition was accordingly inhibited in the cancer cells [249]. The inhibitory effect of

curcumin on metastasis was suggested to be mediated via an inhibition of the Rac1/protein-activated kinase 1 (PAK1) pathway [250]. In fact, Rac1 is an essential GTPase that plays important roles in cell adhesion, migration, invasion and metastasis by triggering MMPs production in different cell types [259]. Activated Rac1, or Rac1L61, was shown to increase MMP-2 and MMP-9 in a great extent, and thus accelerate cell invasion. PAK1 is known as a downstream protein of Rac1, which is involved in cell invasion and migration. Curcumin was demonstrated to abate merely PAK1 phosphorylation, rather than the total PAK1 level, indicating that the anti-invasive activity of curcumin is plausibly associated with Rac1-dependent phosphorylation of PAK1. The study of Senft *et al*. manifested the non-toxic and anti-metastatic properties of curcumin in several human glioblastoma (GBM) cell lines [252]. Decreased levels of p-STAT3, c-Myc and Ki-67 were obtained in the curcumin-treated GBM cells. Their results were in agreement with some early studies that STAT3 expression was positively correlated to cancer cell invasion in glial and non-glial neuro cells [260-261]. In the SCC-25 oral squamous cell carcinoma cells, curcumin treatment led to a notable down-regulation of the EMT promoters Snail, Twist, MMP-2 and MMP-9, but an up-regulation of the EMT repressor E-cadherin [254,262]. Besides EMT regulatory factors, increased expression of HLJ1, which is a DnaJ-like heat shock protein 40 (HSP40), was also observed in the curcumin-treated SCC-25 cells [254]. In a xenograft breast cancer model, curcumin exhibited anti-metastatic effect, mostly through suppression of NF-κB and NF-κB-mediated genes [263]. The expression of several metastatic proteins including MMP-9, VEGF and ICAM-1 was also significantly suppressed by this pharmaceutically safe compound.

5.1.2. Honokiol

Honokiol ($C_{18}H_{18}O_2$, MW: 266.33, **Figure 5**) is a lignin biphenol extracted from Magnolia plant species, particularly *Magnolia officinalis* and *Magnolia grandiflora*. This biphenol is widely used in Japan, China and South Korea for the treatment of inflammation, allergic

diseases, cough, gastrointestinal disorders, stroke and anxiety [264-265]. It also has cardio-protective, neuroprotective, antitumor and antiangiogenic activities [266-268]. Honokiol induced apoptosis through the repression of Ca^{+2} channels, EMT events and the PI3K/Akt/mTOR and Wnt signaling cascades in glioblastoma, breast and lung cancer cells, as well as xenograft and metastatic tumors [269]. Moreover, honokiol suppressed the EGFR signaling pathway in head and neck squamous cell carcinoma (HNSCC) and breast cancer cells via the blockage of EGFR expression or EGFR phosphorylation. Nox1 expression and oxidative stress were dose-dependently decreased in the A375, Hs294t, SK-Mel119 and SK-Mel28 melanoma cells upon the treatment of honokiol by Prasad and colleagues [270]. They also found that honokiol increased the cytosolic p47phox protein accumulation and decreased the membrane-bound p22phox protein levels in the melanoma cells, therefore, the Nox1 activation was prevented. As such, the migration/extravasation and growth of intravenously injected melanoma cells to distant organs, such as liver, lungs, kidneys, and spleen, were largely restricted as shown in their *in vivo* bioluminescence imaging results. In a renal cell carcinoma cellular model with high metastatic behavior, honokiol dose-dependently increased the expression of metastasis suppressor gene KISS1 and its receptor KISS1R at both mRNA and protein levels and resulted in inhibition of cell invasion and colony formation. However, the anti-metastatic effect of honokiol was abolished under the knockdown of KISS1 [271]. It is well acknowledged that EMT events are crucial to cancer metastasis [272]. According to Avtanski *et al.*, honokiol inhibited EMT in breast cancer cells with a considerable down-modulation of mesenchymal inducers and up-modulation of epithelial markers following the inactivation of STAT3 [273].

5.1.3. Magnolol

Magnolol ($C_{18}H_{18}O_2$, MW: 266.34, **Figure 5**) is a hydroxylated biphenolic compound derived from the stem bark and root of *Magnolia officinalis*. This hydroxylated biphenol induced apoptosis and suppressed cell proliferation in glioblastoma, leukemia, colon cancer,

melanoma, hepatoma, fibrosarcoma, thyroid carcinoma and squamous carcinoma cells [274-277]. The highly invasive property of MDA-MB-231 breast cancer cells was significantly inhibited as the transcriptional activity of NF-κB and the DNA binding of NF-κB to MMP-9 promoter were blocked by the magnolol treatment [278]. On the other hand, the levels of MMP-2, MMP-9, COX-1 and COX-2 were all reported with substantial reduction in the PC-3 human prostate cancer cells after the incubation with magnolol [279].

5.2. Monophenolic compounds

5.2.1. 6-Shogaol

6-Shogaol ($C_{17}H_{24}O_3$, MW: 276.38, **Figure 5**) is a major bioactive compound that is plentiful in Ginger (*Zingiber officinale*). This ginger constituent has been shown to provide a wide spectrum of therapeutic effects including anticancer, anti-oxidant, analgesic, anti-inflammatory, antipyretic and antitussive activities, and used for the treatment of different central nervous system disorders [280-281]. Hong *et al.* observed significant reduction of cell motility and invasion in the MDA-MB-231 breast cancer cells as a consequence of MMP-2 and MMP-9 inhibition by 6-shogaol. In addition, various invadopodia markers such as the c-Src kinase, cortactin, tyrosine kinase substrate with five Src homology 3 domains (Tks5), membrane type 1 MMP (MT1-MMP), Twist1, and platelet-derived growth factor receptor-alpha (PDGFR-α) were all repressed upon the 6-shogaol treatment. Invadopodia produced by active c-Src and other proteins including cortactin, Tks5, cofilin, F-actin and actin-related proteins (Arp2/3) are indeed the actin-rich structures responsible for the focal ECM degradation in cancer invasiveness and metastasis [282-284]. The newly formed invadopodia become mature upon the secretion of various ECM degrading proteases, including MT1-MMP, disintegrin, dipeptyl dipeptidase IV, seprase, and a disintegrin and metalloproteinase 10 (ADAM10) [285]. The anti-metastatic action of 6-shagol, therefore, appears highly associated with the inhibition of the key regulators of invadopodium maturation as aforementioned. However, the anti-invasive and

anti-metastatic activities of 6-shogaol were also suggested to be mediated through the up-regulation of plasminogen activator inhibitor (PAI-1) and the resulting down-regulation of MMP-2, MMP-9 or uPA in HCC. The molecular mechanism in PAI-1 modulation may involve the inhibition of MAPK phosphorylation, PI3K/Akt signaling and NF-κB or STAT3 activation [286]. The same research group also reported dose-dependent anti-migratory and anti-invasive activities of 6-shogaol in PMA-treated HepG2 and PMA-untreated Hep3B cells accompanied by an increased expression of TIMP-1 [287]. Ling *et al.* evaluated the inhibitory ability of different shogaols (6-, 8- and 10-shogaol) in PMA-induced breast cancer cells. Among the shogaol analogues, 6-shogaol showed the most potent anti-invasive effect conjointly with its suppressive actions on MMP-9 expression, NF-κB nuclear translocation and JNK activation [288].

5.2.2. Ferulic acid

Ferulic acid ($C_{10}H_{10}O_4$, MW: 194.18, **Figure 5**) is a dietary plant phenolic compound available in corn, wheat and flax as well as in different fruits and vegetables such as citrus fruit, bananas, cabbages, eggplants and bamboo shoots [289]. Ferulic acid treatment significantly inhibited cell invasion and migration of MIA PaCa-2 pancreatic cancer cells, in which notable cell cycle arrest and apoptotic events were obtained [290]. Similar anti-invasive activity of ferulic acid was also observed in TT medullary thyroid cancer cells. In those ferulic acid-treated TT cells, MMP-2, MMP-9 and URG4/URGCP levels were significantly reduced, but the expression of TIMP-1 was induced [291]. Tsai *et al*. claimed that the derivatives of cinnamic acid, namely ferulic acid, caffeic acid and chlorogenic acid, inhibited PMA-induced invasion of A549 cells via modulating levels of MMP-9, uPA, TIMP-1, PAI-1 and PAI-2 as well as the MAPK, PI3K/Akt, NF-κB, AP-1 and STAT3 signaling pathways [292].

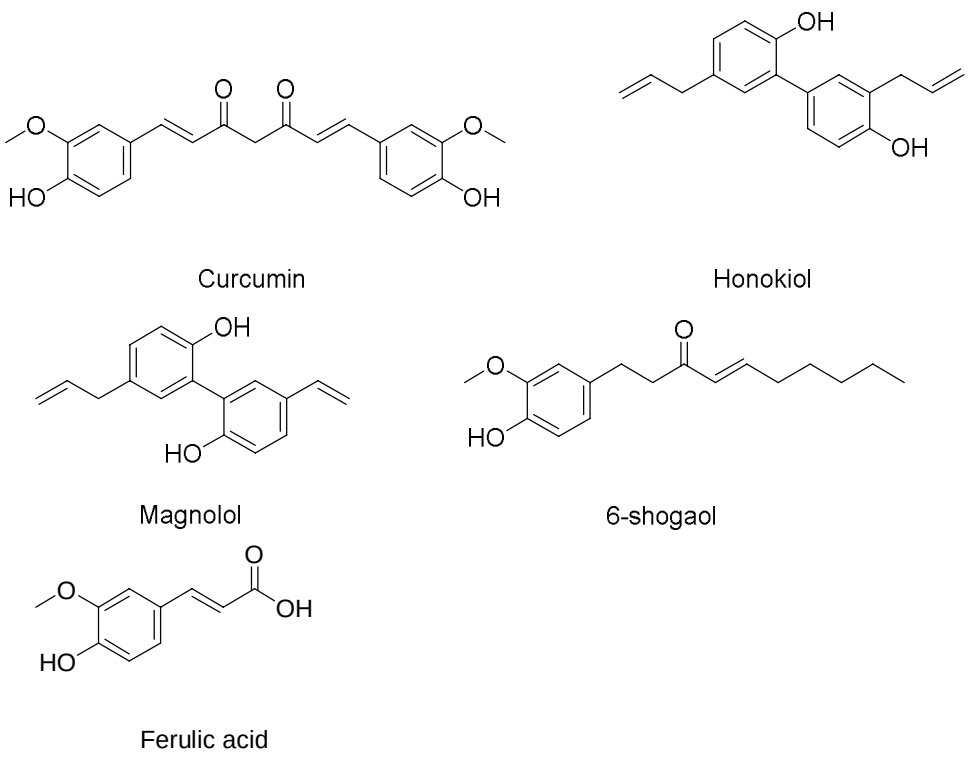


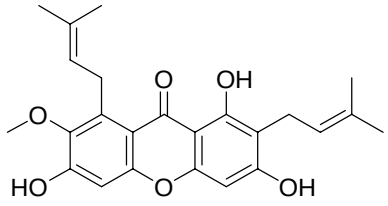
Figure 5. The chemical structures of common phenolics

6. XANTHONE

6.1 α-Mangostin

α-Mangostin ($C_{24}H_{26}O_6$, MW: 410.45, **Figure 6**) is a polyphenolic compound of the xanthone class, which is available in the pericarp of the fruit of *Garcinia mangostana L* [293]. This xanthonoid has numerous pharmacological activities such as antioxidant, anti-inflammatory, anti-allergic, antiviral and antibacterial actions [294-295]. Antineoplastic activity of α-mangostin has been established on breast [296], tongue mucoepidermoid [295], colon [297], liver [298] and pancreatic cancer cells [299]. α-Mangostin at 15 μM significantly inhibited the metastatic property of B16-F10 melanoma cells by decreasing the expression of MMP-9 and intracellular protoporphyrin IX (PpIX) [300]. Yuan and colleagues demonstrated that α-mangostin at non-cytotoxic concentrations, i.e. <5 μM significantly reduced the expression levels of MMP-2 and MMP-9 and attenuated ERK signals in MIA PaCa-2 and BxPC-3

pancreatic cancer cells [301]. Moreover, a study from an Australia group reported the anti-invasive activity of α-mangostin in A-431 and SK-MEL-28 melanoma cells was mediated by reducing MMP-2 and MMP-9 activities via the inhibition of Akt and NF-κB signaling cascades [302].



α-Mangostin

Figure 6. The chemical structure of α-mangostin

7. Sulfur-Containing Compounds

7.1. Sulforaphane

Sulforaphane ($C_6H_{11}NOS_2$, MW: 177.29, **Figure 7**) is an isothiocyanate isolated from broccoli sprouts and cruciferous vegetables of the brassica oleracea species [303]. The anticarcinogenic activity of sulforaphane in breast, prostate, pancreatic, hepatocellular and oral carcinoma cells has been backed up by substantial reports [304-306]. In the U251MG glioblastoma cells, sulforaphane inhibited cell invasion by increasing the expression of E-cadherin and a considerable reduction of MMP-2, MMP-9 and Galectin-3 [307]. In the study of Mondal *et al.*, the anti-migratory effect of sulforaphane in the AGS gastric cancer cells was linked to the down-regulation of EGFR and p-ERK1/2 [308]. Moreover, sulforaphane significantly inhibited the invasion of 87MG and U373MG glioblastoma cells with a suppression on ERK1/2 phosphorylation and MMP-2, but an induction of cell adhesion molecule CD44v6 [309]. Lee *et al.* demonstrated potent anti-invasive activity of sulforaphane in MCF-7 breast cancer cells, in which the TPA-induced MMP-9 expression and NF-κB activation were efficiently reduced [310].

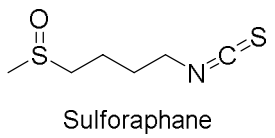


Figure 7. The chemical structure of sulforaphane

8. OTHERS

8.1. Bufalin

Bufalin ($C_{24}H_{34}O_4$, MW: 386.53, **Figure 8**), a cardiotonic steroid, is an active component of traditional Chinese medicine Chan Su [311-312]. The antitumor activity of bufalin on lung, liver, breast, colorectal, prostate, gastric, osteosarcoma, hepatocellular, gallbladder and pancreatic carcinoma cells has been evidenced by recent studies [313-318]. The anti-metastatic activity of bufalin in HCC, both *in vitro* and *in vivo*, was suggested to be associated with decreased levels of mesenchymal mediators, namely N-cadherin, vimentin, Snail, and HIF-1α, an elevation of E-cadherin and a down-regulation of the PI3K/Akt/mTOR/HIF-1α pathway [319]. According to Wu *et al.*, bufalin at sub-lethal concentrations, exhibited anti-invasive and anti-migratory activities in the NCI-H460 lung cancer cells. In the presence of bufalin, expression levels of MMP-2, MMP-9, PKC, PI3K, p-Akt, growth factor receptor bound protein 2 (GRB2), p-ERK, p-p38, and p-JNK were notably suppressed, so as the nuclear translocation of cytoplasmic NF-κB. The anti-metastatic action of bufalin was related to its down-regulation on different metastasis-related genes such as Rho A, Rock1 and FAK [320]. According to Chen *et al.*, the anti-invasive activity of bufalin in SK-Hep1 cells was associated with the suppression of MMP-2, MMP-9, PI3K, p-Akt and nuclear NF-κB activity. Bufalin treatment also inhibited the levels of FAK, Rho A, MEKK3, MKK7, VEGF and uPA in cancer cells [321]. Therefore, the effect of bufalin appears to be modulated via the PI3K/Akt/NF-κB signals. Hong and colleagues demonstrated the potent inhibitory effect of bufalin on claudins, particularly claudin-2, -3 and -4, in the T24

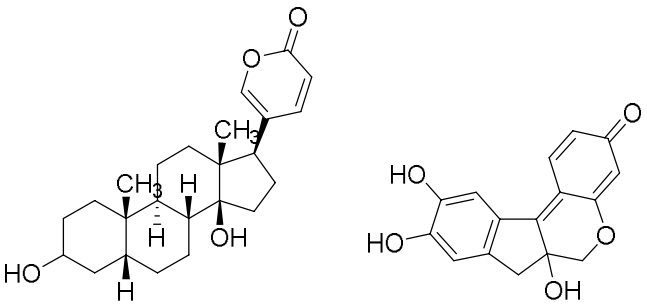
human bladder carcinoma cells. Importantly, the bufalin action on claudins was determined to be ERK-dependent [322].

8.2. RA-XII

RA-XII ($C_{46}H_{58}N_6O_{14}$, MW: 918, **Figure 8**) is a cyclopeptidic glucoside isolated from *Rubia yunnanensis* and *Rubia cordifolia* that has been found effective against several cancer cell lines [323-324]. This plant-derived compound inhibited adhesion of collagen, fibronectin and laminin to cancer cells, and reduced the expression levels of VCAM, ICAM and integrins [323]. Moreover, breast cancer cell migration was significantly inhibited post RA-XII treatment as the cofilin signaling and chemokine receptors were diminished. RA-XII also reduced the activities of MMP-9, uPA as well as ECM-associated proteinases. The molecular mechanism underlying the anti-migratory effect of RA-XII involves the suppression of MAPK, EGFR, PI3K/Akt, NF-κB and FAK/pSRC signaling molecules.

8.3. Brazilein

Brazilein ($C_{16}H_{12}O_5$, MW: 284.27, **Figure 8**) is a bioactive homoisoflavonoid extracted from the dried heartwood of *Caesalpinia sappan* L. that exhibited anticancer effect in various cancer cell lines such as A549 (lung), HepG2 and Hep3B (liver), MDA-MB-231 and MCF-7 (breast), and Ca9-22 (gingival) [325-326]. In the study of Hsieh *et al.*, the inhibitory effect of brazilein on breast cancer cell migration and invasion was correlated to a suppression of MMP-2 and p-NF-κB [327]. The brazilein treatment significantly reduced the phosphorylation of p38 MAPK, PI3K and Akt, but the phosphorylation of ERK1/2 and JNK was not affected. These results suggested that the anti-metastatic activity of brazilein in breast cancer cells was regulated through the inactivation of both PI3K/Akt and p38 MAPK signaling cascades, which engendered the inhibition of metastasis.



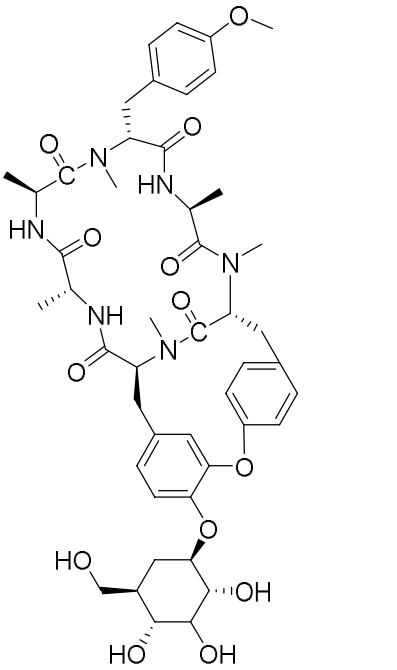


Figure 8. The chemical structures of bufalin, brazilein and RA-XII

Table 1. Anti-metastatic natural compounds with their sources and biological targets

Compounds	Chemical Class	Source	Targets	References
Evodiamine	Quinolone alkaloid	*Evodia rutaecarpa*	MMP-2/-9, NF-κB, ERK1/2, uPA, uPAR, JNK, p38, p-ERK	[29-32,36]
Matrine	Sophora alkaloid	*Sophora flavescens*	MMP-2/-9, Akt, miR-133a, Ki67, EGFR, p-ERK, p-EGFR, PTEN	[44,49]
Sanguinarine	Benzophenanthridi-	*Sanguinaria*	MMP-2/-9, p38,	[58-60]

	ne alkaloid	*canadensis*, *Chelidonium majus*, *Macleaya cordata*	TIMP-1/-2, Akt, COX-2, PGE2, NF-κB, AP-1, ERK, HO-1, VEGF, VE-cadherin, claudin-3/-4	
Glaucine	Alkaloid	*Corydalis turtschaninovii*	MMP-9, NF-κB, IκBα	[61]
Hirsutine	Indole alkaloid	Uncaria genus	MMP-2/-9, NF-κB	[64]
α-Tomatine	Glycoalkaloid	*Lycopersicon esculentum*	MMP-2/-7/-9, FAK, PI3K, Akt, IκBα, NF-κB, PKCα, ERK	[72-74]
α-Solanine	Steroidal glycoalkaloid	*Solanum nigrum*, *Solanum tuberosum*	MMP-2/-9, JNK, CD44, eNOS, EMMPRIN, Akt, E-cadherin, vimentin, VEGF, mTOR, STAT3, β-catenin, TCF-1, NF-κB, RECK, TIMP-1/-2, PI3K miR-21, miR-138	[79-82]
Wogonin	O-methylated flavone	*Scutellariae radix*, *Scutellaria baicalensis*	MMP-2/-9, uPA, p-ERK1/2	[92-94]
Naringenin	Flavanone	*Citrus sinensis*, *Lycopersicon esculentum* Mill.	VEGF, AP-1, MMP-2/-9, ERK, NF-κB, Smad3, PI3K/Akt, JNK, vimentin, N-cadherin	[96,99,101, 105]
Apigenin	Flavone	Onions, parsley, oranges, chamomile,	MMP-9, Wnt/β-catenin, TCF, lymphoid	[109-112]

		wheat, sprouts, tea	enhancer factor, IKKα, NF-κB, caspase-3, PI3K, transgelin, AKT Ser473/Thr308, integrin β4	
Kaempferol	Flavonol	Tea, broccoli, apples, strawberries, beans, citrus fruits	MMP-2/-9, Bax, Bcl-2, Fas, Src, caspases-3/-8/-9 cleaved-PARP, ERK1/2, Akt, AP-1, uPA, JNK, p38 MAPK, PKC, TIMP-2	[113-117]
Genistein	Isoflavone	*Glycine max* L., *Genista tinctoria* L., *Nicotiana tabacum* L	MMP-2/-9, AP-1, NF-κB, ERK, JNK, PI3K, Akt, FLT4, MUC1, ICAM-1, OPG, RANKL, uPA, E-cadherin, vimentin, Smad4, claudin-3/-4, IGF-1, Snail, thrombospondin-1, FAK, kangai-1	[120-127]
Isorhamnetin	O-methylated flavonol	*Hippophae rhamnoides* L., *Oenanthe javanica*	MMP-2/-9, p38 MAPK, STAT3, uPA	[129]
Oroxylin A	O-methylated flavone	*Scutellaria baicalensis*, *Scutellaria radix*	MMP-2/-9, TIMP-2, PKCδ, ERK1/2, AP-1, KDR/Flk-1, p38 MAPK, Akt	[132-134]
Myricetin	Ubiquitous flavonoid	Fruits, vegetables, nuts, berries,	MMP-2/-9/-13, VEGF, NF-κB, uPA, HIF-1α,	[141-143]

		tea, red wine	ERK1/2, c-Fos, c-Jun, AP-1	
Deguelin	Rotenoid	*Derris trifoliate, Mundulea sericea*	MMP-1/-2/-7/-9/-13, NF-κB, IκB, CD4, TIMP1, Rac1, Rock1, uPA, VEGF, Rho A	[146-149]
Silibinin	Flavonoid	*Silybum marianum*	MMP-2/-9, AP-1, AMPK, mTOR, E-cadherin, Zeb1, EGFR, ERK1/2, JNK, β-catenin, Hakai, Snail, Src, Slug, Akt, uPAR, uPA, cathepsin B, Raf-ERK/c-Jun, FAK	[151-158]
Nobiletin	O-methylated flavone	*Citrus sinensis*, *Citrus reticulata*	MMP-2/-9, ERK, JNK, NF-κB, CREB, SP-1, PI3K/Akt, FAK, CXCR4, IκBα, Ras, c-Raf, Rac-1, Cdc42, RhoA, RhoB	[166-169]
Delphinidin	Anthocyanidin	Pigmented fruits and vegetables	MMP-9, AKT, P70S6K, JNK, ERK1/2, MAPK, Met receptor, HGF-mediated tyrosyl, FAK, Src, paxillin, Gab-1, GRB-2, Ras-ERK, PKCα PI3K/Akt, STAT3, NF-κB	[172-174]
Aromatic	Sesquiterpene	*Curcuma longa*	MMP-9, COX-2,	[181]

turmerone			NF-κB, PI3K, Akt, ERK1/2	
α-Bisabolol	Sesquiterpene	*Matricaria chamomilla* L.	EGR1, KISS1R	[184]
Celastrol	Quinone triterpene	Thunder of God Vine, Tripterygium wilfordii	MMP-9, Wnt, β1, β4, αv, β-catenin, LRP6, NF-κB	[194-196]
Raddeanin A	Triterpinoid saponin	*Anemone Raddeana* Regel	MMP-2/-9/-14, Rhoc, RECK	[201]
Tubeimoside-1	Triterpinoid saponin	*Bolbostemma paniculatum*	CXCR4, NF-κB, Wnt/β-catenin	[208-209]
Maslinic acid	Pentacyclic triterpene	Skin of olive fruit	MMP-2/-9, uPA, VEGF, TIMP-1, uPAR, ICAM, VCAM, TGFβ1 E-cadherin, TIMP-2, HIF-1α, pAkt, pERK	[212-213]
Gamma-tocotrienol	Bicyclic monoterpenoids	Palm oil and rice bran	MMP-2/-9, TIMP-1/-2, Wnt, β-catenin, CD44, cyclin D1, p-VEGFR-2	[216-217]
Emodin	Anthraquinone	*Rheum palmatun*, *Radix rhizome* Rhei, *Polygonum cuspidatum*, *Polygonum multiflorum*, Aloe vera	MMP-2/-9, Akt, RhoB, VEGF, bFGF, NF-κB, survivin, eNOS, caspase-3, uPAR, KDR/Flk-1, ERK1/2, p38	[228-229]
Rhein	Anthraquinone	*Rheum undulatum*, *Rheum palmatum*	Akt, NF-κB, SHH	[230-231]

Shikonin	Naphthoquinone	L*ithospermum erythrorhizon*, *Arnebia euchroma*, *Arnebia guttata*	MMP-2/-9/-13, β-catenin, c-Jun, p-PI3K, p-Akt, ERK, p38, JNK, AKT, mTOR, ERK1/2, ROS, NF-κB, AP-1, c-Fos	[235-238]
Tanshinone IIA	Diterpene quinone	*Salvia miltiorrhiza*	MMP-2/-7/-9, uPA, TIMP-1/-2, NF-κB, COX-2	[243-245]
Curcumin	Biphenolic	*Curcuma longa*	MMP-2/-9/-14, STAT3, Ki-67, PI3K/AKT, Rac1/PAK1, Snail, Twist, c-Myc, NF-κB, E-cadherin, HLJ1, VEGF, IAM-1	[249,250,252, 254,262,263]
Honokiol	Biphenolic	*Magnolia officinalis*, *Magnolia grandiflora*	PI3K, Akt, mTOR, Wnt, STAT3, EGFR, Nox1, p47phox, p22phox, KISS1, ZEB1	[269-271, 273]
Magnolol	Biphenolic	*Magnolia officinalis*	MMP-2/-9, NF-κB, COX-1/-2	[278-279]
Ferulic acid	Monophenolic	Citrus fruit, bananas, cabbages, eggplants and bamboo shoots	MMP-2/-9, uPA, TIMP-1, MAPK, URG4/URGCP, PAI-1/-2, PI3K/Akt, AP-1, NF-κB, STAT3	[282,286, 288]
6-Shogaol	Monophenolic	*Zingiber officinale*	MMP-2/-9, c-Src, Tks5, TIMP-1, MT1-MMP, uPA,	[290-292]

			Twist1, MAPK, PDGFR-α, PAI-1, STAT3, AP-1, PI3K/Akt, NF-κB, IκB	
α-Mangostin	Xanthone	*Garcinia mangostana* L	MMP-2/-9, Akt, E-cadherin, ERK, NF-κB	[300-302]
Sulforaphane	Isothiocyanate	Broccoli, sprouts	MMP-2/-9, E-cadherin, Galectin-3, EGFR, NF-κB, p-ERK1/2,	[307-310]
Bufalin	Cardiotonic steroid	Chan Su	MMP-2/-9, PKC, PI3K, AKT, mTOR, HIF-1α, N-cadherin, uPA, E-cadherin, FAK, vimentin, Snail, GRB2, ERK, p-p38, TIMP-1/-2, VEGF, p-JNK, Rho A, Rock1, MEKK3, MKK7, claudin-2/-3/-4	[319-322]
RA-XII	Cyclopeptide glucoside	*Rubia yunnanensis, Rubia cordifolia*	MMP-9, EGFR, VCAM, ICAM, integrins, cofilin, MAPK, NF-κB PI3K/AKT, uPA, FAK/pSRC	[323]
Brazilein	Homoisoflavonoid	*Caesalpinia sappan*	MMP-2, NF-κB, p38, PI3K, Akt	[327]

CONCLUSION

In recent years, natural products have received much attention from pharmacists, chemists and biologists for their potential to be served as new anticancer compounds, particularly for the treatment of metastatic cancers. Increasing evidence from *in vitro* and *in vivo* models demonstrated that natural compounds isolated from plants can be a promising option to inhibit cancer cell invasion and migration, thus the metastatic circumstances. Majority of the plant-derived compounds discussed in this review article target at suppressing the activities of MMPs; nevertheless, they may also have inhibitory actions on other invasive and metastatic mechanisms, or even more diverging pharmacological properites. We hope this review provides an excellent avenue for researchers in linking up the phytocompounds to their corresponding mechanisms of action. However, only limited numbers of these compounds have been undergoing clinical trials for their efficacy and/or safety in cancer patients. In the future, we hope more promising anti-metastatic compounds will be identified by in-depth scientific research studies, as they are the basics for randomized controlled clinical trials. Above all, the additive or synergistic effect of combination treatment with potential anticancer phytocompounds and mainstay therapeutic agents also worths detailed investigation.

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COMPETING INTEREST

The authors have no competing interest.

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