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REVIEW

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Naturally occurring anti-cancer compounds: shining from Chinese herbal medicine

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Abstract

Numerous natural products originated from Chinese herbal medicine exhibit anti-cancer activities, including anti-proliferative, pro-apoptotic, anti-metastatic, anti-angiogenic effects, as well as regulate autophagy, reverse multidrug resistance, balance immunity, and enhance chemotherapy in vitro and in vivo. To provide new insights into the critical path ahead, we systemically reviewed the most recent advances (reported since 2011) on the key compounds with anti-cancer effects derived from Chinese herbal medicine (curcumin, epigallocatechin gallate, berberine, artemisinin, ginsenoside Rg3, ursolic acid, silibinin, emodin, triptolide, cucurbitacin B, tanshinone I, oridonin, shikonin, gambogic acid, artesunate, wogonin, β-elemene, and cepharanthine) in scientific databases (PubMed, Web of Science, Medline, Scopus, and Clinical Trials). With a broader perspective, we focused on their recently discovered and/or investigated pharmacological effects, novel mechanism of action, relevant clinical studies, and their innovative applications in combined therapy and immunomodulation. In addition, the present review has extended to describe other promising compounds including dihydroartemisinin, ginsenoside Rh2, compound K, cucurbitacins D, E, I, tanshinone IIA and cryptotanshinone in view of their potentials in cancer therapy. Up to now, the evidence about the immunomodulatory effects and clinical trials of natural anti-cancer compounds from Chinese herbal medicine is very limited, and further research is needed to monitor their immunoregulatory effects and explore their mechanisms of action as modulators of immune checkpoints.

Keywords: Cancer, Chinese herbal medicine, Natural products, Bioactive compounds, Traditional Chinese medicine

Background

Cancer is a leading public health problem worldwide with an estimated 18.1 million new cases and 9.6 million cancer deaths in 2018 [1]. Chinese herbal medicine has been used as anti-cancer agents for a long time, they exhibit anti-inflammatory activities and contain abundant anti-cancer compounds that exert direct cytotoxicity effects and indirect regulation in tumor microenvironment and cancer immunity, as well as improve chemotherapy [2–5]. For examples, *PNAS* reported that epigallocatechin gallate (EGCG) targeting Laminin receptor (Lam 67R) shows promising efficacy in treating prostate cancer [6]. *British Journal of Pharmacology* described that ginsenoside Rh2 inhibits P-glycoprotein (P-gp) activity to reverse multidrug resistance [7]. *The American Journal of Chinese Medicine* demonstrated that curcumin induces autophagy to enhance apoptotic cell death [8]. *Journal of Ethnopharmacology* reviewed that berberine potentially represses tumor progression and is expected to be safe, effective and affordable agent for cancer patients [9]. *Chinese Medicine* presented that shikonin exerts synergistic effects with chemotherapeutic agent [10]. However, the anti-cancer targets of these pharmacodynamic compounds are still not clear, and this is the major obstacle for the application and development of Chinese herbal medicine.

This review in Chinese herbal medicine and cancer focuses on summarizing experimental results and conclusions from English literatures reported since 2011.

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Literature search was conducted in peer-reviewed and clinical databases, which include PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Web of Science (http://www.webofknowledge.com), Medline (https://www.medline.com), Scopus (https://www.scopus.com), and Clinical Trials (https://clinicaltrials.gov) using the following keywords: Cancer, Tumor, Neoplasm, Chinese herbs, Chinese medicine, Herbal medicine. To provide new insights into the critical path ahead, the pharmacological effects, novel mechanism of action, relevant clinical studies, innovative applications in combined therapy, and immunomodulation of the popular compounds originated from Chinese herbal medicine were reviewed systemically.

Different natural products derived from Chinese herbal medicine, including curcumin, EGCG, berberine, artemisinins, ginsenosides, ursolic acid (UA), silibinin, emodin, triptolide, cucurbitacins, tanshinones, ordonin, shikonin, gambogic acid (GA), artesunate, wogonin, β-elemene, and cepharanthine, were identified with emerging anti-cancer activities, such as anti-proliferative, pro-apoptotic, anti-metastatic, anti-angiogenic effects, as well as autophagy regulation, multidrug resistance reversal, immunity balance, and chemotherapy improvement in vitro and in vivo. These compounds are considered popular with over 100 supported publications and are selected to be discussed in more details. Figure 1 shows the word cloud of these compounds. In this review, the advantages and drawbacks of representative Chinese herbal medicine-derived compounds in different types of cancers were also highlighted and summarized.

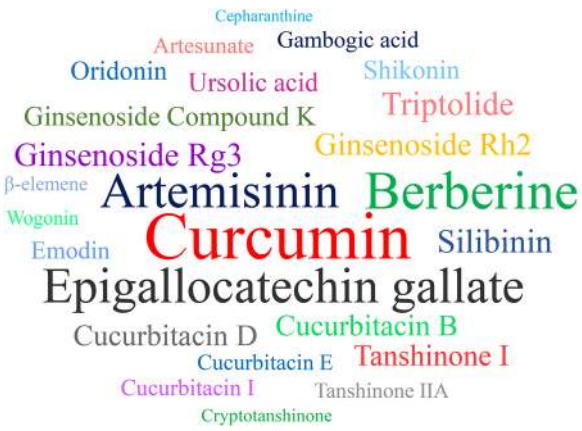

Fig. 1 The anti-cancer compounds from Chinese herbal medicine (CHM). The popular anti-cancer compounds in CHM presented as a "word cloud", in which the size of each name is proportional to the number of publications of the compounds

Curcumin

Curcumin (Fig. 2) is a polyphenol compound extracted mainly from the rhizomes of *Curcuma longa*, *Curcuma zedoaria* and *Acorus calamus* L. with many biological activities, but it has poor water solubility and stability [11]. Clinical evidence and extensive studies showed that curcumin has various pharmacology effects, including anti-cancer, anti-inflammatory, and anti-oxidative activities [12–14]. Curcumin and its analogues are shown to be emerging as effective agents for the treatment of several malignant diseases such as cancer. Numerous studies have shown that curcumin and its preparations can inhibit tumors in almost all parts of the body, including head and neck, ovarian, skin and gastric cancers [15–20]. Curcumin is shown to exhibit many anti-cancer effects through the inhibition of cell proliferation, promotion of cell apoptosis, prevention of tumor angiogenesis and metastasis, and the induction of autophagy [21–25].

Curcumin inhibits cell growth, induces cell cycle arrest and apoptosis in esophageal squamous cell carcinoma EC1, EC9706, KYSE450, TE13 cells through STAT3 activation [12]. It also induces oxidative stress, which disrupts the mitochondrial membrane potential and causes the release of cytochrome c, thus inducing apoptosis [26]. Besides, curcumin is shown to induce autophagy [8, 21, 27–30]. It induces autophagy through 5′AMP-activated protein kinase (AMPK) activation, leading to Akt degradation, thus inhibiting cell proliferation and migration in human breast cancer MDA-MB-231 cells [21], while it inhibits cell growth partially through autophagy induction in human hepatocellular carcinoma HepG2 cells [29]. Moreover, curcumin can ameliorate Warburg effect in human non-small cell lung cancer (NSCLC) H1299, breast cancer MCF-7, cervical cancer HeLa and prostate cancer PC-3 cells through pyruvate kinase M2 down-regulation, a key regulator of Warburg effect [18]. In addition, tumor metastasis has always been a frustrating problem for anti-cancer therapy, and curcumin also exhibits anti-metastasis effects [31–35]. Curcumin inhibits cell invasion via AMPK activation in human colorectal cancer SW-480 and LoVo cells [31], whilst low-toxic level of curcumin efficiently inhibits cell migration and invasion through the inhibition of Ras-related C3 botulinum toxin substrate 1/p21 (Rac1) activated kinase 1 (Rac1/PAK1) pathway in human NSCLC 801D cells, and this effect is also confirmed in 801D xenograft mice [32]. By pulmonary administration of curcumin in mice, it overcomes the problem of its low bioavailability, and inhibits lung metastasis of melanoma [35].

The main target molecules and signaling involved in the pharmacological processes include reactive oxygen species (ROS), matrix metalloproteinases (MMPs), nuclear factor kappa-light-chain-enhancer of activated B cells

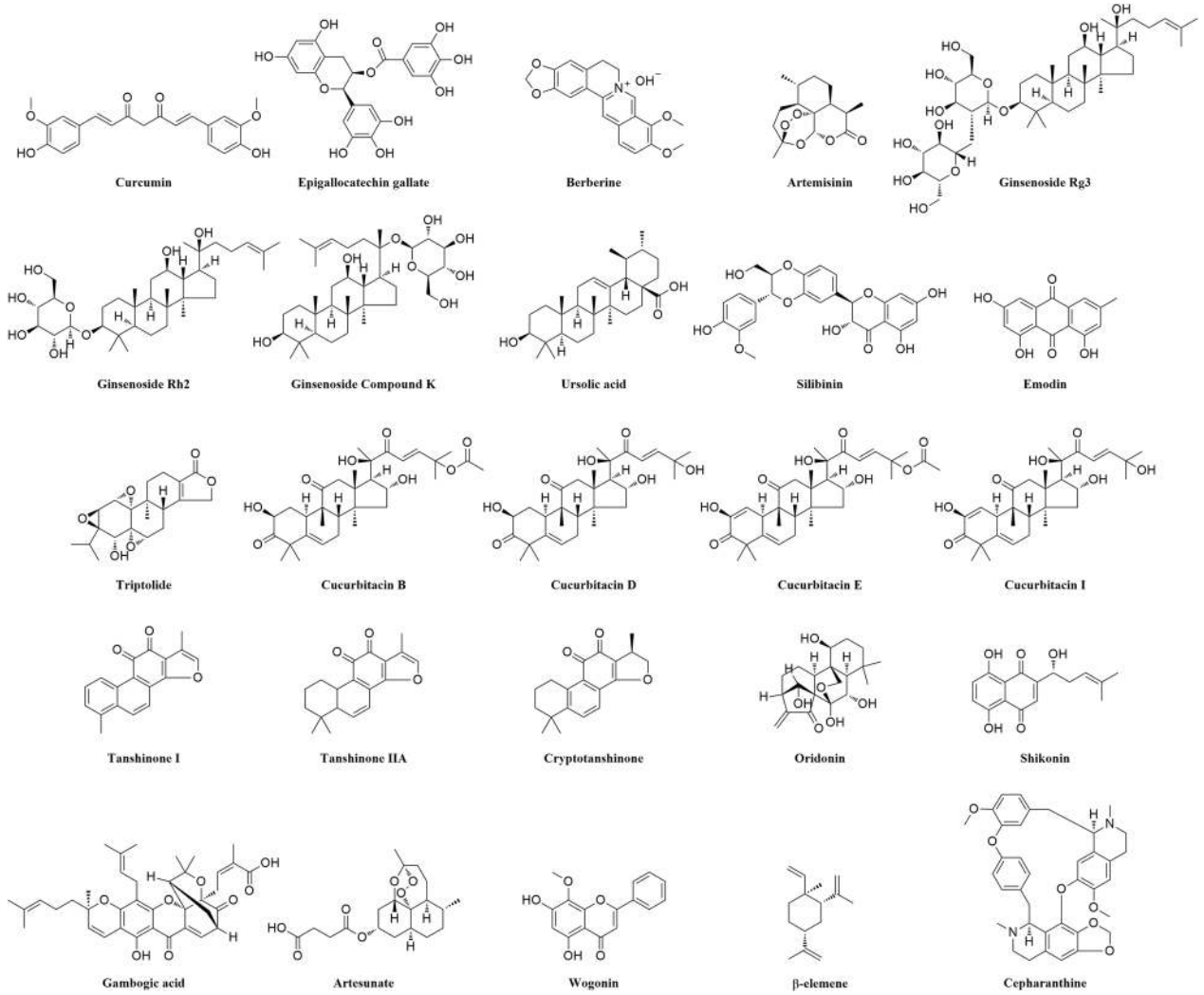

Fig. 2 Chemical structures of anti-cancer compounds from Chinese herbal medicine

(NF-κB), signal transducer and activator of transcription and cell cycle-related proteins [36–46]. Curcumin is shown to induce anti-cancer activities through the disruption of mitochondrial membrane potential and blockade at G2/M phase of the cell cycle in human epidermoid carcinoma A-431 cells [47]. In addition, mammalian target of rapamycin (mTOR) plays a vital role in curcumin-induced autophagy and apoptosis [30, 48–50]. Curcumin induces apoptosis and autophagy through the inhibition of phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway in human NSCLC A549 cells [30], while it induces autophagy by reducing Akt phosphorylation and mTOR in human melanoma A375 and C8161 cells [49].

Curcumin can also exert immunomodulatory effects against cancer cells. Theracurmin, a highly bioavailable form of curcumin, decreases pro-inflammatory cytokine secretion from activated T cells, and enhances T cell-induced cytotoxicity in human esophageal adenocarcinoma OE33 and OE19 cells, so it increases the sensitivity of the cells to T cell-induced cytotoxicity [51]. The natural killing (NK) cells can directly kill cancer cells, and curcumin can enhance the cytotoxicity effect of NK cells when NK cells are co-cultured with human breast cancer MDA-MB-231 cells, which is highly associated with signal transducer and activator of transcription 4 (STAT4) and signal transducer and activator of transcription 5 (STAT5) activation [52]. Besides, myeloid-derived suppressor cells (MDSCs) are immune-suppressive cells which are found in most cancer patients. Curcumin decreases interleukin (IL)-6 levels in the tumor tissues and serum of Lewis lung carcinoma (LLC)-bearing mice to impair the growth of MDSCs, so targeting MDSCs is

important for the treatment of lung cancer [13]. Moreover, the anti-tumor immune response of curcumin is mediated through increased cluster of differentiation (CD)8^+ T cell population and decreased regulatory T cell (T_{reg}) population in tongue squamous cell carcinoma [53–55].

In order to overcome the solubility issues of curcumin and facilitate its intracellular delivery, a curcumin-loaded nanoparticle, curcumin-PLGA-NP, is synthesized. It has a tenfold increase in water solubility compared to curcumin, and shows threefold increased anti-cancer activities in human breast cancer MDA-MB-231 and NSCLC A549 cells [56]. Another curcumin-capped nanoparticle exhibits promising anti-oxidative and selective anti-cancer activities in human colorectal cancer HT-29 and SW-948 cells [57]. Moreover, a curcumin analog, WZ35, has high chemical stability, and higher efficacy in anti-cancer effects compared to curcumin in human gastric cancer SGC-7901 cells and SGC-7901 xenograft mice [20]. Another analog, B63, induces cell death and reduces tumor growth through ROS and caspase-independent paraptosis in human gastric cancer SGC-7901, BGC-823 and SNU-216 cells, 5-fluorouracil-resistant gastric cancer cells, and SGC-7901 xenograft mice [58].

Curcumin can be used with other chemotherapeutic agents to achieve synergistic effects, reduce adverse effects and enhance sensitivity. Tamoxifen and curcumin are packed into a diblocknanopolymer, and this nanopolymer reduces the toxicity of tamoxifen in normal cells and exhibits better anti-proliferative and pro-apoptotic effects in human breast cancer tamoxifen-sensitive and -resistant MCF-7 cells [59]. Triptolide has strong liver and kidney toxicities, and when combined with curcumin, they exert synergistic anti-cancer effects in ovarian cancer, as well as reduce the side effects of triptolide [60]. In addition, adriamycin, sildenafil, 5-fluorouracil, irinotecan, doxorubicin, paclitaxel, sorafenib, Kruppel-like factor 4, emodin, docosahexaene acid and apigenin are shown to exhibit synergistic effects with curcumin [61–71]. Similarly, copper supplementation significantly enhances the anti-tumor effects of curcumin in several oral cancer cells [72], while epigallocatechin-3-gallic acid ester (EGCG) increases the ability of curcumin to inhibit cell growth and induce apoptosis in human uterine leiomyosarcoma SKN cells [73].

Clinical trials can confirm or reveal the effects, adverse reactions and pharmacokinetics of the drugs. As the bioavailability of curcumin is very poor, many curcumin preparations are synthesized and tested in clinical trials [74–76]. A phase I study was conducted to investigate the safety and pharmacokinetics of theracurmin in pancreatic and biliary tract cancer patients who failed with standard chemotherapy [76]. They administered theracurmin every day with standard gemcitabine-based chemotherapy. No new adverse effects and no increase in the incidence of adverse effects were observed among these patients. A pilot phase II study demonstrated encouraging results for the combination of docetaxel/prednisone and curcumin in patients with castration-resistant prostate cancer. It was found that 59% of patients had prostate-specific antigen response and 40% of patients achieved partial response. This study has provided additional evidence for a high response rate and better tolerability with the use of curcumin during cancer therapy [77].

Epigallocatechin gallate (EGCG)

EGCG, also known as epigallocatechin-3-gallate (Fig. 2), is the main polyphenol in green tea (*Camellia sinensis*). Epidemiological studies have indicated that consumption of green tea has potential impact of reducing the risk of many chronic diseases, such as cardiovascular diseases and cancer [78, 79]. EGCG possesses various biological effects including anti-obesity and anti-hyperuricemia, anti-oxidative, anti-viral, anti-bacterial, anti-infective, anti-angiogenic, anti-inflammatory and anti-cancer activities [80–84]. It is reported to present anti-cancer effects in variety of cancer cells, including lung, colorectal, prostate, stomach, liver, cervical, breast, leukemia, gastric, bladder cancers [85–90]. Among its anti-cancer activities, EGCG exhibits multiple pharmacological actions, including the suppression of cell growth, proliferation, metastasis and angiogenesis, induction of apoptosis, and enhancement of anti-cancer immunity [85, 86, 91–94].

EGCG can inhibit cell proliferation through multiple ways in many types of cancer cells. It inhibits cell proliferation in human bladder cancer SW-780, breast cancer MDA-MB-231 and NSCLC A549 cells, and inhibits tumor growth in gastric cancer SGC-7901 xenograft mice [89, 94, 95]. It also induces apoptosis in human oral cancer KB, head and neck cancer FaDu, NSCLC A549, and breast cancer MCF-7 cells [96, 97]. Besides, EGCG induces autophagy, and inhibition of autophagy can enhance EGCG-induced cell death in human mesothelimoa ACC-meso, Y-meso, EHMES-10, EHMES-1 and MSTO-211H, and primary effusion lymphoma BCBL-1 and BC-1 cells [98, 99]. In contrast, it induces cell death via apoptosis and autophagy in oral squamous cell carcinoma SCC-4 cells [84], so autophagy plays a dual role in EGCG-induced cell death. It can also suppress metastasis in human melanoma SK-MEL-5, SK-MEL-28, A375 and G361, NSCLC CL1-5, A549 and H1299 cells, and lung metastasis mice [85, 93, 100]. In addition, EGCG suppresses tumor angiogenesis in human NSCLC A549 cells and A549 xenograft mice [101].

EGCG mediates apoptosis which involves pro- and anti-apoptotic proteins in various cancer cells. It up-regulates pro-apoptotic proteins such as Bcl-2-associated X protein (Bax), and down-regulates anti-apoptotic proteins including B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra large (Bcl-xL) and survivin [97, 102–104]. ER stress also plays an important role in EGCG-induced cell death. EGCG inhibits endoplasmic reticulum (ER) stress-induced protein kinase R-like endoplasmic reticulum kinase (PERK) and eukaryotic translation-initiation factor 2α (eIF2α) phosphorylation [105]. Besides, poly (ADP-ribose) polymerase (PARP) 16 is shown to activate ER stress markers, PERK and inositol-requiring enzyme 1α (IRE1α) [106]. ER stress-induced apoptosis, PERK and eIF2α phosphorylation by EGCG are suppressed in PARP16-deficient hepatocellular carcinoma QGY-7703 cells, so EGCG mediates apoptosis through ER stress, which is dependent on PARP16 [105]. Similarly, EGCG causes 78-kDa glucose-regulated protein (GRP78) accumulation in the ER, which up-regulates ER stress markers such as activating transcription factor 4 (ATF-4), X-box binding protein 1 (XBP-1) and C/EBP homologous protein (CHOP), and shifts into pro-apoptotic ER stress, leading to increased caspase-3 and -8 activities [107]. Furthermore, it suppresses cell migration and invasion by blocking tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6), MMP-2/c-Jun N-terminal kinase (JNK) and transforming growth factor-β (TGF-β) pathways [85, 93, 100].

In addition to anti-cancer effects, EGCG shows a significant inhibitory effect on interferon-γ (IFN-γ)-induced indoleamine 2,3-dioxygenase (IDO) expression, an enzyme that guides cancer to regulate immune response, in human colorectal cancer SW-837 cells [108], so this suggests that EGCG might be useful for chemoprevention and colorectal cancer treatment, and could be a potential agent for anti-tumor immunotherapy. EGCG is also found to be a potential immune checkpoint inhibitor, which down-regulates IFN-γ-induced B7 homolog 1 (B7-H1) levels, an immunoglobulin-like immune suppressive molecule, in human NSCLC A549 cells [109].

Although EGCG has numerous biological activities through different pathways, its efficacy demonstrated in in vivo studies is not always consistent with the results of in vitro studies. This can be due to its low oil solubility, metabolic instability and poor bioavailability [110]. Therefore, EGCG analogs and EGCG-loaded nanoparticles by modifying EGCG are developed, and they have been reported to enhance anti-cancer effects [111–113]. The peracetate-protected (−)-EGCG, a prodrug of EGCG obtained by modifying the reactive hydroxyl groups with peracetate groups, is shown to increase the bioavailability of EGCG and inhibit angiogenesis in endometrial cancer xenograft mice [111]. Besides, EGCG-DHA (docosahexaenoic) ester, a lipophilic derivative of EGCG, shows improved anti-oxidative effects compared to EGCG, and suppresses colon carcinogenesis in mice [112, 113]. In the last decade, many studies were carried out using EGCG-loaded nanoparticles including FA-NPS-PEG and FA-PEG-NPS (epigallocatechin gallate-β-lactoglobulin nanoparticles), EGCG-SLN (solid lipid nanoparticle), DT-EGCG-nanoethosomes, FCS-EGCG-NPs (chitosan coated nanoparticles), EGCG-dispersed selenium nanoparticles, ^{198}AuNP-EGCg (gold nanoparticles), EGCG-loaded microspheres (EGCG/MS), and FCMPs (ferritin-chitosan Maillard reaction products) [6, 110, 114–121]. These EGCG nanoparticles can improve the targeting ability and efficacy of EGCG, which greatly promote the clinical application and development of EGCG analogs.

EGCG antagonizes toxicity induced by anti-cancer chemotherapeutic agents, and sensitizes chemo-resistant cancer cells. It also exerts synergistic effects with anti-cancer agents in various cancer cells, such as cisplatin, oxaliplatin, temozolomide, resveratrol, doxorubicin, vardenafil, curcumin, erlotinib [122–129]. EGCG can enhance the sensitivity of cisplatin through copper transporter 1 (CTR1) up-regulation, which results in the accumulation of cellular cisplatin and cisplatin–DNA adducts in human ovarian cancer SKOV3 and OVCAR3 cells, and the combination of EGCG and cisplatin suppresses tumor growth in OVCAR3 xenograft mice [122]. The combined low concentration of EGCG and curcumin remarkably inhibits cell and tumor growth in human NSCLC A549 and NCI-H460 cells, and A549 xenograft mice through cell cycle arrest [123].

To evaluate the tolerance, safety, pharmacokinetics and efficacy of EGCG in humans, clinical trials have been or are currently being conducted for cancer treatment. During a phase I clinical trial for the treatment of radiation dermatitis, patients with breast cancer received adjuvant radiotherapy and EGCG solution. It was found that the maximum dose (660 μM) of EGCG was well tolerated and the maximum tolerated dose was undetermined [130]. It was concluded that EGCG was effective for treating radiation dermatitis. Moreover, a phase II clinical trial was conducted to investigate the benefits of EGCG as a treatment for acute radiation-induced esophagitis (ARIE) for patients with stage III lung cancer. The oral administration of EGCG was shown to be effective and phase III clinical trial to study the potential effects of EGCG to ARIE treatment was anticipated [131].

Berberine

Berberine (Fig. 2) is an isoquinoline alkaloid mainly extracted from medicinal plants such as *Coptidis*

chinensis Franch., *Mahonia bealei* (Fort.) Carr., and *Phellodendron chinense* Schneid. [132]. Berberine has diverse pharmacological effects and is normally used for the treatment of gastroenteritis [133, 134]. It exhibits significant anti-cancer effects in a wide spectrum of cancers including ovarian, breast, esophageal, and thyroid cancers, leukemia, multiple myeloma, nasopharyngeal carcinoma, and neuroblastoma, through inducing cell cycle arrest and apoptosis, inhibiting metastasis and angiogenesis [135–143].

Berberine can induce cell cycle arrest in various cancer cells [137, 144, 145]. Berberine induces G1 and G2/M phase arrest in murine prostate cancer RM-1 cells, and G1 cell arrest by regulating cyclins D1 and E expressions in human HER2-overexpressed breast cancer cells [144, 145]. However, berberine induces G1 phase arrest in human estrogen receptor positive breast cancer MCF-7 cells but not in estrogen receptor negative MDA-MB-231 cells [137]. Besides, it inhibits cell proliferation by inducing apoptosis in human colorectal cancer HCT-8 cells [146]. In p53-null leukemia EU-4 cells, berberine induces p53-independent and X-linked inhibitor of apoptosis protein (XIAP)-mediated apoptosis, which is associated with mouse double minute 2 homolog (MDM2) and proteasomal degradation [135]. Mitochondrial-mediated apoptosis with Bcl-2-like protein 11 (Bim) up-regulation and Forkhead box O (FoxO) nuclear retention is vital in berberine-induced apoptosis [147]. In addition, berberine can induce autophagic cancer cell death through increased GRP78 levels and enhancing the binding ability of GRP78 to VPS34 in human colorectal cancer HCT-116 cells [148], whilst it induces autophagy through inhibiting AMPK/mTOR/UNC-51-like kinase 1 (ULK-1) pathway in human glioma U251 and U87 cells [149]. In contrast, berberine induces protective autophagy in human malignant pleural mesothelioma NCI-H2452 cells, and inhibition of autophagy promotes berberine-induced apoptosis [150]. Therefore, autophagy plays a dual role in berberine-induced apoptosis. Furthermore, berberine also inhibits tumor migration and invasion [143, 151]. It up-regulates plasminogen activator inhibitor-1 (PAI-1), a tumor suppressor that down-regulates urokinase-type plasminogen activator (uPA) and antagonizes uPA receptor to suppress metastasis in human hepatocellular carcinoma Bel-7402 and SMMC-7721 cells [143]. Berberine also inhibits epithelial mesenchymal transition through PI3K/Akt pathway in murine melanoma B16 cells, [151], and suppresses angiogenesis in glioblastoma U87 xenograft mice and HUVECs [152, 153].

Berberine interacts with diverse molecular targets as it binds to nucleic acids via specific deoxyribonucleic acid (DNA) sequences [154]. Several mechanisms have been identified for the anti-proliferative effects of berberine, including down-regulation of cyclins A, D, cyclin-dependent kinase (CDK) 1, CDK4, MMP-2 and janus kinase 2 (Jak2)/vascular endothelial growth factor (VEGF)/NF-κB/activator protein 1 (AP-1) pathway, and induction of autophagic cell death via mTOR signaling pathway [149, 155, 156]. Berberine also induces mitochondrial-mediated apoptosis through the loss of mitochondrial membrane potential, cytochrome c release, caspase and PARP activation, up-regulation of pro-apoptotic Bcl-2 family proteins, and down-regulation of anti-apoptotic Bcl-2 family proteins [150, 157–159]. It can also activate apoptosis-inducing factor to induce ROS-mediated cell death in pancreatic, breast, and colon cancers [158, 160, 161].

Immunotherapy has made great progress to cancer treatment over the past few years. Toll-like receptors (TLRs) can activate innate immune responses for host defense [162]. Berberine inhibits proto-oncogene tyrosine kinase Src activation and TLR4-mediated chemotaxis in lipopolysaccharide (LPS)-induced macrophages [163]. Besides, IDO1 inhibitors are promising candidates for cancer immunotherapy [164]. Berberine and its derivatives are shown to exhibit anti-cancer activity through cell killing by NK cells via IDO1 [165]. IL-8 is associated with metastasis, and berberine decreases IL-8 levels to inhibit cell growth and invasion in triple-negative breast cancer cells [166].

Berberine has low oral bioavailability as well as poor intestinal absorption [167]. As it has pronounced antimicrobial activity against gut microbiota, high dosage can translates into adverse events [168]. This limits the clinical use of berberine, and different approaches have been applied to improve the bioavailability of berberine. D-α-Tocopheryl polyethylene glycol 1000 succinate enhances the intestinal absorption of berberine by inhibiting P-gp activity in rats [167]. A self-microemulsifying drug delivery system is developed to improve the bioavailability of berberine, the bioavailability is increased by 2.42-fold [169]. Ber8, a 9-alkylated derivative of berberine, has better cytotoxicity and cellular uptake than berberine, and further inhibits cell proliferation and induces cell cycle arrest in different cell lines, including SiHa, HL-60, and A549 cells [170].

The combination of berberine and chemo- or radiotherapies provides synergistic anti-cancer effects [171, 172]. Taxol combined with berberine significantly slows down cell growth in human epidermal growth factor receptor 2 (HER2)-overexpressed breast cancer cells [145], while the combined administration of berberine and caffeine enhances cell death through apoptosis and necroptosis in human ovarian cancer OVCAR3 cells [173]. The combination therapy of berberine and niraparib, a PARP inhibitor, markedly enhances apoptosis

and inhibits tumor growth in ovarian cancer A2780 xenograft mice [174]. Therefore, combination of berberine with other therapies is a promising treatment for the alternative cancer therapy.

Previous pre-clinical research and animal studies have demonstrated the anti-tumor action of berberine hydrochloride. The people with a history of colorectal cancer might be at higher risk for adenomas, thus they are particularly suitable for the study of the chemopreventive effects of berberine hydrochloride in adenomas. A randomized, double-blind, placebo-controlled trial was designed to determine whether the daily intake of 300 mg of berberine hydrochloride could decrease the occurrence of new colorectal adenomas in patients with a history of colorectal cancer, and it is currently ongoing. Another phase II clinical trial of berberine and gefitinib is also ongoing in patients with advanced NSCLC and activating EGFR mutations.

Artemisinins

Artemisinin (Fig. 2) is a sesquiterpene peroxide derived from annual wormwood (*Artemisia annua* L.), which was originally used as Traditional Chinese Medicine for treating malaria and related symptoms such as fever and chills [175]. Since the 2015 Nobel Prize in Physiology or Medicine conferred to Chinese scientist, Youyou Tu, artemisinin drew attention to worldwide [176]. Beside from their well-established anti-malarial effects, artemisinin and its derivatives (ARTs), including dihydroartemisinin (DHA), artesunate, artemether and arteether, are also found to exhibit potent anti-cancer activities in many studies [177–182]. DHA and artesunate are the most studied ART derivatives for cancer treatment, and artesunate will be discussed in a separate section. The anti-cancer effects of ARTs are demonstrated in a broad spectrum of cancer cells including lung, liver, pancreatic, colorectal, esophageal, breast, ovarian, cervical, head and neck, and prostate cancers [183–191]. The anti-cancer activities of ARTs include induction of apoptosis and cell cycle arrest, inhibition of cell proliferation and growth, metastasis and angiogenesis [189, 192–195].

ART inhibits cell proliferation, migration and invasion, and induces apoptosis in human breast cancer MCF-7 cells [193, 196], while DHA suppresses cell growth through cell cycle arrest and apoptosis in human hepatocellular carcinoma HepG2 cells and HepG2 xenograft mice [178]. Similarly, ART induces apoptosis in murine mastocytome P815 cells and hamster kidney adenocarcinoma BSR cells, and inhibits tumor growth in P815 xenograft mice [177]. Moreover, autophagy plays a vital role in ART-mediated anti-cancer activities [190, 197–201]. DHA can induce autophagy-dependent cell death in human cervical cancer HeLa cells, cholangiocarcinoma KKU-452, KKU-023 and KKU-100, and tongue squamous cell carcinoma Cal-27 cells [190, 198, 199], while ART induces autophagy-mediated cell cycle arrest in human ovarian cancer SKOV3 cells [200]. DHA is also shown to induce autophagy by suppressing NF-κB activation in several cancer cells including RPMI 8226, NB4, HCT-116, and HeLa cells [202]. Furthermore, ART and DHA can also inhibit metastasis in various cancer cells such as non-small-cell lung carcinoma (NSCLC), ovarian and lung cancer cells [184, 189, 203]. Apart from apoptosis and metastasis, the inhibition of angiogenesis is also a crucial approach in cancer treatment. ART inhibits angiogenesis through mitogen-activated protein kinase (MAPK) activation in osteosarcoma [204], whilst DHA exerts strong anti-angiogenic effect by repressing extracellular signal–regulated kinase (ERK) and NF-κB pathways in human umbilical vein endothelial cells (HUVECs) and pancreatic cancer, respectively [194, 195].

In the past decades, studies have been focused on studying the anti-cancer mechanisms of ARTs, but there are contentions. ARTs inhibit cancer cell proliferation mainly by the induction of apoptosis through mitochondrial-dependent pathways [196, 205, 206]. ART mediates the release of cytochrome c and caspase-9 cleavage, leading to increased apoptosis in human breast cancer MCF-7 cells [196]. DHA induces apoptosis through Bcl-2 down-regulation in human cervical cancer HeLa and Caski cells [205], and via Bim-dependent intrinsic pathway in human hepatocellular carcinoma HepG2 and Huh7 cells [206]. Interestingly, ART is demonstrated to be an inhibitor of anti-cancer target, histone deacetylases (HDAC) [196]. In addition, another mechanism of killing tumor cells by ARTs is iron-dependent cell death called ferroptosis, a new form of cell death, so ferroptosis becomes an attractive strategy for cancer treatment [183, 207].

DHA can enhance the anti-tumor cytolytic activity of γδ T cells against human pancreatic cancer SW1990, BxPC-3 and Panc-1 cells [208], and ART also potentiates the cytotoxicity of NK cells to mediate anti-tumor activity [209]. Similarly, ART inhibits tumor growth through T cell activation and T_{reg} suppression in breast cancer 4T1 xenograft mice [188]. Therefore, this provides a novel strategy for treating pancreatic cancer with immunotherapy.

ART has poor water solubility and bioavailability. In order to solve this issue, ART is encapsulated into micelles by nanoprecipitation to form ART-loaded micelles [210]. The ART-loaded micelles enhance the drug exposure time and accumulation in breast cancer 4T1 xenograft mice, and shows specific toxicity in human and murine breast cancer MCF-7 and 4T1 cells. A mitochondrial-targeting analog of ART is also synthesized to specifically target mitochondria for enhancing

the inhibition of cell proliferation in various cancer cells including HCT-116, MDA-MB-231, HeLa and SKBR3 cells [211]. Moreover, dimmers of ART are also synthesized by polyamine linkers, and they further inhibit cell proliferation in human breast cancer MCF-7 cells and angiogenesis in HUVECs [212].

Many studies show the synergistic effects of ARTs with other compounds or therapeutic approaches. The combined treatment of ART and resveratrol markedly inhibits cell proliferation and migration, and enhances apoptosis and ROS production in human cervical cancer HeLa and hepatocellular carcinoma HepG2 cells [213]. Similarly, the use of combined DHA and gemcitabine exhibits strong synergistic effects on the loss of mitochondrial membrane potential and induction of apoptosis in human NSCLC A549 cells [214]. DHA also reinforces the anti-cancer activity of chemotherapeutic agent, cisplatin, in cisplatin-resistant ovarian cancer cells [215]. Studies also demonstrate the enhancement of sensitivity by DHA in photodynamic therapy in esophageal cancer [182, 216]. Therefore, this suggests that ARTs could be potential anti-cancer agents.

The population pharmacokinetic properties of DHA were investigated using the plasma and saliva of breast cancer patients for long-term treatment (> 3 weeks) [217]. The salivary DHA concentration was proportionally correlated with the plasma DHA concentration, so saliva is a good use for monitoring DHA levels in the body. An artemisinin analog, Artenimol-R, was shown to improve clinical symptoms and tolerability in patients with advanced cervical cancer [218].

Ginsenosides

Ginsenosides (Fig. 2) are the main bioactive dammarane triterpenoids derived from the rhizomes of many plants including *Panax notoginseng* (Burk.) F. H. Chen, *Panax ginseng* and *Cinnamomum cassia* Presl., with various biological effects including anti-oxidative, anti-inflammatory, and anti-cancer activities [219–222]. Ginsenosides mainly exert anti-cancer effects in colorectal, breast, liver and lung cancers, through inhibiting cell proliferation and migration, angiogenesis, and reversing drug resistance [7, 223–230]. Ginsenoside Rg3, ginsenoside Rh2, and compound K are the primary bioactive compounds among ginsenosides for cancer prevention.

Ginsenoside Rg3 inhibits cell viability and induces cell apoptosis in human ovarian cancer HO8910 cells [231], hepatocellular carcinoma Hep1-6, HepG2 and SMMC-7721, breast cancer MCF-7, MDA-MB-231, MDA-MB-453 and BT-549, and NSCLC A549, H23 and Lewis lung carcinoma cells [232–238]. It induces cell cycle arrest at G1 phase in human melanoma A375, and multiple myeloma U266, RPMI 8226 and SKO-007 cells [239, 240], and inhibits cell migration in human colorectal cancer LoVo, SW-620 and HCT-116 cells [240]. Ginsenoside Rg3 can also modulate the tumor environment through inhibiting angiogenesis and enhancing anti-tumor immune responses [241]. Moreover, ginsenoside Rh2 exhibits anti-tumor activity in human NSCLC H1299 cells and H1299 xenograft mice, through the induction of ROS-mediated ER-stress-dependent apoptosis [242]. It also suppresses cell proliferation and migration, and induces cell cycle arrest in human hepatocellular carcinoma HepG2 and Hep3B cells, and inhibits tumor growth in HepG2 xenograft mice [243]. Compound K, an intestinal bacterial metabolite of ginsenosides, also induces cell cycle arrest and apoptosis in human colorectal cancer HCT-116 cells, and suppresses tumor growth in HCT-116 xenograft mice [244]. It also efficiently inhibits cell proliferation and induces apoptosis through mitochondrial-related pathways in human hepatocellular carcinoma MHCC97-H cells [245]. Furthermore, 20(S)-ginsenoside Rg3 induces autophagy to mediate cell migration and invasion in human ovarian cancer SKOV3 cells [246]. In contrast, it sensitizes NSCLC cells to icotinib and hepatocellular carcinoma cells to doxorubicin through the inhibition of autophagy [247, 248]. Besides, ginsenoside Rh2 inhibits cell growth partially through the coordination of autophagy and β-cateninin signaling in human heptocellular carcinoma HepG2 and Huh7 cells [249]. Compound K induces autophagy-mediated apoptosis through AMPK/mTOR and JNK pathways in human NSCLC A549 and H1975 cells [250], while it also induces autophagy and apoptosis through ROS and JNK pathways in human colorectal cancer HCT-116 cells [251]. Therefore, autophagy plays a dual role in cancer via different signaling routes.

In recent years, the potential anti-cancer mechanisms of ginsenoside Rg3 have been demonstrated in various cancer models, which include the inhibition of cell proliferation and induction of apoptosis via down-regulating PI3K/Akt, and activation of caspase-3 and -9 and Bcl-2 family proteins [234, 252], induction of cell cycle arrest by regulating CDK pathway [240], inhibition of metastasis through reducing the expressions of aquaporin 1, C–X–C chemokine receptor type 4 (CXCR4) and hypoxia-inducible factor 1α (HIF-1α) [253–255]. Moreover, 20(S)-ginsenoside Rh2 is shown to bind to recombinant and intracellular annexin A2 directly, and this inhibits the interaction between annexin A2 and NF-κB p50 subunit, which decreases NF-κB activation [256]. NF-κB is important in cell survival, and 20(S)-ginsenoside Rh2 can inhibit cell survival through NF-κB pathway. Furthermore, p53 also plays a vital role in ginsenoside-induced anti-cancer activities [244, 257, 258]. Ginsenoside Rh2 induces cell death through p53 activation

in human colorectal cancer HCT-116 and SW-480 cells [257], while ginsenoside Rg3 and compound K induces apoptosis and cell cycle arrest through p53/p21 up-regulation in human colorectal cancer HCT-116, SW-480 and HT-29, and gallbladder cancer NOZ and GBC-SD cells, respectively [244, 258].

For the promotion of immunity, ginsenoside Rg3 can enhance lymphocyte proliferation and T helper type 1 cell (Th1)-related cytokine secretion including IL-2 and IFN-γ in hepatacellular carcinoma H22-bearing mice, and inhibit tumor growth partly through the induction this cellular immunity [259]. Ginsenoside Rg3 can also down-regulate the levels of B7-H1 and B7 homolog 3 (B7-H3), immunoglobulin-like immune suppressive molecules, to modulate tumor microenvironment and enhance anti-tumor immunity, and these molecules are negatively associated with overall survival in colorectal cancer patients [241]. It also ameliorates cisplatin resistance by down-regulating B7-H1 levels and resuming T cell cytotoxicity in human NSCLC A549 and A549/DDP cells [260]. In addition, ginsenoside Rh2 can also enhance anti-tumor immunity in melanoma mice by promoting T cell infiltration in the tumor and cytotoxicity in spleen lymphocytes [261].

The combination of ginsenosides with other chemotherapeutic agents provides significant advantages for cancer treatment. Ginsenoside Rg3 alone demonstrates modest anti-angiogenic effects, and displays additive anti-angiogenic effects in B6 glioblastoma rats when combined with temozolomide [262]. When it is combined with paclitaxel, it enhances cytotoxicity and apoptosis through NF-κB inhibition in human triple-negative breast cancer MDA-MB-231, MDA-MB-453 and BT-549 cells [233].

Ginsenosides have a long history of use as traditional medicine to treat many diseases in China. Relatively few clinical studies have been performed in humans even-though ginseng products are widely recognized to have therapeutic effects when used alone or in combination with other chemotherapeutic agents. Therefore, clinical studies are needed to confirm the safety of such uses. A phase II clinical trial is conducting to assess the safety and efficacy of ginsenoside Rg3 in combination with first-line chemotherapy in advanced gastric cancer. Patients with advanced NSCLC and epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) mutation were recruited in a study that investigated the safety and efficacy of the combined therapy, ginsenoside Rg3 and EGFR-TKI. It was shown that this therapy increased progression-free survival, overall survival and objective response rate compared to EGFR-TKI alone [263]. In another study, the safety and efficacy of combined ginsenoside Rg3 and transcatheter arterial chemoembolization (TACE) were studied in patients with advanced hepatocellular carcinoma. The results showed that this therapy ameliorated TACE-induced adverse effects and prolonged the overall survival compared to the use of TACE alone [264].

Ursolic acid (UA)

As an ursane-type pentacyclic triterpenic acid, UA (Fig. 2) can be found in the berries and leaves of a series of natural medicinal plants, including *Vaccinium macrocarpon* Ait. (cranberry), *Arctostaphylos uva-ursi* (L.) Spreng (bearberry), *Rhododendron hymenanthes* Makino, *Eriobotrya japonica, Rosemarinus officinalis, Calluna vulgaris, Eugenia jambolana* and *Ocimum sanctum,* as well as in the wax-like protective coatings of fruits such as pears, apples and prunes [265]. UA has numerous biochemical and pharmacological effects including anti-inflammatory, anti-oxidative, anti-proliferative, anti-atherosclerotic, anti-leukemic, anti-viral, and anti-diabetic effects [266–272]. It also exerts anti-cancer activities in ovarian, breast, gastric, prostate, lung, liver, bladder, pancreatic, and colorectal cancers [273–281].

UA can be used as a potential therapeutic agent for the treatment of various cancers [281–289]. It induces apoptosis through both extrinsic death receptor and mitochondrial death pathways in human breast cancer MDA-MB-231 cells [289], and inhibits cell proliferation and induces pro-apoptosis in human breast cancer MCF-7 cells by FoxM1 inhibition [282]. UA also inhibits cell and tumor growth through suppressing NF-κB and STAT3 pathways in human prostate cancer DU-145 and LNCaP cells, and DU-145 xenograft mice [283], and induces apoptosis in human prostate cancer PC-3 cells [284]. Similarly, UA induces apoptosis and inhibits cell proliferation in human colorectal cancer HCT-15, HCT-116, HT-29 and Caco-2 cells [286, 287]. UA is also shown to induce autophagy to mediate cell death in murine cervical cancer TC-1 cells [290], and promote cytotoxic autophagy and apoptosis in human breast cancer MCF-7, MD-MB-231 and SKBR3 cells [291]. It also inhibits cell growth by inducing autophagy and apoptosis in human breast cancer cells T47D, MCF-7 and MD-MB-231 cells [279]. In contrast, UA induces autophagy, but the inhibition of autophagy enhances UA-induced apoptosis in human oral cancer Ca922 and SCC2095, and prostate cancer PC-3 cells [265, 292]. Therefore, autophagy plays a dual role in UA-induced apoptosis via different signaling pathways. In addition, UA inhibits tumor angiogenesis through mitochondrial-dependent pathway in Ehrlich ascites carcinoma xenograft mice [293].

Increasing evidence has linked the anti-cancer activities of UA to the activation of mitochondrial-dependent signaling pathways, including mitochondrial energy

metabolism, oxidative stress and p53-mediated mitochondrial pathways [289, 291, 293]. UA is demonstrated to have apoptosis-promoting and anti-proliferative capacities via modulating the expressions of mitochondrial-related proteins such as Bax, Bcl-2, cytochrome c and caspase-9 [289, 293]. It can also induce oxidative stress and disruption of mitochondrial membrane permeability to mediate apoptosis in human osteosarcoma MG63 and cervical cancer HeLa cells [294, 295]. In addition, p53 pathway also contributes to the anti-cancer effects of UA. UA induces apoptosis and cell arrest through p21-mediated p53 activation in human colorectal cancer SW-480 and breast cancer MCF-7 cells [296, 297], and this p53 activation is through inhibiting negative regulators of p53, MDM2 and T-LAK cell-originated protein kinase (TOPK) [297].

Studies have reported the cancer immunomodulatory activities of UA [279, 293]. UA down-regulates NF-κB to inhibit cell growth and suppress inflammatory cytokine levels including TNF-α, IL-6, IL-1β, IL-18 and IFN-γ in human breast cancer T47D, MCF-7 and MDA-MB-231 cells [279]. It also modulates the tumor environment by modulating cytokine production such as TNF-α and IL-12 in ascites Ehrlich tumor [293].

UA is insoluble in water, with poor pharmacokinetic properties including poor oral bioavailability, low dissolution and weak membrane permeability [298]. Some new drug delivery technologies have been developed to overcome these problems including the uses of liposomes [280, 299–302], solid dispersions [303], niossomal gels [304], and nanoliposomes [278]. Liposome is the most commonly used drug delivery system. A chitosan-coated UA liposome is synthesized with tumor targeting and drug controlled release properties, and has fewer side effects [302]. It enhances the inhibition of cell proliferation and tumor growth in human cervical cancer HeLa cells and U14 xenograft mice. Besides, a pH-sensitive pro-drug delivery system is also synthesized, and this pro-drug enhances cellular uptake and bioavailability of UA [305]. It further inhibits cell proliferation, cell cycle arrest and induces apoptosis in human hepatocellular carcinoma HepG2 cells.

UA can also be used in combination with other drugs. The combined treatment of zoledronic acid and UA enhances the induction of apoptosis and inhibition of cell proliferation through oxidative stress and autophagy in human osteosarcoma U2OS and MG63 cells [306], whilst the combination of UA and curcumin inhibits tumor growth compared to UA alone in skin cancer mice [307]. Moreover, UA combined with doxorubicin enhances the cellular uptake of doxorubicin, and reverses multi-drug resistance (MDR) in human breast cancer MCF-7/ADR cells [308].

A human clinical study was conducted to investigate the toxicity and pharmacokinetics of UA-liposomes (UAL) including dose-limiting toxicity and maximum tolerated dose in healthy adult volunteers and patients with advanced solid tumors [309]. UAL had manageable toxicities under the dose of 98 mg/m^2, as well as a linear pharmacokinetic profile, so it was suggested that UA could be developed as a potential and safe drug [309].

Silibinin

Silibinin (Fig. 2), one of the flavonoids isolated from *Silybum marianum* L. Gaertn, is commonly exploited for the treatment hepatic diseases in China, Germany and Japan. In addition, silibinin is also found to display various biological activities including anti-oxidative, anti-proliferative, anti-bacterial, anti-fungal, neuro-protective, anti-leishmanial, anti-osteoclastic and anti-metastatic activities [310–317]. Previous studies have reported that silibinin exerts remarkable effects in numerous cancers such as renal, hepatocellular and pancreatic carcinoma, bladder, breast, colorectal, ovarian, lung, salivary gland, prostate and gastric cancers, through the induction of apoptosis, inhibition of tumor growth, metastasis and angiogenesis [318–328].

Silibinin suppresses epidermal growth factor-induced cell adhesion, migration and oncogenic transformation through blocking STAT3 phosphorylation in triple negative breast cancer cells [329]. It strongly suppresses cell proliferation and induces apoptosis in human pancreatic cancer AsPC-1, BxPC-3 and Panc-1 cells, and induces cell cycle arrest at G1 phase in AsPC-1 cells [330]. It can also induce apoptosis via non-steroidal anti-inflammatory drug-activated gene-1 (NAG-1) up-regulation in human colorectal cancer HT-29 cells [331], and induces mitochondrial dysfunction to mediate apoptosis in human breast cancer MCF-7 and MDA-MB-123 cells [332]. Moreover, silibinin induces autophagic cell death via ROS-dependent mitochondrial dysfunction in human breast cancer MCF-7 cells [333]. In contrast, it induces autophagy to exert protective effect against apoptosis in human epidermoid carcinoma A-431, glioblastoma A172 and SR, and breast cancer MCF-7 cells [334–336], and autophagy inhibition enhances silibinin-induced apoptosis in human prostate cancer PC-3 cells [337]. Silibinin also induces autophagy to inhibit metastasis in human renal carcinoma ACHN and 786-O cells, and salivary gland adenoid cystic carcinoma cells [317]. Therefore, autophagy plays a dual role in silibinin-induced anticancer effects. In addition, silibinin inhibits angiogenesis in human prostate cancer PCa, LNCaP and 22Rv1 cells [327].

Silibinin exhibits anti-cancer activities mainly due to the cell cycle arrest [330, 338–341]. It induces G1 phase

arrest in human pancreatic cancer SW1990 and AsPC-1, and breast cancer MCF-7 and MCF-10A cells [330, 339, 340], whilst it causes G2 phase arrest in human cervical cancer HeLa, and gastric cancer MGC-803 and SGC-7901 cells [338, 341]. It also decreases the expressions of CDKs such as CDK1, CDK2, CDK4 and CDK6 that are involved in G1 and G2 progression [338, 339]. Besides, silibinin suppresses metastasis through ERK1/2 and MMP-9 down-regulation in human thyroid cancer TPC-1, breast cancer MCF-7, renal carcinoma ACHN, OS-RC-2 and SW-839, and epidermoid carcinoma A-431 cells [342–344]. In addition, silibinin induces apoptosis and inhibits proliferation through the suppression of NF-κB activation [345–348]. On the other hand, silibinin is shown to induce apoptosis through the promotion of mitochondrial dysfunction, including increased cytochrome c and Bcl-2 levels, the loss of mitochondrial membrane potential, and decreased adenosine triphosphate (ATP) levels [332, 333, 349, 350].

Silibinin has immunomodulatory effects in cancer and immunity. The MDSCs are associated with immunosuppression in cancer, and silibinin increases the survival rate in breast cancer 4T1 xenograft mice, and reduces the population of MDSCs in their blood and tumor [351]. There was also a reduction in macrophage infiltration and neutrophil population in silibinin-treated prostate cancer TRAMPC1 xenograft mice [352]. These studies suggest a role of immunity in its anti-tumor effects.

Silibinin has poor water solubility and bioavailability, so it limits its efficacy in anti-cancer activities [353]. Advanced technologies such as nanoprecipitation technique are used to solve this issue [325, 353–356]. Silibinin is encapsulated in Eudragit® E nanoparticles in the presence of polyvinyl alcohol, and these nanoparticles enhance apoptosis and cytotoxicity in human oral cancer KB cells [353]. The silibinin-loaded magnetic nanoparticles further inhibit cell proliferation in human NSCLC A549 cells [325], while silibinin-loaded chitosan nanoparticles enhances cytotoxicity compared to silibinin alone in human prostate cancer DU-145 cells [356].

The combination of silibinin and other drugs are used in cancer treatment to enhance the efficacy of anti-cancer effects [324, 357–359]. The combination of curcumin and silibinin enhances the inhibition of cell growth and reduction in telomerase gene expression compared to silibinin alone in human breast cancer T47D cells [357]. The mixture of luteolin and silibinin also shows synergistic effects on the attenuation of cell migration and invasion, and induction of apoptosis in human glioblastoma LN18 and SNB19 cells [358]. Silibinin and paclitaxel combination enhances apoptosis and up-regulates tumour suppressor genes, p53 and p21, in human ovarian cancer SKOV3 cells [324].

Silibinin has been widely used as anti-cancer drug in vitro and in vivo, and its combination with other therapies is a promising treatment for cancer, so clinical trials are needed to confirm its safety and efficacy in humans, and to develop as an anti-cancer drug.

Emodin

Emodin (Fig. 2) is an anthraquinone derivative isolated from many plants including *Rheum palmatum*, *Polygonum cuspidatum*, *Polygonum multiflorum*, and *Cassia obtusifolia*. It exhibits remarkable biological effects such as anti-inflammation, anti-oxidant, prevention of intrahepatic fat accumulation and DNA damage [360–366]. Many studies have shown that emodin can attenuate numerous cancers including nasopharyngeal, gall bladder, lung, liver, colorectal, oral, ovarian, bladder, prostate, breast, stomach and pancreatic cancers, through the inhibition of cell proliferation and growth, metastasis, angiogenesis, and induction of apoptosis [367–379].

Emodin suppresses ATP-induced cell proliferation and migration through inhibiting NF-κB activation in human NSCLC A549 cells [380], and induces apoptosis through cell cycle arrest and ROS production in human hepatocellular carcinoma HepaRG cells [381]. It also induces autophagy to mediate apoptosis through ROS production in human colorectal cancer HCT-116 cells [382]. Moreover, emodin can inhibit tumor growth and metastasis in triple negative breast cancer cells, and human colorectal cancer HCT-116 cells [383, 384], whilst it suppresses cell migration and invasion through microRNA-1271 up-regulation in human pancreatic cancer SW1990 cells [385]. In addition, emodin can also inhibit angiogenesis in thyroid and pancreatic cancers [386–388].

Emodin exerts anti-cancer effects through various mechanisms. It effectively suppresses cell proliferation through inhibiting estrogen receptor α (ERα) genomic and PI3K/Akt non-genomic pathways in human breast cancer MCF-7 and MDA-MB-231 cells [389]. Besides, mitochondria and ER stress also play an important role in mediating emodin-induced anti-cancer effects [381, 390–392]. Emodin induces apoptosis through the loss of mitochondrial membrane potential, modulation of Bcl-2 family proteins, and caspase activation in human colorectal cancer CoCa cells and hepatocellular carcinoma HepaRG cells [381, 390]. ER stress is activated in emodin-treated human osteosarcoma U2OS cells, and emodin-induced apoptosis is suppressed by ER stress inhibition with 4-phenylbutyrate (4-PBA) in human NSCLC A549 and H1299 cells [391, 393].

Emodin has immunomodulatory effects in cancer and immunity. It inhibits cell growth and metastasis through blocking the tumor-promoting feed forward loop between macrophages and breast cancer cells [394].

It also down-regulates CXCR4 to suppress C–X–C motif chemokine 12 (CXCL-12)-induced cell migration and invasion in hepatocellular carcinoma HepG2 and HepG3 cells [395]. In addition, emodin inhibits the differentiation of maturation of DCs [396], and can modulate macrophage polarization to restore macrophage homeostasis [397].

Aloe-emodin is a derivate of emodin, which exhibits superior bioactivities in some cancers. It can inhibit cell proliferation through caspase-3 and caspase-9 activation in human oral squamous cell carcinoma SCC-15 cells [398], and induce apoptosis in human cervical cancer HeLa and SiHa cells, which is associated with glucose metabolism [399]. Another derivative of emodin, rhein, can also induce apoptosis in human pancreatic cancer Panc-1 cells, and inhibit tumor growth in pancreatic cancer xenograft mice [400]. It also inhibits cell migration and invasion through regulating Rac1/ROS/MAPK/AP-1 signaling pathway in human ovarian cancer SKOV3-PM4 cells [401].

The combination of emodin and other chemotherapies is widely used for cancer treatment. Emodin can promote the anti-tumor effects of gemcitabine in pancreatic cancer [402–404]. It enhances apoptosis in human pancreatic cancer SW1990 cells, and further inhibits tumor growth in SW1990 xenograft mice, through suppressing NF-κB pathway [402, 403]. The combination of emodin and curcumin can also enhance the inhibition of cell proliferation, survival, and invasion in human breast cancer MDA-MB-231, MDA-MB-435 and 184A1 cells [64]. Moreover, emodin enhances cisplatin-induced cytotoxicity through ROS production and multi-drug resistance-associated protein 1 (MRP1) down-regulation in human bladder cancer T24 and J82 cells [405].

Emodin has been shown to have remarkable anti-cancer effects in vitro and in vivo, and its combination with other therapies is very effective in treating cancer, therefore it is important to evaluate the safety and efficacy of emodin as an anti-cancer drug as the next step.

Triptolide

Triptolide (Fig. 2) is a natural constituent derived from the root of a traditional Chinese medicine, *Tripterygium wilfordii* Hook. F., which possesses diverse effects including anti-inflammatory, anti-oxidative, and anti-cancer activities [60, 406, 407]. For cancer therapy, it has been used to treat breast, lung, bladder, liver, colorectal, pancreatic, ovarian, stomach, prostate, cervical, and oral cancers, melanoma, myeloma, leukemia, neuroblastoma, osteosarcoma, lymphoma, renal, nasopharyngeal, and endometrial carcinoma, through apoptosis, cell cycle arrest, inhibition of cell proliferation, metastasis and angiogenesis [406, 408–426].

Various effects have been disclosed as key contributions to the anti-cancer effects of triptolide. Triptolide is shown to exhibit pro-apoptosis effects in various cancers [427–431]. It induces mitochondrial apoptotic pathway to mediate apoptosis in Burkitt's lumphoma Raji, NAMALWA and Daudi cells, and inhibits tumor growth in Daudi xenograft mice [432], and inhibits cell proliferation through microRNA-181a up-regulation in human neuroblastoma SH-SY5Y cells [433]. Moreover, triptolide induces autophagy to induce apoptosis and inhibit angiogenesis in human osteosarcoma MG63 cells, and breast cancer MCF-7 cells [431, 434]. In contrast, triptolide induces protective autophagy through calcium (Ca^{2+})/calmodulin-dependent protein kinase kinase β (CaMKKβ)-AMPK pathway in human prostate cancer PC-3, LNCaP and C4-2 cells, and through Akt/mTOR down-regulation in human cervical SiHa cells [420, 435]. Therefore, autophagy plays a dual role in triptolide-induced anti-cancer effects. In addition, triptolide is able to inhibit cell migration and invasion in human prostate cancer PC-3 and DU-145 cells, and in tongue squamous cell carcinoma SAS cells co-inoculated with human monocytes U937 cells [417, 419]. Furthermore, triptolide also possesses anti-angiogenic effect by inhibiting VEGFA expression in human breast cancer MDA-MB-231 and Hs578T cells, and through COX-2 and VEGF down-regulation in human pancreatic cancer Panc-1 cells [436, 437].

Triptolide is a natural substance, which exerts its anti-cancer effects through multiple targets. Triptolide is shown to induce mitochondrial-mediated apoptosis in various cancer cells, through decreased mitochondrial membrane potential, Bax and cytochrome c accumulation, PARP and caspase-3 activation, decreased ATP levels, and Bcl-2 down-regulation [432, 438–441]. Moreover, ERK is also shown to be important in mediating triptolide-induced anti-cancer activities. Triptolide induces apoptosis through ERK activation in human breast cancer MDA-MB-231 and MCF-7 cells [434, 442], and ERK activation leads to caspase activation, Bax up-regulation and Bcl-xL down-regulation [442]. On the other hand, it can also inhibit metastasis through ERK down-regulation in esophageal squamous cell cancer KYSE180 and KYSE150 cells, and murine melanoma B16F10 cells [443, 444]. Interestingly, ERα is shown to be a potential binding protein of triptolide and its analogues [445]. In addition, triptolide-induced metastasis is shown to be through MMP-2 and MMP-9 down-regulation in human neuroblastoma SH-SY5Y cells, via decreased MMP-3 and MMP-9 expressions in T-cell lymphoblastic lymphoma cells, and through MMP-2, MMP-7 and MMP-9 down-regulation in human prostate cancer PC-3 and DU-145 cells [417, 423, 433].

Indeed, immunology has been frequently validated to be associated with cancer. The combined use of triptolide and cisplatin enhances the plasma levels of IL-2 and TNF-α in ovarian cancer SKOV3/DDP xenograft mice, which can promote the differentiation of T cells and inhibit tumorigenesis respectively, thus resulting in an inflammatory microenvironment and leading to cancer cell death [446].

The derivatives of triptolide are always needed to improve its ant-cancer therapy. Triptolide derivative, MRx102, shows positive effects on anti-proliferation and anti-metastasis through Wnt inhibition in human NSCLC H460 and A549 cells, and H460 xenograft mice [447]. Minnelide, a water-soluble pro-drug of triptolide, can inhibit tumor growth in pancreatic cancer MIA PaCa-2 xenograft mice. Meanwhile, the combination of minnelide and oxaliplatin further inhibits tumor growth [448]. Moreover, triptolide is poorly soluble in water and exhibits hepatotoxicity and nephrotoxicity, selective delivery is an effective strategy for further application in cancer treatment. Triptolide loaded onto a peptide fragment (TPS-PF-$A_{299-585}$) is specifically targeted to the kidney and with less toxicity [449]. Some modified triptolide-loaded liposomes are reported to contribute a targeted delivery with lower toxicity and better efficacy in lung cancer treatment [450]. Similarly, triptolide-loaded exosomes enhances apoptosis in human ovarian cancer SKOV3 cells [451].

Triptolide has some side effects in various organs because of excessive dosage, so researchers have been looking for alternative triptolide therapies, and combination therapy has become a hot spot. Triptolide combined with gemcitabine markedly enhances pro-apoptosis through Akt/glycogen synthase kinase 3β (GSK3β) pathway in human bladder cancer EJ and UMUC3 cells [452]. Triptolide plus ionizing radiation synergistically enhances apoptosis and anti-angiogenic effects through NF-κB p65 down-regulation in human nasopharyngeal carcinoma cells and xenograft mice, which provides a new chemotherapy to advanced nasopharyngeal malignancy [425]. The combined therapy of triptolide and 5-fluorouracil further promotes apoptosis and inhibits tumor growth through down-regulating vimentin in human pancreatic cancer AsPC-1 cells and AsPC-1 xenograft mice [453]. Besides, low concentration of triptolide potentiates cisplatin-induced apoptosis in human lung cancer HTB-182, A549 and CRL-5810 and CRL-5922 cells [454], and triptolide with cisplatin synergistically enhances apoptosis and induces cell cycle arrest in human bladder cancer cisplatin-resistant cells [409].

Triptolide has wide-spectrum activities in pre-clinical studies, but it has strong side effects and water insolubility, so it is not used in clinical studies. However, some of its derivatives and analogs have been used in clinical studies to test the safety and efficacy on anti-cancer effects [432, 455–457]. Omtriptolide, a derivative of triptolide, is highly water soluble, and a phase I clinical trial was conducted in Europe with patients who had refractory and relapsed acute leukemia [432]. Another phase I clinical trial was completed in patients with refractory gastrointestinal malignancies to study the dose escalation and pharmacokinectics of minnelide, a pro-drug of triptolide [457]. The doses used were 0.16 to 0.8 mg/m^2 and they were well tolerated except from the common hematologic toxicity. LLDT-8, another triptolide derivative, has anti-cancer and immunosuppressive effects, and is going to proceed into phase II clinical trial to test its anti-cancer effects in China [455, 456]. Moreover, minnelide is currently under phase II clinical trial to test anti-cancer effects in patients with advanced pancreatic cancer [458].

Cucurbitacins

Cucurbitacins (Fig. 2) is a cluster of tetracyclic triterpenoids originated from various plants like *Bryonia, Cucumis, Cucurbita and Lepidium sativum*. Cucurbitacins A–T are twelve main curcurbitacins belonging to this family. Cucurbitacins have multiple therapeutic effects such as anti-inflammation, anti-proliferation, anti-angiogenesis, and anti-cancer [452, 459–462]. Besides, cucurbitacins have also been elucidated as a potential candidate for various cancer therapies, including oral cell carcinoma, breast, ovarian, prostate, lung, gastric, bladder, and thyroid cancers, neuroastoma, hepatoma, and osteosarcoma [463–475]. Most of cucurbitacins have been reported with various anti-cancer activities, such as pro-apoptosis, anti-angiogenesis, autophagy induction, and inhibition of metastasis [452, 460–462, 476].

Cucurbitacin B is the most abundant source of cucurbitacins which can explain why it receives more attention from researchers than other cucurbitacins do. It suppresses cell proliferation and enhances apoptosis in human NSCLC A549 cells, colorectal cancer SW-480 and Caco-2 cells [462, 477], and induces G1 phase cell cycle arrest in human colorectal cancer SW-480 and Caco-2, and gastric cancer MKN45 cells [477, 478]. Cucurbitacin D inhibits cell survival in human gastric cancer AGS, SNU1 and Hs746T cells [479], while cucurbitacin E induces cell cycle arrest at G2/M phase in triple negative breast cancer cells [480]. Moreover, cucurbitacins B, E and I are shown to induce autophagy, however inhibition of autophagy can enhance cucurbitacin-induced apoptosis [481–483]. They also inhibit cell migration and invasion in human breast cancer MDA-MB-231 and SKBR3, NSCLC H2030-BrM3 and PC9-BrM3, and colorectal cancer COLO-205 cells [484–487], as well as angiogenesis in HUVECs [461, 488].

Various targets have been demonstrated to be responsible for the anti-cancer effects of cucurbitacins. STAT3 signaling is a very common target for cancer treatment. Cucurbitacins B and D are reported to inhibit proliferation and induce apoptosis through STAT3 suppression in human NSCLC A549 cells and doxorubicin-resistant breast cancer MCF-7/ADR cells, respectively [462, 489]. On the other hand, cucurbitacin E induces cell arrest and apoptosis via STAT3 inhibition in human breast cancer Bcap-37 and MDA-MB-231 cells [468], and cucurbitacin I can inhibit STAT3 pathway to suppress cancer stem cell properties in anaplastic thyroid cancer ATC–$CD133^+$ cells [463]. Besides, cucurbitacin E induces cell cycle arrest through cyclins B1 and D1 down-regulation [480, 490], while cucurbitacin D inhibits cyclin B expression [491]. Moreover, mitochondria and ER stress also play an important role in cucurbitacin-induced anti-cancer effects. Cucurbitacins mediate apoptosis through mitochondrial-related pathway, which is characterized by the loss of the mitochondrial membrane potential, Bcl-2 down-regulation, Bax up-regulation, cytochrome c release, that eventually leads to caspase activation [470, 492]. Cucurbitacin I induces cell death through ER stress, by up-regulating ER stress markers such as IRE1α and PERK in human ovarian cancer SKOV3 cells and pancreatic cancer Panc-1 cells [493].

Cancer immunotherapy also plays a vital role in cucurbitacin treatment. Cucurbitacins may influence the production of cytokines and transcription factors that suppress the immune system, and these mechanisms may help to prevent the development of cancer. Cucurbitacin B is able to promote DC differentiation and anti-tumor immunity in patients with lung cancer [494]. The combined therapy of cucurbitacin I and recombinant IL-15 is also reported to exhibit immunologic anti-cancer activities in lymphoma with increased $CD4^+$ and $CD8^+$ T cell differentiation, and promote DC function through TNF-α up-regulation [495].

Although cucurbitacin B has very effective anti-tumor effects, it is shown to exhibit high toxicity, which restricts its clinical application on cancer therapy. Therefore, studies have been focused on tackling this side effect, and some cucurbitacin B derivatives have been synthesized to screen for effective cancer therapy with safety and tolerability. Compound 10b, one of the derivatives of cucurbitacin B, shows more potent anti-cancer activity than cucurbitacin B [496]. The in vivo acute toxicity study also shows that compound 10b has better tolerability and safety than cucurbitacin B. In addition, some other strategies have been applied to accelerate the clinical use of cucurbitacin B. The collagen peptide-modified nanomicelles with cucurbitacin B were synthesized to enhance the oral availability of cucurbitacin B, and these nanomicelles show a higher bioavailability and better tumor inhibition [497].

For a better cancer therapy, some combinations between cucurbitacins and other drugs have been employed. Low doses of cucurbitacin B or methotrexate cannot inhibit tumor growth in osteosarcoma xenograft mice, however when combined together, they synergistically inhibit tumor growth [498]. The combination therapy of cucurbitacin B and curcumin enhances apoptosis and reverses MDR in human hepatocellular carcinoma Bel-7402/5-Fu cells [499]. Recently, cucurbitacin B is suggested to be a potential candidate when it is applied with withanone, this combination can enhance cytotoxicity in human NSCLC A549 cells, and inhibit tumor growth and metastasis in A549 xenograft mice [500]. Cucurbitacin I is also shown to be a STAT3 inhibitor to mediate cell survival and proliferation, and when it is combined with irinotecan, and they further inhibit cell proliferation in human colorectal cancer SW-620 and LS174T cells [501].

The derivatives of cucurbitacins, cucurbitacin B-nanomicelles, and the combination therapies show promising treatment for cancer in vitro and in vivo, so clinical trials are needed to confirm their safety and efficacy in cancer treatment.

Tanshinones

Tanshinone (Fig. 2) is a derivative of phenanthrenequinone isolated from the dried root or rhizomes of *Salvia miltiorrhiza* Bunge. Tanshinone IIA is the primary bioactive constituent of tanshinones [502], which has various pharmacological effects, including anti-inflammatory, anti-cancer and anti-atherosclerotic activities, and cardiovascular protection [503–506]. Tanshinone exhibits anti-cancer activities in stomach, prostate, lung, breast, and colon cancers, through inducing cell cycle arrest, apoptosis, autophagy, and inhibiting cell migration [507–515].

Tanshinone IIA suppresses cell proliferation and apoptosis in numerous cancer cells, including human breast cancer BT-20, MDA-MB-453, SKBR3, BT-474, MCF-7 and MD-MB-231 [508, 516, 517], and gastric cancer MKN45 and SGC-7901 cells [518]. It also induces cell cycle arrest at G1 phase in human breast cancer BT-20 cells [517], and inhibits cell migration in human gastric cancer SGC-7901 cells [514], and cell migration and invasion in cervix carcinoma stemness-likes cells [519]. Tanshinone I and cryptotanshinone are two other major bioactive compounds, which also induce cytotoxicity against cancer cells. Tanshinone I induces apoptosis and pro-survival autophagy in human gastric cancer BGC-823 and SGC-7901 cells [510], while cryptotanshinone suppresses cell proliferation and induces cell cycle arrest at G1 phase in murine melanoma B16 cells, and

G2/M phase in melanoma B16BL6 cells [520]. In addition, tanshinones I and IIA and cryptotanshinone also inhibit tumor angiogenesis in endothelial and cancer cells [521–525]. Furthermore, tanshinone IIA induces autophagy to inhibit cell growth in human osteosarcoma 143B and MG63 cells and tumor growth in NOD/SCID mice [526], while it induces autophagy to mediate anticancer activities through activating beclin-1 pathway and inhibiting PI3K/Akt/mTOR pathway in human oral squamous cell carcinoma SCC-9, melanoma A375, and glioma U251 cells [527–529]. Moreover, tanshinone IIA is shown to exhibit anti-cancer activities through the interplay between autophagy and apoptosis in human prostate cancer PC-3 cells, mesothelioma H28 and H2452 cells [502, 530].

Tanshinone IIA induces apoptosis through mitochondrial- and caspase-dependent pathways, which includes caspase-3, -9 and PARP activation, cytochrome c release, and increased ratio of Bax/Bcl-2 in human gastric cancer MKN45 and SGC-7901 cells, and tumor-bearing mice [518]. It inhibits epithelial–mesenchymal transition by modulating STAT3-chemokine (C–C motif) ligand 2 (CCL2) pathway in human bladder cancer 5637, BFTC and T24 cells [531], and suppresses cell proliferation and migration via forkhead box protein M1 (FoxM1) down-regulation in human gastric cancer SGC-7901 cells [514]. On the other hand, tanshinone I induces apoptosis via Bcl-2 down-regulation in human gastric cancer BGC-823 and SGC-7901 cells [510], while cryptotanshinone induces apoptosis through mitochondrial-, cyclin- and caspase-dependent pathways in human NSCLC A549 and NCI-H460 cells [532], as well as via ER stress in human hepatocellular carcinoma HepG2 and breast cancer MCF-7 cells [533].

Tanshinone IIA is also shown to exhibit immunomdulatory effects in cancer [534]. The combination of tanshinone IIA with cyclophosphamide increases $CD4^+$ T cell, $CD4^+/CD8^+$ T cell and NK cell populations compared to single treatment in NSCLC Lewis-bearing mice, so it can improve the immunological function in lung cancer [534]. Furthermore, cryptotanshinone becomes a new promising anti-tumor immunotherapeutic agent [535]. It induces mouse DC maturation and stimulates IL-1β, TNF-α, IL-12p70 secretion in DCs, and enhances T cell infiltration and Th1 polarization in Lewis-bearing tumor tissues [535].

Tanshinone IIA has poor bioavailability, so a mixed micelle system is developed to form a tanshinone-encapsulated micelle [536]. This micelle has higher cytotoxicity and pro-apoptotic effects in human hepatocellular carcinoma HepG2 cells compared to tanshinone IIA alone. The tanshinone IIA-loaded nanoparticles improve the bioavailability tanshinone IIA and enhance its leukemic activity in human leukemia NB4 cells [537], while the nanoparticles containing tanshinone IIA and α-mangostin show increased cytotoxicity in human prostate cancer PC-3 and DU-145 cells [538].

Tanshinone IIA is shown to enhance chemosensitivity and its efficacy when combined with other therapeutic agents. Tanshinone IIA can be an effective adjunctive agent in cancer, and it enhances the chemosensitivity to 5-fluorouracil therapy in human colorectal cancer HCT-1116 and COLO-205 cells through NF-κB inhibition [539]. The combination of tanshinone IIA with doxorubicin does not only enhance the chemosensitivity of doxorubicin, but also reduces the toxic side effects of doxorubicin in human breast cancer MCF-7 cells [540]. In addition, tanshinone IIA and cryptotanshinone synergistically enhance apoptosis in human leukemia K562 cells [541].

The anti-cancer effects of Tanshinone IIA have been demonstrated in various cancers in vitro and in vivo, and it can enhance chemosensitivity and its efficacy is very effective when combined with other therapeutic agents. Up to now, the clinical trials of Tanshinone IIA are completed only for the treatment of other diseases [542], so well-designed clinical trials should be done to further confirm its safety and efficacy in cancer treatment.

Oridonin

Oridonin (Fig. 2) is an ent-kaurane diterpenoid isolated from *Rabdosia rubescens* (Hemsl.) Hara, which is also the main active constituent of *Rabdosia rubescens* (Hemsl.) Hara [543]. As an orally available drug, oridonin is demonstrated to have anti-cancer activities in multiple cancers over the past decades, including leukemia, lymphoma, osteosarcoma, myeloma, uveal melanoma, neuroblastoma, hepatocellular, laryngeal, esophageal, and oral squamous cell carcinoma, lung, colorectal, breast, gastric, pancreatic, and prostatic cancers [543–558]. The anti-cancer effects of oridonin are shown in many aspects, including the induction of cell apoptosis, autophagy, cell cycle arrest, and the suppression of angiogenesis, cell migration, invasion and adhesion [554, 559–564].

Oridonin induces apoptosis in human hepatocellular carcinoma HepG2 and Huh6, oral squamous cell carcinoma WSU-HN4, WSU-HN6 and CAL27, and laryngeal cancer HEp-2 cells [550, 559, 561, 565]. It also induces G2/M cell cycle arrest in human oral squamous cell carcinoma WSU-HN4, WSU-HN6 and CAL27, gastric cancer SGC-7901, prostate cancer PC-3 and DU-145, and breast cancer MCF-7 cells [555, 561, 566, 567]. Oridonin is also shown to induce autophagy in many cancer cells, which is associated positively or negatively with apoptosis. It induces autophagy to mediate apoptosis in human

NSCLC A549 and neuroblastoma SHSY-5Y cells [558, 568]. On the other hand, autophagy provides a protective role against oridonin-induced apoptosis, as autophagy inhibitor enhances oridonin-induced apoptosis in human cervical carcinoma HeLa, multiple myeloma RPMI 8266, laryngeal cancer HEp-2 and Tu212, and epidermoid carcinoma A-431 cells [569–572]. The anti-cancer effects of oridonin are also shown to be through suppressing angiogenesis and metastasis, which are the primary causes of tumor growth and metastasis. It can inhibit cell migration and invasion, and tube formation in human breast cancer 4T1 and MDA-MB-231, human and murine melanoma A375 and B16F10, osteosarcoma MG63 and 143B, and HUVECs, as well as tumor metastasis in HepG2 xenograft zebrafish and mice, 4T1 xenograft mice, and 143B xenograft mice [554, 562–564, 573].

Proteomic and functional analyses reveal that ER stress and poly(rC)-binding protein 1 (α-CP1) are potential pathways involved in the anti-proliferative and pro-apoptotic activities of oridonin [546]. Oridonin inhibits cell growth and induces apoptosis through ER stress and ASK1/JNK signaling pathways in human hepatocellular carcinoma Huh6 cells [559]. Besides, the mitochondrial redox change is proved to be a potential mediator for the pro-apoptosis effect of oridonin [565]. The anti-proliferative effect of oridonin is also shown to be associated with mitochondrial-mediated apoptosis, which is characterized by mitochondrial membrane potential reduction, subsequent cytochrome c release, PARP, caspase-3 and -9 activation, and decreased Bcl-2/Bax ratio [551, 565, 574, 575]. Oridonin also inhibits cell proliferation through bone morphogenetic protein 7 (BMP7)/p38 MAPK/p53 pathway in human colorectal cancer HCT-116 and SW-620 cells [553, 576, 577], and induces apoptosis via hydrogen peroxide (H_2O_2) production and glutathione depletion in human colorectal cancer SW-1116 cells [578]. Furthermore, the down-regulation of *AP-1* is reported to be the initial response to oridonin treatment, which decreases the expressions of NF-κB and MAPK to inhibit cell proliferation [579].

Oridonin possesses an immunosuppressive effect which modulates microglia activation, enhances T cell proliferation, alters the balance of Th1-T helper type 2 cells (Th2), reduces inflammatory cytokine secretion such as IL-2, IL-4, IL-6, IL-10 and TNF-α, and modulates an anti-inflammatory target, B lymphocyte stimulator [580]. It also decreases inflammatory cytokine secretion in human pancreatic cancer BxPC-3 cells, including IL-1β, IL-6 and IL-33 [581].

The derivatives and analogs of oridonin usually exhibit more potent anti-cancer activities than oridonin. Geridonin, a novel derivative of oridonin, inhibits cell growth and induces G2/M phase arrest through ROS production in human gastric cancer MGC-803 cells and MGC-803 xenograft mice [582]. Oridonin phosphate, another derivative, is reported to induce autophagy, which can enhance apoptosis in human breast cancer MDA-MB-436 cells [583]. A novel analog of oridonin, CYD 6-17, inhibits tumor growth in bladder cancer UMUC3 xenograft mice and renal carcinoma 786-O xenograft mice [584, 585]. In addition, drug delivery system is also developed to improve the bioavailability of oridonin. The inhalable oridonin-loaded microparticles exhibit strong pro-apoptotic and anti-angiogenic effects through mitochondrial-related pathways in NSCLC rats [586], whilst the oridonin-loaded nanoparticles enhance cellular uptake and exert better anti-cancer effects in human hepatocellular carcinoma HepG2 cells [587].

The combination of oridonin with other agents plays a potential role in cancer therapy. AG1478, a specific epidermal growth factor receptor (EGFR) inhibitor, augments oridonin-induced apoptosis through oxidative stress and mitochondrial pathways in human epidermoid carcinoma A-431 cells [588]. The combination of γ-tocotrienol and oridonin exerts synergistic anti-cancer effects in murine + SA mammary adenocarcinoma epithelial cells, which are mainly through the induction of autophagy [589]. Moreover, oridonin can enhance the pro-apoptotic activity of NVP-BEZ235 in human neuroblastoma SHSY-5Y and SK-N-MC cells through autophagy [558], whilst the combination of oridonin and cetuximab exhibits potent pro-apoptotic effect in human laryngeal cancer HEp-2 and Tu212 cells [572].

Clinical trials are essential to test the safety and efficacy of oridonin before drug approval. A derivative of oridonin, HAO472, is currently under a phase I clinical trial for the treatment of acute myelogenous leukemia in China [590].

Shikonin

Shikonin (Fig. 2) is an active naphthoquinone, which is derived from the dried root of *Lithospermum erythrorhizon*, *Arnebia euchroma* and *Arnebia guttata*, and it possesses anti-oxidative, anti-inflammatory, and anti-cancer activities [591–594]. It is effective in treating different kinds of cancers, including breast, prostate, ovarian and thyroid cancers, Ewing sarcoma, and myelomonocytic lymphoma [595–600]. Shikonin exerts anti-cancer effects mainly by inducing apoptosis, necroptosis, autophagy, cell cycle arrest, and by inhibiting cell proliferation, growth and metastasis [593, 601, 602].

Shikonin is reported to inhibit cell growth by inducing cell cycle arrest and promoting apoptosis in human NSCLC A549, gallbladder cancer NOZ and EHGB-1, esophageal cancer EC109, and epidermoid carcinoma A-431 cells [601, 603–605]. It can also induce necroptosis

via autophagy inhibition in human NSCLC A549 cells [593], and through ROS overproduction in human nasopharyngeal carcinoma 5-8F, and glioma SHG-44, U87 and U251 cells [606, 607]. Moreover, shikonin induces autophagy in human melanoma A375, pancreatic cancer BxPC-3, and hepatocellular carcinoma Bel-7402 and Huh7 cells [608–610]. However, autophagy provides a protective role in shikonin-induced apoptosis in human melanoma A375 cells [608]. In addition, shikonin can suppress metastasis by the inhibition of tyrosine kinase c-Met and integrin (ITG) β1 in human NSCLC A549 cells [602, 611].

There are multiple mechanisms involved in the anti-cancer effects of shikonin, including ER stress, ROS generation, glutathione (GSH) depletion, mitochondrial membrane potential disruption, p53, superoxide dismutase (SOD) and Bax up-regulation, PARP cleavage, catalase and Bcl-2 down-regulation [591, 612–614]. The pro-apoptotic effect of shikonin is also caused by the disruption of intracellular Ca^{2+} homeostasis and mitochondrial dysfunction, which involves enhanced Ca^{2+} and potassium (K^{+}) efflux, caspase-3, -8 and -9 activation, and Bcl-2 family protein modulation [615, 616]. ERK pathway also plays a role in shikonin-induced anti-cancer effects. Shikonin induces apoptosis and inhibits metastasis through suppressing ERK pathway in human NSCLC NCI-H460 and A549 cells, respectively [611, 617]. c-Myc down-regulation along with inhibition of ERK/JNK/MAPK and Akt pathways are also involved in shikonin-induced apoptosis and anti-proliferation in acute and chronic leukemia [618–620]. Moreover, the activation of necroptosis initiators, receptor interacting serine-threonine protein kinase (RIP) 1 and RIP3, by shikonin does not only contribute to DNA double strand breaks via ROS overproduction [621], but also facilitates glycolysis suppression via intracellular H_2O_2 production [622]. In addition, shikonin induces cell cycle arrest through p21 and p27 up-regulation, cyclin and CDK down-regulation [605]. Therefore, numerous pathways involved in shikonin-induced anti-cancer effects may explain the broad range of its activities.

Shikonin is also shown to modulate the function of the immune system. It can enhance the proliferation of NK cells and its cytotoxicity to human colorectal cancer Caco-2 cells by regulating ERK1/2 and Akt expressions [623]. It can also bind directly to heterogeneous nuclear ribonucleoprotein A1 to induce immunogenic cell death in human breast cancer MDA-MB-231 cells [624]. Shikonin is also reported to be used as an immunotherapy modifier in cell-based cancer vaccine systems, suggesting its potential application in cancer immunotherapy [625].

Derivatives are developed to enhance the anti-cancer and tumor targeting effects of shikonin. The naphthazarin ring of shikonin is modified to produce DMAKO-05, which can specifically target cancer cells instead of normal cells [626]. DMAKO-05 can also suppress cell survival in human colorectal cancer HCT-116 cells, and inhibits tumor growth in colorectal cancer CT-26 xenograft mice [627]. Besides, it inhibits cell proliferation and migration, and induces cell cycle arrest and apoptosis in murine melanoma B16F0 cells [626]. Another novel shikonin derivative, cyclopropylacetylshikonin, exhibits strong anti-tumor and pro-apoptotic effects in human melanoma WM164 and MUG-MEL2 cells [628]. In addition, drug delivery system is also developed to promote the intracellular delivery of shikonin. The shikonin-loaded nanogel enhances RIP1- and RIP3-dependent necroptosis in human osteosarcoma 143B cells [629]. There is an increased accumulation of shikonin-loaded nanogel in the tumor tissue, and this nanogel can further inhibit tumor growth and metastasis in 143B xenograft mice. Furthermore, the modified shikonin-loaded liposomes have higher cytotoxicity, and inhibit cell proliferation, metastasis in human breast cancer MDA-MB-231 cells [630].

The combination therapy is widely used to provide synergistic effects of anti-cancer activities. Shikonin can enhance the pro-apoptotic effect of taxol in human breast cancer MBA-MD-231 cells, and this combination improves mice survival and inhibits tumor growth in MDA-MB-231 xenograft mice [631]. Besides, shikonin can also potentiate the anti-cancer effects of gemcitabine through NF-kB suppression and by regulating RIP1 and RIP3 expressions in human pancreatic cancer [632, 633]. Shikonin is also reported to promote the efficacy of adriamycin in lung cancer and osteosarcoma [634, 635], and enhance sensitization to cisplatin in colorectal cancer [636]. Apart from the synergistic effect of shikonin, the combination of shikonin and paclitaxel reverses MDR in human ovarian cancer A2780 cells [10].

The single or combined therapies with shikonin show promising anti-cancer effects in vitro and in vivo, so preclinical data has confirmed its therapeutic use in cancer treatment, as a result, clinical trials will be carried out to further to confirm its safety and efficacy in humans.

Gambogic acid (GA)

GA (Fig. 2) is one of the major compounds derived from gambogethe resin exuded from Garcinia species including *G. hanburyi* and *G. Morella* [637]. It has multiple biological activities such as anti-oxidative, anti-inflammatory, and anti-cancer activities [638, 639]. Plenty of evidence shows that GA inhibits cell proliferation, invasion, survival, metastasis and chemoresistance, and induces angiogenesis in many types of cancers such as gastric and prostate cancers, leukemia,

multiple myeloma, osteosarcoma, and renal carcinoma through multiple signaling mechanisms [640–646].

Many studies have reported the anti-cancer effects of GA in human breast cancer [647–650]. GA at low concentrations (0.3–1.2 μM) can inhibit cell invasion without affecting cell viability, while high concentrations of GA (3 and 6 μM) can induce apoptosis via ROS accumulation and mitochondrial apoptotic pathway in human breast cancer MDA-MB-231 cells [651]. GA also induces apoptosis via ROS production in human bladder T24 and UMUC3 cells [652]. At earlier time points, GA induces ROS-mediated autophagy, which produces a strong cell survival response. However, at later time points, caspases are activated which degrade autophagic proteins and cell survival proteins, and this eventually induces apoptosis. Similarly, GA-induced autophagy via ROS provides a cytoprotective effect to human pancreatic cancer Panc-1 and BxPC-3 cells [653], and ROS scavenger, N-acetylcysteine, can reverse GA-induced autophagy in human NSCLC NCI-H441 cells [654]. Moreover, GA inhibits cell invasion and migration through reversion-inducing-cysteine-rich protein with kazal motifs (RECK) up-regulation in human NSCLC A549 cells and A549 xenograft mice [655], and prevents TNF-α-induced invasion in human prostate cancer PC-3 cells [656]. It also inhibits angiogenesis in HUVECs, and prevents tumor growth through the inhibition of tumor angiogenesis [657].

ROS-related pathways play a vital role in GA-induced cell death [642, 646, 647, 651–654, 658]. GA induces apoptosis mainly through ROS accumulation in human pancreatic cancer Panc-1 and BxPC-3, NSCLC NCI-H441, castration-resistant prostate cancer PCAP-1, melanoma A375, breast cancer MCF-7 cells [642, 646, 647, 653, 654]. It also induces oxidative stress-dependent caspase activation to mediate apoptosis in human bladder cancer T24 and UMUC3 cells [652]. Moreover, GA increases the expressions of ER stress markers such as GRP78, CHOP, activating transcription factor 6 (ATF-6) and caspase-12, and co-treatment with chemical chaperone, 4-PBA, significantly reduces these expressions and apoptosis in human NSCLC A549 cells, so it is suggested that GA induces ER stress to mediate apoptosis [659].

Previous studies have shown some immunomodulatory activities of GA [660, 661]. The activation of TLRs is important to initiate immune responses, and TLR4 forms a complex with myeloid differentiation factor 2 (MD2) to recognize its ligand, like LPS. GA is shown to reduce pro-inflammatory cytokine production in LPS-primed primary macrophages such as TNF-α, IL-1β, IL-6 and IL-12, and also inhibit the activation of TLR4 by disrupting the interaction of TLR4/MD2 complex with LPS [660]. Similarly, it also reduces pro-inflammatory cytokine production including TNF-α, IL-1β and IL-6 by suppressing p38 pathway in murine macrophage RAW 264.7 cells [661].

GA has low solubility, instability and poor pharmacokinetic properties [662]. In order to increase its water solubility, GA is conjugated with a cell-penetrating peptide, trans-activator of transcription, to form GA-TAT [658]. This GA-TAT enhances apoptosis through ROS accumulation in human bladder cancer EJ cells. Another study uses a co-polymer to encapsulate GA to form GA micelles [639]. These GA micelles have better cellular uptake which can further enhance apoptosis in human breast cancer MCF-7 cells and the anti-tumor effects in MCF-7 xenograft mice. Moreover, GA is encapsulated into the core of the nanoparticles to enhance the stability of GA and its circulation time [662]. These nanoparticles have tumor targeting properties, and enhance the anti-tumor activities of GA without inducing higher toxicity.

The combination of GA and other chemotherapy agents has been widely used to improve the therapeutic effects against various cancers such as osteosarcoma, pancreatic and lung cancers [639, 653, 663, 664]. Cisplatin resistance is a main clinical problem for the treatment of lung cancer, and the treatment of cisplatin with GA is shown to enhance apoptosis and decrease the cisplatin resistance index in human NSCLC cisplatin-resistance A549/DDP cells [663]. Moreover, GA and retinoic acid chlorochalcone are loaded into glycol chitosan nanoparticles to form RGNP [639]. The RGNP exhibits synergistic effects to inhibit cell proliferation and induces apoptosis in osteosarcoma. The combination of GA with doxorubicin synergistically reduces cell viability in human ovarian cancer platinum-resistance SKOV3 cells, and this combination also suppresses tumor growth in SKOV3 xenograft mice [665].

The safety and efficacy of GA at different dosages in patients with advanced malignant tumors have been compared in a phase IIa clinical trial [666]. GA had a safety profile at a dosage of 45 mg/m^2. The patients with GA administration on days 1–5 in a 2-week cycle showed a greater disease control rate and only Grades I and II adverse reactions. To further investigate the safety and efficacy of GA, a phase IIb clinical trial involving a larger sample size of patients would be needed.

Artesunate

Artesunate (Fig. 2) is a semi-synthetic compound derived from ART, which is widely used as an anti-malarial agent [667]. As an analog of ART, artesunate exerts better water solubility and higher oral bioavailability, due to its special structure with an additional hemisuccinate group that makes it a better candidate for cancer treatment [668]. The anti-cancer effects of artesunate have

been demonstrated in bladder, breast, cervical, colorectal, esophageal, gastric, ovarian and prostate cancer, renal carcinoma, leukemia, melanoma and multiple myeloma [179, 669–679]. Its anti-cancer effects include induction of cell cycle arrest and apoptosis, inhibition of cell proliferation and growth, metastasis and angiogenesis [670, 678, 680].

Artesunate can induce apoptosis in various cancers including human breast cancer MCF-7, MDA-MB-468 and SKBR3 cells, gastric cancer SGC-7901 and HGC-27, colorectal cancer HCT-116, and esophageal cancer Eca109 and Ec9706 cells [670, 672, 673, 681–683]. It also induces cell cycle arrest at ROS-dependent G2/M phase and ROS-independent G1 phase in human breast cancer MDA-MB-468 and SKBR3, and ovarian cancer HEY1 and HEY2 cells [670, 684], and induces G2/M cell cycle arrest through autophagy in human breast cancer MCF-7 and MDA-MB-231 cells [685]. Artesunate is also shown to induce autophagy to exert cytoprotective effects in human colorectal cancer HCT-116 cells, and the inhibition of autophagy enhances artesunate-mediated apoptosis [179]. Similarly, artesunate-induced mitophagy provides a protective effects against cell death in human cervical cancer HeLa cells [686]. Moreover, it inhibits cell invasion and migration in human prostate cancer DU-145 and LNCaP, cervical cancer Caski and HeLa cells, and uveal melanoma cells [675, 678, 687], and suppresses tumor angiogenesis in HUVECs and renal carcinoma 786-O xenograft mice [676, 680].

In most cases, the inhibition effects of artesunate against cancer cells are resulted from apoptosis. Artesunate induces apoptosis through cyclooxygenase-2 (COX-2) down-regulation in human bladder cancer T24 and RT4, and gastric cancer HGC-27 cells [669, 683]. Mitochondrial pathways also play an important role in artesunate-mediated anti-cancer effects [673, 681, 683]. Artesunate inhibits tumor growth through ROS- and p38 MAPK-mediated apoptosis in human rhabdomyosarcoma TE671 cells [688]. It also exerts anti-tumor activities through the loss of mitochondrial membrane potential, Bcl-2 down-regulation, Bax up-regulation, and caspase-3 activation in human gastric cancer SGC-7901 and HGC-27, esophageal cancer Eca109 and Ec9706 cells, and breast cancer MCF-7 xenograft mice [673, 681, 683]. In addition, gene expression analysis identifies that ER stress is the most relevant pathway for the anti-tumor activity of artesunate in B-cell lymphoma [689]. Interestingly, artesunate selectively inhibits cell growth through iron-dependent and ROS-mediated ferroptosis in human head and neck cancer HN9 cells [690].

Immunomodulation also plays a vital role in artesunate-mediated anti-cancer effects [671, 674, 691, 692]. Artesunate induces Th1 differentiation into $CD4^+$ T cells to mediate apoptosis in murine ovarian cancer ID8 cells [674]. It also exerts anti-tumor effects through suppressing NK killing activity and lymphocyte proliferation, which results in decreased TGF-β1 and IL-10 levels in colorectal cancer Colon-26 and RKO cells [691]. Besides, artesunate also exerts immunosuppression through forkhead box P3 (Foxp3) down-regulation in T cells and decreases prostaglandin E_2 (PGE_2) production in human cervical cancer Caski and HeLa cells [671]. Moreover, it enhances γδ T cell-mediated anti-cancer effect through augmenting γδ T cell cytotoxicity and decreasing TGF-β1 levels to reverse immune escape in human hepatocellular carcinoma HepG2 cells [692].

The treatment of artesunate with other therapies shows promising anti-cancer effects in several studies [693–697]. Artesunate and cisplatin synergistically induce DNA double-strand breaks and inhibit clonogenic formation to mediate cytotoxic effects in human ovarian cancer A2780 and HO8910 cells [693]. The combined treatment of artesunate and erlotinib enhances the inhibition of cell growth in human glioblastoma multiforme U87MG cells [694].

Clinical studies are carried out to investigate the safety and efficacy of artesunate in patients with colorectal and breast cancers, and advanced solid tumor malignancies [698–701]. A phase I study is performed to evaluate the safety and the maximum tolerated dose of artesunate in patients with metastatic breast cancer, the oral administration of artesunate is safe and 2.2–3.9 mg/kg per day is well tolerated [701]. Another phase I study is assessed in patients with advanced solid tumor malignancies, and the maximum tolerated dose of intravenous artesunate is 18 mg/kg [698]. The tolerability and anti-proliferative properties of oral artesunate are also shown in patients with colorectal cancer [699]. Moreover, a study of long term treatment with oral artesunate is performed in patients with metastatic breast cancer, 2.3–4.1 mg/kg per day treatment for up to 1115 cumulative days does not show any major safety concerns [700]. An ongoing phase II clinical trial is carried out to study the safety and effectiveness of neoadjuvant artesunate in patients with stage II or III colorectal cancer awaiting surgical treatment.

Wogonin

Wogonin (Fig. 2) is a plant flavonoid extracted from roots of *Scutellaria baicalensis*, *Scutellaria amoena* and *Scutellaria rivularis,* and stem of *Anodendron affine* Druce, and has many pharmacological effects including anti-viral, anti-oxidative, anti-inflammatory, anti-cancer and neuroprotective activities [702–705]. It has various anti-cancer effects in many cancers, including lung, breast, head and neck, gastric and colorectal cancers, glioma, leukemia, lymphoma, and osteosarcoma, through the induction

of apoptosis and cell cycle arrest, and inhibition of cell growth, migration, invasion, and angiogenesis [706–716].

Wogonin can induce apoptosis and inhibit cell proliferation in human neuroblastoma SK-N-BE2 and IMR-32, NSCLC A549, glioma U251 and U87, and hepatocellular carcinoma HepG2 and Bel-7402 cells [704, 706, 711, 717]. It also induces cell cycle arrest in human colorectal cancer HCT-116, NSCLC A549, chronic myelogenous leukemia imatinib-resistant K562, and ovarian cancer A2780 cells [716, 718–720]. Besides, wogonin induces autophagy in human pancreatic cells Panc-1 and Colo-357, and nasopharyngeal carcinoma NPC-TW076 and NPC-TW039 cells [721, 722]. However, inhibition of autophagy promotes wogonin-induced apoptosis in human nasopharyngeal carcinoma NPC-TW076 and NPC-TW039 cells [722]. It also inhibits metastasis in human hepatocellular carcinoma Bel-7402 and HepG2 cells, and NSCLC A549 cells [717, 723], and through MMP-9 suppression in human hepatocellular carcinoma MHCC97-L and PLC/PRF/5 cells [724]. In addition, wogonin also represses multiple myeloma-stimulated angiogenesis through c-Myc/von Hippel-Lindau tumor suppressor (VHL)/HIF-1α signaling pathway [725], LPS- and H_2O_2-induced angiogenesis through PI3K/Akt/NF-κB pathway [726, 727].

Mitochondrial dysfunction, oxidative stress and ER stress play important roles in wogonin-induced anti-cancer effects. Wogonin activates mitochondrial and ER stress-related pathways including the modulation of Bcl-2 family proteins, cytochrome c release, GRP78 and 94-kDa glucose-regulated protein (GRP94) accumulation, and caspase activation in human neuroblastoma SK-N-BE2 and IMR-32 cells, and induces mitochondrial dysfunction through IRE1α-dependent pathway [704]. ER stress markers and downstream pathways are also activated following wogonin treatment in human leukemia HL-60 and osteosarcoma U2OS cells, including IRE1α, PERK-eIF2α, ATF-6, CHOP, GRP94 and GRP78 [714, 728]. Wogonin also enhances ROS production in human glioma U251 and U87, pancreatic cancer Panc-1 and Colo-357, and NSCLC A549 cells [711, 721, 729]. Moreover, it inhibits cell growth and induces apoptosis through NF-κB suppression in Epstein–Barr virus-positive lymphoma cells [730], and suppresses cell proliferation and invasion through NF-κB/Bcl-2 and EGFR pathways in human hepatocellular carcinoma HepG2 and Bel-7402 cells [717].

Wogonin has immunomodulatory effects in cancer cells. It enhances the recruitment of DCs, T and NK cells into the tumor tissues in gastric cancer MFC xenograft mice, and also down-regulates the level of B7-H1, an immunoglobulin-like immune suppressive molecule, to promote anti-tumor immunity [731]. It also inhibits cell migration through modulating inflammatory microenvironment via IL-6/STAT3 pathway in human NSCLC A549 cells [723]. Moreover, immunization with wogonin-treated tumor cell vaccine effectively inhibits tumor growth in MFC xenograft mice [732]. Targeting TNF receptor with wogonin is also suggested to be a potential strategy for the treatment of chronic lymphocytic leukemia [712].

In order to enhance the accumulation and retention of wogonin in cancer cells, wogonin-conjugated Pt(IV) pro-drug is developed [733]. This pro-drug enhances the anti-proliferative and pro-apoptotic effects through casein kinase 2 (CK2)-mediated NF-κB pathway in human gastric cancer SGC-7901 and cisplatin-resistant SGC-7901/cDDP cells, and reverses cisplatin resistance in cisplatin-resistant SGC-7901/cDDP xenograft mice. It also further induces cell cycle arrest, enhances ROS production and apoptosis, and decreases mitochondrial membrane potential compared to wogonin in SGC-7901 cells [734]. LW-213, a derivative of wogonin, inhibits cell proliferation and induces cell cycle arrest in human breast cancer MCF-7 and MDA-MB-231 cells, and suppresses tumor growth in MCF-7 xenograft mice [735]. A synthetic wogonin derivative, GL-V9, inhibits metastasis in human breast cancer MDA-MB-231 and MCF-7 cells [736], and induces apoptosis and cell cycle arrest in human hepatocellular carcinoma HepG2 and gastric cancer cells MGC-803 cells [737–739]. Moreover, targeting cancer cells specifically is an important strategy in cancer therapy, so wogonin-loaded liposomes are synthesized [740]. These liposomes accumulate in the liver and prolong its retention time and exert better inhibitory effects than wogonin in human hepatocellular carcinoma HepG2 cells.

The combination therapy has been widely used to enhance the anti-cancer effects of wogonin. The combined treatment of wogonin and oxaliplatin synergistically inhibits cell growth in human gastric cancer BGC-823 cells and BGC-823 xenograft zebrafish, through nitrosative stress and disruption of mitochondrial membrane potential [741]. Wogonin also suppresses sorafenib-induced autophagy to exacerbate apoptosis in human hepatocellular carcinoma Hep3B and Bel-7402 cells [742], and augments cisplatin-induced apoptosis through H_2O_2 accumulation in human NSCLC A549 and cervical cancer HeLa cells [743].

As wogonin has various anti-cancer activities, it is currently under phase I clinical trial to test the safety and efficacy as an anti-cancer drug in China [734].

β-Elemene

β-Elemene (Fig. 2) is a sesquiterpene mixture isolated from various Chinese herbs such as *Curcuma wenyujin* Y. H. Chen *et* C. Ling, *Rhizoma zedoariae*, and *Curcuma*

Zedoary. It has various pharmacological effects including anti-oxidative, anti-inflammatory and anti-cancer activities [744–746]. It exerts anti-cancer effects in many cancers, such as lung, gastric, cervical, breast and bladder cancers, osteosarcoma, through apoptosis, inhibition of cell proliferation, migration and invasion, angiogenesis [746–752].

β-Elemene is shown to induce apoptosis in human cervical cancer SiHa, NSCLC A549 cells, primary bladder cancer cells, and Burkitt's lumphoma, and inhibit tumor growth in Lewis tumor-bearing mice [746, 747, 749, 753, 754]. It up-regulates insulin-like growth factor-binding protein 1 (IGFBP1) to induce a reciprocal interaction between microRNA 155-5p and FoxO3a, which leads to the inhibition of cell growth in human NSCLC A549 and H1975 cells [755]. β-Elemene also induces S phase arrest in human NSCLC A549 cells [754], while it induces G0/G1 phase arrest in human glioblastoma U87 cells [756]. Moreover, it induces protective autophagy in human gastric cells MGC-803 and SGC-7901, and NSCLC A549 cells, as autophagy inhibition promotes β-elemene-induced anti-tumor effects [748, 757]. However, autophagy inhibition attenuates β-elemene-induced apoptosis in human NSCLC cisplatin-resistant SPC-A-1 cells [758]. β-Elemene can also inhibit cell migration and invasion in human cervical cancer SiHa, murine breast cancer 4T1 and melanoma B16F10 cells [749, 752, 759], whilst it inhibits cell growth and metastasis through angiogenesis suppression in murine melanoma B16F10 cells [752]. In addition, β-elemene can reverse drug resistance in human NSCLC erlotinib-resistant A549/ER cells by inhibiting P-gp expression and P-gp dependent drug efflux [760].

β-Elemene exerts anti-tumor effects through phosphatase and tensin homolog (PTEN) up-regulation and Akt suppression in human primary bladder cancer cells [746]. It also inhibits cell proliferation and invasion, and induces apoptosis via inhibition of Wnt/β-catenin signaling pathway in human cervical cancer SiHa cells [749]. β-elemene-induced apoptosis is also shown to be through mitochondrial-related pathways, including p21 and Bax up-regulation, caspase-9 activation, Bcl-2 and survivin down-regulation [754]. On the other hand, it reverses drug resistance through mitochondrial-mediated apoptosis in human NSCLC cisplatin-resistant A549/DDP cells, via cytochrome c release, caspase-3 activation, Bcl-2 associated agonist of cell death (Bad) up-regulation and Bcl-2 down-regulation [761]. ER stress also plays a role in β-elemene-induced apoptosis. β-Elemene up-regulates ER stress markers to induce apoptosis in human NSCLC A549 cells, including PERK, IRE1α, ATF-6, ATF-4 and CHOP [747]. Moreover, it also enhances ROS production in human NSCLC A549 cells [747], and up-regulates HIF-1α expression via ROS to induce apoptosis in human osteosarcoma MG63 and Saos-2 cells [751].

β-Elemene has immunomodulatory effects in cancer and immune cells. It inhibits LPS-induced IL-6, TNF-α, IL-1β and IL-10 secretion, as well as inducible nitric oxide synthase in murine RAW264.7 marcophages [745]. M2 macrophages are regarded as tumor-associated macrophages, which can promote tumorigenesis [762]. β-Elemene can induce the polarization of M2 to M1 macrophages, and can also suppress M2 macrophage-treated conditioned medium-induced cell proliferation, migration and invasion in mouse lung cancer Lewis cells [762].

β-Elemene has poor water solubility, low oral bioavailability and severe phlebitis, so different delivery systems have been developed to solve these issues [763–765]. β-Elemene-loaded nanostructured lipid carriers are synthesized to enhance the intravenous delivery of β-elemene, and have higher bioavailiabity [763]. They inhibit tumor growth compared to β-elemene in hepatocellular carcinoma H22 xenograft mice. ETME, a novel β-elemene derivative, synergizes with arsenic trioxide to induce cell cycle arrest and apoptosis in human hepatocellular carcinoma SMMC-7721 cells, which is dependent on p53 [766]. Another β-elemene derivative, 13,14-bis(cis-3,5-dimethyl-1-piperazinyl)-β-elemene (IIi), is shown to inhibit cell proliferation in human gastric cancer SGC-7901 and cervical cancer HeLa cells, and inhibit tumor growth in sarcoma S-180 xenograft mice [767]. It also induces autophagy in human breast cancer MCF-7 cells, so it can be a potential anti-tumor agent.

The combination therapy is commonly used to enhance the efficacy of β-elemene for cancer treatment. β-Elemene when combined with cisplatin synergistically enhances apoptosis and inhibits cell proliferation in human gingival squamous cell carcinoma YD-38 cells and YD-38 xenograft mice [768]. β-Elemene potentiates the anti-proliferation effect of gefitinib as well as the induction of apoptosis and autophagy in human glioblastoma multiforme U251 and U87MG cells, through inhibiting EGFR signaling pathway [769]. It also reverses drug resistance in chemo-resistant breast cancer cells by reducing resistance transmission via exosomes [770], and enhances the sensitivity to TNF-related apoptosis-inducing ligand (TRAIL) partly through death-inducing signaling complex formation in human gastric cancer BGC-823 and SGC-7901 cells [771].

The Elemene Emulsion mainly containing β-elemene has been approved by China's State Food and Drug Administration, and now it is prescribed as an oral or injected drug to improve anti-cancer efficacy and reduce the side effects as adjuvant therapy.

Cepharanthine (CEP)

CEP (Fig. 2), a natural product derived from Chinese herbs such as *Stephania cepharantha* Hayata and *Stephania japonica*, is a cationic and amphipathic alkaloid that has been reported to decrease the fluidity of biological membranes [772]. With the presence of a 1-benzylisoquinoline moiety on alkyl chain, CEP belongs to a class of compounds called biscoclaurine alkaloids that have attracted significant attentions to pharmacologists and clinicians due to their resemblance to polypeptides [773]. CEP is widely used in Japan for the treatment of many acute and chronic diseases [773]. It exhibits antimalarial, anti-viral, anti-inflammatory, anti-metastatic, and anti-cancer activities in various cell lines and animal models [772, 774–776]. Among its anti-cancer activities, CEP exhibits multiple pharmacological actions, including apoptosis and radiation sensitization, inhibition of angiogenesis and metastasis, and reversing MDR [776–789].

CEP induces apoptosis and cell cycle arrest in many types of cancer cells [783–786, 790]. It induces autophagy to mediate apoptosis through suppressing Akt/mTOR signaling pathway in human breast cancer MCF-7 and MDA-MB-231 cells [785], and stimulates AMPK-mTOR-dependent autophagy to induce cell death in apoptosis-resistant cells [791]. In contrast, the inhibition of autophagy is an effective treatment for NSCLC, and CEP is identified as a novel autophagic inhibitor in human NSCLC NCI-H1975 cells [782]. It inhibits autophagy by preventing autophagosome–lysosome fusion and inhibiting lysosomal cathepsin B and cathepsin D maturation. Therefore, this suggests that autophagy plays a dual role in cancer via different signaling routes. Moreover, CEP is suggested to be a potential anti-angiogenic agent, it blocks angiogenesis in endothelial cells, zebrafish and xenograft mice by inhibiting cholesterol trafficking [777]. It can also suppress metastasis in a highly metastatic tumor, cholangiocarcinoma, and markedly inhibit cell migration in human cholangiocarcinoma KKU-M213 and KKU-M214 cells [776].

CEP has anti-tumor action mainly by inducing apoptosis and ROS production [783, 784, 786]. ROS is shown to be an important factor to determine cell fate, and it can be regulated by p21 [792]. CEP efficiently inhibits the growth of p53-mutated colorectal cancer cells that are often resistant to commonly used chemotherapeutic agents [783]. It also effectively induces cell cycle arrest and apoptosis through ROS production, p21 up-regulation, cyclin A and Bcl-2 down-regulation [783]. Similarly, CEP triggers apoptosis via ROS production and reducing mitochondrial membrane potential, thus inducing caspase-3 and PARP activation in human NSCLC H1299 and A549 cells [786]. It also exerts anti-tumor activity through ROS production and JNK activation in human choroidal melanoma MEL15-1 cells and xenograft mice [784]. In addition, CEP is also a potential anti-cancer drug for ovarian cancer by markedly increasing p21 expression and decreasing cyclins A and D levels in human ovarian cancer CaOV-3 and OVCAR3 cells [787].

CEP also plays an important role in immunity. It is shown to reduce IL-6 and TNF-α secretion in LPS-stimulated DCs, and inhibits LPS-stimulated DC maturation and antigen uptake by DCs [793]. CEP-treated DCs becomes a poor stimulator of allogeneic T cell activation and reduces IFN-γ production [793]. Therefore, it is suggested that CEP may have potential to be a cancer immunomodulatory agent.

Targeting P-gp using P-gp inhibitors is one of the main strategies to reverse MDR, and cepharanthine hydrochloride (CEH), a salt form of CEP, is suggested to be a potent P-gp inhibitor [779]. CEH exhibits MDR reversal potency in various cancer cells [779–781, 788]. CEH can reverse MDR-mediated cisplatin resistance in esophageal squamous cell carcinoma [780]. It increases the sensitivity of the cells and induces apoptosis via c-Jun activation, thus down-regulating P-gp and enhancing p21 levels. Similarly, CEH also reverses P-gp-mediated MDR through suppressing PI3K/Akt pathway in human ovarian cancer A2780/Taxol cells [788]. In addition, by reversing MDR, CEH induces cell cycle arrest and apoptosis in human nasopharyngeal carcinoma CNE-1 and CNE-2 cells [789].

In addition to chemotherapy, CEP may act as a radiosensitizer. Radiotherapy in the presence of CEP exhibits significant enhancement of tumor responses in human oral squamous cell carcinoma [778]. This pre-clinical data indicates that CEP has the potential to be used in clinical settings in combination with radiotherapy to treat oral squamous cell carcinoma. Moreover, paclitaxel and CEP co-loaded nano-particles also enhance the anti-cancer effects in human gastric cancer MKN45 cells and xenograft mice, suggesting that these nano-particles could be a potential formulation for gastric cancer [794]. In addition, CEP enhances the anti-cancer effects of dacomitinib in human NSCLC NCI-H1975 cells and NCI-H1975 xenograft mice [782], and cisplatin in lung and breast xenograft mice [777].

Although CEP has not yet been translated into clinical use for the treatment of cancer, the pharmacological activities and pre-clinical data support its significant clinical potential for anti-cancer therapy.

Conclusions

Chinese herbal medicine has played, and still plays, an important role in human health care in China and other Asian countries. Natural products orignianted from Chinese herbal medicine has also become a “hot topic” in anti-cancer research. Chinese herbal medicine is also recognized worldwide as a rich source for the discovery of novel drugs in the past decades. Table 1 illustrates the

Table 1 List of anti-cancer natural compounds from Chinese herbal medicines

Compounds	Origins	Cancer types	In vitro models	In vivo models	Anti-cancer effects	Underlying mechanisms	Dosage	Combinational agents	References
Curcumin	*Curcuma longa*, *Curcuma zedoaria*, *Acorus calamus* L.	Bladder cancer; breast cancer; cervical cancer; colorectal cancer; esophageal squamous cell carcinoma; gastrointestinal cancer; glioma; hepatocellular carcinoma; laryngeal cancer; lung cancer; leukemia; liver cancer; mesothelioma; neuroblastoma; oral squamous cell carcinoma; pancreatic cancer; prostate cancer; renal carcinoma; retinoblastoma	T24, RT4, MDA-MB-231, HeLa, SiHa, HCT-116, HT-29, RKO, HCT-15, DLD-1, EC1, EC9706, KYSE450, TE13, AGS, U87, T98G, HepG2, Tu212, A549, H1299, H460, H292, NCI-H520, NCI-H1373, NCI-H2170, K562, HL-60, PLC/PRF5, WRL68, Huh7, KMCH, RN5, N2a, SCC-25, Patu8988, Panc-1, C4-2, PC-3, LNCaP, VCaP, Caki, O-Rb50, Y79	BxPC-3-GemR xenograft mice; C4-2 xenograft mice; PC-3 xenograft mice; RN5 xenograft mice; U87 xenograft mice	Anti-angiogenesis; anti-metastasis; anti-proliferation; induces cell cycle arrest; inhibits cell viability; pro-apoptosis	Activates caspase-3, -9, PARP; Down-regulates Akt, Bcl-2, Bcl-xL, CTGF, cyclin D1, cyclin E1, ERK1/2, EZH2, FoxM1, GLI1, ITGA5, Jak1, JNK, MMP-2, Mcl-1, NF-κB, Notch1, p15, p16, p62, p70S6 K, ROCK1, RhoA, SHH, SSAT, STAT1, STAT3, Suz12, TROP2, vimentin, WT1, XIAP, YAP/TAZ; Enhances cytochrome c release, ROS accumulation; Inhibits CDK2 activity, PI3K/Akt/mTOR, SHH/GLI1, STAT3, TGF-β pathways; Up-regulates AIF, Bax, Bex-1, -2, -3, -4, -6, HIF-1α, microRNA-15a, microRNA-16-1, microRNA-99a, p21, p53, p73, PKD1, SMOX	0–5 μM; 0–15 μM; 0–16 μM; 0–20 μM; 0–25 μM; 0–40 μM; 0–50 μM; 0–125 μM; 10–40 μM; 15, 25 μM; 25 μM; 30 μM; 0–6 μg/ml; 5 mg/kg; 60 mg/kg; 200 mg/kg; 500 mg/kg; 25 μg/mouse	Gemcitabine; NVP-BEZ235; α-Tomatine	[12, 21, 795–814]
EGCG	*Camellia sinensis*	Biliary tract cancer; bladder cancer; breast cancer; cervical cancer; colorectal cancer; gallbladder cancer; gastric cancer; glioblastoma; head and neck cancer; lung cancer; nasopharyngeal carcinoma; NSCLC; oral cancer; pancreatic cancer; pheochromocytoma; prostate cancer; skin cancer	BDC, CCSW-1, EGI-1, SkChA-1, TFK-1, SW-780, MCF-7, 4T1, T47D, MDA-MB-231, MDA-MB-436, SUM-149, SUM-190, HeLa, DLD-1, HT-29, HCT-116, GBC, MzChA-1, MzChA-2, SGC-7901/FU, MGC-803/FU, AGS, C6, U251, SHG-44, U87, K3, K4, K5, CL1-5, CL1-0, TW01, TW06, NCI-H1299, A549, H460, SCC-9, MIA PaCa-2, Panc-1, PC-12, BCaPT1, BCaPT10, BCaPM-T10, LNCaP, A431, SCC13	4T1 xenograft mice; A549 xenograft mice; BCaPT10 xenograft mice; BCaPM-T10 xenograft mice; CL1-5 xenograft mice; Oral squamous cell carcinoma xenograft mice; PC-12 xenograft mice; SCG-7901/FU xenograft mice; SSC-9 xenograft mice; SUM-149 xenograft mice; SW-780 xenograft mice	Anti-angiogenesis; anti-metastasis; anti-proliferation; induces autophagy, cell cycle arrest; inhibits cell viability, epithelial–mesenchymal transition; pro-apoptosis	Activates caspase-3, -7, PARP; Down-regulates ABCG2, Akt, AXL, Bcl-2, Bcl-xL, E-cadherin, β-catenin, CDK2, CDK4, COX-2, CTTN, cyclin B1, cyclin D1, cyclin D2, cyclin D3, DNMT1, EGFR, ERα, ERK1/2, FAK, FN1, GSK3β, HDAC1, HER2, HSP90, IKKα, JNK, MDR-1, MGMT, MMP-2, MMP-9, NANOG, NF-κB, Notch, Oct-4, u-PA, paxillin, P-gp, PI3K, Raf-1, Snail, SOX2, Sp1, Src, STAT3, survivin, TFAP2A, Tyro3, VEGF, vimentin; Enhances cytochrome c release, ROS accumulation; Induces mitochondrial depolarization; Inhibits MAPK/ERK, PI3K/Akt pathways; Reduces ATP levels; Represses DNA replication; Up-regulates Bax, CK1α, endostatin, microRNA-16, p21, p53, TIMP-1, TIMP-2	0–20 μM; 0–40 μM; 0–50 μM; 0–100 μM; 0–200 μM; 0–400 μM; 2–100 μM; 10 μM; 20 μM; 25, 50, 100 μM; 40 μM; 50, 100 μM; 80 μM; 0–60 μg/ml; 10 mg/kg; 10–20 mg/kg; 15 mg/kg; 16.5 mg/kg; 20 mg/kg; 25 mg/kg; 25–100 mg/kg; 50 mg/kg; 0.025%, 0.05%; 0.06%	Bleomycin; Cisplatin; Curcumin; Docetaxel; 5-Fluorouracil; Oxaliplatin; Pterostilbene; Temozolomide	[93–95, 100, 101, 103, 123–125, 815–834]

Table 1 (continued)

Compounds	Origins	Cancer types	In vitro models	In vivo models	Anti-cancer effects	Underlying mechanisms	Dosage	Combinational agents	References
Berberine	*Coptidis cgubebsus* Franch., *Mahonia bealei* (Fort.) Carr., *Phellodendron chinense* Schneid	Breast cancer; cervical cancer; cholangiocarcinoma; colorectal cancer; endometrial carcinoma; esophageal squamous cancer; gastric cancer; glioblastoma; head and neck cancer; hepatocellular carcinoma; leukemia; lung cancer; medulloblastoma; melanoma; nasopharyngeal carcinoma; oral squamous cell carcinoma; osteosarcoma; ovarian cancer; pancreatic cancer; prostate cancer; skin cancer; uterine leiomyoma	MCF-7, MCF-7/HER2, MCF-7/TAM, MDA-MB157, MDA-MB231, MDA-MB453, BT20, BT549, Hs578T, T47D, SKBR3, BT474, HeLa, SiHa, QBC939, KKU-213, KKU-214, SW-480, SW-620, HT-29, DLD-1; HCT-116, LS174T, LoVo, Eca109, TE13, KYSE-70, EAC, SKGT4, AN3 CA, HEC-1-A, KLE, MGC-803, SGC-7901, AGS, BGC-823, MKN45, U87, U251, U118, SHG-44, FaDu, H22, Hepa1-6, HepG2, Bel-7404, Huh7, WRL68, MHCC97L, K562, A549, B16F10, HONE1, HK1-EBV, CNE-2, KB, U2OS, Panc-1, MIA PaCa-2, LNCaP, DU-145, LAPC-4, PC-3, 22RV1, C4-2B, C42, RM-1, A-431	22RV1 xenograft mice; A2780 xenograft mice; A549 xenograft mice; BGC-823 xenograft mice; Eca109 xenograft mice; H22 xenograft mice; HONE1 xenograft mice; LoVo xenograft mice; LNCaP xenograft mice; MDA-MB-231 xenograft mice; Medulloblastoma xenograft mice; MHCC97L xenograft mice; SGC-7901 xenograft mice; SW-620 xenograft mice; SiHa xenograft mice; U87 xenograft mice	Anti-angiogenesis; anti-proliferation; anti-metastasis; enhances radiosensitivity; induces autophagy, cell cycle arrest; inhibits cell viability, epithelial–mesenchymal transition; pro-apoptosis	Activates caspase-3, -7, -8, -9, PARP; Decreases mitochondrial membrane potential, catalase and superoxide dismutase activities; Down-regulates Akt, AR, Bcl-2, Bcl-xL, Bid, β-catenin, N-cadherin, CDK1, CDK2, CDK4, COX-2, PLA2, cyclin A1, cyclin B1, cyclin D1, cyclin E, DHCR24, DHFR, E2F1, EBNA1, EGFR, EF-Tu, ERK, Ezrin, FAK, FN, HER2, HIF-1α, HMGB1, HNF4α, ITGβ1, Jak2, JNK, Mcl-1, MEK, MMP-1, MMP-2, MMP-9, mTOR, c-Myc, NANOG, NF-κB, iNOS, occludin, Oct-4, p38, p50, p62, p100, p105, p70S6 K, paxillin, u-PA, PCNA, PDK1, PGE_2, PKC-α, PSA, PTEN, PTTG-1, RAD51, b-Raf, c-Raf, Septin-8, Slug, Snail, SOX2, Sp1, Src, STAT3, survivin, UQCRC1, VEGF, vimentin, Wnt5α, ZEBRA; Enhances cytochrome c release, ROS accumulation, SSAT activity; Induces DNA damage; Inhibits Akt/mTOR/p70S6 K/S6, arachidonic acid metabolic, androgen receptor pathways; Reduces NO production; Suppresses Hedgehog signaling pathway; Up-regulates ACC, AIF, AMPKα, Apaf-1, ATF-6, Bad, Bak, Bax, Beclin-1, Bim, E-cadherin, DR5, FasL, FoxO1, FoxO3a, GRP78, HRK, Lig4, MST1, p21, p27, p53, PHLPP2, SSAT, TIMP-2, TRAIL, ULK1	0–10 μM; 0–20 μM; 0–25 μM; 0–40 μM; 0–50 μM; 0–80 μM; 0–90 μM; 0–100 μM; 0–120 μM; 0–150 μM; 0–160 μM; 0–200 μM; 0–250 μM; 0–350 μM; 0–1000 μM; 10–80 μM; 15 μM; 20 μM; 50 μM; 0–1 μg/ml; 0–80 μg/ml; 5 mg/kg; 10 mg/kg; 12.5–50 mg/kg; 20 mg/kg; 50, 100 mg/kg; 50–200 mg/kg; 200 mg/kg; 0.01136 g/kg	Caffeine; Cetuximab; Doxorubicin; Erlotinib; *d*-limonene; Niraparib; Tamoxifen; Taxol; TRAIL	[139, 140, 144, 145, 147–149, 153, 171, 174, 835–870]

Table 1 (continued)

Compounds	Origins	Cancer types	In vitro models	In vivo models	Anti-cancer effects	Underlying mechanisms	Dosage	Combinational agents	References
Artemisinins	*Artemisia annua* L.	Breast cancer; cervical cancer; colorectal cancer; gallbladder cancer; gastric cancer; glioma; hepatocellular carcinoma; Ishikawa endometrial cancer; lung cancer; neuroblastoma; oral carcinoma; pancreatic cancer	MCF-7, MDA-MB-231, HeLa, HCT-116, SW-480, SW-620, GBC-SD, NOZ, MGC-803, C6, HepG2, Hep3B, SMMC-7721, Ishikawa, A375, A549, ASTC-a-1, H1299, BE(2) -C, SHEP1, SK-N-AS, SK-N-DZ, SCC25, RIN	A549 xenograft mice; BE(2)-C xenograft mice; C6 xenograft mice; GBC-SD xenograft mice; HCT-116 xenograft mice; HepG2 xenograft mice; NOZ xenograft mice	Anti-metastasis; anti-proliferation; induces apoptosis, autophagy, cell cycle arrest; inhibits cell viability	Activates caspase-3, -8, -9, PARP; Decreases mitochondrial membrane potential, MMP activity; Down-regulates Bcl-2, CDK2, CDK4, cyclin D1, cyclin E2, Dvl2, ERK1/2, LRP6, MMP-2, NANOG, Oct-4, p38, p62, SOX2, vimentin, Wnt5α/β; Enhances cytochrome c release, ROS accumulation; Induces DNA damage; Inhibits Wnt/β-catenin signaling pathway; Up-regulates Axin2, Bax, E-cadherin, β-catenin, NKD2, p16, TIMP-2	0–75 μM; 0–160 μM; 0–200 μM; 0–250 μM; 0–400 μM; 0–500 μM; 0–1000 μM; 0–1200 μM; 10–320 μM; 40–160 μM; 0–40 μg/ml; 10 mg/kg; 50 mg/kg; 60 mg/kg; 100 mg/kg	3CA; Halofuginone; Holotransferrin; Resveratrol	[184, 186, 213, 871–883]
Ginsenoside Rg3	*Panax notoginseng* (Burk.) F. H. Chen, *Panax ginseng*, *Cinnamomum cassia* Presl.	Breast cancer; colorectal cancer; esophageal carcinoma; gallbladder cancer; gastric cancer; glioblastoma; glioma; hepatocellular carcinoma; leukemia; lung cancer; melanoma; multiple myeloma; ovarian cancer; pancreatic cancer; prostate cancer	BT549, MDA-MB-231, MDA-MB-453, CT-26, HCT-116, LoVo, SW-480, SW-620, EC109, KYSE170, TE1, GBC-SD, Mz-ChA-1, QBC939, SGC-7901, U87MG, U87, Hep1-6, HepG2, Lewis, Jurkat, A549, A549/DDP, H23, H1299, A375, C8161, SK-MEL-28, RPMI 8226, SKO-007, U266, A2780, 3AO, SKOV3, AcPC-1, BxPC-3, Panc-1, SW1990, PC-3	A375 xenograft mice; A549 xenograft mice; BxPC-3 xenograft mice; CT-26 xenograft mice; GBC-SD xenograft mice; HCT-116 xenograft mice; Hep1-6 xenograft mice; H23 xenograft mice; Lewis tumor-bearing mice; LoVo xenograft mice; MDA-MB-231 xenograft mice; MCF-7 xenograft mice; SKOV3 xenograft mice; SW1990 xenograft mice; SW-620 xenograft mice	Anti-angiogenesis; anti-proliferation; anti-metastasis; enhances radiosensitivity; increases cell survival; induces autophagy, cell cycle arrest; inhibits chemotaxis, epithelial–mesenchymal transition; pro-apoptosis	Activates caspase-3, -8, -9, 12, PARP; Decreases mitochondrial membrane potential; Down-regulates Akt, AQP1, B7-H1, B7-H3, Bcl-2, Bcl-xL, VE-cadherin, CDK2, COX-2, CXCR4, cyclin D1, cyclin E, DNMT3A, EGFR, EPHA2, ERK, FUT4, HDAC3, HIF-1α, HK2, IAP, JNK, LeY, MMP-2, MMP-9, mTOR, c-Myc, NF-κB, p38, p53, PCNA, PD-L1, PI3K, PKM2, Rb, STAT3, surviving, VEGF; Enhances cytochrome c release, ROS production; Inhibits the Warburg effect, Wnt/β-catenin pathway; Up-regulates Atg-5, Atg-7, Bax, CHOP, IRE1, microRNA-532-3p, p16, p21, p27, p53, PERK	0–10 μM; 0–30 μM; 0–35 μM; 0–60 μM; 0–80 μM; 0–100 μM; 0–150 μM; 0–160 μM; 0–200 μM; 0–400 μM; 0–600 μM; 25 μM; 0–600 ng/ml; 0–80 μg/ml; 0–100 μg/ml; 0–160 μg/ml; 0–200 μg/ml; 40, 80 μg/ml; 50 μg/ml; 80, 160 μg/ml; 80, 160 mg/ml; 3 mg/kg; 5 mg/kg; 5, 10, 20 mg/kg; 6 mg/kg; 7.5–30 mg/kg; 10 mg/kg; 20 mg/kg	Cisplatin; Cyclophosphamide; Erlotinib; 5-Fluorouracil; Oxaliplatin; Paclitaxel	[227, 232–234, 236–241, 246, 252–255, 260, 884–900]

Table 1 (continued)

Compounds	Origins	Cancer types	In vitro models	In vivo models	Anti-cancer effects	Underlying mechanisms	Dosage	Combinational agents	References
Ursolic acid	*Vaccinium macrocarpon* Ait., *Arctostaphylos uva-ursi* (L.) *Spreng*, *Rhododendron hymenanthes* Makino, *Eriobotrya japonica*, *Rosemarinus officinalis*, *Calluna vulgaris*, *Eugenia jambolana*, *Ocimum sanctum*	Bladder cancer; breast cancer; cervical cancer; colorectal cancer; Ehrlick ascites carcinoma; leukemia; liver cancer; lung cancer; melanoma; ovarian cancer; prostate cancer; skin cancer	BIU-87, T24, MDA-MB-231, MCF-7, MCF-7/ADR, HeLa, HCT-8, HCT-116, HT-29, Caco-2, SW-480, SW-620, HCT-15, CO115, HL-60, HL-60/ADR, Jurkat, K562, K562/ADR, U937, HL-60/ADR, Hep3B, Huh7, HA22T, A549, H3255, Calu-6, M4Beu, SKOV3, DU-145, LNCaP, PC-3	12-dimethylbenz[a] anthracene-induced mice; DU-145 xenograft mice; Ehrlich ascites carcinoma xenograft mice; HCT-116 xenograft mice; HCT-15 xenograft mice; U937 xenograft mice	Anti-angiogenesis; anti-metastasis; anti-proliferation; enhances chemosensitivity; induces apoptosis, autophagy, cell cycle arrest; inhibits MDR	Activates caspase-3, -7, -8, -9, Fas receptor, PARP; Decreases mitochrondrial membrane potential; Down-regulates AEG-1, Akt, Bcl-2, Bcl-xL, Bid, β-catenin, CD31, cyclin D1, EGFR, ERK, cFLIP, FN, HIF-1α, cIAP-1, ICAM-1, IκBα, IKKα/β, IL-8, Jak2, Ki-67, Mcl-1, MMP-2, MMP-9, NF-κB, iNOS, p65, u-PA, P-gp, S6 K, Src, STAT3, survivin, mTOR, TNF-α, VEGF, Wnt5α/β, XIAP; Enhances cytochrome c release, PGE_2 levels, ROS production; Inhibits NO production; Up-regulates ACC, AMPK, ASK1, Bax, CHOP, DR4, DR5, eIF2α, GRP78, GSK3β, IL-12, JNK, c-Jun, NADPH, p21, p52, p53, PERK	0–4 μM; 0–16 μM; 0–17.5 μM; 0–20 μM; 0–40 μM; 0–50 μM; 0–80 μM; 0–100 μM; 4 μM; 20 μM; 0–400 μg/ml; 10 mg/kg; 25–100 mg/kg; 50 mg/kg; 75 mg/kg; 250 mg/kg; 2 μmol/mouse	Capecitabine; 5-Fluorouracil; Oxaliplatin; Resveratrol; TRAIL	[274, 276, 281, 283–289, 293, 901–907]
Silibinin	*Silybum marianum* L. Gaertn	Breast cancer; colorectal cancer; epidermoid carcinoma; glioblastoma; hepatocellular carcinoma; osteosarcoma; pancreatic cancer; prostate cancer; renal carcinoma; thyroid cancer	BT-20, MCF-7, MDA-MB-231, MDA-MB-468, SKBR3, T47D, AsPC-1, BxPC-3, Panc-1, HT-29, HCT-116, LoVo, SW-480, Caco-2, A-431, LN18, SNB19, U87MG, Hep3B, HepG2, SK-Hep-1, SaOS2, PC-3, 769-P, 786-O, ACHN, OS-RC-2, SW839, Caki, TPC-1	786-O xenograft mice; Azoxymethane-induced rats; Diethylnitrosamine-induced mice	Anti-metastasis; anti-proliferation; induces apoptosis, autophagy, cell cycle arrest; inhibits cell viability	Activates caspase-3, -8, -9, PARP; Down-regulates Akt, Bcl-2, EGFR, ERK, GLI1, IL-1β, FN, MMP-2, MMP-7, MMP-9, NF-κB, iNOS, PLA2, TNF-α, mTOR; Enhances CYP2E1 activity, cytochrome c release, ROS production; Up-regulates AIF, Bax, Bid, calpain, EGR1, ICAD, NAG-1, PTEN	0–75 μM; 0–100 μM; 0–200 μM; 0–300 μM; 0–800 μM; 25, 50 μM; 120 μM; 125 μM; 200 mg/kg; 300 mg/kg; 0.5%	Curcumin; luteolin	[318, 319, 329–331, 334, 342–345, 357, 358, 908–910]

Table 1 (continued)

Compounds	Origins	Cancer types	In vitro models	In vivo models	Anti-cancer effects	Underlying mechanisms	Dosage	Combinational agents	References
Emodin	*Rheum palmatum*, *Polygonum cuspidatum*, *Polygonum multiflorum*, *Cassia obtusifolia*	Bladder cancer; breast cancer; colorectal cancer; gallbladder cancer; gastric cancer; hepatocellular carcinoma; lung cancer; nasopharyngeal carcinoma; oral carcinogenesis; ovarian cancer; pancreatic cancer; prostate cancer	MBT2, T24, TSGH8301, 4T1, EO771, MCF-7, MDA-MB-231, MDA-MB-435, MDA-MB-453, HCT-116, LoVo, LS1034, SGC-996, MKN45, C3A, Hep3B, HepG2, PLC/PRF/5, SMMC-7721, A549, CNE-2Z, A2780, SKOV3, AsPC-1, BxPC-3, Panc-1, SW1990, SW1990/GZ, PC-3	4T1 xenograft mice; 7,12-dimethyl benz(a)anthracene-induced golden Syrian hamsters; EO771 xenograft mice; HCCLM3 tumor-bearing mice; LS1034 xenograft mice; MDA-MB-231 xenograft mice; SGC-996 xenograft mice; SKOV3 xenograft mice; SW1990 xenograft mice; T24 xenograft mice	Anti-metastasis; anti-proliferation; induces apoptosis, autophagy, cell cycle arrest; inhibits cell viability, epithelial-mesenchymal transition	Activates caspase-3, -9, PARP, chloride currents; Decreases mitochondrial membrane potential; Down-regulates Akt, Bcl-2, Bcl-xL, Bim-1, β-catenin, CDK1, CSF1, CSF2, CXCL12, CXCR4, cyclin D1, ERα, ERK, FABP4, bFGF, HBP17, HER2, ILK, Jagged1, Jak1, Jak2, Ki-67, Mcl-1, MCP-1, MMP-2, MMP-9, MRP1, NF-κB, p38, p62, u-PA, u-PAR, Slug, Snail, Src, STAT3, survivin, Thy-1, VEGF, vimentin, XIAP, ZEB1; Enhances Ca^{2+} levels, cytochrome c release, ROS production; Up-regulates AIF, Bax, Beclin-1, E-cadherin, GSK3β, microRNA-34, Notch1, SHP-1	0–10 μM; 0–40 μM; 0–50 μM; 0–60 μM; 0–80 μM; 0–100 μM; 0–250 μM; 0–320 μM; 0–1000 μM; 20 μM; 20–80 μM; 40 μM; 0.05 mM; 40 mg/ml; 20, 40 mg/kg; 20, 50 mg/kg; 25, 50 mg/kg; 40 mg/kg; 50 mg/kg	Cisplatin; curcumin; 5-fluorouracil; gemcitabine	[64, 367–378, 380, 382, 383, 385, 389, 394, 395, 402, 403, 405, 911]
Triptolide	*Tripterygium wilfordii* Hook. F.	Bladder cancer; breast cancer; colorectal cancer; endometrial carcinoma; liver cancer; lung cancer; lymphoma; melanoma; myeloma; nasopharyngeal carcinoma; neuroblastoma; osteosarcoma; ovarian cancer; oral cancer; pancreatic cancer; prostate cancer	UMUC3, MDA-MB-231, MCF-7, DLD-1, HCT-116, HEC-1B, MHCC-97H, HepaRG, HepG2, H460, H358, A549, A549/Taxol, HTB182, BEAS-2B, H1299, NCI-H2009, NCI-H460, Jurkat, Molt-3, Raji, NAMALWA, Daudi, B16F10, HS-sultan, IM9, RPMI 8226, U266, CNE, MG63, BE(2)-C, SH-SY5Y, SAOS2, U2OS, SKOV3, SKOV3/DDP, A2780, SAS, Panc-1, AsPC-1, SW1990, BxPC-3, LNCaP, PC-3, DU-145	3LL xenograft mice; A549 xenograft mice; AsPC-1 xenograft mice; BE(2)-C xenograft mice; CNE xenograft mice; Daudi xenograft mice; H358 xenograft mice; H460 xenograft mice; HEC-1B xenograft mice; Jurkat xenograft mice; MHCC-97H xenograft mice; SAS + U937 xenograft mice; SKOV3/DDP xenograft mice; SW1990 xenograft mice	Anti-angiogenesis; anti-metastasis; anti-proliferation; enhances radiosensitivity; induces autophagy, cell cycle arrest; inhibits cell viability; pro-apoptosis	Activates caspase-3, -7, -8, -9, GSK3β, PARP; Decreases mitochondrial membrane potential; Down-regulates Akt, AR, BCAR1, Bcl-2, β-catenin, Cav-1, CD147, CDK2, CHK1, COX IV, CXCR4, cyclin A1, ERK, ETS2, FAK, c-FLIP, GRB2, HIF-1α, HSF1, HSP70, IκBα, ITGβ1, ITGαVβ6, JMJD3, JMJD2B, NK, p38 MAPK, Mcl-1, MKP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-14, MMP-19, c–Myc, NF-κB, iNOS, Nrf2, p65, PCNA, PI3K, PYK2, ROCK1, RhoA, Slug, Snail, SOS1, Src, survivin, mTOR, Twist, UTX, VEGF, vimentin, ZEB1; Enhances Ca^{2+} levels, cytochrome c release, ROS production; Inhibits Wnt/β-Catenin pathway; Up-regulates ATM, Bax, Beclin-1, E-cadherin, cathepsin B, Fas, DKK1, DR5, ENY2, FADD, FRZB, GSK3β, IL-2, γ-H2AX, LMP, LSD1, p53, PPARγ, PTEN, SFRP1, SIRT3, Smac, SUV39H1, TNF-α, Wnt3α	0–10 nM; 0–40 nM; 0–50 nM; 0–80 nM; 0–100 nM; 0–160 nM; 0–200 nM; 0–300 nM; 0–320 nM; 0–400 nM; 0–500 nM; 0–0.1 μM; 0–25 μM; 0–150 μM; 0–200 μM; 10 nM; 50, 72 nM; 100 nM; 0–8 ng/ml; 0–36 ng/ml; 0–50 ng/ml; 0–400 ng/ml; 5, 10 ng/ml; 5–160 ng/ml; 8 ng/ml; 250 μg/kg; 0–0.8 mg/kg; 0.04–0.36 mg/kg; 0.075 mg/kg; 0.15 mg/kg; 0.25 mg/kg; 0.4 mg/kg; 1 mg/kg; 1.5 mg/kg; 2–4 μg/mouse	Cisplatin; epirubicin; 5-fluorouracil; gemcitabine; hydroxycamptothecin	[408, 410, 411, 414, 415, 417, 419, 422, 423, 425–427, 429, 431–434, 438, 444, 446, 453, 454, 912–925]

Table 1 (continued)

Compounds	Origins	Cancer types	In vitro models	In vivo models	Anti-cancer effects	Underlying mechanisms	Dosage	Combinational agents	References
Cucurbitacin B	*Bryonia, Cucumis, Cucurbita and Lepidium sativum*	Breast cancer; cervical cancer; hepatocellular carcinoma; lung cancer; neuroblastoma; prostate cancer	4T1, HCC1937, MCF-7, MCF-7/ADR, MDA-MB-231, MDA-MB-436, SKBR-3, HeLa, T47D, SK-Hep1, Hep3B, HepG2, Bel-7402, Bel-7402/5-Fu, A549, H1299, H23; SH-SY5Y; LNCaP, PC-3	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced mice; 4T-1 xenograft mice; Bel-7402 xenograft mice; MDA-MB-231 xenograft mice; NNK-induced mice; PC-3 xenograft mice	Anti-angiogenesis; Anti-metastasis; Anti-proliferation; Inducing apoptosis, cell cycle arrest; Inhibits epithelial-mesenchymal transition	Activates caspase-3, -8, -9, PARP; Decreases mitochondrial membrane potential; Down-regulates Akt, ACLY, BCAR1, Bcl-2, β-catenin, CD31, CDK1, CIP2A, cyclin B1, cyclin D1, EGFR, ERK, FAK, galectin-3, GSK3β, HER2, HIF-1α, ILK1, ITGA6, ITGB4, Jak2, MMP-2, MMP-9, MRP1, c-Myc, nucleophosmin, P-gp, paxillin, RhoA, ROCK1, STAT3, Src, survivin, TACE, TCF1, mTOR, Twist, VEGF, VEGFR2, Wnt3; Enhances cytochrome c release, PP2A activity, ROS production; Inhibits Wnt/β-catenin pathway; Up-regulates ATM, Bax, Bim, E-cadherin, CDC25C, CHK1, γ-H2AX, JNK, p21, p53	0–100 nM; 0–200 nM; 0–1000 nM; 0.1–1000 nM; 0–0.1 μM; 0–1 μM; 0–1.6 μM; 0–30 μM; 0–100 μM; 0–128 μM; 0.02–62.5 μM; 0–100 μg/ml; 0.1–100 μg/ml; 0.1, 0.2 mg/kg; 0.1, 0.25 mg/kg; 0.5, 1 mg/kg; 1, 5 mg/kg; 2 mg/kg; 10 mg/kg; 0.1 μmol/mouse	Curcumin; docetaxel; gefitinib; gemcitabine	[452, 460–462, 472–475, 485, 499, 926–931]
Tanshinone IIA	*Salvia miltiorrhiza* Bunge	Breast cancer; bladder cancer; cervical cancer; colorectal cancer; esophageal carcinoma; gastric cancer; NSCLC; osteosarcoma; oral squamous carcinoma	BT-20, 5637, BFTC 905, T24, HeLa, C33 A, HCT-116, COLO-205, LoVo, HT-29, SW-620, Eca109, SGC-7901, MKN45, A549, H596, H1299, Calu-1, H460, 143B, SCC090	HT-29 xenograft mice; MKN45 xenograft mice; SGC-7901 xenograft mice; 143B xenograft mice	Anti-angiogenesis; anti-metastasis; anti-proliferation; enhances chemosensitivity, radiosensitivity; induces autophagy, cell cycle arrest; inhibits cell viability, epithelial–mesenchymal transition; pro-apoptosis	Activates caspase-3, -8, -9, -12, PARP; Down-regulates ALDH1, Bcl-2, BIP, N-cadherin, β-catenin, CD31, COX-2, CTGF, FoxM1, HIF-1α, Ki-67, LEF1, MCP-1, Mfn-1, Mfn-2, MMP-2, MMP-9, c-Myc, NANOG, Opa-1, p65, PCNA, Slug, Snail, STAT3, survivin, TCF3, VEGF, vimentin, YAP; Enhances cytochrome c release, ROS accumulation; Reduces mitochondrial membrane potential; Up-regulates ATF-4, Bax, Bak, Bad, E-cadherin, CHOP, Drp-1, DR5, GRP78, p21	0–8 μM; 0–20 μM; 0–40 μM; 0–60 μM; 0–80 μM; 0–100 μM; 0–54.4 μM; 0–20 ng/ml; 0–4 μg/ml; 0–8 μg/ml; 0–18 μg/ml; 0–60 μg/ml; 1 mg/kg; 10, 30 mg/kg; 20 mg/kg	Adriamycin 5-fluorouracil; TRAIL	[514, 515, 517, 519, 523, 531, 539, 932–935]

Table 1 (continued)

Compounds	Origins	Cancer types	In vitro models	In vivo models	Anti-cancer effects	Underlying mechanisms	Dosage	Combinational agents	References
Oridonin	*Rabdosia rubescens* (Hemsl.) Hara	Breast cancer; cervical cancer; colorectal cancer; esophageal cancer; gastric cancer; hepatocellular carcinoma; laryngeal; leukemia; liver cancer; lung cancer; melanoma; multiple myeloma; neuroblastoma; oral squamous carcinoma; osteosarcoma; ovarian cancer; pancreatic cancer; prostate cancer; uveal melanoma	4T1, MCF-7, MDA-MB-231, SW-48, SW-480, SW-620, SW-1116, HeLa, LoVo, HCT-116, HCT-15, COLO-205, RKO, EC9706, KYSE-30, KYSE-150, SGC-7901, AGS, HepG2, Huh6, MHCC97-H HCC, Hep-2, K562, K562/ADR, HL-60, HL-60/ADR, MV4-11/DDP, MOLM-13/DDP, A549, SHSY-5Y, SK-N-MC, LP-1, SCC-25, HSC-3, HSC-4, MG63, U2OS, HOS, Saos-2, 143B, WSU-HN4, WSU-HN6, CAL27, SKOV3, BxPC-3, PC-3, LNCaP, DU-145, RM-1, MUM2B, OCM-1	143B xenograft mice; 4T1 xenograft mice; HCT-116 xenograft mice; HepG2 xenograft mice and zebrafish; HL-60 xenograft mice; HOS xenograft mice; K562 xenograft mice; KYSE-150 xenograft mice; LoVo xenograft mice; MV4-11/DDP xenograft mice; RM-1 xenograft mice; SCC-25 xenograft mice; SHSY-5Y xenograft mice; SW-480 xenograft mice; WSU-HN6 xenograft mice	Anti-angiogenesis; anti-metastasis; anti-proliferation; induces apoptosis, autophagy, cell cycle arrest, epithelial–mesenchymal transition	Activates caspase-3, -8, -9, PARP; Decreases mitochondrial membrane potential; Down-regulates Akt, AMPK, AP-1, Bcl-2, Bcl-xL, N-cadherin, CD31, CD44, CDC25C, CDK1, CDK2, Claudin 1, Claudin 4, Claudin 7, α-CPI, cyclin B1, cyclin D1, cyclin E, DHFR, EGFR, ERK, GLUT-1, GSK3β, HO-1, ICAD, Mcl-1, MCT1, MDM2, MMP-2, MMP-9, c-Myc, NF-κB, Notch, Nrf2, NQO1, p38, p62, PCNA, PI3K, Rac2, Raf, Ras, SERTAD1, Slug, Smad, Snail, Stathmin, SREBP1, mTOR, vimentin; Enhances cytochrome c release, intracellular Ca^{2+} levels, ROS production; Inhibits TrxR activity; Up-regulates AIF, ASK1, ATM, Bad, Bax, Beclin-1, Bim, BMP7, E-cadherin, CHK2, CHOP, CKS2, eIF2α, FADD, GADD45AQ, GRP78, γ-H2AX, HERC5, HSP90, IRE1, JNK, p21, p53, PERK, PPARγ, RECQL4, SFN, PTEN	0–1000 nM; 0–1.5 μM; 0–4 μM; 0–9 μM; 0–12 μM; 0–15 μM; 0–20 μM; 0–25 μM; 0–30 μM; 0–32 μM; 0–40 μM; 0–50 μM; 0–60 μM; 0–64 μM; 0–80 μM; 0–100 μM; 0–160 μM; 36 μM; 0–10 mM; 0–64 μg/ml; 5–30 μg/ml; 1.875, 7.5 mg/ml; 1 mg/kg; 2–8 mg/kg; 2.5–10 mg/kg; 5, 10 mg/kg; 5–10 mg/kg; 5–15 mg/kg; 7.5–30 mg/kg; 10 mg/kg; 10, 20 mg/kg; 15 mg/kg; 30 mg/kg; 50, 100 mg/kg	Cisplatin; NVP-BEZ235; valproic acid	[544–556, 558–567, 573–576, 578, 579, 936–946]
Shikonin	*Lithospermum erythrorhizon*, *Arnebia euchroma*, *Arnebia guttata*	Breast cancer; cervical cancer; colorectal cancer; gallbladder cancer; gastric cancer; glioblastoma multiforme; glioma; hepatocellular carcinoma; leukemia; lung cancer; NSCLC; renal carcinoma; pancreatic cancer; thyroid cancer	MCF-7, MDA-MB-231, SKBR3, HeLa, HCT-116, HT-29, SNU-407, SW-1116, SW-680, SW-620, NOZ, BGC-823, SGC-7901, Primary glioblastoma stem cells, C6, SHG-44, U87, U251, SMMC-7721, NB4, Calu-6, H358, HCC-2279, NCI-H15, NCI-H460, NCI-H1229, NCI-H1437, NCI-H1703, A549, 789-O, Capan-1, Suit-2, 8305C, 8505C, BCPAP, C643, FTC133, IHH4, K1, TPC1	A549 xenograft mice; Glioblastoma stem cell xenograft mice; HCT-116 xenograft mice; NOZ xenograft mice; SGC-7901 xenograft mice	Anti-metastasis; anti-proliferation; enhances chemosensitivity; induces apoptosis, cell cycle arrest, necroptosis	Activates caspases-3, -8, -9, -12, PARP, JNK/c-Jun, p38 MAPK, PERK/eIF2α/CHOP, pathways; Decreases mitochondrial membrane potential; Down-regulates Akt, Bcl-2, CDK4, cyclin D1, FoxO3a, ICBP90, ITGβ1, MDM2, MMP-9, c-Myc, RIPK1; Elevates intracellular Ca^{2+} and ROS levels; Enhances Ca^{2+} and K^{+} efflux; Inhibits ERK pathway, PKM2 activity; Promotes RIP1/RIP3 necrosome formation; Up-regulates Bax, Bim, Cbl-b, CHOP, cytochrome c, EGR1, eIF2α, GRP78, IRE1α, p16, p21, p53, p73, PERK, RIP1, RIP3	0–2 μM; 0–4 μM; 0–5 μM; 0–6 μM; 0–10 μM; 0–20 μM; 0–50 μM; 0.1–0.4 μM; 1 μM; 2 μM; 20 mg/kg; 2 mg/kg	Cisplatin; 5-fluorouracil; oxaliplatin	[593, 595, 600, 603, 607, 611, 614, 615, 617, 620, 636, 947–952]

Table 1 (continued)

Compounds	Origins	Cancer types	In vitro models	In vivo models	Anti-cancer effects	Underlying mechanisms	Dosage	Combinational agents	References
Gambogic acid	*G. hanburyi*, *G. Morella*	Breast cancer; colorectal cancer; glioma; hepatocellular carcinoma; NSCLC; osteosarcoma; ovarian cancer; pancreatic cancer; prostate cancer; renal carcinoma	4T1, MCF-7, MDA-MB-231, HCT-15, HCT-15R, HCT-116, HT-29, SW-480, SW-620, LoVo/L-OHP, LoVo/L-OHP/GA, T98G, Hep3B, Huh7, A549, A549/DDP, SPC-A-1, MG63, SKOV3, BxPC-3, Capan-1, Capan-2, Colo-357, MIA PaCa-2, Panc-1, Suit-007, Suit-2, SW1990, B6WT, DU-145, LAPC-4, LNCaP, PC-3, PCAP-1, $PTEN^{-/-}/p53^{-/-}$, Caki	4T1 xenograft mice; A549 xenograft mice; B16F10 and MC38 xenograft mice; BxPC-3 xenograft mice; C26 xenograft mice; SKOV3 xenograft mice	Anti-angiogenesis; anti-metastasis; anti-proliferation; anti-tumor growth; enhances chemosensitivity; induces apoptosis, autophagy, cell cycle arrest; inhibits cell viability, survival	Activates caspase-3, -7, -8, -9, PARP, JNK pathway; Decreases mitochondrial membrane potential; Down-regulates Akt, ALDOA, ATG4B, Bcl-2, Bcl-xL, β-catenin, $cFLIP_L$, cyclin D1, DLL1, DLL3, DLL4, ERK, Jagged1, Jagged2, LRP, p-53, P-gp, Mcl-1, MMP-2, MMP-9, MRP2, PI3K, RRM2, SIRT1, survivin, TOPIIα, VEGF, XIAP; Enhances ROS accumulation, cytochrome c release; Inhibits ERK/E2F1/RRM2, MAPK, PI3K/Akt pathways, NF-κB p65 binding activity, Trx activity; Up-regulates AIF, Atg-5, Bax, CHOP, DUSP1, DUSP5, FoxO3a, c-Jun, p27, p53	200–400 nM; 0–1 μM; 0–2 μM; 0–3 μM; 0–5 μM; 0–8 μM; 0–10 μM; 0–40 μM; 0–50 μM; 0–51.8 μM; 0.5 μM; 0–3 μg/ml; 2 mg/kg; 8 mg/kg	Chlorochalcone; Cisplatin; Doxorubicin; 5–Fluorouracil; Gemcitabine; NaI^{131}; Oxaliplatin; Retinoic acid; TRAIL	[639, 644, 646, 647, 650, 656, 657, 663–665, 953–966]
Artesunate	*Artemisia annua* L.	B-cell lymphoma; bladder cancer; breast cancer; colorectal cancer; gastric cancer; head and neck cancer; hepatocellular carcinoma; myelodysplastic syndrome; ovarian cancer; pancreatic cancer; prostate cancer; rhabdomyosarcoma	BL-41, Raji, Ramos, Rec-1, RT4, T24, ACHN, BT-474, MCF-7, MDA-MB-231, BGC-823, HGC-27, MGC-803, SGC-7901, HN3, HN4, HN9, SKM-1, HO8910, SKOV3, AsPC-1, BxPC-3, Colo-357, Panc-1, DU-145, LNCaP, RD18, TE671	BL-41 xenograft mice; A2780 xenograft mice; HO8910 xenograft mice; TE671 xenograft mice; MCF-7 xenograft mice	Anti-angiogenesis; anti-metastasis; anti-proliferation; anti-tumor growth; induces apoptosis, cell cycle arrest, DNA damage, ferroptosis	Activates caspase-3, -9, p38 MAPK pathway; Decreases metabolic capacity, mitochondrial membrane potential, PGE_2 production; Down-regulates Bcl-2, CDC25A, COX-2, cyclin B, cyclin D1, cyclin E2, γ-H2AX, IGF-1R, Keap1, c-Myc, PAX7, RAD51, STAT3, UCA1, xCT; Enhances ROS production; Up-regulates ATF-4, ATM, ATR, Bax, BRCA1, E-cadherin, CHK1, CHK2, CHOP, HO-1, microRNA-16, microRNA-133, microRNA-206, Nrf2, p53	0.1–10 μM; 0–50 μM; 0–100 μM; 0–120 μM; 0–200 μM; 50 μM; 0–50 μg/ml; 0–160 mg/L; 0–200 mg/kg; 50 mg/kg; 50, 150 mg/kg; 100 mg/kg; 200 mg/kg	Cisplatin; Connexin-43; Paclitaxel	[669, 673, 675, 681, 683, 688–690, 693, 695, 967–971]

Table 1 (continued)

Compounds	Origins	Cancer types	In vitro models	In vivo models	Anti-cancer effects	Underlying mechanisms	Dosage	Combinational agents	References
Wogonin	*Scutellaria baicalensis*, *Scutellaria amoena*, *Scutellaria rivularis*, *Anodendron affine* Druce	Breast cancer; gastric cancer; head and neck cancer; hepatocellular carcinoma; leukemia; lymphoma; melanoma; multiple myeloma; neuroblastoma; osteosarcoma; ovarian cancer; pancreatic cancer; NSCLC	MDA-MB-231, BGC-823, MFC, MGC-803, MKN45, SGC-7901, AMC-HN2, AMC-HN3, AMC-HN4, AMC-HN5, AMC-HN9, AMC-HN4-cisR, AMC-HN9-cisR, SNU-1041, SNU-1066, SNU-1076, Bel-7402, Hep3B, HepG2, SMMC-7721, K562, K562/A02, K562R, Raji, B16F10, RPMI 8226, U266, IMR-32, SK-N-BE2, $CD133^+$ CAL72, A549, A2780, Colo-357, Panc-1	MDA-MB-231 xenograft mice; Raji xenograft mice; AMC-HN4-cisR xenograft mice; AMC-HN9-cisR xenograft mice; B16F10 xenograft mice; BGC-823 xenograft mice and zebrafish; MFC xenograft mice; RPMI 8226 xenograft mice	Anti-angiogenesis; anti-metastasis; anti-proliferation; anti-tumor growth; induces apoptosis, autophagy, cell cycle arrest, ER stress, mitochondrial dysfunction; reverses drug resistance	Activates caspase-3, -4, -8, -9, -12, PARP, IRE1α-dependent pathway; Decreases mitochondrial membrane potential; Down-regulates Akt, B7H1, Bcl-2, CDK4, CDK6, cyclin D1, cyclin E, EGFR, ERK, HIF-1α, IL-8, IκB, IKKα, Ki-67, MMP-2, MMP-9, c-Myc, PDK1, PI3K, Rac1, RAE-1ε, SGK1, ULK1, VEGF; Enhances calreticulin, HMGB1, cytochrome c release, ROS accumulation; Inhibits 5-LO/BLT2/ERK/IL-8/MMP-9, NF-κB pathways; Up-regulates ASK, Bax, Bid, GRP78, GRP94, IRE1α, JNK, p21, p53, PU.1, PUMA	0–20 μM; 0–40 μM; 0–50 μM; 0–60 μM; 0–80 μM; 0–100 μM; 0–150 μM; 0–200 μM; 40 μM; 50 μM; 0–40 μg/ml; 0–60 mg/kg; 0–80 mg/kg; 8 mg/kg; 20 mg/kg; 60 mg/kg; 12.5 ng/zebrafish	Cisplatin; Paclitaxel; Oxaliplatin; Sorafenib	[704, 708, 709, 716, 717, 719, 721, 725, 730, 731, 741, 742, 972–976]
β-Elemene	*Curcuma wenyujin* Y. H. Chen *et* C. Ling, *Rhizoma zedoariae*, *Curcuma Zedoary*	Bladder cancer; bone neoplasms; breast cancer; cervical cancer; gastric cancer; melanoma; NSCLC; osteosarcoma; thyroid cancer	PBC, Bcap37, MBA-MD-231, MCF-7, MCF-7/ADR, MCF-7/DOC, 5637, SiHa, T-24, BGC-823, MKN45, SGC-7901, B16F10, A549, H358, H460, H1299, H1650, H1975, Lewis, PC9, MG63, U2OS, FTC-133	A549 xenograft mice; B16F10 xenograft mice; BGC-823 xenograft mice; Lewis tumor-bearing mice; MG63 xenograft mice; U2OS xenograft mice	Anti-angiogenesis; anti-metastasis; anti-proliferation; anti-tumor growth; enhances radiosensitivity; induces apoptosis, autophagy, cell cycle arrest; reverses chemoresistance	Activates caspase-3, -7, -8, -9, -10; Down-regulates Akt, Bcl-2, β-catenin, CDC25C, CDK1, cyclin B1, cyclin D1, endostatin, ERK, DNMT1, MMP-2, MMP-3, MMP-9, MTA3, c-Myc, STAT3, Sp1, survivin, TCF7, TIMP-1, TIMP-2, VEGF; Enhances ROS accumulation; Induces polarization from M2 to M1 macrophages; Inhibits Wnt/β-catenin pathway; Up-regulates ATF-4, ATF-6, Bad, Bax, BTF, CHK2, CHOP, FoxO3a, IGFBP1, IRE1α, p15, p21, p53, Pak1, PAK1IP1, PERK, TOPIIα	0–25 μM; 0–1000 μM; 67.5–1000 μM; 0–40 μg/ml; 0–50 μg/ml; 0–120 μg/ml; 0–160 μg/ml; 0–200 μg/ml; 0–320 μg/ml; 0–500 μg/ml; 0–800 μg/ml; 0–0.16 mg/ml; 15, 30 μg/ml; 100 mg/ml; 1 mg/kg; 20 mg/kg; 50 mg/kg; 75 mg/kg; 200 mg/kg	Cisplatin; Paclitaxel; Rapamycin	[746, 747, 749, 752, 754, 755, 762, 977–987]

Table 1 (continued)

Compounds	Origins	Cancer types	In vitro models	In vivo models	Anti-cancer effects	Underlying mechanisms	Dosage	Combinational agents	References
Cepharanthine	*Stephania cepharantha* Hayata, *Stephania japonica*	Choroidal melanoma; colorectal cancer; breast cancer; gastric cancer; leukemia; nasopharyngeal carcinoma; NSCLC; ovarian cancer; renal carcinoma	MEL15-1, COLO-205, HCT-116 HT-29, SW-620, MCF-7, MDA-MB-231, Jurkat T-cells, A549, H1299, HCC827, NCI-H1299, NCI-H1650, NCI-H1975, CNE-1, CNE-2, A2780, A2780/Taxol, CaOV-3, OVCAR3, Caki	A549 xenograft mice; NCI-H1975 xenograft mice	Anti-angiogenesis; anti-metastasis; anti-proliferation; anti-tumor growth; induces apoptosis, autophagy, cell cycle arrest; Reverses multi-drug resistance	Activates caspase-3, -9, PARP; Decreases mitochondrial membrane potential; Down-regulates Akt, Bcl-2, Bcl-xL, CDK4, cyclin A, cyclin D, c-FLIP, mTOR, p50, p52, survivin; Enhances cytochrome c release, ROS accumulation; Inhibits lysosomal cathepsin B and cathepsin D maturation, Akt/mTOR, NF-κB, pathways; Up-regulates Atg-7, Bak, Bax, Beclin1, DR5, p38 MAPK, Mcl-1, $p21^{Waf1/Cip1}$, p53	0–15 μM; 0–20 μM; 0–80 μM; 0–100 μM; 0–120 μM; 2–8 μM; 4, 5 μM; 5–80 mM; 25 mg/kg; 50 mg/kg	Cisplatin; Dacomitinib; Paclitaxel; TRAIL	[777, 782–790, 794, 988]

experimental models and conditions, pharmacological effects, as well as mechanistic actions of the natural compounds derived from Chinese herbal medicine. Despite the unique anti-cancer beneficial features of many compounds derived from Chinese herbal medicine, their clinical applications are disproportionally limited. As of 2019, only preliminary clinical studies have been performed with artemisinins, emodin, cucurbitacins, tanshiones, shikonin, and CEP in various cancers, without any approved clinical applications. The phase I safety studies of UA-liposomes, oridonin derivative (HAO472), and wogonin were evaluated in patients with advanced solid tumors. Curcumin, pro-drug of triptolide (minnelide™), triptolide derivative (LLDT-8), and GA have been investigated on cancer therapy in phase II clinical trials. The phase II clinical trials of berberine hydrochloride, ginsenoside Rg3, and artesunate are being conducted in patients with cancer. EGCG was shown to have potential anti-cancer effects in a phase III clinical trial. Elemene Emulsion mainly containing β-elemene was approved by China's State Food and Drug Administration as a Class 2 new drug in China. Based on our critical review of those clinical studies, we conclude that Chinese herbal medicine is a promising source and could be used as a complementary approach for cancer therapy.

We believe that as the evidence for safety and efficacy continues to develop, this will improve the understanding about the mechanistic actions and clinical potential of these compounds. Chinese herbal medicine will also serve as a huge community from which many promising compounds will be developed for clinical use.

Abbreviations

4-PBA: 4-phenylbutyrate; 5-LO: 5-lipoxygenase; ABCG2: ATP-binding cassette super-family G member 2; ACC: acetyl-CoA carboxylase; ACLY: ATP-citrate lyase; AEG-1: astrocyte elevated gene-1; AIF: apoptosis inducing factor; ALDOA: aldolase A; ALDH1: aldehyde dehydrogenase 1; AMPK: 5′AMP-activated protein kinase; AP-1: activator protein 1; Apaf-1: apoptotic protease activating factor 1; AQP1: aquaporin 1; AR: androgen receptor; ARIE: acute radiation-induced esophagitis; ART: artemisinin; ASK: apoptosis signal-regulating kinase; ATF-4: activating transcription factor 4; ATF-6: activating transcription factor 6; ATG4B: autophagy related 4B cysteine peptidase; Atg-5: autophagy related 5 protein; ATM: ataxia-telangiectasia mutated protein kinase; ATP: adenosine triphosphate; ATR: ataxia telangiectasia and Rad3-related protein; Axin2: axis inhibition protein 2; B7-H1: B7 homolog 1; B7-H3: B7 homolog 3; Bad: Bcl-2 associated agonist of cell death; Bak: Bcl-2 homologous antagonist killer; Bax: Bcl-2-associated X protein; BCAR1: breast cancer anti-estrogen resistance protein 1; Bcl-2: B cell lymphoma 2; Bcl-xL: B-cell lymphoma-extra large; Bex: brain-expressed and X-linked; Bid: BH3 interacting-domain death agonist; Bim: Bcl-2-like protein 11; BIP: binding immunoglobulin protein; BLT2: leukotriene B_4 receptor 2; BMP7: bone morphogenetic protein 7; BRCA1: breast cancer type 1 susceptibility protein; BTF: Bcl-2-associated transcription factor 1; Ca^{2+}: calcium; CAMKKβ: Ca^{2+}/calmodulin-dependent protein kinase kinase β; Cav-1: caveolin-1; Cbl: casitas B-lineage lymphoma; CD: cluster of differentiation; CDC25A: cell division cycle 25A; CDC25C: cell division cycle 25C; CDK: cyclin-dependent kinase; CEH: cepharanthine hydrochloride; CEP: cepharanthine; CHK: checkpoint kinase 1; CHOP: C/EBP homologous protein; CIP2A: cancerous inhibitor of protein phosphatase 2A; CK1α: casein kinase 1α; CKS2: cyclin-dependent kinases regulatory subunit 2; COX-2: cyclooxygenase-2; COX IV: cytochrome c oxidase subunit 4; α-CP1: poly(rC)-binding protein 1; CSF: colony stimulating factor; CTGF: connective tissue growth factor; CTR1: copper transporter 1; CTTN: cortactin; CXCL-12: C–X–C motif chemokine 12; CXCR4: C–X–C chemokine receptor type 4; CYP2E1: cytochrome P450 2E1; DC: dendritic cell; DHA: dihydroartemisinin; DHCR24: 24-dehydrocholesterol reductase; DHFR: dihydrofolate reductase; DLL: delta-like canonical Notch ligand; DKK1: Dickkopf-related protein 1; DNA: deoxyribonucleic acid; DNMT: DNA (cytosine-5)-methyltransferase; DR4: death receptor 4; DR5: death receptor 5; Drp-1: dynamin-related protein 1; DUSP: dual-specificity phosphatase; Dvl2: dishevelled segment polarity protein 2; E2F1: E2F transcription factor 1; EBNA1: Epstein–Barr nuclear antigen 1; EF-Tu: elongation factor thermo unstable; EGCG: epigallocatechin gallate; EGFR: epidermal growth factor receptor; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor; EGR1: early growth response protein 1; ENY2: enhancer of yellow 2 transcription factor homolog; eIF2α: eukaryotic translation-initiation factor 2α; EphA2: ephrin type-A receptor 2; ER: endoplasmic reticulum; ERα: estrogen receptor α; ERK: extracellular signal-regulated kinase; Ets2: ETS proto-oncogene 2; EZH2: enhancer of zeste homolog 2; FABP4: fatty acid binding protein 4; FADD: Fas-associated protein with death domain; FAK: focal adhesion kinase; FasL: Fas ligand; bFGF: basic fibroblast growth factor; c-FLIP: FLICE-like inhibitory protein; FN: fibronectin; FoxM1: forkhead box protein M1; FoxO: forkhead box O; Foxp3: forkhead box P3; FRZB: frizzled-related protein; FUT4: fucosyltransferase 4; GA: gambogic acid; GADD45AQ: growth arrest and DNA damage-inducible 45; GLI1: glioma-associated oncogene homolog 1; GLUT-1: glucose transporter 1; GRB2: growth factor receptor-bound protein 2; GRP78: 78-kDa glucose-regulated protein; GRP94: 94-kDa glucose-regulated protein; GSH: glutathione; GSK3β: glycogen synthase kinase 3β; γ-H2AX: phosphorylated H2A histone family member X; HBP17: human fibroblast growth factor binding protein 1; HO-1: heme oxygenase 1; H_2O_2: hydrogen peroxide; HDAC: histone deacetylases; HER2: human epidermal growth factor receptor 2; HERC5: HECT domain and RCC-1-like domain-containing protein 5; HIF-1α: hypoxia-inducible factor 1α; HK2: hexokinase 2; HMGB1: high mobility group box 1; HNF4α: hepatocyte nuclear factor 4α; HRK: activator of apoptosis harakiri; HSF1: heat shock factor 1; HSP: heat shock protein; HUVEC: human umbilical vein endothelial cell; IAP: inhibitor of apoptosis protein; ICAD: apoptosis protease activating factor-1; ICAM-1: intercellular adhesion molecule 1; ICBP90: inverted CCAAT box-binding protein of 90 kDa; IDO: indoleamine 2,3-dioxygenase; IFN-γ: interferon-γ; IGFBP1: insulin-like growth factor-binding protein 1; IGF-1R: insulin-like growth factor 1 receptor; IκB: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; IKK: IκB kinase; IL: interleukin; ILK: integrin-linked kinase; iNOS: inducible nitric oxide synthase; IRE1α: inositol-requiring enzyme 1α; ITG: integrin; Jak1: Janus kinase 1; Jak2: Janus kinase 2; JMJD3: Jumonji domain-containing protein D3; JMJD2B: Jumonji domain-containing protein 2B; JNK: c-Jun N-terminal kinase; K^+: potassium; Keap1: Kelch-like ECH-associated protein 1; LEF1: lymphoid enhancer-binding factor 1; LeY: Lewis Y; Lig4: DNA ligase 4; LLC: Lewis lung carcinoma; LMP: Epstein–Barr virus latent membrane protein; LRP: low density lipoprotein receptor-related protein; LPS: lipopolysaccharide; LSD1: lysine-specific histone demethylase 1; MAPK: mitogen-activated protein kinase; Mcl-1: myeloid cell leukemia 1; MCT1: monocarboxylate transporter 1; MCP-1: monocyte chemoattractant protein 1; MD2: myeloid differentiation factor 2; MDM2: mouse double minute 2 homolog; MDR: multi-drug resistance; MDSCs: myeloid-derived suppressor cells; MEK: MAPK kinase; MGMT: *O*-6-methylguanine-DNA methyltransferase; MHC: major histocompatibility complex; Mfn: mitofusin; MKP-1: MAPK phosphatase 1; MMP: matrix metalloproteinase; MRP1: multi-drug resistance-associated protein 1; MST1: macrophage-stimulating 1; MTA3: metastasis-associated 1 family member 3; mTOR: mammalian target of rapamycin; NADPH: nicotinamide adenine dinucleotide phosphate oxidase; NAG-1: non-steroidal anti-inflammatory drug-activated gene 1; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NK: natural killing; NKD2: naked cuticle 2; NQO1: NADPH quinone oxidoreductase 1; Nrf2: nuclear factor erythroid 2-related factor 2; NSCLC: non-small-cell lung carcinoma; Oct-4: octamer-binding transcription factor 4; Opa-1: optic atrophy protein 1; p70S6K: p70S6 kinase; u-PA: urokinase-type plasminogen activator; u-PAR: urokinase-type plasminogen activator receptor; PAI-1: plasminogen activator inhibitor 1; PAK1: p21-activated protein kinase 1; PAK1IP1: p21-activated protein kinase-interacting protein 1; PARP: poly (ADP-ribose) polymerase; PAX7: paired box 7; PCNA: proliferating cell nuclear antigen; PERK: protein kinase R-like endoplasmic reticulum kinase; PD-L1: programmed death-ligand 1; PDK1: pyruvate dehydrogenase kinase 1; PGE_2: prostaglandin E_2; P-gp:

P-glycoprotein; PHLPP2: pH domain and leucine Rich repeat protein phosphatase 2; PLA2: phospholipase A2; PI3K: phosphoinositide 3-kinase; PKC-α: protein kinase Cα; PKD1: polycystin 1; PKM2: pyruvate kinase isozyme M2; PP2A: pyrophosphatase (inorganic) 2; PPARγ: peroxisome proliferator-activated receptor γ; PSA: prostate-specific antigen; PTEN: phosphatase and tensin homolog; PTTG-1: pituitary tumor-transforming gene 1 protein; PU.1: spleen focus forming virus proviral integration oncogene; PUMA: p53 upregulated modulator of apoptosis; PYK2: proline-rich tyrosine kinase 2; Rac1: Ras-related C3 botulinum toxin substrate 1; Rac2: Ras-related C3 botulinum toxin substrate 2; RAE-1ε: ribonucleic acid export 1ε; Rb: retinoblastoma-associated protein; RECK: reversion-inducing-cysteine-rich protein with kazal motifs; RECQL4: ATP-dependent DNA helicase Q4; RhoA: Ras homolog family member A; RIP: receptor-interacting serine/threonine protein; RIPK1: receptor-interacting serine/threonine protein kinase 1; RRM2: ribonucleotide reductase regulatory subunit M2; ROCK1: Rho-associated protein kinase 1; ROS: reactive oxygen species; S6: ribosomal protein S6; S6K: ribosomal protein S6 kinase; SERTAD1: SERTA domain-containing protein 1; SFRP1: secreted frizzled related protein 1; SFN: stratifin; SGK1: serum and glucocorticoid-regulated kinase 1; SHH: sonic hedgehog; SHP-1: Src homology region 2 domain-containing phosphatase 1; SIRT: sirtuin; Smac: second mitochondria-derived activator of caspase; SMOX: spermine oxidase; SOS1: son of sevenless homolog 1; SOD: superoxide dismutase; SOX2: sex determining region Y-box 2; Sp1: specificity protein 1; SREBP1: sterol regulatory element-binding protein 1; SSAT: spermidine/spermine N1-acetyltransferase; STAT: signal transducer and activator of transcription; SUV39H1: suppressor of variegation 3-9 homolog 1; Suz12: suppressor of zeste 12 protein homolog; TACE: TNF-α-converting enzyme; TAZ: tafazzin; TFAP2A: transcription factor AP-2-alpha; TCF: T-cell factor; TGF-β: transforming growth factor-β; Th1: T helper type 1 cell; Th2: T helper type 2 cell; Thy-1: THYmocyte differentiation antigen 1; TIMP: TIMP metallopeptidase inhibitor; TLR: toll-like receptor; TNF: tumor necrosis factor; TOPK: T-LAK cell-originated protein kinase; TOPIIα: DNA topoisomerase IIα; TRAF6: TNF receptor-associated factor 6; TRAIL: TNF-related apoptosis-inducing ligand; TROP2: tumor-associated calcium signal transducer 2; T_{reg}: regulatory T cells; Trx: thioredoxin; TrxR: thioredoxin reductase; Tyro3: tyrosine-protein kinase receptor; UA: ursolic acid; UAL: UA-lipsomes; UCA1: urothelial cancer-associated 1; ULK-1: UNC-51-like autophagy activating kinase 1; UQCRC1: ubiquinol-cytochrome c reductase core protein 1; UTX: ubiquitously transcribed tetratricopeptide repeat protein X-linked; VEGF: vascular endothelial growth factor; VEGFR2: vascular endothelial growth factor receptor 2; VHL: von Hippel–Lindau tumor suppressor; XBP-1: X-box binding protein 1; xCT: solute carrier family 7 member 11; XIAP: X-linked inhibitor of apoptosis protein; WT1: Wilms tumor 1; YAP: Yes-associated protein 1; ZEB1: zinc finger E-box binding homeobox 1; ZEBRA: BamHI Z Epstein–Barr virus replication activator.

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Authors' contributions
YW and ZZ designed, organized, and supervised the study. HL, ZZ, HC, YG, PL, LQ, MZ, QL, ZC, JZ, PY, and CG drafted the manuscript. CV, HL, and HC analyzed the literature. CV and ZZ revised the manuscript. JW, CU, and SW participated in the revision. All authors read and approved the final manuscript.

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