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REVIEW

Artemisinin and its derivatives: a promising cancer therapy

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Abstract

The world is experiencing a cancer epidemic and an increase in the prevalence of the disease. Cancer remains a major killer, accounting for more than half a million deaths annually. There is a wide range of natural products that have the potential to treat this disease. One of these products is artemisinin; a natural product from *Artemisia* plant. The Nobel Prize for Medicine was awarded in 2015 for the discovery of artemisinin in recognition of the drug's efficacy. Artemisinin produces highly reactive free radicals by the breakdown of two oxygen atoms that kill cancerous cells. These cells sequester iron and accumulate as much as 1000 times in comparison with normal cells. Generally, chemotherapy is toxic to both cancerous cells and normal cells, while no significant cytotoxicity from artemisinin to normal cells has been found in more than 4000 case studies, which makes it far different than conventional chemotherapy. The pleiotropic response of artemisinin in cancer cells is responsible for growth inhibition by multiple ways including inhibition of angiogenesis, apoptosis, cell cycle arrest, disruption of cell migration, and modulation of nuclear receptor responsiveness. It is very encouraging that artemisinin and its derivatives are anticipated to be a novel class of broad-spectrum antitumor agents based on efficacy and safety. This review aims to highlight these achievements and propose potential strategies to develop artemisinin and its derivatives as a new class of cancer therapeutic agents.

Keywords Artemisinin · Cancer · Cell lines · Transgenics · Flavonoids · Combination therapy

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Abbreviations

AA	Artemisinic Acid
A&D	Artemisinin and its derivatives
ACTs	Artemisinin based combination therapies
AN production	Artemisinin production
CDK	Cyclin-dependent kinase
MVA	Cytosolic Mevalonate Pathway
DTP	Developmental Therapeutics Program
DHAA	Dihydroartemisinic Acid
DW	Dry Weight
ERK	Extracellular Signal-Regulated Kinases
MA	Mevalonic Acid
NCI	National Cancer Institute
TSTs	Non-glandular T-shaped Trichomes
ROS	Reactive Oxygen
SA	Salicylic Acid
TFAR1	Trichome-specific fatty acyl-CoA reductase 1
TDZ	Thidiazuron
TAR1	Trichome and artemisinin regulator 1
TAFR1	Trichome-Specific Fatty Acyl-CoA Reductase 1

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WHO	World Health Organization
PLGA	L-lactic-co-glycolic acid

Introduction

Cancer is the foremost cause of deaths around the world. Approximately 14.1 million deaths were reported in 2012 and there is an estimate of 20 million deaths in 2030. The death rate is increasing every year because of different forms of cancer including stomach, liver, lung, breast and colon cancer. Cancer cells are produced by the mutations or genetic factors attained by the cell due to external agents. According to the World Health Organization [1], up to 30% of deaths due to cancer can be prevented.

Drug resistance and significant levels of drug toxicity related to existing anticancer treatments are the main cause of difficulty in cancer control. The formulation of effective medications to reduce the cancer burden with insignificant side effects on healthy mammalian cells [2] is the most challenging task.

Self-reliance in growth signals, obdurate to growth-inhibitory signals, vesting replicative eternity, tissue invasion and metastasis, insistent angiogenesis, and evasion of apoptosis are main molecular and cellular hallmarks of cancer [3].

New chemotherapies are being investigated to treat malignant tumors by investigating the anticancer potentials of novel compounds together with testing the anticancer properties of the drugs utilized for the treatment of other diseases. Bioactive compounds isolated from natural resources are found most effective against tumours with the least side effects. Natural compounds in the herbal medications could contain potential anticancer compounds with minimum or no side effects at all. One of such compounds is artemisinin which is found in *Artemisia* plant and it has both anticancer as well as antimalarial effects [4]. Artemisinin and its derivatives pose promising anticancer activity against various cancer cell lines [5–9].

Artemisinin is the most promising drug molecule isolated from *Artemisia* plants with minimum adverse effects [10, 11]. WHO has approved it as an antimalarial drug and it is successfully used to treat malaria, cough, cold and diarrhoea. It is also used to treat hepatitis, cancer, inflammations, bacterial, fungal and viral infections, and has proven record for being anthelmintic, antiseptic, antipyretic, carminative, antispasmodic, stimulant and stomachic [12–14]. Among other properties of artemisinin in-vitro activity against HIV has also been found [15]. *Artemisia* plant is also effective in inhibiting osteoporosis and osteoclast induced bone diseases [16]. Artemisinin and its derivatives successfully prevented ovarian cancer growth and metastasis [17], breast cancers [18] and other variety of cancer types [4, 5, 7, 19–25].

This review will reexamine some of the critical issues in the implementation of artemisinin and its derivatives as anticancer agents. Moreover, this review will also explore the mechanisms of their antitumor effects in the light of new research. Furthermore, current and future development of artemisinin by considering its limitations and benefits will be highlighted to assess its importance in the field of cancer drug discovery.

Mechanism of action of artemisinin and its derivatives in cancer pathway(s)

Artemisinin is one of the bioactive molecules belonging to an effective family of anticancer agents. Its isolation and characterization is considered one of the most novel discoveries in recent research into medicinal plants. In 1972, it was isolated and characterized from *Artemisia annua* L plant [26], and its structure was analyzed by X-ray analysis in 1979 [27].

Artemisinin is an endoperoxide sesquiterpene lactone. The empirical formula of Artemisinin is C, H, O and has a unique structure lacking nitrogen-containing heterocyclic ring. Numerous studies have widely documented the anticancer effects of artemisinin and its derivatives. The molecule is potent against various cancers namely breast cancer [28–31], lung cancer [31, 32], prostate cancer [31, 33], head and neck cancer [34], bladder and renal cancer [31], ovarian cancer [35] cervical carcinoma [36], pancreas carcinoma [37], colon carcinoma [31], thyroid medullary carcinoma, endometrial and oral squamous carcinomas [34].

Endocytosis of artemisinin and derivatives and iron

Artemisinin permeates through the cell membrane due to its hydrophobic nature and induces its anti-cancer actions. A significant number of pharmacological studies [4, 24, 38, 39] have demonstrated the mechanism of action of artemisinin against different cancer types. Usually, cancer cells require vast quantities of iron for their proliferation and have transferrin receptors that are involved in endocytosis and uptake of the plasma iron-carrying protein. The endoperoxide moiety of artemisinin reacts with the iron in cancer cells to produce ROS (Reactive Oxygen Species) including superoxide and hydroxyl radicals which elicit cellular destruction.

Artemisinin and iron are transported into the cell and artemisinin-transferrin conjugate causes the release of iron which reductively cleaves the artemisinin molecule and produces the destructive free radicals [5–7, 40–43]. Therefore, artemisinin transforms into cytotoxic carbon because of free iron centred radicals for cellular destruction. Consequently, artemisinin and artemisinin-tagged iron-carrying molecules

are very selective and effective and can be altered to develop powerful anticancer drugs [44, 45].

Artemisinin and artemisinin-based synthetic dimers are also known to effectively reduce cell propagation, angiogenesis and induce apoptosis in cancer cells [4, 5, 7, 46–50].

Artemisinin and its derivatives stop multiplication of cancer cell

Artemisinin compounds impart cytotoxic and cytostatic effect on cancer cells. To regulate cell division, inhibitors involving the Cyclin-dependent kinase (CDK) associated protein (CIP)/kinase-inhibitory protein (KIP) such as p57, p27 and p21 [51] play a modulatory role. Artemisinin and its derivatives affect the cell division by intervening the different stages of the cell cycle. Growth arrest induced by artemisinin has commonly observed at G0/G1 to S transition,however, growth arrest at all cell cycle phases has been commonly observed [52].

Cell cycle arrest

Artemisinin and its derivatives exert their proliferation inhibitory activity on tumours by distressing different stages of the cell cycle. Generally, G0/G1 or S phase inhibition is the most common target, through an alteration in the activity and expression of cell cycle regulatory enzymes [53–55]. Dihydroartemisinin mediated cell cycle arrest (G0/G1 phase) through downregulation of cyclins and CDKs. DHA exhibits its effect by reducing the activity of the CDK promoter or increasing the potential of CDK inhibitors [56]. Artemisinin can inhibit CDK-4 gene expression directly [57]. Artesunate obstructs the regulators of the mitotic spindle checkpoint in the G2/M phase such as Bub3, Mad3,andMad2 [58]. The proliferation of pancreatic cancer can be prevented by dihydroartemisinin through inhibition of the activity of nuclear transcription factor NF-κB [59]. ART and DHA induced apoptosis in human hepatoma cells through a caspase-dependent mitochondrial pathway, arresting G1-phase by regulating G1-checkpoint proteins in vivo [56]. DHA arrested lung cancer A549 cell cycle at the G1 phase and inhibited cell proliferation through downregulation of the AKT/Gsk-3β/ cyclinD1 signalling pathway. It also mediated apoptosis by overexpressing the ratio of Bax/Bcl-2 and active caspase-3 and cytochrome-c [60–62]; (Table 1).

Induction of apoptosis

ARTs have been studied to hold apoptosis prompting characteristics in countless cancer cell lines by regulating proapoptotic and antiapoptotic genes [19, 20, 54, 60, 61, 66, 69]. Artesunate helps in proliferation inhibition and induction of apoptosis mainly through iron transporters [75, 76].

Improvement of cell pro-apoptotic protein Bax and downregulation of antiapoptotic protein Bcl-2 can be controlled by dihydroartemisinin by enhancing Fas and activating caspase-8. Inhibition of translocation as well as DNA-binding activity of nuclear factor-κappa gene (NF-κB) can also be improved by DHA [35, 59, 77, 78]. It has also been demonstrated that apart from apoptosis, dihydroartemisinin also participates in the programmed cell death process of autophagy [79, 80]. Also, DHA treatment in HeLa, HCT116, HepG2 and SKOV3 cell lines caused stress-inducible protein p8 to be upregulated along with the upregulation of ATF4 and CHOP expressions, these events lead to autophagy [81, 82].

Induction of autophagy and ferroptosis (iron-dependent cell death)

Autophagy in cancer is regarded as bearing both prosurvival and tumour suppressive functions [83] and ARTs have shown effectiveness in autophagy modulated cell death [66, 81, 84, 85]. Artesunate prompts cell cycle arrest in the G2/M phase by increasing the expression of the initiator of autophagy i.e. Beclin1 [86].

Artemisinin has been linked to non-apoptotic cell death called ferroptosis which is a form of iron dependant cell death [87, 88]. Since ARTs induces iron-dependent cytotoxicity, they have been linked to causing ferroptosis [89].

Inhibition of tumour angiogenesis

ARTs have proved to be good candidates in the inhibition of tumour angiogenesis by down-regulating the production of growth factors and up-regulating the inhibitory factors. To further progress and metastasize, malignant tumours undergo neovascularization. This is controlled by proangiogenic signals including growth factors and cytokines, for example, VEGF (vascular endothelial growth factor), basic bFGF (fibroblast growth factor), IL-1 (interleukin-1), IL-8, angiopoietin, MMPs (matrix metalloproteinases), antiangiogenesis factors like the endostatin, angiostatin, TIMPs (tissue inhibitor of matrix metalloproteinases), etc. [88]. Meanwhile, angiogenesis is critical in cancer progress and metastasis, consequently one major approach of cancer chemotherapy is its inhibition [90].

Among artemisinin derivatives, DHA and especially artesunate are the most ideal candidates for cancer treatment. DHA inhibits angiogenesis through the NF-κB pathway [67, 91]. Artesunate achieves its inhibitory effect on angiogenesis by targeting molecules like EGF, VEGF, VEGFR, etc. [63, 77, 78, 92–94]. Artemisinin, dihydroartemisinin and

Table 1 Summary of Artemisinin and its Derivatives affectivity against cancer

Compound	Cytotoxicity studies	Pathway effected	Mode of action	References
Artemisinin	Non-small-cell lung cancer (NSCLC) A549 and H1299 cells	Wnt/ β-catenin pathway	Cell cycle arrest in G1 phase β-catenin downregulation by decrease Wnt5-a/b increase NKD2 and Axin2	[55]
Artesunate	Non-small-cell lung cancer (NSCLC) A549 and H1299 cells	Wnt/ β-catenin pathway	Cell cycle arrest in G1 phase β-catenin downregulation by decrease Wnt5-a/b increase NKD2 and Axin2	[55]
	A549 human lung cancer cells	Epidermal growth factor receptor (EGFR), Akt and ATP-binding cassette subfamily G member 2 (ABCG2)	Down-regulation of EGFR and its downstream factor Akt artemisinin and its derivatives down-regulates the expression of ABCG2 in vitro and in vivo	[63]
Dihydro-artemisinin	Nasopharyngeal cancer (NPC) cells	Cell cycle	Cell cycle G1 arrest and apoptosis suppression of Cell motility, colony formation invasion	[54]
	Glioma cell lines BT325 and C6	Raf/MEK/ERK PI3K/AKT signaling pathways anti-apoptotic proteins Mcl-1 and	Inactivation of the Raf/MEK/ERK and PI3K/AKT downregulation of Mcl-1 and Bcl-2	[64]
	Human umbilical vein endothelial cells (HUVECs)	JNK pathway	Increased the expression of p-JNK blocks the JNK pathway	[65]
	Non-small-cell lung cancer (NSCLC) A549 and H1299 cells	Wnt/ β-catenin pathway	Cell cycle arrest in G1 phase β-catenin downregulation by decrease Wnt5-a/b increase NKD2 and Axin2	[55]
	acute myeloid leukemia (AML) HL-60 and NB4 cells	Noxa-mediated pathway	Induces Noxa expression upregulates FOXO3a	[66]
	Lung cancer A549 cell line	AKT/GSK3β/cyclinD1 pathway	Suppresses the AKT/Gsk-3β/ cyclinD1 signalling pathway increases the ratio of Bax/Bcl-2, caspase-3 and cytochrome-c	[60, 61]
	Human Umbilical Vein Endothelial Cell, HUVEC	NF-kB pathway	Inhibits VEGFR2 expression down-regulates VEGFR2 mRNA and VEGFR2 protein expression in endothelial cells increase IkB-a and inhibit NF-kB p65 nuclear translocation	[67]
	Human Fibrosarcoma HT- 1080 cells		Inhibits the PKCa/ Raf/MEK/ERK/NF-kB and JNK/AP-1 cascades suppresses MMP-9 expression	[68]
	Pancreatic cancer cell line BxPc3-RFP	Not studied	Interferes with cell proliferation Induces apoptosis	[69]
	Human ovarian cancer cells A2780, OVCAR-3	Not studied	Induction of death receptor, mitochondrion-mediated, caspase-dependent, apoptosis	[19, 20]
	prostate cancer DU145, PC3 and LNCaP	PI3-K/Akt and ERKl pathways	Suppresses the PI3-K/Akt and ERK induces death receptor DR5 activates extrinsic and intrinsic cell death signaling	[70]

Table 1 (continued)

Compound	Cytotoxicity studies	Pathway effected	Mode of action	References
	Human hepatoma cells,HepG2 (p53 wild-type),Huh-7 andBEL-7404 (p53mutant), and Hep3B (p53 null), and a normal human liver cell line, 7702	Cell cycle analysis	Induced G1-phase arrest, decreases levels of cyclin D1, cyclin E, cyclin-dependent kinase 2, cyclin-dependent kinase 4, and E2F1 increased levels of Cip1/p21 and Kip1/p27	[56]
	Glioma cell lines BT325 and C6	Raf/MEK/ERK and PI3K/AKT signaling pathways	Inactivates Raf/MEK/ERK and PI3K/AKT signaling pathways downregulates Mcl-1 and Bcl-2	[64]
	Breast cancer cells	Mitocondrial pathway	G0/G1 cell cycle arrest increased expression of Bim decreased expression Bcl-2	[71]
Artemether	ConA- or alloantigen-induced splenocyte proliferation	Cell Cycle	Cell cycle arrest in G0/G1 phase	[72]
	Impairment of both antigen- and anti-CD3-induced phosphorylation of ERK	Cell Cycle	Cell cycle arrest in G1 phase	[72]
	Inhibition of ConA-induced T cell proliferation	Cell Cycle	Cell cycle arrest in G1 phase	[72]
	Brain tumor cells	Cell Cycle	Cell cycle arrest in G1 phase	[73]
Arteether	Ovarian cancer	Not studied	Cellular proliferation	[74]
	Prostate cancer	Not studied	Cellular proliferation	[28]

artesunate repress Wnt/β-catenin pathway through β-catenin downregulation [55].

Altered cancer metabolism

The remarkable difference between the metabolic pathways of normal and cancer cells can serve as an active target for cancer therapy. ARTS have shown an indication of being a good cancer-specific modulator of glucose metabolism. Artemisinin inhibited glycolytic metabolism by inhibition of glucose uptake through the reduction in the glucose transporter GLUT1, altering lactate production and reducing ATPS in NSCLC cell lines [95, 96] demonstrated similar effects with dihydroartemisinin, a derivative of artemisinin.

Some proteomics studies performed by [97] on human bronchial epithelial cells identified about 8 artesunate interacting enzymes that were crucial for glucose metabolic pathways. Artemisinin has shown similar outcomes/results by interacting with 11 target enzymes of the cancer pathway [98].

Anticancer activities of the derivatives of artemisinin

Artesunic acid (Artesunate) in the treatment of cancer

Besides artemisinin, derivatives of artemisinin are also considered as natural antimalarial [99] and anticancer agents [47, 100]. In primary cell lines and cancer cultures, their antitumor activities were evident as they prevented cancer metastasis, proliferation and angiogenesis [42, 101]. Chaturvedi et al. [102] summarised that the antitumor properties of artemisinin derivatives on the development and characterization of several artemisinin combinations including two, three, or four monomers are possible 'leads' for anticancer drugs. Artesunate has proven for cytotoxic effects against ovarian, breast, colon, melanoma, leukemia, renal and prostate cancer cell culture [4–7, 103]. Recent studies have revealed that artesunate could efficiently delay the growth rate of leukemia (J-Jhan), colon carcinoma (HCT-116), small-cell lung carcinoma (H69) and glioma (U251) cancer cell cultures by promoting M/G2 phase cell cycle arrest [58]. Artesunate treatment with glioma cells followed by irradiation showed enhanced apoptotic activity, M/G2 arrest and higher DNA damage as presented by an increased quantity of cH2AX nucleus/foci [104].

Artesunate has proved itself as an effective antitumor agent with IC_{50} values of 2.69 μM as compared with artemisinin ($IC_{50} > 50$ μM) against the cell line of neuroblastoma. It was also found that artesunate may activate caspase-3, which is responsible for apoptosis in both

chemoresistant and chemosensitive neuroblastoma cell lines [105]. Artesunate can induce apoptosis in breast cancer cells (T47D, MCF-7 and MDAMB231) and leukemia cells (J16, CEM and Molt4) through Fe dependent ROS generation along with cytochrome c dynamic release and breakdown of different procaspases [103, 106–108]. Nevertheless, some reports are suggesting that along with apoptosis, artesunate also induced necrosis in some pancreatic cancer cells lines including CFPAC-1, BxPC-3 and Panc-1 [109].

Numerous reports have demonstrated that artesunate is well correlated with differentially regulated 30 genes of angiogenesis in different human cancer cell cultures [110, 111]. Artesunate has significant and independent anticancer action and can reduce tumours to minimize the potential risk of hepatic metastases [112, 113]. Concentration-dependent inhibition of angiogenesis was reported for the artesunate with the range of 12.5–50 μM [114]. Nude mice (BALB/c) induced with ovarian cancer (HO-8910) expressed enhanced levels of VEGF along with KDR/flk-1 receptors. Artesunate at the concentration of 50 mg/kg/d can suppress the amount of VEGF, KDR/flk-1 receptors and can also reduce the growth of tumours [33]. Artesunate also prevents VEGF expression and prevents angiogenesis in myeloid leukemia cells (K562) [115]. In human endothelial cells of the umbilical vein, apoptosis induced by the artesunate is connected with its regulation of Bcl-2 and enhanced regulation of BAX [32]. Youns et al. [116] reported that artesunate can act as a key topoisomerase IIa blocker which suppresses pancreatic cancer development by regulation of multiple signalling pathways.

Similarly, in the lung cancer cell (H1299 and H460), artesunate prevented the metastasis by evading NF-κB and MMPs pathways [117]. In human low differentiated colorectal carcinoma culture, artesunate upregulated E-cadherin which indicated blocking of Wnt-signaling pathway leading towards apoptosis of tumor cells [118]. A review of the literature would suggest that conjugation of transferrin with artemisinin derivatives shows higher anticancer potential [38, 119–121]. Iron(II) glycine sulphate is known to increase the anticancer activity of free artesunate toward U373 astrocytoma cell line and CCRF-CEM leukemia cell line 1.5–10.3 fold compared to the molecules without iron [40]. Combine action of artesunate with Glioblastoma multiforme cells and OSI-774 which is an inhibitor of tyrosine kinase has shown supra additive reduction of tumor cell growth in U-87MG, G-599GM, G-210GM [40].

In a case report, 70% tumor inhibition of laryngeal squamous cell melanoma was recorded in the artesunate treated patients [122]. Moreover, artesunate has the potential to reduce tumor size and enhance the survival of the patients suffering metastatic uveal carcinoma [123]. In a randomized controlled trial including 120 patients having lung cancer, the control group (60 patients) was treated with standard chemotherapy (cisplatin and vinorelbine) and the rest of the patients (60) were given 120 mg artesunate intravenously along with chemotherapy. The 60 patients dosed with artesunate showed enhanced short-term and long-term (up to 1 year) survival rates, an increase in cancer progression time and minimal detectable side effects when compared to the control group [124].

Dihydroartemisinin (DHA) in the treatment of cancer

DHA is one of the most potent derivatives of artemisinin [42] which can induce cell apoptosis just after twelve-hour of the treatment. Artemisinin could produce the same apoptotic effect when it is used 10 times more in quantity compared to DHA [19, 20]. The main apoptotic responses driven by DHA are connected with the activation of the caspase-9 or/and caspase-3 [28, 125–127]. Treatment of the cancer cells with DHA also increases the pro-apoptotic protein BAX and reduces the levels of BCL2 in Hep3B and HepG2 cells [56]. In the PC14 cell line (lung cancer), DHA induced apoptosis and also enhanced p38 MAPK (mitogen-activated protein kinase) phosphorylation [128]. Additionally, DHA induced prominent apoptosis in HCT116 and HL-60 cancer cell lines and permanently down-regulates the c-myelocytomatosis (c-MYC). These findings are consistent with persistent G1 phase arrest mediated by DHA [125, 127]. Low doses of DHA showed more inhibitory effects in hypoxia, while high doses were more effective in normoxia [129]. Induction of apoptosis by DHA treatment was connected to the release of cytochrome c, mitochondrial membrane depolarization, DNA fragmentation and activation of caspases [130, 131].

DHA exhibited antitumor response against ovarian, breast, glioma, colon, lung and pancreatic cancer cells [19–24]. DHA showed anti-cancer action through G2/M cell cycle arrest against ovarian cells (OVCA-420) [35]. On the other hand, in AsPC-1 and BxPC-3 (pancreatic cancer, DHA induced G0/G1 progression towards S-phase. In this case, DHA decreased the expression of cyclin E CDK6, CDK4, CDK2 and NF-κB activity,nevertheless increased the p27 expression [77, 78]. In another report, DHA reduced the levels of MMP9 or/and MMP2, metastasis in HO8910PM (ovarian cancer) and in pancreatic cancer cells (BxPC-3 and PANC-1) through NF-κB inhibition [68, 132–134]. In contrast, DHA significantly reduced HCC tumor growth both in vivo and in vitro by activating cell cycle arrest at G2/M and cell apoptosis. The inhibition of cyclin B, induction of p21 pathway and blocking of CDC25C all participated in ultimate G2/M arrest by DHA. The inhibition phenomenon includes induction of K562 and downregulation of TfR expression resulting in the growth arrest of the G2/M phase [135].

DHA strongly suppressed angiogenesis in a concentration-dependent manner with 2.5–50 µM range [114]. Proliferation and migration of endothelial cells on a fibronectin matrix in a human was evaluated and data showed significant anti-angiogenic activity with DHA treatment [23, 136]. Studies on rat glioma cancer cell lines suggest that DHA may cause ROS production possibly by genotoxic damage [54]. In MCF-7 (breast cancer) cell lines, DHA conjugated with transferrin and demonstrated 280 times higher antitumor activity than normal breast cells [137] which proved the synergistic effect of DHA [56].

Artemether and arteether in the treatment of cancer

Oral administration of artemether for over a period of 12 months, helps in the reduction of tumour density [138]. In vitro, studies reported that artemether has a suppressive effect against alloantigen mediated splenocyte proliferation. Artemether upregulates the production of different cytokines including IL-2 and IFN-γ, and it is also responsible for the cell cycle arrest through G0/G1 transition. Further, artemether showed impairment of both antigens- and anti-CD3-induced phosphorylation of extracellular signal-regulated kinases (ERK). Artemether is responsible for the inhibition of anti-CD3 mediated phosphorylation of Raf1 protein along with activation of Ras protein in primary T-cells [72]. Artemether also suppress the growth of tumor cells in BALB/c mice by depleting splenic Foxp3+, CD4+, CD25+and regulatory T-cells, and increasing the expression of IL-4 in splenic cells [139]. Moreover, artemether displayed a reduction of ConA mediated T-cell expression up to IC50 of 3.8×10^{-6} µg ml^{-1} and inhibition of LPS mediated B-cell expression up to IC_{50} of 1.8×10^{-6} µg ml^{-1} [102]. In another study, artemether exhibited strong inhibitory effects in MTT assay on C6 glioma cells in brain tumour-bearing SD rat and authors suggested that artemether penetrated the blood–brain barrier to inhibit angiogenesis [73]. Different assays were conducted to evaluate the genotoxic and cytotoxic potential of artemether in gastric carcinoma (PG100) and the results revealed that artemether mediated necrosis in lymphocytes at concentrations of 238.8 µg ml^{-1} and 477.6 µg ml^{-1} in PG100 cell lines [140]. Cytotoxic potential of artemether was tested against lung carcinoma (A549) and IC_{10} value was obtained at different concentrations of artemether using the MTT test. The results suggest that artemether decreased cell survival in a concentration-dependent manner with an IC_{10} value of 28.9 µM which was lesser than artemisinin (43.7 µM) [141].

Artemether, as well as arteether, also displayed anticancer response against CNS, ovarian, breast, prostate and renal carcinomas [28, 38]. Artemether and arteether exhibited anticancer activities at 10 µmol L^{-1} for 24 h exposure on cell survival of adenoma cells OVCAR-432 and SK-OV-3 of human ovarian in MTT assays. This lead to the reduction of cells viability ~ 35–40%, which was comparable to the reduction in the cells viability by artemisinin [74]. Efferth and Oesch [142] documented the anticancer effects of artemisinin, arteether and artemether against 60 cancer cell cultures along with anthracyclines. They also compared the IC_{50} values of anthracyclines and artemisinin with the expression of mRNA from 170 genes responsible for oxygen tension response and metabolism. Artemether and arteether reveal remarkable antineoplastic activity through simple mechanisms of tumor cell inhibition in which genes responsible for cellular expression may play a prime role [38].

Synergistic effect of artemisinin, its derivatives and flavonoids on cancer

Phenolics are aromatic organic compounds with a benzene ring attached to one hydroxyl group [143]. Phenolics have a unique position among natural products owing to their ubiquitous distribution in the plant kingdom. They are protective against a broad range of ailments including coronary heart diseases, stroke and various types of cancer. They also possess antimicrobial, insecticidal, algicidal, estrogenic and keratolytic activities [144]. The hydroxyl groups of phenolics donate hydrogen ions, thus scavenging ROS and stopping the cycle of the generation of new free radicals. They can inhibit free radical-mediated oxidative damage to the biomacromolecules e.g. lipids, proteins and DNA. They also inhibit the enzymes involved in new free radical production [144].

Polyphenols are a class of phenolic compounds that characteristically contain more than one phenol group in the molecule and they are good antioxidants as they tend to retard the detrimental effects of free radicals [145]. Polyphenols are sub-classified as tannins and flavonoids. Tannins are astringent and bitter compounds that mainly function in the binding or precipitation of proteins. If we look at the skeleton of Flavonoids (which belong to the polyphenols) it is a 15-carbon (C6-C3-C6) structure also known as hydroxylated polyphenols [146]. Their amount varies from species to species, also based on stages and conditions of the plant growth [147]. They are ubiquitously found in plants mainly produced by the phenylpropanoid pathway in response to microbial infection. They have a diverse function with structure-dependent characteristics. The antioxidant effect of flavonoids is mediated by the hydroxyl group attached, which act as scavengers of free radicals and metal chelators [148]. Regarding the chemical structure of flavonoids, there is a backbone of the skeleton which contains fifteen-carbon molecules along with the presence of two benzene rings

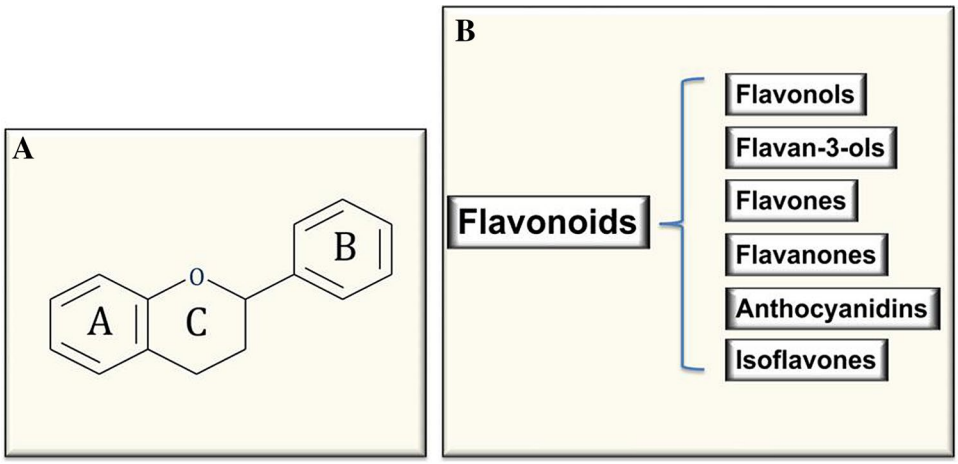

Fig. 1 Flavonoid basic skeleton (**a**) and classification (**b**) [149]

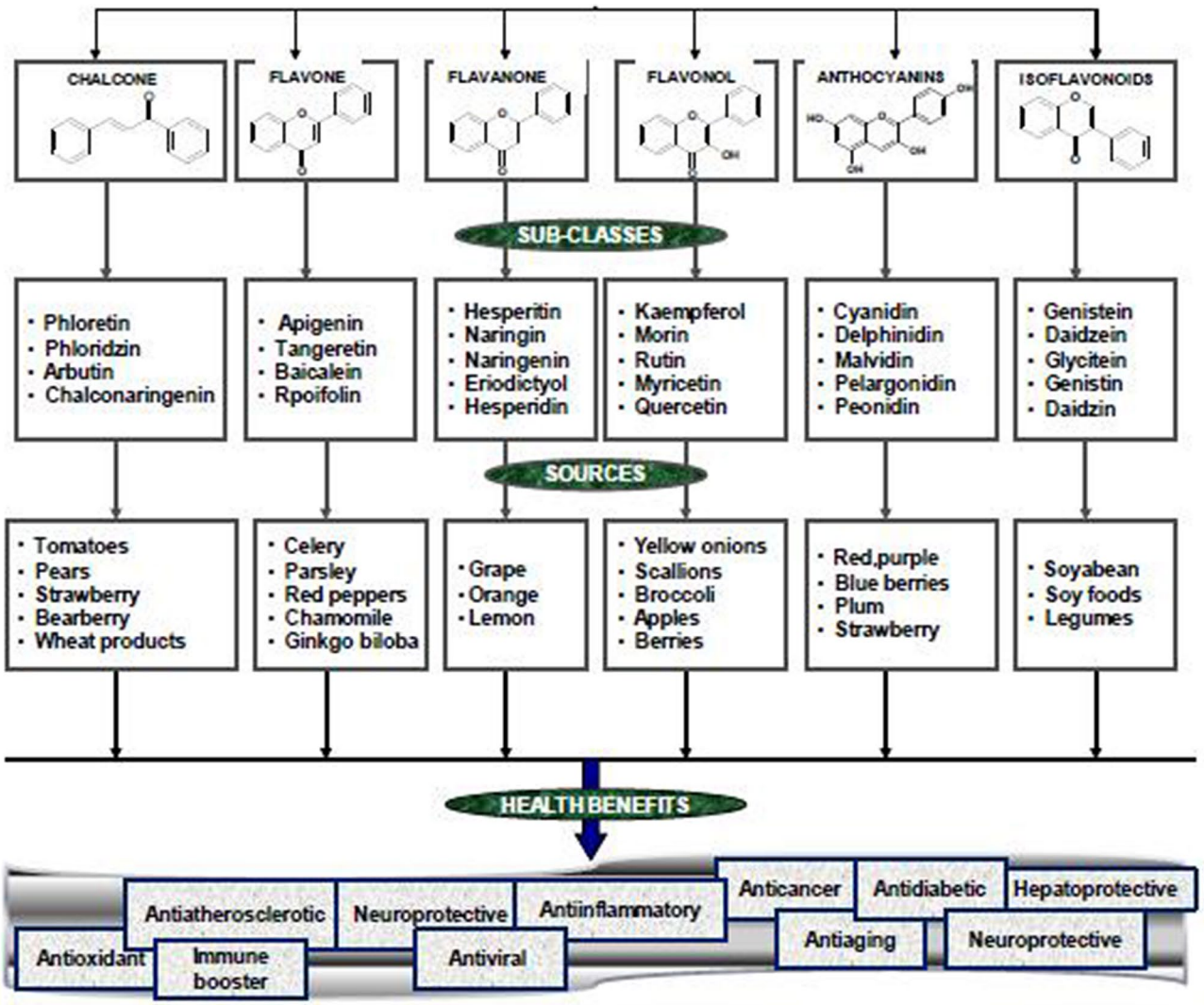

Fig. 2 Flavonoids sources and health benefits [150]

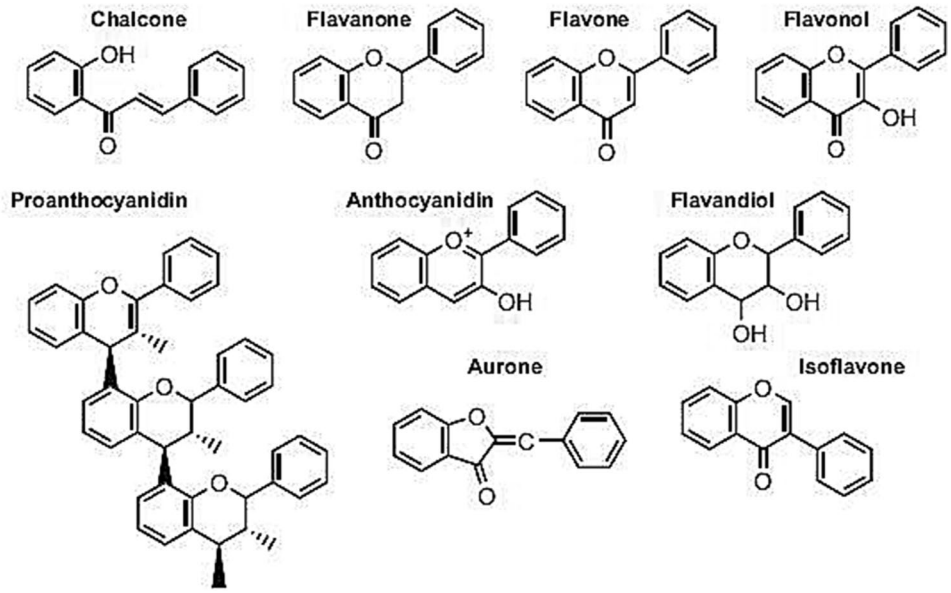

Fig. 3 Structure of different classes of flavonoids [151]

(A and B) connected through a heterocyclic pyran ring (C) (Figs. 1a) and 2.

There are numerous classes of flavonoids as shown in Fig. 1b. Their general structures are given in Fig. 3. The distinction in the classes of flavonoids is mainly due to the difference in the oxidation level and the way ring C is substituted, whereas different molecules inside a class vary in the replacement pattern of the A and B rings [150].

Over 4500 different flavonoids have been reported in plants [146]. The genus *Artemisia* consists of more than 300 species and is one of the richest sources of these flavonoids [145]. Within this genus, *A. annua* is the most extensively studied species from which around 50 flavonoids have been isolated, however, several flavonoids have been detected in other species too like *A. absinthium* L. [152, 153], *A. asiatica* [154], *A. herba-alba* [155], *A. abrotanum* [156], *A. lactiflora* [157] and *A. sphaerocephal* [130, 131]. Phenolics isolated from *A. annua* have been summarized in the scheme shown in Fig. 4.

Potential synergistic interactions among anticancer and antimalarial drugs including flavonoids and artemisinin respectively have not been entirely investigated. It could prove appreciable to search the treatment against cancer by exploring the biological effect of flavonoids, artemisinin and its potential derivatives [145]. The combination of flavonoids along with artemisinin might improve the efficacy of artemisinin. The well-known anticancer effects of flavonoids state that iron and copper metals are chelated during this activity of flavonoids [158]. In that regard, flavonoids could assist artemisinin by converting Fe+3 to Fe+2, the latter being important in the biological activity of artemisinin [40], leading to the release of momentary toxic free radicals that are part of the antimalarial and anticancer mode of action of artemisinin. Furthermore, the anti-cancer activity of artemisinin can be significantly improved by the flavonoids in terms of bioavailability and serum shelf-life [159], hindering metabolically active enzymes [160] or by targeting important anti-apoptotic and pro-apoptotic factors in different cancer cells. To date, there is only a single report stating the synergism between flavonoids and artemisinin treatment against cancer cell lines. In that report, Resveratrol was combined with Artemisinin and tested against HepG2 and HeLa cell cultures for hepatoma and cervical cancers respectively. The combination significantly increased apoptosis as well as necrosis in two tested cancer cell cultures [161, 162]. Moreover, pterostilbene was found to be toxic to the normal hematopoietic cells very minutely. There are some reports which also support potential synergism between artemisinin and flavonoids [163, 92]. It is found that both *A. annua* and *A. carvifolia* extracts contained flavonoids in methanolic and artemisinin in n-hexane fractions and both of the fractions inhibited proliferation of HeLA, MCF7 and HePG2 cancer cell lines individually. When cancer cells were treated with both fractions combined, an enhanced effect was observed compared to individual fractions, thus providing an enhanced synergistic anticancer activity, also supported by the findings of Tolomeo et al. [93].

Although there is a possibility that synergism can sometimes result in drug overdose, its positive features can still be discovered to increase the bioavailability of a drug with a wider protective margin such as artemisinin [145]. Therefore, further investigation should be carried out on the positive interactions between artemisinin and these natural antioxidant metabolites.

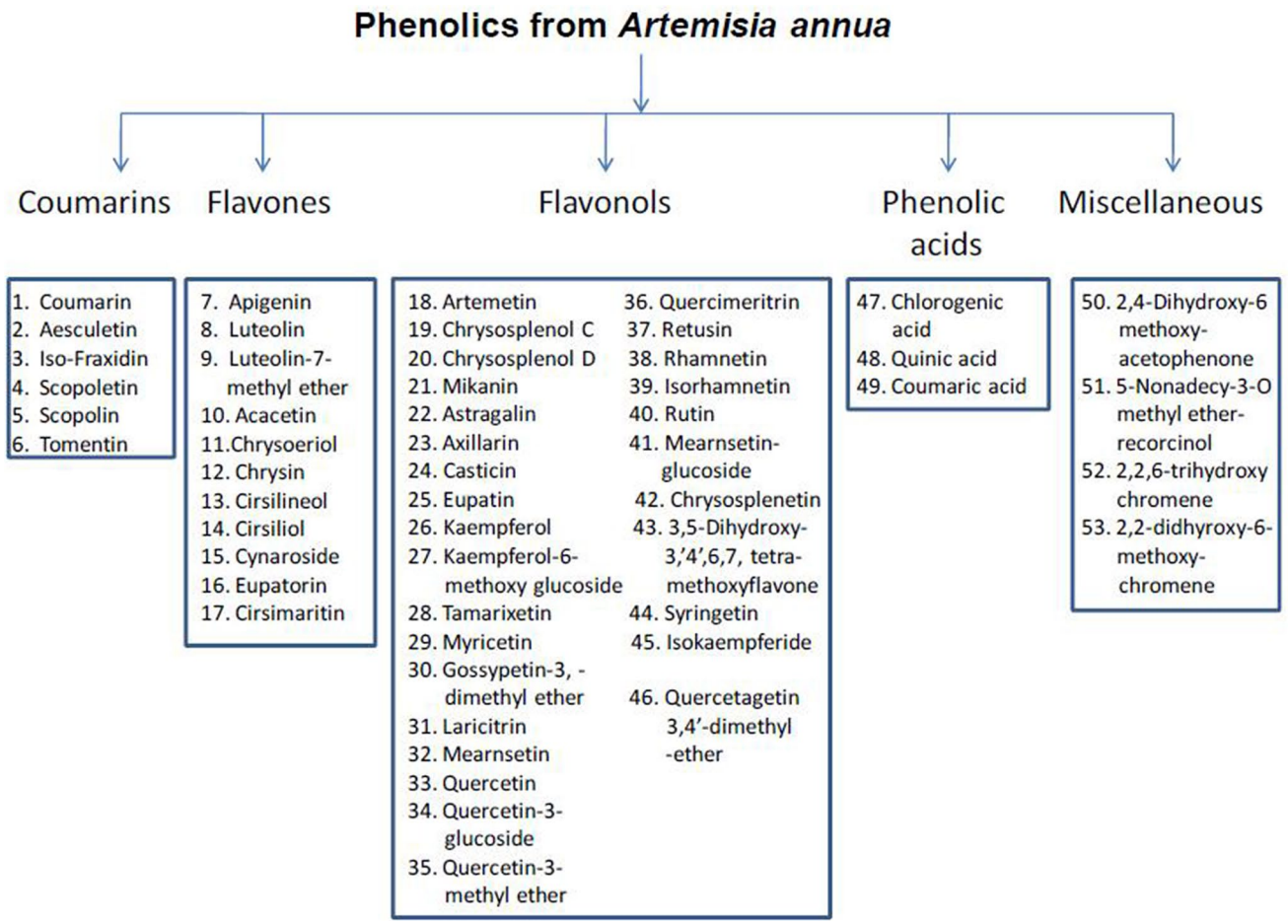

Fig. 4 A schematic diagram showing phenolics isolated from *A. annua* [145]

Combination therapy and nano-targeted drug delivery system

Progress in the field of nanotechnology has opened up massive opportunities for functional combination chemotherapy. Countless nanocarriers like liposomes and poly-drug conjugates have flagged their way into additive synergistic therapy. They not only lower the chemotherapeutic dose and toxicity but also change the physiochemical properties by modifying the bioavailability and biodegradability of therapeutic agents [94], 113]. ARTs encounter challenges in the design of drug delivery formulations despite their broad-spectrum anticancer therapeutics, because of their poor solubility and rapid degradation. To overcome these obstacles, several nano targeted drug delivery systems have been proposed for them [82]. Combination therapy of ARTs with known cancer drugs have proved to be an excellent therapeutic combination, for example, DHA in combination with doxorubicin significantly enhanced the effectiveness of DOX in MCF-7 cells [80] while the combination of Paclitaxel with artemether loaded in liposome nanostructure proved to be a good option in enhancing their therapeutic value while decreasing toxicity [161, 162]. Transferrin loaded magnetic nanoliposomes were used in combination therapy with artemisinin. Their cytotoxicity in breast cancer cell line MCF-7 and MDA-231 resulted in an increased antiproliferative effect than their individual effects [82]. A similar effective drug delivery system was acknowledged for artemether, with its activity enhanced by transferrin loaded lipid nanospheres [62]. The biodegradable polymer Poly-D, L-lactic-co-glycolic acid (PLGA) was used as a nanocarrier for the artesunate, increasing its half-life [171].

Combination therapy is the most effective way to treat major diseases and a combination of two or more anticancer agents using ARTs has proved to be more effective for chemotherapeutics. Artesunate displayed a strong effect on cell proliferation and apoptosis in osteosarcoma cells when used in combination with Allicin (a compound derived from garlic) [26]. DHA's synergistic effect with gemcitabine improved the therapeutic action in the pancreatic cancer model both in vivo and in vitro by the inactivation of the NF-κB pathway [59]. The synergistic effect of artesunate

in the inhibition of angiogenesis with various other agents is also reported [55, 157]. In breast cancer cells, DHA was found to be involved in inhibiting proliferation and cell cycle arrest involving the mitochondrial pathway by increasing the expression of pro-apoptotic gene Bim while decreasing the expression of the anti-apoptotic gene Bcl-2 [71].

Conclusions and perspectives

Artemisinin has been widely utilized as an antimalarial drug for many years. However, several of its other biological activities were reported in the previous years and among them anticancer activity was highlighted the most. Artemisinin and its derivatives served better in extremely metastatic and vigorous cancer growth with no side effects. In this regard, significant work has been done to evaluate the anticancer activity of artemisinin and its derivatives and promising results have been observed against cancer both in vitro and in vivo. Moreover, antimalarial endoperoxides might synergise with other anticancer drugs with negligible side effects. Similarly, the synergistic effect of A&D and flavonoids against cancer is yet to be investigated in detail and requires more attention from the scientific community.

Although the capacity of artemisinin to kill tumor cells is established but the mechanism and the molecular basis of artemisinin-initiated cell death need to be further investigated. In this regard, current research is focusing on the investigation of the mechanism of bioactivation and other molecular events together with new targets for artemisinin against cancer. The likelihood of artemisinin integration into the category of anticancer medications has opened the path for fact-finding exploration in this field and that would be helpful in various ways.

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Compliance with ethical standards

Conflict of interest The authors declare that they do not have any competing interests.

Ethical approval No ethical considerations apply for this review paper.

References

1. WHO (2008) Cancer statistics. WHO, Geneva
2. Hsiao WLW, Liu L (2010) The role of traditional Chinese herbal medicines in cancer therapy from TCM theory to mechanistic insights. Planta Med 76(11):1118–1131
3. Hanahan D, Weinberg RA (2011) The hallmarks of cancer: the next generation. Cell 144:646–674
4. Efferth T, Dunstan H, Sauerbrey A, Miyachi H, Chitambar C et al (2001) The anti-malarial artesunate is also active against cancer. Int J Oncol 18:767–773
5. Efferth T, Saverbrey A, Olbrich A et al (2003) Molecular modes of action of artesunate in tumour cell lines. Mol Pharmacol 64(2):382–394
6. Efferth T (2003) Molecular modes of action of artesunate in tumor cell lines. Mol Pharmacol 64(2):382–394
7. Efferth T, Sauerbrey A, Olbrich A, Gebhart E, Rauch P, Weber HO et al (2003) Molecular modes of action of artesunate in tumor cell lines. Mol Pharmacol 64:382–394
8. Reungpatthanaphong P, Mankhetkorn S (2002) Modulation of multidrug resistance by artemisinin, artesunate and dihydroartemisinin in K562/adr and GLC4/adr resistant cell lines. Biol Pharm Bull 25(12):1555–1561
9. Woerdenbag HJ, Moskal TA, Pras N et al (1993) Cytotoxicity of artemisinin-related endoperoxides to Ehrlich ascites tumor cells. J Nat Prod 56(6):849–856
10. Dondorp AM, Nosten F, Yi P et al (2009) Artemisinin resistance in *Plasmodium falciparum* malaria. New Engl J Med 361(5):455–467
11. Gordi T, Lepist EI (2004) Artemisinin derivatives: toxic for laboratory animals, safe for humans? Toxicol Lett 147(2):99–107
12. Abad MJ, Bedoya LM, Apaza L, Bermejo P (2012) The *Artemisia* L. genus: a review of bioactive essential oils. Molecules 17(3):2542–2566
13. Bora KS, Sharma A (2011) The genus *Artemisia*: a comprehensive review. Pharm Biol 49(1):101–109
14. Sadiq A, Hayat MQ, Ashraf M (2014) Ethnopharmacology of Artemisia annua L.: A review. Artemisia annua-pharmacology and biotechnology. Springer, Cham, pp 9–25
15. Lubbe A, Seibert I, Klimkait T, Van der Kooy F (2012) Ethnopharmacology in overdrive: the remarkable anti-HIV activity of *Artemisia annua*. J Ethnopharmacol 141(3):854–859
16. Lee SK, Kim H, Park J, Kim H-J, Kim KR, Son SH et al (2017) Artemisia annua extract prevents ovariectomy-induced bone loss by blocking receptor activator of nuclear factor kappa-B ligand-induced differentiation of osteoclasts. Sci Rep 7(1):17332
17. Li X, Ba Q, Liu Y, Yue Q, Chen P, Li J et al (2017) Dihydroartemisinin selectively inhibits PDGFRα-positive ovarian cancer growth and metastasis through inducing degradation of PDGFRα protein. Cell Discov 3:17042
18. Feng M-X, Hong J-X, Wang Q, Fan Y-Y, Yuan C-T, Lei X-H et al (2016) Dihydroartemisinin prevents breast cancer-induced osteolysis via inhibiting both breast cancer cells and osteoclasts. Sci Rep 6:19074
19. Chen H, Sun B, Pan S, Jiang H, Sun X et al (2009) Dihydroartemisinin inhibits growth of pancreatic cancer cells in vitro and in vivo. Anticancer Drugs 20:131–140
20. Chen T, Li M, Zhang R, Wang H et al (2009) Dihydroartemisinin induces apoptosis and sensitizes human ovarian cancer cells to carboplatin therapy. J Cell Mol Med 13(7):1358–1370
21. Kim SJ, Kim MS, Lee JW, Lee CH, Yoo H, Shin SH et al (2006) Dihydroartemisinin enhances radio sensitivity of human glioma cells in vitro. J Cancer Res Clin Oncol 132:129–135
22. Lu JJ, Chen S, Zhang M, Ding XW, Meng LH et al (2011) The anti-cancer activity of dihydroartemisinin is associated

with induction of iron-dependent endoplasmic reticulum stress in colorectal carcinoma HCT116 cells. Invest New Drugs 29:1276–1283
23. Mu D, Chen W, Yu B, Zhang C, Zhang Y, Qi H et al (2008) Calcium and survivin are involved in the induction of apoptosis by dihydroartemisinin in human lung cancer SPC-A-1 cells. Methods Find Exp Clin Pharmacol 29:33–38
24. Singh NP, Lai H (2001) Selective toxicity of dihydroartemisinin and holotransferrin toward human breast cancer cells. Life Sci 70:49–56
25. Zhang Y, Xu G, Zhang S, Wang D, Prabha PS, Zuo Z (2018) Antitumor research on artemisinin and its bioactive derivatives. Nat Prod Bioprospect 8(4):303–319
26. Roth RJ, Acton N (1989) The isolation of sesquiterpenes from *Artemisia annua*. J Chem Educ 66:349–350
27. Brown TA (1993) Gene cloning and DNA analysis and introduction. In: Brown TA (ed), Blackwell Science, pp 139–144
28. Nam W, Tak J, Ryu JK, Jung M, Yook JI, Kim HJ et al (2007) Effects of artemisinin and its derivatives on growth inhibition andapoptosis of oral cancer cells. Head Neck 29:335–340
29. Posner GH, McRiner AJ, Paik IH, Sur S, Borstnik K, Xie S, Shapiro TA, Alagbala A, Foster B et al (2004) Anticancer and antimalarial efficacy and safety of artemisinin-derived trioxane dimers in rodents. J Med Chem 47:1299–1302
30. Singh NP, Lai H (2004) Artemisinin induces apoptosis in human cancer cells. Anticancer Res 24:2277–2280
31. Thomas E, Axel S, Armin O, Erich G, Pia R, Oliver W et al (2003) Molecular modes of action of artesunate in tumor cell lines. Mol Pharmacol 64:382–394
32. Wu GD, Zhou HJ, Wu XH et al (2006) Apoptosis of human umbilical vein endothelial cells induced by artesunate. Vasc Pharmacol 41(6):205–212
33. Chen HH, Zhou HJ, Wu GD, Lou XE et al (2004) Inhibitory effects of artesunate on angiogenesis and on expressions of vascular endothelial growth factor and VEGF receptor KDR/flk-1. Pharmacology 71:1–9
34. Yamachika E, Habte T, Oda D et al (2004) Artemisinin: an alternative treatment for oral squamous cell carcinoma. Anticancer Res 24:2153–2160
35. Jiao Y, Ge C, Meng Q, Cao J, Tong J, Fan S et al (2007) Dihydroartemisinin is an inhibitor of ovarian cancer cell growth. Acta Pharmacol Sin 28(7):1045–1056. https://doi.org/10.1111/j.1745-7254.2007.00612.x
36. Disbrow GL, Baege AC, Kierpiec KA et al (2005) Dihydroartemisinin is Cytotoxic to papillomavirus-expressing epithelial cells in vitro and in vivo. Cancer Res 65:10854–10861
37. Wu JM, Shan F, Wu GS, Li Y, Ding J, Xiao D, Han JX, Atassi G, Leonce S, Caignard DH, Renard P et al (2001) Synthesis and cytotoxicity of artemisinin derivatives containing cyanoarylmethyl group. Eur J Med Chem 36:469–479
38. Efferth T, Olbrich A, Bauer R et al (2002) mRNA expression profiles for the response of human tumor cell lines to the antimalarial drugs artesunate, arteether, and artemether. Biochem Pharmacol 64(4):617–623
39. Sadava D, Phillips T, Lin C, Kane SE et al (2002) Transferrin overcomes drug resistance to artemisinin in human small-cell lung carcinoma cells. Cancer Lett 179:151–156
40. Efferth T, Benakis A, Romero MR, Tomicic M, Rauh R, Steinbach D et al (2004) Enhancement of cytotoxicity of artemisinins toward cancer cells by ferrous iron. Free Radic Biol Med 37:998–1009
41. Efferth T (2004) Combination treatment of glioblastoma multiforme cell lines with the anti-malarial artesunate and the epidermal growth factor receptor tyrosine kinase inhibitor OSI-774. Biochem Pharmacol 67(9):1689–1700
42. Firestone GL, Sundar SN (2009) Anticancer activities of artemisinin and its bioactive derivatives. Expert Rev Mol Med 11:32
43. O'Neill PM, Barton VE, Ward SA et al (2010) The molecular mechanism of action of artemisinin–the debate continues. Molecules 15:1705–1721
44. Henry L, Tomikazu S, Narendra PS et al (2005) Oncologic, endocrine and metabolic treatment of cancer with artemisinin and artemisinin tagged iron-carrying compounds. Expert Opin Ther Targets 9(5):995–1007
45. Rowen RJ (2002) Artemisinin: from malaria to cancer treatment. Townsend Lett Doct Patients 86–88
46. Gong Y, Gallis BM, Goodlett DR, Yang Y, Lu H, Lacoste E et al (2013) Effects of transferrin conjugates of artemisinin and artemisinin dimer on breast cancer cell lines. Anticancer Res 33:123–132
47. Krishna S, Bustamante L, Haynes RK, Staines HM et al (2008) Artemisinins: their growing importance in medicine. Trends Pharmacol Sci 29:520–527. https://doi.org/10.1016/j.tips.2008.07.004
48. Paik IH, Xie S, Shapiro TA, Labonte T, Narducci Sarjeant AA, Baege AC et al (2006) Second generation, orally active, antimalarial, artemisinin-derived trioxane dimers with high stability, efficacy, and anticancer activity. JMedChem 49:2731–2734
49. Sertel S, Plinkert P, Efferth T et al (2013) Activity of artemisinin-type compounds against cancer cells. In: Wagner H, Ulrich-Merzenich G (eds) Evidence and rational based research on chinese drugs. Springer, Vienna, pp 333–362
50. Stockwin LH, Han B, Yu SX, Hollingshead MG, ElSohly MA, Gul W et al (2009) Artemisinin dimer anticancer activity correlates with heme-catalyzed reactive oxygen species generation and endoplasmic reticulum stress induction. Int J Cancer 125:1266–1275
51. Yoon MK, Mitrea DM, Ou L, Kriwacki RW et al (2012) Cell cycle regulation by the intrinsically disordered proteins p21 and p27. Biochem Soc Trans 40:981–988
52. Tin AS, Sundar SN, Tran KQ, Park AH, Poindexter KM, Firestone GL et al (2012) Antiproliferative effects of artemisinin on human breast cancer cells requires the downregulated expression of the E2F1 transcription factor and loss of E2F1-target cell cycle genes. Anticancer Drugs 23:370–379
53. Chen G, Gong R, Shi X, Yang D, Zhang G et al (2016) Halofuginone and artemisinin synergistically arrest cancer cells at the G1/G0 phase by upregulating p21Cip1 and p27Kip1. Oncotarget 7(31):50302–50314
54. Huang Z, Huang X, Jiang D, Zhang Y, Huang B, Luo G et al (2016) Dihydroartemisinin inhibits cell proliferation by induced G1 arrest and apoptosis in human nasopharyngeal carcinoma cells. J Cancer Res Ther 12(1):244–247. https://doi.org/10.4103/0973-1482.151855
55. Tong Y, Tong Y, Liu Y, Zheng H, Zheng L, Liu W, Wu J, Ou R, Zhang G, Li F, Hu M, Liu Z, Lu L et al (2016) Artemisinin and its derivatives can significantly inhibit lung tumorigenesis and tumor metastasis through Wnt/β-catenin signaling. Oncotarget 7(21):31413–31428
56. Hou J, Wang D, Zhang R, Wang H et al (2008) Experimental therapy of hepatoma with artemisinin and Its derivatives: In vitro and in vivo activity, chemosensitization, and mechanisms of action. Clin Cancer Res 14(17):5519–5530. https://doi.org/10.1158/1078-0432.CCR-08-0197
57. Willoughby JA, Sundar SN, Cheung M, Tin AS, Modiano J, Firestone GL et al (2009) Artemisinin blocks prostate cancer growth and cell cycle progression by disrupting Sp1 interactions with the cyclin-dependent kinase-4 (CDK4) promoter and inhibiting CDK4 gene expression. J Biol Chem 284(4):2203–2213. https://doi.org/10.1074/jbc.M804491200

58. Steinbrück G, Pereira I, Efferth T et al (2010) Effects of artesunate on cytokinesis and G2/M cell cycle progression of tumour cells and budding yeast. Cancer Genom Proteom 7(6):337–346
59. Wang SJ, Gao Y, Chen H, Kong R, Jiang HC, Pan SH, Sun B et al (2010) Dihydroartemisinin inactivates NF-??B and potentiates the anti-tumor effect of gemcitabine on pancreatic cancer both in vitro and in vivo. Cancer Lett 293(1):99–108. https://doi.org/10.1016/j.canlet.2010.01.001
60. K Liao, J Li, Z Wang et al (2014) Dihydroartemisinin inhibits cell proliferation via AKT/GSK3β/cyclinD1 pathway and induces apoptosis in A549 lung cancer cells. Int J Clin Exp Pathol 7(12):8684–8691. Retrieved from www.ijcep.com
61. Liao K, Li J, Wang Z et al (2014) Dihydroartemisinin inhibits cell proliferation via AKT/GSK3β/cyclinD1 pathway and induces apoptosis in A549 lung cancer cells. Int J Clin Exp Pathol 7(12):8684–8691
62. Xu Q, Li Z-X, Peng H-Q, Sun Z-W, Cheng R-L, Ye Z-M, Li W-X (2011) Artesunate inhibits growth and induces apoptosis in human osteosarcoma HOS cell line in vitro and in vivo. J Zhejiang Univ Sci B 12(4):247–255
63. Ma H, Yao Q, Zhang AM, Lin S, Wang XX, Wu L, Chen ZT et al (2011) The effects of artesunate on the expression of EGFR and ABCG2 in A549 human lung cancer cells and a xenograft model. Molecules 16(12):10556–10569. https://doi.org/10.3390/molecules161210556
64. Du W, Pang C, Xue Y, Zhang Q, Wei X et al (2015) Dihydroartemisinin inhibits the Raf/ERK/MEK and PI3K/AKT pathways in glioma cells. Oncol Lett. https://doi.org/10.3892/ol.2015.3699
65. Zhang J, Ling G, Xia Z, Fengyun D, Liqun L, Zuowang C, Yinghua X, Jiyong L, Qi X, Liu Ju et al (2016) Dihydroartemisinin induces endothelial cell anoikis through the activation of the JNK signaling pathway. Oncol Lett 12:1896–1900
66. Zhao X, Zhong H, Wang R, Liu D, Waxman S, Zhao L, Jing Y et al (2015) Dihydroartemisinin and its derivative induce apoptosis in acute myeloid leukemia through Noxa-mediated pathway requiring iron and endoperoxide moiety. Oncotarget 6(8):5582–5596
67. Dong F (2014) Dihydroartemisinin targets VEGFR2 via the NF-κB pathway in endothelial cells to inhibit angiogenesis. Cancer Biol Ther 15(11):1479–1488
68. Hwang YP, Yun HJ, Kim HG, Han EH, Lee GW, Jeong HG et al (2010) Suppression of PMA-induced tumor cell invasion by dihydroartemisinin via inhibition of PKCα/Raf/MAPKs and NF-κB/AP-1-dependent mechanisms. Biochem Pharmacol 79(12):1714–1726
69. Aung W, Sogawa C, Furukawa T, Saga T et al (2011) Anticancer effect of dihydroartemisinin (DHA) in a pancreatic tumor model evaluated by conventional methods and optical imaging. Anticancer Res 31:1549–1558
70. He Q, Jingxue S, Xiao-Ling S, Jie A, Hong S, Lu W, Ying-Jie H, Qing S, Lin-Chun F, Saeed SM, Ying H et al (2010) Dihydroartemisinin upregulates death receptor 5 expression and cooperates with TRAIL to induce apoptosis in human prostate cancer cells. Cancer Biol Ther 9(10):819–824
71. Mao H (2013) Involvement of the mitochondrial pathway and Bim/Bcl-2 balance in dihydroartemisinin-induced apoptosis in human breast cancer in vitro. Int J Mol Med 31(1):213–218
72. Wang JX, Tang W, Shi LP, Wan J, Zhou R, Ni J, Fu YF, Yang YF, Li Y, Zuo JP et al (2007) Investigation of the immunosuppressive activity of artemether on T-cell activation and proliferation. Br J Pharmacol 150:652–661
73. Wu ZP, Gao CW, Wu YG, Zhu QS, Chen Y, Liu X, Liu C et al (2009) Inhibitive effect of artemether on tumor growth and angiogenesis in the rat C6 orthotopic brain gliomas model. Integr Cancer Ther 8:88–92
74. Jiao Y, Tong J (2007) Dihydroartemisinin is an inhibitor of ovarian cancer cell growth. Acta Pharmacol Sin 28(7):1045–1056
75. Cheng R, Li C, Li C, Wei L, Li L, Zhang Y, Gao G et al (2013) The artemisinin derivative artesunate inhibits corneal neovascularization by inducing ROS-dependent apoptosis in vascular endothelial cells. Invest Ophthalmol Vis Sci 54(5):3400–3409
76. Yang ND, Shi-Hao T, Shukie N, Yin S, Jing Z, Kevin S, Wei T, Wai-Shiu FW, Han-Ming S (2014) Artesunate induces cell death in human cancer cells via enhancing lysosomal function and lysosomal degradation of ferritin. J Biol Chem 289(48):33425–33441
77. Chen H, Shi L, Yang X, Li S, Guo X, Pan L et al (2010) Artesunate inhibiting angiogenesis induced by human myeloma RPMI8226 cells. Int J Hematol 92(4):587–597. https://doi.org/10.1007/s12185-010-0697-3
78. Chen H, Sun B, Wang S, Pan S, Gao Y, Bai X, Xue D et al (2010) Growth inhibitory effects of dihydroartemisinin on pancreatic cancer cells: involvement of cell cycle arrest and inactivation of nuclear factor-kappaB. J Cancer Res Clin Oncol 136(6):897–903
79. Jia G, Rui K, Zhi-Bin M, Bing H, Yong-Wei W, Shang-Ha P, Ying-Hua L, Bei S et al (2014) The activation of c-Jun NH2-terminal kinase is required for dihydroartemisinin-induced autophagy in pancreatic cancer cells. J Exp Clin Cancer Res 33:8–15
80. Thomas S, Quinn BA, Das SK, Dash R, Emdad L, Dasgupta S et al (2013) Targeting the Bcl-2 family for cancer therapy. Exp Opin Ther Targets 17:61–75
81. Chen Y, Zhang D, Liao Z et al (2015) Anti-oxidant polydatin (piceid) protects against substantia nigral motor degeneration in multiple rodent models of parkinson's disease. Mol Neurodegener 10:4
82. Morrissey C, Gallis B, Solazzi JW, Kim BJ, Gulati R, Vakar-Lopez F, Sasaki T (2010) Effect of artemisinin derivatives on apoptosis and cell cycle in prostate cancer cells. Anticancer Drugs 21(4):423
83. Mizushima N, Levine B, Cuervo AM, Klionsky DJ et al (2008) Autophagy fights disease through cellular self-digestion. Nature 451(7182):1069–1075
84. Chen SS, Hu W, Wang Z, Lou XE, Zhou HJ et al (2015) p8 attenuates the apoptosis induced by dihydroartemisinin in cancer cells through promoting autophagy. Cancer Biol Ther. https://doi.org/10.1080/15384047.2015.1026477
85. Galluzzi L, Pietrocola F, Bravo-San Pedro JM, Amaravadi RK, Baehrecke EH, Cecconi F, Kroemer G et al (2015) Autophagy in malignant transformation and cancer progression. EMBO J 34(7):856–880. https://doi.org/10.15252/embj.201490784
86. Chen K, Shou L-M, Lin F, Duan W-M, Wu M-Y, Xie X, Tao M et al (2014) Artesunate induces G2/M cell cycle arrest through autophagy induction in breast cancer cells. Anticancer Drugs 25:652–662
87. Gao M, Monian P, Pan Q, Zhang W, Xiang J, Jiang X et al (2016) Ferroptosis is an autophagic cell death process. Cell Res 26(9):1021–1032. https://doi.org/10.1038/cr.2016.95
88. Li Z (2016) Artemisinin and its derivatives as a repurposing anticancer agent: what else do we need to do? Molecules 21(10):1331–1339
89. Wong YK, He Y, Wang J, Xu C, Kalesh KA, Shen H, Wong WSF et al (2017) Artemisinin as an anticancer drug: recent advances in target profiling and mechanisms of action. Med Res Rev 2017(37):1492–1517. https://doi.org/10.1002/med.21446
90. Giuliano S, Pagès G (2013) Mechanisms of resistance to anti-angiogenesis therapies. Biochimie 95(6):1110–1119. https://doi.org/10.1016/j.biochi.2013.03.002
91. Wang SJ, Sun B, Cheng ZX, Zhou HX, Gao Y, Kong R, Bai XW et al (2011) Dihydroartemisinin inhibits angiogenesis in pancreatic cancer by targeting the NF-??B pathway. Cancer Chemother

Pharmacol 68(6):1421–1430. https://doi.org/10.1007/s00280-011-1643-7
92. Boyeva SA, Brezhneva TA, Maltseva AA, Buzlama AV, Slivkin AI (2007) Saponins of the *Polemonium caeruleum* L. and *Beta vulgaris* L. plants. The features of obtaining, the comparative assessment of the hypoglycemic activity. Proc Voronezh State Univ Chem Biol Pharm 1:139–141
93. Cavallo F, De Giovanni C, Nanni P, Forni G, Lollini P-L (2011) 2011: the immune hallmarks of cancer. Cancer Immunol Immunother 60(3):319–326
94. Efferth T, Albini A, Pfeffer U et al (2006) Microarray expression profiles of angiogenesis-related genes predicttumor cell response to artemisinins. Pharmacogenom J 6:269–278
95. Martinez-Outschoorn UE, Peiris-Pagés M, Pestell RG, Sotgia F, Lisanti MP et al (2017) Cancer metabolism: a therapeutic perspective. Nat Rev Clin Oncol 14(1):11–31. https://doi.org/10.1038/nrclinonc.2016.60
96. Mi Y, Geng G, Zou Z, Gao J, Luo X, Liu Y et al (2015) Dihydroartemisinin inhibits glucose uptake and cooperates with glycolysis inhibitor to induce apoptosis in non-small cell lung carcinoma cells. PLoS ONE 10(3):1–21. https://doi.org/10.1371/journal.pone.0120426
97. Ravindra KC, Ho WE, Cheng C, Godoy LC, Wishnok JS, Ong CN, Wong WS, Wogan GN, Tannenbaum SR et al (2015) Untargeted proteomics and systems-based mechanistic investigation of artesunate in human bronchial epithelial cells. Chem Res Toxicol 28(10):1903–1913
98. Zhou Y, Weichao L, Xiao Y et al (2016) Profiling of Multiple Targets of Artemisinin Activated by Hemin in Cancer Cell Proteome. ACS Chem Biol 11:882–888. https://doi.org/10.1021/acschembio.5b01043
99. Li Y (2012) Qinghaosu (artemisinin): chemistry and pharmacology. Acta Pharmacol Sin 33:1141–1146. https://doi.org/10.1038/aps.2012.104
100. Ho WE, Peh HY, Chan TK, Wong WS et al (2014) Artemisinin: pharmacological actions beyond anti-malarial. Pharmacol Ther 142:126–139. https://doi.org/10.1016/j.pharmthera.2013.12.001
101. Crespo-Ortiz MP, Wei MQ (2012) Antitumor activity of artemisinin and its derivatives: from a well-known antimalarial agent to a potential anticancer drug. J Biomed Biotechnol 2012:247597. https://doi.org/10.1155/2012/247597
102. Chaturvedi D, Goswami A, Saikia PP, Barua NC, Rao PG et al (2010) Artemisinin and its derivatives: a novel class of anti-malarial and anti-cancer agents. Chem Soc Rev 39(2):435–454
103. Efferth T (2006) Molecular pharmacology and pharmacogenomics of artemisinin and its derivatives in cancer cells. Curr Drug Targets 7:407–421
104. Reichert S, Reinboldt V, Hehlgans S, Efferth T, Rodel C, Rodel F et al (2012) A radiosensitizing effect of artesunate in glioblastoma cells is associated with a diminished expression of the inhibitor of apoptosis protein survivin. Radiother Oncol 103:394–401. https://doi.org/10.1016/j.radonc.2012.03.018
105. Michaelis M (2010) Anti-cancer effects of artesunate in a panel of chemoresistant neuroblastoma cell lines. Biochem Pharmacol 79(2):130–136
106. Efferth T, Merling A, Krammer PH, Li-Weber M et al (2007) Artesunate induces ROS-mediated apoptosis in doxorubicin-resistant T leukemia cells. PLoS ONE 2(8):693
107. Hamacher-Brady A, Stein HA, Turschner S, Toegel I, Mora R, Jennewein N, Efferth T, Eils R, Brady NR et al (2011) Artesunate activates mitochondrial apoptosis in breast cancer cells via iron-catalyzed lysosomal reactive oxygen species production. J Biol Chem 286(8):6587–6601
108. Zeng QP, Zhang PZ (2011) Artesunate mitigates proliferation of tumor cells by alkylating heme-harboring nitric oxide synthase. Nitric Oxide 24(2):110–112
109. Du JH, Zhang HD, Ma ZJ, Ji KM et al (2010) Artesunate induces oncosis-like cell death in vitro and has antitumor activity against pancreatic cancer xenografts in vivo. Cancer Chemother Pharmacol 65(5):895–902
110. Anfosso L, Efferth T, Albini A, Pfeffer U et al (2006) Microarray expression profiles of angiogenesis-related genes predict tumor cell response to artemisinins. Pharmacogenom J 6:269–278
111. Lai HC, Singh NP, Sasaki T et al (2013) Development of artemisinin compounds for cancer treatment. Invest New Drugs 31(1):230–246
112. Li LN, Zhang HD, Yuan SJ, Tian ZY, Wang L, Sun ZX et al (2007) Artesunate attenuates the growth of human colorectal carcinoma and inhibits hyperactive Wnt/β-catenin pathway. Int J Cancer 121(6):1360–1365
113. Eling N, Reuter L, Hazin J, Hamacher-Brady A, Brady NR et al (2015) Identification of artesunate as a specific activator of ferroptosis in pancreatic cancer cells. Oncoscience 2(5):517–532
114. Chen HH, Zhou HJ, Fang X et al (2003) Inhibition of human cancer cell line growth and human umbilical vein endothelial cell angiogenesis by artemisinin derivatives in vitro. Pharmacol Res 48(3):231–236
115. Zhou HJ, Wang WQ, Wu GD, Lee J, Li A et al (2007) Artesunate inhibits angiogenesis and downregulates vascular endothelial growth factor expression in chronic myeloid leukemia K562 cells. Vascul Pharmacol 47(2):131–138
116. Youns M, Efferth T, Reichling J, Fellenberg K, Bauer A, Hoheisel JD et al (2009) Gene expression profiling identifies novel key players involved in the cytotoxic effect of Artesunate on pancreatic cancer cells. Biochem Pharmacol 78:273–283
117. Rasheed SAK, Efferth T, Asangani IA, Allgayer H et al (2010) First evidence that the antimalarial drug artesunate inhibits invasion and in vivo metastasis in lung cancer by targeting essential extracellular proteases. Int J Cancer 127:1475–1485
118. Li LN, Zhang HD, Yuan SJ, Yang DX, Wang L, Sun ZX et al (2008) Differential sensitivity of colorectal cancer cell lines to artesunate is associated with expression of beta-catenin and E-cadherin. Eur J Pharmacol 588(1):1–8
119. Lai H, Nakase I, Lacoste E, Singh NP, Sasaki T et al (2009) Artemisinin-transferrin conjugate retards growth of breast tumors in the rat. Anticancer Res 29(10):3807–3810
120. Nakase I, Gallis B, Takatani-Nakase T, Oh S, Lacoste E, Singh NP, Goodlett DR, Tanaka S, Futaki S, Lai H, Sasaki T et al (2009) Transferrin receptor-dependent cytotoxicity of artemisinin–transferrin conjugates on prostate cancer cells and induction of apoptosis. Cancer Lett 274(2):290–298
121. Nakase I, Lai H, Singh NP, Sasaki T et al (2008) Anticancer properties of artemisinin derivatives and their targeted delivery by transferrin conjugation. Int J Pharm 354:28–33
122. Singh NP, Verma K (2002) Case report of a laryngeal squamous cell carcinoma treated with artesunate. Arch Oncol 10(4):279–280
123. Berger TG, Dieckmann D, Efferth T, Schultz ES, Funk JO, Baur A, Schuler G et al (2005) Artesunate in the treatment of metastatic uveal melanoma-first experiences. Oncol Rep 14:1599–1604
124. Zhang Z, Yu SQ, Miao LY, Huang XY, Zhang XP, Zhu YP, Xia XH, Li DQ et al (2008) Artesunate combined with vinorelbine plus cisplatin in treatment of advanced non-small cell lung cancer: a randomized controlled trial. Zhong Xi Yi Jie He Xue Bao = J Chin Integr Med 6(2):134–138
125. Lu JJ, Meng LH, Shankavaram UT, Zhu CH, Tong LJ, Chen G, Lin LP, Weinstein JN, Ding J et al (2010) Dihydroartemisinin accelerates c-MYC oncoprotein degradation and induces apoptosis in c-MYC-overexpressing tumor cells. Biochem Pharmacol 80(1):22–30

126. Lu YY, Chen TS, Qu JL, Pan WL, Sun L, Wei XB et al (2009) Dihydroartemisinin (DHA) induces caspase-3-dependent apoptosis in human lung adenocarcinoma ASTC-a-1 cells. J Biomed Sci 16:16–20
127. Lu YY, Chen TS, Wang XP, Qu JL, Chen M et al (2010) The JNK inhibitor SP600125 enhances dihydroartemisinin-induced apoptosis by accelerating Bax translocation into mitochondria in human lung adenocarcinoma cells. FEBS Lett 584:4019–4026
128. Riganti C, Doublier S, Viarisio D, Miraglia E, Pescarmona G, Ghigo D et al (2009) Artemisinin induces doxorubicin resistance in human colon cancer cells via calcium-dependent activation of HIF-1αand P-glycoprotein overexpression. Br J Pharmacol 156:1054–1066
129. D'Alessandro S, Basilico N, Corbett Y, Scaccabarozzi D, Omodeo-Sale F, Saresella M, Marventano I, Vaillant M, Olliaro P, Taramelli D et al (2011) Hypoxia modulates the effect of dihydroartemisinin on endothelial cells. Biochem Pharmacol 82:476–484
130. Zhang J, Li L, Liu X, Wang Y, Zhao D et al (2012) Study on chemical constituents of *Artemisia sphaerocephala*. China J Chin Materia Med 37(2):238–242
131. Zhang CZ, Zhang H, Yun J, Chen GG, Lai PB et al (2012) Dihydroartemisinin exhibits antitumor activity toward hepatocellular carcinoma in vitro and in vivo. Biochem Pharmacol 83(9):1278–1289
132. Wang SJ (2010) Dihydroartemisinin inactivates NF-??B and potentiates the anti-tumor effect of gemcitabine on pancreatic cancer both in vitro and in vivo. Cancer Lett 293(1):99–108
133. Wang SJ (2011) Dihydroartemisinin inhibits angiogenesis in pancreatic cancer by targeting the NF-??B pathway. Cancer Chemother Pharmacol 68(6):1421–1430
134. Wu XL, Zhang WG, Shi XM, An P, Sun WS, Qiao CL, Wang Z et al (2011) Effect of artemisinin on the expressions of GRalpha mRNA, GRbeta mRNA and P300/CBP protein in lupus nephritis mice. J Chin Med Mater 17(4):277–282
135. Wang J, Zhang C-J, Chia WN et al (2015) Haem-activated promiscuous targeting of artemisinin in *Plasmodium falciparum*. Nat Commun 6:10111
136. D'Alessandro S, Gelati M, Basilico N, Parati EA, Haynes RK, Taramelli D et al (2007) Differential effects on angiogenesis of two antimalarial compounds, dihydroartemisinin and artemisone: implications for embryotoxicity. Toxicology 241(1):66–74
137. Wei-Ling X, Pei-Hui Y, Zeng X, Ji-Ye C et al (2009) Effect of 4-(12-dihydroartemisininoxy) benzoic acid hydrazide transferrin tagged drug on human breast cancer cells. Chin J Anal Chem 37(5):671–675
138. Singh NP, Panwar VK (2006) Case report of a pituitary macroadenoma treated with artemether. Integr Cancer Ther 5:391–394
139. Farsam V, Hassan ZM, Zavaran-Hosseini A, Noori S, Mahdavi M, Ranjbar M et al (2011) Antitumor and immunomodulatory properties of artemether and its ability to reduce CD4+ CD25+ FoxP3+ T reg cells in vivo. Int Immunopharmacol 11:1802–1808
140. Alcântara DDFÁ, Ribeiro HF, Cardoso PCS, Araújo TMT, Burbano RR, Guimarães AC, Khayat AS, Oliveira BM et al (2013) In vitro evaluation of the cytotoxic and genotoxic effects of artemether, an antimalarial drug, in a gastric cancer cell line (PG100). J Appl Toxicol 33:151–156
141. Zhao Y, Jiang W, Li B, Yao Q, Dong J, Chen Y, Pan X, Li J, Zheng J, Pang X et al (2011) Artesunate enhances radiosensitivity of human non-small cell lung cancer A549 cells via increasing no production to induce cell cycle arrest at G 2/M phase. Int Immunopharmacol 11:2039–2046
142. Efferth T, Oesch F (2004) Oxidative stress response of tumor cells: microarray-based comparison between artemisinins and anthracyclines. Biochem Pharmacol 68:3–10
143. Luthria DL (2006) Significance of sample preparation in developing analytical methodologies for accurate estimation of bioactive compounds in functional foods. J Sci Food Agric 86(14):2266–2272
144. Castellano G, Tena J, Torrens F et al (2012) Classification of phenolic compounds by chemical structural indicators and its relation to antioxidant properties of *posidonia oceanica* (L.) Delile. Environment 2:6–9
145. Ferreira JF, Luthria DL, Sasaki T, Heyerick A et al (2010) Flavonoids from *Artemisia annua* L. as antioxidants and their potential synergism with artemisinin against malaria and cancer. Molecules 15(5):3135–3170
146. Croteau R, Kutchan T, Lewis N et al (2000) Natural products (secondary metabolites). Biochem Mol Biol Plants 24:1250–1319
147. Debeaujon I, Peeters AJ, Léon-Kloosterziel KM, Koornneef M et al (2001) The TRANSPARENT TESTA12 gene of Arabidopsis encodes a multidrug secondary transporter-like protein required for flavonoid sequestration in vacuoles of the seed coat endothelium. Plant Cell 13(4):853–871
148. Kitamura S (2006) Transport of flavonoids: from cytosolic synthesis to vacuolar accumulation. The science of flavonoids. Springer, Cham, pp 123–146
149. Grassi D, Desideri G, Ferri C et al (2010) Flavonoids: antioxidants against atherosclerosis. Nutrients 2:889–902
150. Middleton JR (1998) Effect of plant flavonoids on immune and inflammatory cell function. Flavonoids in the living system. Springer, Cham, pp 175–182
151. Falcone Ferreyra ML, Rius S, Casati P et al (2012) Flavonoids: biosynthesis, biological functions, and biotechnological applications. Front Plant Sci 3:222
152. Aberham A, Cicek SS, Schneider P, Stuppner H et al (2010) Analysis of sesquiterpene lactones, lignans, and flavonoids in wormwood (*Artemisia absinthium* L.) using high-performance liquid chromatography (HPLC)—mass spectrometry, reversed phase HPLC, and HPLC—solid phase extraction—nuclear magnetic resonance. J Agric Food Chem 58(20):10817–10823
153. Singh R, Verma PK, Singh G et al (2012) Total phenolic, flavonoids and tannin contents in different extracts of *Artemisia absinthium*. J Intercult Ethnopharmacol 1(2):101–104
154. Hajdú Z, Martins A, Orbán-Gyapai O, Forgo P, Jedlinszki N, Máthé I, Hohmann J et al (2014) Xanthine oxidase-inhibitory activity and antioxidant properties of the methanol extract and flavonoids of *Artemisia asiatica*. Rec Nat Prod 8(3):299
155. Qnais E, Raad D, Bseiso Y et al (2014) Analgesic and anti-inflammatory effects of an extract and flavonoids from *Artemisia* herba-alba and their mechanisms of action. Neurophysiology 46(3):238–246
156. Suresh J, Ahuja J, Paramakrishnan N, Sebastian M et al (2012) Total phenolic and total flavonoids content of aerial parts of *Artemisia abrotanum* Linn. and *A. pallens* wall. Anal Chem Lett 2(3):186–191
157. Xiao M, Luo D, Ke Z, Ye J, Tu PF (2014) A novel polyacetylene from the aerial parts of *Artemisia lactiflora*. Phytochem Lett 8:52–54
158. Mabeza GF, Loyevsky M, Gordeuk VR, Weiss G et al (1999) Iron chelation therapy for malaria: a review. Pharmacol Ther 81(1):53–75
159. Lai H, Singh NP (1995) Selective cancer cell cytotoxicity from exposure to dihydroartemisinin and holotransferrin. Cancer Lett 91(1):41–46
160. Moore JC, Lai H, Li JR, Ren RL, McDougall JA, Singh NP, Chou CK et al (1995) Oral administration of dihydroartemisinin and ferrous sulfate retarded implanted fibrosarcoma growth in the rat. Cancer Lett 98(1):83–87

161. Li XY, Zhao Y, Sun MG, Shi JF, Ju RJ, Zhang CX, Lu WL et al (2014) Multifunctional liposomes loaded with paclitaxel and artemether for treatment of invasive brain glioma. Biomaterials 35(21):5591–5604. https://doi.org/10.1016/j.biomaterials.2014.03.049
162. Li P, Yang S, Dou M, Chen Y, Zhang J, Zhao X et al (2014) Synergic effects of artemisinin and resveratrol in cancer cells. J Cancer Res Clin Oncol 140(12):2065–2075
163. Dilshad E, Zafar S, Ismail H, Waheed MT, Cusido RM, Palazon J, Mirza B (2016) Effect of rol genes on polyphenols biosynthesis in *Artemisia annua* and their effect on antioxidant and cytotoxic potential of the plant. Appl Biochem Biotechnol 179(8):1456–1468
164. Dilshad E, Ismail H, Khan MA, Cusido RM, Mirza B (2020) Metabolite profiling of *Artemisia carvifolia* Buch transgenic plants and estimation of their anticancer and antidiabetic potential. Biocatal Agric Biotechnol 24:101539
165. Tolomeo M, Grimaudo S, Di Cristina A, Roberti M, Pizzirani D, Meli M, Dusonchet L, Gebbia N, Abbadessa V, Crosta L et al (2005) Pterostilbene and 3′-hydroxypterostilbene are effective apoptosis-inducing agents in MDR and BCR-ABL-expressing leukemia cells. Int J Biochem Cell Biol 37(8):1709–1726
166. Yeon J, Raj C, Thapa K, Soon C, Jong Y, Kim O et al (2016) Nanoparticle-based combination drug delivery systems for synergistic cancer treatment. J Pharm Investig. https://doi.org/10.1007/s40005-016-0252-1
167. Ochiuz L, Grigoras C, Popa M, Stoleriu I, Munteanu C, Timofte D, Grigoras AG et al (2016) Alendronate-loaded modified drug delivery lipid particles intended for improved oral and topical administration. Molecules 21(7):858. https://doi.org/10.3390/molecules21070858
168. Gharib A, Faezizadeh Z, Mesbah-Namin SA, Saravani R et al (2014) Preparation, characterization and in vitro efficacy of magnetic nanoliposomes containing the artemisinin and transferrin. Daru 22(1):44–50. https://doi.org/10.1186/2008-2231-22-44
169. Wu GS (2013) Synergistic anti-cancer activity of the combination of dihydroartemisinin and doxorubicin in breast cancer cells. Pharmacol Rep 65(2):453–459
170. Eltayeb SE, Su Z, Xiao Y, Ping Q et al (2016) Antitumor activity of transferrin-modified- artemether lipid nanospheres in cancer cell lines. J Drug Deliv Sci Technol 31:118–129. https://doi.org/10.1016/j.jddst.2015.12.003
171. Nguyen DX, Massague J (2014) Genetic determinants of cancer metastasis. Nat Rev Genet 8:341–352
172. Jiang W, Huang Y, Wang J, Yu X, Zhang L et al (2013) The synergistic anticancer effect of artesunate combined with allicin in osteosarcoma cell line in vitro and in vivo. Asian Pac J Cancer Prev 14:4615–4619
173. Krusche B, Arend J, Efferth T et al (2013) Synergistic inhibition of angiogenesis by artesunate and captopril in vitro and in vivo. Evid Based Complement Altern Med. https://doi.org/10.1155/2013/454783