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REVIEW

Development of artemisinin compounds for cancer treatment

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Summary Artemisinin contains an endoperoxide moiety that can react with iron to form cytotoxic free radicals. Cancer cells contain significantly more intracellular free iron than normal cells and it has been shown that artemisinin and its analogs selectively cause apoptosis in many cancer cell lines. In addition, artemisinin compounds have been shown to have anti-angiogenic, anti-inflammatory, anti-metastasis, and growth inhibition effects. These properties make artemisinin compounds attractive cancer chemotherapeutic drug candidates. However, simple artemisinin analogs are less potent than traditional cancer chemotherapeutic agents and have short plasma half-lives, and would require high dosage and frequent administration to be effective for cancer treatment. More potent and target-selective artemisinin-compounds are being developed. These include artemisinin dimers and trimers, artemisinin hybrid compounds, and tagging of artemisinin compounds to molecules that are involved in the intracellular iron-delivery mechanism. These compounds are promising potent anticancer compounds that produce significantly less side effect than traditional chemotherapeutic agents.

Keywords Artemisinins · Anticancer properties · Drug development

Introduction

Artemisinin (Fig. 1), a chemical isolated from the sweet wormwood *Artemisia annua L*, is a sesquiterpene lactone with potent antimalarial activity. Its effectiveness on malaria is due to its endoperoxide moiety that reacts with heme, which is abundant in malaria parasites, leading to the formation of carbon-based free radicals which in turn cause death of the parasite. Artemisinin is also being developed into an anticancer therapeutic agent. The rationale is that cancer cells, like the malaria parasites, contain high concentration of free iron. Cell death also results from the formation of free radicals by the artemisinin-iron reaction. The advantage of artemisinin as an anticancer agent is not only in its potency as a toxic agent to cancer cells, but also in its selectivity in killing cancer cells and low toxicity to normal cells. In a paper published in 1995 [1], we demonstrated that dihydroartemisinin is 100 times more toxic to human leukemia cells than normal lymphocytes. This was again shown later in human breast cancer cells versus normal breast cells [2]. In addition, we showed that an increase in intracellular iron by preincubating cancer cells with holotransferrin could potentiate the toxicity of artemisinin toward the cells. This gave support to the hypothesis that artemisinin kills cancer cells via its reaction with free iron and its selectivity toward cancer cells was due to their high rate of uptake of iron via transferrin receptors compared to normal cells. This property of artemisinin enables it to be effective against many different types of cancer cells.

Over the years, various forms of molecules containing artemisinin/endoperoxide moiety have been developed for more effective cancer treatment. In this review, we will summarize these developments and discuss some of the problems.

Artemisinin and its monomer analogs are generally not potent enough to assure cancer cure due to their relatively low toxicity toward cancer cells and short half lives. More potent compounds are needed. Many attempts have been made to increase the cancer cytotoxicity potency. These include artemisinin dimers, tetraoxanes and hybrids. Another approach is to deliver artemisinin compounds to cancer cells by tagging them to cancer cell targeting molecules.

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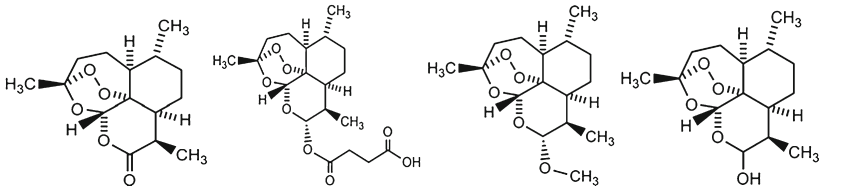

Fig. 1 Molecular structures of several common artemisinin monomers

Artemisinin monomers

The anticancer effects of artemisinin have been reported in the early 1990s *by* Woerdenbag et al. [3]. Most of the earlier research was mainly on the monomer analogs. The most prolific researcher in this area has been Thomas Efferth of the Johannes Gutenberg University.

The common artemisinin monomers (artemisinin, dihydroartemisinin, artesuante and artemether (Fig. 1)) have been tested on many different types of cancer cells (Table 1). Results indicate they are toxic to cancer cells with IC_{50}s in the 10–20 μM range. Only few studies had simultaneously tested the compounds on normal cells [1, 2, 4–11]. In general, artemisinin compounds have been shown to be more toxic toward cancer cells than their corresponding normal cells. Many molecular mechanisms have been investigated. Artemisinins affect many different cellular pathways that are involved in cellular development, proliferation, and apoptosis. Apoptosis is a commonly reported effect [6, 7, 12–31], as well as arrest in cell cycle [9, 11, 32–37], particularly at the G_0/G_1 phases. Thus, both cell death and growth inhibition occur. However, the site of action is not clear. There are reports of involvement of mitochondria and the apoptotic pathway [5, 7, 9, 20–22, 38–41]. There are also reports suggesting extra-mitochondrial mode of action [7, 30, 44]. Involvements of iron/heme [1, 2, 9, 14, 23, 38, 40–45] and reactive oxidative species [5, 7, 12, 20, 30, 46–51] have also been implicated as we had previously hypothesized [1].

Many cellular molecular pathways involved in cell growth and processes of cancer development have been studied. Two processes that have repeatedly been reported to be affected by artemisinins are inhibition of nuclear factor kappaB (NF-κB) [27, 32, 52–56] and decrease in vascular endothelial growth factor (VEGF) [16, 57–63] activities. Effects on other cellular pathways have also been reported including NOXA [5], mitogen-activated protein kinase (MAPK) [53, 64], hypoxia-inducible factor 1α (HIFα) [59, 65], Wnt/β − catenin [66, 67], survivin [24], COX [68], c-MYC oncoprotein [18, 23, 69], epidermal growth factor (EGF) [70], and tumor necrosis factor α (TNFα) [56]. These molecular effects could explain the apoptotic, anti-angiogenic [15, 16, 54, 58–63, 71–86]; anti-inflammatory [55, 56, 68, 87–90]; anti-metastasis [61, 91–95], and cell cycle inhibition effects of artemisinin compounds. Of course, most of these changes in cellular molecular activities could result from an increase in free radical activity in cancer cells due to the reaction of artemisinins with iron.

Artemisinin monomers have been tested on many animal models of cancer, including sarcoma, leukemia, fibrosarcoma, glioma, oesteosarcoma, and cancers of the breast, pancreas, ovary, liver, and colon. Studies are summarized in Table 2. A general conclusion is that these monomers can retard cancer growth. However, high doses up to 100 mg/kg/day are required to achieve significant effect. No significant side effects have been reported. Several studies [6, 8, 96, 97] have shown that dihydroartemisinin is synergistic with various traditional chemotherapeutic anticancer drugs. These findings warrant the use of artemisinin compounds as primary or adjuvant agents for cancer treatment. However, only five human case reports have so far been published: laryngeal squamous cell carcinoma/artesunate [98]; metastatic uveal melanoma/artesunate [99]; pituitary macroadenoma/artemether [100]; non-small cell lung cancer/artesunate [101]; and cervical cancer/dihydroartemisinin [102].

Other monomers and artemisinin hybrids

In addition to the basic monomeric compounds, other artemisinin-like compounds have been developed. These other compounds include: artemisone, tehranolide, artemisinin-glycolipid, deoxoartemisinin, and artemisinin deveriatives.

Deoxoartemisinin compounds have actively been studied in Yansei University in Korea. A group of deoxoartemisinins was synthesized [103] and found to be more potent antimalarials than artemisinin. These compounds are hydrolytically stable and orally active. Lee et al. [104] tested anticancer cell activity of deoxoartemisinin and carboxypropyldeoxoartemisinin on cancer cell lines. Their compounds have different profiles of toxicity on the different cell lines. They proposed that the antitumor activity of artemisinin compounds was not dependent on lipophilicity and 'artemisinin derivatives have specific target proteins in each type of cancer'. However, no further information on this hypothesis is available. Jung et al. [105] tested a series of deoxoartemisinin monomers, dimers and trimers on cancer cell lines. Some of these compounds are more active in killing cancer cells than adriamycin, mitomycin, and taxol. A trimer, particularly, was shown to be very active. However, the study also showed that different cell lines have different

Table 1 A list of cancer cell lines investigated in artemisinin in vitro studies (all cell lines were human cells unless otherwise specified)

Brain cancer-
Rat C6 glioma cells- dihydroartemisinin [65, 85, 163]
U373MG cells- dihydroartemisinin [50]
18 neuroblastoma cell lines- artemisinin, dihydroartemisinin, artesunate [51]
Glioblastoma multiforme cell lines- artesunate [162]
Breast cancer-
MDA-MB-231cells-artesunate [171]
Murine Ehrlich ascites EN2 tumor cells- artemisinin [125, 172]
MCF-7, MDA-MD-231, and T47D cells- artesunate [7]
MCF-7 cells-artemisinin [173, 174]
HTB-27 radio-resistant cells- dihydroartemisinin [2]
MCF-7 cells- artesunate [175]
MCF-7, MDA-MB-231, MCF-10AT, MCF-10A cells-artemisinin [11]
Cervical cancer-
HeLa cells- artesunate [27]
Colorectal cancer-
Mouse colorectal cancer cells- artesunate [176]
CLY cells- artesunate [66, 67]
HCT116 cells- dihydroartemisinin [42]
HCT116 and HCT116/R cells- dihydroartemisinin [177]
Endometrial cancer-
RL95-2 endometrial carcinoma cells- artesunate [31]
Gastric cancer-
PG100 cells- artemether [4]
Hepatoma-
H22 cells- artemisinin [178]
HepG2, Huh-7, BEL-7404, Hep3B-artemisinin, dihydroartemisinin, artesunate, artemether [8]
HepG2 and SMMC-7721 hepatocellular carcinoma cells- artemisinin [94]
BEL-7402 cells-artesunate [179]
BEL-7402 cells-dihydroartemisinin [180]
Leukemia-
Multidrug-resistant human CCRF-CEM cells- artesunate [181]
Doxorubicin-resistant T leukemia cells- artesunate [12]
Molt-4 cells- dihydroartemisinin [1]
Chronic myeloid leukemia K562 cells- dihydroartemisinin [16]
K562 cells- artesunate [63]
HL60 leukemia cells- DHA [44, 182]
K562/adr chemoresistant myelogenous leukemia cells- artemisinin, dihydroartemisinin, artesunate [169]
K562 cells- dihydroartemisinin [183]
CCRF-CEM and multi-drug resistant leukemia cells- artemisinin and artesunic acid [131]
Lung cancer-
ASTC-a-1 lung adenocarcinoma cells- dihydroartemisinin [19]
SPC-A-1 cells- dihydroartemisinin [24]
PC-14 cells- dihydroartemisinin [184]
GLC4/adr small cell lung cancer cells- artemisinin, dihydroartemisinin, artesunate [182]
Small cell lung cancer cells- artemisinin [185]
A549 lung adenocarcinoma cells- artesunate [186]
ASTC-a-1 lung adenocarcinoma cells-artemisinin [30]
Murine Lewis lung carcinoma cells- dihydroartemisinin [96]
Lymphoma-
Romos cells- artesunate [164]

Table 1 (continued)

There are studies in which a panel of different types of cancer cells was investigated, e.g., Beekman et al. [125], Efferth et al. [194]

Melanoma-
A375, G361, LOX melanoma cells- dihydroartemisinin [5]
Myeloma-
SP2/0 cells- artesunate [17, 187]
RPM18226 multiple myeloma cells- dihydroartemisinin [62]
Nasopharyngeal cancer-
CNE-1 and CNE-2 nasopharyngeal carcinoma cells- artemisinin [35]
Oral cancer-
YD-10B cells- dihydroartemisinin [25]
Oral squamous cell carcinoma (IHGK) cells- artemisinin [188]
Osteosarcoma-
Canine osteosarcoma cells- dihydroartemisinin [189]
HOS cells- artesunate [29]
Ovarian cancer-
A2780 and OVCAR-3 cells- dihydroartemisinin [6]
Ten human ovarian cancer cell lines- dihydroartemisinin, artesunate, artemether, arteether, arteannuin [10]
SKOV3 and OVCAR3 cells- dihydroartemisinin [64, 190]
HO8910PM cells- dihydroartemisinin [95]
Pancreatic cancer-
BxPC-3 and AsPC-1 cells- dihydroartemisinin [191]
Panc-1 cells-artesunate [47]
BxPC-3 and PANC-1 cells- dihydroartemisinin [97]
Papillomavirus-expressed epithelial cells- dihydroartemisinin [46]
Prostate cancer-
PC-3, LNCaP, C4-2 and DU145 cells- dihydroartemisinin [23]
LNCaP (lymph node carcinoma of the prostate) cells- artemisinin [34]
PC-3 cells- Artesuante [192]
Skin cancer-
A431 human epidermoid carcinoma cells-artesunate [9]
Thyroid cancer-
8 medullary thyroid carcinoma cell lines- artesunate [193]

responsiveness to these compounds. The variation can be hundreds of folds. For the dimers, linkages with one amide- or one sulfur centered two ethylene groups are essential for high anticancer activity. Antitumor activity of deoxoartemisinin dimers has also been studied by Jeyadevan et al. [106] and Posner et al. [107]. Cho et al. [108] synthesized 10-substitured triazolylartemisinin compounds and tested them on various cancer cell lines (human colorectal adenocarcinoma, human glioma, human cervical carcinoma and mouse melanoma). The GI_{50}s of most of these compounds were less than 1 μM. However, in most of these cell lines, paclitaxel has significantly lower GI_{50}s. Nam et al. [25] tested deoxoartemisinin and its dimers and trimers on oral cancer cells. The deoxoartemisinin compound 12-(2′-hydroxyethyl) deoxoartemisinin was not very active against the cancer cells. However, the dimer and trimer showed potent antiproliferative effect on the cells. The trimer was actually more potent than paclitaxel. Apoptosis was observed. Jung et al. [109] tested C-12 non-acetal deoxoartemisinins on various cancer cell lines and reported potent activity. However, these compounds were significantly less potent than doxorubicin.

Oh et al. [79] (on oxo-olefinated deoxortemisinin) and Jung et al. [77] (on non-acetal deoxoartemisinin) have reported potent anti-angiogenic activity of deoxoartemisinin compounds. They also reported no direct correlation of anti-angiogenic and anticancer activity of these compounds.

Ricci et al. [81] studied artemisinin-glycolipid hybrids and reported high antiangiogenic activity of these compounds comparable to fumagillin and thalidomide. Glycolipids have been shown to have anti-angiogenic effects. Recently, artemisinin-glycolipid hybrids from 12β(c-c)-type deoxoartemisinin and glycolipids have also been tested on cancer cells [110]. They have potent anticancer activity above that of artemisinin or glycolipid alone on several cancer cell lines. Notably, they are five times more potent than cisplatin and paclitaxel on oral cancer cells.

Table 2 In vivo studies of artemisinin-compounds on cancer growth

	Treatments	Results
Bachmeier et al. [171]	MDA-MB231 human breast cancer mouse xenograft; started when tumors at 5-6 mm diameter, artesuante (200 or 400 mg/kg/day, i.p., for five consecutive days), doxorubicin (8 mg/kg, i.v., once a week for two weeks), monitored to 38 days.	'Marginal' growth inhibition at 400 mg/kg dose (tumor size~60 % of control); doxorubicin was more potent.
Chen et al. [195]	BxPC-3 human pancreatic cancer mouse xenograft; started when tumors reached ~120 mm^3, dihydroartemisinin (2, 10, 50 mg/kg, i.p. for 18 days).	Inhibited tumor growth in a dose-dependent manner; at 50 mg/kg, tumor volume on day 18 was 27 % of control.
Chen et al. [6]	A2780 and OVCAR-3 human ovarian cancer mouse xenografts; started when tumor reached ~70 mg, dihydroartemisinin (10 or 25 mg/kg/5 days/week for three weeks, i.p.), carboplatin (120 mg/kg, i.p. on first day), and combined dihydrartemisinin/carboplatin treatment.	Significant growth inhibition observed. A2780 xenograft- dihydroartemisinin-24 % and 41 % inhibition for the two dosages); carboplatin- 56 % inhibition; combine- 70 % inhibition. OVCAR xenograft- dihydroartemisinin-14 % and 37 % inhibition for the two dosages); carboplatin- 46 % inhibition; combine- 70 % inhibition.
Dell'Eva et al. [76]	Kaposi's sarcoma mouse xenograft; started immediately after cancer implantation, artesunate (167 mg/kg/day in drinking water) for 27 days.	Artesunate inhibited tumor growth, at the end of the experiment, tumor volume of artesunate –treated animals was ~30 % of control.
Disbrow et al. [46]	Canine oral papillomavirus tumor model; direct application of dihydroartemisinin (2.22 mg in 100 μl (78 mM) DMSO once daily, 5 days a week).	Dihydroartemisinimn abolished tumor formation, tumor developed regressed faster than control.
Du et al. [196]	Panc-1 human pancreatic cancer mouse xenograft; started when tumors reached 130 mm^3, artesunate (20, 50, 100 mg/kg/day, daily i.p.), gemcitabine (100 mg/kg/day, i.p., every three days).	Retarded tumor growth dose-dependently, response to 100 mg/kg artesunate dose similar to gemcitabine treatment. However, body weight loss was observed in gemcitabine-treated and not in artesunate-treated mice.
Farsam et al. [197]	Spontaneous mammary ductal carcinoma in mice; started when tumors reached 500 mm^3, artemether (10 mg/kg/day, i.p.) or cyclophosphamide (20 mg/kg/day, i.p.) given first in three consecutive days and then on days 5, 7, and 9.	On day 10, volume of tumors of artemether-treated animals was 24 % of controls; response similar to cyclophosphamide.
Gao et al. [198]	U937 human leukemia cell mouse xenograft; started 3 days after inoculation, dihydroartemisinin (50 mg/kg, i.p., 5 times per week).	52, 60, and 70 % inhibition of tumor growth on days 10, 15 and 20.
Hou et al. [8]	HepG2 and Hep3B human hepatoma mouse xenograft; started at 100 mg tumor mass, artemisinin or dihydroartemisinin (50 or 100 mg/kg/day, p.o.), artemisinin or dihydroartemisinin+ gemcitabine (80 mg/kg, i.p. on days 7, 11 and 15).	HepG2 xenograft: artemisinin and dihydrartemisinin reduced tumor growth dose-dependently (30 %, 39.4 % for artemisinin; 36.1 % and 60.6 % for dihydroartemisinin 36.1 % and 60.6 %); dihydroartemisinin more potent than artemisinin; synergistic with gemcitabine. Hep3B xenograft: dihydroartemisinin more potent than artemisnin in reducing tumor growth; dihydroartemisinin synergistic with gemcitabine, but not artemisinin.
Lai and Singh [170]	DMBA-induced breast cancer in rat; artemisinin mixed in food (~8 mg/kg/day, 40 weeks).	Delayed and prevention of cancer development; fewer tumors developed in artemisinin-treated animals.
Lai et al. [158]	MTLn3 cell implantation-induced breast cancer in rat; started when tumors reached 1 cm in diameter, dihydroartemisinin (20 mg/kg/day, p.o., 5 consecutive days).	Tumor growth reduction (on day 6, tumors size of dihydroartemisinin-treated rats was ~75 % of control).
Langroudi et al. [119]	Implanted mouse spontaneous mammary ductal carcinoma, started when tumors reached 500 mm^3, artemisinin (2.8 mg/kg/day, i.p.) or cyclophosphamide (20 mg/kg/day, i.p.) daily for 20 days.	Artemisinin decreased tumor growth (~50 % on day 20); no significant difference between artemisinin- and cyclophosphamide-treated groups until day 19, when cyclophosphamideshowed bigger inhibition.
Li et al. [66]	CLY human colorectal carcinoma mouse xenograft, started when tumors reached 100 mm^3 (stopped when control tumors reached 1000 mm^3); Artesunate (100 mg/kg, i.v., daily; 300 mg/kg, i.v., every 3 days), cyclophosphamide (100 mg/kg, i.v., every 7 days).	Artesunate inhibited tumor growth at 35.4 % and 50.5 % for the two dosages. Cyclophosphamide at 67.1 % (with weight loss and two animals died).
Ma et al. [199]	A549 human non-small cell lung carcinoma mouse xenograft; started when tumors reached 100 mm^3, artesunate (60 or 120 mg/kg/day, p.o., 2 weeks).	Artesunate at 120 mg/kg/day significantly reduced tumor growth (not at 60 mg/kg/day). On day 14, tumor size of artesunate-treated animals was ~56 % of control.
Moore et al. [200]	Implanted fibrosarcoma in rats; started with tumors reached 340 mm3, dihydroartemisinin (2 mg/kg/day for 1-3 days, 5 mg/kg/day on 4-10 days, p.o.), some animals were also	Tumor growth of dihydroartemisinin treatment alone not different from control.

Table 2 (continued)

	Treatments	Results
	given ferrous sulfate (20 mg/kg, p.o.) together with dihydroartemisinin.	'Dihydroartemisinin+ferrous sulfate'-treated animals: tumor growth was retarded (70 % of control on day 11).
Noori and Hassen [201]	Implanted mouse spontaneous mammary ductal carcinoma, started when tumors reached 1500 mm^3, dihydroartemisinin (4.85 μg/mouse/day, i.p. for 6 days). *(The dosage given by the authors was probably incorrect.)*	Dihydroartemisinin reduced tumor growth (at the end of the experiment, dihydroartemisinin-injected tumor volume was almost the same as on day 1).
Noori et al. [115]	Implanted mouse spontaneous mammary ductal carcinoma, started when tumors reached 1500 mm^3, dihydroartemisinin (intratumoral injection, 11.28 μg/mouse/day for 9 days).	Dihydroartemisinin significantly retarded tumor growth (at the end of the experiment, dihydroartemisinin-injected tumor volume was almost the same as on day 1).
Rasheed et al. [92]	Chicken embryo metastasis assay with non-small cell lung cancer cells placed on upper chorion-allantoic membrane (CAM), artesunate (i.v., or applied on upper CAM).	Artesunate decreased liver metastasis and reduced primary tumor size on upper CAM.
Soomro et al. [82]	Zebra fish embryos angiogenesis model; various dihydroartemisinin derivatives added to water	Some dervicatives have potent anti-angiogenesis effect- effective at 1 μg/ml.
Tin et al. [11]	MCF-7 breast cancer mouse xenograft; started when tumors about 35 mm^3; artemisinin (100 mg/kg/day, SC) for two weeks.	Inhibition of tumor growth (at the end of two weeks, tumor size smaller than at start), anti-angiogenic effect implied.
Wang et al. [202]	Eca109 human esophageal carcinoma cell mouse xenograft; artesunate (100, 200, 300 mg/kg/day, i.p.; 7 days, stopped one week and then injected for another 7 days), tumors measured one day after last injection.	Artesunate inhibited cancer growth (maximum inhibition rate 76.4 % in the 200 mg/kg group)
Wang et al. [61]	Mouse Lewis lung carcinoma cells inoculated in ear skin of mice; artemisinin (50 mg/kg/day, p.o., 2 weeks) started the day after inoculation; animals examined on day 30 after inoculation; others for survival study up to 60 days.	Artemisinin caused no significant change in tumor growth rate; presence and number of lung metastasis were reduced by 50 and 63.5 %, respectively; also less metastasis in lymph nodes-metastasis in deep cervical and mediastinal lymph nodes fully prevented; lymphangiogenisis was inhibited by 63 %; survival prolonged from 38 days (in control) to 54 days.
Wang et al. [97]	BxPC-3 human pancreatic cancer mouse xenograft; started when tumors reached 120 mm^3, dihydroartemisinin (10 mg/kg/day, daily, i.p.), gemcitabine (100 mg/kg, i.p., 2 times a week), dihydroartemisinin+gemcitabine, for 21 days.	Dihydroartemisinin reduced tumor growth (~30 % inhibition on day 21), dihydroartemisinin and gemcitabine are synergistic.
Wang et al. [54]	BxPC-3 human pancreatic cancer mouse xenograft; started when tumors reached 120 mm^3, dihydroartemisinin (2, 10, 50 mg/kg/day, i.p. for 21 days).	Dose-dependent inhibition of tumor growth; on day 21, tumor size of 50 mg/kg-group was 33 % of control.
Weifeng et al. [94]	HepG2 human hepetocellular carcinoma orthotropic xenograft implanted in liver of mice; artemisinin (50 or 100 mg/kg/day, p.o., 4 weeks) beginning at 24 hr after tumor implantation.	Lung tumor (metastasis) fewer in artemisinin-treated groups compared to control (51.8 % and 79.6 % inhibition for the two dosages).
Wu et al. [95]	Mouse orthotropic ovarian cancer tissue implanted on ovarian capsule; started at two weeks after tumor inoculation, dihydroartemisinin (50 mg/kg, i.p., 3 X a week for 4 weeks)	No significant difference in tumor size from control; metastesis to other organs was moderately reduced in dihydroartemisinin-treated animals.
Wu et al. [85]	Rat orthotropic glioma model (C6 rat glioma cells injected into brain white matter of rats); started on third day after implantation, artemether (50, 33.3, 66.6 mg/kg/day, p.o., 10 days), artemether (50 mg/kg/day)+ferrous sulfate (1.5 mg/kg/day, p.o., 10 days).	Artemether reduced tumor growth (volume ~40 % of control); no significant different among the different dosages. Ferrous sulfate enhanced the effect of artemether.
Xu et al. [29]	HOS human osteosarcoma mouse xenograft; started when tumors reached 120 mm^3, artesunate (50, 100, 200 mg/kg/day, i.p., 18 days), cisplatin (2 mg/kg, i.p., twice weekly).	Artesunate caused dose-dependent reduction in tumor growth. Inhibition of artesunate at 200 mg/kg/day similar to that of cisplatin.
Zhang et al. [203]	HepG2 hepatocellular carcinoma mouse xenograft, dihydroartemisinin (20 mg/kg/day, i.p., 5 times a week, 27 days).	On day 26, tumor size of dihydroartemisinin-treated rats was ~40 % of control.
Zhou et al. [96]	Lewis lung carcinoma mouse xenograft (subcutaneous implantation of piece of tumor), started immediately after tumor implantation, dihydroartemisinin (50, 100, 200 mg/kg/day, i.p., 25 days), cyclophosphamide (50 mg/kg/day. i.p., every other day, 5X), and dihydroartemisinin+cyclophosphamide. A549 non-small cell lung cancer mouse xenograft, similar treatments as above except cisplatin (2 mg/kg, i.p) was used instead of cyclophosphamide.	Dihydroartemisinin and the chemotherapeutic drugs reduced tumor growth. Combined treatment better than either drug alone in both models. Spontaneous pulmonary metastasis completely inhibited by drug combinations.

Artemisone (Fig. 2) is being developed mainly in the Hong Kong University of Science and Technology for use in malaria treatment. It is structurally different from the artemisinin derivatives currently used in malaria treatment and has been suggested to be a possible replacement in case resistance develops to the current artemisinin compounds [111]. Recently, artemisone has been tested on several cancer cell lines [112] and found to have more potent antiproliferative effect (mainly in arresting cell cycling) than artemisinin. It also acted synergistically with the chemotherapeutic drugs oxaliplatin and gemcitabine. However, earlier studies have shown that artemisone is less anti-angiogenic than dihydroartemisinin [75] and has significant embryo- and fetotoxic effects [113]. These latter effects are common to other artemisinin compounds.

Tehranolide (Fig. 3) is a sesquiterpene lactone with an endoperoxide moiety. It is isolated from *Artemisia diffusa* and investigated mainly by researchers at the Tarbiot Medares University in Iran. An important aspect of the research is that, in addition to its selective toxicity to cancer cells, Tehranolide has been shown to modify immune responses and enhance antitumor immunity. Tehranolide decreased breast tumor growth when injected directly into the tumor in the mouse and attenuate Treg-cell-mediated immune suppression that the researcher interpreted as an antitumor immunity against cancer [114]. A further study [115] showed that intraperitoneally injected Tehranolide could also reduce tumor growth in mice and caused a significant decrease in sphenic CD4(+)CD25(+) Foxp3(+) T-lymphocytes. In vitro study showed that it inhibited cell growth of RIN pancreatic cancer cells and had no significant effect on normal lymphocytes. Interestingly, similar effects of artemisinin on the immune system were also reported by these researchers. Noori et al. [116] reported that

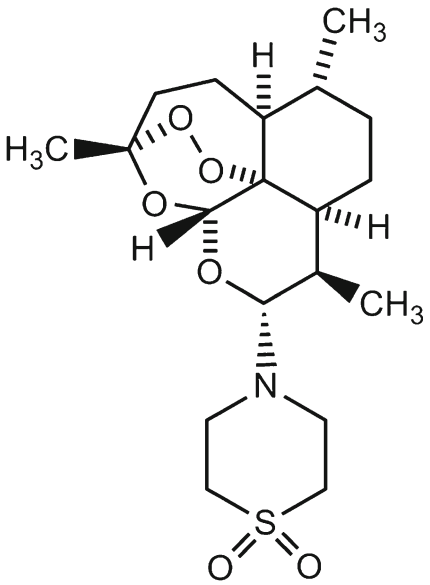

Fig. 2 Molecular structure of artemisone

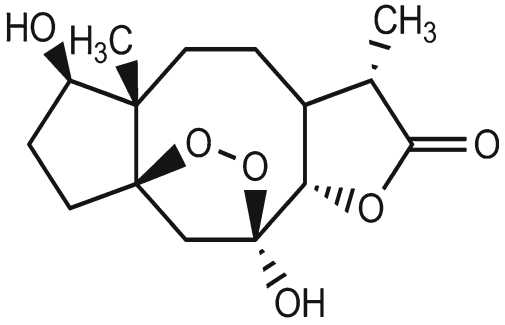

Fig. 3 Molecular structure of Tehranolide

artemisinin was an immunosuppressive agent. It was shown to suppress delayed hypersensitivity to sheep blood cells in mice. More recently, Noori et al. [117] reported that dihydroartemisinin stimulated the delayed hypersensitivity against sheep blood cells and reduced growth of ductal carcinoma in mice. Noori and Hassan [118] further reported that dihydroartemisinin decreased IL-4 and the level of CD4(+)CD25(+)Foxp3 (+) T-lymphocytes in mice. Laugroudi et al. [119] reported that artemisinin reduced Treg cells in tumor and increased IFN gamma/IL-4 ratio in splenoctye cultures. Increase in Treg cells in tumors is correlated with tumor progression. More recently, Noori and Hassan [120] reported that Tehranolide inhibited proliferation of MCF-7 breast cancer cells by induction of G_0/G_1 cell cycle arrest and apoptosis.

Yang et al. [121] tested 15 dihydroartemisinin-chalcone hybrids on human HL-60 leukemia and mouse P388 lymphoma cells. Chalcone was used to form the hybrids because it also has been shown to have anticancer activity. The researcher reported that the hybrids had higher toxicity toward the cancer cells than dihydroartemisinin alone. The IC_{50}s were all <1 μM. Hybrids linked by ether are more potent than those linked by ester. Xie et al. [122] have also tested artemisinin-chalcone hybrids on five cancer cell lines. The IC_{50}s on human HT-29 colon and HeLa cervical cancer cells were between 0.12 and 0.85 μM. Xie et al. [123] have also synthesized artemisinin-guanidine hybrids. The Guanidine moiety would make the molecule more water soluble. These hybrids were tested on human non-small cell lung cancer, colon cancer, and breast cancer cells. The IC_{50}s were between 0.02 and 0.53 μM, which were significantly lower than those of dihydroartemisinin (IC_{50}s 7.8–12 μM) on these cancer cells. Liu et al. [124] synthesized artemisinin derivatives containing lipophilic alkyl carbon chains. They reported that these compounds were more cytotoxic toward cancer cells than artemisinin (up to 200 times). The length of the carbon chains correlated with the cytotoxicity toward human heptocellular carcinoma cells. However, toxicity of these compounds on normal cells is not known. More lipophilic artemisinin compounds, e.g., artemether and arteether, are in general more neurotoxic.

More recently, Soomro et al. [82] reported the cytotoxic effects of a group of dihydroartemisinin derivatives that they synthesized. Some of these compounds were found to be more potent than artesunate (EC_{50} 17–62 μM on acute lymphoblastic leukemia cell lines). The compounds also have anti-angiogenic property. Interestingly, drug-resisitant cancer cells were more sensitive to some of these compounds than the drug-sensitive wild types.

Artemisinin dimers and trimers

The first study on artemisinin dimers was reported by Beekman et al. in 1998 [125]. The pioneer work in the development of artemisinin dimers was carried out in the laboratory of Gary Posner in the Johns Hopkins University. Artemisinin dimers (Fig. 4) have been tested in many different cancer cell lines and found to be effective in either retarding their growth or causing cell death (apoptosis) (e.g. [126–129]). In general, cancer cell cytotoxicity of dimers is more potent than that of the monomers. The increase in potency varies from 10- to 200-fold [106, 127, 128, 130–132]. Artemisinin dimers have also been shown to be as or even more potent than some chemotherapeutic agents, such as doxorubicin [133], and much less toxic to normal cells than cancer cells [130, 134]. Posner et al. [135] reported a high therapeutic index (>150) for some of the dimers they synthesized. Nam et al. [25] reported that deoxoartemisinin dimers and trimers are more potent than the monomer on cancer cells. Deoxoartemisinin trimers are even more potent than pacilitaxel, 5-fluorouracil, and cisplatin on oral cancer cells. The artemisinin-guanidine dimers of Xie et al. [123] are more potent than its monomer and have IC_{50}s of 20–60 nM against HT-29 human colon cancer cells. The highly selective cytotoxicity of artemisinin dimers towards cancer cells makes them an attractive option for development for cancer treatment.

Not very many studies have been carried out to investigate the effect of artemisinin-dimers in vivo. Galal et al. [136] reported that daily subcutaneous injection (25–50 mg/kg/day) of a dimer caused a significant growth delay of HL-60 human leukemia xenografts in the mouse. However, one of the dimer tested was found to be toxic to animals. Recently, we [137] have shown in both in vitro and in vivo experiments that artemisinin dimers (dimer-alcohol and dimer-hydrazone) are more potent than dihydroartemisinin in regard to rat mammary adenocarcinoma cancer cell (MTLn3) toxicity and retardation of tumor growth (daily oral administration of 20 mg/kg).

The mechanism of action of artemisinin dimers on cancer cells is not known. However, it must be pointed out that the presence of two endoperoxides in one molecule would not guarantee its effectiveness towards cancer cells. Other molecular features also play a role on its potency. For example, not all dimers tested were found to have an effective antiproliferative effect on cancer cells and those that do also have different potencies towards different cancer cell lines (e.g. 23, 133, 136). In our recent study [137], we tested two artemisinin-dimers synthesized in our laboratories and found that one was slight but significantly more potent effect than the other both in vitro and in vivo.

Beekman et al. [138] speculated that the spatial positions of the active groups are an important consideration. They found that non-symmetric DHA dimers are more potent than symmetric dimers in killing EN2 cancer cells. The linkers of the dimers also play an important role. Chadwick et al. [139], in testing their C10 carba artemisinin dimers, found that changing the number of carbon atoms in the linker changed the potency of the dimer in killing HL-60 cells: dimers with more carbon atoms in their linkers were more active. Jung et al. [105] reported that linker size affected the potency of their artemisinin dimers. Jeyadevan et al. [106], from their study on artemisinin phosphate ester dimers, also concluded that the nature of the linker in the dimers played an important role in their antiproliferative effect on cancer

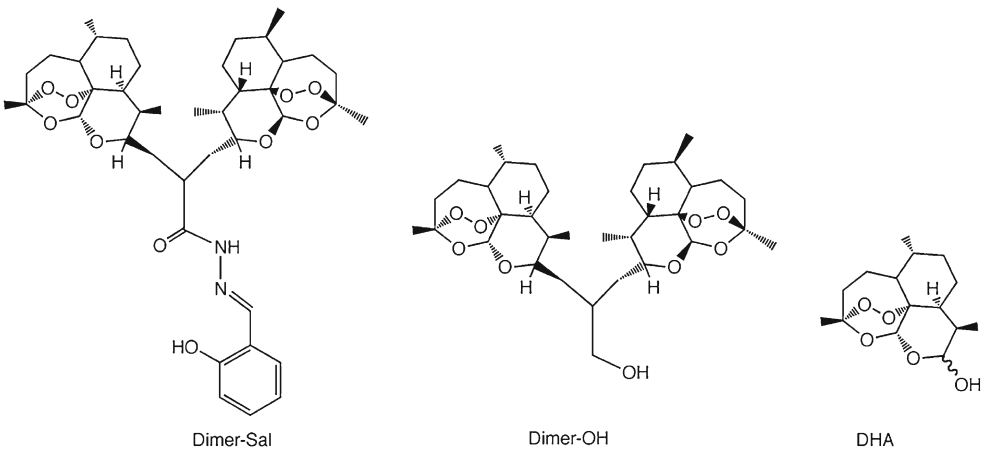

Fig. 4 Molecular structures of two artemisinin dimers (Dimer-Sal and Dimer-OH) and the monomer dihydroartemisinin (DHA)

cells. Reiter et al. [129] also reported that the nature and length of the linkers of the artesunic acid homodimers they synthesized are important in the biological effect and may be involved in overcoming cross-resistance in drug-resistant cancer cells. Furthermore, it is also not known why the dimers are more potent than monomers. One possibility is that dimers, with two active groups, after activation by iron, can form cross-linking of biological molecules, which could cause a more devastating effect on cellular functions leading to cell death. Interestingly, Beekman et al. [125] concluded that the ether linkage of their artemsinin dimers was the component that kills cancer cells, whereas the endoperoxides only played a minor role. However, Stockwin et al. [128] found that both the antioxidant L*N*-acetylcysteine and the iron-chelator desferroxamine were able to block the cancer cell cytotoxicity of their dimers, which would suggest an involvement of the endoperoxide moieties. They suggested that formation of reactive oxygen species causes endoplasmic reticulum stress leading to apoptosis.

Therefore, artemisinin dimers cannot be considered as a single group of compounds with similar general properties. The arrangement of atoms in the molecule, the chemical characteristics of the linkers, and the in vivo pharmacokinetics of a dimer can determine the cytotoxic effectiveness and action of the compound on cancer cells.

Tetraoxanes

Tetraoxanes are structurally different from artemisinin-like compounds. However, they also contain endoperoxide moiety that can react with heme or ferrous iron to form free radicals. They were developed mainly as antimalarials [140]. Vennerstrom et al. [141] tested a series of tetraoxanes on neuroblastioma cells and reported IC_{50}s in the low μM range. Opsenica et al. [142] also tested tetraoxanes on 14 cancer cell lines, including those from non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian caner and renal cancer. They also reported GI_{50} and IC_{50} values in the μM range (<10 μM). There was indication that tetraoxanes induced apoptosis in cancer cells. Two compounds described by Terjic et al. [143] have IC_{50}s of 22 and 69 nM on melanoma cells. This low IC_{50} again was reported by Opensiac et al. [144] on melanoma and ovarian cancer cells (60 nM). Cvijetic et al. [145] recently pointed out hydrophobicity and H-bond donor properties are the main factors affecting the cytotoxic potency of tetraoxane compounds. Apparently, tetraoxanes are generally more potent than artemisinin compounds on cancer cells. There is indication that different free radical species are produced by these two groups of compounds. A study by Kumura et al. [146] reported oxidative degradation of unsaturated phospholipids in the presence of Fe^{2+} and absence of oxygen, whereas no such degradation was observed with artemisinin. It must be pointed out that not all tetraoxanes tested are toxic to cancer cells. Kumar et al. [147] tested a series of tetraoxanes on 4 cancer and 2 non-cancer cell lines and found no significant effects up to a concentration of 25 μM. Certain structural requirements seem to be necessary for these compounds to work as effective antimalarials. Similar requirements may be needed for them to affect cancer cells. These molecular structural considerations have been discussed in a recent review by Kumar et al. [148]. The toxicity of these compounds on normal cells needs to be investigated.

Artemisinin tagged to molecules involved in cellular iron transport

In mammalian cells, iron is transported into the cytoplasm via a receptor-mediated endocytosis process [149]. Binding of the plasma iron-carrying protein transferrin to cell surface transferrin receptors triggers endocytosis. A drop in pH in the endosome causes the release of iron from transferrin. Iron is then actively pumped out into the cytoplasm. Transferrin and transferrin receptors are recycled back to the cell surface. Since cancer cells require a large amount of iron, e.g., as a cofactor in the synthesis of deoxyriboses before cell division, they express a high number of transferrin receptors on their cell surface. For example, breast cancer cells have 5–15 times more transferrin receptors on their cell surface than normal breast cells [150], and breast cancer cells do take up more iron than normal breast cells [151]. We speculate that if artemisinin is covalently attached to holotransferrin (iron-loaded transferrin), it would be transported in the same package into cells and react with the iron within the endosome where iron would be released from holotransferrin. This may enhance the cytotoxic potency and selectivity of artemisinin on cancer cells.

Transferrin is a glycoprotein. Its protein moiety is mainly involved in its binding to cell surface transferrin receptors, whereas the carbohydrate chains are not involved in receptor binding [152]. Transferrin has two N-glycosides attached to Asn residues in the C-terminal domain [153]. Periodate oxidation of these carbohydrate chains generate reactive aldehyde groups that can be modified with a variety of hydrazine or aminoxy derivatives of artemisinin. Assuming that all 1,2-diol moieties are oxidized to the corresponding aldehyde group, we estimate that at least ten artemisinin derivatives could be tagged to one molecule of transferrin. Thus, we have tagged an artemisinin analog artelinic acid to the gycosylate-moiety of holotransferrin using a relatively simple process. Holotransferrin was first treated with NaIO4 to oxidize the N-glycoside chains to expose aldehyde groups on the surface. Artelinic acid hydrazide was then reacted with the oxidized holotransferrin to form a covalent conjugate (Art-

Tf). On an average, more than 16 artelinic acid moieties can be tagged to one transferrin molecule.

Using this 'Trojan Horse' strategy, chemotherpeutic drugs have been tagged to transferrin for specific delivery to cancer cells. However, tagging with artemisinin offers an addition advantage. In this situation, artemisinin is a pro-drug and becomes activated after it is transported inside the cell when iron is released from transferrin inside acidified endosome.

We [154] first tested the Art-Tf in human leukemia (Molt-4) cells and normal human lymphocytes and compared it with the effectiveness of dihydroartemisinin. We found that Art-Tf is about two times more potent than DHA in killing cancer cells. However, its toxicity toward normal lymphocytes was much lower (IC_{50}s: Molt-4-Tagged-compound 0.98 μM; Molt-4-DHA 1.64 μM; lymphocyte-tagged compound 33 mM; lymphocyte-DHA 58.4 μM.) This enhanced cancer versus normal cell toxicity ratio was further confirmed by a more recent experiment by an independent research group [155]. They tested ART-Tf on human breast cancer cell (MCF-7) and normal breast cells (HNB) (IC_{50}s: MCF-7/ART-Tf 0.08 μM; MCF-7/DHA 0.20 μM; HNB/ART-Tf 22.89 μM; HNB/DHA 0.69 μM). Thus, in line with our data on human leukemia cells/lymphocytes, these researchers reported that ART-Tf was more cytotoxic and selective in killing cancerous than normal breast cells. A further study by the same researchers [156] reported a difference in ultrasturcture of plasma membrane of breast cancer cells treated with Art-Tf or DHA. Large holes were observed on the membrane after Art-Tf treatment, whereas small irregular shape holes were observed with DHA treatment.

A study [157] has been carried out to investigate the mechanisms of action of Art-Tf. In prostate cancer cells (DU-145), Art-Tf induced apoptosis via activation of mitochrondial apoptotic pathways. Leakage of cytochrome c from mitochondria, cleavages of procaspase-9 and caspase-3, and PARP-degradation were observed. The action required expression of transferrin receptors, thus, validating the endocytotic intake of Art-Tf. Furthermore, the toxicity is related to the number of artemisinin-moieties tagged and independent of the concentration of cells in the culture (whereas the effectiveness of DHA decreased with an increase in cell concentration). Interestingly, Art-Tf is less effective to PC-3 cells, another type of human prostate cancer cell line, than DU-145. A recent study *(Gong* et al. *unpublished results)* has found that transferrin tagged with artemisinin-dimer was more potent in killing breast cancer cells than transferrin-tagged with the monomer.

We have also tested ART-Tf on an animal model of breast cancer and found that it (at 13 nmol/day, iv) significantly retarded the growth of breast tumor in the rat and it was significantly more effective than DHA (at 20 mg/kg/day, po) [158].

A major drawback of Art-Tf is that it is large molecule and has to be injected intravenously. This limits the dosage that can be given at a time. In addition, Art-Tf has to compete with endogenous transferrin for binding to transferrin receptors on cancer cells.

In another research to achieve specific delivery of artemsinin to cancer cells, we [159] covalently conjugated artemisinin to a transferrin-receptor targeting peptide HAIYPRH that binds to a cavity on the surface of the transferrin receptor. This enables artemisinin to be co-internalized with receptor-bound transferrin. One (ART-peptide) or two (ART2-peptide) artemisinin moieties were covalently tagged to the peptide. The artemisinin-peptide conjugates showed potent anti-cancer activity against Molt-4 leukemia cells with a significantly improved cancer/normal cells selectivity. (The IC_{50} values of ART-peptide and ART2-peptide on Molt-4 cells were 1.06±0.08 and 0.61±0.05 μM at 72 h, respectively. ART2-peptide was significantly more potent than ART-peptide, consistent with a higher anti-cancer activity of artemisinin dimers compared to monomeric artemisinin derivatives. The artemisinin-tagged peptides were virtually non-toxic to normal leukocytes (IC_{50}>10,000 μM). Under the same assay conditions, DHA showed IC_{50} values of 5.01±0.35 and 43±22 μM for Molt-4 cells and normal leukocytes, respectively. Thus, the peptide conjugates showed markedly improved efficacy and selectivity in killing the leukemia cells.

Artemisinin-tagged natural iron-carrying molecules can also be used to treat other diseases. In an earlier paper [160], we proposed the use of artemisinin-tagged transferrin and lactoferrin for treatment of bacterial infection, because some bacteria pick up host transferrin and lactoferrin as their sources of iron. We also proposed that artemisinin-tagged bacterial specific siderophores can be developed into effective antibiotics. Most bacteria use siderophores to acquire iron from the environment. A recent study by Miller et al. [161] showed that artemisinin-tagged mycobactin, a bacterial siderophore, had selective and potent activity against multi- and extensively drug-resistant strains of Mycobacterium tuberculosis. Furthermore, in addition to artemisinin monomers, other artemisinin-compounds, e.g., dimers, trimers, or tetraoxanes, can also be tagged to these targeting carriers. This may further enhance their efficacies.

Discussion

A good cancer treatment should have high specificity toward cancer cells and not normal cells. It should have a broad spectrum of action. Thus, it is effective against different types of cancer and acts on different mechanisms that affect cancer growth and development. It should be easy to administer, e.g., orally, and have a high therapeutic index. An additional preferable quality is that it is economical, thus, it can be available to patients who cannot afford the expensive traditional cancer therapies. Artemisinin derivatives satisfy

all these criteria. In particular, it is very unusual that a chemotherapeutic agent has also antiproliferation, antiangiogenic, and anti-inflammatory properties. All of them are beneficial to cancer treatment. With the different types of artemisinin-like compounds described in the above sections, it is likely that some will eventually developed into effective and simple cancer treatment agents. However, there are several aspects that will require further research to understand the mechanisms of action of these compounds and to achieve this goal of a better treatment strategy.

(1) The reason why artemisinin is less toxic to normal cells than cancer cells is still a mystery. In one of our early experiments on breast cancer cells and normal breast cells [2], it was found that artemisinin has virtually no significant toxicity on normal breast cells in log phase in culture, when uptake of iron for cell division occurs. It can be speculated that normal cells have better regulation of free iron intracellularly, such that removal of iron from the endosome, transfer to sites of usage, and storage in ferritin are much more efficient than in cancer cells. In the study of artemisinin-tagged transferrin [154], the same low toxicity to normal dividing cells was again observed. Since iron is released from holotransferrin inside the endosome when it acidifies, the released iron can immediately react with the artemisinin moieties attached to the transferrin molecule. This indicates a fast removal of released iron from the endosome in normal cells.

(2) It is clear that the artemisinin monomers alone are not effective enough for use in cancer treatment. Combination of these compounds with traditional chemotherapeutic agents may achieve a synergistic effect with fewer side effects. Synergism has been reported between artesunate with fotemustine and dacarbazine on human uveal melanoma [99]; artesunate and epidermal growth factor receptor tyrosine kinase inhibitor on glioblastoma multiforme cells [162]; artesunate and vinovelbine and cisplatin on human non-small cell lung cancer [101]; dihydroartemisinin and temozolomide on rat C6 glioma cells [163]; artemisinin and dihydroartemisinin with gemcitabine on hapatoma xenograph in mice [8]; Dihydroartemisinin and carboplatin on ovarian cancer cells in vitro and vivo [6]; dihydroartemisinin and gemcitabine on pancreatic cancer xenograft in mice [97]; dihydroartemisinin with cisplatin and cyclophosphamide on lung cancer xenographs in mice [96]; artesuante with lenalidomide on A549 lung cancer cells and MCF7 breast cancer cells (not on HCT116 colon cancer cells); artemisone with gemcitabine, oxaliplatin and thalidomide on human colon and breast cancer cells [112]; and artesunate and the anti-CD20 antibody rituximab [164]. However, this interaction requires further investigation before implementation. Gravett et al. [112] have reported antagonism between artemisinin and oxaliplatin on colon cancer cells, and Riganti et al. [165] reported that artemisinin induced doxorubicin resistance in human colon cancer cells. On the other hand, artemisinin compounds have been shown to be toxic towards various multiple drug-resistant cancer cell lines [131, 166–168]. Interestingly, Reungpatthanaphong and Mankhetkorn [169] reported that artemisinin, artesunate, and dihydroartemisinin were synergistic with pirarubicin and doxorubicin on drug-resistant K562/adr and GLC4/adr cells, but not in their corresponding drug-sensitive cell lines. This further supports the use of artemisinin compounds as supplements to traditional chemotherapy.

(3) Some of these compounds have not been tested adequately. For example, the effects of most of these compounds on normal cells have not been studied. Most mechanism studies were carried out on monomers. It is likely that the more complex artemisinin-compounds may have different anticancer mechanisms. For example, the high toxicity of dimers and trimers on cancer cells could be due to their ability to form crosslinks among biological molecules. In that sense an optimal length of the linker to the two endoperoxide-moieties would affect the effectiveness of the dimer or trimer in killing cells. Too short a linker arm would be less effective, since intermolecular crosslinks would be more damaging that intramolecular crosslinks. However, if the arms are too long, both endoperoxides would not be accessible to the source of free iron and get activated at the same time. In addition, the atomic composition of the linker could also affect the effectiveness of the dimer/trimer molecule such that negative charges in the linker could make the molecule more attracted to positive charged free iron atom.

(4) A very puzzling fact is that different artemisinin compounds have different effectiveness on different types of cancer cells. It is very important to understand this phenomenon in order to develop an effective treatment using artemisinin drugs. This puzzle can probably be resolved by understanding the mechanism of action of these compounds. Several possibilities can be investigated. One possibility is that differences in iron metabolism in different types of cancer cells [e.g., see 45] may alter the amount and location of cellular iron available for interaction with artemisinin compounds in the cell. This may also explain the observation that increase iron availability to cells (via an iron supplement of holotransferrin) does not always enhance the effectiveness of artemisinin compounds. The location of a compound inside the cell compartments can affects its effectiveness in killing the cell. Oxidative stress is a major mechanism of action of artemisinin compounds. Cells with different oxidative/

antioxidative profiles will have different susceptibilities to artemisinin compounds.

(5) The effect of long term intake of artemisinin has not yet been investigated. In one of our experiments [170], we gave artemisinin to rats at ~8 mg/kg/day continuously for 40 weeks. We did not observe any adverse side effects in the animals. It is possible in the future that artemisinin compounds could be used to turn cancer into a chronic disease or as cancer preventive agents. However, effects of longer period of administration at higher dosage, particularly neurotoxicity, should be investigated.

(6) In addition to the property of selective toxicity toward cancer cells. Artemisinin compounds have been shown to have other properties that could be beneficial for cancer treatment. Further studies on these properties are needed. These properties are anti-angiogenic, anti-inflammatory, anti-metastatic, and immunological effects.

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Conflict of interest statement The authors are co-inventors of technologies, of which the patents are owned by the University of Washington, related to artemisinin-tagged transferrin, artemisinin-tagged transferrin receptor binding peptides, and artemisinin-dimer hydrazone. These technologies are licensed to Holley Pharmaceuticals (China) and Artemisia Biomedical (USA) for commercial development.

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