Anticancer Effects and Mechanisms of Artemisinin and Its Derivatives on Hematological Malignancies

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Abstract: Traditional Chinese medicine believes that artemisinin (ART) could treat malaria which are extracted from artemisia. Modern medicine found that except the use of curing malaria, artemisinin and its derivatives also show anticancer activities in vitro and in vivo by reducing the proliferation, migration, invasion, tumorigenesis and metastasis of cancer cells. As the components of natural plants, artemisinin and its derivatives demonstrated multi-specific manner in the treatment of hematological malignancies. The major mechanisms of effects of artemisinin and its derivatives on anticancer activities include induction of apoptosis, inhibition of angiogenesis, inhibition of proliferation, etc., through regulating multiple pathways, such as JNK, KDR / Flk-1, MAPK, STAT3 and Wnt/β-catenin signalling pathways. This review discusses the anticancer activity of artemisinin, artesunate and dihydroartemisinin (DHA) in the treatment of hematological malignancies, and from which it is demonstrated that ART and its derivatives are effective in vitro and in vivo. Future research is required in this promising field of cancer drug discovery.

1 INTRODUCTION

Hematological malignancies is the general name of a large class of malignant tumors originated from hematopoietic system, mainly including leukemia, lymphoma and myeloma. It has become a severe challenge to public health and public hygiene. According to the statistics of common malignant tumors in China, the acute leukemia and lymphoma in hematological malignancies rank the top ten in the "ten common malignant tumors", and the incidence rate is increasing year by year. Multiple myeloma is the second most common malignancy in the blood system. The incidence rate has also increased in recent years. Except the old way of treating cancer such as chemotherapy, World Health Organization publicated that artemisinin is one of the most efficient drugs for the treatment of resistant malaria (World Health Organization 1998). In recent years, increasing amount of artemisinin's other functions have been discovered and applied, such as treatment potential on pulmonary hypertension, anti-diabetes effects, anti-fungal, immune regulation, antiviral effects (Kapepula 2020). Importantly, anti-cancer effects of artemisinin within the scientific and medical community are evidenced by the fact that the Nobel Prize in Medicine and Physiology was awarded in 2015 for the discovery of artemisinin in China by the pharmaceutical chemist Tu Youyou (Su 2015). Hence, among these numerous effects, anticancer effect of artemisinin and its derivatives attracted attention of researchers with its properties of well-tolerance by human body and no significant side-effect.

As a derivant of artemisinin, artsunate also presents potential anticancer activity. Several studies showed varying degrees of inhibitory effect on liver cancer cells, breast cancer cells as well as lung cancer cells *in vitro* (Sun 2015, Dong 2014). This review summarizes its potential anticancer mechanisms on

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inducing tumor apoptosis and inhibiting angiogenesis.

Dihydroartemisinin (DHA), which is another derivative of artemisinin with better water solubility, could be more easily absorbed by the human body (Adam 2018). This review discusses the treatment with hematological malignancies with DHA and the potential mechanisms including its role of inhibiting cancer cell proliferation (Zhang 2019), as well as inducing cancer apoptosis (Yan 2018, Hu 2018).

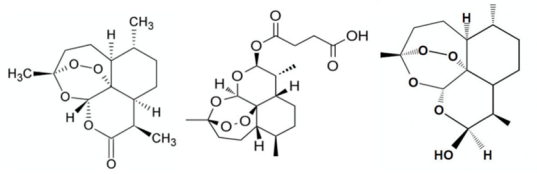

Figure 1: The chemical structure of artemisinin, artesunate and dihydroartemisinin.

2 CONSTRUCTION AND ANTICANCER EFFECT OF ARTEMISININ

2.1 Description of Specimens

Artemisinin, with the formula of $C_{15}H_{22}O_5$, is a sesquiterpene (Fig1) (Kumar 2017). High-resolution mass spectrometry (HRMS) showed a molecular ion at m/z 282.1470 which is corresponding to the formula C15H20 (Zheng 1994). The reaction with triphenylphosphine to give the phosphine oxide proved that there's a peroxide group in artemisinin (Kumar 2017). However, research showed that there existed some shortcomings such as short half-life and poor solubility when artemisinin was applied to cancer cells (Zhang 2020). Hence, efforts have been made to synthesis hybridization of artemisinin as well as other anticancer physicochemical for triggering a solution toward these problems (Meunier 2008).

2.1.1 The Cytotoxicity Activity of Artemisinin

Nine sesquiterpene compounds were tested for their cytotoxicity toward several cancer cell lines, though only artemisinin exhibited potent cytotoxicity toward A-549 (human lung carcinoma), P-388 (murine lymphocytic leukemia) and HT-29 (human colon adenocarcinoma) cells with ED_{50} values of 0.0962, 4.16, and 4.41μg/ml, respectively (Zheng 1994). Apart from these cell lines, another group tested the cytotoxicity of artemisinin to Ehrlich ascites cancer cells by microculture tetrazolium (MTT) assay and found a dramatic inhibition of cell proliferation with IC_{50} of 29.8μM (Woerdenbag 1993).

Hence, Artemisinin showed higher cytotoxicity toward most of cancer cells, implying a potential therapeutic way to treat cancers in clinical medicine. However, importantly, artemisinin has stronger cytotoxicity effects on normal cells than its derivatives which may lead to the death of normal tissues and consequently potential side effect, which makes it urgent to find more derivatives with efficient anticancer effects while less cytotoxicity on normal cells.

2.1.2 Artemisinin Induces Apoptosis

It was found that B cell-specific Moloney murine leukemia virus integration site 1 (BMI1) inhibitors induced apoptosis with a fluorescence-activated cell sorting (FACS) assay (Ohtaka 2017). Artemisinin, as one of the BMI1 inhibitors, was found potential therapeutic effects on six acute myeloid leukaemia and two normal lymphoblastic cell lines (Hu 2018). It's showed in the Dose-response curves that ART suppressed multiplication of Jurkat cells, which provided another evidence that artemisinin inhibits some certain cancer cells proliferation (Ohtaka 2017).

Besides the inhibition function, ART also didn't weaken the multiplication of normal cells within the concentration range used (Ohtaka 2017). In this case, a potential advantage of using artemisinin as a treatment toward leukemia is that it may minimize leukemia cell proliferation while seldom infect the normal lymphocyte. Studies on patients with artemisinin also showed well-tolerance and did not show severe side effects based on a large number of clinical trials of artemisinin (Efferth 2010).

Artemisinin decreased the expression of BMI1, NOTCH1, and in Jurkat cells it nullified NOTCH1 and the downstream targets of NOTCH, indicating that a potential mechanism of artemisinin inducing apoptosis is to down-regulate the expression of BMI1 and NOTCH1 (Ohtaka 2017). BMI inhibitors might be used as drugs targeting leukemia stem cells owing to its ability to regulate cell stemness (Ohtaka 2017). However, there should be more experiments to clarify molecular pathways targeted by BMI inhibitors, as well as test their effects for normal hematopoietic stem cells.

2.2 Artesunate

Artesunate is a water-soluble esterification derivative of artemisinin. The anticancer mechanisms of artesunate involve induction of reactive oxygen species (ROS) production and ROS dependent DNA damage, inhibition of angiogenesis, induction of apoptosis and cell cycle stagnation (Zhang 2015).

2.2.1 Pro-apoptosis Effect

It was found that ART may induce cell proliferation and programmed cell death in human leukemia cells, which have been proven in *in vitro* tests on cell line K562 (Sun 2015). The effects of different concentrations of Artesunate on the viability of K562 cells decreased (98.9 ± 2.3 % to 37.9 ± 6.2 %) with the increase of drug concentration (0 to 400 μmol/L) as a dose-dependent manner (Sun 2015). Specifically, Artesunate played an pro-apoptosis effect of K562 cells, as the study showed that after 24 hours of treatment with 100μmol/L Artesunate, there were increasing number of cells in early apoptosis (2.48 ± 0.9%), late apoptosis (9.96 ± 1.5)% and necrotic cells (3.25 ± 0.5)% compared with the control group (1.46 ± 0.7)%, (2.79 ± 0.6)%, and (1.68 ± 0.4)%, respectively (Sun 2015). Hence, the Bcl-2 family members play an important role in regulating apoptosis in intrinsic pathway, which can be divided into anti-apoptosis including Bcl-2 and Bcl XL, as well as pro-apoptosis including Bid, Bax, Bad, and Bim. Bcl-2 may suppress the apoptosis-inducing signals while Bax may antagonize Bcl-2 by promoting apoptosis. Furthermore, the ratio of these two molecules determines the survival or apoptosis of cells. Artesunate was displayed the dual role for the anti-apoptotic Bcl-2 protein in mitochondria and endoplasmic reticulum of cancer cells (Alk 2014). Studies showed that after 24 hours with 100μmol/L of Artesunate treatment, it exerted a positive effect on the expression of Bcl-2 while did not change the expression of Bcl-2 significantly (Alk 2014), indicating that the pro-apoptosis effect of Artesunate may be related to the regulation of Bcl-2 family and potentially the intrinsic pathway.

The cell cycle of K562 cell lines was also affected under Artesunate treatment, with a decreasing cell population in the S phase while increasing the cell population in the G2M phase in a dose-dependent manner. After the treatment with a higher concentration of Artesunate (200μmol/L), the percentage of apoptosis was up to 39.65%, and the cells in the S and G2M phase were reduced (Sun 2015). Moreover, with an increase of drug concentration, cell proliferation was significantly inhibited in a dose-dependent manner. Applying 12.5, 25, 50, 100, 200 and 400 μmol/L ART inhibits rates of cell proliferation by (6.90 ± 3.3)%, (17.8 ± 5.5)%, (38.4 ± 5.8)%, (52.8 ± 6.1)%, (64.0 ± 5.8)%, (69.9 ± 7.2)%, respectively, and the 50% proliferation inhibition concentration (IC_{50}) was about 95.0 μmol/L (Sun 2015).

In summary, Artesunate could regulate cell cycle change, inhibit cell proliferation, and induce apoptosis through the intrinsic pathway, which may be related to the down-regulating expression level of Bcl-2 and the up-regulating expression level of Bax (Solaini 2011). The *in vitro* methods that usually used in related studies include cell culture, cell vitality detection, apoptosis detection, cell proliferation detection, cell cycle analysis, etc. (Sun 2015), while further *in vivo* studies as well as potential clinical research are required to further understanding the influence of Artesunate on cell proliferation process.

2.2.2 Anti-angiogenesis Effects

Angiogenesis is one of the critical process to migration, division, and differentiation of vascular endothelial cells or stromal stem cells, followed by the formation of lumen structure, and consequently malignant growth and metastasis of tumors (Zhang 2007). Various research showed an inhibition effect of Artesunate on angiogenesis. For instance, at the concentration range of 0.5-50 μmol/L, Artesunate significantly supressed angiogenesis in a concentration-dependent manner (Li 2013). However, the mechanisms of Artesunate induced anti-angiogenesis effects have not been fully recognized.

Tumor cells and endothelial cells may interact with each other to regulate tumor angiogenesis. During this process, the vascular endothelial growth factor (VEGF) is one of the most important major ligand for angiogenesis leading to malformation and dysfunctional vascular system, activates two tyrosine kinase receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR / Flk-1). After the activation of these two receptors, the sign for angiogenesis will be enabled (Shibuya 2011). Studies have found that Artesunate may play a role in mitigating the activation of KDR / Flk-1 and consequently affects the process of angiogenesis with limited production of pro-angiogenic cytokines from tumor cells (Wei 2017). It was found that Artesunate significantly inhibited the proliferation, migration, and subsequent tube formation of human umbilical vein endothelial cells (HUVEC), with a significantly decreased expression

of Flt-1 and KDR / Flk-1 in endothelial cells. Moreover, in embryonic samples derived from mouse embryonic stem cells, Artesunate down-regulated HUVEC Bcl-2 while up-regulated Bax levels, caused changes in the proportion of Bcl-2 and Bax, and significantly induced HUVEC apoptosis (Wu 2004). Importantly, the mRNA expression of more than 6 angiogenic genes is related to the sensitivity and drug resistance of tumor cells to eight artemisinin derivatives (Anfosso 2006), which provided a clue as to potential clinical precise therapy.

Taken together, the anti-angiogenesis mechanisms of Artesunate may be related to disarranging pathways including JNK, p38 MAPK, KDR / Flk-1 and Akt, etc. (Table 1). Subsequently, Artesunate could inhibit endothelial cell proliferation, induce endothelial cell apoptosis, and play an anti-tumor angiogenesis role by inhibiting VEGF expression, downregulating Flt-1 and KDR / Flk-1 expression levels, downregulating Bcl-2, as well as upregulating Bax levels, and in turn suppression the vessel formation.

Table 1. Mechanisms underlying the anti-angiogenesis effects of Artesunate (modified from Ref. (Wei 2017)).

Cell types	Mechanisms	Artesunate effect	Ref(s)
HUVECs	JNK activation ↓	Proliferation ↓	(Cheng 2013)
	p38 MAPK activation ↑	Apoptosis ↑	(Cheng 2013)
	KDR / Flk-1 activation ↓	Angiogenesis ↓	(Wu 2004)
RAFLS	Akt phosphorylation ↓	Production of VEGF and IL-8↓ IL-8	(Uckun 2021)
	Akt phosphorylation ↓	production↓	(Xu 2007)

2.3 Dihydroartemisinin

Dihydroartemisinin (DHA) is semi-synthesized from artemisinin which is modified to retain the antimalarial active group. Thus, DHA contains the hydroxyl group, which greatly improves its antimalarial effect. As shown in Fig.1, its anticancer effect mainly depends on its unique peroxide bridge structure. The DHA is more water-soluble than artemisinin and is easier to be absorbed by the human body. Hence, it has been showing the great advantages of a faster metabolism rate, more efficient effect, and lower toxicity (Adam 2018).

The anticancer activity of DHA in the treatment of hematologic malignancies was discussed from three aspects: inhibition of cancer cell proliferation and DHA induction of cancer cell death.

2.3.1 DHA Inhibits Cancer Cell Proliferation

DHA can inhibit the proliferation of leukemia cell K562 by inhibiting aerobic glycolysis mediated by Pyruvate kinase M2 (PKM2) and glucose transporter 1 (GLUT1). Gao et al. illustrated the inhibitory effect of DHA on the proliferation of human chronic myeloid leukemia cells by presenting an example of the inhibitory effect of DHA on human chronic myeloid leukemia K562 cells (Gao 2020).

The rapid growth of cancer cells requires a dramatic increase in glucose and glucose metabolites. Normal cells obtain energy mainly through oxidative phosphorylation of mitochondria, while most cancer cells rely on aerobic glycolysis. Glycolysis produces large amounts of lactic acid and induces metabolic waste. Lactic acid, in turn, promotes the development of cancers (Zhang 2019). Thus, the specific dependence of cancer cells on glycolysis makes them susceptible to specific glycolysis target inhibitors.

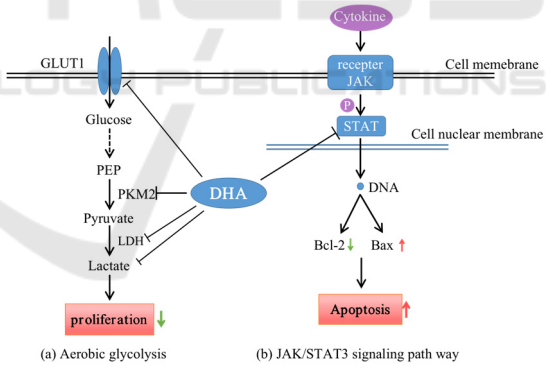

Figure 2: mechanisms of DHA induced proliferation inhibition and apoptosis.

Overexpression of glucose transporters (GLUTs) can be usually observed in cancer cells to regulate the "Warburg effect" in cancer cells. It was found that DHA can gradually inhibit the expression of GLUT1 at protein levels (Gao 2020). These results indicated that DHA could inhibit lactate secretion, block glucose uptake and inhibit GLUT1 expression in K562 cells through inhibition. At the same time, DHA may also inhibit PKM2, which is important for phosphoenolpyruvate (PEP) to generate pyruvate. Therefore, DHA may regulate the metabolism of

cancer cells by inhibiting the expression of GLUT1 and PKM2, thus inhibiting the proliferation of cancer cells as shown in Fig.2a (modified from Ref. (Gao 2020)).

2.3.2 DHA Induced Cancer Apoptosis

The increase of abnormal cell response is mainly through increasing the transmembrane response of GLUT1. Studies have shown that the low expression level of cells GLUT1 is related to abnormal conditions. GLUT1 is the most widely distributed glucose transporter known, and is highly expressed in brain, blood-brain barrier, myocardium, adipose tissue and skeletal muscle, which are adapted to the glucose needs of the body's microenvironment (Cai 2004, Takata 1990). It has been showing that GLUT1 played an important role in cancer progression and abnormal expression of GLUT1 has been found in many cancers. Studies have found that GLUT was overexpressed in juvenile hemangioma, and an abnormally elevated expression of GLUT1 was found in multiple cancers such as pancreatic cancer, gastric cancer, ovarian cancer, cervical cancer, lung cancer, and nasopharyngeal cancer (Drut 2004). Thus, GLUT1 could be regarded as a potential biomarker of cancer early diagnosis, differentiation of benign and malignant, as well as prognostic evaluation.

To better understand the anti-cancer effects of DHA, it has been found that its mechanism of inducing cancer cell apoptosis is related to multiple signal pathways, such as PI3K/Akt, MAPK, STAT3, Wnt/β-catenin, NF-κB and other signal pathways (Table 2).

Table 2: DHA targets in cancer cell signaling.

Reported target	Function/pathway of target	DHA Effect	Ref(s)
PI3K/Akt	Activates downstream target of rapamycin, mTOR	Inhibits proliferation; Promotes apoptosis; Abnormal invasion	(Li 2017) (Tang 2014)
MAPK	Decreases DNA repair enzyme (PARP) expression Down-regulates mRNA and protein expression Induces caspase-dependent apoptosis	Inhibits proliferation Promotes apoptosis	(Dong 2015) (Zhang 2017)
STAT3	Regulates of transcription of target genes Activates Bax and leads to programmed cell death	Inhibits proliferation Promotes apoptosis	(Hu 2018)
Wnt/β-catenin	Reduces the adhesion between cells Promotes the interstitial transformation of cells	Promotes apoptosis	(Qiao 2016)
Notch	Down-regulatesof mRNA expression in cells	Promotes apoptosis	(Liu 2014)
NF-κB	Leads to the accumulation of ROS	Promotes apoptosis	(Hu 2014)

JAK-STAT signaling pathway is one of the critical pathways during tumorigenesis by which DHA induces apoptosis. JAK/STAT signaling pathway is a widely expressed intracellular signal transduction pathway stimulated by a variety of cytokines, which is mainly involved in many important biological processes such as cell proliferation, differentiation, and apoptosis. Lymphocyte adaptor protein (LNK) gene was found to play an important role in regulating hematopoietic stem regeneration and proliferation. The protein encoded by the LNK gene is lymphocyte linker (SH2B3), which belongs to the SH2B connexin family and is a key factor in normal hematopoietic. LNK was highly expressed in hematologic cancer cells. It was found that LNK mutation could cause mutations in corresponding domains such as SH2 or/and PH, which may weaken or lose the inhibitory function of activated JAK receptor and its downstream genes, and in turn leads to the high expression of STAT3, as a consequence causing abnormal proliferation of hematopoietic cells and accelerating the occurrence and development of hematologic cancer cells (Vainchenker 2011). Importantly, studies have showing that expression level of LNK protein increased after DHA application, and LNK protein inhibited STAT3 protein expression, so DHA further inhibited STAT3 protein expression. Furthermore, the Bcl-2 protein level was decreased while Bax protein level was increased, which promoted the apoptosis of AML cells (Fig2a) (Yan 2018, Hu 2018).

The effect of DHA on laryngeal cancer was investigated and it was demonstrated that the treatment of DHA can prolong the survival time of mice and inhibit the activation of STAT3 in cancer cells. These results indicated that DHA inhibits the invasion and metastasis induced by cancer STEM cells by inhibiting the activation of STAT3 in laryngeal cancer (Wang 2020). It was found that DHA inhibited melanoma proliferation in a time- and dose-dependent manner by studying the effect of DHA on melanoma (Yu 2020). Moreover, DHA significantly promoted mitochondrial apoptosis in melanoma by regulating the STAT3 pathway. Researchers studied the antitumor activity of DHA in head and neck squamous cell carcinoma and found that DHA showed significant specific inhibitory effect on STAT3 activation through selective blocking of Jak2/STAT3 signaling pathway (Jia 2016). In addition, DHA could also inhibit the growth of squamous cell carcinoma of the head and neck *in vitro* and *in vivo*, possibly by inducing apoptosis and inhibiting cell migration (Jia 2016).

In summary, DHA may be a STAT3 inhibitor and may represent a new effective drug for the treatment of cancer and for the treatment of sensitization in cancer patients.

3 CONCLUSION

Artemisinin and its derivatives, including artemisinin, DHA, and artesunate, have been showing remarkable anticancer effects on hematological malignancies. Artemisinin and its derivatives may regulate multiple pathways, such as JNK, KDR / Flk-1, MAPK, STAT3 and Wnt/β-catenin. A better understanding of the common mechanisms under similar conditions in different cell systems would greatly contribute to the development of targeted artemisinin derivativesas well as improving the cytotoxicity of artemisinin by reducing IC_{50}, emergence of drug resistance, drug-related toxicity and enhancing drug interaction. At present, there have been a large number of studies applying artemisinin and its derivatives to the treatment of various types of cancers. This article reviews the latest advances in the research of artemisinin and its derivatives in hematological malignancies. Various studies have shown that it can play a role through a variety of mechanisms, such as inducing cell cycle arrest, inducing autophagy and apoptosis. In addition, artemisinin and its derivatives also show anti-cancer effects in many drug-resistant hematological malignancies, and have a synergistic effect with other drugs. Nevertheless, the potential drug reaction, drug interaction, drug resistance, as well as the side effects toward normal cells remains a concern. An increasing number of studies have been focusing on determining the biological activation mechanism and molecular events behind the artemisinin effect. However, how artemisinin exerts its antitumor activity after activation remains unclear. Besides, future investigation may be required to futher understand the effects of artemisinin to reveal potential of artemisinin as a clinical drug on not only malaria, but also hematological malignancies.

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