

# Artemisinin Derivatives: Anti-cancer Effects and Mechanisms

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**Abstract:** Abstract-Artemisinin derivatives have been studied as anti-malaria drugs in many aspects, while were found anti-cancer affects recently. However, the mechanisms of their anti-cancer effect remain unclear. Research has showed that Artemisinin derivatives may affect the cell cycle of cancer cells through blocking G1 to S phase, and subsequently reduce cell proliferation. Artemisinin derivatives may also cause oncosis and cancer cell apoptosis by promoting Ferroptosis. A new water-soluble derivative, SM1044, was found its anti-cancer ability through inducing apoptosis and blocking cell cycle. Future research is required to better understand the potential mechanisms as well as to expand their clinical applications.


## 1 INTRODUCTION


Cancer is a serious hazard to human health and is listed as one of the most important public health problems in the world, which needs to be solved urgently (Yang, 2020). The cancer epidemiology data released by Bray et al. indicated a great burden caused on society (Bray, 2018). There were 1,806,590 new cancer cases and 606,520 deaths in 2020 in the United States. It was estimated that there would be 28.4 million cancer cases worldwide in 2040 (Liu, 2021).


Artemisinin has been known as an effective anti-malaria drug. This active ingredient is isolated from the Chinese herbal medicine Artemisinin annua. Artemisinin and its derivatives can usually be extracted from plant species at the same time as a mixture. They are sesquiterpene lactones with peroxy bridges, which have strong anti-malarial effects. Through the structural modification of artemisinin scientists designed and synthesized new derivatives of artemisinin. Obtained dihydroartemisinin (DHA) and new derivatives with different substituents introduced at each point of dihydroartemisinin.

Through research in recent years, artemisinin and its derivatives have been confirmed to have anti-

cancer effects, though the mechanisms of their anti-cancer effects remain unclear. Current researchers found that the possible mechanism may include the following aspects: (1) blocking the growth of cancer cells by inhibiting the cell cycle, such as ART inducing apoptosis of human retinoblastoma cells (Yang, 2019); (2) causing cell death through oncosis; (3) reacting with a huge number of ferrous ions in cells which are cancerous. Importantly, during the oncosis and ferroptosis in cancer cells, the oxidative stress was caused by artemisinin derivatives through producing of reactive oxygen species, which leads to the expansion of intracellular organelles, the disorder of the antioxidant mechanism in cancer cells, as well as other factors which caused cell death. Though the mechanisms of oncosis and Ferroptos remain unclear. The anti-cancer mechanism of the newly synthesized artemisinin derivative SM1044 and its advantages over the anti-cancer mechanism of traditional artemisinin derivatives is a new direction to preparation and innovation of anticancer drugs.

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## 2 THE MECHANISM OF ARTEMISININ DERIVATIVES

### 2.1 Properties of Artemisinin and Its Derivatives

Artemisinin is a sesquiterpene lactone. There are several names. Artemisinin, Arteannuin, Artemisinine, Qinghaosu. It is chemically known as (1R,4S,5R,8S,9R,12S,13R)-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.0.4,13.0.8,13]hexadecan-10-one (Fig.1).

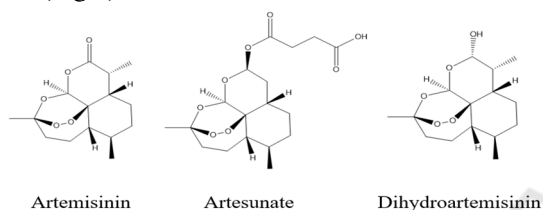


Figure 1: Chemical structure diagram.

Artemisinin is colorless needle crystal and tastes bitter, soluble in organic solvent. Though by modifying the structure of the Artemisinin such as doubling hydrogen of artemisinin, in order to improve the double hydrogen artemisinin molecules chemically unstable hemiacetal structure, obtained derivatives showed better antimalarial activity. Further structure modification could get the artemether, artemisia ether, artesunate (Fig.1) and other dissolved solution and better compound (Mercer, 2007).

The common feature of artemisinin compounds is that they all have a peroxide bridge structure in their components. Studies have shown that the peroxide bridge is an essential structure for artemisinin to exert its pharmacological activity, and its pharmacological activity is significantly reduced after the loss of the peroxide bridge structure (Mercer, 2007).

### 2.2 Affecting the Cell Cycle by Blocking G1 to Enter S

Blocking proliferation of uncontrolled cell growth is one of the important ways to inhibit tumorigenesis. In the normal cells, cyclin will express special proteins at specific periods and activate CDK to drive cells to complete the cell cycle and proliferation. There are two important stages: G1 to S and G2 to M. This review focuses on the G1 to S, which rely on the CyclinD1 combine with the CDK4 (Li, 2018).

CyclinD1 regulates the cell proliferation cycle by binding and activating to CDK4 protein, which promotes cell proliferation. Then the complexes promote the phosphorylation of Rb protein, promoting the cell cycle from G1 phase to S phase, and finally accelerating the cell cycle, which improves the cell proliferation. Researchers found that high expression of CyclinD1 protein would accelerate the cell cycle and rapid abnormal proliferation (Vermeulen, 2003). Eventually, when cancer cells were inhibited, the expression of CyclinD1 and CDK4 would be significantly reduced (Li, 2018). As a result, cell cycle would be negatively regulated, and cell proliferation would be inhibited.

P16 plays a key role in regulating cell cycle through preventing the CyclinD1 combining with the CDK4 (Ding, 2019). In normal cells, the balance of P16 and cyclinD1 maintains a stable state, which keeps the cells in a relatively stable cell cycle. One possible mechanism of conversion from normal cells to cancer cells is losing control of the cell cycle (Lutful Kabir, 2013).

DHA, as another derivative apart from Artesunate, showed an inhibition effect on the proliferation of cancer cells by blocking the process from G1 to S phase, which reduced the DNA synthesis and replication of cells in vitro (Gao, 2020, Caglar, 2020) (Tab.1). Through determination of intracellular protein levels, it was found that cyclinD1 and P16 play an important role in the regulation of cancer cell cycle. With the increase of DHA concentration, cyclinD1 protein expression was gradually down-regulated, while P16 protein up-regulated (Caglar 2020). DHA reduced the combining of cyclinD1 to CDK4 and up-regulated P16 protein, thus achieving cell cycle arrested from G1 to S phase and inducing apoptosis of cancer cells. Importantly, normal cells also have a complete cell cycle which may also be one of the targets of anti-cancer drugs together with cancer cells. Researchers found that compared with traditional anticancer drugs, DHA has the advantage of specific selection for cancer cells (Caglar, 2020). Future research may focus on explanation of the specific expression of DHA in cancer cells. If the cancer specificity of DHA can be combined with molecular targeting technology to find the specific antigen sites of cancer cells, it might be able to achieve a breakthrough in the synthesis of anticancer drugs.

Table 1: Effect to different cell models within Artemisinin derivatives.

Cell line	Drug	Effect	Ref.
BGC-823	DHA	Inhibit cell growth. Induction of apoptosis. Make cell cycle stay in G1.	(Gao 2020)
Panc-1	ART	Mitochondria with decreased matrix density and swelling of cristae, cells severely damaged.	(Du 2010)
BJeLR and DRD	siGPX4	Cell death	(Yang 2014)
BJeH and BJeHLT	siGPX4	No cell death	(Yang 2014)
HL60	SM1044	Inhibited the proliferation, promoted the apoptosis of HL60 cells	(Yu 2013)
Kasumi-1	SM1044	Change cell cycle apoptosis-related protein to inhibit the proliferation of Kasumi-1 cells	(Liu 2011)
SU-DHL-4 (DLBCL)	SM1044	Induced he apoptosis of SU-DHL-4cells in a dose-dependent manner up-regulated the expression of caspase 3 nd PARP fragments	(Yu 2014)

### 2.3 Oncosis

The effect of artemisinin derivatives on cancer cells can lead to cell oncosis (Weerasinghe, 2012). Oncosis originated in the Greek word “onkos” which means swelling. Oncosis and apoptosis have obvious morphological differences. Apoptosis is a process in which cells actively die through gene regulation. The main manifestations of apoptosis are cell atrophy and nuclear fragmentation. Oncosis is passive cell death caused by some factors such as the physical and chemical properties of drugs or other chemical reagents or the environment (Leppo, 2003). The main manifestations of oncosis are the expansion of cells and organelles, the increase of cell membrane permeability and the dissolution of cell nuclei (Majno, 1995).

It was exerted that artemisinin derivatives caused mitochondrial dysfunction when acting on cancer cells, leading to the expansion of the intracellular mitochondrial plasma reticulum (Du, 2010). In addition, the cells undergoing oncosis did not appear to undergo apoptosis after the Hoechst dye entering the cells.

The mechanisms of oncosis induced by artemisinin derivatives remain unclear. Du et al. found that on the death of pancreatic cancer cells induced by artesunate, artemisinin derivatives induced changes in mitochondrial membrane potential (MMP, or  $\Delta\psi_m$ ) and reactive oxygen species mediated cell death in pancreatic cancer cells (Du, 2010) (Tab.1).

The change of mitochondrial membrane potential is one of the most important signs of cell physiological state (Guan, 2018). Through the detection of mitochondrial membrane potential, it can be roughly inferred whether cell homeostasis is disrupted, etc. (Xiao, 2020). Thus, the change of MMP may be a manifestation of cell oncosis. The excessive production of ROS (reaction oxygen species) leads to oxidative stress and damage to intracellular molecules and organelles.

Overall, oncosis, as a different pathway of cell death from apoptosis, could be induced by partial derivatives of artemisinin, which might be a new and effective anti-cancer approach for cancer cells with defective apoptotic pathways. Further research is required to better understand the mechanisms of oncosis induced by artemisinin derivatives and potential of artemisinin derivatives as anti-cancer drugs.

### 2.4 Ferroptosis

Ferroptosis is an iron-dependent way of inducing apoptosis by attacking the cell's antioxidant system, which was named by Dr. Brent R. Stockwell (Dixon, 2012). Different from other types of apoptosis such as necroptosis, autophagic cell death and apoptosis, normal apoptosis inhibitors are ineffective against ferroptosis, but iron chelator can inhibit the production of ferroptosis (Dixon, 2012). These facts indicated that ferroptosis refers to an iron-dependent, non-apoptotic cell death (Imai, 2017). Here are some of the mechanisms of ferroptosis.

Cancer cells are usually over proliferating with high metabolism level and oxygen consumption, which requires more haemoglobin. In turn, with overcrowded haemoglobin, excessive Fe<sup>2+</sup> can produce ferroptosis in cells through Fenton reaction. The Fenton reaction means that Fe<sup>2+</sup> reacts with the peroxy group (the -OOH) in DHA to produce OH•, which belongs to Reactive oxygen species (ROS). Normal doses of ROS are metabolized by cells through a series of reactions (such as peroxide can be degraded by CAT into water and oxygen) while excess ROS can overwhelm the antioxidant system in cells, leading to cell death.

GSH plays a crucial role in the antioxidant system of the body through specifically combining with ROS and eliminating the toxicity of ROS to cells. The expression of GSH is regulated by SLC7A11/XcT, GR and GPX4 (Yang, 2014) (Tab.1). SLC7A11/XcT can transport Cystine into cells to provide raw material for GSH synthesis. GR provides hydrogen for converting GSSG to GSH. GPX4 not only eliminates peroxide, but also converts excess GSH into GSSG for storage. Although there are so many mechanisms in the cell to promote GSH production, the rate of any chemical reaction has an upper limit. When the ROS production rate exceeds the GSH clearance rate, the cell would be enriched in ROS and ROS will attack the cell, leading to cell death.

It was found that intracellular ROS levels of SMMC-7721 and Huh-7, of which the genomic characteristics are very sensitive to the number of passages and detecting gene expression is a convenient and inexpensive way, increased 2.6 times and 2.1 times respectively at DHA 35 μmol/L, and lipid peroxides increased 2.3 times and 1.7 times (Li 2019). In the SMMC-7721 cells GSH decreased by 59% and GPX4 decreased by 81.3% at DHA 35 μmol/L (Li, 2019).

These findings suggested that the inhibitory effect of DHA on the proliferation and anticancer mechanism of Hepatocellular Carcinoma (HCC) cells may not only be limited to cell apoptosis, but also iron death plays an important role in the anti-HCC mechanism of DHA. However, the interaction between iron death and apoptosis in inhibiting hepatocellular carcinoma cell activity and its mechanisms require to be further studied.

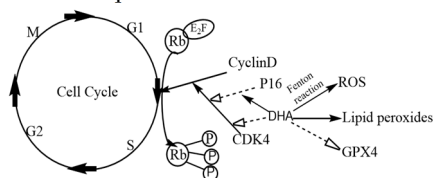


Figure 2: Mechanisms of anti-cancer effect of DHA.

## 2.5 SM1044

In recent years, artemisinin and its derivatives have been making great contributions to drug research. Fat-soluble drugs have been proved to be very inefficient in drug absorption in experiments, and their efficacy is usually not fully utilized. Among the many artemisinin derivatives, SM1044 is a newly developed water-soluble artemisinin derivative. It is superior to fat-soluble drugs in blocking cell growth cycle, inducing cell apoptosis and other therapeutic regimens.

Another study of the effects of artemisinin derivative SM1044 is on acute myeloid leukemia cell line HL60 to analyse the anti-cancer effects of SM1044 on AML and related mechanisms. It was found that SM1044 inhibited the proliferation of HL60 cells; promoted the apoptosis of HL60 cells with an increase of the percentage of apoptosis population with a dose-dependent manner. There are two main pathways of apoptosis: external pathway and internal pathway respectively. The external pathway is the activation of death receptors by extracellular signals, which causes the self-activation of apoptosis promoter caspase -8. The internal pathway is that when it is activated, mitochondrial transmembrane potential is lost, then releasing cytochrome C to stimulate the self-activation of the apoptotic promoter cystein-9. However, after the activated caspase 8 and caspase 9 react each other and stimulate the production of caspase 3, which in turn degrades important proteins including PARP leading to apoptosis. Therefore, apoptosis may occur when both cysteinase-8 and cysteinase-9 are activated and mitochondrial transmembrane potential is lost after the action of SM1044 (Yu, 2013). Hence, the effect of SM1044 on the expression of apoptosis-related proteins was similar as that of SM1044 on kasumi-1 cells and effect of SM1044 on mitochondrial transmembrane potential of HL60 cells was the same as that of SM1044 on transmembrane expression of SU-DHL-4 cells. Therefore, the in vitro studies showed an anti-AML effect of the SM1044, though in vivo studies and potentially clinical studies are required to better understanding the mechanisms and its therapeutic effects (Yu, 2013) (Tab.1).

Kasumi-1 cells were used as the model to test the effect of SM1044, and the results showed that SM1044 could inhibit the proliferation of Kasumi-1 cells through alter in cell cycle and apoptosis-related proteins. The main possible mechanism is that with an increasing concentration of SM1044 ( $\mu_{24}=0.92$ ,  $\mu_{48}=0.98$ ,  $\mu_{72}=0.97$ ,  $p<0.05$ ) an increasing portion of Kasumi-1 cells were blocked in the G0/G1 phase,

which in turn inhibited the proliferation of Kasumi-1 cells with a time- and dose-dependent manner, stopped the cell growth, and thus induced cell apoptosis. Second, L Caspase inhibitor was added in the experiment of co-incubation with different concentrations of SM1044 and cells for 24 hours, and it was found that Caspase was the main mediating mode leading to cell apoptosis. Finally, examination the expression of apoptosis-related proteins showed that SM1044 could induce apoptosis by activating apoptosis-related proteins, including associated protein Caspase 3, PARP and the fusion protein AML1-ETO (Liu, 2011) (Tab.1).

NHL is a hematologic malignancy that causes more than 60,000 new cases in the United States each year, with Diffuse Large B-cell lymphoma (DLBCL) being the most common, so the development of new drugs to combat this disease has become a priority (Cultrera, 2012). In 2006, artemisinin-based ACTs were found to have a 95% cure rate against plasmodium falciparum malaria (Njuguna, 2012). In the study of DLBCL cell line SU-DHL-4 treated with SM1044, it was found that SM1044 induced the apoptosis of SU-DHL-4 cells in a dose-dependent manner, with a possible mechanism through up-regulated the expression of caspase 3 and PARP fragments which were related to apoptosis. It was known that artemisinin may directly act on membrane structures such as the endoplasmic reticulum (ER) which plays an important role in the endogenous apoptosis pathway. Therefore, future studies may focus on endoplasmic reticulum stress and the mechanism of SM1044 inducing SU-DHL-4 cell apoptosis. Thus, according to the recent study, SM1044 can induce the expression of ER stress-related genes and proteins in SU-DHL-4 cells. Artemisinin exerted their anti-malaria effect by targeting the calcium dependent ATPase PfATP6 in plasmodium/sarcoplasmic reticulum, thus greatly increasing the calcium ion level in parasites and leading to the death of plasmodium parasites (Yu, 2014). The role of calcium ion SM1044 in inducing endoplasmic reticulum stress and apoptosis of SU-DHL-4 cells was determined. Hence, SM1044 induced apoptosis of SU-DHL-4 cells may be a complex process involving multiple mechanisms. Due to the greater safety of SM1044 and the strong water solubility of other artemisinin derivatives, SM1044 might be a promising new anti-cancer drug (Yu, 2014) (Tab.1).

Until now, most studies have concluded that the mechanism of artemisinin-induced apoptosis is similar to its antimalarial mechanism, that is, the reaction between the internal peroxide group and iron

ions produces free radicals or electron-philic intermediates, which increases the intracellular reactive oxygen species level and then activates the upstream apoptotic signalling pathway (Mercer, 2007). Follow-up work may continue to investigate the mechanisms of anti-cancer effects of SM1044 as well as its potential clinical application.

### 3 CONCLUSIONS

In conclusion, the results of different studies and experiments indicate that uncontrolled cell growth is known to cause cancer and many complications in vivo and inducing apoptosis is the primary treatment for blocking the overgrowth of cancer cells. Firstly, in terms of the stages of cell division, the G1 to S stages play a key role in regulating proteins that block cancer cell growth which SM1044 could induce Kasumi-1 cell cycle and block Kasumi-1 cells at G0/G1 phase, and at the same time, S phase cells decreased significantly. Secondly, through antimalarial mechanisms, the Fenton reaction between the peroxide bridge and iron destroys cancer cells and blocks cell growth. Finally, among artemisinin derivatives, water-soluble derivatives are more efficient in absorption and function than fat-soluble derivatives.

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