Scholar Publishing Group
International Journal of Public Health and Preventive Medicine
https://doi.org/10.38007/IJPHPM.2020.010404
ISSN 2789-8377 Vol. 1, Issue 4: 34-45

Anti-tumor Activity and Mechanism of Artemisinin Galactoside

Jianzhang Du

Oriental School of Beijing University of Chinese Medicine, Hebei, China
Djianzh@bucmdf.edu.cn

Keywords: Artemisinin Galactosides, Antitumor Mechanism, Tumor Proliferation Rate, Artemisinin Drugs

Abstract: Artemisinin is a highly effective antimalarial component isolated from the Chinese medicine Artemisia annua. In addition to its antimalarial effect, artemisinin and its derivatives can also inhibit the activity of tumor cells. The glycosylation modification of artemisinin can solve the problem that it is prone to oxidation and isomerization and decompose and deteriorate. It is based on the principle that glycosyltransferase catalyzes the glycosylation reaction. This article aims to study the anti-tumor activity and mechanism of artemisinin galactosides, so this article selects derivatives with artemisinin as the mother core for structural transformation, screens them for activity, and selects a compound with high comprehensive evaluation. Its in vivo anti-tumor mechanism is studied. The selected dose is 20 mg / kg, 40 mg / kg, 80 mg / kg. During the experiment, the tumor diameter was measured every other day to calculate the tumor volume (V) and relative tumor volume (RTV). The relative tumor proliferation rate T / C (%) was used as the evaluation index of the drug's anti-MDA-MB-231 tumor activity in vivo. If T / C (%)> 60%, the drug was judged to be ineffective. The research data found that the tumor weight of artemisinin galactoside decreased as the dose increased, indicating that the tumor was dose-dependent on artemisinin galactoside and inhibited tumor at the highest dose (80 mg / kg) The rate reached 73.25%. Artemisinin drugs have a broad spectrum, high efficiency, and low toxicity, can selectively kill tumor cells, reverse the multi-drug resistance of tumors, and have a synergistic and synergistic effect with a variety of chemotherapy drugs.

1. Introduction

Tumor is still the leading cause of life-threatening disease and death, and current anti-tumor therapies are often accompanied by the emergence of significant toxicity and drug resistance. Therefore, there is an urgent need to develop a drug with high efficiency, low toxicity, and selective killing effect on tumor cells. Artemisinin and its derivatives, as conventional antimalarial drugs,

have potential antitumor activity and no obvious toxic side effects on sensitive, drug-resistant or radiation-resistant cell lines in the nanomolar and micromolar concentration range. But its anti-tumor mechanism is still controversial. In this article, we will elaborate on some key issues of artemisinin and its derivatives as anti-tumor drugs in order to better understand the mechanism of its anti-tumor effect.

As the global aging trend intensifies and carcinogenicity-related behavioral activities increase, the incidence of cancer continues to rise. The 2014 World Health Organization's latest "World Cancer Report" shows that in 2012 China added 3.07 million cancer patients and caused approximately 2.2 million deaths, accounting for 21.9% and 26.8% of the global total. Traditional tumor treatment methods include surgery, radiotherapy and chemotherapy. Although they can remove most tumors, they are also prone to cause tumor cell proliferation, drug resistance and large side effects. Therefore, there is an urgent need to find high-efficiency, high specificity, anti-tumor cell resistance of drugs [1-2].

Dell et al. Found that artesunate can not only induce apoptosis of Kaposi's sarcoma cells, but also inhibit tumor cell angiogenesis [3]. The inhibitory effect of artemisinin on tumor angiogenesis is mainly related to its inhibition of vascular endothelial cell proliferation, differentiation and migration, and it is also related to the inhibition of the expression of vascular endothelial growth factor VEGF and its receptor KDR / flk-1. Efferth et al. Screened the inhibitory activity of 22 traditional Chinese medicines on multi-drug resistant tumor cells and found that artemisinin had the highest growth inhibitory activity on multi-drug resistant tumor cells, and artesunate can significantly increase Adriamycin in human leukemia The accumulation of cell lines in epirubicin-resistant CEM / E100 cell lines [4]. The combined use of artemisinin and daunorubicin can play a regulatory role in multi-drug resistant cell lines. At the same time, the study found that artemisinin has a growth inhibitory activity on P-gp-mediated multi-drug resistant cell lines Also higher.

Through the research in this article, we can see that the anti-tumor research of artemisinin and its derivatives has become a hot spot, so this article selects a series of derivatives with artemisinin as the core for structural transformation, screens them for activity, and chooses a comprehensive The highly evaluated compounds are further studied on their anti-tumor mechanisms in vivo. The experimental results show that the tumor weight of artemisinin galactosides decreases with increasing dose, indicating that the tumor is dose-dependent on artemisinin galactosides and inhibits tumors at the highest dose (80 mg / kg) The rate reached 73.25%. Artemisinin compounds have strong anti-tumor activity and low toxicity. They can inhibit tumor growth by inhibiting tumor cell proliferation, inducing tumor cell apoptosis, inhibiting tumor angiogenesis, reversing tumor cell multidrug resistance, etc. Research in the field of anti-tumor is very active, it is a class of anti-tumor compounds with in-depth research value.

2. Proposed Method

2.1. Anti-Tumor Mechanism of Artemisinin and Its Derivatives

1) Internal peroxide group has important anti-tumor effect

The internal peroxide groups of artemisinin and its derivatives have been shown to have important antimalarial activity. Heme or ferrous iron activates the internal peroxide group, producing cytotoxic carbon-centered free radicals, alkylating important biological macromolecules such as DNA or proteins in the body of Plasmodium, thereby causing the death of Plasmodium [5]. The potent anti-tumor effect of artemisinin and its derivatives can also be attributed to internal

peroxide groups. The partial lack of peroxide group does not completely block its anti-tumor activity, but it will significantly reduce its cytotoxicity.

2)Iron and heme are involved in the activation and action of artemisinin and its derivatives

The existing research results have reached a general consensus: iron, heme or heme binding protein is involved in the activation and biological activity of artemisinin and its derivatives. In some cell lines, anti-tumor activity of artemisinin and its derivatives can be increased by up to 100 times with iron or ferritin pretreatment. In addition, artemisinin combined with iron-containing compounds has greater activity than artemisinin alone. The experiment found that intracellular heme can mediate the artemisinin's cytotoxicity. Increasing the precursor substance of heme synthesis will enhance the effect of artemisinin, and adding inhibitors to interfere with the heme synthesis pathway will reduce the cytotoxicity. Non-heme iron can enhance the effect of artemisinin by participating in the heme synthesis process [6]. This is consistent with previous research. Similarly, the addition of deferoxamine, an iron chelating agent, can reduce its activity. The metabolism of iron and heme may be related to the selective antitumor effect of artemisinin and its derivatives. The growth and proliferation of malignant cells require high levels of iron metabolism to maintain, so tumor cells exhibit high levels of transferrin receptor, which can absorb iron and regulate the concentration of iron in the cell. In different tumor cells, the expression level of transferrin receptor may be different, depending on different cell lines, however, they are significantly different from normal cells, resulting in high artemisinin and its derivatives Selective.

3)ROS-mediated cytotoxicity

It is speculated that iron works by activating artemisinin to release alkylated carbon free radicals and active oxygen species (ROS) [7]. The generation of ROS may lead to the selective effect of artemisinin on tumor cells. Compared with normal cells, tumor cells are more susceptible to damage by ROS because they exhibit low expression of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase. Therefore, enhancing oxidative stress is a common antitumor mechanism of antitumor drugs. The abnormal sensitivity of Plasmodium to artemisinin indicates that there are specific parasitic targets in the body. In contrast, in tumor cells, the effects of artemisinin and its derivatives seem to be more commonly mediated through the generation of ROS. There is direct evidence that in human leukemia cells HL-60 cells, early and rapidly generated ROS (1 h) is related to artemisinin-induced apoptosis and cell damage. In addition, its IC 50 is directly related to ROS levels. . A recent study showed that human cervical cancer cells HeLa cells produced ROS under the effect of artesunate for 16 h, and their cytotoxicity was found at 48 h, suggesting that ROS may be the initial mechanism of artemisinin-induced damage .

Studies have shown that the mitochondrial electron transport chain plays a key role in the cytotoxicity of artemisinin drugs. When using HeLa ρ0 cells (HeLa cells without mitochondrial DNA), the inhibitory effect of artesunate on cells and cytotoxicity Significantly weakened, but a large amount of ROS can still be detected, suggesting that there may be other sources of ROS in the cell. Indeed, new evidence shows that in breast cancer cells, artesunate is activated by iron, and oxidative stress initially occurs in the lysosome, a process that appears to be similar to that of Plasmodium. Therefore, the activation of apoptotic pathways in the mitochondria is a downstream mechanism leading to cell death. In this model, artemisinin may promote heme synthesis and further increase cytotoxicity [8]. Despite increasing evidence that ROS mediates cell damage in many cell systems, cell damage has been independently associated with oxidative stress. In particular, the new artemisinin dimer seems to produce anti-tumor effects with little or no reactive oxygen generation. However, its mechanism of cytotoxicity is still under study. Is artemisinin-induced cell necrosis independent of ROS? The mechanism of action is also unclear.

4)Other molecular targets and cytotoxicity of artemisinin and its derivatives

Artemisinin's cytotoxicity seems to be regulated by calcium metabolism, endoplasmic reticulum stress, and translationally controlled tumor protein (TCTP) expression. The sarcoplasmic reticulum calcium pump (SERCA) as a target of artemisinin in Plasmodium has also been found in tumor cells. There is evidence that 10 uM artemisinin can increase the calcium concentration after inhibiting the sarcoplasmic reticulum calcium pump. . However, studies have shown that ROS-induced endoplasmic reticulum stress after treatment with artemisinin is independent of the effect of inhibiting the sarcoplasmic reticulum calcium pump. The results of the study show that the highly active artemisinin dimer and the sarcoplasmic reticulum calcium pump inhibitor, thapsigargin, appear to be similarly mediated by different molecular events [9]. In fact, thapsigargin lacks peroxide groups and only produces low levels of ROS. However, the endoplasmic reticulum seems to be a relevant point for the action of artemisinin, because fluorescent derivatives preferentially accumulate in this organelle in human liver cancer cells HepG 2 cells. In addition, microarray analysis found that artemisinin had a negative correlation with the IC 50 translation control tumor protein expression of tumor cell lines in the National Cancer Institute. Tumor cells that highly expressed translation control tumor protein were sensitive to artesunate, while Low expressions are not sensitive. The flow chart of the anti-tumor mechanism of artemisinin and its derivatives is shown in Figure 1:

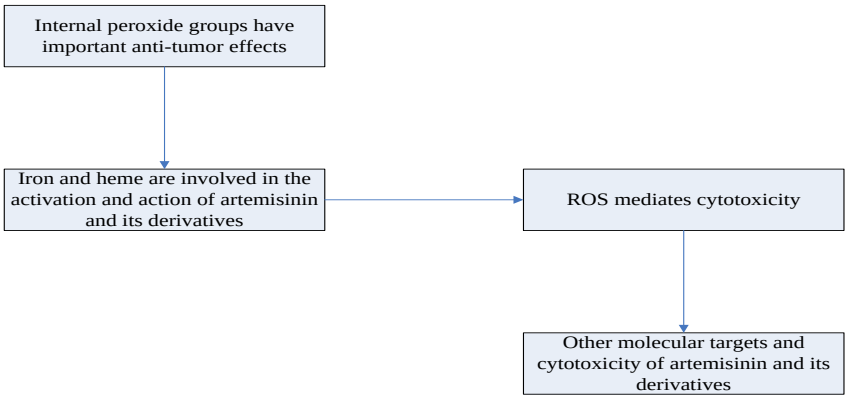

Figure 1. Flow chart of anti-tumor mechanism of artemisinin and its derivatives

2.2. Antitumor Effect of Artemisinin and Its Derivatives

Artemisinin and its derivatives can inhibit and kill various tumor cells in vivo and in vivo. 55 human tumor cells were selected from the National Cancer Institute (NCI) to study its anti-tumor activity. The results showed that artesunate has an effect on leukemia, pancreatic cancer, colon cancer, melanoma, breast cancer, ovarian cancer, prostate cancer Malignant cells such as kidney cancer have an inhibitory effect. Dihydroartemisinin also has significant anti-tumor activity, such as pancreatic cancer, leukemia, osteosarcoma, lung cancer and other malignant cells [10].

Studies have found that artemisinin plays a role either through direct induction of DNA damage or through a series of signal transduction pathways that indirectly interfere with some malignant tumor markers. In pancreatic cancer cells (PANC-1), artesunate causes DNA breaks and membrane damage. Low concentrations of artesunate are associated with cell swelling, while higher concentrations of artesunate induce cell apoptosis [11]. The type and degree of cell damage seem to depend on the phenotype and origin of the cell line, and may also depend on different times and

doses. It is worth noting that the faster the cell line grows, the easier it is to observe its sensitivity to artesunate. Some of its anti-tumor effects mainly manifest as:

(1) To effectively inhibit the proliferation of tumor cells by blocking the cell cycle or interfering with the proliferation pathway;

(2) Induce apoptosis of tumor cells;

(3) Inhibit the invasion and metastasis of tumor cells;

(4) Inhibit the formation of tumor neovascularization;

(5) Reverse the multiple drug resistance of the tumor;

(6) Combined with a variety of conventional chemotherapy drugs, it has synergistic and sensitizing effects, and can increase the sensitivity of drug-resistant tumor cell lines to conventional chemotherapy drugs [12]. In addition, artemisinin and its derivatives can selectively kill tumor cells with little toxic side effects on normal cells. In clinical trials also showed good tolerance, and no obvious toxic and side effects.

2.3. Chemical Structure and Biological Characteristics of Artemisinin and Its Derivatives

Artemisinin is insoluble in water and oil, has a half-life of about 2.5 h, and has a low bioavailability. It is a sesquiterpene ester compound containing a peroxy bridge. This internal peroxide is derived from the Chinese medicine Artemisia annua. Isolated, it has long been used only to control fever symptoms. Endoperoxide artemisinin semi-synthetic and fully-synthetic derivatives have been developed. Two types of semi-synthetic artemisinin derivatives such as artesunate and artemether have been used clinically to treat malaria, with good efficacy. It has been proved that the peroxygen bridge of artemisinin is the main active group and has very important pharmacological activity in the treatment of malaria. It is believed that the activation of the artemisinin peroxygen bridge is related to the reduction of heme (FPFeII) or ferrous ions (FeII). The activated peroxygen bridge leads to the generation of a large number of carbon radicals, which undergo an alkylation reaction with surrounding molecules. The carbon free radicals are the key factor to enter the worm body to produce a killing effect. However, the mechanism of this killing effect and the target of the main effect are still under study. There is a hypothesis that artemisinin targets the organelles of Plasmodium such as mitochondria, endoplasmic reticulum and vacuole, and there are also hypotheses that artemisinin will alkylate heme, protein alkylate and inhibit calcium Ion ATP enzyme etc. Although the target of artemisinin has always been controversial, most views believe that the hemolytic effect of ferrous heme or ferrous ions on plasmodium is essential. A large number of studies have proved this point. For example, in the study of blood-sucking insects, artemether has a strong effect of destroying the inner membrane of blood-sucking insects, and this effect is more intense under the action of ferrous ions.

Through the research in this article, it is generally believed that the anti-tumor active site of artemisinin is also attributed to the peroxygen bridge of artemisinin, but the lack of peroxygen bridge is not a complete loss of anti-tumor activity, but a significant reduction Cytotoxicity, cytotoxicity is one-fiftieth when there is a peroxygen bridge. At the same time, heme or ferrous ion binding protein also participates in the bioreduction activation of artemisinin.

2.4. Artemisinin Compounds Inhibit Tumor Multidrug Resistance

In the course of chemotherapy, the most important self-defense mechanism of tumor cells is the generation of multi-drug resistance (MDR), which is also an important reason for the failure of treatment. The adenosine triphosphate binding cassette transporter (ATP-binding cassette

transponer, ABC transporter) superfamily is a group of unidirectional substrate transport pumps, which have an ATP binding region and complete multiple molecular transmembrane transports by active transport. Many members of the membrane protein ATP-binding cassette ABC transporter superfamily are involved in the mechanism of multidrug resistance, including multidrug resistance-related protein (MRP) and its encoded P-glycoprotein (permeability glycoprotein, P-gp), etc. . In a series of in vitro and animal model experiments, artemisinin and its derivatives have shown good anti-tumor effects, and have obvious effects on leukemia, colorectal cancer, melanoma, breast cancer, ovarian cancer, prostate cancer and renal cancer cells Inhibition and killing effect. Studies on artemisinin and its derivatives in inhibiting the proliferation, invasion and metastasis of tumor cells, inducing apoptosis and inhibiting the formation of tumor blood vessels have found that it can not only act on tumor cells alone, but artemisinin and its derivatives The main mechanism of tumor function is to regulate the expression of genes and proteins related to tumor cell proliferation, apoptosis, invasion and metastasis, and vascularization.

2.5. Artemisinin and Cell Death

Cell death is the final stage of cell life, mainly divided into: exogenous apoptosis, caspase-dependent and non-dependent endogenous apoptosis, autophagic cell death, iron death and so on. Apoptosis refers to the orderly death of cells controlled by genes in order to maintain the stability of the internal environment. Autophagy, or cell self-digestion, is a process used by eukaryotes to degrade and recycle intracellular biological macromolecules and damaged organelles in order to achieve the metabolic needs of the cells themselves and the renewal of certain organelles. Iron death is a new type of cell death. Glutathione peroxidase activity decreases, leading to dyslipidemia, which reacts with intracellular ferrous ions and generates a large amount of reactive oxygen species (ROS) to cause cell death. Studies have shown that artemisinin and its derivatives can kill tumor cells by inducing apoptosis, causing iron death and autophagic death. On the one hand, artemisinin and its derivatives can promote apoptosis by inducing caspase expression. Artesunate stimulates high expression of caspase and caspase, and induces apoptosis in human osteosarcoma cells. It shows that artemisinin and its derivatives up-regulate caspase content through the mitochondrial pathway, thereby promoting tumor cell apoptosis. On the other hand, artemisinin and its derivatives can also regulate Bcl-2 family genes.

2.6. Anti-Tumor Cell Proliferation and Cell Cycle Arrest Effect of Artemisinin Compounds

In normal cells, the cyclin family of cyclins (including Cyclin A, Cyclin B, Cyclin C, and Cyclin D) and cyclin-dependent kinases (CDK) are the key proteins that allow the cell cycle to proceed smoothly. The growth of normal cells depends on the effective replication and division of signaling molecules, and the uncontrollable proliferation of tumor cells can induce mutations in signaling molecules and protein factors in the cells, the weakening of protein molecule recognition ability, and the loss of certain dangerous protein inhibitors. Abnormal cell growth can also trigger programmed cell death or apoptosis. Artemisinin and its semi-synthetic derivatives can effectively induce tumor cell growth arrest by blocking the cell cycle or interfering with cell proliferation, and artesunate and dihydroartemisinin are very effective tumor cell growth inhibitors, dihydroqing Artemisinin derivatives are considered to be the most effective anti-tumor compounds (the activity is as follows: DHA> artesunate> artemether> artemether). Artemisinin compounds can induce cell growth arrest at various stages of the cell cycle, the most common of which is arrest in the G0 / G1 and S phases. In leukemia, pancreatic cancer, osteosarcoma and ovarian cancer, DHA can block the

cell cycle in the G2 / M phase. Similarly, in osteosarcoma and ovarian cancer, artesunate can block the cell cycle in G2. period. The mechanism by which artemisinin compounds stop the growth of tumor cells is to change the enzymes that control cell cycle regulation. For example, cyclin-dependent kinases CDK2, CDK4 and CDK6 can promote the cycle from G1 phase to S phase, or cyclin-dependent kinase CDK1 Promote the completion of the G2 / M period. Artemisinin-like compounds can induce down-regulation of cyclin-dependent kinase family CDK, inhibit activation of CDK factors or up-regulate P21 and P27 proteins. Inhibition of tumor cell proliferation is also due to down-regulation of interacting proteins in multiple pathways. DHA has been shown to act on pancreatic cancer cells (BxPC3, AsPC-1) by down-regulating cyclin D1 and pro-proliferating nuclear antigen (PCNA), while simultaneously up-regulating p21 Protein to jointly inhibit the proliferation of tumor cells.

3. Experiments

3.1. Experimental Setup

(1) Experimental Instruments

Vortex mixer, micro pipette, electronic balance, SHB-Ⅲ circulating water type multi-purpose vacuum pump.

(2) Experimental animals

1) KM mice 18 g ~ 22 g, half male and female, are housed in SPF animal house.

2) BALB / c nu mice, 4-6 weeks old, are housed in female SPF animal houses.

(3) Experimental cells

Human breast cancer MDA-MB-231

(4) Main reagents and materials

Distilled water, 1 ml syringe, mouse No. 12 applicator, paclitaxel

3.2. Experimental Method

Nine 18 g-22 g KM mice, 3 of each group were divided into 3 groups, referring to the literature, to find the corresponding dose of 0% and 100% mouse mortality. Then 50 KM mice were selected and randomly divided into 5 groups, 10 mice in each group, half male and female, according to the dose ratio of 1: 0.8, respectively 262 mg / kg, 328 mg / kg, 410 mg / kg, 512 mg / kg , 640 mg / kg, given by intragastric administration according to 0.1 ml / 10g. Observe closely after administration, and observe the number of deaths during the observation period of one week.

After 50 female nude mice were inoculated with MDA-MB-231 cells until the average tumor volume reached 100 mm3, they were randomly divided into 5 groups with 10 mice in each group: blank group, that is, saline and DHX01 high, medium and low Group (20 mg / kg, 40 mg / kg, 80 mg / kg) and positive control paclitaxel group (Taxol, 20 mg / kg) were given intravenously three times a week. Artemisinin galactoside is administered by intragastric administration once a day at a body mass of 10 ml / kg, weighed once a day, and a record is made. After continuous administration for 21 days, nude mice were sacrificed after the last administration, the tumor body was immediately peeled off, the longest and shortest diameters were measured and weighed.

4. Discussion

4.1. Test Study on the Weight Change of Nude Mice

(1) Through the test of acute toxicity of artemisinin galactosides as shown in Table 1, it is concluded that the LD50 of artemisinin galactose is 375mg / kg. 1. The weight of the first three days is gradually decreased compared with the previous three days after the weight loss before the drug administration. The doses selected in this experiment were 20 mg / kg, 40 mg / kg, and 80 mg / kg. During the experiment, the tumor diameter was measured every other day to calculate the tumor volume (V) and relative tumor volume (RTV). The relative tumor proliferation rate T / C (%) is used as the evaluation index of the anti-MDA-MB-231 tumor activity in the drug. If T / C (%)> 60%, the drug is judged to be ineffective; if T / C (%) ≤ 60 %, And after statistical treatment P <0.05, the drug is judged to be effective. Compare the relative tumor proliferation rate of the blank group and the drug group to determine whether the test drug has an anti-tumor effect in vivo. Tables 1 and Figure 2 show the survival of animals at different doses of artemisinin galactosides:

Table 1. Artemisinin galactoside survival at different doses

Dose	Day1	Day2	Day3	Day4	Day5	Day6	Day6
640 mg/kg	2	0	0	0	0	0	0
512 mg/kg	3	2	2	2	2	2	2
410 mg/kg	4	3	2	2	2	2	2
328 mg/kg	9	7	6	6	6	6	6
260 mg/kg	10	10	10	10	10	10	10

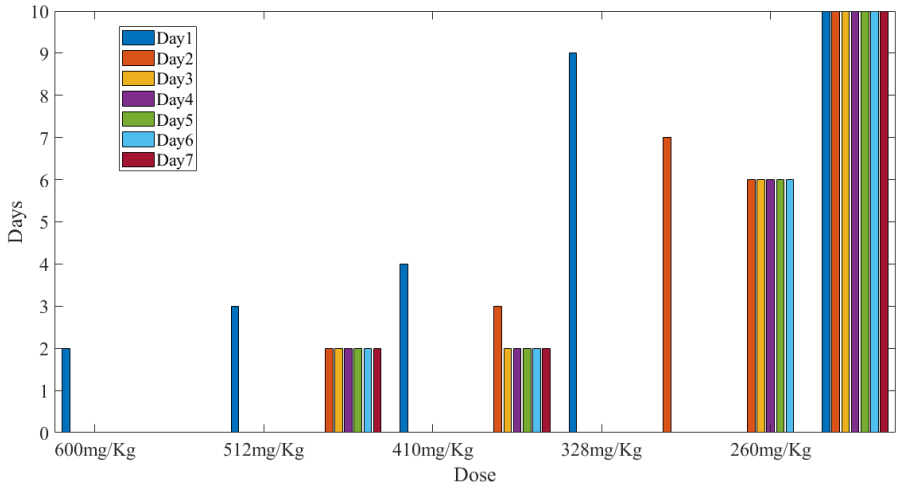

Figure 2. Artemisinin galactoside survival at different doses

(2) The body weight of nude mice showed that the weight of nude mice in the medium-dose (40 mg / kg) and high-dose (80 mg / kg) artemisinin galactosides groups had a certain degree of weight loss after administration, of which 40 The body weight of the mg / kg group decreased significantly after the administration, and the average body weight of the animals in the 80 mg / kg group continued to be at the level before the administration, and did not increase with the growth of the

animal and the increase in tumor volume. As the dose of artemisinin galactoside increased, the tumor weight also decreased, indicating that the tumor was dose-dependent on artemisinin galactoside, and the tumor inhibition rate reached 73.25% at the highest dose (80 mg / kg) , Artemisinin galactosides caused changes in tumor weight in the MDA-MB-231 model shown in Table 2 and Figure 3:

Table 2. Artemisinin-galactoside-induced changes in tumor weight in MDA-MB-231 model

Group	Dose	Initial	End	Tumour wt/g	Inhibition (%)
DHX01	20 mg/kg	18.2 ±0.97	19.9 ±0.46	1.62 ±1.21	33.30
DHX01	40 mg/kg	18.3 ±0.67	17.2 ±0.37	1.34 ±0.57	44.86
DHX01	80 mg/kg	18.9 ±0.77	18.7 ±0.43	0.65 ±0.59	73.25

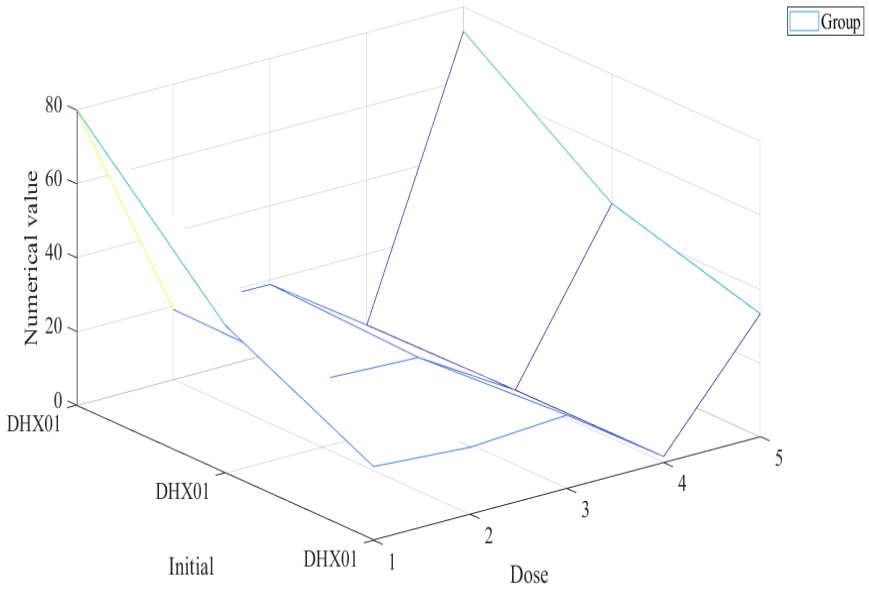

Figure 3. Artemisinin-galactoside-induced changes in tumor weight in MDA-MB-231 model

4.2. Analysis of Tumor Growth Changes in Nude Mice

(1) The tumor growth of nude mice in each group showed that the tumor weight inhibition rate of artemisinin galactosides 20 mg / kg group was 33.3%, and the relative tumor proliferation rate was 64.6%. The tumor weight inhibition rate in the 40 mg / kg group reached 44.9%, the tumor weight inhibition rate in the 60 mg / kg group reached 44.9% and 61.4%, the tumor weight inhibition rate in the 80 mg / kg group was 73.25%, and the relative tumor proliferation rate (T / C) 38.22 %. The high-dose group met the effective criteria for evaluating antitumor activity (T / C (%) $\leqslant$ 60%). DHX01 caused the change in tumor volume data in the MDA-MB-231 model as shown in Figure4:

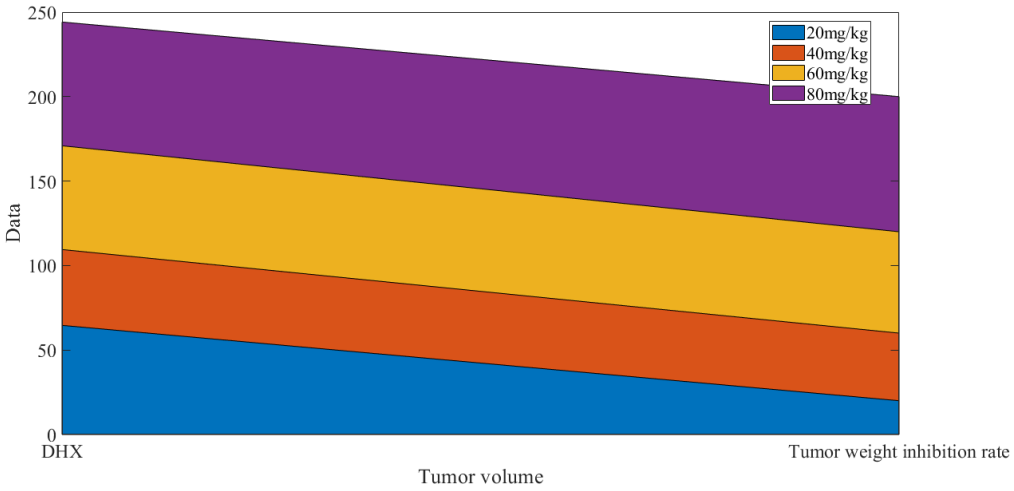

Figure 4. DHX01 causes changes in tumor volume data in the MDA-MB-231 model

Artemisinin galactoside has a certain inhibitory effect on the tumor growth of MDA-MD-231 model animals and is related to the dose administered. Compared with the solvent and the control group, the tumor volume of the three groups of nude mice was significantly reduced. Before the middle of the experiment, the tumor volume growth of the three-dose group was smaller than that of the control group, and showed a certain dose-effect relationship. Although MDA-MB-231 tumor-bearing mice were given intragastric administration of higher doses of artemisinin galactosides, some toxic and side effects occurred, and the middle and high dose groups lost weight. However, it shows obvious antitumor activity in vivo, and its effect is weaker than that of paclitaxel for clinical injection. However, oral administration has fewer safety and side effects, and has the value of in-depth research. Given that artemisinin galactosides exhibit higher anti-proliferative activity against drug-resistant cell lines MCF-7 / Adr in vitro, if an in vivo model of MCF-7 / Adr cells is established, it may have a more significant antitumor effect in vivo. Artemisinin galactosides have a certain tumor-inhibiting effect on MDA-MB-231 tumor-bearing mice, the highest dose (80 mg / kg) tumor inhibition rate reached 73.25%, and it was dose-dependent, the data is shown in Figure 5 Show:

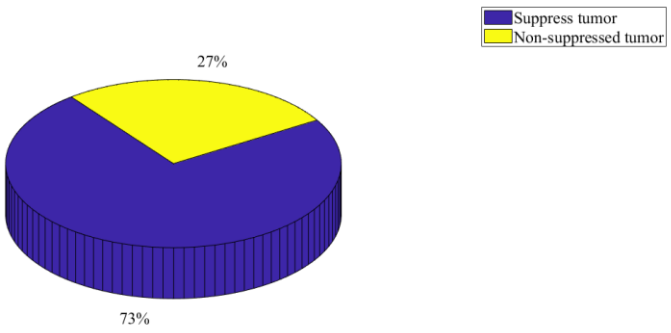

Figure 5. Maximum dose (80 mg / kg) tumor inhibition rate

5. Conclusion

(1) According to the experimental research in this article, artemisinin drugs have been widely used in anti-malarial treatment for many years. Such drugs have many biological activities, especially their powerful anti-tumor effects. Through the research in this paper, it is found that artemisinin drugs may be an alternative treatment for highly malignant or metastatic tumors that are ineffective for long-term treatment or generally resistant. In general, the true potential and benefits of artemisinin drugs have yet to be discovered. The study of artemisinin drugs as anti-tumor drugs is very challenging, and cracking their anti-tumor mechanisms will meet the expectations of many people.

(2) According to the research in this article, artemisinin is one of the few drugs with strong anti-malarial properties without any toxic and side effects, and has potential anti-tumor activity on certain sensitive cells and radiation-resistant cell lines The activity range is between nanomolar and micromolar. During the experiment in this paper, the tumor diameter was measured every other day to calculate the tumor volume (V) and relative tumor volume (RTV). The relative tumor proliferation rate T / C (%) is used as the evaluation index of the drug's anti-MDA-MB-231 tumor activity in vivo. If T / C (%)> 60%, the drug is judged to be ineffective; if T / C (%) $\leqslant$ 60 %, And after statistical treatment P <0.05, the drug is judged to be effective. Compare the relative tumor proliferation rate of the blank group and the drug group to determine whether the test drug has an anti-tumor effect in vivo. Through the test of acute toxicity of artemisinin galactosides, it was found that the LD50 of DHX01 was 375mg / kg. The mice were slow in action after administration, flaccid, closed their eyes, and lost weight for the first three days. Weight gradually increased compared with the previous three days.

(3) The experimental results in this paper show that the tumor weight decreases with increasing dose of artemisinin galactoside, indicating that the tumor is dose-dependent on artemisinin galactoside and the highest dose (80 mg / kg) Tumor inhibition rate reached 73.25%. The artemisinin galactoside raw materials have poor water solubility and cannot be directly administered via tail vein injection. In order to better compare the antitumor activity of artemisinin galactoside against transplanted tumors in mice, the drug was prepared the solid dispersion improves the water solubility of the drug. Artemisinin galactosides can selectively down-regulate the Cyclin D1 level of MCF-7 cells in a dose- and time-dependent manner at 0.25 μM and 0.5 μM concentrations, and down-regulate the Cyclin B1 level in a time-dependent manner; 0.025 μM, 0.05 μM Time-dependent and selective down-regulation of Cyclin D1 and Cyclin B1 levels in MCF-7 / Adr cells and up-regulation of P27 levels did not affect the expression of P-gp in MCF-7 / Adr cells. Intragastric administration of artemisinin galactosides against MDA-MB-231 tumors in vivo, in the three dose groups of 20 mg / kg, 40 mg / kg and 80 mg / kg, artemisinin galactosides against MDA-The inhibition rates of tumor weight in nude mice bearing MB-231 cells were 33.3%, 44.86% and 73.25%, respectively, and the relative tumor proliferation rate (T / C%) was 38.22% at high doses.

Funding

This article is not supported by any foundation.

Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Conflict of Interest

The author states that this article has no conflict of interest.

References

[1] Jian Qiao, Zhida Liu, & Yang-Xin Fu. (2016). "Adapting Conventional Cancer Treatment for Immunotherapy", Journal of Molecular Medicine,94(5), pp.489-495.

[2] Yusuke Inagaki, Eiji Kubota, Yoshinori Mori, Mineyoshi Aoyama, & Takashi Joh. (2017). "Anti-tumor Efficacy of Oncolytic Reovirus Aagainst Gastrointestinal Stromal Tumor Cells",Oncotarget, 8(70), pp.115632-115646. DOI: 10.18632/oncotarget.23361

[3] Lougheed, M. D., Lemière, C., Dell, S. D., Ducharme, F. M., Fitzgerald, J. M., & Leigh, R., et al. (2016). "Canadian Thoracic Society Asthma Management Continuum – 2010 Consensus Summary for Children Six Years of Age and Over, and Adults", Canadian Respiratory Journal Journal of the Canadian Thoracic Society, 17(1), pp.15.

[4] Sara Iverson, Field, C., Bowen, D., Blanchard, W., Connie Stewart, & Shelley Lang, et al. (2016). "Qfasa: Quantitative Fatty Acid Signature Analysis", Ecological Monographs, 74(2), pp.211-235. DOI: 10.1890/02-4105

[5] LU BINBIN, RYAN MENG, LYNNE WISSE, & JIAO YANFU. (2016). "Comparison of Cytotoxicity of Cigarette Smoke of Different Tar Deliveries", Tobacco Science & Technology, 49(6), pp.45-49.

[6] D.-Y. Xie. (2016). "Artemisia Annua, Artemisinin, and the Nobel Prize: Beauty of Natural Products and Educational Significance", Science Bulletin,61(1), pp.1-3. DOI: 10.1007/s11434-015-0989-3

[7] Heiko Blaser, Catherine Dostert, Tak W. Mak, & Dirk Brenner. (2016). "Tnf and Ros Crosstalk in Inflammation", Trends in Cell Biology, 26(4), pp.249-261. DOI: 10.1016/j.tcb.2015.12.002

[8] Brent R. Stockwell, José Pedro Friedmann Angeli, & Hülya Bayir. (2017). "Ferroptosis: Aregulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease", Cell, 171(2), págs. pp.273-285.

[9] Jennifer M Fox, James R Moynihan, Bryan T Mott, Jennifer R Mazzone, & Xiaochun Chen. (2016). "Artemisinin-derived Dimer Art-838 Potently Inhibited Human Acute Leukemias, Persisted in Vivo, and Synergized with Antileukemic Drugs", Oncotarget, 7(6), pp.7268-7279.

[10] Rui Zhao, Tao Zhang, Baoling Ma, & Xing Li. (2016). "Antitumor Activity of Portulaca Oleracea l. Polysaccharide on Hela cells Through Inducing Tlr4/nf-κb Signaling", Nutrition & Cancer, 69(1), pp.1-9.

[11] Hua Zhang, Xia Li, Xufeng Dai, Juanjuan Han, & Ji-jing Pang. (2017). "The Degeneration and Apoptosis Patterns of Cone Photoreceptors in Rd11 Mice", Journal of Ophthalmology, 2017(7), pp.1-13.

[12] Aline G. Souza, Karina Marangoni, Patrícia T. Fujimura, Patrícia T. Alves, & Vivian A. Goulart. (2016). "3d Cell-selex: Development of Rna Aptamers as Molecular Probes for Pc-3 Tumor Cell Line", Experimental Cell Research,341(2), pp.147-156.