Anticancer Potential of Artemisinin and Its Derivatives

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Abstract. Chinese scientist Tu Youyou discovered artemisinin in the 1970s, and she extracted it from Artemisia annua. The greatest contribution of artemisinin is to the treatment of malaria, and in 2015, Tu Youyou received the Nobel Prize in Medicine for her discovery. This article presents recent studies showing that artemisinin and its derivatives have some anti-cancer effects in addition to treating malaria. Cancer, the disease with the highest mortality rate, has been the subject of human efforts to find ways to overcome it. Artemisinin was already found to slow down the growth of tumor cells through various mechanisms, such as by preventing cell invasion, promoting apoptosis, causing cell cycle arrest, and controlling the tumor microenvironment, but further studies are needed to demonstrate its better efficacy and safety. This article first describes the basic structure and physical and chemical properties of artemisinin, then describes the various anticancer mechanisms of artemisinin and its derivatives, as well as the clinical trials that have been completed for the study and proof of these mechanisms, and finally describes the anticancer effects of artemisinin in combination with other drugs.

Keywords: Arteminsinin, Cancer, Ferroptosis, Artesunate, Apoptosis, Cell Cycle.

1. Introduction

Cancer is a lethal disease that certain cells in the body proliferate uncontrollably, resulting in aggressive and metastatic malignant tumors. It has long been the most fatal problem confronting humanity, and it contributes to the world's second leading cause of death [1]. According to GLOBOCAN cancer statistics from the International Institute for Research on Cancer, in 2020, the new cases of cancer were approximately 19.3 million and the deaths from cancer were almost 10.0 million globally [2]. Female breast cancer, lung cancer, and prostate cancer were the three malignancies that were most frequently diagnosed, while lung, liver, and stomach cancers were the three that claimed the most lives from the disease [2]. With such a high number of deaths, scientists have also been researching various ways to treat cancer. On the molecular level, cancer alters the interactions between cells and key genes, causing aberrant growth. Genetic mutation turns proto-oncogenes into oncogenes, endangering the viability of cells. Uncontrolled cell division is triggered when tumor suppressor genes are absent [3]. Application of nanotechnology, extracellular vesicles, magnetic hyperthermia, targeted therapy, natural antioxidants, gene therapy, thermal ablation, pathomics and radiomics are promising approaches for developing precise and effective cancer treatments [4]. These technologies optimize the release profile of the medications, boost their bioavailability and concentration near the tumor tissues, and target certain areas while sparing the surrounding area [4]. In addition to these advanced anti-cancer technologies already in development, artemisinin and artemisinin's derivatives have been studied for their anti-cancer properties as well. Artemisinin is a plant-derived and bioactive compound that was obtained from the ancient Chinese herb Artemisia annua by a Chinese scientist Tu Youyou and has various derivatives, including artemether, arteether, dihydroartemisinin, and artesunate. Artemisinin has been found as an antimalarial drug, and artemisinin and artemisinin's derivatives as well as have been studied for their prospective use in treating human cancers [5].

2. The Structure and Properties of Artemisinin and Its Derivatives

Artemisinin was successfully extracted from Artemisia annua in the 1970s, and its structure was identified by X-ray crystallography, spectrophotometry, mass spectroscopy, and poly-arithmetic

analysis [6, 7]. Fig. 1 shows the molecular structure of artemisinin, which contains an unusual endoperoxide component, 1,2,4-trioxane ring, which mostly accounts for the antimalarial function, and the anti-tumor activities of artemisinin is also from this component [8]. However, the hydrogenation of the endoperoxide part of artemisinin yields deoxy artemisinin, which does not have the ability to inhibit malaria. By using sodium borohydride, the lactone portion of artemisinin can be converted into a lactol, which was the starting point for creating a modified artemisinin derivative [6]. The majority of the stages of the malaria parasite in the blood, including the sexual stages that spread the infection to others, are efficiently eliminated by artemisinin. Unfortunately, they have little effect on certain kinds of malaria parasites' early liver stages. Artemisinin's precise mode of action is yet unknown. However, it is thought to include ion-dependent alkylation, with sarcoplasmic endoplasmic reticulum calcium adenosine triphosphatase as a potential target [9]. In addition to its chemical properties, artemisinin also has several uncommon physical properties: its solubility is low in both water and oil, and it is one of the deficiencies of artemisinin because it cannot dissolve in both polar or nonpolar solvents, but it can dissolve in aprotic solvents [6]. Artemisinin can endure heating up to 156-157°C, but at 190°C, it decomposes. However, in the presence of an alkali or acid, it becomes unstable and forms mixed products [6]. As for derivatives, artemisinin derivatives like dihydroartemisinin, artesunate, artemether, and arteether have been developed and found to have significant antitumor activities besides their original use as antimalarials. The last two are quickly metabolized into dihydroartemisinin in the body [10]. As the only anti-malarial drug, there are now no substitute medications on the market, and artemisinin sensitivity and resistance are widely spreading. A serious health disaster could result from this condition, particularly in Africa, where the majority of fatalities occur. The WHO has issued a warning on the need to prevent a regional public health emergency, and initiatives are being made to extend the shelf life of artemisinins and find other medications with comparable mechanisms of action [11].

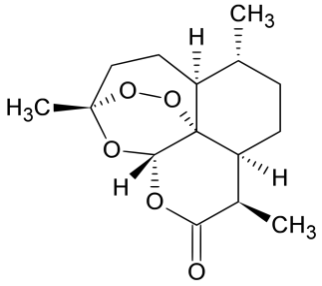

Figure 1. The structure of Artemisinin [12]

3. The Anti-Cancer Mechanism of Artemisinin

Current studies suggest that by interfering with intracellular pathways, artemisinin, and its derivatives can slow several types of cancer cell growth, such as the breast, melanoma, ovarian, lung, and prostate cancer. These substances have been shown to prevent cell invasion, promote apoptosis, cause cell cycle arrest, and control the tumor microenvironment [13]. The cell cycle phases G1 to S and G2 to M are crucial for the development of tumors. It has been discovered that artemisinin and its derivative dihydroartemisinin prevent tumor growth by causing cell cycle arrest to happen specifically in the G1 phase and inducing G1 cell cycle arrest in prostate and lung cancer cells via controlling cyclin expression and boosting the activity of cyclin-dependent kinase inhibitors [14]. Dihydroartemisinin (DHA) can also inhibit the cancer cell by impacting its metabolism. The Warburg effect describes how cancer cells differ from healthy cells in their predilection for glycolysis to make lactate, and DHA has the ability to prevent cancer cells from utilizing glucose and inhibits glycolysis. This is most likely due to the downregulation mechanism of Hypoxia-inducible factor 1-alpha (HIF-1) and pyruvate kinase M2 and suppression of the Phosphoinositide 3-kinases/Protein kinase B (PI3K/AKT) pathway [8]. The oxidative pentose phosphate pathway, which is crucial for the metabolism of cancer cells, can also be inhibited by DHA. By downregulating particular proteins,

DHA can also inhibit the fatty acid synthesis pathway and lessen colon cancer cell proliferation [8]. Artemisinin can make cancer cells more susceptible to ferroptosis, which can promote apoptosis. The current work examined whether artemisinin compounds can control ferroptosis and found that several artemisinin compounds sensitized cells to ferroptosis brought on by various agents in a time- and dose-dependent manner [15, 16]. Cells were more sensitive to ferroptosis when they were exposed to the active metabolite of artemisinin drugs, DAT. The ferroptosis inhibitor Ferrostatin-1 inhibited cell death in these circumstances, and the degree of cell death was associated with the production of lipid peroxide, indicating that the observed cell death was ferroptosis in origin [15]. The study also discovered that independent of autophagy and chaperone-mediated autophagy, the dopamine transporter regulates cellular iron homeostasis and makes cells susceptible to ferroptosis [15]. By causing the lysosomal breakdown of ferritin, a protein involved in iron storage, DAT enhanced the quantity of cellular free iron in both autophagy-competent cells and autophagy-defective cells [16]. This action was reversed by the lysosomal inhibitor BafA1, which also prevented the ferroptosis brought on by DAT and the ferroptosis inducer erastin. The autophagy cargo receptor Ncoa4 was not affected by erastin's rise in ferritin lysosomal degradation in autophagy-competent cells, and DAT's induction of ferritin lysosomal degradation was unrelated to Ncoa4 lysosomal degradation [15, 16].

4. Clinical Trials of the Anti-cancer Performance of Artemisinin

The effectiveness and safety of artemisinin-derived compounds artesunate (ARS) in the treatment of cervical carcinoma, non-small cell lung cancer (NSCLC), and colorectal carcinoma have been studied in a number of clinical trials. Patients who received an intravenous ART injection regimen of vinorelbine and cisplatin for eight days in the trial of upgraded NSCLC outperformed the control group in terms of disease control rates and time to progression [14]. Comparable results were seen in a pilot study of DHA in patients with cervical cancer, which indicated improvements in clinical symptoms, tolerability, and survival rates. In a double-blind, placebo-controlled trial, ART treatment resulted in higher apoptosis rates and lower expression of tumor markers in patients having the type of colorectal cancer [14]. Patients with metastatic breast cancer had their ART and DHA pharmacokinetics assessed. However, tumor response and survival durations were not disclosed. Studies conducted in vitro indicate that ARS-type medications bind to several targets, which makes them ideal options for cancer treatment [14]. While some clinical trials have attained phase II level recently, no conclusive final outcomes have yet been shown in recent clinical studies that have focused on the use of ARS as a cancer treatment [14]. In patients with strong tumor malignancies and metastatic breast cancer, studies have demonstrated that ARS was relatively safe and tolerated to a certain extent [14]. Nevertheless, dose-limiting toxicities and adverse events associated with ARS have been identified, highlighting the need for safety monitoring and additional study [13, 14]. Future research should thoroughly investigate how various factors, such as administration method, dosage, and drug administration time, affect the effectiveness of ARS [8, 13]. To give more persuasive evidence for the use of ARS in clinical oncology, further clinical studies of various ARTs, such as ARE, DHA, and ARM, as well as larger size phase II, III, and IV trials, should be carried out [8]. In a few case reports, the use of artemisinin-based medications (ARS) in cancer treatment has yielded promising outcomes. One patient with metastatic stage 4 breast cancer who received ARS treatment exhibited tumor shrinkage, and another breast cancer patient also responded favorably 2.5 years after starting ARS, a patient with advanced abdominal ascites and hepatocellular cancer were still active [14]. Also, two patients with uveal melanoma who received sympathetic therapies with ARS after failed standard chemotherapy demonstrated disease stability and transient response, which is surprising given the average median survival lengths for this particular form of malignancy [14]. Nevertheless, unpleasant reactions could occur if ARS is taken with other drugs [14]. One patient with glioblastoma multiforme who had treatment with temozolomide, ART, and Chinese medicines experienced reversible hepatotoxicity [14]. Another patient with GBM who received dichloroacetate plus ART died a few days after suffering from significant liver and bone marrow toxicity [14]. Hence,

it is advised against using unapproved combinations of drugs from complementary and alternative medicine.

5. The Anti-cancer Effect of Artemisinin Combined with Other Drugs

The combination therapy approach of artemisinin and other drugs can improve efficacy, reduce toxicity, and overcome drug resistance. In cancer therapy, combinations of artemisinin-based drugs with chemotherapeutics or phytochemicals have shown promising results [8]. These combinations have multiple mechanisms, such as inhibiting mTOR, reducing tumor microvessel density, downregulating RAD51, and activating different apoptotic pathways [8]. Moreover, the combinations of ARTs with existent medications have also shown potential in overcoming drug resistance in cancer treatment. These new combination methods have enhanced anticancer activity and developed novel medicaiton coworkers for clinical trials. The following are some kinds of combination therapies of artemisinin: for the combination with standard chemotherapy, a number of recent research papers have explored the potential for combining artemisinin-derived drugs (ARS) with established anticancer drugs to enhance tumor cell killing [17]. Because ARS drugs cause DNA oxidation abnormalities and break the double-strand structure, they may be effective when combined with anticancer drugs that cause Dna damage. When ARS drugs are combined with established anticancer drugs or other drugs that target tumor cells, studies have shown supplement to synergistic effects in both in vitro and in vivo. These consequences are caused by effects on DNA reconstruction, signaling pathways, angiogenesis, and cell death induction [17]. In combination with radiotherapy, which is a mainstay of cancer treatment and works by damaging tumor DNA, the development of resistance is a major obstacle, but radiosensitizers like ART and DHA are being investigated to overcome radioresistance by generating ROS, cell cycle arresting and cell death induction [17]. The development of new cytotoxic compounds, in conjunction with new synthetic compounds, is critical in the development of anticancer drugs. There is still a lot of interest in incorporating existing compounds with medically tested or interventional drugs [17]. Glutathione metabolism, glucose-6-phosphate dehydrogenase, glutamine utilization, and histone deacetylase activity are all potential targets for sensitizing tumor cells to ARS-type drugs. However, there is a need to carefully consider potential unwanted interactions when combining ARS-type medications with new synthetic compounds, as some combinations may attenuate the cytotoxic consequences of the ARS-type medications [17]. In conjunction with therapeutic antibodies or recombinant proteins, rituximab and artemisinin (ART) combination therapy has been reported to boost cytotoxicity toward B-NHL cells by triggering mitochondrial intrinsic and extrinsic apoptosis and decreasing cellular antioxidant capability. It has also been shown that using tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in combination with DHA or ART can increase apoptosis induction by generating ROS, increasing DR5 expression, and decreasing the levels of other apoptosis-regulating proteins [17]. Last but not least, combination with RNA interference, according to several studies, the combination of ARS-type medications and short hairpin RNA (shRNA) and short interference RNA (siRNA) targeting particular genes led to the cell death induction in glioblastoma cells with ARS and VCAM1 siRNA, while the combination of ARS and BMI1 siRNA prevented the growth of nasopharyngeal carcinoma cells [17]. Rac1 expression was reduced by siRNA, which improved the reactions of DHA on cell cycle arrest, death, and migration in cancer cells [17]. In DHA-resistant cells, the PARK7 (DJ-1) protein was abundantly expressed, and siRNA was used to show the protein's contribution to DHA resistance [17].

6. Conclusion

Antimalarial medication using artemisinin has been proven to have high anticancer activity and no negative side effects. Both studies in vitro and in vivo have produced encouraging results, and artemisinin may also work in concert with other anticancer medications. Further research is still

required to be conscious of the molecular mechanism and basis of artemisinin-induced cell death and identify new artemisinin targets for cancer treatment. The promise of artemisinin as an anticancer drug has created new avenues for this field of study. Furthermore, Dna methylation, capillary inhibition, signaling pathways inhibition, apoptosis and lysosomal suppression, as well as DNA damage, are additional or combinatorial methods by which these combined therapies with other medications improve tumor cell killing. ARS-type medications can be used with a wide range of medications, including radiation, macromolecules, synthetic or natural chemical substances, and other medications. Because the precise mechanisms for synergistic effects between ARS medications as well as other medications are mostly unidentified, more extensive research is required to identify the most efficient and secure drug combinations. The effectiveness and tolerance of innovative combinations of ARS-type medicines with other cancer treatment modalities must be evaluated in clinical trials.

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