Synthetic Derivatives of Artemisinin and Cancer

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ABSTRACT

Curing of cancer or at least prolonging the life of a cancer patient can be done by the development of anticancer drugs which can kill the cancer cells selectively. Artemisinin (ART), a natural endoperoxide containing sesquiterpene lactone, is a naturally occurring antimalarial with potent anticancer properties. Despite high efficacy, the therapeutic value of ART is limited by its low solubility in oil and water, short half-life after administration, poor bioavailability etc. In order to avoid these limitations, several derivatives of artemisinin have been synthesized which are more active than the parent artemisinin molecule and also exhibit enhanced anticancer activity in nano-to-micro molar range. Thus, ART derivatives can be a good treatment option for cancer treatment. However, further research is needed in order to develop better ART derivatives with greater efficacies. Again, the use of ART derivatives in cancer treatment must be addressed by better understanding of the mechanism of action of the derivatives which will help to increase the clinical effectiveness of the derivatives. The aim of this review paper is to provide an overview about ART, its synthetic derivatives and their anticancer properties.

Keywords: Artemisinin, Synthetic Derivatives, Cancer

INTRODUCTION

Cancer is a life threatening disease. The global incidence of cancer is increasing day by day. Globally, the five most common cancers in both male and female include lung cancer, breast cancer, colorectal cancer, prostate cancer and cancer of cervix uteri. In United States, 1 in 4 deaths is due to cancer. Though the pattern of cancer incidence varies among geographical regions, it has become a public health burden all over the world [1,2]. Curing of cancer or at least prolonging the life of a cancer patient can be done by the development of anticancer drugs which can kill the cancer cells selectively. Natural products are good source of compounds having inhibitory effects against a range of diseases. Thus, the isolation of artemisinin (ART) from Artemisia annua L. is a great success of pharmacognosy [3]. Though ART is well known for its anti-malarial properties, ART and its derivatives also have anti-inflammatory, anti-tumor, anti-angiogenic and anti-proliferation properties. Thus, it has received a special attention in cancer research [4].

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Artemisinin:

Artemisinin (ART) is a natural endoperoxide containing sesquiterpene lactone isolated from an ancient Chinese herb Artemisia annua L. (Qinghao), one kind of wormwood native to Asia. ART is also known as Qinghaosu and it was discovered by Tu Youyou in the early 1970s [5]. The use of Artemisia annua L. for treatment of diseases was reported in Chinese scripts as early as 168 BC. Later on, Qinghaosu was isolated from the shoots of Artemisia annua L. in pure form and its structure was determined in 1979 [6]. It is a potent anti-malarial drug approved by the Food and Drug Administration (FDA). It is also a best therapeutic against drug resistance and has shown effectiveness against infectious diseases like hepatitis B and schistosomiasis. Recently, effectiveness of ART against different cancer cell lines including colon cancer, breast cancer and human leukemia has been reported and it may be effective in the treatment of drug resistant cancers. As ART is a natural product, it has no or fewer side effects [5-7]. Recent studies have also suggested the immunosuppressive activity of ART and it is used to treat autoimmune disease like rheumatoid arthritis, systemic lupus erythematosus and collagen-induced arthritis [8].
Biosynthesis of Artemisinin:

*Artemisia annua* L. uses the sugars produced by photosynthesis in plants and convert them to two-carbon acetyl-CoA in the cytosol. The two-carbon acetyl-CoA enters into the cytosolic mevalonate biosynthesis pathway and produces 15-carbon farnesyl diphosphate (FDP). The next step is the conversion of FDP into 15-carbon isoprenoid hydrocarbon amorphadiene by amorphadiene synthase (ADS) which is the first committed step of artemisinin biosynthesis. Amorphadiene is oxidized enzymatically to either dihydroartemisinic acid or artemisic acid. Dihydroartemisinic acid is a direct precursor of artemisinin and in presence of sunlight it is converted spontaneously into artemisinin [7, 9, 10].

Artemisinin and Its Derivatives:

ART is a potent antimalarial and can kill malarial parasite very quickly. Despite high efficacy and quick action over malarial parasites, the therapeutic value of ART is limited by its low solubility in oil and water which causes difficulties in the intravenous administration of ART. ART has also short half-life after administration. Again, ART has relatively high recurrence rate of infection in monotherapy. Although ART is considered to be of low toxicity, there are evidences of reproductive toxicity and neurotoxicity. ART has also poor bioavailability which also limits its effectiveness. These limitations inspired the development of synthetic ART with better pharmacological properties than parent molecule. Thus, development of new drugs based on the parent ART has become a new area of investigation [10-12].

To overcome some of these limitations, several synthetic and semi-synthetic derivatives of ART have been developed. The semi-synthetic derivatives of ART include artesunate (ARS), dihydroartemisinin (DHA), artemether (AM), arteether (AE) etc. ART along with its semi-synthetic derivatives are considered as first-generation endoperoxides. Though ART has low solubility in water and oil, ARS is water-soluble and AM and AE are oil-soluble. The synthetic derivatives of ART exhibit increased stability and potency and are considered as second-generation endoperoxides. All these semi-synthetic and synthetic derivatives of ART show greater potency, improved solubility and are effective at micromolar to nanomolar concentrations [13]. For example, artsunic acid, a semi-synthetic analog of ART, shows greater toxicity towards cancer cells but exhibits low toxicity towards normal cells [14]. DHA and ARS both act as radiosensitiser for cervical cancer cells [15].

Again, anticancer activity of ART can be improved by preparing hybrid drugs. Hybrid drugs are prepared by incorporating two drugs into a single molecule. Hybrid drugs are less prone to drug resistance and have the capacity to impact multiple targets simultaneously. For instance, the strong antiangiogenic activity of ART-glycolipid hybrid has been reported in recent times [16].

Table 1: Artemisinin and its derivatives.

<table>
<thead>
<tr>
<th>Code</th>
<th>Artemisinin and its derivatives</th>
<th>Molecular Weight (g/mol)</th>
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<tbody>
<tr>
<td>ART</td>
<td>Artemisinin</td>
<td>282.33</td>
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<tr>
<td>ARS</td>
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<td>DHA</td>
<td>Dihydroartemisinin</td>
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<td>AD1</td>
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<td>10-dihydroartemisinol butyrate</td>
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<td>10-(2-butyloxy)dihydroartemisin</td>
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<td>10-dihydroartemisinol 2’-propylpentanoate</td>
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<td>AM</td>
<td>Artemether</td>
<td>298.375</td>
</tr>
<tr>
<td>AE</td>
<td>Arteether</td>
<td>312.401</td>
</tr>
</tbody>
</table>

Figure 1: Chemical structure of artemisinin and its several derivatives. A. Chemical structure of artemisinin (ART). B. Chemical structure of dihydroartemisin (DHA). C. Chemical structure of artemisinin (ART). D. Chemical structure of arteether (AM).
Mechanism of Action of Artemisinin:

The structure of ART contains an endoperoxide bridge (C-O-O-C). This endoperoxide bridge is pharmacologically very important because this is required for the antimalarial activity. Although the precise mechanism of action of ART is not very clear, it is thought that the endoperoxide bond is activated by ferrous iron (FeII) or by reduced heme (FPFeII). The activation of endoperoxide bond generates cytotoxic carbon-centered free radicals. These carbon-centered free radicals are potent alkylating agent which may target the macromolecules of malarial parasite leading to the death of the parasites [17].

The antitumor mechanism of action of ART is not clearly defined. But, it is proposed that the antitumor mechanism of action of ART is based on the similar antimalarial mechanism of action of ART. Thus, the endoperoxide bridge is also thought to be responsible for the antitumor mechanism of action of ART [14]. Cancer cells possess more intracellular free iron than normal cells because cancer cells require high amount of iron for their proliferation and growth. Thus, for uptaking higher amount of iron, cancer cells exhibit higher amount of transferrin receptors (TfR). Although the level of TfR may vary in different cell lines, they differ significantly from normal cells. It is thought that iron-activation of endoperoxide bridge of ART is a crucial event for cytotoxicity because compounds without endoperoxide bridge don’t exhibit cytotoxicity. Iron-activated endoperoxide bridge of ART generates radical oxygen species (ROS) and carbon-centered radicals which lead to cell alterations or cell death. Cancer cells are vulnerable to ROS-induced damage because they exhibit low levels of antioxidant enzymes than normal cells [17-19].

Generally, cell death can proceed either via apoptosis or necrosis. Previously, it was thought that necrosis is an accidental cell death which occurs in response to physicochemical insults. But, recent studies suggest that necrosis can also be a regulated event and thus it is now defined as genetically controlled cell death event resulting in cellular leakage and characterized by cell swelling, cell lysis, cytoplasmic granulation and organelle dysfunction [20, 21]. On the other hand, apoptosis is a distinctive form of programmed cell death characterized by distinct biochemical mechanisms and morphological characteristics. It is an intrinsic cell-suicide program which ensures proper development by maintaining tissue homeostasis and safeguarding the organism through the elimination of unwanted or virus-infected cells. This active, metabolic, genetically encoded and evolutionary selected death pathway can occur under either pathological or physiological conditions and this pathway is characterized by membrane blebbing, chromatin condensation, nuclear fragmentation, cell shrinkage etc.

Anticancer Activity of Artemisinin and Its Derivatives:

Anticancer activity of ART and its derivatives have been reported in various types of cancers like breast cancer [29–31], prostate cancer [33], leukemia [34], cervical cancer [32]. Recent studies suggest that ART derivatives can induce apoptosis in cancer cell lines. It can also downregulate proteins involved in cell cycle, oncogenesis and apoptotic resistance like cyclin D1, c-myc, surviving etc. In breast cancer cells, ART derivatives have role in inhibiting growth of breast cancer cells through induction of downregulation of HER family members [35]. Leukemic cells generally contain excess iron in their cytoplasm. These excess iron increases the reactivity of ART for leukemic cells. Thus, ART has also inhibitory effects on leukemic cells [34]. In cervical cancer treatment, ART is considered as a potent radiosensitizer. It acts as a radiosensitizer through regulation of G-2 check-point related proteins. Thus, it improves the therapeutic ratios of cervical cancer treatment by combination of ART with ionizing irradiation. Again, the anti-cancer action of ART and its derivatives on prostate cancer cells is also reported. Morrissey et al. have reported that ART derivatives can induce apoptosis which follows mitochondrial pathway in prostate cancer cells. Thus, ART derivatives can be a treatment option against prostate cancer cells [36].

Ultimately, the cells break into apoptotic bodies which are cleared by phagocytosis [22-24]. Again, there are two major known signaling cascades of classical apoptosis. One major pathway of classical apoptosis is the receptor-mediated pathway or the extrinsic pathway. Another major pathway for the initiation of apoptosis is the mitochondrial pathway or the intrinsic pathway [25, 26]. Both of these pathways are linked and involve caspases. It has been found that endoperoxide-mediated cytotoxicity can proceed via initiation of caspase-dependent apoptosis in cancer cells. But, the chemical basis of this initiation event is not clearly defined [19, 24].

Furthermore, recent studies suggest that antitumor mechanism of action of ART also involves growth inhibition, increase in the levels of oxidative stress, the inhibition of angiogenesis and metastasis, DNA double strand breakage [14, 15, 27]. Mechanisms like down regulation of the expression of vascular endothelial growth factor and suppression of hyperactive Wnt/β-catelin pathway have also been suggested for anticancer activity of ART [28].
DISCUSSION:

ART derivatives are not only good anti-malarials, but also they have anti-inflammatory, anti-angiogenic and anti-proliferation properties. They have a broad range of action and are effective against different types of cancer cell lines. They have high specificity towards cancer cells than normal cells. Thus, ART derivatives can be considered as a good treatment option for cancer. But, still there are several aspects which require further research in order to develop better ART derivatives with greater efficacies. Further research is also required for better understanding of the molecular mechanism of action of ART derivatives because it will help to increase the clinical effectiveness of ART derivatives.

ABBREVIATIONS:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ART</td>
<td>Artemisinin</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FDP</td>
<td>Farnesyl Diphosphate</td>
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<tr>
<td>ADS</td>
<td>Amorphadiene Synthase</td>
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<tr>
<td>ARS</td>
<td>Artesunate</td>
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<tr>
<td>DHA</td>
<td>Dihydroartemisin</td>
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</tr>
<tr>
<td>AE</td>
<td>Arteether</td>
</tr>
<tr>
<td>TIR</td>
<td>Transferrin Receptors</td>
</tr>
<tr>
<td>ROS</td>
<td>Radical Oxygen Receptors</td>
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REFERENCES: