Letter to Editor

Could artemisinin increase the sensitivity of photodynamic therapy against SARS-CoV-2 infection?

Dear Editor

Artemisinin (ART) is a traditional Chinese medicine with various biological activities, including antibacterial, antiviral, and anti-inflammatory. It is a famous malaria agent in China. A series of questions require consideration, such as "Is this a good choice for the treatment of SARS-CoV-2?" "Could ART be a photosensitizer (PS) similar to curcumin, pheophorbide a (Pa), and hypocrellin B?" "What is the role of ART in photodynamic therapy (PDT)?"

ART belongs to the "*Asteraceae*" family derived from the sweet wormwood plant, *Artemisia annua* L. Its derivatives include dihydroartemisinin, artesunate, and artemether, unique structures consisting of 1,2,4-trioxane peroxide pharmacophore. These are the antimalarial agents used for chemotherapy. ART is also a natural product and an anti-inflammatory phytomedicine that possesses broad-spectrum antiviral activity. The function of ART is clearing heat and detoxification with the ability to suppress immune responses according to the traditional Chinese medicine theory. In 2015, Nobel Prize in Physiology or Medicine was awarded to Professor Youyou Tu for the significant discovery of ART and its usage in malaria (1).

The principle of photodynamic therapy (PDT) involves a PS combined with a suitable visible wavelength to undergo the photon absorption process. PS absorbs the appropriate wavelength and reaches an excited state that reacts with ambient oxygen in the formation of reactive oxygen species (ROS) for targeting the unwanted cells or tissues to achieve cell apoptosis and death (2).

PDT's major components are PS, visible light, and oxygen. However, ART and its derivatives are different from the other natural Chinese medicines for PS, such as curcumin, pheophorbide a (Pa), and hypocrellin B. ART cannot act as a PS alone because of the short wavelength and absorption peak (215 nm). Tan ideal should have a strong absorption peak in the red to the near-infrared spectral region between 650 and 800 nm. The absorption of single photons with wavelengths longer than 800 nm does not provide enough energy to excite oxygen to its singlet state. Thus, it is better to design the ART as chemodynamic, combined with PDT therapy, or develop the ART into nanomedicine for PDT therapy (3).

Growing evidence has shown that artemisinin enhances the sensitivity of PDT. Li Y et al. reported dihydroartemisinin (DHA) increases the sensitivity of PDT via NF-κB/HIF-1α/VEGF pathway in an esophageal cancer cell *in vitro* and *in vivo*. The combined PDT and DHA treatment inhibited tumor growth nearly double that of the DHA or PDT alone. It might be the DHA increases the sensitivity of esophageal cancer cells to PDT. 5-aminolevulinate acid (5-ALA) was used as a PS and DHA-assisted 5-ALA to promote the sensitivity of cancer cells. The irradiation was carried out using a 630-nm wavelength at a fluence rate of 25 W/cm^2 (4).

In 2019, Osaki, et al. discovered that ART derivatives such as artesunate and artemether could enhance the cytotoxicity of 5-ALA-based PDT against the mammary tumor cells of mice. Artesunate and artemether rapidly convert to ROS inside cells, ultimately disrupting cellular functions (5) for improving the efficacy of 5-ALA-PDT. The ROS induction of 5-ALA-PDT with artesunate was higher (>20%) when compared to 5-ALA-PDT with artemether. The irradiation was carried out using a 630-nm wavelength at 20 mW/cm^2 and 10 J/cm^2 (6). Wang J et al. also identified ART and its combination with 5-ALA for PDT, enhancing anti-colorectal cancer activity. The specific cytotoxicity of ART toward colorectal cancer cells that the sensitivity increased with the addition of 5-ALA promoted the heme level and dramatically improved its anticancer effects at least 10 folds. The irradiation was carried out using a 630-nm wavelength at 20 mW/cm^2. This novel ART/ALA combination therapy proves to be more effective without toxic effects (7).

Besides, the combination of 5-ALA with ART. Feng G et al. discovered there was another light-up probe of ART for (tetraphenylethenethiophene(TPETH)-Mito-1ART), which used to co-deliver artemisinin ART and an aggregation-induced emission (AIE) photosensitizer for cancer cell ablation. This co-delivery strategy increased inducing cancer cell apoptosis and promoted PDT

efficiency (8).

Up to the present, we realized that the spike S glycoprotein engages the angiotensin-converting enzyme 2 (ACE2) receptor that facilitates viral entry into the cells for its replication in the respiratory and gastrointestinal tract. Thus, the PDT action for SARS-CoV-2 is mainly on the antiviral treatment by the generation of ROS to inactivate the SARS-CoV-2 (9).

Some traditional Chinese medicines have been used as a photosensitizer for PDT to fight against SARS-CoV-2, such as curcumin and hypocrellin B. These are different from ART. As discussed above, ART cannot be a photosensitizer because of its short wavelength and difficulty in undergoing excitation to generate ROS in PDT.

However, ART can assist PDT to increase the sensitivity to corresponding target cells. We may also suggest the use of nanotechnology. This is expected that nano-ART is more effective in combining a PS to combat SARS-CoV-2 when PDT is applied since nanotechnology has enhanced the bioavailability, solubility, transport, and effectiveness of ART as well as the PS for PDT efficacy.

The above information demonstrates that ART could increase the sensitivity of photodynamic therapy against SARS-CoV-2 infection. Still, much more works need to be done, including the dosage and safety assessment of the ART or nano-ART combined with PS for the PDT in a human clinical study.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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