Letter to Editor

Could Celastrol Be a Photosensitizer for Photodynamic Therapy to Combat SARS-CoV-2?

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Dear Editor

Celastrol is a quinone methide triterpenoid isolated from the traditional Chinese medicine *Tripterygium wilfordii* Hook F and belongs to the Celastraceae family. It possesses a wide range of antiviral, anti-inflammatory, and anti-cancer properties [1]. These biological activities are related to its unique structural features [2]. It is a pentacyclic triterpenoid consisting of triterpene quinine methides (Figure 1) [3]. The molecular weight of celastrol is 450.61 g/mol with absorption in 425 nm ultra-violet (UV) wavelength [4].

An ideal photosensitizer (PS) should have an absorbance band in the range of 600 to 800 nm in the red to the near-infrared spectral region. If the wavelength is longer than 800 nm, the absorption of single photons does not provide enough energy to excite the oxygen at its singlet state, causing a poor production of reactive oxygen species (ROS) for some biological mechanisms, even in the activated light [5]. PS is expected to localize in different subcellular locations, such as mitochondria, lysosomes, endoplasmic reticulum, and plasma membrane for the photodynamic damage leading to cell apoptosis [6].

Compared to a much well-known traditional Chinese herb PS, curcumin (Figure 1) has a molecular weight of 368.38 g/mol and absorption from 420-580 nm UV wavelength [7]. Curcumin has a broad absorption wavelength but is similar to celastrol; both face the same problem of lower water solubility. The water solubility of celastrol and curcumin are 13.25±0.83 mg/mL, and less than 8 μg/mL respectively [8, 9] which are limited for the photodynamic therapy efficacy. How can we minimize this issue?

Growing evidence has shown that the biocompatibility of celastrol could be improved by nanotechnology. Accordingly, Li J et al. reported the semiconductor nanomaterials called "titanium dioxide" (TiO_2) nanofibers. This nanomaterial was applied in the drug carriers and photodynamic therapy (PDT) to cure diseases, such as cancer. Celastrol was incorporated with the TiO_2 nanofibers which enhanced the cytotoxicity of celastrol for HepG2 cancer cells and cut down its consumption. Celastrol inhibited HepG2 cancer cell proliferation to induce apoptosis and cell cycle arrest at the G2/M phase. TiO_2 nanofibers assisted celastrol to increase its PS functions. It promoted the cellular interaction between HepG2 cancer cells upon the association of PDT [10].

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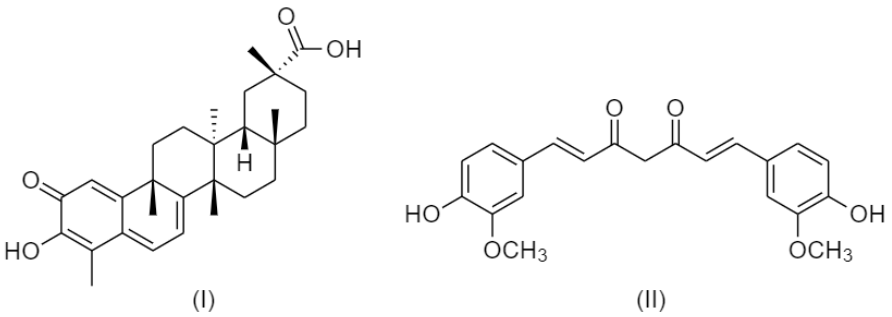

Figure 1. Chemical structure of (I) Celastrol and (II) curcumin

Recently, Caruso F et al. identified celastrol as a potential methide quinone inhibitor for the action of coronavirus disease 2019 (COVID-19) which was mainly about the structure of celastrol rings. The proton transfers and π interaction can scavenge the superoxide radical in SARS-CoV-2 and destroy the major protease [11]. Fernández-Quintela A et al. also indicated that celastrol could interact with the angiotensin-converting enzyme 2 (ACE2) receptor to reduce the inflammatory response induced by SARS-CoV-2 [12]. In early 2010, Ryu YB et al. discovered celastrol as an inhibitor of SARS-CoV $3CL^{pro}$, and the IC50/EC50 was around 10.30 μM which was less than curcumin's 23.50 μM [13].

According to the above evidence, we confirmed that the functions of celastrol and curcumin are much alike in their antiviral, anti-inflammatory, and anti-cancer properties. If celastrol is a PS itself and with the help of nanotechnology and photodynamic effect, its functions must be enhanced, especially in the treatment of SARS-CoV-2. There is a strategy of the celastrol nanotechnology upon the PDT for combating SARS-CoV-2: (1) celastrol is attached to the surface of TiO_2 nanofibers; (2) celastrol undergoes light activated with a suitable wavelength (425 nm); and (3) PDT processes of celastrol induce SARS-CoV-2 death. Only the TiO_2 nanofibers remain and these nanofibers would be degraded in a short time (Figure 2).

The principle of PDT for celastrol is expected to be similar to curcumin. The light activation of celastrol/TiO_2 nanofibers decreases the loading of SARS-CoV-2 in the upper respiratory tract. The PDT processes generate ROS and $^1O_2$ to prevent or block the attachment of SARS-CoV-2 on the ACE2 receptor [14].

Based on our previous celastrol research, it has toxicity but this could be minimized by nano-formulation. One of the papers, "Folic Acid-Modified Celastrol Nanoparticles: Synthesis, Characterization, Anticancer Activity in 2D and 3D Breast Cancer Models" was published in 2020. We used folic acid as a target agent to select the

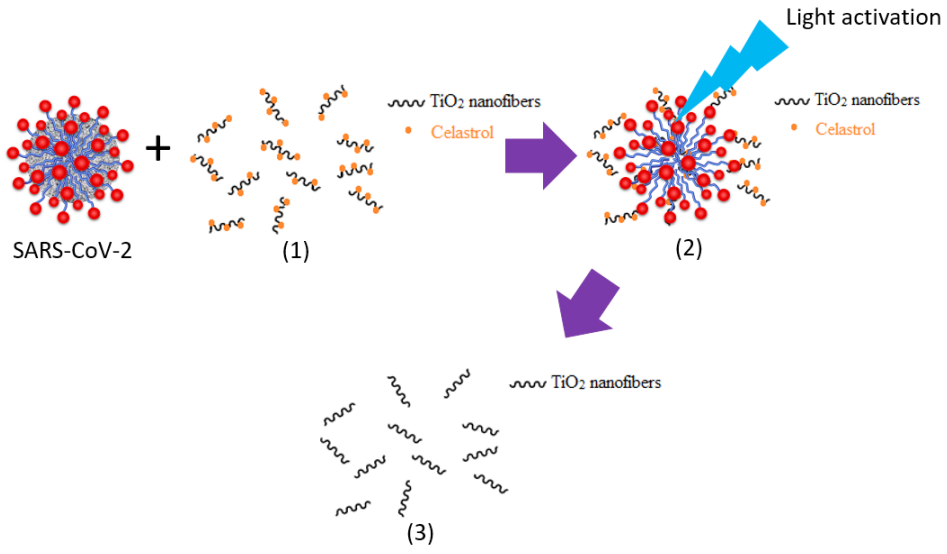

Figure 2. Celastrol/TiO_2 nanofibers upon the PDT for combating SARS-CoV-2

cancer cells only. It combines with the celastrol and is encapsulated by a polymer, PVP-co-2-dimethylaminoethyl methacrylate to control the releasing rate and toxicity, and it is also conjugated with the gold nanoparticle [15]. The results have shown that it could be further applied in the PDT to enhance its functions for various cancer diseases, and even be used in treating SARS-CoV-2. Huang T et al. also reported high drug-loading celastrol nanosuspensions and their anti-breast cancer activities in vitro and in vivo. The celastrol nanosuspensions with poloxamer 188 were approved by the FDA for intravenous injection [16].

Recently, Alam ST et al. reported that celastrol could be used as a PS agent in PDT. He found out that there were 6 active compounds from the extract of *tripterygium wilfordii* which consisted of pheophorbide compounds and possessed strong antimicrobial activities for the inactivation of bacteria and fungi by a red light at 660 nm (aPDT). It was implied in a Caenorhabditis elegans model for producing ROS to induce apoptosis of pathogenic bacteria without any side effects [17].

All of the information demonstrates that celastrol/TiO_2 nanofibers and celastrol gold nanoparticles upon the PDT for combating SARS-CoV-2 are proposed. Celastrol with the help of a nano-system is easier to be a good PS than using only celastrol because the nano-system enhances the celastrol bioavailability and increases the PDT efficacy. However, further research needs to be conducted, including the dosage, cytotoxicity of celastrol gold nanoparticles, and celastrol/TiO_2 nanofibers, in addition to the safety assessments in the human body.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Conflict of interest

The author declares no conflict of interest.

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