

## Letter to Editor

## Effectiveness of 5-aminolevulinic Acid-mediated Photodynamic Therapy Combined With Curcumin

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## Dear Editor

**5**-Aminolevulinic acid (5-ALA) is the mitochondria metabolite produced from glycine and succinyl-CoA, which is converted to protoporphyrin IX (PpIX) by the conjugation of eight itself molecules forming the “heme” group in the porphyrin ring (Figure 1) [1]. The PpIX is used as a photosensitizer (PS) with an absorption wavelength of 410 nm, and 5-ALA acts as a precursor or prodrug for PpIX in photodynamic therapy (PDT). Exogenous administration of excessive amounts of 5-ALA increases the production of PpIX during heme biosynthesis. It is eliminated after 24-48 h with a lower risk of long-term photosensitivity [2]. However, ALA/PDT has several disadvantages. For instance, the concentration of ALA is affected by its absorption and pharmacokinetics that do not fully cover the treatment area [3-5]. It also limits the depth of tumor penetration and causes pain [6].

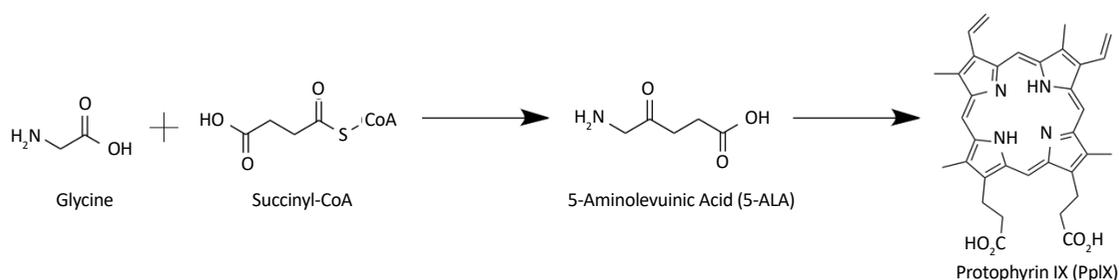
Unsurprisingly, most plant extracts have no pharmaceutical activity on abnormal cells if they are not exposed to light. When the plant extracts are activated by light with a suitable wavelength, they act as a PS, which is strongly toxic to malignant cells [7]. Curcumin is a famous PS obtained from herbal plants, consisting of hydrophobic polyphenols found in the turmeric rhizome (*Curcuma longa* L.). It has various pharmaceutical properties, including anti-inflammatory, antioxidant, anti-

bacterial, and antiviral properties [8, 9]. Curcumin has a broad absorption spectrum from 300 to 500 nm with a relatively high extinction coefficient [10]. Curcumin produces reactive oxygen species (ROS) and more specifically, singlet state oxygen (<sup>1</sup>O), hydrogen peroxide, and hydroxyl radicals [11]. ROS undergoes a destruction process in the PDT for treatment of cancers and diseases. A PS accumulates in the tumor tissue and illuminates it with light [12].

Curcumin-mediated PDT, combined with autophagy inhibitor, can further suppress epithelial-mesenchymal transition (EMT) in lung cancer cells. It may be a potential strategy against the invasion and migration of lung cancer. Shao et al. investigated the apoptosis mechanism of curcumin-mediated PDT by detecting the levels of ROS, mitochondrial membrane potential, and related proteins [13]. Libby et al. examined the effect of curcumin-mediated PDT on oxidized low-density lipoprotein (ox-LDL)-treated vascular smooth muscle cells (VSMCs) to confirm whether these effects are mediated by autophagy. The therapy significantly promoted the autophagy level and inhibited the phenotypic transformation induced by ox-LDL [14]. Paolillo et al. examined the effect of combined curcumin-mediated PDT and artificial skin on *Staphylococcus aureus* infected wounds in rats. The PDT was performed with a curcumin gel and a blue LED light (450 nm, 80 mW/cm<sup>2</sup>) at the dose of 60 J/cm<sup>2</sup> which accelerated the wound contraction [15].

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**Figure 1.** Formation of PpIX through the 5-ALA molecules

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Şueki et al. in a study in 2019 on the efficacy of 5-ALA-mediated PDT, used 10  $\mu$ M of non-toxic doses of curcumin, which significantly reduced the PDT resistance in Caco-2 cells. They concluded that 5-ALA-mediated PDT, combined with curcumin, synergistically improves the antitumor efficacy of PDT on Caco-2, which is considered a highly resistive cancer cell line [16]. Tumor cell lines from adult T cell leukemia or lymphoma (ATL) are susceptible to specific cell death by visible light exposure after a short-term culture with 5-aminolevulinic acid, indicating that 5-ALA mediates the efficiency of PDT [17]. It is much better to use the PDT with other conventional therapies such as curcumin. Evidence showed that curcumin combined with PDT can overcome the limitation of curcumin's low bioavailability, which is used to enhance the reactivity of curcumin and the efficacy of PDT [18].

The above mentioned materials demonstrates that 5-ALA-mediated PDT combined with curcumin may have some positive outcomes, such as enhancing the bioavailability and efficacy of PDT. However, more studies are needed to further investigate the effective concentrations (dosages) of the 5-ALA and curcumin in the human body. Hypocrellin-b and pyropheophorbide-a are other PS from herbal plants whose effects need to be studied.

## 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 declared no conflict of interest.

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