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Letter to the Editor

A Potential Approach to Amplify the Therapeutic Effects of Caffeic Acid Phenethyl Ester (CAPE) on Lung Adenocarcinomas

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Abstract

Caffeic acid phenethyl ester (CAPE) is a candidate molecule to increase the therapeutic window of lung cancer. However, CAPE is of a hydrophobic nature. While dimethyl sulfoxide (DMSO) solution was employed in this study to solubilize CAPE, its potential toxicity at low doses hinder the clinical applications. To address this, we propose the utilization of micellar systems to encapsulate hydrophobic CAPE using regulator-approved amphiphilic materials like polysorbate and poloxamer. These materials are capable of self-assembly in aqueous environments, significantly enhancing CAPE's water solubility. Furthermore, given their ease of preparation and high potential for large-scale manufacturing, micellar CAPE emerges as a promising candidate for lung carcinoma radiotherapy nutra-pharmaceuticals. This letter offers a novel strategy for promoting the clinical application of CAPE.

Keywords: caffeic acid phenethyl ester, lung cancer, DMSO

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TO THE EDITOR

We recently read the work by Prades-Sagarra et al.[1] with great interest, which was upon the application of caffeic acid phenethyl ester (CAPE) on lung cancer radiotherapy. In the study, the cytotoxic, radiosensitizing, and radioprotective effects of CAPE in lung cancer were confirmed, and the underlying mechanisms regarding cell cycle, glycolysis, mitochondrial membrane depolarization and pro-inflammatory markers inhibition were investigated. It was revealed that CAPE was a candidate molecule to increase the therapeutic window of lung cancer. As CAPE was extracted from honeybee propolis, it could be recognized as a nutra-pharmaceutical.

We appreciated that the cellular and animal models used in the study were reasonable and feasible, and thus the results were credible. On this basis, we supposed some supplementary discussion might strengthen the value of the

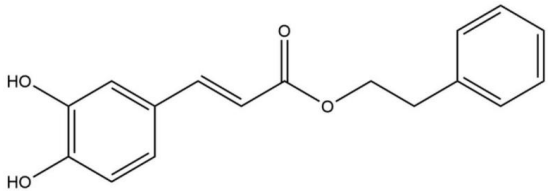

Figure 1. Molecular Structure of CAPE.

study. A point that attracted our attention was that CAPE was dosed to the cells or mice in the form of dimethyl sulfoxide (DMSO) solution, according to the Material and Methods Section. It should be noted that DMSO could provoke toxicity issues, especially ophthalmological toxicities[2], even at a dosage as low as ~2%[3]. Given safety concerns, CAPE DMSO solutions were less appropriate for future clinical applications. A safer delivery system should be tailored for CAPE.

After a further survey, we fully understood the reason behind utilizing DMSO. Seen from the molecular structure (Figure 1), CAPE is of a hydrophobic nature. The literature reported the water solubility of CAPE was approximately 21μg/mL[4], which was a quite low value. As a result, CAPE could not be directly dissolved in aqueous systems, and organic solvents like DMSO should be chosen to dissolve it. To avoid using DMSO and the safety concerns, techniques to improve the water solubility must be adopted.

With the purpose of boosting the clinical translation of CAPE-based nutra-pharmaceuticals, based on our expertise on drug delivery system development, we proposed that micellar systems would be proper to enhance the water solubility of CAPE. Micellar systems self-assembles in aqueous environment by amphiphilic materials that contain both hydrophilic and hydrophobic motifs, and the hydrophobic CAPE could be solubilized in the hydrophobic motifs. They are easy to prepare, with high possibility in manufacture on large scale. Generally, the water solubility can be significantly raised after micellization. Regulator-approved amphiphilic materials includepolysorbate, poloxamer, etc.[5], which can be employed to fabricate micellar CAPE.

Encouraged by commercialized products like Estrasorb™ (micellar estradiol)[6], micellar CAPE hold great promises for clinical translation. Notably, the encapsulation into micelles may alter the pharmacokinetic and toxicokinetic profiles of CAPE; we should pay particular attention to these issues during investigation and development processes.

In summary, we put forward that micellar CAPE might be a promising candidate as lung carcinoma radiotherapy nutra-pharmaceuticals. Such an idea could be added to the scientific and clinical value of the original study. It is envisioned that relevant laboratories, preclinical and clinical studies can be conducted as soon as possible.

Acknowledgements
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Conflicts of Interest
The authors declared no conflict of interest.

Data Availability
All data generated or analyzed during this study are included in this published article.

Author Contribution
Fan Jia drafted the original manuscript; Yuan Yao and Qingying Mu participated in the information cellection; Xin Pan made the conceptualization; Wenhao Wang and Zhengwei Huang carefully revised the manuscript.

Abbreviation List
CAPE, Caffeic acid phenethyl ester
DMSO, Dimethyl sulfoxide

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