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Genomic study of the absorption mechanism of cantharidin and its solid dispersion

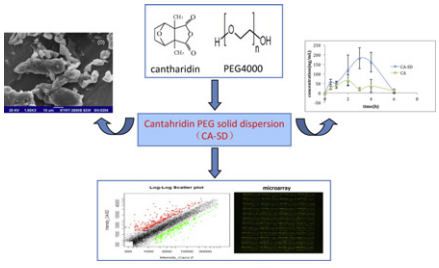
Dang Yun-jie, Zhu Chun-yan*

Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Ministry of Education, Beijing 100193, China

HIGHLIGHTS

- Cantharidin solid dispersion was prepared to increase the solubility and oral bioavailability.
- The physicochemical properties of solid dispersion were investigated by DSC, PXRD and SEM.
- CA-PEG4000 solid dispersion had higher bioavailability than free CA after oral dosing.
- DNA microarray was carried out to investigate genes expression after Caco-2 exposed to the drug.

GRAPHICAL ABSTRACT



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ABSTRACT

Over the past decade, numerous in vitro screening techniques have been developed to predict human intestinal absorption including the rat intestinal perfusion model and the cell lines model. But there is limited information about the holistic evaluation of these transporters, so we try to find a useful, sensible and simple method to study the relative proteins participated in the absorption. This research employs cDNA microarrays to identify the changes of gene expression in Caco-2 cells exposed to cantharidin and cantharidin-PEG4000 solid dispersion, and explored the permeability behavior of catharidin and the solid dispersion preparation in order to reveal the mechanism of absorption improvement. We prepared cantharidin solid dispersion with PEG4000, evaluate the oral bioavailability in rat and study the genetic changes that occurred in Caco-2 cell lines during the permeability of cantharidin alone and cantharidin solid dispersion. The in vivo results showed that CA-PEG4000 solid dispersion had higher bioavailability than free CA after oral dosing, the relative bioavailability of CA-SD to free CA was 295.4%. DNA microarray was carried out to investigate the involvement of two transport families, ATP binding cassette (ABC) and solute carrier transporter (SLC). The action of drug and solid dispersion significantly changed the expression of some genes in these two families, which may influence the absorption rate of the drug.

1. Introduction

According to the record in Shen Nong's *Herbal Classic*, the dry body of *Mylabris phalerata* Pallas or *Mylabris cichorii* Linnaeus [1] has the biological action of eliminating toxic material, eroding mycosis, removing blood stasis, dispersing obstructions and lumps, and so on. Recent pharmacological studies showed that cantharidin (CA) (Fig. 1) is the most active ingredient, which has an inhibitory effect on the primary hepatomas and other carcinomas, e.g., uterine and cervical cancer, nasopharyngeal carcinoma, cutaneous cancer and leukemia [2–4]. Several *Mylabris-based* pharmaceutical preparations used in Chinese market have been reported to have good anticancer properties.

However, processing various pharmacological effects and the antitumor activities, CA is partially water-soluble and has displayed poor intestinal absorption and low bioavailability (26.7%) in

* Corresponding author. Tel.: +86 10 57833263; fax: +86 10 57833276.
E-mail address: cyzhu@implad.ac.cn (C.-y. Zhu).

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