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Enhanced pulmonary bioavailability of curcumin by some common excipients and relative therapeutic effects on sepsis-induced acute lung injury in rats

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ABSTRACT

Application of curcumin in clinic was limited due to its poor solubility, stability and low bioavailability. The purpose of this study is to investigate the efficacy of some common excipients including Poloxamer 188, polyvinyl pyrrolidone K30 (PVP K30), Tween 80, Gelucire 4414 and polyethylene glycol 400 (PEG 400) for overcoming these limitations of curcumin. Results showed that these excipients were efficient in improving the solubility and stability of curcumin and moreover significantly increased curcumin absorption in a concentration-dependent manner after their administrations to rat lungs. Studies of pulmonary membrane damage evaluated by measuring amount of protein and activity of lactate dehydrogenase (LDH) released from rat lung demonstrated that these excipients at studied concentrations did not cause obvious membrane damage to lung tissues. The bio-efficacy studies showed that combinatorial treatment of curcumin and PEG 400 (45%, v/v) resulted in a therapeutic effect on the sepsis-induced acute lung injury (ALI) of rats, characterized by obvious reduction of lung W/D weight ratio, protein content, MPO activity, and alleviated pathological symptoms of lung tissues. These findings suggested that intrapulmonary delivery of curcumin combined with these excipients, especially 45% (v/v) PEG 400, was promising for treating pulmonary diseases including ALI.

1. Introduction

Curcumin, chemically diarylheptanoid (as shown in Fig. 1), is a hydrophobic yellow powder extracted from the rhizomes of the curcuma longa (turmeric) [1]. It has been traditionally used by India and Southeast Asia as colorant, dietary spice and also for medicinal purposes as an antiseptic and wound healing compound. Recent studies have demonstrated curcumin's diverse biological activities, such as anti-inflammatory, anti-oxidant, anti-diabetic, anti-coagulant, anti-microbia, anti-HIV properties and anti-cancer activity in various cancer cell lines [2–8]. Additionally, the safety studies of curcumin have proved that curcumin is nontoxic for human even at a high dose of 12 g/day [9,10]. Accordingly, the excellent pharmacological efficacy and safety of curcumin makes it a potential compound for treatment and prevention of a wide variety of human diseases.

However, despite those positive actions of curcumin on multiple diseases, curcumin has not yet been approved as a therapeutic agent and the poor bioavailability of curcumin has greatly hindered the widespread use in clinic due to low plasma levels, limited tissue distribution, rapid metabolism and short half-life [11,12]. Dhillon et al. found that only 22–41 ng/mL curcumin was detected in plasma, even with an oral dose of 8 g/day in human [13]. And oral administration of curcumin in rats resulted in approximately 75% being excreted in the feces and only traces appeared in the urine [14]. In addition, curcumin has low solubility in water (0.4 μg/mL at pH 7.3) [15] and degrades rapidly at neutral pH condition as well. It was reported that when curcumin was incubated in 0.1 M phosphate buffer and serum-free medium, pH 7.2 at 37 °C, about 90% decomposed within 30 min [16]. To date, numerous attempts have

Abbreviations: PVP K30, polyvinyl pyrrolidone K30; PEG 400, polyethylene glycol 400; ALI, acute lung injury; DMSO, dimethylsulfoxide; PBS, phosphate buffer solution; BALF, bronchoalveolar lavage fluid; BCA, bicinchoninic acid; LDH, activity of lactate dehydrogenase; NaDC, sodium deoxycholate; HPLC, high performance liquid chromatography; SD, Sprague-Dawley; CLP, cecum ligation and puncture; MPO, myeloperoxidase; W/D, lung wet/dry weight; BA, bioavailability; LPS, lipopolysaccharide; CD, hydroxypropyl-γ-cyclodextrin.

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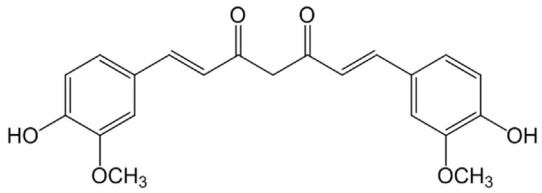

Fig. 1. Chemical structure of curcumin.

been made to overcome these limitations through encapsulating curcumin into nanoparticles [17], microspheres [18], solid dispersions [19], micelles [20], liposomes [21], and so on. However, the complicated process of encapusulation and the unstability of these formulations are most likely to limit their practical utilization. Comparatively, formulation with physical mixture by adding functional excipients might be a simple and efficient way to improve the solubility of curcumin and thereby promoting curcumin absorption.

On the other hand, drug delivery route is another important factor for drug absorption. Yang et al. showed that treatment of curcumin intravenously at the dose of 10 mg/mL in rats produced a maximal serum curcumin level of 0.36 ± 0.05 μg/mL, whereas 500 mg/mL curcumin administrated orally only created 0.06 ± 0.01 μg/mL maximal serum level in rats [22]. Although there was much higher absorption of curcumin injected intravenously than administrated orally, intravenous injection of curcumin was still limited due to the poor patient compliance and inconvenience to patients. Recently, pulmonary administration has attracted much attention as a valid and noninvasive route for delivering drugs to the lung or systemic circulation and it seems that many small molecules probably have pulmonary bioavailabilities approaching 100% [23]. Compared with oral delivery, drug degradation in the gastrointestinal tract and hepatic first pass metabolism can be avoided by administration from lung [24]. In addition, there are several favorable unique features of lung: the large alveolar surface area (approximately 100 m^2), thin alveolar epithelium (0.1–0.5 μm), a highly vascularized mucosa and relatively low enzymatic activity [25], all of which create good conditions for effective drug absorption. As for treating lung diseases, pulmonary delivery can directly target the therapeutic agents to lung as the site of action and generate faster onset of drug [26]. Until now, there have been many studies investigating the pharmacokinetics of curcumin [22,27] and its pharmacodynamics for pulmonary diseases by oral, intravenous or intraperitoneal administration [28–31], but few study is conducted by administration via the lungs.

In the present study, therefore, effects of some common excipients including Poloxamer 188, polyvinyl pyrrolidone K30 (PVP K30), Tween 80, Gelucire 44/14 and polyethylene glycol 400 (PEG 400) on the solubility, stability and pulmonary bioavailability of curcumin were evaluated. In addition, we also estimated pulmonary membrane damage of these excipients by measuring the activity of lactate dehydrogenase (LDH) and the amount of protein in bronchoalveolar lavage fluids (BALF). Finally, the bio-efficacy studies were carried out to investigate the therapeutic effect of curcumin on treating sepsis-induced acute lung injury (ALI) by directly administration to rat lung.

2. Materials and methods

2.1. Materials

Curcumin (~98%, Lot# C1301014), PEG 400, Tween 80, Poloxamer 188, PVP K30, dianisidine dihydrochloride and dimethylsulfoxide (DMSO), were obtained from Aladdin Industrial Corporation (Shanghai, China). Gelucire 44/14 was obtained from GATTEFOSSE (Saint Priest Cedex, France). LDH assay Kit was purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). Bicinchoninic acid (BCA) protein assay kit was purchased from Applygen Technologies Inc. (Beijing, China). All other regents were commercially available and of analytical grade.

2.2. Solubility studies

Solubility of curcumin in presence of various excipients was determined by the shake flask method as described earlier [32,33]. Briefly, excess amounts of curcumin were placed in glass vials and mixed with various excipients to yield various final concentrations of curcumin solutions. Then the vials were sealed, vortexed and equilibrated in a shaker water bath at 150 rpm for 24 h in dark. At the end of 24 h, all mixtures were centrifuged at 12,000 rpm for 10 min and the supernatant was filtered through a 0.45 μm filter. The clear filtrate was diluted appropriately with mobile phase and analyzed for curcumin by high performance liquid chromatography (HPLC).

2.3. Stability studies

The stability of curcumin with excipients was investigated according to the method described previously [34,35]. Curcumin solutions including excipients were incubated at 37 °C for 6 h in dark. At predetermined time intervals, appropriate aliquots of the solutions were taken and filtered through 0.45 μm filters to quantify the stability of curcumin in presence of those excipients by HPLC.

2.4. Pulmonary absorption study

In vivo pulmonary absorption of curcumin in rats was conducted according to earlier reports [36,37]. All rats were housed and fed in the animal center of Xi'an Jiaotong University before use. The acquisition, housing, care and disposition of rats and the animal studies including anaesthetizing, operation methodology were all performed and approved in accordance with the guidelines of animal ethics committee at Xi'an Jiaotong University. Male Sprague-Dawley (SD) rats weighing 220–250 g were fasted overnight but water was freely available. Rats were firstly anesthetized by an intraperitoneal injection of sodium pentobarbital (40 mg/kg body weight). Then the trachea was exposed and a section of polyethylene tube was inserted through the tracheal incision between the forth and fifth tracheal rings caudal to the thyroid cartilage. Subsequently, drug solution (100 μL) was instilled through the tube with a calibrated syringe. After that, the blood samples were withdrawn from jugular vein at each predetermined time interval for 4 h, and immediately separated by centrifugation (12,000 rpm, 5 min, 4 °C), then stored in ice until processed and analyzed.

2.5. Evaluation of pulmonary membrane damage

The pulmonary membrane damage of various excipients was evaluated with the method described previously [37,38]. Briefly, various excipients, phosphate buffer solution (PBS) and 1% (w/v) sodium deoxycholate (NaDC) were administrated to the tracheas of the anesthetized rats, respectively. 4 h later, the rats were bled and the BALF were collected, centrifuged (12,000 rpm, 5 min, 4 °C) and the supernatants were separated for measuring the activities of LDH and the amounts of protein. The activity of LDH and the amount of protein were measured by an assay LDH kit and BCA protein assay kit, respectively.