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Improved pharmacokinetic characteristics of ursolic acid in rats following intratracheal instillation and nose-only inhalation exposure

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Abstract:

Ursolic acid (UA) is a common pentacyclic triterpene phytochemical with various pharmacological activities. However, UA is classified as a class IV drug in BCS system and its development as an oral drug is limited. Pulmonary delivery is an effective way to improve the bioavailability of drugs with low absorption. In this study, the differences in pharmacokinetic behaviors of UA after pulmonary and oral administration was explored in rats. Compared with oral administration, the plasma concentration of UA increased rapidly after pulmonary administration, and the bioavailability increased about 80 times. UA instantly accumulated in the lungs after pulmonary administration, and the pulmonary AUC_{0-t}/dose increased by 114 times compared to oral dosing. Incubation experiments showed that the metabolism of UA in rat lung microsomes was significantly reduced compared with that in liver microsomes, in which the clearance rate of phase I and phase II metabolism was reduced by 14.7 times and 1.4 times respectively. These results indicated that pulmonary administration could improve the bioavailability of UA and reduce its metabolism. This study not only provides a preferable route of administration for the application of UA but also offers new insights for the development of phytochemical drug candidates with poor pharmacokinetic properties.

Keywords: Aerosol, bioavailability, pulmonary drug delivery, pharmacokinetics, lung metabolism

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the number of animals used. All animal experiments were performed under the National Institute of Health guidelines for the care and were approved by the Animal Ethics Committee of China Pharmaceutical University, Nanjing, China (Permit Number: 2020-06-001).

2.3. Nose-only inhalation exposure experimental setup and aerosol delivery

Male Sprague-Dawley (SD) rats were exposed to the UA aerosol using a nose-only exposure system (Beijing Huironghe Technology Co., Ltd., Beijing, China). Before inhalation, the rats were placed radially in a fixed cylinder with a push rod to adjust the length and plugged into the exposure tower tightly as shown in Figure 2 (A). The drug solution was added into the liquid bottle matched with the aerosol generator, and then the liquid was atomized into aerosol with the MMAD (mass median aerodynamic diameter) 1-3 μm (GSD:1.5-3) by the aerosol generator. The aerosol generated can be evenly distributed to each exposure chamber through the exposure tower for rats to inhale. In this case, all rats were confined so that only the mouth and nose (a small amount of skin or fur) were exposed to the aerosol under identical conditions. The aerosol mass concentration monitoring system with data analysis software was used to cooperate with the computer control to realize on-line monitoring and to adjust the aerosol particle distribution and concentration trend.

2.4. Pulmonary delivery by intratracheal instillation

The specialized tracheal quantitative drug delivery device is expensive and difficult to obtain, thus the self-assembled endotracheal intubation device (as shown in Figure 2 (B)) was used in this experiment. The specific intratracheal instillation method was as follows: rats were anesthetized by intraperitoneal injection of urethane (1.2 g/kg) and fixed on an operating fix table. Then the throat skin was incised and the muscle tissue above the trachea was separated by blunt dissection to expose the trachea. The next step was tilting the operating fix table in 45° to raise the rat's head upward, opening the mouth and cleaning the saliva in the oral cavity and pharynx. A No.12 gavage needle connected with a 1 mL syringe was inserted into the trachea from the oral cavity cling to the maxacoria. The entry of the gavage needle could be observed from the exposed trachea when it was inserted successfully. After injecting the drug solution into the trachea, the syringe was pulled out quickly, and the rats were kept upright for a minute to