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Application of a high-resolution benchtop quadrupole-Orbitrap mass spectrometry for the pharmacokinetics and tissue distribution of Danhong injection in guinea pig

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ABSTRACT

Danhong injection (DHI) is a compound preparation of traditional Chinese medicine Salviae miltiorrhiza (a.k.a. Danshen) and Flos Carthami tinctorii. Phenolic acids, such as salvianic acid A sodium (SAS), protocatechualdehyde (PAL), salvianolic acid B (SAB) and flavonoids, such as rutin, are the main bioactive ingredients of DHI. This paper presents an application of ultra high-performance liquid chromatography and quadrupole-Orbitrap high-resolution mass spectrometry (UHPLC-Q-Orbitrap HR MS) to quantify salvianic acid A sodium, protocatechualdehyde, salvianolic acid B, and rutin in guinea pig plasma and tissues for pharmacokinetic and tissue distribution studies. Biological samples were processed with methanol extraction, and calibration curves were determined with indometacin as internal standard (I.S.). The analytes were separated by a Hypersil GOLD aQ C_{18} column and detected using negative ion full MS/dd-MS^2 (data-dependent MS^2) mode. The full MS scan acquired data for identification and quantification, and dd-MS^2 scan obtained product ion spectra for confirmation. The response showed good linear relationship over the concentration range between 10.22 and 5110 ng/mL for salvianic acid A sodium, 10.06–5030 ng/mL for salvianolic acid B, 11.12–5560 ng/mL for protocatechualdehyde, and 10.58–5290 ng/mL for rutin, all the coefficients of correlation (r^2) >0.9990. The lower limit of quantification (LLOQ) was 10 ng/mL for the analytes. Overall, the novel UHPLC-Q-Orbitrap has demonstrated great performance for rapidity, accuracy, high sensitivity, and high selectivity. It was successfully applied to the pharmacokinetic and tissue distribution studies of Danhong injection. These acquired data would provide helpful information for the clinical applications, mechanism studies, and technology promotion of DHI in the future.

1. Introduction

Danhong injection (DHI), a compound preparation, is made up of aqueous extracts of traditional Chinese medicine Salviae miltiorrhiza (a.k.a. Danshen) and Flos Carthami tinctorii [1]. It has been used for the treatment of myocardial infarction, atherosclerosis, and ischemic cerebrosis [2]. The four components of DHI have been isolated and identified as the main active constituents among the water-soluble compounds (Fig. 1) [3–5], such as salvianic acid A sodium (SAS), protocatechualdehyde (PAL), and salvianolic acid B (SAB), which are phenolic acids, and rutin are flavonoids. In recent years, growing evidence suggests that the phenolic compounds are extremely important in the therapeutic activities of Danshen. Among the phenolic acids, Danshensu and SAB have notable pharmacological activities [6–12]. They are, therefore, regarded as the main active constituents of Danshen. Meanwhile, these components are the control indexes in quality standards [13–15]. Since most Chinese medicine injections (CMIs) presumably exert their therapeutic efficacies through the synergistic effects of multiple components acting on multiple targets, the simultaneous determination of various components' in vivo pharmacokinetic properties and tissue distributions is particularly important for the appropriate medication management when applying these injections.

Orbitrap is the newest addition to the family of high-resolution mass spectrometry (HRMS). With its revolutionarily design, the resolution is capable of resolving power in excess of 1,000,000

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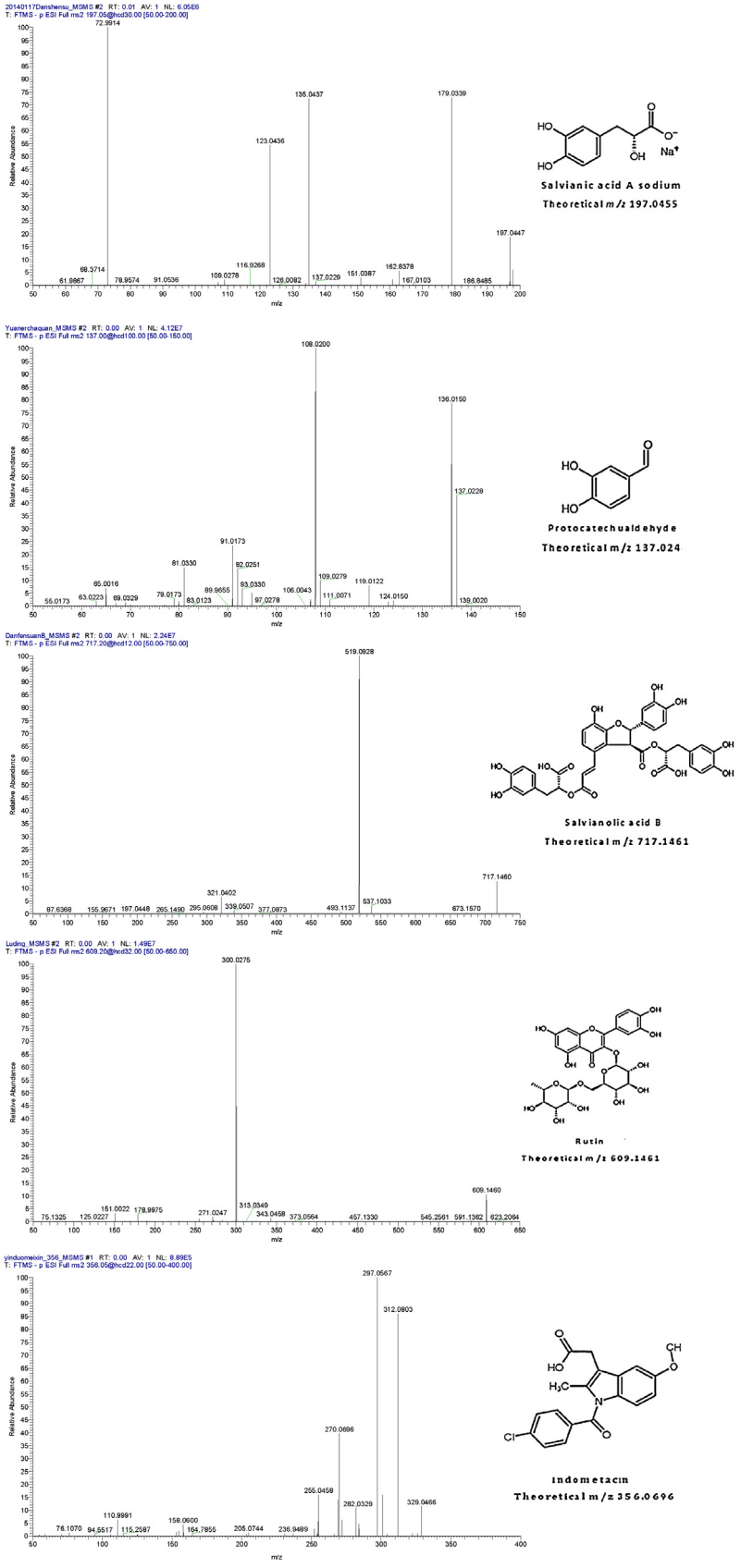

Fig. 1. Chemical structures and MS^2 productions of SAS, PAL, SAB, rutin and IS.