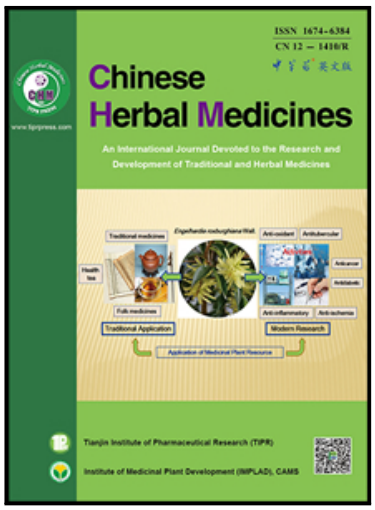
# Accepted Manuscript




Salidroside shows a particular pharmacokinetic property in the model rats of myocardial ischemia

Hui-lin Gu , Run-bin Sun , Fei Fei , Li-xiang A , Hao-xue Gao , Ming-xue Tao , Si-qi Feng , Na Yang , Yue Zhang , Ji-ye Aa , Guang-ji Wang

PII: S1674-6384(18)30037-6
DOI: 10.1016/j.chmed.2018.03.009
Reference: CHMED 28

To appear in: *Chinese Herbal Medicines*

Received date: 29 January 2018
Revised date: 19 March 2018
Accepted date: 19 March 2018

Please cite this article as: Hui-lin Gu , Run-bin Sun , Fei Fei , Li-xiang A , Hao-xue Gao , Ming-xue Tao , Si-qi Feng , Na Yang , Yue Zhang , Ji-ye Aa , Guang-ji Wang , Salidroside shows a particular pharmacokinetic property in the model rats of myocardial ischemia, *Chinese Herbal Medicines* (2018), doi: 10.1016/j.chmed.2018.03.009

# Salidroside shows a particular pharmacokinetic property in the model rats of myocardial ischemia

Hui-lin Gu[a], Run-bin Sun[a], Fei Fei[a], Li-xiang A[a], Hao-xue Gao[a], Ming-xue Tao[a], Si-qi Feng[a], Na Yang[a], Yue Zhang[a], Ji-ye Aa[a,*], Guang-ji Wang[a]

a Jiangsu Province Key Laboratory of Drug Metabolism and Pharmacokinetics, Jiangsu Key laboratory of drug design and optimization, State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, China

**Abstract Objective** Salidroside showed potential pharmacological effect on plateau hypoxia and cardiovascular disease like myocardial ischemia. However, pharmacokinetic differences have not been assessed between the pathological model and the normal animals. This study focused on evaluating the pharmacokinetic properties of salidroside in animals with myocardial ischemia. **Methods** A reproducible and sensitive method was established and optimized based on liquid chromatography tandem mass spectrometry (LC–MS/MS) to determine salidroside in rats plasma. The data showed the $AUC_{0-\infty}$ and $C_{max}$ of salidroside proportionally increased along with dose elevation after singly intragastric administration of salidroside at a dose of 20, 50, and 100 mg/kg. **Results** Compared to the single dose, the $C_{max}$, and $AUC_{0-8h}$ of salidroside markedly decreased while CL/F and V/F increased after multiple dosing. However, the $C_{max}$ and $AUC_{0-8h}$ of ischemic model rats were 0.35 and 0.39 fold lower than those in normal rats after a single dose at 50 mg/kg, with an increased CL/F and V/F. Surprisingly, after a consecutive administration of salidroside for 7 d, the mean $C_{max}$, $AUC_{0-8h}$ increased 2.89 and 2.61 fold higher than a single dose in model rats, and even 2.28 and 4.03 fold higher than the normal controls after multiple doses. All the above fold values were statistically different ($P < 0.01$). **Conclusion** The particular PK properties of salidroside in ischemic model rats were presented in our study for the first time, suggesting that myocardial ischemia greatly affected pharmacokinetics exposure of the orally administrated salidroside after a single or multiple doses.

**Keywords** LC–MS/MS; method validation; pharmacokinetics; salidroside

## 1.Introduction

Cardiovascular disease (CVDs) is one of the most prevalent diseases of high mortality and morbidity worldwide. Not only in the developing countries, but also in the developed countries, ischemic heart disease is now a general health issue (Moran et al., 2014). It refers to the reduction of blood perfusion in the heart, leading to reduced oxygen supply in the heart, abnormal cardiac energy metabolism, and a pathological condition that does not support the normal work of the heart (Sabatine et al., 2005). The main cause of myocardial ischemia includes decreasing blood pressure, reducing blood supply to the aorta, myocardium disease itself, while the most common etiology is coronary atherosclerosis (Greco et al., 2014). Clinically, treatment of myocardial ischemia includes surgical intervention, such as coronary artery bypass grafting, the setting of intravascular stent, and the drug therapy. All methods are greatly desirable for clinic patients although surgical practice costs high and has some post-surgery sequela, while drug therapy has some side effects. Traditional Chinese medicine has a long history for the therapy of myocardial ischemia, angina, coronary heart disease and other cardiovascular diseases (Xin et al., 2013; Zhu et al., 2015; Zou et al., 2015). *Rhodiola rosea* L., a typical traditional Chinese herb medicine widely distributed in the mountainous regions, has a history to be used for the prevention and therapy of plateau diseases and enhancement of body's resistance to fatigue (Szu-Fu Chen, 2012; Zhu et al., 2016). Recent studies suggested that it can remove free radical damage, improve myocardial ischemia, and enhance cognitive function (Li et al., 2008).

Salidroside is the primarily bioactive ingredients extracted from the root of herb *R. rosea*, which has various pharmacological properties in the treatment of diabetes, hypertension, inflammatory, hypoxia, as well as neuroprotection, liver protection, and cardiac protection (Guo et al., 2014; Qi et al., 2016; Zhang et al., 2015). The application of salidroside to plateau hypoxia and myocardial ischemia has attracted much attention recently (Chang et al., 2016; Zhou et al., 2017). Previously, although pharmacokinetic study has been evaluated in animals like SD rats (Guo et al., 2012), the pharmacokinetic property has never been assessed in model animals of myocardial ischemia. In general, both plateau hypoxia and myocardial ischemia can reduce the oxygen supply which affects the contractile efficiency of myocardial cells, the pump of blood stream, and the flow rate of blood in various tissues. Hence, salidroside is absorbed through gastro intestine, distributed in various organs, metabolied and eliminated, filtrated and excreted in kidney (Sun et al., 2012). Pharmacokinetic assessment of a candidate drug in the model animal is of crucial importance and special significance for this type of agents.

During this research, a sensitive and reproducible technique was developed and optimized for quantitative assay of salidroside by means of LC–MS/MS. A single and multiple doses of salidroside was administrated in both model rats of myocardial ischemia (Liu et al., 2013) and the normal controls. Pharmacokinetic profile and exposure of salidroside were evaluated and compared to evaluate the effect of myocardial ischemia on pharmacokinetic properties of the determinand, salidroside.

## 2. Materials and methods

### 2.1. Reagents and chemicals

Salidroside ($C_{14}H_{20}O_7$, Lot Number: 10338-51-9, purity: 98.96%) was synthesized by the Mansite Bio-technology Co., Ltd. (Chengdu, China). Paeoniflorin ($C_{23}H_{28}O_{11}$, Lot Number: 110736-201337, purity > 98%), which was used as internal standard (IS) during this study, was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Both formula of salidroside and paeoniflorin (IS) are shown in Fig.1. HPLC-grade methanol was straightly provided by Merck (Merck, Germany). All deionized water used in the research was obtained by Milli-Q Ultrapure water purification system (Millipore Corporation, Billerica, MA) , while the minimum resistance of this system was 18.2 MΩ. Remaining analytic grade solvents and reagents could be available commercially