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Quantitatively metabolic profiles of salvianolic acids in rats after gastric-administration of *Salvia miltiorrhiza* extract

Zhanli Liu [a], Xunyang Zheng [a], Yanlei Guo [b], Weihan Qin [b], Lei Hua [b], Yong Yang [b,*]

[a] Department of Pediatrics, Hangzhou First People's Hospital (Hangzhou Hospital affiliated Nanjing Medical University), Hangzhou 310006, China
[b] Chongqing Academy of Chinese Materia Medica, No.34, Nanshan Road, Nan'an District, Chongqing 400065, China

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ABSTRACT

Salvianolic acids, the well-known active components in *Salvia miltiorrhiza*, have been shown to possess markedly pharmacological activities. However, due to the complex in vivo course after administration, the pharmacologically active forms are still poorly understood. In present study, we evaluated the stability of eight major salvianolic acids from Danshen extract under different chemical and physiological conditions. We also quantitatively explained the absorption, metabolism and excretion of these salvianolic acids in rats after gastric-administration, which was carried out by simultaneously determining the amounts of salvianolic acids and their metabolites in the rat gastrointestinal contents, gastrointestinal mucosa, plasma, bile and urine. We found that: 1) protocatechuic aldehyde (PAL) was much stable whether in acidic environment (pH 4.0) or in alkaline environment (pH 8.0), while other salvianolic acids were stable in acidic environment and instable in alkaline environment; 2) PAL, salvianoli acid A (SAA) and salvianolic acid B (SAB) were instable whether in rat stomach or in small intestine, while other salvianolic acids were stable in rat stomach and instable in small intestine; 3) after gastric-administration, except PAL and Danshensu (DSS), other phenolic acids would be metabolized into DSS and caffeic acid (CA) in the rat gastrointestinal tract before absorption, and only free and glucuronidated PAL, CA and DSS were detected in rat plasma, bile and urine. In conclusion, it was the free and glucuronidated PAL, CA and DSS rather than the prototypes of other salvianolic acids that were present in plasma with considerable concentrations after gastric-administration.

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1. Introduction

Salvianolic acids are a group of water-soluble phenolic compounds isolated from *Salvia miltiorrhiza*, which can be divided into single phenolic acids and polyphenolic acids. The single phenolic acids include protocatechuic aldehyde (PAL), Danshensu (DSS) and caffeic acid (CA). The polyphenolic acids are the conjugate of DSS and CA or CA dimmer, such as lithospermic acid A (LAA), lithospermic acid B (LAB), rosmarinic acid (RA), salvianolic acid A (SAA), salvianolic acid B (SAB) and salvianolic acid D (SAD), et [1]. The chemical structures and molecular weights of them were shown in Fig. 1.

Many traditional Chinese medicine preparations (TCMPs) containing Salvia miltiorrhiza, such as Fufang Danshen tablets (FDT) and Compound Danshen dripping pills (CDDP), have been widely used for the treatment of coronary arteriosclerosis, angina pectoris, and hyperlipaemia [2–4]. As the most abundant components in Salvia miltiorrhiza, Salvinolic acids have also been proved to have markedly pharmacological activities such as anti-oxidation, anti-inflammation and anti-tumor, et al. [5]. However, because of the complex in vivo course after administration, the exactly therapeutic mechanism for salvianolic acids is still poorly understood.

Nowadays various investigations have been performed to hunt for the pharmacologically active forms in Salvia miltiorrhiza after administration. Studies showed that orally administered PAL (40 mg kg^{-1}) can be rapidly metabolized into glucuronidated PAL and prtocatechuic acid (PAC) in rats, and a small amount of free PAL (C_{max} < 2.5 μg mL^{-1}) can be detected in plasma after i.m administration (23 mg kg^{-1}) [6]. RA is present as the free or conjugated and/or methylated forms in plasma (C_{max} of free RA < 0.18 ng mL^{-1}) in rats after oral administration (50 mg kg^{-1}) [7]. After orally administered SAB (105 mg kg^{-1}), it was detected as the free form in plasma (C_{max} < 1.0 μg mL^{-1}) [8]. Only a trace amount of CA derivatives and DSS can be detected in rat urine and feces after oral administration of the salvinolic acid extract composed of DSS, SAB and PAL [9]. On the contrary, in vitro and in vivo studies have shown that the curative concentration for most of salvianolic acids is >10 μg mL^{-1} [10–14]. Therefore, we presumed that the biotransformation of salvianolic acids may have occurred before and/or after their absorption into body circulation, and the prototypes of salvianolic acids may not play the key role in their pharmaceutical activities. Regretfully, previously pharmacokinetic studies were mainly focused on the qualitative identification of the metabolites, so it was

* Corresponding author.
E-mail address: yangychem@126.com (Y. Yang).

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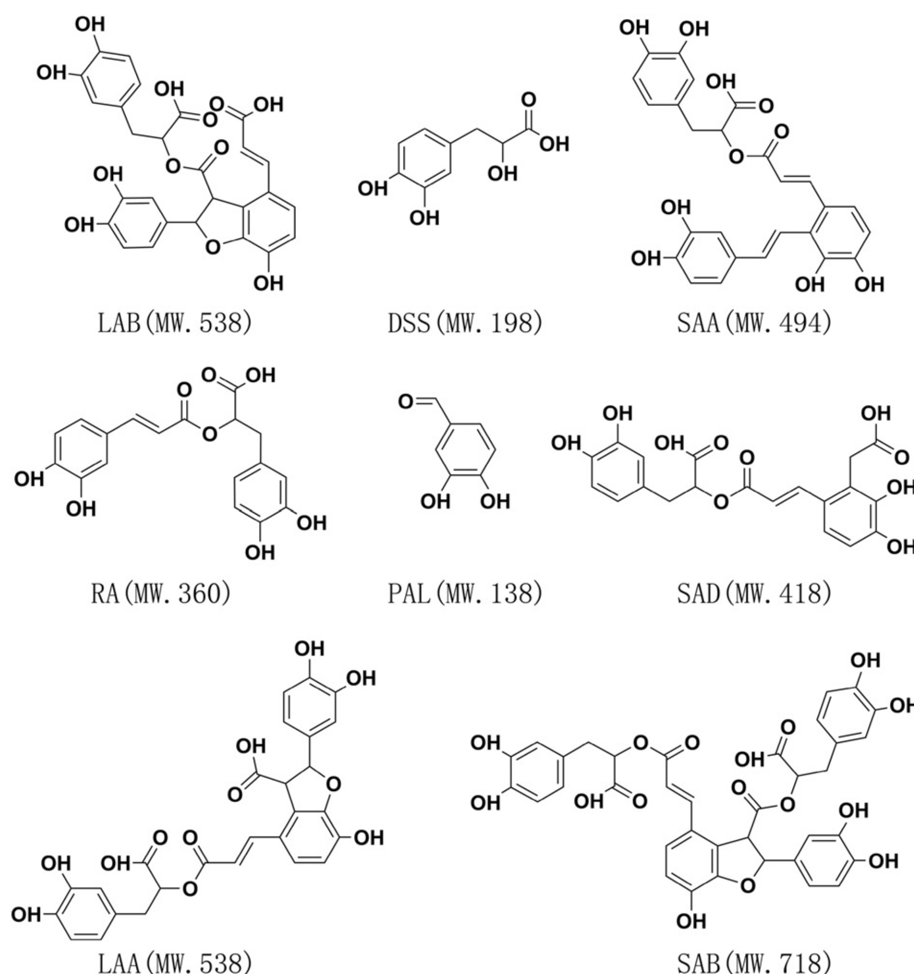

Fig. 1. Chemical structures and molecular weights of major phenolic acids in *S. miltiorrhiza*.

impossible to clearly elucidate where, in what forms and especially how many salvianolic acids were absorbed into blood to bring into therapeutic effects after oral administration.

Limited information has showed that SAB can be degraded into LAA and LAB under alkaline conditions [15]. The gastrointestinal bacterial may also contribute to the biotransformation of SAB [16]. So far, no similar studies to other salvianolic acids were reported. Hence, the stability of salvianolic acids in in vitro or in vivo environment should be shed more light.

In the present study, we evaluated the stability of eight salvianolic acids from Salvia miltiorrhiza extract under different chemical and physiological conditions, namely, DSS, PAL, LAA, LAB, RA, SAA, SAB and SAD. We also quantitatively explained the absorption, metabolism and excretion of these salvianolic acids in rats after gastric-administered Salvia miltiorrhiza extract, which was carried out by simultaneously determining the salvianolic acids and their metabolites in the gastrointestinal contents, the gastrointestinal mucosa, plasma, bile and urine. We found that, it was the free and glucuronidated PAL, CA and DSS rather than the prototypes of other salvinolic acids that were present in plasma with considerable concentrations after gastric-administration.

2. Materials and methods

2.1. Materials

β-Glucuronidase (EC 3.2.1.31, type HP-2, from *Helix pomatia*) and Sulfatase (EC 3.1.6.1, Type H-2, Helix pomatia) were from Sigma (Shanghai, China). The *S. miltiorrhiza* extract was obtained from *S. miltiorrhiza* Bunge by water extraction and 70% ethanol deposition. DSS (>99%), PAL (>99%), PAC (>99%) and CA (>99%) were obtained from Yi-Fang Science & Technology Co., Ltd. (Tianjin, China). Ethyl-*p*-hydroxybenzoate (>99%) was of analytical grade from Chang-Yuan Chemicals Co., Ltd. (Dalian, China) as the internal standard (IS). Acetonitrile and methanol were of HPLC-grade from Fisher Scientific (Fair Lawn, NJ, USA). All the other reagents were of analytical grade.

2.2. Instruments and conditions

HPLC analysis was performed on a Shimadzu VP Series workstation system (Kyoto, Japan), a SCL-10 A system controller and a SPD-10AV UV detector at 280 nm. Chromatographic separation was achieved on a Kromasil-C_{18} column (4.6 mm × 250 mm, 5 μm, China). The flow rate was 0.80 mL min^{-1}. The mobile phase consisted of solvent A (acetonitrile) and solvent B (0.021% aqueous phosphonic acid, *v*/v). Gradient programs at 30 °C were performed as follows: 10–22% A at 0–8 min, 22–26% A at 8–15 min, 26–39% A at 15–36 min, 39–10% A at 36–40 min, then the column was equilibrated with 10% A for 5 min.

HPLC-MS identification was performed on a Shimadzu HPLC-MS-2010 EV system (Shimadzu Corp, Kyoto, Japan) equipped with an ESI source. The MS analysis worked in negative ion mode using an interface voltage of −3.5 kV. The tube lens offset was set to 25 V and the interface temperature at 250 °C. N_2 was used as both nebulizing gas with a flow rate of 1.5 L min^{-1} and as auxiliary gas with a pressure of 0.1 kPa. Total ion chromatograms (TIC) were recorded over a mass range of *m*/*z* 100–800.

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