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Metabolic characteristics of *Rhizoma Coptidis* intervention in spontaneously hypertensive rats: Insights gained from metabolomics analysis of serum

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Abstract. The present study aimed to investigate the intervention mechanisms of *Rhizoma Coptidis* using spontaneously hypertensive rats. A serum metabolomics analysis was performed with high performance liquid chromatography-quadrupole/time of flight mass spectrometer in positive mode. The obtained data were further analyzed by principal component and partial least-squares discriminant analysis to reveal differentiating metabolites. The pattern of metabolites in the serum after *Rhizoma Coptidis* exhibited distinct alterations. A total of 10 potential biomarkers were significantly altered in the serum and may be associated with the underlying mechanism. Alterations were primarily associated with phospholipid metabolism, fatty acid metabolism, amino acid metabolism and arachidonic acid metabolism. In addition, biochemical alterations in potential biomarkers were associated with inflammation, nitric oxide production, platelet aggregation and endothelial function. By analyzing and verifying the specific biomarkers, metabolomics may be helpful to further understand the underlying therapeutic mechanism of *Rhizoma Coptidis*. Metabolomics is a powerful tool used to investigate the therapeutic effects of herbal medicine with multiple targets.

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Introduction

Individuals with high blood pressure are at greater risk of developing coronary heart disease and peripheral artery disease (1). It is a complex, multi-factorial disease, and the underlying physiological and metabolic drivers remain to be fully elucidated. However, patients with hypertension exhibit metabolite alterations.

As an important branch of system biology, metabolomics, developed following genomics and proteomics, deals with a small number of molecules (<1,000 Da) contained within a cell or organism under a given set of conditions. It is a 'discovery' driven holistic evaluation of changes in the expression patterns of hundreds of metabolites, for example, following exposure to environmental stimuli or certain medicines (2). Metabolomics technology has been widely applied in the medical field, and has great potential in the diagnosis of disease and understanding the underlying mechanisms of drugs (3-5). Therefore, performing metabolomic analysis of the metabolic perturbations during hypertension may result in an enhanced understanding of the pathogenesis and effects of drugs.

In the treatment of hypertension, traditional Chinese medicine (TCM) possesses a unique theoretical system and methods of control. Chinese herbal medicines provided a rational means for hypertension. *Rhizoma Coptidis*, a classical heat-clearing and detoxifying herb, possesses multispectrum therapeutic activities, including antihyperlipidemia, anti-hypertension, anti-inflammatory and antioxidant effects (6). *Rhizoma Coptidis* contains a number of isoquinoline alkaloids, in which berberine is the primary component and accounts for ~5-8%. Berberine has a protective effect on high blood pressure and cardiac dysfunction in myocardial hypertrophy model rats induced with L-thyroxine, associated with increased nitric oxide (NO) content (7). Recent studies have indicated that *Rhizoma Coptidis* serves an important role in treating

hypertension (8,9). The present study used serum metabolomics based on data generated from high performance liquid chromatography (HPLC)-quadrupole/time of flight (TOF) mass spectrometer (MS), to clarify the underlying therapeutic mechanism of *Rhizoma Coptidis* treatment in spontaneously hypertensive rats (SHRs).

Materials and methods

Chemicals and reagents. Acetonitrile, methanol and formic acid of HPLC grade were purchased from Tedia Co., Inc. (Fairfield, OH, USA). All aqueous solutions were prepared using ultrapure Milli-Q water (EMD Millipore, Billerica, MA, USA).

Preparation of Rhizoma Coptidis. Dried *Rhizoma Coptidis* (a member of the Ranunculaceae family; collected in Mount Emei, Sichuan, China; lot no. 120906) was authenticated on the basis of chemical analysis in accordance with the Chinese Pharmacopoeia (10). The berberine content (pharmacologically active component) was determined by referring to high-performance liquid chromatography-mass spectrometry (unpublished data) and was 7.63 $mg \cdot g^{-1}$. Other alkaloids included jatrorrhizine hydrochloride (6.01 $mg \cdot g^{-1}$), epiberberine (6.91 $mg \cdot g^{-1}$), coptisine (5.09 $mg \cdot g^{-1}$) and palmatine chloride (7.22 $mg \cdot g^{-1}$). Powdered *Rhizoma Coptidis* (100 g) was extracted three times with 95% ethanol (1,000 ml) under thermal reflux for 1 h. Following filtration, the ethanol extract was combined and concentrated under reduced pressure at 60˚C. The resulting residue was dissolved in and extracted with water three times under the same conditions as with ethanol. Following filtration, water was evaporated at 60˚C. Extracted solutions were combined to obtain a 1.0 $g \cdot ml^{-1}$ extract and were stored at 4˚C.

Animal experiment. A total of 12 male SHRs (age, 12 weeks; body weight, 200-250 g) and six male Wistar-Kyoto (WKY) rats (age, 12 weeks; body weight, 230-270 g) were supplied by the Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China), certificate no.: SCXK (Beijing) 2012-0001. All studies were performed according to the guidelines of the National Research Council of China and approved by the Animal Ethics Committee of Affiliated Hospital of Shandong University of Traditional Chinese Medicine (Shandong, China). The 12 SHRs were divided randomly into the model group (n=6) and *Rhizoma Coptidis* group (n=6) and the 6 WKY were defined as the healthy control group. All rats were kept under standard animal conditions at a regulated temperature (17-25˚C), humidity (45-60%) and a 12-h light/dark cycle. They were allowed free access to food and water throughout the study. The *Rhizoma Coptidis* group was administered with *Rhizoma Coptidis* at a dose of 10.001 $g \cdot kg^{-1}$. The normal control group and the model group received an equal volume of physiological saline. In accordance with the principle of the same volume and the different concentration, all animals were administered by gastric infusion once daily for 4 continuous weeks.

Blood pressure measurement. Blood pressure was measured via the tail artery prior to and following *Rhizoma Coptidis* administration at 1, 2, 3 and 4 weeks. Measurement data was expressed as the mean ± standard error and for multiple group comparisons one-way analysis of variance was used followed by Tukey's test. Data were analyzed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Collection and preparation of serum samples. Serum was collected from the abdominal aorta at day 28 and was immediately centrifuged at 1,780 x g for 15 min at 4˚C. The supernatant was transferred into a glass sampling vial and stored at -80˚C. Prior to analysis, 300 μl serum was mixed with 600 μl acetonitrile and vortexed for 1 min. Following centrifugation at 1,780 x g for 15 min at 4˚C, the serum sample was filtered through a 0.22-μm membrane and transferred to a 1.5-ml glass vial, prior to storage at -20˚C until analysis.

HPLC-TOF/MS analysis. HPLC-TOF/MS analysis was performed using an Agilent-1260 LC system coupled with an electrospray ionization source (Agilent Technologies, Inc., Santa Clara, CA, USA) and an Agilent 6230 time-of-flight (TOF) mass spectrometer (Agilent Technologies, Inc.). Chromatographic separations were performed on a 2.1x100 mm Halo-C_{18} column (2.7 μm) with a binary solvent system (solvent A: water with 0.1% formic acid; solvent B: acetonitrile). The gradient elution program for analysis of serum samples started from 10% B to 60% B at 0-15 min, held at 60% for 7 min, changed to 100% B over 22-24 min, maintained a strong elution for 10 min, then returned to the initial status and re-equilibrated for 10 min. The flow rate was 0.35 $ml \cdot min^{-1}$ and the injection volume was 5 μl. The column was maintained at 25˚C.

Mass detection was operated in positive mode with the following optimized conditions: Capillary voltage, 4,000 V; drying gas flow, 11 $l \cdot min^{-1}$; gas temperature: 350˚C; nebulizer pressure, 35 psig; fragmentor voltage, 140 V; skimmer voltage, 60 V. Data were collected in centroid mode from 100 to 1,000 m/z. Samples were analyzed randomly for unbiased measurement with tune mixture solution (m/z 121.050873 and 922.009798) as internal standards to ensure accuracy and reproducibility.

Data processing and statistical analysis. The raw data were converted to CEF format by Mass Hunter Qualitative Analysis software version B.06.00 (Agilent Technologies, Inc.), imported into Mass Profiler Professional (MPP; Agilent Technologies, Inc.) to continue the preliminary calibration of retention time, abundance and mass range. The data from each sample was then normalized to the summed total area and was inputted into Mass Hunter Qualitative Analysis software a second time to execute regression analysis. Subsequently, data were processed by MPP to continue filter flags and significance analysis. The significance of variation between multiple groups was determined by one-way analysis of variance followed by Tukey's test and the fold-change (≥2). $P<0.05$ was considered to indicate a statistically significant difference. The resulting three-dimensional matrix, including sample name, peak intensity and peak retention time was introduced into the SIMCA-P software package (version 11.5; Sartorius AB, Göttingen, Germany),

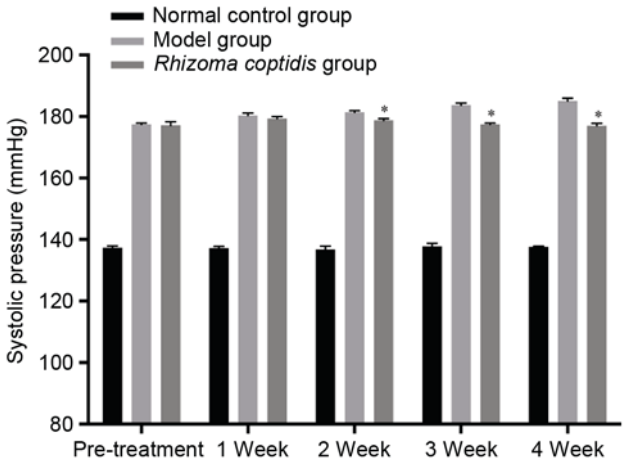

Figure 1. Systolic blood pressure in the normal control, model or *Rhizoma Coptidis* groups prior to treatment, or following 1, 2, 3 and 4 weeks of administration. *P<0.05 vs. model group.

where multivariate analysis, including principal component analysis (PCA) and partial least-squares-discriminant analysis (PLS-DA) were performed for pattern recognition. The R^2Y and Q^2 parameters indicated the goodness of fit and the ability of prediction, respectively. Importance for projection (VIP) values produced during PLS-DA was applied to identify a variable that contributed greatly to the classification. Variables with VIP values >1 were considered to be statically significant and treated as candidate difference variables (11). In order to further identify these variables, publicly-accessible metabolomics databases were used, including the Human Metabolome Database (www.hmdb.ca), METLIN metabolomics database (metlin.scripps.edu) and the Kyoto Encyclopedia of Genes and Genomes database (www.kegg.com). In order to explore the metabolic pathways between variables, the MetaboAnalyst 3.0 pathway analysis module (www.metaboanalyst.ca) was used to carry out enrichment analysis and topological analysis of metabolic pathways.

Results and Discussion

Blood pressure of rats in different groups. Systolic blood pressure (SBP) in the model group and *Rhizoma Coptidis* group was elevated prior to intervention compared with the healthy control group (Fig. 1). SBP of SHRs treated with *Rhizoma Coptidis* was decreased compared with the model group ($P<0.05$) at 2, 3 and 4 weeks, which reached a minimum at 4 weeks (Fig. 1).

Multivariate data analysis and pattern recognition. Fig. 2 demonstrates examples of HPLC-TOF/MS total ion chromatograms (TIC) of serum samples from each experimental group. PCA was initially used as a starting point for analysis to visualize possible intrinsic clusters and trends among the observations. PCA is additionally used to investigate whether each group is separated and determine metabolic distinction (12). The unsupervised PCA model was used to separate serum samples into three blocks following intervention, which indicated that they had different metabolic profiles (Fig. 3).

PLS-DA, a more sophisticated supervised projection method with the adoption of a UV scale, may be applied to an MS data set (13). In the PLS-DA scores and trajectory analysis of score plots (Fig. 4), the samples from different groups were sorted into different quadrants, with no overlap, which demonstrated that *Rhizoma Coptidis* effectively altered the

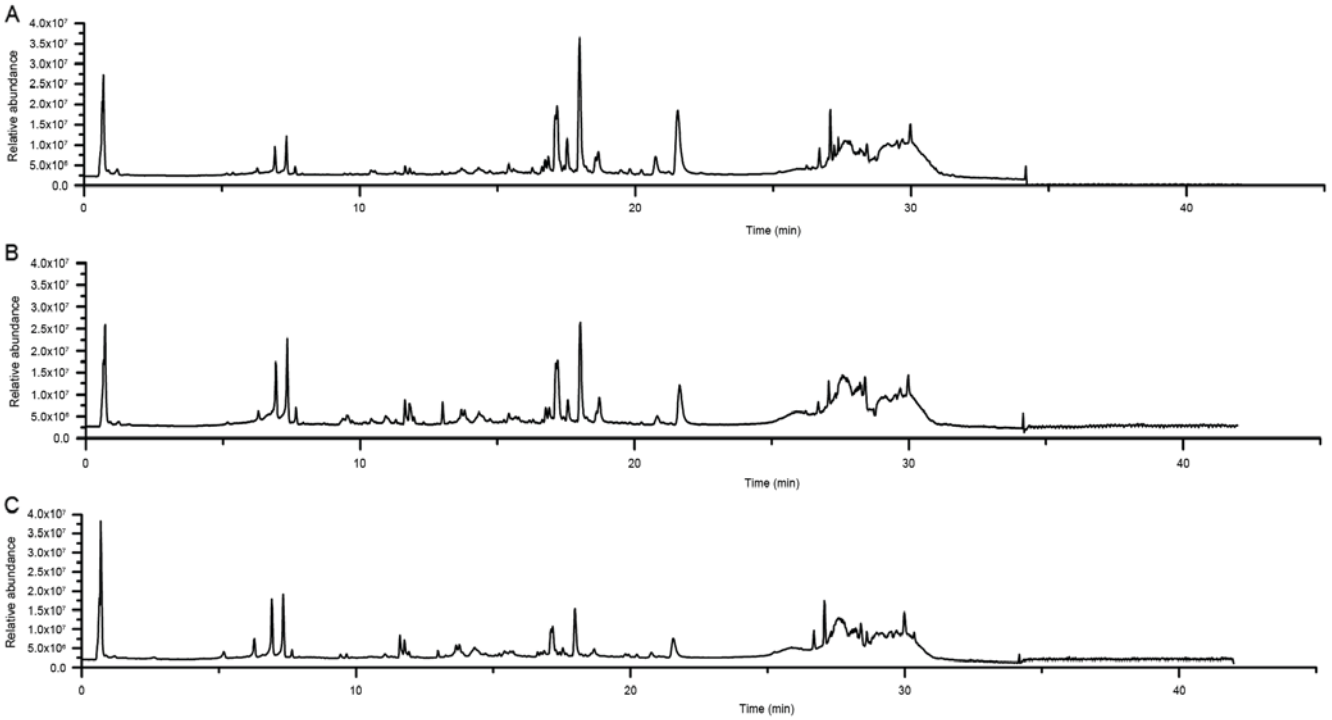

Figure 2. High performance liquid chromatography-quadrupole/time of flight/mass spectrometer total ion chromatograms of serum samples from the (A) normal control group, (B) model group and (C) *Rhizoma Coptidis* group, in positive mode.

Table I. Identification of ions and their alteration trend in positive mode.

No.	Retention time (min)	Exact mass	Formula	Identification	Change trend[a]		Pathway
					Healthy control group	*Rhizoma coptidis* group	
1	0.70	220.0848	$C_{11}H_{12}N_2O_3$	5-Hydroxy-L-tryptophan	↑	↑	Tryptophan metabolism
2	26.68	256.2402	$C_{14}H_{29}COOH$	Fatty acid	↓	↓	Glycerolipid metabolism
3	28.82	296.3079	$C_{20}H_{40}O$	Thromboxane	↓	↓	Arachidonic acid metabolism
4	27.08	284.2715	$C_9H_{13}N_2O_9P$	Stearic acid	↓	↓	Biosynthesis of unsaturated fatty acids
5	32.19	757.5622	$C_{42}H_{80}NO_8P$	PC (18:2(9Z,12Z)/16:0)	↓	↓	Glycerophospholipid metabolism
6	27.21	332.2715	$C_{22}H_{36}O_2$	Adrenic acid	↓	↓	Biosynthesis of unsaturated fatty acids
7	33.13	702.5676	$C_{39}H_{79}N_2O_6P$	SM (d18:0/16:1(9Z))	↑	↑	Sphingolipid metabolism
8	15.67	330.2559	$C_{22}H_{34}O_2$	Docosapentaenoic acid	↑	↑	Biosynthesis of unsaturated fatty acids
9	28.67	715.5516	$C_{39}H_{74}NO_8P$	PE (18:1(9Z)/16:1(9Z))	↓	↓	Glycerophospholipid metabolism
10	19.36	509.3481	$C_{25}H_{52}NO_7P$	LysoPC (17:0)	↑	↑	Glycerophospholipid metabolism

[a]Compared with the model group. ↑, increased; ↓, decreased; PC, phosphatidylcholine; SM, sphingomyelin; PE, phosphatidylethanolamine; LysoPC, lysophospholipids.

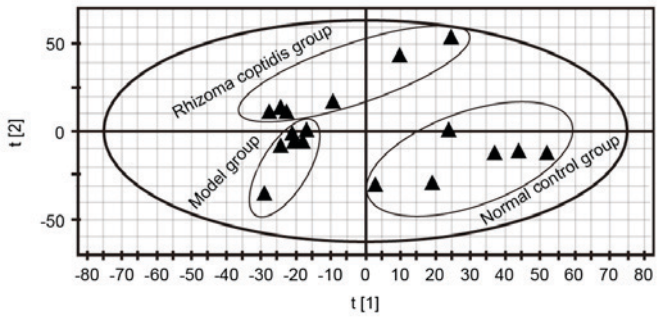

Figure 3. The principal component analysis plot of serum data from the normal control group, model group and *Rhizoma Coptidis* group (n=6/group). t[1], first principle component score; t[2], second principle component score.

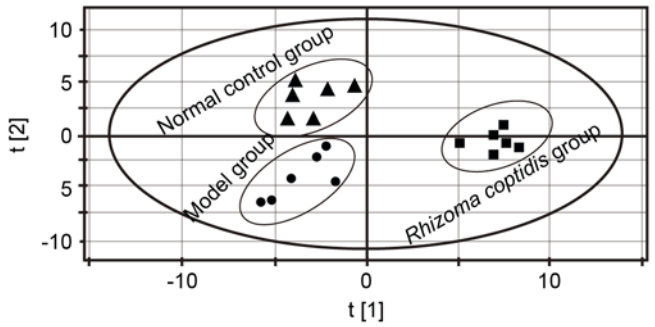

Figure 4. The partial least-squares-discriminant analysis plot of serum data from the normal control group, model group and *Rhizoma Coptidis* group (n=6/group). t[1], first principle component score; t[2], second principle component score.

physiological and metabolic conditions of rats. R^2Y and Q^2 of the PLS-DA model were 0.856, 0.793 and 0.841, respectively. The result indicated that a well-fitted PLS-DA model was established.

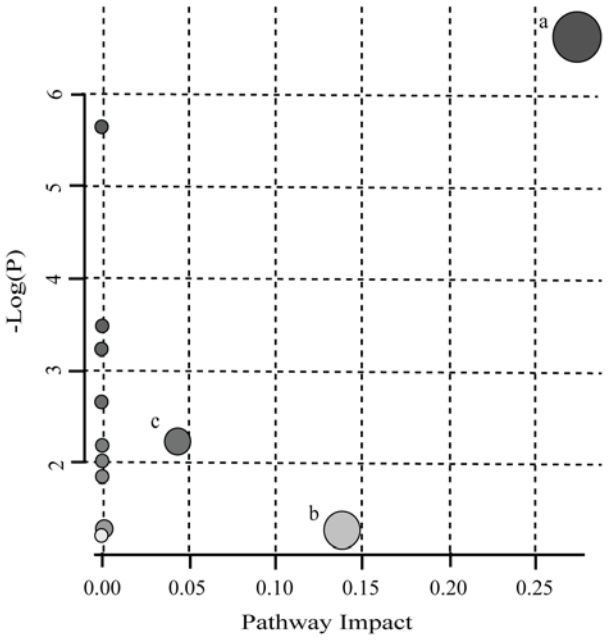

Figure 5. Summary of pathway analysis using the pathway analysis module. The color and size of each circle are determined by the P-value of the metabolic pathway and the importance of the pathway. a, glycerophospholipid metabolism; b, tryptophan metabolism; c, glycosylphosphatidylinositol-anchor biosynthesis.

Identification of potential biomarkers. After the processing of PCA and PLS-DA, metabolites that significantly contributed to the clustering were identified according to a threshold of VIP. Ions with VIP values >1 demonstrated potential endogenous components. Ultimately, 10 potential biomarkers were identified. Compared with the model group, serum levels of fatty acid, stearic acid, thromboxane (TX), phosphatidylcholine (PC) [18:2 (9Z, 12Z)/16:0], adrenic acid and phosphatidylethanolamine (PE) [18:1 (9Z)/16:1 (9Z)] were increased following

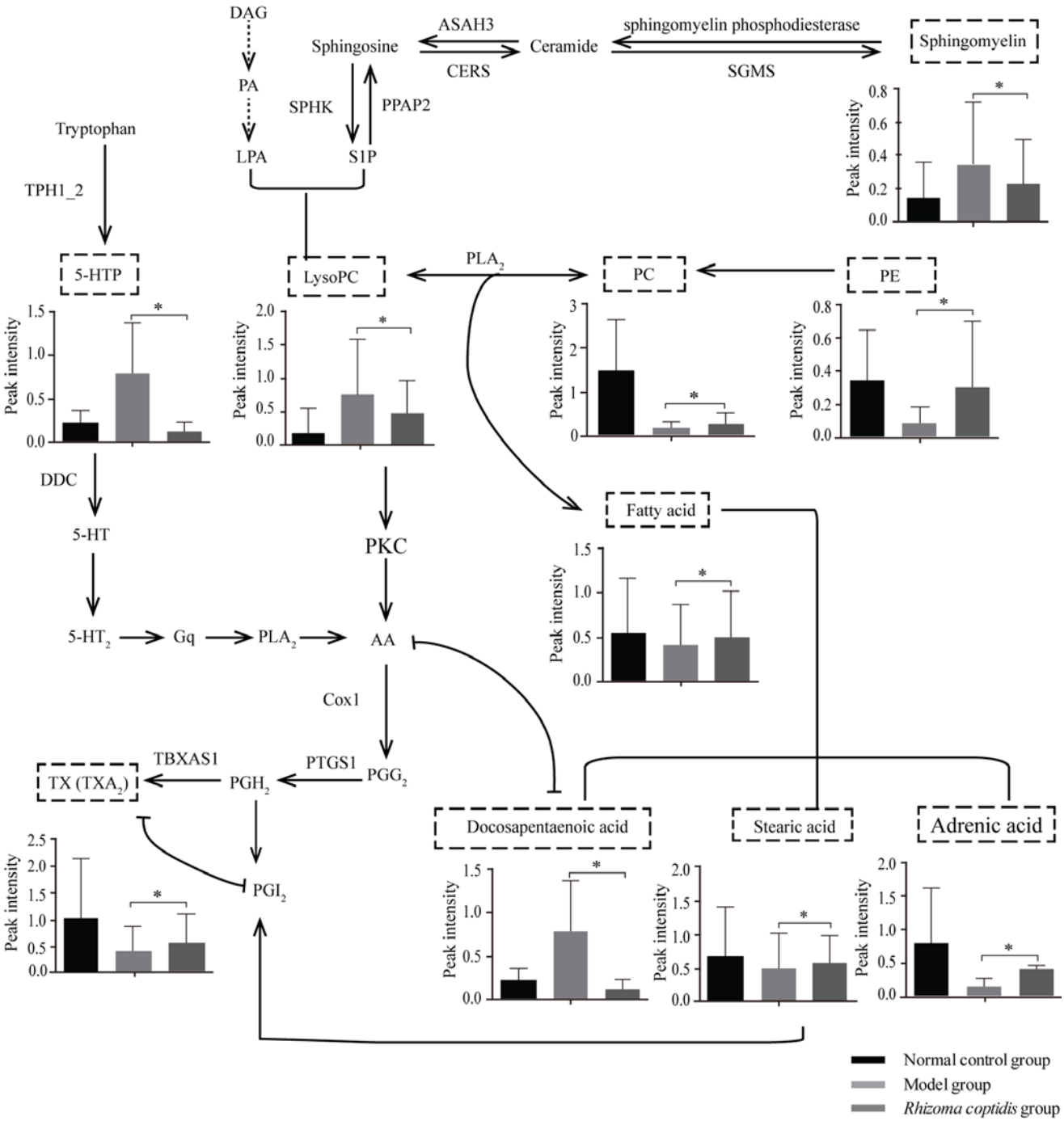

Figure 6. Metabolic network of the altered biomarkers in the normal control group, model group and *Rhizoma Coptidis* group. P-values were calculated using analysis of variance. n=6/group. *P<0.05. Dashed line boxes represent potential biomarkers. Straight arrows represent the association between metabolites. Dashed arrows represent indirect reaction generation. TPH1_2, tryptophan 5-monooxygenase; 5-HTP, 5-hydroxy-l-tryptophan; DDC, aromatic-l-amino-acid decarboxylase; 5-HT, 5-hydroxytryptamine; PLA, lysophosphatidic acid; PA, phosphatidic acid; DAG, diacylglycerol; S1P, sphingosine 1 phosphate; SPHK, sphingosine kinase; PPAP2, phosphatidate phosphatase; ASAH3, alkaline ceramidase; CERS, ceramide synthetase; SGMS, sphingomyelin synthase; LysoPC, lysophospholipids; PLA2, phospholipase A2; AA, arachidonic acid; COX1, cyclooxygenase 1; PTGS1, prostaglandin-endoperoxide synthase 1; PGG2, prostaglandin G2; PGH2, prostaglandin H2; TBXAS1, thromboxane-A synthase; PGI2, prostaeyelin; TX, thromboxane; TXA_2, thromboxane A2; PE, phosphatidylethanolamine; PC, phosphatidylcholine; Gq, guanine nucleotide-binding protein G(q) subunit α.

intervention, while 5-hydroxy-L-tryptophan (5-HTP), sphingomyelin [d18:0/16:1 (9Z)], docosapentaenoic acid and LysoPC (17:0) were decreased. The differences and alteration trend of these biomarkers are summarized in Table I.

Metabolic pathway analysis and biological function analysis. The 10 identified biomarkers were imported into the pathway analysis module to explore the possible signaling pathways that were affected by *Rhizoma Coptidis*. The metabolic pathway analysis with the pathway analysis module revealed that glycerophospholipid metabolism, tryptophan metabolism and glycosylphosphatidylinositol anchor biosynthesis were identified to be important metabolic pathways (Fig. 5). Based on the knowledge of these biomarkers and online databases,

a network of *Rhizoma Coptidis* intervention-associated metabolic pathways was generated (Fig. 6), indicating that the antihypertensive effect of *Rhizoma Coptidis* is associated with the certain endogenous metabolites.

Phospholipid metabolism disorders and inflammation. There is widespread evidence that altered lipid metabolism is involved in the pathogenesis of hypertension (14,15). Numerous studies have demonstrated that abnormal phospholipid metabolism serves an essential role in the development of intimal injury and vascular disease (16,17). Traditionally, total serum cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) concentrations are considered important and clinically useful biomarkers of hypertension (18,19). With the rapid development of metabolomics, the identification of potential lipid biomarker signatures may provide clues for the investigation of the pathogenesis of hypertension. Kulkarni *et al* (20) demonstrated through plasma lipidomic profiling that a disturbance in diacylglycerol metabolism is an independent biomarker of hypertension. In the present study, four different phospholipids species were identified: Lysophospholipids (LysoPC), PE, PC and sphingomyelin (SM). The results of the present study revealed that PC [18:2 (9Z, 12Z)/16:0] and PE [18:1 (9Z)/16:1 (9Z)] were significantly decreased in the model group compared with the healthy control group, whereas sphingomyelin [d18:0/16:1 (9Z)] and LysoPC (17:0) were significantly increased. There is a tendency to return to normal following intervention by *Rhizoma Coptidis*. The results suggested that *Rhizoma Coptidis* may correct phospholipid metabolism disorder.

LysoPC is a simple phospholipid signaling molecule. Lysophosphatidic acid (LPA) and sphingosine 1 phosphate (S1P) are two primary bioactive lysophospholipids. They may couple with multiple types of G proteins to activate a range of downstream effectors. LPA and S1P regulate endothelial functions, and serve a role in the regulation of angiogenesis and blood vessel integrity (21-23). LysoPC additionally promotes the development of inflammation. LysoPC induces the activation of phospholipase A2 via activation of protein kinase C, and then induces the hydrolysis of membrane phospholipids and release of free arachidonic acid (24). The proportion of PE and PC combined is 75% in glycerol phospholipid composition. In the lipid metabolism network, PC is the primary source of arachidonic acid that is a precursor of eicosanoids, which serve an important role in inflammatory processes. During inflammation, PC is converted to arachidonic acid. PE is an instantaneous source and may be quickly added. When inflammation subsides, PC is converted to arachidonic acid at a slower pace. SM is the only sphingolipid class that additionally belongs to the phospholipid class (25). The biologically active sphingomyelin metabolites (SMM), sphingosine-1-phosphate (S1P), sphingosylphosphorylcholine, sphingosine and ceramide are important lipid mediators, which are generated upon cell activation from membrane phospholipids as part of the sphingomyelin cycle (26). S1P is the most potent intercellular signaling molecule in the sphingolipid family. S1P serves vital roles in angiogenesis, endothelial cell proliferation and migration and vascular permeability (27). Yogi *et al* (28) identified a novel signaling pathway linking S1P/S1P1 receptors to specific proinflammatory signaling pathways via epidermal growth factor receptor and platelet-derived growth factor transactivation. Such molecular events may contribute to vascular inflammation in hypertension. The alteration in LysoPC, PE, PC and SM by this test demonstrated that inflammatory reactions exist in hypertension (29), and suggest that *Rhizoma Coptidis* may be an anti-inflammatory drug (6,30).

Fatty acid metabolism and endothelial NO. In the model group, fatty acids and stearic acid were significantly increased and docosapentaenoic acid was decreased compared with the healthy group. This suggested that the aberrant distribution of fatty acids contributes to the pathogenesis of hypertension (31). Stearic acid is a useful type of saturated fatty acid. Docosapentaenoic acid is an essential omega-3 fatty acid. An important function of docosapentaenoic acid is the transport and oxidation of cholesterol. It may reduce plasma cholesterol, triglycerides and LDL, while increasing HDL. In addition, docosapentaenoic acid and arachidonic acid (AA) have the same metabolic pathway, and are the common substrate of a number of metabolic enzymes. When they simultaneously exist, they have a competing inhibition effect. Therefore, docosapentaenoic acid may inhibit the cyclooxygenase metabolic of AA to some extent, thereby reducing inflammation derivatives, including TXA2 and prostaeyelin (PGI_2). The fatty acids in serum may cause vasoconstriction and blood pressure elevation by increasing the concentration of blood Ca^{2+} or exciting the sympathetic nervous system (32,33). Fatty acids may locate to cell membrane phospholipids as the second messengers to alter membrane function, directly affect vascular endothelial cells and endothelial NO synthesis, which may reduce the content or the activity of endogenous NO (34). Table I demonstrates that *Rhizoma Coptidis* successfully reversed the fatty acid metabolism disorder. The results suggested that *Rhizoma Coptidis* may reduce blood pressure by lowering serum fatty acids content and may improve the activity of endothelial NO.

TX, adrenic acid and arachidonic acid metabolism. TX is produced in platelets by TX synthase, which is produced from endoperoxides by the cyclooxygenase (COX) enzyme from AA. TX is a vasoconstrictor, potent hypertensive agent and facilitates the clumping of platelets. The two primary TXs are TXA_2 and TXB_2. Adrenic acid is metabolized by COX, lipoxygenases and cytochrome P450 s to dihomo-eicosanoids (35). Under physiological conditions, TXA_2 and PGI_2 are in a state of dynamic equilibrium. PGI_2 is released and synthesized by endothelial cells. It is a biologically active substance, which has vasodilator and anti-platelet aggregation properties. TXA_2 and PGI_2 imbalance is one of the causes of platelet aggregation, vascular spasm or thrombosis. In the pathologic process of hypertension, high blood pressure damages the endothelium, then collagen and fibers under the skin are exposed to TXA_2 released by platelets (36). Subsequently, TXA_2 may allow blood pressure to continually rise via the inhibition of PGI_2 synthesis, impact on the vascular permeability and promote the proliferation of smooth muscle cells. However, adrenic acid metabolites serve a potential role in the regulation of vasodilation. Adrenic acid is metabolized in human vascular endothelial cells to PGI_2, which inhibited thrombin-induced platelet aggregation (37). The present study revealed that in the

model group, the alteration in TX and adrenic acid suggested that there is an association between hypertension, and TX and adrenic acid. Following intervention with *Rhizoma Coptidis*, TX and adrenal acid metabolism were improved. This suggested that *Rhizoma Coptidis* may be involved in anti-platelet aggregation.

5-HTP and the sympathetic nervous system. 5-HTP is an aromatic amino acid naturally produced by the body from the essential amino acid L-tryptophan. It may affect mood, sleep and appetite. 5-HTP has been used clinically for >30 years, and has been demonstrated to be effective in treating a wide variety of conditions, including depression, chronic headache and insomnia (38-40). In animal and human experiments, 5-HTP promoted the metabolism of catecholamines, in particular to promote dopamine and norepinephrine release (41). These amino acids therefore affect the activity of the sympathetic nervous system. Increased sympathetic activity is a primary cause of hypertension. 5-HTP is the immediate precursor of the neurotransmitter 5-hydroxytryptamine (5-HT) and serves a significant role in the 5-HT pathway. L-tryptophan is hydroxylated by tryptophan 5-hydroxylase to form 5-HTP, following which aromatic amino acid decarboxylases catalyze the formation of 5-HT (42). 5-HT has multiple vascular effects, depending on the different 5-HT receptor subtypes (43). 5-HT_1R mediates vasodilating activity and 5-HT_2R mediates vasoconstriction (44,45). In the present study, the serum levels of 5-HTP in the *Rhizoma Coptidis* group reduced compared with the model group. This suggested that *Rhizoma Coptidis* regulates metabolic pathways of catecholamine and 5-HT to reduce blood pressure. However, the specific underlying mechanism of action of *Rhizoma Coptidis* on 5-HTP requires further investigation.

In conclusion, clinical practice has demonstrated that decreasing blood pressure cannot completely protect and reverse damaged organs or tissue caused by high blood pressure. The primary reason is multiple risk factors in patients with hypertension interact and influence each other. Therefore, treatment of hypertension requires drugs that target multiple targets and metabolic pathways. In the present study, by applying metabolomics technology, the therapeutic efficacies and mechanism of *Rhizoma Coptidis* on SHRs was investigated.

There were metabolic differences between the model group and *Rhizoma Coptidis* groups, and *Rhizoma Coptidis* reversed the levels of 10 perturbed metabolites. These alterations suggested that the antihypertensive effect of *Rhizoma Coptidis* may involve the regulation of phospholipids, fatty acids, amino acid and arachidonic acid metabolism. However, there were limitations of the research, and the results require further validation. This study provides insights into the underlying therapeutic mechanism of *Rhizoma Coptidis* for hypertension.

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