Study on Preparation and Quality of Coicis Semen Damp-clearing Mixture

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Abstract [**Objectives**] To optimize the extraction process of Damp-clearing Mixture and establish the quality control indicators. [**Methods**] The extraction process of Coicis Semen Damp-clearing Mixture was optimized by $L_9(3^4)$ orthogonal design with the content of total flavonoids and the dry yield rate as the evaluation indicators, and the amount of water, extraction time and extraction times as the factors, to determine the formation process of Coicis Semen Damp-clearing Mixture. In addition, the quality of the mixture was studied by thin layer chromatography (TLC). [**Results**] The optimal extraction process of Coicis Semen Damp-clearing Mixture was as follows: decocting twice, one hour each time, adding 8 times of water in the first time and 6 times of water in the second time, standing the extract in a cool place, adding 0.1% stevioside to facilitate the formation of the mixture; Acori Tatarinowii Rhizoma and Dendrophenol in the mixture were well separated by TLC with good reproducibility and specificity. [**Conclusions**] The preparation process and quality control indicators determined by the experiment are reasonable and feasible. It can provide a reference for the pilot production and quality standards of Coicis Semen Damp-clearing Mixture.

Key words Coicis Semen Damp-clearing Mixture, Preparation process, Quality standard, Orthogonal experiment

1 Introduction

Essential Prescriptions of the Golden Chamber first defined "dampness disease" in a narrow sense. It considered that dampness disease was caused by exogenous dampness (often accompanied by wind and cold), and when dampness diarrhea invaded the human body, it was easy to invade the spleen, while the spleen likes dryness and hates dampness, and dampness diarrhea is easy to damage the muscles, surface and joints. In a broad sense, dampness disease refers to the disease caused by the invasion of exogenous dampness, or the abnormal metabolism of dampness and the retention of dampness in the body caused by the imbalance of the functions of the internal organs of the human body[1]. Modern studies have shown that dampness disease is closely related to water metabolism, especially local tissue water metabolism and microcirculation disorders, and the level of plasma vasopressin (AVP), aldosterone (ALD) and neurotensin (NT) metabolism in rats with dampness blocking the middle energizer syndrome are abnormal[2-4]. Dampness disease shows inflammatory reaction and tissue infiltration of inflammatory cells in various ways. The occurrence of dampness and turbidity can not only be mediated by the invasion of pathogenic bacteria and inflammation, but also be induced by the material components produced by metabolic disorders[5-7].

With the acceleration of people's life rhythm, the increasing pressure of life, and a variety of unhealthy living habits in modern times, the number of people suffering from damp diseases is increasing. Coicis Semen Damp-clearing Formula consists of five medicines, namely, Coicis Semen, Acori Tatarinowii Rhizoma, *Polygala fallax* Hemsl., Dendrobii Caulis, and Zingiberis Rhizoma Recens. The prescription is derived from clinical experience, and it has the efficacy of eliminating dampness and detoxifying, strengthening the spleen and invigorating qi, and is used for treating heaviness of the head, lassitude, chest distress, abdominal distension, aching pain of limbs and joints, heavy aching pain of joints, sticky stool, chronic gastroenteritis, gout, pneumonia and hyperlipidemia caused by dampness. Since the appearance of Coicis Semen Damp-clearing Formula, it has been used in the form of decoction in clinic. In order to facilitate the use and carrying of patients and the storage of drugs, and to better retain the active components and clinical efficacy, Coicis Semen Damp-clearing Formula was developed into a mixture in this study. With the dry yield rate and the content of total flavonoids as the indicators, the extraction process conditions were screened by orthogonal experiment, and the TLC identification of the mixture was studied, so as to establish stable and reliable preparation process and quality control items.

2 Materials and methods

2.1 Drugs and reagents All drugs were purchased from Guangxi Xianzhu Traditional Chinese Medicine Technology Co., Ltd. Coicis Semen, Acori Tatarinowii Rhizoma, Dendrobii Caulis and Zingiberis Rhizoma Recens comply with the relevant provisions of the *Chinese Pharmacopoeia* (Edition 2020). *P. fallax* Hemsl accords with that *Quality Standard of Zhuang Medicine of Guangxi Zhuang Autonomous Region*; rutin reference substance (batch No.: 100080-201811), Acori Tatarinowii Rhizoma reference substance (batch No.: 121098-201406) and Dendrophenol reference substance (batch No.: 111875-201202) were purchased from China National Institute for Food and Drug Control; chemical reagents were analytically pure, ultra-pure water (self-made).

Received: January 12, 2025 Accepted: April 3, 2025

Supported by Self-funded Research Project of Administration of Traditional Chinese Medicine of Guangxi Zhuang Autonomous Region (GXZYA20220142); Key R&D Project of Guangxi Science and Technology Department (Guike AB21196057).

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2.2 Instruments TU1901 UV-Vis spectrophotometer produced by Beijing Persee General Instrument Co., Ltd.; ME155DU electronic balance produced by Mettler Toledo Instrument Co., Ltd.; PHG-9206A electric heating constant temperature blast drying oven produced by Shanghai Yiheng Scientific Instrument Co., Ltd.; Basic-Q30 deionized water purifier produced by Shanghai Hitech Instrument Co., Ltd.

2.3 Plotting of standard curve The preparation process of the stock solution of reference substance is as follows: accurately weighed 11.80 mg of rutin reference substance, dissolved it in 60% ethanol, fixed the volume in a 25 mL volumetric flask, and shook it up to obtain the stock solution of reference substance with a concentration of 0.472 mg/mL. Then, 0.4, 0.7, 1.0, 1.2 and 1.5 mL of the stock solution were put into a 10 mL volumetric flask separately, and 0.3 mL of 5% $NaNO_2$ solution was added and allowed to stand still for 6 min, and then 0.3 mL of 10% $Al(NO_3)_3$ solution was added and allowed to stand still for another 6 min. Then 4 mL of 1 mol/mL NaOH solution was added, and 60% ethanol was added to the scale. After shaking, the solution was allowed to stand still for 10 min. Finally, the absorbance of each solution was determined at the wavelength of 510 nm. With the mass concentration of rutin as the abscissa (x) and the absorbance as the ordinate (y), the standard curve was plotted and the regression equation was obtained: $y = 11.552x + 0.0063$ ($R^2 = 0.9993$), showing that there was a good linear relationship between concentration and absorbance in the range of 0.019 – 0.0708 mg/mL.

2.4 Sample extraction and total flavonoid content determination Weighed 95 g of each drug according to the proportion of the prescription, added water to extract, filtered, cooled to a constant volume of 150 mL, and shook well to obtain the test solution. Took a proper amount of test solution, developed the color and determined the absorbance according to the steps in Section **2.3**, and calculated the total flavone content according to the regression equation.

2.5 Determination of dry yield rate Weighed 95 g of each drug according to the proportion of the prescription, added water for extraction, filtered, properly concentrated the filtrate, fixed the volume to 150 mL, precisely pipetted 20 mL, put it into an evaporating dish dried to constant weight, evaporated it to dryness, dried it at 105 ℃ for 3 h, took it out, cooled it in a dryer for 0.5 h, and quickly weighed it. Calculated the dry yield rate according to the formula: Dry yield rate = (Dry yield mass/20) × 150/Total medicinal material mass × 100%.

2.6 Orthogonal experiment and verification of extraction process The water addition amount (A), extraction time (B) and extraction times (C) were selected as the factors of orthogonal experiment, and the comprehensive score of total flavonoids and dry yield rate was used as the evaluation indicators. The extraction process of Coicis Semen Damp-clearing Mixture was optimized by $L_9(3^4)$ orthogonal design, and the factor levels are shown in Table 1. According to the prescription, weighed 9 portions of medicinal materials, 95 g for each portion, extracted, filtered, concentrated and fixed the volume to 150 mL according to the orthogonal experiment in Table 1. Comprehensive score = Total flavonoids/The highest total flavonoids × 60 + Dry yield rate/The highest dry yield rate × 40.

Table 1 Factor levels of orthogonal design to optimize the extraction process of Coicis Semen Damp-clearing Mixture

Level	Factor		
	Water addition amount (A) times	Extraction time (B) min	Extraction times (C) time
1	6	30	1
2	8	60	2
3	10	90	3

Process validation was carried out according to the above extraction process optimization results. Weighed 285 g of each medicinal material according to the prescription, added 8 times of water for the first time, added 6 times of water for the second time, and decocted twice, one hour each time. The decoctions were combined and concentrated to a relative density of 1.05 to 1.15 (60 ℃). The experiment was repeated three times consecutively to determine the total flavonoid content and dry yield rate of the sample.

2.7 Purification process First, 475 g of each medicinal material was weighed according to the prescription, and the liquid medicine was extracted according to the optimized process parameters, and the experiment was repeated three times. The extract was divided into two parts, and one part of the concentrated solution was placed in a cool place overnight, and the total flavonoid content and dry yield rate of the sample before and after standing were determined.

2.8 Investigation on the dosage of flavoring agent Weighed 475 g of each medicinal material according to the prescription, and extracted the liquid medicine according to the optimized process parameters, stood still and filtered, and appropriate amount of liquid medicine was added with 0.05%, 0.1% and 0.2% steviosin (corresponding to the name of "stevioside" in Volume of the *Chinese Pharmacopoeia*, 2020 edition), respectively, and the dosage was investigated with the taste as the evaluation indicator.

2.9 Quality study

2.9.1 TLC identification of Acori Tatarinowii Rhizoma. Took 20 mL of the prepared mixture and added 20 mL of petroleum ether (60 – 90 ℃) for shaking extraction. Pipetted the petroleum ether solution, evaporated to dryness, and dissolved the residue with 1 mL of petroleum ether (60 – 90 ℃) as the test solution. In addition, took 0.5 g Acori Tatarinowii Rhizoma of the control medicinal material, added 10 mL of petroleum ether (60 – 90 ℃), carried out ultrasonic treatment for 30 min, filtered and evaporated the filtrate to dryness, and dissolved the residue with 1 mL of petroleum ether (60 – 90 ℃) as the control medicinal material solution. Took the negative preparation without Acori Tatarinowii Rhizoma, and prepared the negative control solution according to the preparation method of the test solution. Carried out the experiment according to the thin layer chromatography (General Rule 0502),

pipetted 10 μL of the test solution, 10 μL of the negative control solution and 5 μL of the control medicinal material solution, dropped them on the same silica gel G thin layer plate separately, developed them with petroleum ether (60 – 90 ℃)-ethyl acetate (7∶3) as the developing agent, took them out and dried them in the air, placed under UV light (365 nm) for inspection.

2.9.2 TLC identification of Dendrobii Caulis. Took 20 mL of the prepared mixture and added 20 mL of ethyl acetate for shaking extraction, pipetted the ethyl acetate solution, evaporated to dryness, and dissolved the residue in 1 mL of methanol as the test solution. In addition, took Dendrophenol reference substance and prepared a solution containing 0.2 mg per mL with methanol as the reference substance solution. Took the negative preparation without Dendrobii Caulis and prepared the negative control solution according to the preparation method of the test solution. Carried out the experiment according to the thin layer chromatography (General Rule 0502), pipetted 3 – 5 μL of the test solution, 3 μL of the control solution and 3 μL of the negative control solution, respectively drip them on the same silica gel G thin layer plate, use cyclohexane-dichloromethane-acetone (5∶3∶2) as the developing agent, took out and air dried, sprayed with 10% sulfuric acid ethanol solution and heated at 105 ℃ until the color of the spot was clear.

3 Results and analysis

3.1 Orthogonal experiment The orthogonal experiment design scheme and results are shown in Table 2, and the comprehensive score variance analysis results are shown in Table 3. The results showed that factors A, B and C had significant effects on the extraction process ($P < 0.05$), and the order of the factors was C > B > A, that is, the extraction times had the greatest effect, followed by the extraction time and the amount of water. In the factor, $C_2 > C_3 > C_1$, $B_2 > B_3 > B_1$, and $A_2 > A_1 > A_3$. The optimum process combination was $C_2B_2A_2$. Considering the actual production operation and economic factors, the extraction process of the product was determined as follows: weighing each medicinal material according to the prescription, decocting twice with water, adding 8 times of water for the first time and 6 times of water for the second time, one hour each time.

Table 2 Results of orthogonal design optimization of Coicis Semen Damp-clearing Mixture extraction process

Level	A	B	C	D	Total flavonoids mg/mL	Dry yield rate//%	Comprehensive score
1	1	1	1	1	0.53	6.780	35.82
2	1	2	2	2	1.55	10.990	84.81
3	1	3	3	3	0.89	17.720	74.45
4	2	1	2	3	1.51	9.260	79.35
5	2	2	3	1	1.21	15.050	80.81
6	2	3	1	2	0.96	8.320	55.94
7	3	1	3	2	0.76	12.970	58.70
8	3	2	1	3	0.79	7.670	47.89
9	3	3	2	1	1.39	12.670	82.41
Comprehensive score	K_1	65.027	57.957	46.550	66.347		
	K_2	72.033	71.170	82.190	66.483	$G = 600.16$	
	K_3	63.000	70.933	71.320	67.230	$GT = G^2/9 = 40\,021.20$	
	R	9.033	13.213	35.640	0.883		

Table 3 Analysis of variance of comprehensive score

Source of variance	Sum of squares of deviations	Degrees of freedom	Variance	F	P
A	134.802	2	67.401	99.377	< 0.05
B	343.042	2	171.521	252.894	< 0.05
C	2 001.919	2	1 000.960	1 475.834	< 0.05
Error	1.356	2	0.678		

3.2 Verification test The verification results showed that the average content of total flavonoids was 1.48 mg/mL and the average dry yield rate was 16.49% according to the Coicis Semen Damp-clearing Mixture extracted by the optimized process, and the process was stable and feasible (Table 4).

Table 4 Verification results of Coicis Semen Damp-clearing Mixture extraction process

Experiment No.	Total flavonoids //mg/mL	Dry yield rate//%
1	1.44	16.26
2	1.52	16.43
3	1.49	16.79
Mean value	1.48	16.49

3.3 Purification process test The quality of the mixture is required to be clear, and a small amount of precipitates that are easy to disperse are allowed[8], so the impurities that are easy to precipitate need to be removed in the molding process. The test re-

sults showed that there was little difference in the content of total flavonoids in the concentrated solution of the mixture after standing compared with that before standing, but the content of precipitates in the concentrated solution after standing was significantly reduced, and the clarification effect was better than that before standing (Table 5). The results also showed that the concentrated solution of the mixture was placed in a cool place, which could not only retain the medicinal ingredients of the product, but also obtain a clear liquid medicine.

Table 5 Investigation on purification process of Coicis Semen Damp-clearing Mixture

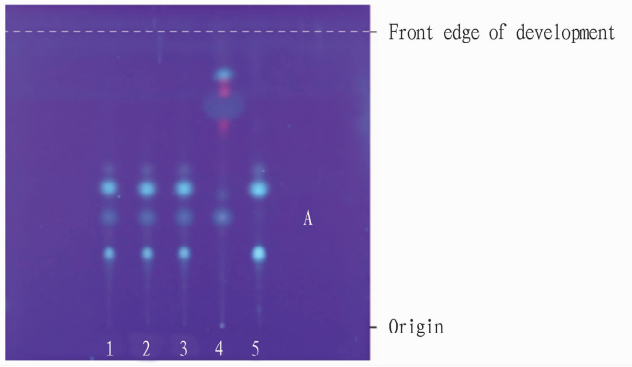
Experiment No.	Indicator	Total flavonoids mg/mL	Dry yield rate//%
1 – 1	Before standing	1.50	16.96
1 – 2	After standing	1.44	12.75
2 – 1	Before standing	1.56	16.51
2 – 2	After standing	1.52	11.59
3 – 1	Before standing	1.45	16.72
3 – 2	After standing	1.49	12.61
Mean value	Before standing	1.50	16.73
	After standing	1.48	12.32

3.4 Investigation on the dosage of flavoring agent The sweetness of steviosin is 200 – 300 times that of sucrose, with high sweetness and low dosage. It is widely used in oral preparations of traditional Chinese medicine, and its safety and stability are recognized. It is also applicable as the main flavor additive in the production process of oral preparations of traditional Chinese medicine[9-11]. The results showed that the mixture with 0.05% steviosin tasted bitter, the mixture with 0.2% steviosin tasted too sweet, and the mixture with 0.1% steviosin tasted sweet and good.

3.5 Quality study

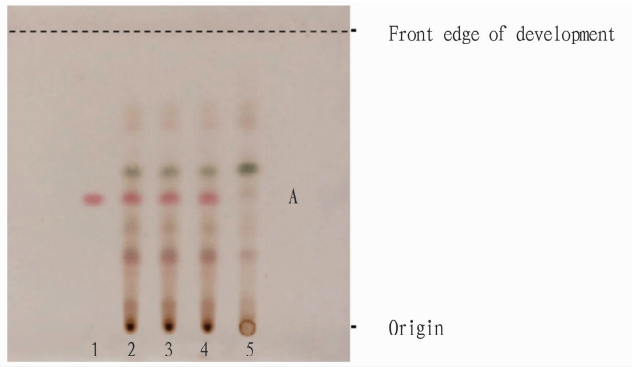
3.5.1 TLC identification of Acori Tatarinowii Rhizoma. As can be seen from Fig. 1, in the chromatogram of the test sample, fluorescent spots of the same color appear at positions corresponding to the chromatogram of the control drug. The negative control did not have this spot. Three batches of samples of Coicis Semen Damp-clearing mixture were tested by this method, and the results showed that the thin layer chromatography effect was the same, which met the requirements, and the thin layer chromatography had good separation effect, round and clear spots, good reproducibility, no negative interference, and strong specificity.

3.5.2 TLC identification of Dendrobii Caulis. It can be seen from Fig. 2 that in the chromatogram of the test sample, the same red spot appears at the position corresponding to the chromatogram of the control sample, while the Dendrobii Caulis negative control has no such spot. Three batches of samples of Coicis Semen Damp-clearing mixture were tested by this method, and the results showed that the thin layer chromatography effect was the same, which met the requirements, and the thin layer chromatography had good separation effect, clear spots, good reproducibility, no negative interference, and strong specificity.



NOTE 1. Sample 200601; 2. Sample 200602; 3. Sample 200603; 4. Reference material of Acori Tatarinowii Rhizoma; 5. Negative solution of Acori Tatarinowii Rhizoma; A. Acori Tatarinowii Rhizoma main characteristic spot of the control medicinal material.

Fig. 1 TLC chromatogram of Acori Tatarinowii Rhizoma in Coicis Semen Damp-clearing Mixture



NOTE 1. Dendrophenol reference substance; 2. Sample 200601; 3. Sample 200602; 4. Sample 200603; 5. Dendrobii Caulis negative solution; A. Dendrophenol reference substance characteristic spot.

Fig. 2 TLC chromatogram of Dendrobii Caulis in Coicis Semen Damp-clearing Mixture

4 Conclusions

In this study, we explored the preparation process and quality of Coicis Semen Damp-clearing Mixture. With the content of total flavonoids and dry yield rate as the evaluation indicators, we used the orthogonal design to optimize the extraction conditions of Coicis Semen Damp-clearing Mixture, and obtained the optimal extraction process as follows: weighing each medicinal material according to the prescription, decocting twice with water, adding 8 times of water at the first time, adding 6 times of water for the second time, and one hour each time. After further investigation, we determined the purification process of Coicis Semen Damp-clearing Mixture as follows: the drug solution was placed in a cool place overnight, and 0.1% steviosin was added at the same time to obtain a mixture with suitable taste. The TLC identification methods of Acori Tatarinowii Rhizoma and Dendrophenol in the Coicis Semen Damp-clearing Mixture are specific and reproducible, and can be used as the quality control indicators of the mixture.

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G. jasminoides on hyaluronidase was also increased by 90.30% after fermentation. The results showed that the fermentation could increase the content of total flavonoids in *G. jasminoides* and improve the efficacy of its active components, which provided a reference for the comprehensive development and utilization of active components in *G. jasminoides*.

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