Original Article

Research on the treatment of settling sediments in the production process of Ich mau extracts

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ABSTRACT

In Vietnam, Ich mau (*Leonurus japonicus* Houtt, Lamiaceae) is curently used as a medicine to regulate menstruation and treat dysmenorrhea. This research will determine the parameters of the time to settle the liquid extract and the amount of settling liquid S obtained in each production batch to contribute to the completion of the production process on an industrial scale. Medicinal herbs will be collected in different seasons of the year, meeting the standards of Vietnam's Pharmacopoeia V. Excipients included ethanol, sugar, and benzoic acid. Prepare Ich mau extracts medicine according to the formula of Vietnam's Pharmacopoeia with the volume of 1 packing unit is 100 ml. Evaluation of the quality of Ich mau extracts according to the standards of Vietnam's Pharmacopoeia V. The batches of preparation with or without the use of liquid S all obtained the products that met the requirements of testing criteria. Ich mau extracts meet the requirements of the test criteria after 3, 6, 9, and 12 months of storage. With raw materials from different regions and seasons, the project has researched to standardize the technical parameters of the production process such as: settling time t, the volume of clear liquid T, volume of settling liquid S. We will continue to monitor the product's long-term stability to prolong the life of the medicine.

Keywords: Sediment concentration, *Leonurus japonicus*, Ich mau, Settling sediments

Introduction

Ich mau (*Leonurus japonicus* Houtt, Lamiaceae) has the effect of increasing the tonus and frequency of uterine contractions. Also, it increases myocardial contractility and increases respiratory rate, and amplitude. In addition, it also has hemolytic, diuretic, and sedative effects [1, 2]. Currently, in Vietnam, China, and other Southeast Asian countries, the herb is used as a medicine to regulate menstruation and treat dysmenorrhea [3-6]; often used in combination with ngai cuu (*Artemisia vulgaris* L., Asteraceae), huong phu (*Rhizoma Cyperi* L., Cypcraceae) [1, 2]. Ich mau extracts medicine - prepared according to the formula of Vietnam's Pharmacopoeia V [1, 2] - is produced and widely circulated on the Vietnamese market.

Ich mau extracts medicine (liquid extracts of Leonurus japonicus) is produced according to the diagram in **Figure 1**. Accordingly, medicinal herbs (Ich mau (*Leonurus japonicus* Houtt, Lamiaceae), Ngai cuu (*Artemisia vulgaris* L., Asteraceae), Huong phu (*Rhizoma Cyperi* L., Cypcraceae)) are extracted with hot water (liquid extracts), then let it settle and separate the clear liquid, combine with the remaining ingredients such as sugar, ethanol, benzoic acid to achieve the specified standards [2]. Because the ingredients of medicinal herbs often change according to the weather, the growing region, etc., and the amount of settling sediment in the production batches is often different, lead to the amount of clear liquid obtained after the settling phase of the medicine batches is often different. From there, it is necessary to determine the parameters of the separated clear liquid volume (liquid T), the volume of the remaining sediment-containing liquid (liquid T') after settling, and the settling time (t) to verify the production process, and at the same time, research the settling sediment treatment process to recover the medicine

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liquid. This makes economic and environmental sense when produced on an industrial scale.

The project investigated the production process of Ich mau extracts medicine with raw materials collected from many regions and many seasons of the year. Accordingly, Ich mau extracts medicine is produced according to the diagram in **Figure 2**, so the research will determine the parameters of the time to settle the liquid extract and the amount of settling liquid S obtained in each production batch to contribute to the completion of the production process on an industrial scale.

Materials and Methods

Research subjects

- Medicinal herbs such as Ich mau (*Leonurus japonicus* Houtt, Lamiaceae), Ngai cuu (*Artemisia vulgaris* L., Asteraceae), Huong phu (*Rhizoma Cyperi* L., Cypcraceae) are grown in Bac Giang, Dong Thap and will be collected in different seasons of the year, meeting the standards of Vietnam's Pharmacopoeia V.
- Excipients such as ethanol, sugar, and benzoic acid.
- Equipment for preparing Ich mau extracts: water bath, decanter.
- Centrifuge Rotanta 460 Hettich (Germany).

Research contents

- Prepare the liquid extract (CIM) from medicinal herbs such as ich mau (*Leonurus japonicus* Houtt, Lamiaceae), ngai cuu (*Artemisia vulgaris* L., Asteraceae), huong phu (*Rhizoma Cyperi* L., Cypcraceae) harvested seasonally in Bac Giang, Dong Thap according to the diagram in **Figure 1**.
- The liquid extract is placed in a settling vessel, then let it cool off and settle, separate the clear liquid (liquid T) for the next stage of preparation, determine the settling time t and the amount of clear liquid (liquid T)
- The remaining sediment-containing liquid (liquid T') is treated, and the clear liquid (liquid S) is separated according to the diagram in **Figure 2** to be reused for the next production batch. And monitor the stability of this liquid S.
- Carrying out the production of Ich mau extracts medicine with a larger batch size to verify the above parameters according to the diagram in **Figure 2** and monitor the stability of Ich mau extracts medicine

Research methods

Recipe for preparing Ich mau extracts

Ich mau (*Leonurus japonicus* Houtt, Lamiaceae), ngai cuu (*Artemisia vulgaris* L., Asteraceae), huong phu (*Rhizoma Cyperi* L., Cypcraceae) which coding batches of medicinal herbs are grown in Bac Giang province with Spring (from January to March) – M and Summer (from April to June) – N; and Dong Thap province in two seasons: Spring (from January to March) - P, Summer (from April to June) - Q,

Prepare Ich mau extracts medicine according to the formula of Vietnam's Pharmacopoeia with the volume of 1 packing unit is 100 ml. The recipe ingredients for the preparation of Ich mau extracts medicine are presented in **Table 1** [1, 2].

Table 1. Recipe ingredients for the preparation of Ich mau extracts medicine

Recipe ingredients	Mass /volume per packing unit
Huong phu (*Rhizoma Cyperi*) for making vinegar (g)	25
Ich mau (*Leonurus japonicus* Houtt, Lamiaceae) (g)	80
Ngai cuu (*Artemisia vulgaris* L., Asteraceae) (g)	20
Benzoic Acid (g)	0.2
Ethanol 90 % (mL)	18
White sugar (g)	60
Water is sufficient (mL)	100

The process of preparing Ich mau extracts medicine

The preparation process of Ich mau extracts medicine is presented as shown in **Figure 1**. The medicinal herbs (Ich mau (*Leonurus japonicus* Houtt, Lamiaceae), Ngai cuu (*Artemisia vulgaris* L., Asteraceae), Huong phu (*Rhizoma Cyperi* L., Cypcraceae)) are extracted with hot water (liquid extracts), so we collected the liquid extract of CIM (liquid extracts of *Leonurus japonicus*), then settled it and separated the clear liquid T, then combine sugar, ethanol, benzoic acid into the clear liquid T to get the product. Next is to check the quality of the product.

The remaining sediment-containing liquid T' is kept separate and processed according to the procedure shown in **Figure 2**.

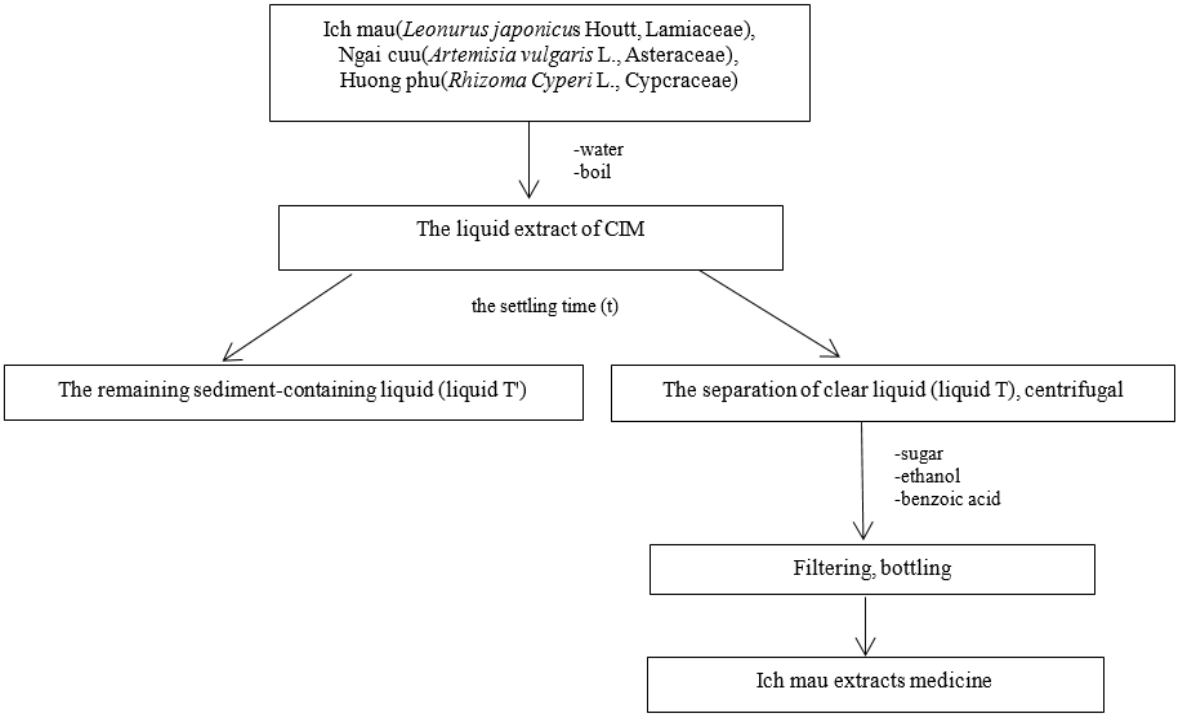

Figure 1. The preparation process of Ich mau extracts medicine

Separation of clear liquid T

The liquid extract of CIM **(Figure 1)** is placed in a settling vessel, then let it cool off and settle. Use the tube connected to the vacuum pump to withdraw the clear liquid from high to low until the clear liquid is gone. Check the clarity of the settling liquid by centrifugation method. Determine the settling time (t), volume, and density of the obtained clear liquid (liquid T).

Check the clarity of the settling liquid

Centrifuge the clear liquid for 10 minutes at speed of 5,000 rpm.

- Evaluate the appearance of sedimentation by observing with the naked eye
- Compare the turbidity of the centrifugal liquid by the method of determining the clarity of the liquid (Appendix 9.2, Vietnam's Pharmacopoeia V). The clarity of the centrifugal liquid was determined by comparison with reference mixtures.

The reference mixture was prepared from hydrazine sulfate, hexamethylenetetramine, and water. The comparisons are conducted in identical test tubes of neutral, clear, colorless, flat-bottomed glass and have a diameter between 15 mm and 25 mm. The liquid extract is considered clear if it is equivalent to the clarity of distilled water or the solvent used when tested under the conditions as described or if slightly turbid, do not be more turbid than the reference mixture I.

Requirements: clear liquid, no sedimentation

Treatment of sediment-containing liquid (liquid T')

The sediment-containing liquid is treated by adding the same amount of water and then boiling, settling, and separating the clear liquid (liquid S) to reuse for the next production batch **(Figure 2)**. Determine the settling time (t') and the amount of liquid S obtained. Monitor the stability of liquid S with the criterion of limiting infection.

Steps to treat the sediment-containing liquid are shown in **Figure 2**.

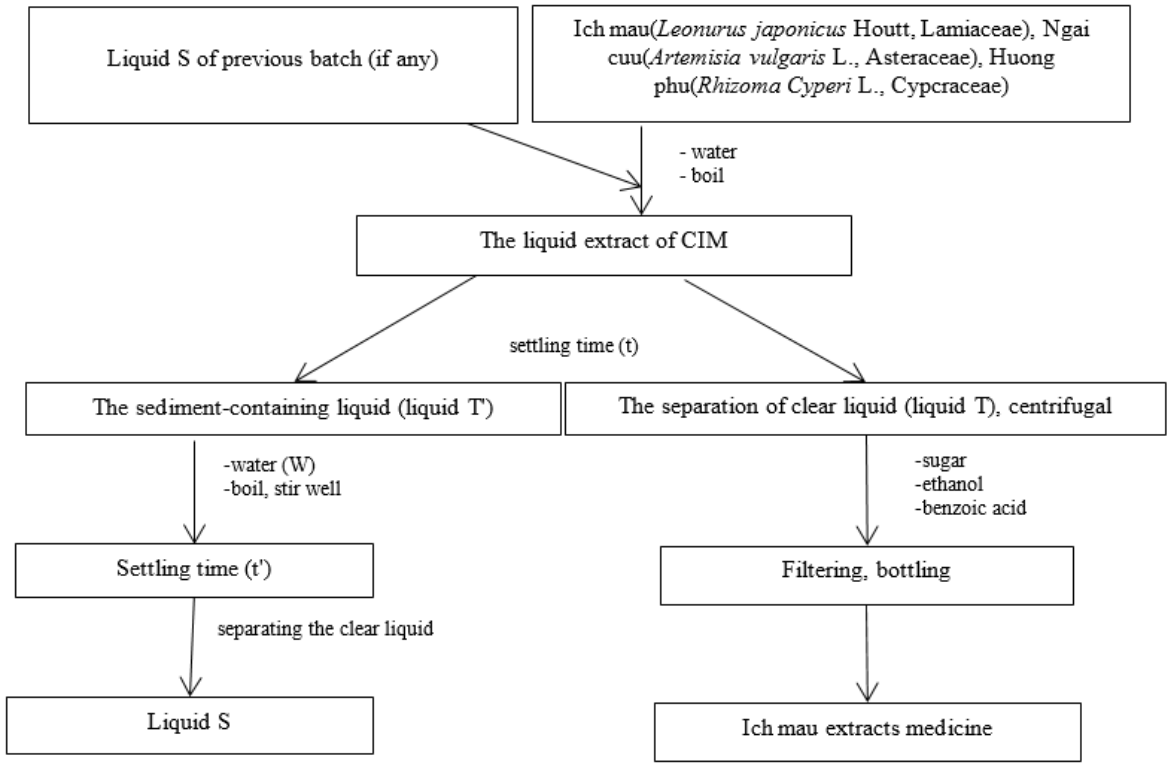

Figure 2. Steps to treat the sediment-containing liquid T'

Monitor the stability of the liquid S

Liquid S is stored in a sealed container at 25°C for 30 days. Check the criterion of limiting infection of liquid S every 10 days by membrane filter method according to Appendix 13.6. Infectious Limit Test, Vietnam's Pharmacopoeia V.

Verification

Prepare batches of Ich mau extracts medicine with defined parameters T, T', t, t'. Test finished products with the following criteria: Qualitative of ich mau (*Leonurus japonicus* Houtt, Lamiaceae), ngai cuu (*Artemisia vulgaris* L., Asteraceae), clarity and uniformity, density, ethanol content, microbiological limit, stability.

Stability monitoring method

Evaluation of the stability of Ich mau extracts at the time: 0, 3, 6, 9, and 12 months under normal conditions [7].

Evaluation criteria: Clarity and uniformity, color, the smell of the liquid, qualitative of ich mau (*Leonurus japonicus* Houtt, Lamiaceae), ngai cuu (*Artemisia vulgaris* L., Asteraceae); density, ethanol content, infection limit [7].

Quality standards of Ich mau extract medicine

Evaluation of the quality of Ich mau extracts according to the standards of Vietnam's Pharmacopoeia V.

Properties: Viscous liquid, dark brown, the aroma of medicinal herbs, slightly bitter.

Solubility: Liquid extracts must be completely soluble in the solvent used to prepare them.

Clarity and uniformity: Viscous, uniform liquid, must be free of mold, medicinal residues, and foreign matter (Appendix 1.1, Vietnam's Pharmacopoeia V). Add the same volume of water that is not turbid.

Density: At 20°C: From 1.20 to 1.23 (Appendix 6.5, use density meter).

Qualitative of Ich mau extracts: *Qualitative of ich mau (Leonurus japonicus Houtt, Lamiaceae) by thin layer chromatography method (Appendix 5.4, Vietnam's Pharmacopoeia V)*

Procedure: Thin sheet of silica gel G, and development solvent: Toluene - ethyl acetate - acetone - formic acid (15:2:2:1).

Test solution: Take 10 ml of the preparation, dilute with 70 ml of water, transfer to a decanter, and shake with 30 ml of ethyl acetate (TT). Decant the ethyl acetate liquid extract, and evaporate in a water bath to dry. Dissolve the sediment in 1 ml of ethanol 96 % (TT).

Reference solution: Take 6 g of ich mau(*Leonurus japonicus* Houtt, Lamiaceae) (standard pattern) chopped, add 100 ml of water, boil gently for 1 h (addition of evaporated water),

and filter. Extract the filtrate in a water bath to about 30 ml, then let it cool, transfer it to a decanter, and shake it with 30 ml of ethyl acetate (TT). Decant the ethyl acetate liquid extract, and evaporate in a water bath to dry. Dissolve the sediment in 1 ml of ethanol 96 % (TT).

Dot separately on a thin sheet 20 µl each of the above solutions. Develop chromatography, allow the thin sheet to dry at room temperature, spray iron(III) chloride solution 5% in ethanol (TT), and observe in normal light. The chromatogram obtained with the test solution shall have spots of the same color and the same Rf value as the spots in the chromatogram obtained with the reference solution.

Qualitative of ngai cuu (Artemisia vulgaris L., Asteraceae) by thin layer chromatography method (Appendix 5.4, Vietnam's Pharmacopoeia V)

Procedure: Thin sheet of silica gel G, and development solvent: Toluene - ethyl acetate - acetone - formic acid (15:2:2:1).

Test solution: Use the test solution in the qualitative of ich mau (*Leonurus japonicus* Houtt, Lamiaceae) section.

Reference solution: Take 2 g of Ngai cuu (*Artemisia vulgaris* L., Asteraceae) (standard pattern) chopped, add 100 ml of water, boil gently for 1 hour (addition of evaporated water), and filter. Extract the filtrate in a water bath to about 30 ml, then let it cool, transfer it to a decanter, and shake it with 30 ml of ethyl acetate (TT). Decant the ethyl acetate liquid extract, and evaporate in a water bath to dry. Dissolve the sediment in 1 ml of ethanol 96 % (TT).

Dot separately on a thin sheet 20 µl each of the above solutions. Develop chromatography, allow the thin sheet to dry at room temperature, and observe under ultraviolet light at 366 nm. The chromatogram obtained with the test solution shall have luminescent spots of the same color and the same Rf value as the spots in the chromatogram obtained with the reference solution.

Ethanol content: Ich mau extracts have an ethanol content of 14% to 17% (Appendix 10.12, Vietnam's Pharmacopoeia V)

Heavy Metals: Not more than twenty parts per million.

Procedure: Take 1.0 g of the preparation and conduct the test according to method 3, Appendix 9.4.8 (Vietnam's Pharmacopoeia V). Use 2 ml color Plumbum solution of ten parts per million Pb (TT) to prepare the reference sample.

Residues of plant protection chemicals: Meet the requirements specified in Appendix 2.17, Vietnam's Pharmacopoeia V.

Infection limit: Meet the requirements specified in Appendix 13.6 Infectious Limit Test Vietnam's Pharmacopoeia V. Usage method: Filter membrane method.

Results and Discussion

Preparation of liquid extract

The liquid extract of CIM is prepared from medicinal herbs such as ich mau (*Leonurus japonicus* Houtt, Lamiaceae), ngai cuu (*Artemisia vulgaris* L., Asteraceae), huong phu (*Rhizoma Cyperi* L., Cypcraceae) which are harvested seasonally in Bac Giang, Dong Thap according to the diagram in **Figure 1**.

Recipe for batch size 1,000 ml

The recipe for the preparation of a batch size of 1,000 ml is including Huong phu (Rhizoma Cyperi) for making vinegar (250g); Ich mau (Leonurus japonicus Houtt, Lamiaceae) (800g); Ngai cuu (Artemisia vulgaris L., Asteraceae) (200g); Benzoic Acid (2g); Ethanol 90 % (180 mL); White sugar (600g); Water is sufficient (1000 mL). Prepare batches N1, M1, P1, and Q1 (raw materials are grown in the region and harvested according to the respective seasons).

Probe for settling time t

The settling time t of Ich mau extracts is presented in **Table 2**. The batches of medicinal herbs are different but have the same sedimentation time on the 3rd day after settling.

Table 2. Settling time of Ich mau liquid extract

Batches	Day 1	Day 2	Day 3	Day 4	Day 5
N1	clear liquid, no sedimentation	clear liquid, no sedimentation	clear liquid, sedimentation at the bottom	clear liquid, sedimentation at the bottom	clear liquid, sedimentation at the bottom
M1	clear liquid, no sedimentation	clear liquid, no sedimentation	clear liquid, sedimentation at the bottom	clear liquid, sedimentation at the bottom	clear liquid, sedimentation at the bottom
P1	clear liquid, no sedimentation	clear liquid, no sedimentation	clear liquid, sedimentation at the bottom	clear liquid, sedimentation at the bottom	clear liquid, sedimentation at the bottom
Q1	clear liquid, no sedimentation	clear liquid, no sedimentation	clear liquid, sedimentation at the bottom	clear liquid, sedimentation at the bottom	clear liquid, sedimentation at the bottom

Separation of liquid T

Let the liquid settle for 3 days, collect the settling liquid from high to low, check the settling sediment by centrifugation for 10 minutes, and stop collecting the liquid when the sediment appears in the centrifuge tube. The volume of clear liquid T of each batch is different and > 800 ml. The project chooses T = 800 ml as a parameter of the production process.

Treatment of liquid T' and stability monitoring of liquid S

Treatment of liquid T':

Boiled liquid T' for 30 minutes, then let it cool for 8 hours at room temperature and settle, separate the clear liquid, and measure the density of liquid S. = The volume of clear liquid S of each batch is different and > 150 ml. The project selected S = 150 ml as a parameter of the production process.

Liquid volume T, T'; Density and clarity of liquid T, T' are presented in **Table 3**.

Table 3. Volume T, T'; density and clarity of liquid T and Treatment results of liquid T'

Parameters	Batch N1	Batch M1	Batch P1	Batch Q1	Average ± SD
Volume T, T'; density and clarity of liquid T					
Volume of liquid T (ml)	805	812	821	830	817 ± 10.9
Volume of liquid T' (ml)	195	188	179	170	183 ± 10.9
Density of liquid T	1.05	1.07	1.10	1.08	1.08 ± 0.02
Clarity of liquid T	crystal-clear	crystal-clear	crystal-clear	crystal-clear	crystal-clear
Treatment results of liquid T'					
Liquid T' (ml)	195	188	179	170	183 ± 10.9
Amount of water W added (ml)	195	188	179	170	183 ± 10.9
Time to settle t' (days)	3	3	3	3	3 ± 0.0
Liquid S (ml)	155	160	171	185	167.8 ± 13.3
Density of liquid S (g/cm^3)	1.03	1.04	1.05	1.05	1.04 ± 0.01

Stability monitoring of liquid S

The results of stability monitoring of the liquid S are presented in **Table 4**. After 30 days of storage, liquid S still met the requirements for clarity and infection limit.

Table 4. Results of stability monitoring of the liquid S

Criteria	Liquid S of batch N1	Liquid S of batch M1	Liquid S of batch P1	Liquid S of batch Q1
Clarity				
After 10 days	pass	pass	pass	pass
After 20 days	pass	pass	pass	pass
After 30 days	pass	pass	pass	pass
Infection limit				
After 10 days	pass	pass	pass	pass
After 20 days	pass	pass	pass	pass
After 30 days	pass	pass	pass	pass

Verification

Verification preparation

Prepare 8 batches of Ich mau extracts medicine with a batch size of 1,000 ml of finished product/batch according to the diagram in **Figure 2**, of which 4 batches N2, M2, P2, and Q2 do not use the liquid S of the previous batch and batches of N3, M3, P3, Q3 using liquid S from batches N2, M2, P2, Q2 (respectively). Check the quality criteria of the finished product. The results are presented in **Table 5**. The batches of preparation with or without the use of liquid S all obtained the products that met the requirements of testing criteria.

Stability monitoring

Monitor the stability of the above medicine batches under normal conditions, and check at the time of 3 months, 6 months, 9

months, and 12 months. The results are presented in **Table 5**. Ich mau extracts meet the requirements of the test criteria after 3, 6, 9, and 12 months of storage.

Table 5. Results of testing criteria for 8 batches of Ich mau extracts

Criteria	N2	M2	P2	Q2	N3	M3	P3	Q3
Results of testing criteria for 8 batches of Ich mau extracts								
Properties	pass	pass	pass	pass	pass	pass	pass	pass
Solubility	pass	pass	pass	pass	pass	pass	pass	pass
Heavy metal	pass	pass	pass	pass	pass	pass	pass	pass
Residues of plant protection chemicals	pass	pass	pass	pass	pass	pass	pass	pass
Qualitative of ich mau (*Leonurus japonicus* Houtt, Lamiaceae)	positive	positive	positive	positive	positive	positive	positive	positive
Qualitative of ngai cuu (*Artemisia vulgaris* L., Asteraceae)	positive	positive	positive	positive	positive	positive	positive	positive
Clarity and uniformity	pass	pass	pass	pass	pass	pass	pass	pass
Density	1.22	1.23	1.22	1.24	1.21	1.23	1.18	1.22
Ethanol content	14.5	14.7	15.3	14.9	16.1	15.7	15.4	16.6
Infection limit	pass	pass	pass	pass	pass	pass	pass	Pass
Results of stability monitoring after 3, 6, 9, and 12 months								
Results of stability monitoring after 3 months								
Qualitative of Ich mau (*Leonurus japonicus* Houtt, Lamiaceae)	positive	positive	positive	positive	positive	positive	positive	positive
Qualitative of Ngai cuu (*Artemisia vulgaris* L., Asteraceae)	positive	positive	positive	positive	positive	positive	positive	positive
Clarity and uniformity	pass	pass	pass	pass	pass	pass	pass	pass
Density	1.25	1.18	1.20	1.17	1.21	1.20	1.24	1.20
Ethanol content	14.2	15.3	15.8	14.5	16.4	15.3	14.5	16.0
Infection limit	pass	pass	pass	pass	pass	pass	pass	Pass
Results of stability monitoring after 6 months								
Qualitative of ich mau (Leonurus japonicus	positive	positive	positive	positive	positive	positive	positive	positive
Qualitative of ngai cuu (*Artemisia vulgaris* L., Asteraceae)	positive	positive	positive	positive	positive	positive	positive	positive
Clarity and uniformity	pass	pass	pass	pass	pass	pass	pass	pass
Density	1.17	1.25	1.25	1.21	1.23	1.21	1.20	1.23
Ethanol content	14.6	15.1	15.2	15,9	15.4	14.9	15.0	15.8
Infection limit	pass	pass	pass	pass	pass	pass	pass	pass
Results of stability monitoring after 9 months								
Qualitative of ich mau (Leonurus japonicus	positive	positive	positive	positive	positive	positive	positive	positive
Qualitative of ngai cuu (*Artemisia vulgaris* L., Asteraceae)	positive	positive	positive	positive	positive	positive	positive	positive
Clarity and uniformity	pass	pass	pass	pass	pass	pass	pass	pass
Density	1.25	1.19	1.18	1.24	1.22	1.23	1.20	1.21
Ethanol content	15.0	14.9	16.5	16.1	15.5	16.4	15.9	15.7
Infection limit	pass	pass	pass	pass	pass	pass	pass	pass
Results of stability monitoring after 12 months								
Qualitative of ich mau (*Leonurus japonicus)*	positive	positive	positive	positive	positive	positive	positive	positive
Qualitative of ngai cuu (*Artemisia vulgaris*)	positive	positive	positive	positive	positive	positive	positive	positive
Clarity and uniformity	pass	pass	pass	pass	pass	pass	pass	pass
Density	1.23	1.22	1.23	1.19	1.17	1.18	1.24	1.24
Ethanol content	14.9	16.3	16.1	16.5	14.9	16.0	15.5	16.2
Infection limit	pass	pass	pass	pass	pass	pass	pass	pass

The project has investigated the source raw materials of ich mau (*Leonurus japonicus* Houtt, Lamiaceae), ngai cuu (*Artemisia vulgaris* L., Asteraceae), huong phu (*Rhizoma Cyperi* L., Cypcraceae), which are grown in Bac Giang and Dong Thap regions. These are two of the main medicinal growing areas in Vietnam. In the production of Ich mau extracts medicine, the settling phase

before separating and extracting liquid T is necessary to minimize the appearance of sediment in the finished product during storage and circulation. On an industrial scale (volume of liquid medicine > 1,000 liters), this process requires the use of suitable tanks. The research period of the settling phase is 3 days to ensure continuous production deployment, less equipment occupation, and easy process control. This time may vary depending on the conditions of each actual production unit.

Determine the parameter T = 800 ml/recipe for 1000 ml of the finished product to ensure that all batches of preparation can separate the same amount of clear liquid T to put into the preparation. This parameter is very important to ensure that the medicine batches meet the requirements of density criteria. Determine the parameter S = 150 ml/recipe for the preparation of 1,000 ml of the finished product to ensure that all batches of preparation can separate the same amount of clear liquid S, convenient in preparing tools for storage and preservation. When this parameter is selected, the fact is that the remaining clear liquid has not been recovered. If the production facilities are equipped with suitable sedimentation and extraction equipment (for example centrifuge…) then a more optimal amount of clear liquid can be recovered for remanufacturing [8]. Determining the fixed volume of liquid T and liquid S for production batches is very important for building and verifying the production process, helping to ensure the quality of the medicine is always controlled regardless of the source of medicinal herbs is a factor that changes according to the season of the year [9].

Research the stability of liquid S for one month to effectively use the recovered liquid extract when the production process goes on continuously. Depending on actual conditions, it is possible to research the preservation for a longer time. However, long-term storage will affect the quality of the medicine. Therefore, the preservation time and conditions of liquid S must be researched and controlled.

Conclusion

With raw materials from different regions and seasons, the project has researched to standardize the technical parameters of the production process such as: settling time t, the volume of clear liquid T, volume of settling liquid S. These are important parameters used to build production processes and ensure product quality. Conducted production verification on a pilot scale and monitored product stability after 12 months under normal conditions, the results showed stable product quality. We will continue to monitor the product's long-term stability to prolong the life of the medicine.

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Conflict of interest: None

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Ethics statement: This study conducted on herbal materials with lab-working only. No intervention was generated on human being.

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