RESEARCH ON PRODUCTION OF INSTANT TEA USING *GARDENIA JASMINOIDES* ELLIS. TO SUPPORT NOURISHING BRAIN AND ACTIVATING BLOOD CIRCULATION ON HEART FUNCTION

NGHIÊN CỨU BÀO CHẾ TRÀ HÒA TAN SỬ DỤNG MỘC ĐAN TRONG VIỆC HỖ TRỢ HOẠT HUYẾT DƯỠNG NÃO VÀ TĂNG TUẦN HOÀN MÁU, CẢI THIỆN CHỨC NĂNG TIM

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ABSTRACT

This study has demonstrated the presence of two compounds Genipin and Geniposide in *Gardenia jasminoides* Ellis.) collected in Thanh Luong commune, Thanh Chuong district, Nghe An province using the ^{1}H-NMR and ^{13}C-NMR. Genipin and Geniposide have biological activities such as anti-inflammatory, anti-oxidant, inhibiting *α*-glycosidase enzyme, antiplatelet effect, improving thrombosis, *etc*. The anti-inflammatory role of *Gardenia jasminoides* Ellis. can be helps prevent vascular diseases such as fibrosis and atherosclerosis. This study has successfully prepared instant tea from *Gardenia jasminoides* Ellis. combined with *Millettia dielsiana* Harms. and *Lycopodium cernuum* L.. Instant tea has physicochemical indicators. such as moisture content of about 3.73%, ash level of 10.46% according to TCVN 9739:2013 standard and heavy metal content all meet regulations according to National Technical Regulations, QCVN8-2:2011/BYT.

Keywords: *Gardenia jasminoides* Ellis*., instant tea.*

TÓM TẮT

Nghiên cứu này đã chứng minh sự có mặt của hai hợp chất Genipin và Geniposide trong cây Mộc đan *(Gardenia jasminoides* Ellis.) được thu hái tại xã Thanh Lương, huyện Thanh Chương, tỉnh Nghệ An bằng phương pháp quang phổ cộng hưởng ^{1}H-NMR và ^{13}C-NMR. Genipin và Geniposide có hoạt tính sinh học tốt như chống viêm, chống oxy hóa, ức chế enzyme *α*-glycosidase, tác dụng kháng tiểu cầu, cải thiện tình trạng huyết khối, tắc mạch,… Vai trò chống viêm của mộc đan có thể giúp ngăn ngừa các bệnh về mạch máu như xơ hóa và xơ vữa động mạch. Nghiên cứu này đã bào chế thành công trà hòa tan từ Mộc đan *(Gardenia jasminoides* Ellis.) kết hợp với kê huyết đằng *(Millettia dielsiana* Harms.) và thông đất *(Lycopodium cernuum* L.) Trà hòa tan có các chỉ tiêu hóa lý như độ ẩm khoảng 3,73%, độ tro 10,46% theo tiêu chuẩn TCVN 9739:2013 và hàm lượng kim loại nặng đều đạt quy định theo Quy chuẩn kỹ thuật quốc gia. QCVN8-2:2011/BYT.

Từ khóa: *Mộc đan, trà hòa tan.*

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1. INTRODUCTION

Gardenia jasminoides Ellis. is a familiar shrub of the *Rubiaceae family*. It has the bitter taste, cold, non-toxic, *etc* [1]. The modern researchs have carried out that *Gardenia jasminoides* Ellis. is proved to be influential in gallbladder, inhibit secretion gastric juice, and stomach; intestine; antibacterial; anti-flammatory; antihypertensive, pain-relief, *etc* [2, 3]. Additionally, in traditional medicine, *Gardenia jasminoides* Ellis. is also used to treat sore throat, mouth sores, swelling, fibroids, atherosclerosis and thrombosis, *etc* [2, 4].

Currently, there has been research in the country on the use of *Gardenia jasminoides* Ellis. in food colouring. Studies on acute toxicity of those extracts also show that *Gardenia jasminoides* Ellis. can be used at does of 6 - 12g for safe treatment [5]. However, presently research products on *Gardenia jasminoides* Ellis. are almost stopped at the application to food or medicine, there is no product in the form of supplements to support blood circulation and nourish the brain. Therefore, this study presents the results of determining some chemical components presented in *Gardenia jasminoides* Ellis., thereby applying the use of *Gardenia jasminoides* Ellis. in

combination with some other medicial herbs in the preparation of instant tea.

2. MATERIALS AND METHOD

2.1. Material, Equipment, Chemical

Plant material: *Gardenia jasminoides* Ellis. was collected in April 2022 at Thanh Luong commune, Thanh Chuong district, Nghe An province. Samples were separated from seeds and pods, transferred to a sealed chamber of the Memmert VO200 (Memmert, Berlin, Germany) at 45°C, 10mbar, and dried until the moisture content was 10%. And then crushed by hammer mill with a sieve of 60 Mesh to obtain samples of *Gardenia jasminoides* Ellis. powder. After that, samples were stored in a sealed bag to avoid hygroscopic phenomena during the research.

Millettia dielsiana Harms.: samples after being cleaned, separated, removed impurities, sliced thin. *Lycopodium cernuum* L.: samples including stems, roots, and leaves, after preliminary treatment, washed, and chopped. Then, two samples were transferred to a sealed chamber of the vacumn dryer with pump mode: pressure 10 mbar, temperature 40 - 45°C, dried until the moisture content reached 10% and then crushed by hammer mill with a sieve of 60 Mesh to obtain powder.

Chemicals: *n*-hexane (China, 99%), Dichloromethane (China, 99%), ethyl acetate (China, 99%), H_2SO_4 (China, 98%), ethanol (China, 99%). Silicagel 60: 0.04 - 0.06mm (Merck), thin plate TLC Silicagel 60 F_{254} (Merck), alcohol 70^0.

Equipment:: NMR spectroscopy was measured in solvent DMSO-d_6 on the Bruker Avance machine (Brucker, Berlin, Germany) at frequencies of 600MHz for ^{1}H-NMR and 150MHz for ^{13}C-NMR at the Institute of Chemistry, Vietnam Academy of Science and Technology.

2.2. Research some pharmaceutical substances presented in *Gardenia jasminoides* Ellis. by isolation using column chromatography

300g samples of *Gardenia jasminoides* Ellis. powder were extracted with EtOH 70° for 24 hours (3 times). Filter the extract, distillation to recover the solvent under reduced pressure to obtain crude EtOH extract (60.2g). Distribute extraction with *n*-hexane and EtOAC, respectively, obtained n-hexane extract (11.6g) and EtOAc extract (10.8g). The EtOAc extract was subjected to silica gel column chromatography, using gradient solvent with increasing polarity from *n*-hexane to EtOAc, MeOH to obtain 8 fractions (GE1~GE8).

The fraction GE4 (0.7g) was fractionated by silica gel column chromatography, with increasing polarity from *n*-hexane to MeOH, obtained 3 fractions (GE4.1~ GE4.3). Sub-fraction GE4.2 (461,2mg) was further purified by silica gel column chromatography, (CH_2Cl_2-MeOH, 100/0 - 80/20 *(v/v)*) yielding three fractions with symbols from GE4.2.1 to GE4.2.3. Sub-fraction GE4.2.3 (141,7mg) was purified by Sephadex LH-20 column, using gradient solvent (CH_2Cl_2/MeOH 1/9) to obtain 2 fractions: GE4.2.3.1 and GE4.2.3.2. Recrystallizing sub-fraction GE4.2.3.1 and eluting by MeOH solvent to obtain compound **GJE2** (112.3mg).

Sub-fraction GE7 (1,43g) was further purified by increasing polarity (CH_2Cl_2-MeOH, 100/0 - 70/30 *(v/v)*) yielding four fractions (GE7.1 to GE7.4). Sub-fraction GE7.3 (512,3mg) was purified by Sephadex LH-20 column, and eluted by 100% MeOH, to obtain 3 fractions from GE7.3.1 to GE7.3.3. Sub-fraction GE7.3.2 (431,6mg) was purified by Sephadex LH-20column, eluted by 100% MeOH, to obtain 3 fractions from GE7.3.2.1 đến GE7.3.2.3. Sub-fraction GE7.3.2.3 was purified by Sephadex LH-20 column, using solvent (CH_2Cl_2/MeOH), recrystallizing and eluting in acetone to obtain compound **GJE3** (296.4mg).

2.3. Process of production of instant tea

Millettia dielsiana Harms. powder and *Lycopodium cernuum* L. powder were mixed with *Gardenia jasminoides* Ellis. powder at a ratio shown in Table 1. After mixing, the medicinal mixture was extracted by the alcohol-water solvent and then sublimed by Lyovapor™ L300 freeze-drying machine (BUCHI, BÜCHI Labortechnik AG, Switzerland) to not more than 5% moisture content, added galactose, created seeds and packed, preserved during the use according to the Figure 1.

Table 1. The ratio of material mixture [6]

No.	Material	Unit	Weight
1	*Gardenia jasminoides* Ellis.	g	900
2	*Millettia dielsiana* Harms.	g	50
3	*Lycopodium cernuum* L.	g	50

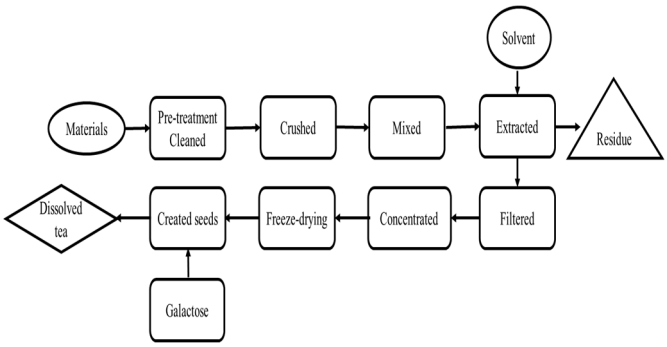

Figure 1. The process of making instant tea from *Gardenia jasminoides* Ellis.

Analytical method for quality indicators of instant tea

- Moisture content was determined by drying to constant weight.

- Ash content determined according to TCVN 5611-1991.

- The heavy metals content was determined by atomic absorption spectroscopy (AAS).

3. RESULTS AND DISCUSSION

3.1. Some pharmaceutical substances presented in *Gardenia jasminoides* Ellis.

Cardiovascular disease is the leading cause of morbidity and mortality worldwide, affecting the health, lives and activities of patients. In the United States, an estimated 62

million people have cardiovascular disease and 50 million have high blood pressure. According to WHO statistics, in 2000, about 946,000 deaths were due to cardiovascular disease, accounting for 39% of all deaths in the US [7]. According to statistics from the Vietnam Heart Association, cardiovascular diseases claim about 200,000 lives every year, and 1 in 3 adults is at risk of developing cardiovascular disease. The causes of this disease often depend on the patient's lifestyle habits, such as smoking, being overweight, stress, having hypercholesterolemia, having high blood pressure, *etc* [8].

Many researchs have been published around the world proving the biological activity of *Gardenia jasminoides* Ellis. In particular, the compound genipin has the effect of significantly reducing the increase in serum aminotransferase activity and lipid peroxidation; in addition to its good hepatoprotective ability [9], Geniposide and aglycone Genipin have anti-inflammatory effects [10], antioxidant and antiplatelet effects, improve thrombosis [11], and embolism, and *Gardenia jasminoides* Ellis.'s anti-inflammatory role may help prevent vascular diseases like fibrosis and atherosclerosis [12].

During the research, Geniposide and Genipin were found in the materials *Gardenia jasminoides* Ellis. used to make instant tea. The structures of these two compounds are demonstrated specifically by proton magnetic resonance spectroscopy and carbon magnetic resonance:

3.1.1. Substances GJE2

^{1}H-NMR (600MHz, $CDCl_3$): δ_H 3.183 (1H, m, H-1); 2.525 (1H, t, *J* = 8.4Hz, H-2); 4.816 (1H, dd, *J* = 12 - 5.4Hz, H-3); 7.523 (1H, s, H-4); 2.039 (1H, ddt, *J* = 9.6 - 1.8 - 1.2Hz, H-6); 2.858 (1H, ddt, *J* = 9.6 - 1.8 - 1.2Hz, H-6); 5.87 (1H, s, H-7); 3.734 (3H ,s, H-10); 4.269 (2H, d, *J* = 12.6Hz, H-11). ^{13}C-NMR (150MHz, $CDCl_3$): δ_C 36.07 (C-1); 48.10 (C-2); 96.37 (C-3); 152.59 (C-4); 110.72 (C-5); 39.02 (C-6); 130.78 (C-7); 142.15 (C-8); 168.03 (C-9); 51.33 (C-10); 61.27 (C-11).

Combining the above spectral data and comparing with the data published by Ryousuke *et al.* [13] the result allows to confirm the structure of GJE2 as Genipin.

3.1.2. Substances GJE3

^{1}H-NMR (600MHz, CD_3OD): δ_H 7.529 (1H, s, H-1); 5.181 (1H, d, *J* = 7,8Hz, H-3); 3.187 (1H, d, *J* = 7.8Hz, H-4); 2.828 (1H, dd, *J* = 16.2 - 8.4Hz, H-5); 5.819 (1H, s, H-8); 2.091 (1H, m, H-9); 2.735 (1H, t, *J* = 7.8Hz, H-9); 3.732 (3H, s, H-13); 3.869 (1H, d, *J* = 7.8Hz, H-21); 4.319 (1H, d, *J* = 14.4Hz, H-14); 4.726 (1H, d, *J* = 7.8Hz, H-16); 3.305 - 3.335 (1H, m, H-19); 4.194 (1H, dd, *J* = 12.6 - 1.8Hz, H-14); 3.395 (1H, m, H-22); 3.650 (1H, m, H-22). ^{13}C-NMR (150MHz, CD_3OD): δ_C 153.31 (C-1); 98.27 (C-3); 47.01 (C-4); 51.73 (C-5); 112.54 (C-6); 144.77 (C-7); 128.33 (C-8); 39.68 (C-9); 169.51 (C-10); 36.65 (C-13); 62.64 (C-14); 100.34 (C-16); 78.35 (C-18); 71.52 (C-19); 74.84 (C-20); 77.83 (C-21); 61.40 (C-22).

Combining the above spectral data and comparing with the data published by Lelono *et al.* [14] the result allows to confirm the structure of GJE3 as Geniposide.

The structure of Genipin and Geniposide has been established using spectral data. That further establishes the existence of two priceless substances that aid in the treatment of cardiovascular conditions including atherosclerosis contained in material *Gardenia jasminoides* Ellis. Atherosclerosis can affect all large and medium arteries, including the coronary, carotid, and cerebral arteries. It includes many factors, including factors such as high blood pressure, high cholesterol, and diabetes [15].

3.2. Instant tea products from *Gardenia jasminoides* Ellis.

In the preparation of instant tea, to increase the therapeutic effect, the authors collaborated *Gardenia jasminoides* Ellis. with *Millettia dielsiana* Harms. and *Lycopodiella Cernua* L. with ratio shown in Table 1.

Lycopodiella Cernua L. is an herb with diverse biological activities: bitter, spicy, cold, and non-toxic. *Lycopodiella Cernua* L. has the effect of the effect of nourishing blood, promoting blood circulation in the brain, protecting the nervous system, improving sleep quality and memory [16]. Especially, Huperzine A is found in high concentrations in the plant's composition [17]. This substance can easily penetrate the blood-brain barrier and act directly on brain neurons [18]. Huperzine A enhances neurotransmitters, prevents the formation of plaques and plexuses in the brain, and nourishes brain cells, to support *Gardenia jasminoides* Ellis, to avoid atheroma and prevent cerebral infarction [19]. To increase blood circulation, a small amount of *Millettia dielsiana* Harms. is added. This plant has a bitter taste, is neutral, has the effect of tonic blood on the blood meridians, and enhances the excretion of water and salt, thereby helping to lower blood pressure in cases of high blood pressure [20].

The conditions for extraction of the raw material mixture were investigated as Table 2.

Table 2. Survey results on the influence of solvent concentration on the extraction process

Solvent EtOH	Material weight (g)	Extraction solvent volume (L)	Extract volume (L)	Total Extraction (g)	Extraction efficiency (%)
90°	1000	4	3.3	257	25.7
80°	1000	4	3.3	268	26.8
70°	1000	4	3.3	287	28.7
60°	1000	4	3.2	271	27.1
50°	1000	4	3.2	243	24.3

In the survey Table 2, it was shown that the extraction of the raw material mixture using an ethanol solvent in the range of 60° to 80° gave the highest extraction yield. The color of the extract became darker with increasing ethanol concentration.

The solvent distillation process in extracts with 60° and 50° alcohols is more difficult than using 70° alcohol. When distilling the solvent recovery type for extracts using 60° and 50° alcohols as extraction solvents, the extract is frequently foamed, reducing extraction efficiency.

Therefore, in the survey conditions, the selection of 70% alcohol is the most optimal, and the extraction of the raw material mixture achieved an efficiency of 28.7%.

Table 3. Survey results on the influence of the solvent/dry material mixture ratio

Ratio of solvent/ materials (L/kg)	Material weight (g)	Extraction solvent volume (L)	Extract volume (L)	Total Extraction (g)	Extraction efficiency (%)
2/ 1	1000	2	1.5	224	22.4
3/ 1	1000	3	2.4	264	26.4
4/ 1	1000	4	3.3	291	29.1
5/ 1	1000	5	4.3	302	30.2
6/ 1	1000	6	5.4	308	30.8

The results of the investigation on the influence of the extraction solvent/materials mixture ratio shown in Table 3. When performing the extraction process with the ratios of 2/1 and 3/1, the extraction efficiency was low. Because the extraction process was not thorough, many pharmaceutical substances were still in the medicinal residues. When increasing the ratio to 6/1 L/kg, the extraction process takes place quickly, thoroughly, and with high efficiency. However, using a large amount of solvent will increase cost, prolong solvent removal time, and yield more extract. When surveyed with the ratio of 4 liters per kilogram, the extraction efficiency was 29.1%; the difference was not significant compared to when using the ratios of 5 liters per kilogram and 6 liters per kilogram, but it was significantly reduced. Obtain the recovery time. Therefore, choose a solvent/mixture ratio of 4L/kg to continue using in the extraction process.

Table 4. Results of the investigation of the effect of temperature on the extraction efficiency

Extraction temperature (°C)	Material weight (g)	Extraction solvent volume (L)	Extract volume (L)	Total Extraction (g)	Extraction efficiency (%)
80	1000	4	3.2	256	25.6
70	1000	4	3.3	268	26.8
60	1000	4	3.3	289	28.9
50	1000	4	3.2	251	25.1
40	1000	4	3.2	247	24.7

The results of the investigation of the effect of the extraction temperature on the extraction process and the formation of the raw material mixture shown in Table 4.

When performing the extraction process at a temperature of 40°C to 50°C, the obtained extract has a bright color. However, because the extraction efficiency of the raw material mixture is not high, it is possible that the extraction process at this temperature threshold does not take place thoroughly. The implementation at the threshold of 70°C shows that the extraction process takes place faster. However, the evaporation time is slow, the extraction efficiency is low, and the color of the extract is darker than using the lower temperature. It is likely that due to the influence of high temperatures, some compounds are plasticized and hinder the evaporation of alcohol-based solvents. Therefore, 60°C is selected as the extraction temperature for the product preparation process.

The results from Table 5 shown that, when choosing the ratio of solvent/ materials to be 4L/1kg to investigate the extraction efficiency, it showed that the extraction volume decreased gradually after each extraction time, the third time efficiency decreased significantly.

Table 5. Survey results on the effect of extraction times per batch on process efficiency

Time for extraction	1	2	3
Extraction solvent volume (L)	4	3.3*	3.2*
Extraction volume (L)	3.3	3.2	3.5
Extraction (g)	293.6	71.8	1.2
Extraction efficiency (%)	29.36	7.18	0.012

Note: *: further solvents

Although theoretical basis shows that the longer the extraction time, the higher the extraction efficiency will be. But only at a certain point when the process reaches equilibrium, the extraction efficiency will not increase anymore and it may also be influenced by temperature, which produces some chemical changes of the extracted substances, this problem also depends a lot on the nature of each plant. Therefore, only 2 extractions may be needed to optimize the process, time and cost in the preparation process.

Table 6. Moisture and ash content of instant tea samples

Targets	Measurement times			Average	SD (%)	RSD (%)	TCVN 9739:2013 ISO 6079:1990
	1	2	3				
Moisture (%)	3.76	3.79	3.65	3.73	0.07	1.97	≤ 6.0
Ash (%)	10.42	10.51	10.45	10.46	0.05	0.44	≤ 20.0

The results of the moisture and ash content of instant tea samples from *Gardenia jasminoides* Ellis. mixed with *Millettia dielsiana* Harms. and *Lycopodium cernuum* L. The results shown that the instant tea sample has a moisture content of 3.73% and total ash of about 10.46%. The results reached the requirements of TCVN 9739:2013 and ISO 6079:1990 for solid instant tea which require less than 6% moisture content and less than 20% total ash. The heavy metal indicators (Cd, Pb and Hg) in instant tea are all below the detection threshold compared with QCVN 8-2:2011/BYT on heavy metal standards for dietary supplements. The permissible limit for heavy metals is Cd 1.0mg/kg; Pb 3.0mg/kg; and Hg 0.1mg/kg. The results showed that the instant tea sample was prepared from *Gardenia jasminoides*

Ellis. combined with *Lycopodium cernuum* L. and *Millettia dielsiana* Harms. and met the allowable limit of heavy metal content.

4. CONCLUSION

From the sample *Gardenia jasminoides* Ellis. was collected in Thanh Luong commune, Thanh Chuong district, Nghe An province, created the extract and determined the presence of the compounds Genipin and Geniposide in this sample. In addition, the extraction process was optimized to create an extract of the mixture of ingredients and successfully prepare instant tea from *Gardenia jasminoides* Ellis. and other medicinal herbs such as *Millettia dielsiana* Harms. and *Lycopodium cernuum* L.at the condition: 70% ethanol solvent, solvent/material ratio is 4L kg^{-1}, extraction temperature 60°C with 2 time extraction. The instant tea products have physicochemical criteria: the moisture content reached 3.73% and the ash level reached 10.46%. The content of heavy metals included Cd, Pb and Hg were not detected in the instant tea samples. The results of this study pave the way for further studies on the use of magnolia to create products related to cardiovascular diseases.

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