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The Stem Components and Antitumor Activities of Three Medicinal Herbal Plants

Shiting Hong,[1,#] Wan Adibah Wan Mahari,[2,#] Rock Keey Liew,[3,#] Guanyan Li,[1] Xiaochen Yue,[1,*] Xiangmeng Chen,[1,*] Haiping Gu,[1] Wanxi Peng[1,*] and Yuli Dang[1,*]

Abstract

Study on the stem chemical composition and in vitro anti-tumor activity of three perennial medicinal herbaceous plants, namely *Begonia palmata*, *Rubia ovatifolia* and *Boehmeria nivea*. Extract and separate ethanol extracts from three plants, systematically and deeply identify and analyze the physicochemical properties of plant ethanol extracts using Gas chromatography-mass spectrometry (GC-MS) and Ultra High-Performance Liquid Chromatography-Tandem Mass Spectrometry (UPLC-QTOF-MS) methods, and evaluate the in vitro anti-tumor activity of compounds using Cell viability was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay colorimetric method. GC-MS detected 28 compounds in *Begonia palmata*, 23 compounds in *Rubia ovatifolia*, and 24 compounds in *Boehmeria nivea*. The killing rates of three plant summer stem extracts on NCI-H1703 lung squamous cell carcinoma cells were ranked from high to low as *Begonia palmat* (52.77%) > *Rubia ovatifolia* (51.26%) > *Boehmeria nivea* (50.55%). The findings of this study not only enhance the chemical database of three plant stem metabolites, but also confirm their anti-tumor material basis, and provide candidate compounds and network pharmacological target reference for the development of new plant-derived anti-tumor drugs.

Keywords: *Begonia palmata*; *Rubia ovatifolia*; *Boehmeria nivea*; Gas chromatography-mass spectrometry; Lung squamous cell carcinoma.
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1. Introduction

Cancer poses a significant threat to human health worldwide. According to the global cancer data statistics in 2022, Lung cancer (LC) is the primary contributor to both the incidence rate and mortality associated with cancer in 2022, accounting for 12.4 % of all cancers in the world, With the trend of tobacco epidemic, it indicates that the overall burden of LC will be higher in the next few decade.[1] The combination of natural products with other anti-tumor agents has strong prospects, and plants play a crucial role in it.[2,3] In China, reports of plants being used to treat cancer are not uncommon. The research progress on anti-tumor effects of plant drugs has shown that the effective medicinal ingredients in plant extracts are commonly used sources of anti-tumor drugs.[4-6] In traditional medicine systems (TMS), products containing plants, other plant materials or tissues as active ingredients are referred to as herbal medicines and used as complementary or alternative medicines, and their safety and efficacy in treating human life and health are widely recognized.[7]

Begonia palmata D. Don is a rhizomatous plant of the Camellia genus in the Rosaceae family. *Rubia ovatifolia Z. Ying Zhang* is a plant of the Rubiaceae family and the Rubiaceae genus. *Boehmeria nivea (L.) Gaudich.* is a plant of the nettle genus in the Urticaceae family. All three are perennial medicinal herbs.[8] Modern pharmacological research has shown that the active ingredients of ramie, which

[1] *College of Forestry, College of Science, College of Landscape Architecture and Art, Henan Agricultural University, Zhengzhou, 450002, China*
[2] *Higher Institution Centre of Excellence (HICoE), Institute of Tropical Aquaculture and Fisheries, University Malaysia Terengganu, Kuala Nerus, Terengganu, 21030, Malaysia*
[3] *Center for Global Health Research (CGHR), Saveetha Medical College, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, 602105, India*
[#] *These authors contributed equally to this work.*
**Email:* yuexiaochen95@163.com (X. Yue); xmchen0610@163.com (X. Chen); wanxipeng2024@163.com (W. Peng); dangyuli2020@163.com (Y. Dang)

has the effect of clearing heat and detoxifying, have clear anti-tumor activity.[9,10] *Rubia ovatifolia* as a traditional Chinese medicine and *Begonia palmata* have a diverse range of pharmacological effects such as anti-inflammatory, antibacterial,[11,12] anti-tumor and immune protection.[13] Modern research mostly focuses on the whole grass or root parts of medicinal plants,[14,15] plant stems are also important parts of traditional Chinese medicine, such as Dendrobium officinale.[16] However, there are few reports on the stem composition and anti-tumor activity of medicinal herbaceous plants. Under high temperature, high humidity, and strong light conditions in summer, the biomass and active ingredient content of herbaceous and vine stems are relatively high. The traditional harvesting period for most medicinal plants is concentrated in summer and autumn.[17] Moreover, studies have shown that in terms of medicinal parts, herbaceous plants utilize more root and stem medicinal plants.[18] Therefore, to delve deeper into the chemical constituents and anti-tumor activities of the stems of three perennial medicinal herbs, *Begonia palmata*, *Rubia ovatifolia* and *Boehmeria nivea* in summer, this paper studied the stems of these plants, focusing on the compounds related to anti-tumor activity, and discussed the potential mechanism of promoting anti-tumor effect.

2. Materials and methods

2.1 Instruments and materials

High speed universal crusher (FW-400A, Beijing Zhongxing Weiye Instrument Co., Ltd.); 120 target screening; Intelligent digital multifunctional oil-water bath pot (H//SH-3L/5L, Zhengzhou Boke Instrument Equipment Co, Ltd.), thermal desensitization and cracking gas chromatography-mass spectrometry instrument (Agilent Technologies Co., Ltd.); Orbitrap ExplorisTM 120 liquid chromatography-mass spectrometer (Thermo Fisher Scientific); Carbon dioxide incubator (QB-80, Boko); Electric hot air drying oven (101-1A, Xinyu Instrument): electric constant temperature incubator (FXB303-, standing instrument); Medical low-temperature storage box (-80 ℃) (BDF-86V348, Boko); LED digital display heating metal bath (HB120-S, Dalong); Biosafety Cabinet (BSC-1500IIB2-X, Boko); Flow cytometry (FACSCaliburTM, BD); Desktop low-speed centrifuge (TD-4C, Boko); Enzyme linked immunosorbent assay analyzer (DR-200Bc, Huaweilang instrument); Ultra clean workbench (SW-CJ-2FD, Shanghai DuTe Scientific Instrument Co., Ltd.).

Serum free cell cryopreservation solution (C40100, Xinsaimei) and premium fetal bovine serum (E600001-0500, Shenggong); PBS (G0001，Servicebio); Pancreatic enzyme (G4004, Servicebio); RPMI-1640 (PM150110, Pronose); MTT Cell Proliferation and Cytotoxicity Test Kit (C0009M, Biyuntian). NCI-1703 human lung squamous cell carcinoma cells, from Wuhan Ponosi Life Technology Co., Ltd.

Begonia palmata was collected on September 2, 2021, near the hemlock in Qihe Forest Farm, Lushi County, Sanmenxia City, Henan Province; *Rubia ovatifolia* was harvested from the northern part of Boshan Forest Farm in Queshan County, Zhumadian City, Henan Province on September 2, 2021; *Boehmeria nivea* was collected on September 5, 2021 from Yihezhai Forest District, Biyang County, Zhumadian City, Henan Province. After sampling, the samples were sent back to the laboratory for separation according to the leaf, stem and root parts. The stems were selected for cleaning, air drying, freeze-drying, crushing, sieving, and making into powder samples that were packaged for testing purposes.

2.2 Experimental methods

2.2.1 Extraction and separation of plant samples

Weigh 10g of three types of plants, *Begonia palmata*, *Rubia ovatifolia* and *Boehmeria nivea* summer stem powder samples were placed in flat bottomed flasks and 300 mL of anhydrous ethanol was added. The flasks were sealed with plastic wrap and soaked at room temperature for 8 hours. The water bath was set to a temperature of 78 ℃ and heated for 5 hours before filtration. The filtered extract was then subjected to rotary evaporation at 45 ℃ and 0.01 MPa to a volume of 10ml to obtain the plant summer stem ethanol extract, which was stored in a refrigerator at 4 ℃ and shaken well before use for gas chromatography-mass spectrometry (GC-MS), MTT assay, and ultra high performance liquid chromatography-tandem mass spectrometry (UPLC-QTOF-MS) detection.

2.2.2 GC-MS detection

Regarding *Begonia palmata*, GC-MS detection of ethanol extracts from summer stems of *Rubia ovatifolia* and *Boehmeria nivea* plants.

Gas chromatography condition setting: Elastic quartz capillary column HP-5MS (60 m × 250 μm × 0.25 μm); Injection port: 280 ℃; Injection volume: 1 μL, without diversion; Carrier gas: helium gas (99.99 %); Column flow rate: 1.5 mL/min; Heating program: The initial temp is 50 ℃, and it is heated to 250 ℃ at a rate of 8 ℃/min. After 2 minutes, it is further heated to 280 ℃ at a rate of 5 ℃/min and left for 5 minutes.

Mass spectrometry condition setting: EI ion source; Ionization voltage 70eV; Ion source temp: 230 ℃; Quadrupole rod temp: 150 ℃; Scanning range: 30-600 amu; Mass spectrometry library: NIST08.

Mass spectrometry scanning was performed on each peak in the obtained total ion chromatogram to obtain corresponding mass spectra. These spectra were compared and analyzed with the mass spectra of reference materials in the NIST08 database to confirm the summer stem components of *Begonia palmata*, *Rubia ovatifolia*, and *Boehmeria nivea*. The relative abundance of the compounds corresponding to each chromatographic peak was quantified by area normalization method.

2.2.3 Cytotoxicity assay

Using MTT assay,[19-21] NCI-H1703 lung squamous cell carcinoma was used as a blank control group to determine the growth inhibition rate of three different summer stem ethanol

extract samples, *Begonia palmata*, *Rubia ovatifolia*, and *Boehmeria nivea*. Three samples were sterilized by UV irradiation for 30 minutes. The recovered cells were cultured under conditions of 37 ℃ and 5 % CO_2. Different cells in logarithmic phase were collected and counted to prepare a cell suspension (5 × 104 cells / mL, 100 μL / well) was seeded in a 96 well microplate and cultured for 24 hours. Add the prepared test drug to the culture plate. Continue to cultivate for 24 hours. Add 10 μL of MTT solution to with a concentration of 5 mg/mL each well and continue incubating in the incubator for 4 hours. Discard the supernatant, add 100 μL of Formazan solution to each well, mix well and incubate at 37 °C for 3-4 hours. MTT assay The succinate dehydrogenase in the mitochondria of living cells can reduce the yellow soluble MTT solution to a purple crystal formazan that is insoluble in water under a common optical microscope, while dead cells do not have this function.[21] The absorbance (A) of each well was based on ELISA Reader at 570 nm, and calculate the cell killing rate as (1-A experimental group/A control group) × 100 %.

2.2.4 UPLC-QTOF-MS detection

UPLC-QTOF-MS detection of ethanol extract from summer stem parts of *Begonia palmata*. Chromatographic condition setting: chromatographic column 1.8 um (2.1 × 100 mm); Column temperature: 40 ℃; Injection volume: 1 μ L; Mobile phase : positive ion mode, Mobile phase A: formic acid (0.10 %); mobile phase B: acetonitrile, formic acid (0.10 %), flow rate: 0.3ml/min. Elution program gradient: [0 min, 5 %], [2 min, 5 %], [25 min, 100 %], [25.1 min, 5 %], [35 min, 5 %].

Mass spectrometry condition setting: ESI (+/-) positive and negative ion mode; Voltage: 3.5KV; Temperature of ion transport tube; 350 ℃; Sheath gas flow rate: 4.82 L/min, auxiliary sheath gas flow rate; 9.53 L/min; The scanning quality range is 50-1200 m/z.

Process and analyze the detection data of UPLC-QTOF-MS, calculate the common peaks and relative contents of each component in the UPLC-QTOF-MS graph.

2.2.5 Target acquisition and construction of intersection targets

Screen the effective active components of UPLC-QTOF-MS detection data, identify the target proteins corresponding to these active components, and confirm the relevant target genes using Pubchem database and SwissTarget Prediction target database. Search for Non-Small Cell Lung Cancer (NSCLC) related data in the GeneCards database to obtain lung cancer related target information. Cytoscape 3.8.0 software was used to create the correlation network diagram of active ingredient-target-lung squamous cell carcinoma cells, and screen for the main components for lung cancer treatment.

3. Results and analysis

3.1 GC-MS results and analysis

The GC-MS total ion diagrams of summer stem ethanol extracts from *Begonia palmata*, *Rubia ovatifolia*, and *Boehmeria nivea* are shown in Fig. 1, The test results of extract compounds are shown in Table 1. Through analysis, a total of 64 peaks were detected in the summer stem of *Begonia palmata*, and 28 compounds were identified; 61 peaks were detected in the stem of *Rubia ovatifolia* during summer, and 23 compounds were identified; 48 peaks were detected in the stem of *Boehmeria nivea* during summer, and 24 compounds were identified.

Table 1: GC-MS analysis of summer stem ethanol extract compounds from Begonia palmata, Rubia ovatifolia, and Boehmeria nivea.

No.	Name	Relative content of ethanol extract from summer stems (%)		
		Begonia palmata	*Rubia ovatifolia*	*Boehmeria nivea*
1	E-10, 13, 13-Trimethyl-11-tetradecen-1-ol acetate	0.78	-	-
2	2-Octen-1-ol, 3, 7-dimethyl-, isobutyrate, (Z)-	0.68	0.75	0.60
3	2, 4, 6-Cycloheptatrien-1-one, 3, 5-bis-trimethylsilyl-	18.05	-	-
4	2, 2-Dimethyl-6-methylene-1-[3, 5-dihydroxy-1-pentenyl] cyclohexan-1-perhydrol	10.73	21.2	7.45
5	Triisobutyl (3-phenylpropoxy) silane	1.47	0.70	0.92
6	2-Aminobenzoxazole, 2TBDMS derivative	1.45	-	-
7	1, 3-Propanediol, TBDMS derivative	0.27	-	0.26
8	1, 3-Propanediol, TMS derivative	0.41	20.86	-
9	2-Butyloxycarbonyloxy-1, 1, 10-trimethyl-6, 9-epidioxydecalin	0.11	-	-
10	Phenol, 3, 5-bis (1, 1-dimethylethyl)-	5.19	-	1.37
11	4, 5-Dihydrooxazole-5-one, 4-chloromethylene-2-phenyl-	0.29	-	0.55

No.	Name	Relative content of ethanol extract from summer stems (%)		
		Begonia palmata	*Rubia ovatifolia*	*Boehmeria nivea*
12	3-Phenyl-3-pentanol	0.68	-	-
13	Hexadecanoic acid, (3-bromoprop-2-ynyl) ester	0.37	-	-
14	1-Butanone, 2-hydroxy-1-phenyl-	1.66	-	-
15	Heptasiloxane, 1, 1, 3, 3, 5, 5, 7, 7, 9, 9, 11, 11, 13, 13-tetradecamethyl-	1.14	-	-
16	Tetradecane, 1-chloro-	1.44	-	-
17	tert-Hexadecanethiol	7.58	0.45	0.53
18	Dodecane, 1-fluoro-	10.21	1.70	0.87
19	Octadecane, 1-chloro-	1.04	-	-
20	Cyclopentasiloxane, decamethyl-	0.20	-	-
21	2, 5-Octadecadiynoic acid, methyl ester	0.22	0.66	2.29
22	9, 12-Octadecadienoic acid (Z, Z)-	4.00	0.95	0.71
23	Hexadecanoic acid, ethyl ester	12.77	-	-
24	9, 12-Octadecadienoyl chloride, (Z, Z)-	9.60	3.89	15.01
25	E-2-Hexenyl benzoate	1.00	-	-
26	Tetraethyl silicate	0.52	-	-
27	1-Propanone, 3-chloro-1-phenyl-	8.03	-	4.46
28	Phenyl tert-butyl ketone	0.10	-	-
29	Z-10-Methyl-11-tetradecen-1-ol propionate	-	2.92	4.29
30	.beta.-D-Mannofuranoside, farnesyl-	-	14.41	-
31	Butyl 6, 9, 12-hexadecatrienoate	-	3.99	-
32	Phthalic acid, butyl oct-3-yl ester	-	10.61	16.21
33	1-Heptatriacotanol	-	4.74	-
34	Geranyl isovalerate	-	1.14	-
35	1-Penten-3-one, 1-(2, 6, 6-trimethyl-1-cyclohexen-1-yl)-	-	1.63	-
36	Albuterol	-	0.11	-
37	4-Cyanothiophenol	-	1.71	-
38	Dasycarpidan-1-methanol, acetate (ester)	-	0.22	-
39	Decanoic acid, 3-hydroxy-, methyl ester	-	0.78	-
40	Vitamin E	-	4.82	-
41	5-Amino-1-benzoyl-1H-pyrazole-3, 4-dicarbonitrile	-	-	0.70
42	17-Octadecynoic acid, methyl ester	-	-	0.36
43	2-(tert.-Butyldimethylsilyl)oxybenzylidene acetophenone	-	-	0.18
44	Undec-10-ynoic acid, tetradecyl ester	-	-	0.37
45	[2-(5-Hydroxypent-2-ynyl)-3-oxocyclopentyl]thioacetic acid, S-t-butyl ester	-	0.59	-
46	8-Bromooctanoic acid, ethyl ester	-	-	3.36
47	Palmitoleic acid	-	-	0.87
48	5, 7-Dodecadiyn-1, 12-diol	-	1.09	0.44
49	Benzoyl isothiocyanate	-	-	2.82
50	(2R, 3R, 4aR, 5S, 8aS)-2-Hydroxy-4a,5-dimethyl-3-(prop-1-en-2-yl)octahydronaphthalen-1(2H)-one	-	-	35.07
51	[2-(5-Hydroxypent-2-ynyl)-3-oxocyclopentyl]thioacetic acid, S-t-butyl ester	-	-	0.31

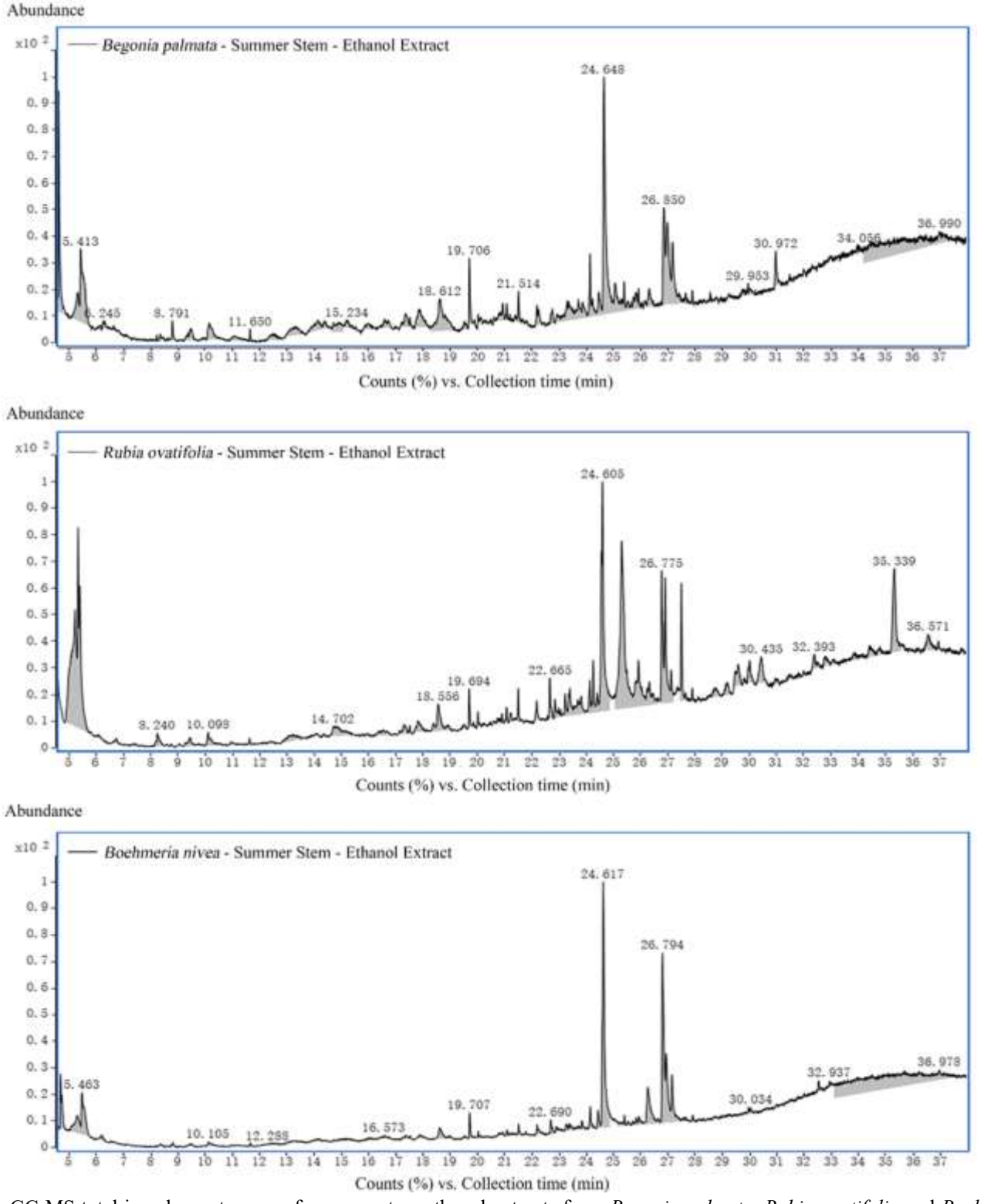

Fig. 1: GC-MS total ion chromatogram of summer stem ethanol extracts from *Begonia palmata*, *Rubia ovatifolia* and *Boehmeria nivea*.

Fig. 2 shows Begonia palmata, Rubia ovatifolia and Boehmeria nivea summer stem ethanol extracts Venn diagram, Table 2 classifies the chemical components in the ethanol extracts of the three plants according to their organic compound properties and calculates their relative percentage content. According to GC-MS data identification and analysis, among the ethanol extracts of summer stems from three plants, Begonia palmata has the richest variety of active ingredients, while Rubia ovatifolia has the least variety of active ingredients. There are 8 common compounds in the ethanol extracts of three plant summer stems, among which 9 and 12 are common compounds in the ethanol extracts of Begonia palmata summer stem and Rubia ovatifolia summer stem, and Boehmeria nivea summer stem, respectively, while 11 are common compounds in the ethanol extracts of Rubia ovatifolia summer stem and Boehmeria nivea summer stem.

Table 2: Chemical composition categories and relative contents of ethanol extracts from summer stems of *Begonia palmata*, *Rubia ovatifolia*, and *Boehmeria nivea*.

Ethanol extracts / Type of compounds	Summer stems - relative content (%)		
	Begonia palmata	*Rubia ovatifolia*	*Boehmeria nivea*
Alcoholic	8.95	41.66	1.24
Ester	16.45	21.66	30.60
Phenolic	5.19	6.54	1.37
Acid	4.00	0.95	1.59
Ketone	27.84	1.63	39.71
Terpenes	10.73	21.27	7.45
Acyl chlorides	9.60	3.89	15.01
Heterocyclic	1.73	-	1.25
Halogenated hydrocarbon	12.69	1.71	0.87
Organic silicon	2.81	0.70	0.92

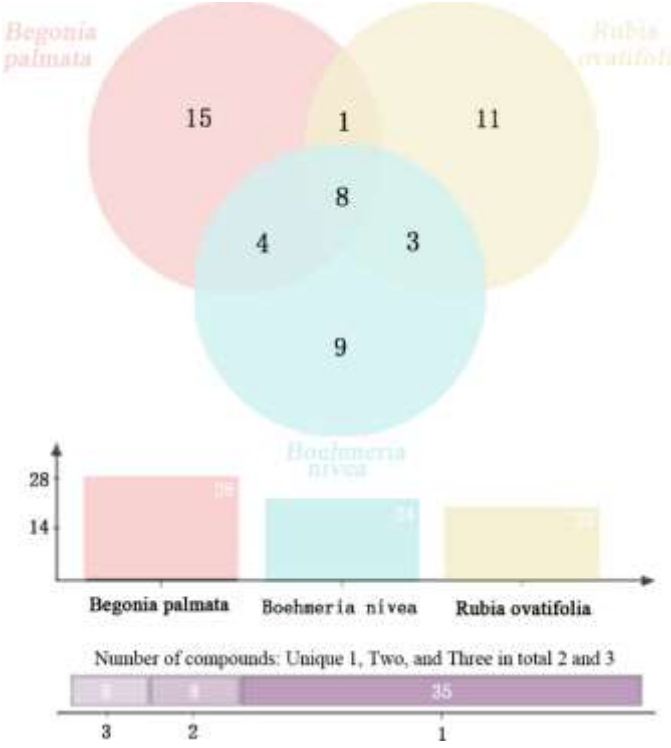

Fig. 2: Venn diagram of ethanol extracts from summer stems of *Begonia palmata*, *Rubia ovatifolia*, and *Boehmeria nivea*.

The relative content of ketone compounds in the ethanol extract of Begonia palmata summer stems is the highest, and the active ingredients include: 2, 4, 6-Cycloheptatrien-1-one, 3, 5-bis-trimethylsilyl-(18.05 %), 1-Propanone, 3-chloro-1-phenyl-(8.03 %), 1-Butanone, 2-hydroxy-1-phenyl-(1.66 %) and Phenyl tert-butyl ketone (0.10 %). Rubia ovatifolia summer stem ethanol extract has the highest relative content of alcohol compounds, and the active ingredients include: 1, 3-Propanediol, TMS derivative (20.86 %), beta.-D-Mannofuranoside, farnesyl- (14.41 %), 1-Heptatriacotanol (4.74 %), 5, 7-Dodecadiyn-1, 12-diol (1.09 %), tert-Hexadecanethiol (0.45 %) and Albuterol (0.11 %). The relative content of ketone compounds in Boehmeria nivea summer stem ethanol extract is the highest, and the active ingredients include: (2R, 3R, 4aR, 5S, 8aS)-2-Hydroxy-4a, 5-dimethyl-3-(prop-1-en-2-yl)octahydronaphthalen-1 (2H)-one (35.07 %), 1-Propanone, 3-chloro-1-phenyl- (4.46 %) and 2-(tert.-Butyldimethylsilyl) oxybenzylidene acetophenone (0.18 %).

By studying Begonia palmata, The GC-MS analysis of

ethanol extracts from summer stems of Rubia ovatifolia and Boehmeria nivea shows that all three plants have abundant active ingredients in their summer stems. Among them, Begonia palmata has the most compound types, followed by Boehmeria nivea, and Rubia ovatifolia has the least. Therefore, MTT assay was used to evaluate the proliferation inhibition rate of three summer stem ethanol extracts on tumor cells.

3.2 Cytotoxicity assay results and analysis

Three sets of experimental control treatments were conducted on the summer stem ethanol extracts of Begonia palmata, Rubia ovatifolia, and Boehmeria nivea.[22] The corresponding cell killing rate was calculated based on the absorbance (A) of each well, and the experimental results were imported into GraphPadPrism for plotting (Fig. 3 and Table 3). The results showed that, the results of Begonia palmata, Rubia ovatifolia, and Boehmeria nivea showed significant differences relative to the CK group ($p < 0.0001$). The killing rates of summer stems of Begonia palmata, Rubia ovatifolia, and Boehmeria nivea on NCI-H1703 cells are shown in Table 3. The ethanol extracts of summer stems from different plants have significant differences in the killing rates of NCI-H1703 cells. The killing rates of summer stems of these three plants on NCI-H1703 lung squamous cell carcinoma cells are in the order of Begonia palmata (52.77 %) >Rubia ovatifolia (51.26 %) >Boehmeria nivea (50.55 %) from high to low. Among them, the stem part of Begonia palmata showed the highest cell killing rate in summer, indicating that Begonia palmata exhibited good cytotoxicity inhibition effects, while the inhibition results shown by Boehmeria nivea were relatively weak.

Based on the cytotoxicity test results of NCI-H1703 lung squamous cell carcinoma cells, The summer stem of Begonia palmata has the highest cell killing rate. Therefore, further UPLC-QTOF-MS analysis was conducted on the summer stem parts of Begonia palmata to explore the more abundant non-volatile active ingredients in Begonia palmata.

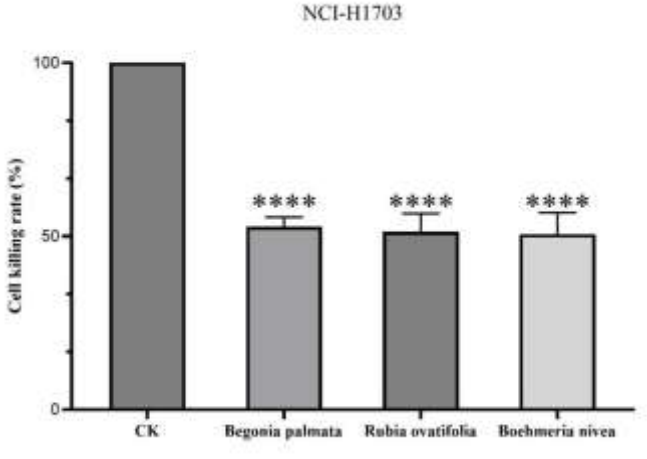

Fig. 3: Comparison of 24-hour changes in *Begonia palmata*, *Rubia ovatifolia*, and *Boehmeria nivea* cultured in NCI-H1703 cells (Note: Relative to the control group (CK), * $P < 0.05$; **** $P < 0.0001$).

Table 3: Cell toxicity results of ethanol extracts from summer stems of Begonia palmata, Rubia ovatifolia, and Boehmeria nivea.

Parts	NCI-H1703 cell killing rate (%)		
	Begonia palmata	*Rubia ovatifolia*	*Boehmeria nivea*
Summer stem	52.77	51.26	50.55

3.3 UPLC-QTOF-MS results and analysis

Place the ethanol extract of Begonia palmata summer stems into a UPLC-MS instrument to detect and identify the chemical components contained in the extract, and analyze and process the data results. As shown in Fig. 4, a total of 153 mass spectrometry peaks were detected, and 127 active chemical components were identified. Among them, the main active ingredients in the ethanol extract of Begonia palmata summer stems are shown in Table 4.

According to the UPLC-QTOF-MS data identification and analysis of Begonia palmata summer stems, the relative content of non-volatile active ingredients in Begonia palmata summer stems was classified and statistically analyzed, as shown in Fig. 5. Among all the chemical components of ethanol extract, esters have the highest content (38.90 %) with 23 types, while alcohols have the lowest content (0.06 %) with 2 types. And there are 2, 17, 11, 1, 3, 15, 15, 2, 6, 4, and 6 types of compounds including acids, phenols, ketones, aldehydes, quinones, terpenes, glycosides, amines, alkaloids, aromatics, and others. The content of esters is the highest, and the types of acids are the most abundant. The inhibitory effect of Begonia palmata summer stem ethanol extract on NCI-H1703 lung squamous cell carcinoma cells may be related to these substances.

Among these 127 non-volatile active ingredients, according to relevant literature searches, they play different roles in different fields such as biopharmaceutical, agriculture, and chemical production. These non-volatile active ingredients exhibit biological activities, including anti-cancer, anti-tumor, and anti-inflammatory properties. For example, Ajugasterone C has been proven to have ethnic pharmacological significance in the treatment of inflammatory diseases.[23] Wedeloactone has been found to induce apoptosis of prostate cancer cells by down-regulating PKCε, and its dose can attack and kill prostate cancer cells without affecting normal PrEC activity.[24] In other studies, Wedelolactone plays a crucial role in inflammatory responses by directly inhibiting IKK complexes to suppress LPS induced caspase-11 expression,[25] and has shown significant cytotoxicity to hepatocytes, breast cancer cells, and NK92-MI cells in some in vitro tissue culture experiments.[26-28] Moreover, a novel PLGA nanoparticles can be synthesized with NP to become a promising anti-cancer therapeutic strategy.[29]

Organic acids play an important role in antioxidant, antibacterial, anti-inflammatory, maintaining acid-base balance, and enhancing resistance.[30] The acid compounds

Table 4: Main active ingredients of Begonia palmata summer stem ethanol extract detected by UPLC-QTOF-MS.

No.	RT	Name	Score (%)	relative content (%)	Compound attribution
1	10.35	Wedelolactone	98.36	1.73	Coumarin lactone
2	22.18	Docosanic acid	95.76	0.03	Saturated fatty acids
3	5.47	Caffeic acid	97.02	0.31	Flavonoids
4	21.92	Montanic acid	97.02	0.03	Saturated fatty acids
5	1.48	Creatine	90.76	0.02	Amino acid derivatives
6	9.07	Xanthine	92.92	0.02	Purine alkaloids
7	10.22	Araloside A	96.21	0.49	Triterpenoid saponin
8	12.80	Caffeine	91.92	0.09	Purine alkaloids
9	10.47	Dimethyl sebacate	91.69	0.09	Esters
10	6.74	Phenol	97.97	1.11	Aromatic phenols
11	15.62	n-Decyl acetate	97.79	0.04	Esters
12	19.09	Elaidic acid	97.49	3.21	Unsaturated fatty acid
13	21.15	Erucic acid	94.46	0.01	Unsaturated fatty acid
14	10.35	Soyasaponin A5	94.08	0.03	Triterpenoid saponin
15	11.77	Asarumin B	98.81	0.69	Phenylpropanoids
16	20.62	Ethyl heptadecanoate	95.78	0.03	Esters
17	4.04	Uralenneoside	93.38	0.14	Glycosides
18	9.58	Dimethyl azelate	96.99	0.21	Esters
19	20.12	L-(-)-alpha-Monopalmitin	98.55	0.04	Monoacylglycerol
20	10.22	Tribulusamide A	98.50	0.87	Amide class
21	16.26	Alchorneine	97.46	0.03	Alkaloid
22	17.16	Bufadienolide	98.87	0.38	Cardiac glycosides
23	13.56	Gingerglycolipid C	90.89	0.15	glycolipid
24	12.15	Pterosin G	93.14	0.05	Sesquiterpenes
25	10.09	Munjistin	93.36	0.06	Anthraquinones
26	9.19	Acaciin	92.29	0.07	Flavonoid glycosides
27	12.80	Damascenine	97.66	0.10	Nitrogen-containing heterocycles
28	8.16	Cinchonic acid	96.82	0.21	quinolines
29	21.15	Arachidic acid	97.77	0.05	Saturated fatty acids
30	17.16	Abietic acid	93.68	0.03	Diterpenoid resin acids
31	11.25	Batatasin I	97.35	0.20	Steroidal sapogenin
32	11.64	Bowdichione	98.99	2.05	Flavonoids
33	11.77	Embelin	99.76	3.30	benzoquinones
34	5.59	Benzoic acid	96.68	0.64	Aromatic carboxylic acid
35	14.46	Coronaric acid	96.53	0.57	Fatty acid
36	12.64	Digitoxin	98.60	2.46	Cardiac glycosides
37	5.57	Swainsonine	92.04	0.04	Alkaloid
38	9.32	Purpurin	90.67	0.04	Anthraquinones
39	5.34	Vulgaxanthin I	95.21	0.06	Folate derivatives
40	19.69	12-Methyl tetradecanoic acid methyl ester	99.09	17.47	Fatty acid ester
41	10.35	7-Methoxy-4'-hydroxyflavone	99.20	1.32	Flavonoids

No.	RT	Name	Score (%)	relative content (%)	Compound attribution
42	9.44	Pelargonidin	90.21	0.08	Flavonoids
43	15.75	Androst-4,6-diene-3, 17-dione	98.10	0.20	Steroid hormone derivatives
44	19.73	14-Methyl hexadecanoic acid methyl ester	96.42	10.56	Fatty acid ester
45	10.17	Peonidin	92.56	0.42	Flavonoids
46	9.59	3-Methoxy quercetin	92.78	0.09	Flavonoids
47	9.19	1, 3, 5, 6-Tetrahydroxy-4-phenylxanthone	99.86	7.01	Xanthone ketone
48	14.98	Guggulsterone M	91.26	0.04	Steroid compounds
49	19.62	Anacardic acid A	94.80	0.04	Phenolic acid derivatives
50	13.31	(-)-Maslinic acid	94.87	0.04	Pentacyclic triterpenoid acid
51	6.63	Ajugasterone C	97.43	1.82	phytoecdysone
52	12.93	Eriocarpin C	98.54	5.95	Triterpenoid glycosides
53	17.69	Sagittin	94.34	1.58	Flavonoids
54	15.75	4', 5, 7, 8-Tetramethoxyflavone	98.10	2.23	Flavonoids

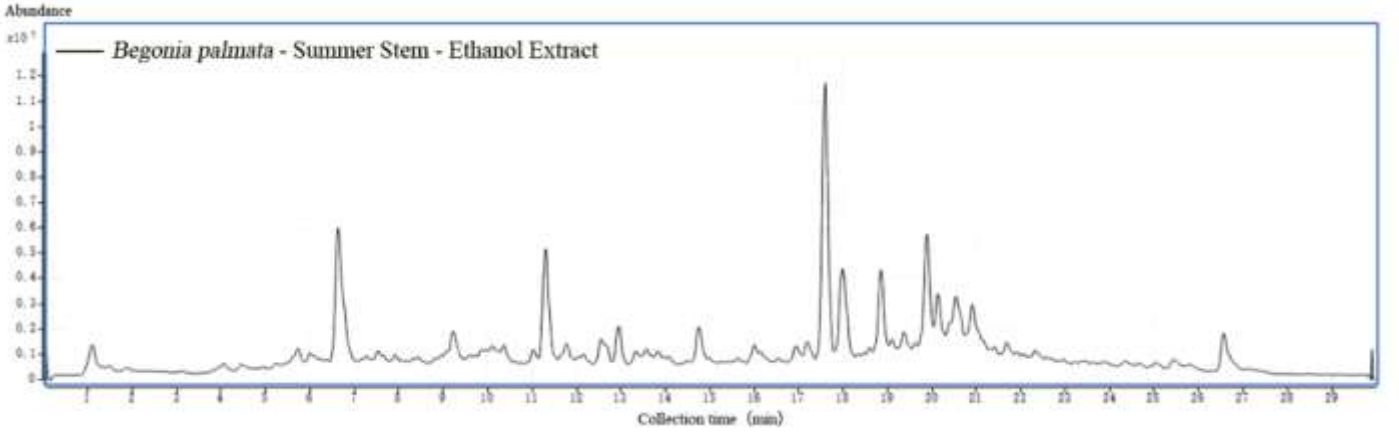

Fig. 4: UPLC-QTOF-MS ion chromatogram of ethanol extract from summer stem of *Begonia palmata.*

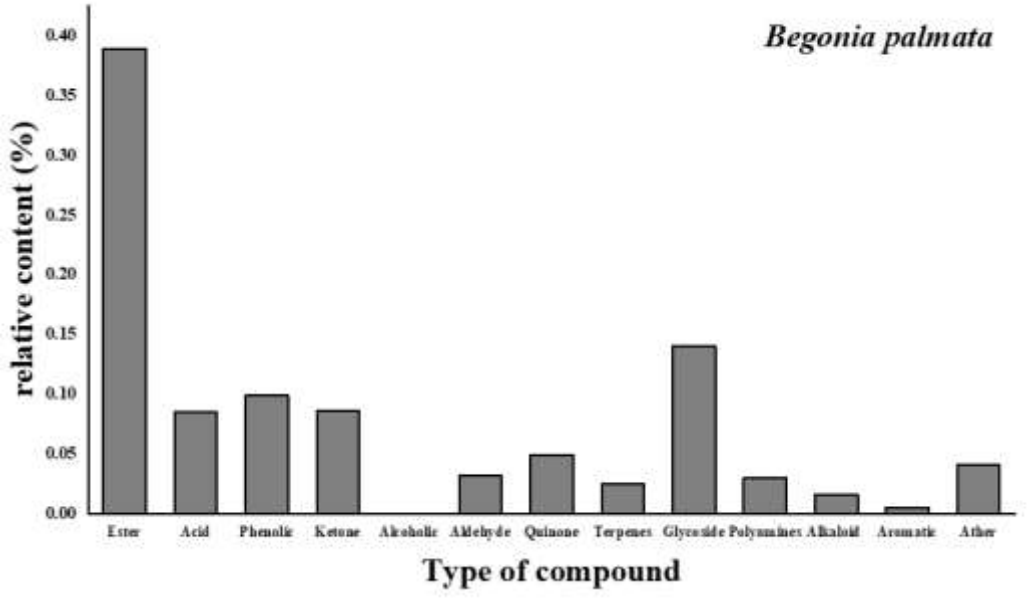

Fig. 5: Relative Content of Different Chemical Composition Types in Ethanol Extracts of *Begonia palmata* Stem Summer.

(8.53 %) identified in Begonia palmata mainly include: Docosanic acid,Elaidic acid, Montanic acid, Creatine, Erucic acid,Embelin, Benzoic acid, Coronaric acid, Anacardic acid A Waiting for research findings. Docosanic acid is a fatty acid containing saturated bonds that is difficult to absorb and has an impact on human cholesterol levels.[31] Elaidic acid is a key selenium (Se) metabolite with anticancer activity. By activating the apoptotic enzyme caspase-3 in the tumor tissue, demonstrated an inhibitory effect on the proliferation of colon tumors in mice. colon tumors in mice.[32] Research has shown that Embelin (3.30 %) has a preventive effect on lipid metabolism and oxidative stress.[33] It is a benzoquinone compound that can penetrate cells and has anti-cancer properties. It can not only down-regulate the apoptosis of human leukemia cells induced by X-linked inhibitor of apoptosis (XIAP),[34] but also deliver paclitaxel to breast cancer and prostate cancer as a nano micellar carrier, showing stronger anti-tumor activity in mouse experiments.[35] Flavonoids in polyphenols have a wide range of therapeutic properties and can serve as fundamental materials for immune regulating, heart protecting, anti-tumor and other related drugs.[36,37] The flavonoids identified in Begonia palmata include: Caffeic acid,3-Methoxy quercetin,7-Methoxy-4'-hydroxyflavone,Peonidin,Sagittin, 4', 5, 7, 8-Tetramethoxyflavone and Caffeic acid. Among them, caffeic acid (0.31 %) has been exerted inhibitory effects on tumorigenesis of colitis associated colorectal cancer (CAC) by suppressing the IL-6/STAT3 signaling pathway.[38] 4 ', 5, 7, 8-Tetramethoxyflavone (2.23 %) has anti-inflammatory and antiallergic activity, It inhibits the activation of HMC-1 cells by interfering with gene expression and mediates the regulation of human body inflammatory response.[39] Swainsonine (0.04) is an alkaloid compound, and research has shown that Swainsonine can inhibit the invasion of esophageal cancer cells by down-regulating Twist1.[40] In cervical cancer research, Swainsonine as an inhibitor, can regulate macrophage phenotype and inhibit T cell activation.[41] The analysis of non-volatile components data provides a reliable theoretical basis and scientific foundation for the systematic advancement and utilization of Begonia palmata, and the anti-tumor activity of Begonia palmata extracts may be mainly related to these active ingredients. Network pharmacology was used to explore the correlation between the active ingredients in the summer stems of Begonia palmata and the target of lung cancer, and to explore the internal mechanism of its anti-tumor activity, which providing new directions for the discovery of plant anti-cancer drugs.

3.4 Intersection target protein interaction network analysis

Six key active ingredients extracted from Begonia palmata that significantly inhibit lung cancer cell function were selected, namely Wedelolactone, Docosanic acid, Caffeic acid, Montanic acid, Xanthan, and Elaidic acid. By inputting NSCLC into the GeneCards database, all NCI-H1703 lung squamous cell carcinoma cell related targets were screened. After integration and deduplication, 2832 targets were finally obtained.[42] Obtain Canonical Smiles of 6 active ingredient compounds from the Pubche database, and import the unique SMILES string of the compounds into the SwissTarget Prediction target database to screen for 339 corresponding effective targets. Using Excel tools to process data and obtain common targets of active ingredients and lung cancer. Using Cytoscape software, the intersection target map of the effective active ingredients of Begonia palmata summer stem and the common target protein of lung cancer was obtained, as shown in Fig. 6. The five yellow nodes represent the active components in the summer stems of Begonia palmata, and the middle blue nodes represent the targets of the joint action of plant active components and lung cancer (150). The closer the distance in the target protein intersection target graph, the larger the degree value. These 20 nodes have higher degree values, including: CCND, PTK2, SRC, AURKB, IGF1R, FEN1, MAOA, EPHB4, BRAF, PFKFB3, AURKA, EPHX1, TEK, PLK4, AKT1, CDK2, FLT4, PLK1, PDGFRB and KDR. From this, it can be seen that these 20 protein targets may be the core targets for Begonia palmata to inhibit NCI-H1703 lung squamous cell carcinoma.

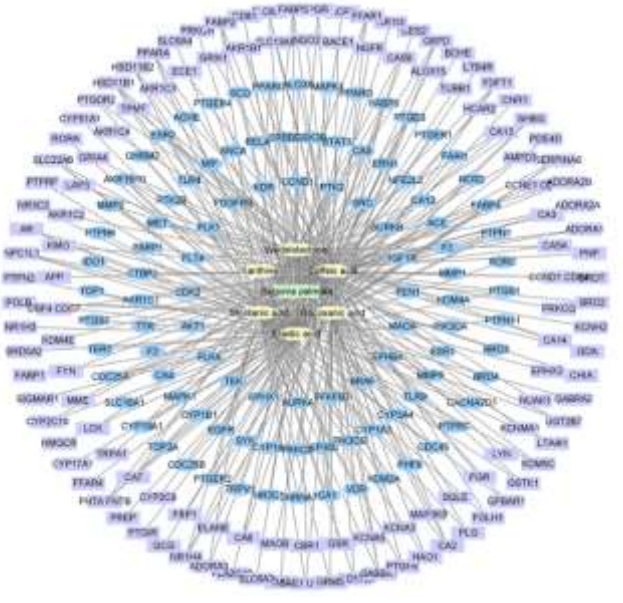

Fig. 6: Intersection target map of effective active ingredients and lung cancer in summer stems of *Begonia palmata*.

4. Conclusion

This study focuses on *Begonia palmata*, The summer stems of three medicinal herbaceous plants, *Rubia ovatifolia* and *Boehmeria nivea*, were studied. GC-MS, MTT assay, UPLC-QTOF-MS and network pharmacology protein interaction target protein intersection target analysis were used to analyze the metabolic chemical components, types, relative contents, and inhibition of LC cells in the ethanol extracts of the three medicinal herbaceous plant parts. The GC-MS analysis results indicate that *Begonia palmata* has the highest variety of active ingredients and the highest content of ketone compounds;

Boehmeria nivea ranks second in terms of active species, with the highest content of ketone compounds; *Rubia ovatifolia* has the least variety of sexual components and the highest content of alcohol compounds. The summer stems of three plants contain eight common compounds. In the MTT colorimetric cytotoxicity results, it was shown that the killing rate of NCI-H1703 lung squamous cell carcinoma cells from high to low was *Begonia palmata* (52.77 %) > *Rubia ovatifolia* (51.26 %) > *Boehmeria nivea* (50.55 %), and there were differences in the killing rate of NCI-H1703 cells among the summer stems of the three plants. In the UPLC-QTOF-MS analysis of *Begonia palmata*, it was found that *Boehmeria nivea* had the best inhibitory effect on NCI-H1703 cells, which may be related to the presence of anticancer ingredients such as Wedelolactone, Caffeic acid, Elaidic acid, Embelin, and Swainsonine. Flavonoids and acid compounds are important anti-tumor active ingredients in *Begonia palmata*. Through statistical analysis of the effective ingredients of *Begonia palmata* and the targets associated with NCI-H1703 lung squamous cell carcinoma cells, it was found that six active ingredients, Wedelolactone, Docosanic acid, Caffeine acid, Montanic acid, Xanthan, and Elaidic acid, share multiple common targets with NCI-H1703 lung squamous cell carcinoma cells. Therefore, it is inferred that due to the presence of these active ingredients, they have a high killing rate on lung cancer cells and show a good lung cancer inhibition effect.

Anyway, through in-depth identification and analysis of the active ingredients in three medicinal herbaceous plants, it was found that medicinal herbaceous plants contain abundant active ingredients, which are suitable for fields such as food, industry, cosmetics, and pharmaceuticals, and have great research and development value. In particular, the anti-tumor activity of Begonia palmata on NCI-H1703 lung squamous cell carcinoma cells in this study provides reference and theoretical support for the advancement of subsequent lung cancer drugs, improving the economic value of the three medicinal herbaceous plants and the high-value utilization of forest resources.

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Conflict of Interest

There is no conflict of interest.

Supporting Information

Not applicable.

CRediT Statement

Shiting Hong: Writing – original draft, Visualization, Methodology, Conceptualization. **Wan Adibah Wan Mahari**: Writing – original draft, Visualization, Methodology, Conceptualization. Rock Keey Liew: Writing – review & editing, Visualization. **Guanyan Li**: Visualization. **Xiaochen Yue**: Writing – review & editing. **Xiangmeng Chen**: Writing – review & editing, Supervision, Conceptualization. Haiping Gu: Writing – review & editing, Supervision. **Wanxi Peng** and **Yuli Dang**: Methodology, Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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