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Q-Markers of Paris Polyphylla var. yunnanensis Based on Hemostatic Efficacy

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Abstract: To enhance the quality control of traditional Chinese medicine (TCM) and ensure clinical medication safety and efficacy, this study developed a quality assessment method for Paris polyphylla var. yunnanensis that was aligned with its hemostatic efficacy. The methodology involved a multi-tiered screening strategy that used plasma recalcification time (PRT) and prothrombin time (PT) as pharmacodynamic endpoints to systematically evaluate the crude herb, bioactive fractions, and purified compounds. Based on these evaluations, the weights of the core criteria (efficacy, measurability, specificity) were determined using the Analytic Hierarchy Process (AHP), supported by objective data quantification from the Entropy Weight Method (EWM). The results showed that all compounds except water-soluble fraction A significantly shortened PRT and PT ($P < 0.001$). Eleven active constituents were identified, with polyphyllin VII and H exhibiting the most significant activity. Consequently, the AHP-EWM model prioritized five saponins as core Q-markers based on their integrated hemostatic efficacy contributions, ranked as follows: Paris saponin I > Paris saponin II > Paris saponin VII > Paris saponin H > Paris saponin D. This study thereby provides a scientific basis for improving the quality control of Paris polyphylla var. yunnanensis and its formulations by elucidating its multi-component hemostatic mechanism and quantitatively identifying five core Q-markers.

Keywords: Paris polyphylla var. yunnanensis; Q-markers; hemostatic activity; AHP-EWM; constituents knockout; identification model of target components

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1. Introduction

Paris polyphylla Smith var. yunnanensis (Franch.) Hand.-Mazz, a renowned genuine medicinal material from Yunnan, serves as the key ingredient in various hemostatic Chinese patent medicines such as “Gong Xue Ning” Capsules, which has reliable curative effects for abnormal uterine bleeding. However, wild resources are nearing extinction due to over-harvesting. At the same time, cultivated varieties face challenges of mixed seed sources and extended growth cycles (7–10 years), leading to significant quality variations that threaten the sustainable development of the Chinese medicine industry. The current Chinese Pharmacopoeia (2025 edition) utilizes content levels of only a few saponins, including Polyphyllin I, II, and VII, as quality control indicators [1]. Yet, these existing metrics fail to explain the differences in hemostatic efficacy between wild and cultivated P. polyphylla var. yunnanensis.

In recent years, the core concept of Q-markers in traditional Chinese medicine, proposed by Academician Liu Changxiao, has provided a novel perspective for systematically evaluating the overall quality of Chinese medicinal materials [2]. The component knockout method, an efficacy-oriented tracing mode for identifying bioactive fractions, systematically screens efficacy compounds across three chemical levels: the whole medicine, active fractions, and active constituents [3]. The AHP-EWM model integrates expert judgment on effectiveness, measurability, and specificity via the Analytic Hierarchy Process (AHP), while objectively reflecting intrinsic data variability through the Entropy Weight Method (EWM). This combined approach enables a multidimensional, subjective-objective integrated quantitative evaluation of candidate compounds, ensuring that the identified Q-markers are both significant and measurable [4]. Therefore, this study innovatively integrates component knockout-based efficacy verification with the AHP-EWM comprehensive evaluation model to establish a quantitative screening system for Q-markers. This framework provides scientific evidence and specific candidate indicators for enhancing the quality control standards of P. polyphylla var. yunnanensis and related Chinese medicinal preparations.

2. Materials and Methods

2.1. Instruments

Analytical Balance FA2004 (Shanghai Sunny Hengping Scientific Instrument Co., Ltd.); Electric Thermostatic Water Bath (Shanghai Yiheng Scientific Instrument Co., Ltd.); Heidolph Rotary Evaporator Hei-VAP Core HL/G (Germany Heidolph); LC-2010A Preparative Liquid Chromatograph (Japan Shimadzu Corporation); Ultimate3000 High-Performance Liquid Chromatograph (Thermo Fisher Scientific, USA).

2.2. Materials and reagents

Rhizome of P. polyphylla var. yunnanensis were provided by GAP of Wuding Planting Base of Yunnan Baiyao, Yunnan Province, People's Republic of China, in December 2022. A voucher specimen (No. 20221218) was deposited at the Natural Medicine Research Laboratory of the Yunnan Pharmaceutical Research Institute. Polyphyllin VI (National Institutes for Food and Drug Control, batch number: 111592-201604, purity: 97.0%); Polyphyllin V (Senlan Technology Co., Ltd., batch number: 030141-202301, purity: 98%). HPD-100 macroporous adsorption resin (Cangzhou Baoen Adsorption Material Technology Co., Ltd.); RP-C18 (Merck); column chromatography silica gel (Qingdao Marine Chemical Co., Ltd.); water is ultrapure, acetonitrile is chromatographic grade, and other reagents are analytical grade. 0.9% sodium chloride injection (Kunming Nanjiang Pharmaceutical Co., Ltd.); anhydrous calcium chloride (Xilong Science Co., Ltd.); rabbit brain powder (Beijing Boersi Technology Co., Ltd.); chloral hydrate (China National Medicines Co., Ltd.); normal saline (Kunming Nanjiang Pharmaceutical Co., Ltd.); 2% sodium citrate disposable vacuum blood collection tube (Jiangsu Yuli Medical Equipment Co., Ltd.); vitamin K1 injection (Qingdao High-Tech Industrial Park Biotechnology Co., Ltd.).

2.3. Animals

Healthy male Sprague–Dawley (SD) rats, weighing 180–220 g, were obtained from Beijing Sibei Fu (SPF) Biotechnology Co., Ltd., License No.: SCXK (Jing) 2019-0010. Laboratory Animal Use License: SYXK (Dian) K2022-0002, issued by the Kunming Municipal Bureau of Science and Technology. The use of experimental animals was approved by the Experimental Animal Management and Use Committee of Yunnan Institute of Materia Medica. Animal feed was purchased from Beijing Ke'ao Xieli Feed Co., Ltd. The experimental animals were housed under the following conditions: temperature 22–25°C, humidity 40–60%, and a 12-hour light/dark cycle.

2.4. Preparation of 70% Ethanol Extract, Fractions, and Compounds from P. polyphylla

The air-dried aerial parts of P. polyphylla var. Yunnanensis (15 kg) were extracted by refluxing 2 times with 70% ethanol,

and the filtered solution was concentrated in vacuo to obtain the supernatants and sediments. The supernatant was first fractionated on an HPD-100 macroporous resin column by sequential elution with water and 85% ethanol. The water eluate was concentrated and dried to yield Fraction A (310.3 g). The 85% ethanol eluate was then further purified by ODS column chromatography using a stepwise ethanol gradient (40%, 55%, 85%), affording Fractions B (32.8 g), C (7. 1 g), and D (21.35 g). Fraction B was subjected to RP18 CC using a methanol-water as the eluent, which afforded 3 subfractions (B1~B3). SubfractionB1 was further purified by semi-preparative HPLC (acetonitrile-water, 20:80) to yield compound 1 (18.2 mg) and compound 2 (22.5 mg), followed by another run (acetonitrile-water, 25:75) to afford compound 3 (20.3 mg). Subfraction B2 was purified by semi-preparative HPLC (acetonitrile-water, 33:77) to afford compound 4 (53.8mg). Subfraction B3 was purified by semi-preparative HPLC (acetonitrile-water, 37:63) to afford compound 5 (100.5 mg). Fraction C was subjected to silica gel column chromatography using a dichloromethane -methanol-water gradient elution system to afford subfractions C1–C4. Subfraction C4 was recrystallized from dichloromethane to afford compound 6 (179.2 mg). Subfraction C3 was purified by semi-preparative HPLC (acetonitrile-water, 40:60) to afford compound 7 (24.3 mg). Subfraction C2 was recrystallized fromdichloromethane to afford compound 8 (110.6 mg). Fraction D was subjected to silica gel column chromatography using a dichloromethane-methanol-water gradient elution system to afford subfractions D1–D5. Subfraction D5 was recrystallized from dichloromethane to afford compound 10 (88.5 mg). Subfraction D4 was purified by semi-preparative HPLC (acetonitrile-water, 45:55) to afford compound 11 (20.2 mg). Subfraction D3 was recrystallized from dichloromethane to afford compound 12 (58.2 mg). Subfraction D2 was recrystallized from dichloromethane to afford compound 13 (253.3mg). A quantity of each sample was dissolved in methanol and analyzed by HPLC under the following conditions: Mobile phase: Acetonitrile (A)–water (B) gradient elution (0–30 min, 14%–45% A; 30–55 min, 45%–90% A). Flow rate: 1 mL·min-1. Detection wavelength: 203 nm. nmInjection volume: 10 μL. Column temperature: 30 °C.

2.5. Hemostatic Activity Assays

2.5.1. Solution Preparation

The calcium chloride solution (25 mmol/L) was prepared by dissolving 83.25 mg of anhydrous calcium chloride in normal saline to a total volume of 30 mL. The thromboplastin solution (rabbit brain powder suspension) was freshly prepared by adding 900 mg of rabbit brain powder to 15 mL of normal saline, followed by stirring in a 37 °C water bath for 10 min. The control solutions included: (1) negative control: normal saline containing 2% DMSO; (2) positive control: 2 $mg \cdot mL^{-1}$ vitamin K_1 injection. The test sample solution was prepared by dissolving an accurately weighed sample in 1 mL of DMSO to prepare a stock solution, which was then diluted to the target concentration with the negative control solution immediately before use.

2.5.2. Measurement of Plasma Recalcification Time (PRT) and Prothrombin Time (PT)

Specifically, fresh rat blood was mixed with 38 g/L sodium citrate (9:1, v/v) and centrifuged for 10 min at 3500 rpm. The supernatant was used as platelet-rich plasma (PRP). For the plasma recalcification time (PRT) assay, 100 μL of PRP was mixed with 100 μL of different sample solutions in test tubes, incubated at 37°C for 1 minute, and then 100 μL of $CaCl_2$ (0.025 M) was added. The time required for visible clot formation was recorded as the PRT. Similarly, for the prothrombin time (PT) assay, 100 μL of PRP was mixed with 100 μL of thromboplastin solution, followed by the addition of 100 μL of the sample solution, incubated at 37°C for 1 minute, and then 100 μL of $CaCl_2$ (0.025 M) was added to trigger coagulation, with the clot formation time recorded as the PT. Differences among multiple groups were analyzed using one-way ANOVA with SPSS 20.0 software, and graphs were generated using Origin 2021.

2.6. Construction of Q-marker Evaluation Dataset

Evidence on Efficacy: Experimental research literature was included as efficacy data, using search terms such as “P. polyphylla”, “Blood coagulation”, or “Hemostasis”, along with common constituents found in P. polyphylla. Evidence on

Quantifiability: Quantifiable scoring data for measurability were obtained by retrieving and collating content information using keywords combining the Chinese name or Latin name of P. polyphylla and the Chinese/English names of its active compounds with “content”. This involved calculating the average content and the coefficient of variation for the active compounds. Evidence on Specificity (Uniqueness): Databases such as TM-MC and SymMap were utilized to search for the presence of compounds identified in P. polyphyllaacross other related medicinal materials. Concurrently, literature searches were conducted to compile statistics on the frequency of occurrence of these compounds within plants of the genus Paris.

3. Results

3.1. Identification of Fractions and Compounds

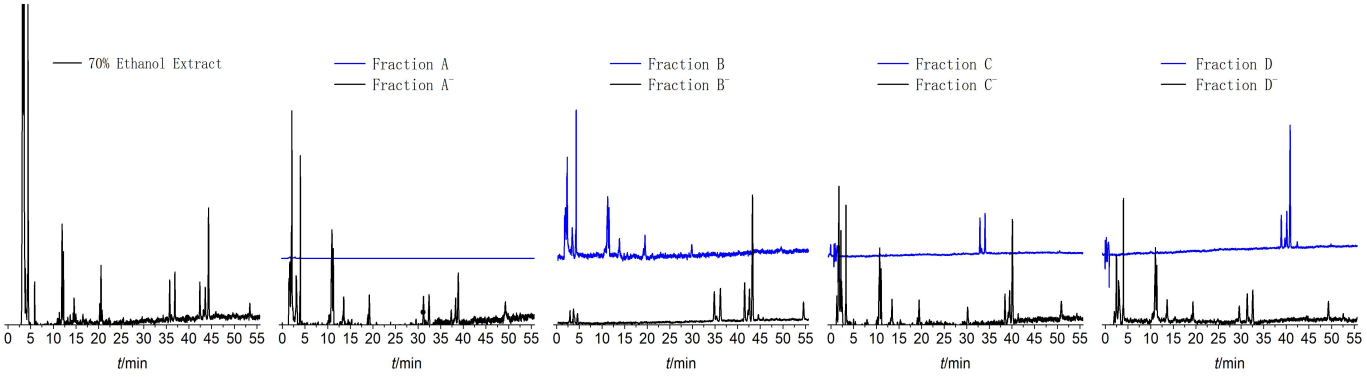

Figure 1. Comparative HPLC analysis: P. polyphylla fractions and knockout samples

Based on the yield proportions, the corresponding fractions were pooled to prepare knockout samples. Each fractions and its knockout samples were analyzed by HPLC according to the chromatographic conditions described in Section 2.2 (see **Figure 1**). The results showed that fraction A exhibited no significant ultraviolet absorption. The characteristic peaks for fraction B, fraction C, and fraction D were observed at retention times of 10~20 min, 30~36 min, and 37~45 min, respectively. A significant reduction in the signals of the corresponding components in the negative samples confirmed the effectiveness of the knockout process. The known compounds were elucidated as (23S,24S)-spirost-5,25(27)-diene-1β,3β,21,23,24-pentaol-1-O-{3-O-β-D-glucopyranosyl-α-L-rhamnopyranosyl-(1→3)-[β-D-apiofuranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl}-24-O-β-D-fucopyranoside (1)[5]; (23S,24S)-spirost-5,25(27)-diene-1β,3β,21,23,24-pentol-1-O-{α-L-rhamnopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→3)]-β-D-glucopyranosyl}-24-O-β-D-fucopyranoside (2)[6]; (23S,24S,25S)-spirost-5-ene-1β,3β,21,23,24-pentaol-1-O-{3-O-β-D-glucopyranosyl-α-L-rhamnopyranosyl-(1→3)-[β-D-apiofuranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl}-24-O-β-D-fucopyranoside (3)[7]; (25R)-26-O-β-D-glucopyranosyl-22-hydroxyfurost-5-ene-3β,26-diol-3-O-α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside (4)[8]; (25R)-26-O-β-D-glucopyranosyl-22-hydroxyfurost-5-ene-3β,26-diol-3-O-α-L-rhamnopyranosyl-(1→2)-[α-L-arabinofuranosyl-(1→4)]-β-D-glucopyranoside (5)[8]; pennogenin-3-O-α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside (6)[9]; pennogenin-3-O-β-D-glucopyranosyl-(1→3)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside (7)[10]; pennogenin-3-O-α-L-rhamnopyranosyl-(1→2)-[α-L-arabinofuranosyl-(1→4)]-β-D-glucopyranoside (8)[9]; diosgenin-3-O-α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside (10)[12]; diosgenin-3-O-β-D-glucopyranosyl-(1→3)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside (11)[11]; diosgenin-3-O-α-L-rhamnopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside (12)[10]; diosgenin-3-O-α-L-rhamnopyranosyl-(1→2)-[α-L-arabinofuranosyl-(1→4)]-β-D-glucopyranoside (13)[11], by comparing their spectroscopic data with reported data.

3.2. Evaluation of Hemostatic Activity

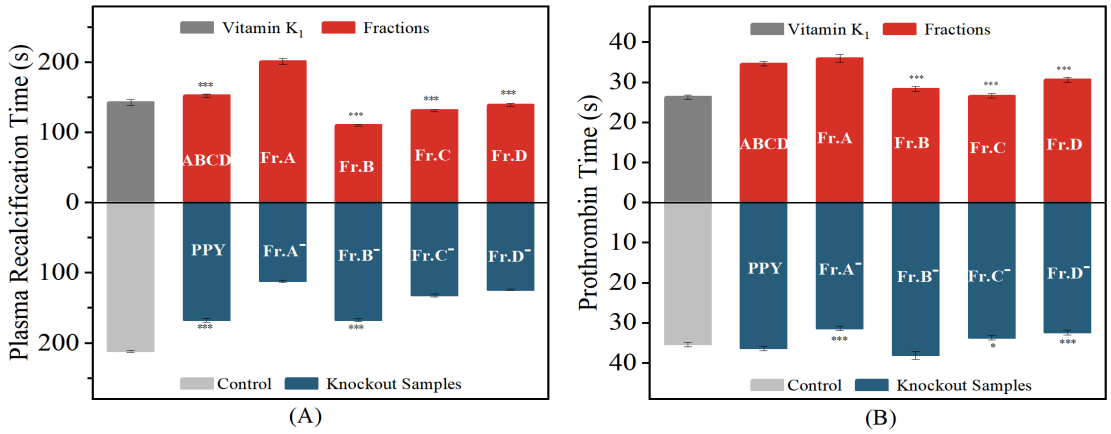

Figure 2. Effects of P. polyphylla fractions and knockout samples on coagulation parameters: (A) PRT (mean ± SD, n = 6), (B) PT (mean ± SD, n = 3). Compared with control group: $^{***}P<0.001$, $^{**}P<0.01$

To evaluate the hemostatic activity of the target fractions, we examined their effects on plasma recalcification time (PRT) and prothrombin time (PT) in rats before and after knockout, as shown in **Figure. 2**. The results demonstrated that at a concentration equivalent to 30 mg·mL-1 of crude drug, fraction B, fraction C, fraction D, and the knockout samples (fraction A^-, fraction D^-) significantly shortened both PRT and PT ($P < 0.001$). With the exception of fraction A, all fractions derived from P. polyphylla var. yunnanensis exhibited strong hemostatic activity and may potentially act in a synergistic manner.

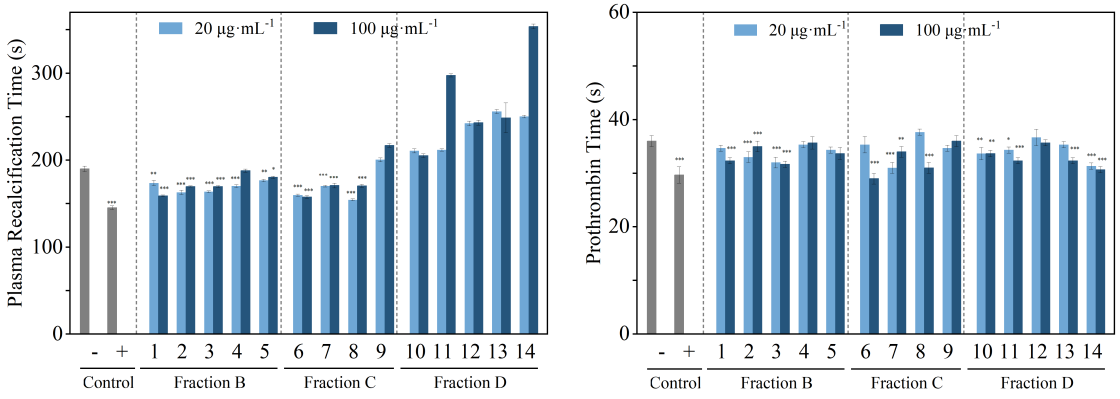

Figure 3. Effects of compounds from P. polyphylla var. yunnanensis on coagulation parameters: (A) PRT (mean ± SD, n = 6), (B) PT (mean ± SD, n = 3). Compared with control group: $^{***}P<0.001$, $^{**}P<0.01$

Furthermore, the PRT and PT of the isolated monomeric compounds were determined. As illustrated in **Figure. 3**, compounds 1–3 and 6–8 significantly reduced both PRT and PT ($P < 0.01$) within the concentration range of 20-100 μg·mL^{-1}.

3.3. Q-Marker Identification Based on AHP-EWM Model

3.3.1. Evaluation of Efficacy, Measurability, and Specificity of Active Compounds

"Effectiveness" constitutes a core attribute of quality markers. Quantitative indicators were derived from literature on platelet aggregation induced by constituents of P. polyphylla var. yunnanensis, as well as from previously obtained experimental data on PRT and PT from our research group. After standardization, information entropy calculation, and entropy weight assignment, the weights for literature data and experimental data under the effectiveness criterion were

determined to be 44.08% and 14.92%, respectively. The quantification of component content is regarded as a crucial method for quality evaluation of traditional Chinese medicine. A higher average content of active constituents in P. polyphylla var. yunnanensis indicates enriched levels, while the coefficient of variation reflects batch-to-batch variability. A larger coefficient suggests that content limits for the component should be more strictly defined [13]. The dry rhizomes of P. polyphylla var. yunnanensis (Franch.) Hand.-Mazz. and P. polyphylla var. chinensis (Franch.) Hara have been documented as rhizoma paridis in the 2025 Edition of the Chinese Pharmacopeia [1]. However, field investigations have revealed that up to 16 species within the genus Paris are used in ethnic and folk medicine [14], with significant interspecific differences in chemical composition and content [15]. The exclusivity of a component is strengthened by its limited distribution among related medicinal materials. Similarly, its specificity within the genus is enhanced by a lower frequency of occurrence across species of Paris. Statistical data are presented in **Table 1**.

Table 1. Comprehensive evaluation data based on efficacy, measurability, and specificity of active compounds

No.	Compound Name	Efficacy	Measurability			Specificity	
		Number of Literature Reports	Number of Quantitative Analysis Papers	Mass Fraction (%)	Coefficient of Variation (%)	Number of Related Medicinal Materials	Number of Distribution Species
1	Paristengoside A	_	_	_	_	_	1
2	_	_	_	_	_	_	1
3	parisverticillatosideA	_	_	_	_	_	1
4	Dichotomin	_	_	_	_	_	6
5	Parisaponin I	_	_	_	_	_	2
6	Polyphyllin VII	4	22	0.141	0.3434	1	8
7	Polyphyllin D	1	5	0.032	0.8214	_	4
8	Polyphyllin H	3	11	0.110	0.2500	1	6
9	Polyphyllin VI	_	17	0.019	1.5357	1	10
10	Polyphyllin II	3	24	0.397	0.4008	_	10
11	Dioscin	_	7	0.116	0.9024	21	11
12	Gracillin	_	8	0.070	0.6074	5	9
13	Polyphyllin I	1	24	0.424	0.5784	_	11
14	Polyphyllin V	_	6	0.024	1.1000	_	11

Table 2. Comprehensive weights of evaluation indicators

Element Layer	Element LayerWeight/%	Control Layer	Control Layer Weight/%	Comprehensive Weight/%
Efficacy	59	Number of Literature Reports	74.71	44.08
		Experimental Data	25.29	14.92
Measurability	31	Number of Quantitative Analysis Papers	30.27	9.38
		Mass Fraction	59.95	18.58
		Coefficient of Variation	9.78	3.03
Specificity	10	Number of Related Medicinal Materials	84.18	8.42
		Number of Distribution Species	15.82	1.58

3.3.2. Quantitative Identification of Hemostatic Q-markers in P. polyphylla var. yunnanensis

The criteria layer was constructed using the Analytic Hierarchy Process (AHP) to evaluate the three core attributes: effectiveness, measurability, and specificity. Weightings for these attributes were assigned based on expert scoring data reported in the literature [4, 16]. For the control layer, the Entropy Weight Method (EWM) was applied to analyze literature data, generating objective entropy weights. The comprehensive weight for each indicator was calculated by multiplying the AHP primary weight by the corresponding EWM secondary entropy weight (Table 2). A composite score for each constituent was then derived by summing the products of its indicator values and their respective comprehensive weights, followed by ranking (Table 3). A threshold of composite score >20 was set, leading to the final selection of Q-markers, a result supported by both expert consensus and objective data [17]. Among the top five constituents identified as hemostatic quality markers was Polyphyllin I. In addition, studies have demonstrated that Polyphyllin H at low to medium concentrations (5–20 μmol/L) induces reversible platelet aggregation in male Wistar rats. This aggregation depends on ADP release following platelet activation and thromboxane A_2 (TXA_2) generation [18]. Similarly, Polyphyllin VII induces platelet activation by triggering substantial ADP release from dense granules. The released ADP subsequently activates the P2Y1 and P2Y12 receptor signaling pathways [19].

Table 3. Comprehensive scores of individual compounds

No.	Compound Name	ChemicalFormula	Comprehensive Score	Rank
1	Paristengoside A	$C_{55}H_{86}O_{28}$	15.6299	9
2	_	$C_{50}H_{78}O_{24}$	16.3106	7
3	parisverticillatosideA	$C_{55}H_{88}O_{28}$	16.3146	6
4	Dichotomin	$C_{57}H_{94}O_{26}$	9.3190	14
5	Parisaponin I	$C_{50}H_{80}O_{22}$	13.0170	11
6	Polyphyllin VII	$C_{51}H_{82}O_{21}$	77.5179	3
7	Polyphyllin D	$C_{45}H_{72}O_{18}$	28.8477	5
8	Polyphyllin H	$C_{44}H_{70}O_{17}$	69.1356	4
9	Polyphyllin VI	$C_{39}H_{62}O_{13}$	11.9344	13
10	Polyphyllin II	$C_{51}H_{82}O_{20}$	81.1851	2
11	Dioscin	$C_{45}H_{72}O_{16}$	13.2056	10
12	Gracillin	$C_{45}H_{72}H_{17}$	15.9169	8
13	Polyphyllin I	$C_{44}H_{70O1}6$	82.7320	1
14	Polyphyllin V	$C_{39}H_{62}O_{12}$	12.8589	12

4. Discussion

This study systematically established a Q-marker screening system through integration of multi-component synergy mechanism analysis and an innovative comprehensive evaluation model, providing scientific support for precise quality control of P. polyphylla var. yunnanensis and related Chinese medicinal preparations. The research demonstrated that the hemostatic effect of P. polyphylla var. yunnanensis originates from multi-pathway synergistic actions of steroidal saponins, with spirostanol saponins (fraction B) and pennogenin saponins (fraction C) as the core efficacious compounds, while diosgenin saponins (fraction D) exert synergistic enhancement effects. Further investigation revealed that the coagulation process is regulated by 11 compounds through concentration-dependent synergistic mechanisms, collectively influencing

both intrinsic and extrinsic coagulation pathways. Among these, polyphyllin VII and H displayed the most significant activity. Based on these findings, this study employed an AHP-EWM model for multi-index quantitative evaluation, focusing on efficacy contribution, detectability, and specificity of compounds, with weights assigned according to data variability characteristics. This approach led to the identification of polyphyllin I, II, VII, H, and D as core Q-markers for the hemostatic function of P. polyphylla var. yunnanensis. The findings by Li Y et al. [20], who identified polyphyllin I, II, VII, H, and D as Q-markers for anti-platelet aggregation in P. polyphylla var. yunnanensis through spectrum-effect relationship analysis, provide strong support for our conclusions regarding hemostatic Q-markers. Our results also align with Li Y et al. [21], whose study based on the Efficacy Component Index (ECI) model suggested that quality control should prioritize compounds with high activity and significant variability, such as polyphyllin D and H, rather than focusing solely on content stability. This methodology effectively excluded interfering compounds exhibiting high variability with low activity (e.g., polyphyllin V and VI) and those with weak specificity (e.g.Dioscin and gracillin), thereby directing weight assignment toward key efficacious substances.

Current research indicates that P. polyphylla var. yunnanensis possesses bidirectional regulatory potential, characterized by hemostatic effects at low concentrations and blood-activating effects at high concentrations. The multi-target regulation of saponin compounds at different concentrations establishes the pharmacological basis for multi-pathway, multi-target synergistic hemostasis in P. polyphylla var. yunnanensis, fully demonstrating the holistic regulatory advantage of traditional Chinese medicine. However, the complex synergistic mechanisms present additional challenges for preparation standardization and quality control. Future research should focus on addressing detection challenges for moderately active compounds (e.g., parisverticillatoside A) using techniques such as UPLC-MS/MS. Furthermore, methods including component knockout experiments, grey relational analysis, and BP neural networks should be employed to optimize Q-marker compatibility ratios, thereby advancing the modernization and precision of quality control systems for P. polyphylla var. yunnanensis.

Disclosure statement

The author declares no conflict of interest.

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