Plant substitution therapy improve hair loss：Potential targets and related pathways

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Abstract:

Objective: To explore the comprehensive efficacy and mechanisms of Platycladus orientalis leaf extract (POL) in combating androgenetic alopecia (AGA).

Methods: Network pharmacology was employed to screen active components and target pathways of POL. Anti-hair loss mechanisms and efficacy were validated through in vitro and human clinical studies, including proliferation assays, anti-apoptotic analysis, and clinical evaluations of hair loss prevention.

Results: Network pharmacology identified the steroid hormone biosynthesis pathway as a key mechanism. Experimental results demonstrated that POL at 31.3 μg/mL increased cell proliferation by 15.63% ($P < 0.01$), comparable to 100 μg/mL minoxidil ($P > 0.05$). At 125 μg/mL, the extract inhibited cell apoptosis by 35.35% ($P < 0.01$). In clinical trials, a rinse-off shampoo containing 500 μg/mL POL reduced hair loss by 61.9% ($P < 0.05$) after 4 weeks, with overall hair density increasing by 25.8% ($P < 0.05$) and localized hair density improving by 8.9% ($P < 0.05$).

Conclusion: POL exhibits multi-pathway anti-hair loss potential, providing scientific support for plant-based alternative therapies in cosmetic strategies for alopecia management.

Key words: Hair loss; Pathway; Plant substitution therapy; Bioinformatics

1. Introduction

Hair loss, characterized by progressive hair thinning or shedding [1], is a multifactorial condition influenced by genetic, physiological, psychological, environmental, and lifestyle factors. It affects both genders but manifests distinct patterns and prevalence. Approximately 50% of middle-aged Caucasian men experience hair loss, increasing to 80% by age 80, while 40% of women over 70 suffer from female AGA [2,3]. In China, prevalence rates are approximately 21.3% in men and 6.0% in women [4,5]. Although not directly impairing physical health, hair loss often causes significant psychological and social distress.

Current treatments include minoxidil, finasteride, and dutasteride. Minoxidil, a repurposed vasodilator, stimulates hair growth but may cause skin irritation and erythema [6]. Finasteride and dutasteride inhibit 5α-reductase, reducing dihydrotestosterone (DHT) levels; however, systemic side effects such as sexual dysfunction and osteoporosis limit their long-term use [7].

Plant-based alternatives with historical efficacy and safety profiles are gaining attention. Platycladus orientalis leaves, the dried branches and leaves of Platycladus orientalis, have

been documented in traditional Chinese medical classics such as Compendium of Materia Medica (Bencao Gangmu), Handbook of Prescriptions for Emergencies (Zhouhou Beiji Fang), and Taiping Holy Prescriptions for Universal Relief (Taiping Shenghui Fang) for their efficacy in treating hair loss [8]. Modern pharmacological studies reveal that Platycladus orientalis leaves are rich in bioactive compounds such as flavonoids and volatile oils, which may interfere with AGA pathogenesis [9]. However, their active components and mechanisms of action remain insufficiently elucidated. This study integrates network pharmacology and experimental approaches to investigate the pathways and efficacy of Platycladus orientalis in AGA intervention, aiming to advance the application of botanical alternatives in cosmetic strategies for hair loss management.

2. Materials and Methods

2.1 Network Pharmacology Research

2.1.1 Drug Target Prediction

The components of POL were analyzed using UPLC-EQ-MS, and the primary and secondary mass spectrometry data of the chromatographic peaks were obtained. The relative molecular mass of high-resolution mass spectrometry was calculated using Thermo Scientific Xcalibur software to infer the corresponding molecular formulas of the compounds. The composition of the compounds was inferred and confirmed by comparing with the secondary fragments recorded in the literature. The active components of POL were imported into the PubChem database to obtain the SMILES structures of each active component. These SMILES structures were then used on the SwissTargetPrediction platform for target prediction.

2.1.2 AGA Disease Target Retrieval

Using “Androgenic alopecia” as the keyword, six disease target databases were searched: Drugbank database, GeneCards database, MalaCards database, OMIM database, NCBI Gene database, and DisGenet database.

2.1.3 Drug-Component-Common Target Mapping and Network Construction

Through the above processes, we obtained the active components of POL and their targets, as well as the disease-related targets of AGA. These two sets of targets were mapped, and the common targets identified were considered as the potential targets of POL for AGA. The “drug-component-common target” network was constructed using Cytoscape 3.7.1 software and visualized.

2.1.4 Protein Interaction Network Construction and Analysis

The common targets were imported into the STRING database to obtain the protein-protein interaction (PPI) network mapping. The network was visualized using Cytoscape software. Additionally, the PPI network was subjected to topological analysis using the Cytoscape plugin CytoHubba to identify key targets, which were considered as the key targets of POL for AGA treatment.

2.1.5 Biological Enrichment Analysis

In this study, biological enrichment analysis was performed on the common targets of drugs and diseases, as well as key sub-module targets. This mainly included KEGG pathway analysis, which was completed using the R package clusterprofiler. The enrichment results were filtered with a threshold of $P < 0.05$, and the top-ranked entries were visualized using R software.

2.2 Study on the Proliferative Effect of POL on Dermal Papilla Cells

The cell experiment utilized POL, a brown powder soluble in dimethyl sulfoxide (DMSO)

with a solubility of 100 mg/mL (at 20° C). High-performance liquid chromatography (HPLC) analysis revealed the total flavonoid content of the extract to be 99.5 mg/g, comprising 12.36 mg/g quercetin, 1110 μg/g afzelin, and 90 μg/g isoquercitrin.

Positive control: Minoxidil, a colorless to pale yellow clear liquid with a concentration of 50 mg/mL.

Cell line: Human primary dermal papilla cells, cultured and passaged in-house.

(1) Preparation of Test Samples

Test sample preparation: Dissolve 100 mg of POL powder in 1 mL DMSO to prepare a 100 mg/mL stock solution.Dilute the stock solution 100-fold with culture medium to achieve the first test concentration (1 mg/mL), followed by a 4-fold gradient dilution to obtain the second test concentration (0.25 mg/mL). Positive control preparation: Dilute 100 μL minoxidil with culture medium to a final volume of 6.25 mL, yielding an 800 μg/mL stock solution. Perform 2-fold serial dilutions with culture medium to generate working concentrations.

(2) Cell Culture and Treatment

①Thaw cryopreserved primary dermal papilla cells and monitor growth. Subculture cells upon reaching ~90% confluency.

②Sample dilution and treatment: Dilute the test sample stock solution 100-fold with complete culture medium to prepare the initial concentration (1 mg/mL), followed by 2-fold serial dilutions to generate final concentrations of 250, 125, 62.5, 31.25, 15.63, 7.81, and 3.91 μg/mL. For the positive control, prepare 2-fold serial dilutions from the stock solution to achieve final concentrations of 800, 400, 200, 100, 50, 25, 12.5, and 6.25 μg/mL. Add 10 μL of each sample or culture medium (control) to designated wells and incubate for 48 h prior to the CCK-8 assay.

③Add 10 μL CCK-8 solution to each well and incubate in the dark at 37°C, 5% CO_2 for 1 h. Measure optical density (OD) at 450 nm using a microplate reader. Analyze cell proliferation using the recorded OD values.

(3) Analytical Methods

Cell viability (%) = [(OD of tset well)-(OD of blank well)/(OD of control well)-(OD of blank well)]×100%

Cell proliferation rate (%) = [(OD of test well)-(OD of control well)/(OD of control well- (OD of blank well)]×100%

2.3 Study on the Anti-Apoptotic Effect on DPCs

2.3.1 Toxicity Test of POL on DPCs

(1) Test Sample Preparation

Accurately weigh 100 mg of POL powder and dissolve it in 1 mL of DMSO to prepare a 100 mg/mL stock solution. Dilute the stock solution 100-fold with culture medium to prepare the first test concentration of 1 mg/mL. Subsequently, perform sequential 2-fold gradient dilutions with culture medium to obtain test concentrations of 0.5 mg/mL, 0.25 mg/mL, etc.

(2) Cell Culture and Treatment

①Thaw cryopreserved primary DPCs. When cell confluency reaches 60%, seed the cells into 96-well plates and culture in a CO2 incubator (37°C, 5% CO2) for 24 h.

②Prepare test concentrations by diluting the stock solution with complete medium via 2-fold serial dilution to achieve final concentrations of 1000 μg/mL, 500 μg/mL, 250 μg/mL, 125 μg/mL, 62.5 μg/mL, and 31.25 μg/mL.

③When cell confluency in the 96-well plate reaches 50%-60%, administer treatments by adding 200 μL of culture medium containing corresponding test concentrations to each well. After 24 h of incubation in the CO2 incubator, discard the supernatant and add MTT working solution (0.5 mg/mL). Incubate at 37°C in the dark for 4 h. Discard the supernatant and add 150 μL DMSO to each well. Measure optical density (OD) at 490 nm using a microplate reader. Calculate relative cell viability using the obtained OD values.

(3) Analytical Methods

Cell viability (%) = [(OD of test well - OD of blank well) / (OD of control well - OD of blank well)] × 100%

2.3.2 Anti-Apoptotic Effect of POL on DPCs

(1) Test Sample Preparation

Based on toxicity test results, select the highest safe concentration of 125 μg/mL for subsequent experiments.

(2) Cell Culture and Treatment

①Thaw cryopreserved primary DPCs. When cell confluency reaches 60%, seed the cells into 6-well plates and culture in a CO2 incubator (37°C, 5% CO2) for 24 h.

②When cell confluency reaches 60%, stimulate the Platycladus group, positive control group, and negative control group with 4.25 μg/mL H2O2 for 1 h to induce apoptosis.

③ After induction, administer treatments:Platycladus group: 2 mL culture medium containing test compound; Negative control: 2 mL culture medium; Positive control: 2 mL minoxidil-containing culture medium; Blank control: 2 mL culture medium. Incubate in a CO2 incubator (37°C, 5% CO2) for 23 h, Using propidium iodide staining.

(3) Analytical Methods

Apoptosis rate (%) = [(OD of control well - OD of test well) / (OD of control well)] × 100%
Data analysis was performed using GraphPad Prism. Results are expressed as Mean ± SD. Intergroup comparisons were analyzed by t-test (two-tailed). $P < 0.05$ was considered statistically significant, and $P < 0.01$ as highly significant.

2.4 Clinical Evaluation of Anti-Hair Loss Efficacy

(1) Testing Methodology

①Test products: POL shampoo (test group).Vehicle shampoo (control group).

②Study design:

This study enrolled 62 volunteers aged 24-60 years with hair loss, following the Testing Methods for Anti-Hair Loss Efficacy of Cosmetics issued by the China National Medical Products Administration (NMPA) [10].

Volunteers were randomly divided into two groups: Platycladus group (n=31), used POL shampoo. Vehicle group (n=31), used the vehicle shampoo.

Application protocol: Trained staff distributed test and control products according to a randomization table and instructed participants on proper usage.

All participants provided informed consent, and 62 volunteers completed the trial.

(2) Anti-hair loss efficacy assessment parameters

①Hair shedding count: At each visit, trained staff performed a 60-stroke combing method to count and record shed hairs.

②Global hair density: Participants' scalp hair was symmetrically parted and maintained in a consistent style for all visits.A 0-7 grading scale was used by dermatologists to evaluate

hair density in the vertex region through in-person and photographic assessments. The mean score of both evaluations was recorded as global hair density.

③Local hair density:A fixed 1.5 cm×1.5 cm scalp area was marked and maintained throughout the study. Dermoscopy images of the target area were captured at each visit. Specialized software quantified hair count and density within the localized region.

(3) Analytical Methods

Differences between baseline and measurements at 2 weeks and 4 weeks were calculated for both groups.SPSS Statistics 25 was used for statistical analysis (two-tailed test, significance level $\alpha = 0.05$). Continuous data: Normality was assessed using Shapiro-Wilk tests. Normally distributed data: Independent t-test. Non-normal data: Mann-Whitney U test. Ordinal data: Analyzed using the Mann-Whitney U test.

3. Results

3.1 Network Pharmacology Study of POL in Treating AGA

3.1.1 Target Prediction of Active Components in POL

A total of 28 active components were identified from POL. Target prediction was performed using SwissTargetPrediction, yielding 612 unique drug targets after removing duplicates.

3.1.2 Construction of the AGA Disease Target Database

620 AGA-related disease targets were retrieved from six databases: GeneCards: 402, DisGeNET: 112, OMIM: 48, NCBI Gene: 33, MalaCards: 14, DrugBank: 11, After deduplication, 506 AGA disease targets were retained.

3.1.3 Drug-Component-Common Target Mapping and Network Construction

The 612 Platycladus orientalis targets and 506 AGA disease targets were intersected, revealing 48 shared targets (Figure 1). A "Drug-Component-Common Target" network was constructed (Figure 1), comprising 28 active components and 48 shared targets.

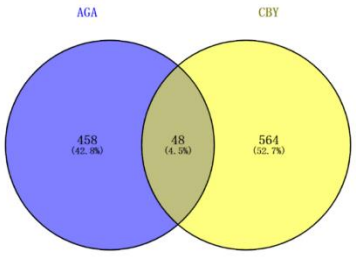

Figure 1. Venn diagram of the common targets between POL and AGA

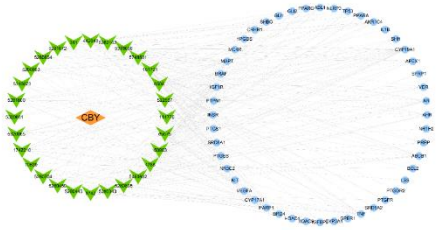

Figure 2. "Drug-Component-Common Target" Network

3.1.4 Protein-Protein Interaction (PPI) Network Construction and Analysis

The 48 shared targets were imported into the STRING platform to generate a PPI network. Visualization using Cytoscape revealed a network with 47 nodes and 212 edges. Node size and color intensity (red-to-white gradient) reflected degree values, with larger, redder nodes

indicating higher connectivity.Top 10 targets by degree value: TP53, TNF, VEGFA, AR, PPARG, IL1B, CYP19A1, HPGDS, IGF1R, CYP3A4.

3.1.5 Functional Enrichment Analysis of Shared Targets

Functional enrichment analysis of the 48 shared targets was performed. KEGG pathway analysis identified the top five significantly enriched pathways: Steroid hormone biosynthesis, MAPK signaling pathway, Ovarian steroidogenesis, Endocrine resistance, Hedgehog signaling pathway. These pathways involved 20 targets, with their interactions visualized in Figure 3. In the chord diagram, white-to-black color gradients represent target importance in the PPI network: whiter hues indicate higher degree values, while darker hues denote lower connectivity.

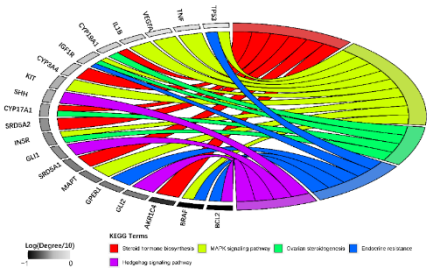

Figure 3. Chord diagram of KEGG pathways and targets (The color blocks of the targets represent log(Degree/10))

3.2 Study on the Proliferative Effect of Extract on DPCs

The effects of POL on the viability and proliferation rate of dermal papilla cells are shown in Table 1.

The results indicate that the five tested concentrations of Platycladus extract (125–7.8 μg/mL) significantly increased cell viability compared to the blank control group (**P < 0.01, *P < 0.05). Among these, the proliferation rate was highest at a concentration of 31.25 μg/mL, reaching 15.63%. Similarly, the five tested concentrations of minoxidil (800–25 μg/mL) also significantly enhanced cell viability compared to the blank control group (**P < 0.01, *P < 0.05). The proliferation rate was highest at a concentration of 100 μg/mL, with a value of 15.49%, which was comparable to that of the 31.3 μg/mL Platycladus extract (P > 0.05).

Table 1. Results of the Proliferative Effects of POL on DPC

Gurop	Concentration（μg/mL）	Cell viability（%）	Cell proliferation rate（%）
Blank control	/	100.00±5.89	/
POL	250	105.96±3.19	5.96±3.19
	125	108.68±4.6*	8.68±4.60
	62.5	113.07±7.24**	13.07±7.24
	31.25	115.63±4.75**	15.63±4.75
	15.63	114.07±6.09**	14.07±6.09
	7.80	111.47±5.3**	11.47±5.30
Positive control	800	106.08±3.78	6.08±3.78

400	104.93±11.76	4.93±11.76
200	125.14±2.62**	25.14±2.62
100	115.49±5.6**	15.49±5.60
50	112.42±4.58*	12.42±4.58
25	112.47±3.85*	12.47±3.85

Note: Compared with the blank control group, **P < 0.01, *P < 0.05

3.3 Study on the Anti-Apoptotic Effect on Hair DPCs

3.3.1 Toxicity Test of POL on DPCs

The effects of POL on the viability of dermal papilla cells are shown in Table 2. The results indicate that the cell viability was above 90% for the three tested concentrations of Platycladus extract (31.25 μg/mL to 125 μg/mL). Therefore, the highest safe concentration of 125 μg/mL was selected for the anti-apoptosis experiment on dermal papilla cells.

Table 2. The cytotoxicity test results of POL on dpcs

Gurop	Concentration（μg /mL）	Cell viability（%）
POL	1000	4.72±0.12
	500	32.23±0.55
	250	89.03±1.57
	125	94.84±1.27
	62.5	95.84±2.68
	31.25	96.60±1.80
Positive control	10%DMSO	25.78±3.69
Blank control	/	100.00±2.18

3.3.2 Anti-Apoptotic Effect of POL on DPCs

The results of the anti-apoptosis experiment of POL on dermal papilla cells are shown in Table 3. The results indicate that at a concentration of 125 μg/mL, the apoptosis rate of cells treated with Platycladus extract was significantly decreased compared with the negative control group (**P < 0.01), with an inhibition rate of 35.35%.

Table 3. Results of the Anti-apoptosis Experiment of POL on DPCs

Gurop	Apoptosis rate（%）	Inhibition rate（%）
POL	17.28±0.90**	35.35%
Positive control	15.06±0.89**	/
Negative control	26.73±0.89##	/
Blank control	11.83±0.85	/

Note: Compared with the blank control group, ##P < 0.01, #P < 0.05; compared with the negative control, **P < 0.01, *P < 0.05

3.4 Clinical Evaluation of Anti-Hair Loss Efficacy

3.4.1 Experiment on the Effect of POL on Reducing Hair Loss

The results of the experiment on the effect of POL on reducing hair loss are shown in Table 4. The hair loss count results indicate that compared to before using the product, the hair loss count in the test group significantly decreased after 2 weeks and 4 weeks of product use ($P < 0.05$), with a reduction rate of 47.8% after 2 weeks and 61.9% after 4 weeks. Compared to the control group, the hair loss count in the Platycladus group also significantly decreased after 2 weeks and 4 weeks of product use ($P < 0.05$).

Table 4. Results of the Experiment on the Effect of POL on Reducing Hair Loss

Group	Hair loss count			Reduction rate of hair loss count relative to the initial value(%)	
	Before use	After 2 weeks	After 4 weeks	After 2 weeks	After 4 weeks
Tset	37.3	19.5	14.2	-47.8%*#	-61.9%*#
Control	35.9	34.2	34.2	-4.8%	-4.8%

Note: Compared with the initial value, *$P < 0.05$; compared with the vehicle group, #$P < 0.05$

4.2 Experiment on the Effect of POL on Improving Overall Hair Density

The results of the experiment on the effect of POL on improving overall hair density are shown in Table 5. The overall hair density results indicate that compared to before using the product, the overall hair density in the test group significantly increased after 2 weeks and 4 weeks of product use ($P < 0.05$), with an improvement rate of 21.3% after 2 weeks and 25.8% after 4 weeks. Compared to the control group, the overall hair density in test group also significantly improved after 2 weeks and 4 weeks of product use ($P < 0.05$).

Table 5. Results of the Experiment on the Effect of POL on Improving Overall Hair Density

Group	Overall Hair Density			Improvement rate of overall hair density relative to the initial value(%)	
	Before use	After 2 weeks	After 4 weeks	After 2 weeks	After 4 weeks
Tset	2.9	3.5	3.6	21.3%*#	25.8%*#
Control	3.3	3.3	3.3	1.0%	1.0%

Note: Compared with the initial value, *$P < 0.05$; compared with the vehicle group, #$P < 0.05$

4.3 Experiment on the Effect of POL on Improving Local Hair Density

The results of the experiment on the effect of POL on improving local hair density are shown in Table 6. The local hair density results indicate that compared to before using the product, the local hair density in the test group significantly increased after 2 weeks and 4 weeks of product use ($P < 0.05$), with an improvement rate of 4.4% after 2 weeks and 8.9% after 4 weeks. Compared to the control group, the local hair density in test group also significantly improved after 2 weeks and 4 weeks of product use ($P < 0.05$).

Table 6. Results of the Experiment on the Effect of POL on Improving Local Hair Density

Group	Local Hair Density	Improvement rate of local hair density relative to the initial value(%)

	Before use	After 2 weeks	After 4 weeks	After 2 weeks	After 4 weeks
Tset	117.69	122.86	128.20	4.4%*#	8.9%*#
Control	115.92	117.76	116.83	1.6%	0.8%

Note: Compared with the initial value, *P < 0.05; compared with the vehicle group, #P < 0.05

4. Discussion

This study employed network pharmacology to preliminarily explore the key molecular pathways and active components of *POL* in treating AGA. The therapeutic effects were further validated through cellular experiments and clinical anti-hair loss efficacy assessments.

Network pharmacology analysis revealed that the steroid hormone biosynthesis pathway was the most significantly enriched among the core shared targets of *POL* and AGA. This pathway, critical in androgen metabolism dysregulation, plays a pivotal role in AGA pathogenesis [11]. The steroid hormone biosynthesis pathway interacts with multiple signaling pathways, such as Wnt/β-catenin and TGF-β, disrupting the normal hair follicle growth cycle and contributing to hair loss [12]. Dysregulated androgen metabolism not only suppresses dermal papilla cell proliferation—accelerating the transition from anagen to catagen and telogen phases—but also upregulates apoptosis-related signals in dermal papilla cells, thereby interrupting normal hair cycling.

The study demonstrated that *POL*, rich in isoquercitrin, quercitrin, and afzelin, significantly promotes dermal papilla cell proliferation and inhibits apoptosis. Quercitrin activates the Wnt/β-catenin pathway to stimulate dermal papilla cell proliferation [13]. Isoquercitrin enhances the bioavailability of quercetin and inhibits TGF-β1 signaling, preventing perifollicular fibrosis [14]. Afzelin upregulates β-catenin signaling to induce dermal papilla cell proliferation [14].

These findings suggest that these components may exert therapeutic effects by modulating the steroid biosynthesis pathway and cross-talking with multiple signaling pathways, expanding our understanding of *Platycladus orientalis*'s mechanisms in AGA treatment.

In vitro dermal papilla cell experiments, at 31.25 μg/mL the extract increased cell proliferation by 15.63%(P< 0.01), comparable to 100 μg/mL minoxidil(P> 0.05), indicating its potential as an alternative or adjunct to minoxidil. At 125 μg/mL, the extract exhibited at 35.35% inhibition of apoptosis(P< 0.01), with efficacy escalating at higher concentrations, suggesting promise for localized high-dose applications.

Clinical anti-hair loss evaluation: A 500 μg/mL rinse-off shampoo formulation reduced hair shedding by 61.9%(P< 0.05), improved global hair density by 25.8%(P< 0.05), and enhanced localized hair density by 8.9% (P< 0.05) after 4 weeks, with significant differences versus the vehicle control (P< 0.05).

These results validate the efficacy of *Platycladus orientalis* in shampoo formulations and highlight the potential of rinse-off products for anti-hair loss applications. Further studies are needed to elucidate its permeation behavior and mechanistic details.

5. Conclusion

In summary, this study reveals that POL may exert anti-apoptotic and proliferative effects on dermal papilla cells by regulating the steroid biosynthesis pathway. These findings were further corroborated through clinical evaluations, which confirmed the efficacy of shampoos

containing POL in improving hair loss. Additionally, flavonoid components in the extract, such as isoquercitrin, quercetin, and afzelin, have demonstrated significant potential. Overall, the study highlights the multifaceted potential of POL in preventing hair loss and provides research support for the application of plant-based therapies in improving hair loss strategies within the cosmetics industry.

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