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A Retrospective Analysis of Acupoint Catgut Embedding Therapy For Overweight/Obesity

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Abstract

[Objective] To retrospectively analyze the clinical efficacy and safety of acupoint catgut embedding therapy in treating overweight/obesity. [Methods] A total of 48 overweight/obese patients were treated with acupoint catgut embedding. Changes in body weight and body mass index (BMI) before and after treatment were observed, and intraoperative/postoperative adverse reactions were recorded. [Results] Both the effective rate and marked effectiveness of the acupoint catgut embedding therapy rate were favorable. [Conclusion] Acupoint catgut embedding therapy is safe and effective for treating overweight/obesity.

Keywords Acupoint Embedding Thread; overweight; obesity
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1 Background

Overweight/obesity represents a significant public health concern, with its global prevalence continuously increasing. According to reports, the overweight/obesity rate among Chinese adults has reached 50.7[1]. Over the past two decades, alongside shifts in dietary patterns and lifestyle habits, there has been a marked rise in the consumption of high-sugar, high-fat, and highly processed foods, while physical activity time has declined due to more sedentary behavior—factors contributing to the rapid increase in overweight and obesity cases.

Obesity is fundamentally a chronic disease influenced by multiple factors, including genetic predisposition and environmental conditions. Research indicates[2] that overweight and obesity are closely associated with increased risks of non-communicable diseases (NCDs), such as type 2 diabetes, non-alcoholic fatty liver disease, hypertension, myocardial infarction, stroke, dementia, osteoarthritis, obstructive sleep apnea, and certain types of cancer. These comorbidities significantly reduce quality of life and elevate the risk of premature mortality.

Current treatment approaches for overweight/obesity include pharmacotherapy, exercise, dietary interventions, and surgical procedures. However, these methods often face limitations such as low patient adherence and procedural invasiveness. Acupoint catgut embedding therapy (ACE)[3], known for its operational simplicity and sustained efficacy, has the potential to improve compliance. ACE integrates multiple therapeutic modalities—including acupoint-blocking effects, acupuncture-like stimulation, bloodletting, tissue repair responses, and localized therapeutic effects—into a single intervention.

In recent years, ACE has seen widespread application in weight management. This study retrospectively analyzed 48 overweight or obese patients who underwent ACE therapy at Longhua District Maternal and Child Health Hospital in Shenzhen between 2023 and 2024, aiming to evaluate its clinical efficacy and safety. Additionally, a comprehensive literature review on ACE for overweight/obesity was conducted using databases such as CNKI, VIP, and PubMed. The objective is to summarize existing findings and explore the potential mechanisms and limitations of ACE, thereby providing a more robust theoretical foundation for its clinical application in obesity treatment.

2 Materials and Methods

This retrospective study included 48 overweight or obese patients who underwent acupoint catgut embedding (ACE) therapy at Longhua District Maternal and Child Health Hospital in Shenzhen between January 2023 and December 2024. Inclusion criteria were: (1) body mass index (BMI) ≥ 24 kg/m^2 for overweight or ≥ 28 kg/m^2 for obesity, and (2) provision of informed consent and signature of the ACE therapy consent form. Patients were excluded if they had obesity secondary to other underlying diseases, were pregnant, suffered from severe primary comorbidities, presented with skin lesions or ulcers at treatment sites, had a history of foreign protein allergy, or had coagulation disorders.

The treatment protocol followed standard procedures. Acupoints were selected based on the national TCM curriculum and WHO nomenclature, including CV 12, ST 25, CV 4, CV 6, ST 28, ST 36, and ST 40. Polyglycolic acid (PGA) absorbable sutures (2 cm) were embedded into either the muscle layer (limbs, ST 36/ST 40) or adipose layer (abdomen, CV and ST points) depending on body region. Treatment was performed biweekly over two months (2 sessions total). The patient lay supine while acupoints were disinfected with iodophor. After strict aseptic preparation, a PGA suture was threaded through a 5 mL syringe needle and inserted into the acupoint to achieve “de qi.” The needle was then withdrawn, leaving the suture embedded. Postoperative care included compression with sterile cotton, application of dressings, and avoidance of bathing, pressure, or spicy foods for a specified time. Patients were instructed to report any adverse reactions such as pain, nodules, redness, or fever.

Observation metrics included body weight, BMI, and waist circumference measured before and after treatment. Fasting weight in undergarments was recorded, and BMI calculated to two decimal places. Efficacy was categorized as: *markedly effective* (weight loss ≥ 5 kg or BMI reduction ≥ 2 kg/m^2), *effective* (weight loss 3–5 kg or BMI reduction 1–2 kg/m^2), or *ineffective* (weight loss < 3 kg or BMI reduction < 1 kg/m^2, or no change). The total effective rate was calculated using the following formula:

$$\text{Total Effective Rate (\%)} = \left(\frac{\text{Markedly Effective Cases + Effective Cases}}{\text{Total Cases}}\right) \times 100\%$$

Adverse events such as syncope, pain, bruising, fever, and suture rejection were monitored, and the incidence of adverse events was calculated as:

$$\text{Adverse Event Incidence (\%)} = \left(\frac{\text{Number of Adverse Events}}{\text{Total Procedures}}\right) \times 100\%$$

Data analysis was performed using SPSS version 26.0. Measurement data were tested for normality; those conforming to a normal distribution were expressed as mean ± standard deviation. Pre- and post-treatment comparisons were made using paired-sample t-tests. A p-value < 0.05 was considered statistically significant.

3 Results

3.1 General Characteristics

Among the 48 overweight or obese patients who completed ACE therapy, the majority were female (43 cases, 89.58%), reflecting the hospital' s focus on maternal and child health. Only 5 participants (10.42%) were male. Most patients (87.5%) were between 20 and 40 years of age. Based on BMI diagnostic criteria, 25 patients (52.08%) were classified as obese (BMI $\geq$ 28 kg/m^2), and 23 patients (47.92%) as overweight (BMI $\geq$ 24 kg/m^2).

Table 1 Baseline Patient Characteristics and Clinical Information

Items	N%
Gender	
Male	5(10.42%)
Female	43(89.58%)
Age/years	
<20	0(0%)
20-30	27(56.25%)
30-40	15(31.25%)
40-50	6(12.50%)
>50	0(0%)
BMI (kg/m^2)	
24-27.9	23(47.92%)
>28	25(52.08%)

3.2 Comparison of Weight and BMI Before and After Treatment

After treatment, patients showed statistically significant reductions in both body weight and BMI compared to their pre-treatment values ($p < 0.05$), as detailed in Table 2.

Table 2 Comparison of Weight, BMI (*n=48*)

	Weight（kg）	BMI（kg/m2）
Pre-ACE	67.7750±7.7921	27.6552±2.0506
Post-ACE	64.2579±7.0869*	26.2535±2.2325**

*Sig: *Compared to pre-treatment, P < 0.05; **Compared to pre-treatment, *P < 0.01.*

3.3 Treatment Efficacy

The total effective rate of catgut embedding therapy was 64.6%, with outcomes categorized as markedly effective, effective, or ineffective. Overall, the therapeutic response was favorable, as summarized in Table 3.

Table 3 Treatment Efficacy

Efficacy (Number of Cases)			Total Effective Rate（%）
Marked Efficacy	Effective	Ineffective	
16	15	17	64.6%

3.4 Adverse Events

Across 96 treatment sessions (two sessions per patient), intraoperative pain and bleeding occurred in 100% of procedures, while no cases of needling syncope were reported (0%). Postoperatively, prolonged pain lasting up to 7 days was observed in 70.8% of cases, but no instances exceeded 7 days (0%). Nodule formation was not observed (0%), and bruising occurred in 2.08% of cases, with half of those lasting more than 7 days. No severe adverse reactions—including suture rejection, fever, infection or abscess, or fat liquefaction—were documented in this retrospective analysis.

Table 4 Adverse Event Incidence (Cases (%))

	Pain	Bleeding	Needling Syncope	Nodule Formation	Bruising	Redness/ Swelling	Fat Liquefaction	Infection	Fever
During ACE	96（100）	96（100）	0	—	—	—	—	—	—
Within 7 Days Post-ACE	68（70.8）	2（20.8）	—	—	2（2.08）	3（31.3）	—	—	—
Beyond 7 Days	0	0	—	—	1（1.04）	—	—	—	—

4 Discussion

Modern medicine considers overweight and obesity to be chronic metabolic disorders characterized by excessive adipose tissue accumulation and abnormal body weight, resulting from a complex interplay of genetic, environmental, and other contributing factors[4]. An energy surplus induces dynamic changes in adipose tissue volume and cellular architecture, leading to adipose tissue remodeling. The imbalance between energy intake and expenditure is widely recognized as the primary driver of overweight and obesity[5]. Scientifically validated strategies for weight management emphasize dietary regulation and increased physical activity. However, many patients struggle to sustain long-term adherence to exercise regimens, underscoring the need for alternative therapeutic approaches.

Acupoint Catgut Embedding (ACE) therapy involves the implantation of absorbable surgical sutures into specific acupoints, where sustained stimulation through needling, thread retention, and micro-bloodletting synergistically dredges meridians, regulates qi-blood balance, and eliminates dampness and turbidity. Functioning as a long-acting form of acupuncture[6], it shares mechanistic similarities with traditional acupuncture by promoting qi circulation and meridian regulation. The insertion of sutures induces localized inflammatory responses, activating immune phagocytic functions that aid in clearing necrotic tissue and triggering apoptosis in senescent cells. Studies[7] have suggested that weight loss following embedding is associated with a reduction in peripheral adipose tissue volume. ACE therapy thus exhibits distinct therapeutic mechanisms and has demonstrated significant clinical efficacy in managing overweight and obesity. By modulating multiple physiological systems, it offers a non-pharmacological and non-surgical option for effective weight control.

4.1 Comparison of Different Suture Materials

Clinically used embedding materials include catgut and collagen sutures, most of which are absorbable surgical sutures (excluding traditional catgut). The flexibility and biocompatibility of these materials are critical for therapeutic outcomes. As ACE therapy relies on sustained acupoint stimulation, preference is given to sutures with optimal absorption duration and safety profiles. Consequently, traditional catgut—

owing to its instability—has been largely replaced by modern absorbable sutures. The composition and characteristics of various suture types are summarized in Table 5.

Commonly used suture lengths include 1 cm, 1.5 cm, and 2 cm. For acupoints located in muscle-rich or adipose-rich areas (e.g., limbs, abdomen), longer sutures (1.5–2 cm) are preferred to enhance stimulation intensity. In contrast, for superficial or pain-sensitive regions, shorter sutures (1 cm) are selected to minimize the risk of suture protrusion and patient discomfort.

Table 5 Comparison of Different Suture Materials

Suture Material	Composition	Absorption Time	Advantages and Disadvantages
Catgut	Submucosal connective tissue from sheep or cattle	4-5d	Low cost, unstable performance, frequent adverse reactions
Collagen	Collagen derived from the bones of higher animals	4-5d	Non-irritating, minimal tissue reaction, easy storage
PGLA	PGA (Polyglycolic Acid) or PLA (Polylactic Acid)	2-4w	Good flexibility, biocompatibility, and biodegradability
PGA	Corn or sugar beet	2-4w	Good flexibility, biocompatibility, and biodegradability
PDS	Polymer of polydioxanone with ≥99% purity	2-4w	Non-allergenic
PLA	Lactic acid	2-4w	Non-toxic material, non-irritating, excellent biocompatibility

4.2 Embedding Depth

Current literature indicates that embedding depths for catgut sutures primarily target the subcutaneous layer, subcutaneous adipose tissue, or muscle layer. Sutures embedded in the adipose layer have demonstrated superior weight-loss efficacy, while those placed in the muscle layer are associated with a lower risk of suture protrusion. Due to anatomical variations in the vertical distance between the skin and underlying adipose or muscle layers, embedding depth should be adjusted based on specific body regions.

The muscle layer, being richer in blood vessels and nerves than the adipose layer, often induces more pronounced local soreness and pain during the embedding process. For patients with low pain tolerance, placement of sutures within the adipose layer is recommended to reduce discomfort and enhance treatment compliance.

4.3 Medical Evaluation of Obesity

In clinical practice, acupoint catgut embedding therapy for obesity often emphasizes treatment over obesity staging or stratified management. However, not all stages of obesity respond equally to this intervention. The severity and progression of obesity influence appropriate therapeutic strategies[8]. According to the guidelines of the American Association of Clinical Endocrinologists (AACE)[9], obesity is defined as a chronic disease characterized by excess adipose tissue, with an emphasis on grading and staging to guide treatment.

When applying embedding therapy, obesity-related comorbidities must be concurrently assessed and addressed. Evidence suggests that ACE therapy has demonstrated clinical efficacy in managing obesity accompanied by hyperlipidemia, hypertension, prediabetes, polycystic ovary syndrome (PCOS), and non-alcoholic fatty liver disease (NAFLD)[10]. However, the severity of comorbidities must be carefully evaluated. In some cases, a combination of ACE therapy and pharmacological treatment may be necessary. For patients with severe complications—such as hypothyroidism, Cushing’s syndrome, acanthosis nigricans, or hypothalamic disorders—standalone embedding therapy is contraindicated.

Patients may present with obesity in the absence of suboptimal health manifestations—such as thermoregulatory dysfunction, constipation, insomnia, or anxiety/depression—and without abnormal laboratory findings. In such cases, where organ function remains intact, significant weight loss can often be achieved through a combination of embedding therapy, dietary regulation, and moderate exercise. These individuals primarily suffer from energy imbalance, making them more responsive to non-pharmacological interventions.

In contrast, patients with underlying metabolic disorders (e.g., diabetes, NAFLD) or endocrine abnormalities (e.g., polycystic ovary syndrome, cortisol excess) require comprehensive, multimodal interventions. For these patients, embedding therapy alone typically yields limited results. Effective management must integrate dietary adjustments, control of comorbidities, and systemic health optimization.

Tailored treatment protocols should be developed based on individual patient characteristics, including adiposity distribution, comorbidity profiles, and metabolic resilience, to ensure sustainable and clinically meaningful outcomes.

4.4 Efficacy of Catgut Embedding for Weight Loss

In this retrospective analysis, acupoint catgut embedding therapy demonstrated favorable outcomes in the management of overweight and obesity, with notable effective and markedly effective rates. Significant improvements were observed in body weight, BMI, waist circumference, and overall clinical efficacy, laying a foundation for achieving target weight reduction. Clinically, individualized treatment protocols should be developed to enhance patient adherence and optimize therapeutic outcomes.

It is noteworthy that some patients in this cohort received combination therapy involving both embedding and pharmacological interventions; however, these cases were excluded from the present analysis. Future studies should employ controlled trial designs to better assess the efficacy of combined therapeutic approaches.

Study Limitations:(1)Limited sample size ($n = 48$) and short follow-up duration (2 months).(2) No patients received more than three treatment sessions, preventing assessment of long-term efficacy.(3)The durability of therapeutic effects—particularly the issue of "weight rebound," a major patient concern—remains undetermined.(4)Potential selection bias exists, as only patients who completed follow-up were included. Expanding the study cohort in future research will improve data reliability and generalizability.

4.5 Safety of ACE for Weight Loss

In terms of treatment safety, no severe intraoperative adverse reactions—such as fat liquefaction, infection, or needling syncope—were observed in this cohort (0% incidence). The most prolonged adverse event was bruising, reported in 2.08% of cases, with symptoms lasting beyond one week. To optimize safety, we recommend shortening the treatment interval from four weeks to two weeks, ensuring complete resolution of prior adverse events before administering the next session. No severe complications (e.g., fever, infected abscesses, or fat liquefaction) were reported, supporting the overall safety profile of ACE therapy.

However, patient willingness to continue treatment is largely influenced by intraoperative and postoperative experiences. Future research should focus on minimizing procedural pain and reducing postoperative adverse effects through technical refinement.

5 Summary

In conclusion, this retrospective analysis demonstrates that acupoint catgut embedding therapy effectively promotes weight reduction in overweight and obese individuals while addressing limitations associated with conventional pharmacological and surgical treatments. Importantly, the therapy's favorable safety profile and tolerability support sustained patient adherence, making it a viable long-term weight management strategy. ACE therapy is recommended as a safe and effective approach to obesity treatment and is worthy of broader clinical application.

Conflict of Interest: The authors declare that they have no conflict of interest.
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Authors' Contributions Ying CHEN drafted the manuscript. Ying CHEN, Jingwen WANG, Dan ZHU, and Xiaoying YI collected the clinical data. Ying CHEN performed the data analysis.
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Effectiveness of Rain Classroom combined with Case-Based teaching in the Gynecological nursing practice for undergraduate interns

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Abstract

[Aims] This study aimed to investigate the effectiveness of combining Rain Classroom with case-based teaching in improving the educational outcomes of undergraduate interns in gynecological nursing. [Methods] A total of 48 full-time undergraduate nursing interns in the gynecology department of the Seventh Affiliated Hospital of Sun Yat-sen University, from August 2023 to April 2025, were selected and divided into a control group (traditional lecture-based teaching, n = 24) and an experimental group (Rain Classroom combined with case-based teaching, n = 24) according to the chronological order of their internships. Teaching effectiveness was evaluated based on theoretical exam scores, nursing assignment scores, and student satisfaction. [Results] The results indicated that the theoretical exam and nursing assignment scores of the experimental group were significantly higher than those of the control group. Furthermore, the combined teaching model effectively stimulated students' interest in learning, improved their mastery of theoretical knowledge, enhanced their initiative and engagement, and increased overall teaching satisfaction. [Conclusions] Integrating Rain Classroom with case-based teaching proves to be an effective strategy for enhancing students' learning initiative, optimizing knowledge acquisition, and supporting the ongoing reform of nursing education.

Keywords Nursing interns; Rain Classroom; Case-based teaching; Teaching satisfaction

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1 Introduction

Nursing internships represent a pivotal stage in the transition from academic study to clinical practice. This phase enables interns to translate classroom-acquired knowledge into real-world clinical scenarios, validate theoretical principles, deepen their understanding of disease management and pharmacological applications, and develop both basic and specialized clinical skills. However, traditional teaching approaches are often limited by low interactivity, inflexible content delivery, repetitive instructional methods, and insufficient student engagement[1-2], all of which impede the effectiveness of learning. In response to the growing trend of educational informatization, the integration of intelligent technologies and innovative pedagogical strategies has emerged as a key avenue for enhancing the quality of clinical education.

Rain Classroom is an innovative AI-powered teaching platform developed by Tsinghua University, and it has been increasingly applied in clinical education. Its key features include: (1) delivering educational materials to students via WeChat; (2) embedding quizzes into PowerPoint slides for real-time formative assessment; (3) enabling teacher-student interaction through randomized roll calls; (4) supporting a variety of question formats for assignments; and (5) providing regular analytics on teaching effectiveness. By integrating high-quality resources with interactive functionalities, Rain Classroom significantly enhances the learning experience and contributes to improved academic performance among interns [3-4].

The platform is user-friendly and accessible across multiple devices, including smartphones, computers, and tablets. Instructors can distribute teaching materials—such as slides, quizzes, videos, and audio files—directly to students' mobile devices. Students can access these materials in real time by scanning QR codes via WeChat or its embedded mini-programs. The system automatically records and analyzes learning data, allowing educators to track student engagement and learning progress before, during, and after class, and to adjust teaching strategies accordingly. This model of flexible and fragmented learning is particularly well-suited to the dynamic and time-constrained environment of clinical nursing education [5-6].

Gynecology wards are characterized by a wide spectrum of disease types, frequent emergencies, complex clinical presentations, and high workloads. In this context, the accumulation and application of typical clinical cases are essential components of nursing education. By analyzing multiple representative cases of common gynecological conditions, educators can effectively cultivate interns' clinical reasoning and problem-solving skills. Case-based teaching (CBT) encourages students to apply theoretical knowledge in practical scenarios, promoting deeper understanding through vivid, context-rich discussions. This approach not only enhances learning motivation but also bridges the gap between theory and practice, thereby fostering the development of clinical thinking abilities [7].

Against this backdrop, the present study investigates the effectiveness of integrating Rain Classroom with case-based teaching for undergraduate interns in gynecological nursing. The aim is to provide evidence-based insights for optimizing instructional strategies and improving the quality of clinical nursing education.

2 Materials and Methods

2.1 Study design

This study employed a comparative design. A total of 48 nursing interns from the gynecology department of the Seventh Affiliated Hospital of Sun Yat-sen University participated, with internships conducted between August 2023 and April 2025. Inclusion criteria were as follows: (1) full-time undergraduate nursing students; (2) provision of informed consent and a serious attitude toward the internship. Exclusion criteria included: (1) interns who violated hospital regulations and had their internship terminated prematurely; (2) those who did not attend in-person lectures; (3) those who missed the theoretical examinations.

Participants were assigned to a control group ($n = 24$) and an experimental group ($n = 24$) based on the chronological order of their internship rotation. There were no significant differences in baseline characteristics, such as age and gender, between the two groups ($P > 0.05$), indicating good comparability.

2.2 Intervention strategies

According to the requirements of the gynecology nursing curriculum, each intern completed a four-week clinical rotation. On the first day, the interns participated in a departmental orientation conducted by the pediatric-gynecological teaching coordinator, followed by specialized training delivered by gynecology educators. Each intern was assigned a clinical mentor and required to complete weekly plans encompassing theoretical instruction, skills practice, and bedside teaching. In the second week, two instructors provided thematic lectures on topics such as perioperative care for cervical cancer and key management points in ectopic pregnancy. During the fourth week, interns' theoretical knowledge and nursing assignments were assessed by both educators and clinical mentors. The head nurse supervised the overall quality control process to ensure the consistency and fairness of evaluations.

The control group received traditional lecture-based instruction, while the experimental group was exposed to a combined teaching model incorporating Rain Classroom and case-based learning. (1) Pre-class Preparation: PowerPoint presentations (PPTs) were designed with 3 4 embedded multiple-choice questions per slide. Nursing educators distributed the materials to interns via the Rain Classroom platform. (2) Group Enrollment and Pre-class Engagement: New interns were invited to join the Rain Classroom group. They were instructed to preview the PPT content in advance, flag slides marked as "difficult to understand," and bookmark key slides for discussion. Pre-class self-assessments, consisting of single- and multiple-choice questions on topics such as clinical symptoms, common etiologies, and treatment modalities of ectopic pregnancy and cervical cancer, were completed to identify knowledge gaps [7-8]. (3) In-class Delivery: Instructors proficient in using Rain Classroom facilitated sessions in multimedia-equipped classrooms. Interns accessed the virtual classroom by scanning a QR code or entering a unique code via WeChat. (4) Adaptive Teaching Strategies: Based on the pre-class self-assessment results, instructors adjusted their teaching strategies to emphasize core concepts, address common misconceptions, and focus on challenging areas. (5) Interactive Case-Based Learning: Clinical case scenarios were integrated into lectures, supplemented by relevant images and video clips to expand and consolidate knowledge. Interactive approaches—including randomized Q&A, group discussions, and real-time feedback tools such as bullet-screen comments—were employed to increase engagement and foster active learning. (6) Post-class Reinforcement: Interns reviewed lecture materials and reinforced key knowledge points using Rain Classroom's mobile mini-program or official WeChat account, supporting flexible, on-demand learning and promoting long-term retention. (7) Final Assessment: In the fourth week, clinical educators administered theoretical examinations and evaluated nursing assignments aligned with the instructional content to assess students' mastery of the material[9-10]] (Figure 1).

2.3 Measurements

The primary outcome indicator was academic performance. In the fourth week of the internship, clinical educators administered a theoretical examination and a nursing assignment, both aligned with the curriculum content. Each component was scored on a 0 100 scale, with higher scores indicating a greater mastery of knowledge among interns [11].

The secondary outcome indicator was student satisfaction. Upon completion of the rotation, the teaching coordinator of the obstetrics and gynecology department distributed an online questionnaire via the Wenjuanxing platform (WeChat-based) to assess interns' satisfaction with the theoretical teaching. The questionnaire covered four dimensions: (1) stimulation of learning interest, (2) mastery of theoretical knowledge, (3) enhancement of learning initiative and engagement, and (4) overall teaching satisfaction. Each dimension was rated on a 100-point scale, with higher scores reflecting greater perceived teaching effectiveness [12]. A total of 48 valid responses were collected, yielding a response rate of 100%.

2.4 Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared using independent-samples t tests. Categorical

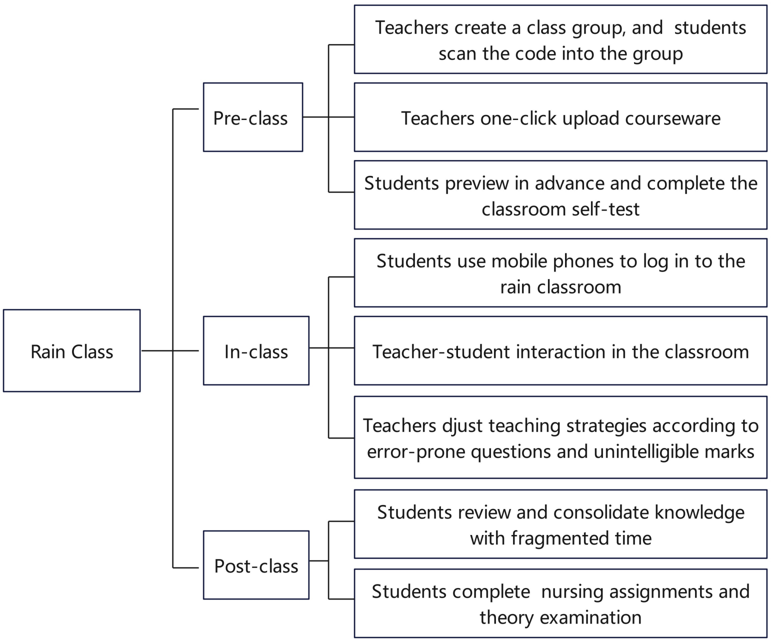

Figure 1: The process of Rain Classroom mode

variables were presented as frequencies and percentages (%) and analyzed using chi-square χ^2 tests. A P-value < 0.05 was considered statistically significant.

3 Results

3.1 Academic Performance

The experimental group performed significantly better than the control group in both the theoretical examination (85.96 ± 10.18 vs. 72.58 ± 10.01; $t = -4.589$, $P < 0.001$) and nursing assignment scores (90.50 ± 1.87 vs. 87.21 ± 3.75; $t = -3.848$, $P = 0.001$) (Table 1).

Table 1. Theoretical Exam and Nursing Assignment Scores of Participants ($N = 48$)

Evaluation index	Control group **($\bar{x} \pm s$)**	Experimental group **($\bar{x} \pm s$)**	t	P
Theoretical Exam Scores	72.58 ± 10.01	87.21 ± 3.75	-4.589	0.000**
Nursing Assignment Scores	85.96 ± 10.18	90.50 ± 1.87	-3.848	0.001**

*$P < 0.05$, **$P < 0.01$.

3.2 Teaching Satisfaction

Compared with the control group, the experimental group demonstrated greater effectiveness in stimulating students' interest in learning (95.83% vs. 62.50%), facilitating the mastery of theoretical knowledge (95.83% vs. 70.83%), enhancing learning initiative and engagement (91.66% vs. 66.66%), and improving overall teaching satisfaction (100% vs. 75%). The scores in the experimental group were significantly higher than those in the control group, and the differences were statistically significant ($P < 0.05$) (Table 2).

Table 2. Comparison of Teaching Satisfaction Between Control and Experimental Groups

Item	Control group (n = 24)		Experimental group (n = 24)		χ^2	P
	Satisfied [n (%)]	Dissatisfied [n (%)]	Satisfied [n (%)]	Dissatisfied [n (%)]		
Stimulate Interest	15（62.50）	9（37.5）	23（95.83）	1（4.17）	8.084	0.005**
Mastery of theoretical knowledge	17（70.83）	7（29.17）	23（95.83）	1（4.17）	5.400	0.024*
Enhance initiatives and engagement	16（66.66）	8（33.33）	22（91.66）	2（8.33）	4.547	0.033*
Overall teaching Satisfaction	18（75）	6（25）	24（100）	0（0）	6.857	0.011*

*$P < 0.05$, **$P < 0.01$.

4 Discussion

4.1 Rain Classroom combined with Case-Based teaching enhances academic performance

A comparative analysis of the two groups revealed that the nursing interns in the experimental group achieved significantly higher scores in both theoretical examinations and nursing assignments compared to those in the control group ($P < 0.05$). These findings are consistent with the experimental results reported by Trullàs[13].

Compared to the traditional teaching model, the integration of Rain Classroom with case-based teaching offers distinct advantages. It effectively identifies core knowledge and skill points, fosters a dynamic and interactive classroom environment, and stimulates students' motivation for inquiry-based learning. This innovative pedagogical model can be implemented through three interconnected phases: (1)Pre-class preparation: The model leverages online resources to enable knowledge preposition and creates a personalized learning space for students with weaker cognitive foundations.(2)In-class interaction: Through functions such as real-time feedback and bullet-screen interactions (barrage), it establishes deep teacher-student dialogue, thereby addressing key limitations of traditional classrooms, including low participation and lack of evaluative feedback.(3)Post-class reinforcement: Digital resource iteration supports knowledge consolidation and promotes higher-order thinking development[14].

This study demonstrated that the experimental group scored significantly higher in the theoretical examination (85.96 ± 10.18) compared to the control group (72.58 ± 10.01; $P < 0.001$). Similarly, nursing assignment scores were significantly higher in the experimental group (90.50 ± 1.87) than in the control group (87.21 ± 3.75; $P < 0.05$). These findings suggest that this blended teaching model not only improves teaching effectiveness in clinical nursing practice but also serves as a reproducible and scalable paradigm for nursing education reform.

4.2 Rain Classroom combined with Case-Based teaching enhances satisfaction

As society rapidly evolves, so too do educational models. In the context of clinical nursing practice teaching, traditional methods exhibit several limitations: (1) the teaching approach is monotonous and lacks innovation; (2) standardized teaching schedules and content fail to accommodate the diverse learning abilities of students; (3) teacher-centered instruction often devotes excessive time to explaining knowledge points, causing students to passively receive information, take notes mechanically, and miss opportunities for critical thinking and interaction.

The case-based teaching method is not merely a tool for knowledge transmission in nursing education; it is also a fundamental strategy for cultivating competency-oriented nursing professionals. Through situational learning, nursing students can integrate fragmented knowledge into systematic clinical capabilities, develop professional values, and build a strong foundation for navigating the complexities of real-world clinical environments[15].

Traditionally, Rain Classroom and case-based teaching were used separately, often resulting in one-way knowledge transmission, with students passively receiving information. This study introduced an innovative integration of the Rain Classroom platform with the case-based teaching method. By leveraging technology-enhanced instruction, this approach significantly improved both learning efficiency and student satisfaction.

Aligned with the modern "student-centered" educational philosophy, this model offers a novel and dynamic teaching experience for both instructors and learners, creating an engaging classroom atmosphere. It effectively stimulates nursing interns' interest in learning, enhances their capacity for active learning, and improves their theoretical performance. Moreover, it fosters the development of clinical thinking skills, strengthens knowledge retention, and elevates overall teaching satisfaction.

This integrated model addresses the shortcomings of traditional teaching approaches and has yielded promising outcomes. It contributes new momentum to the reform of clinical nursing education and provides a replicable framework for future educational innovation.

5 Conclusion and implications for practice

In this study, the integration of Rain Classroom with case-based teaching led to several notable advancements in clinical nursing education. First, dynamic interaction was achieved by enhancing classroom engagement through interactive features such as real-time comments and group discussions. Second, precision instruction was made possible by analyzing preview data to tailor content and focus on key learning areas. Third, the cultivation of clinical thinking was promoted through real-case simulations, which facilitated the integration of theoretical knowledge with practical application. The findings suggest that combining Rain Classroom with case-based teaching can effectively improve the theoretical knowledge and teaching satisfaction of gynecological nursing interns, demonstrating its potential for broader clinical application. Moving forward, this dual-mode instructional approach may be further developed and enriched by integrating cutting-edge educational theories, enabling it to better meet the evolving needs of nursing professionals in modern healthcare settings.

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Medical Research

Reflections on Competency-Based Curriculum Reform in Master's Graduate Education of Basic Medical Sciences

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Abstract

The cultivation of job competency is a core objective of master's graduate education in basic medical sciences and plays a critical role in students' career development. Curriculum reform is a key strategy for enhancing the quality of graduate education. It not only lays the foundation for training high-caliber medical professionals but also facilitates adaptation to the evolving medical landscape, advances scientific research, and promotes the standardization of medical education. Therefore, by focusing on job competency development, we should establish a curriculum-based training pathway for master' s education in basic medical sciences that meets the demands of the new era and aligns with the needs of medical development and public health. This paper presents the reform and implementation of a training model at our university, aiming to provide insights into the improvement of medical graduate education in China and to contribute to raising its overall quality.

Keywords Job competency; Curriculum System Reform; Basic Medicine; Master's graduate Education

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1 Introduction

Medical master's graduate education is a critical component of the broader medical education system and is closely tied to the development of China's healthcare undertakings. The *Guiding Opinions of the General Office of the State Council on Accelerating the Innovative Development of Medical Education*(Guobanfa [2020] No. 34) (hereinafter referred to as the *Opinions*)[1] emphasize the need to "be guided by service needs, focus on the development of new medical disciplines, strive to innovate institutional mechanisms, and cultivate research-oriented, interdisciplinary, and application-oriented talents through classified training." The Opinions further state that "by 2030, a higher-level medical talent training system with Chinese characteristics should be established, with significantly enhanced capacity for scientific research and innovation, and a markedly strengthened ability to support healthcare development," thereby providing strong talent support for building a Healthy China and safeguarding public health.

As basic medicine constitutes the cornerstone of clinical practice, medical research, and the innovation of diagnostic and treatment technologies, basic medical education occupies an irreplaceable role in cultivating high-level, innovative medical professionals[2]. Within this context, master's graduate education in basic medicine serves as a crucial bridge—it not only builds upon undergraduate education but also lays a vital foundation for future professional development. Most graduates pursue careers in universities, research institutes, and healthcare institutions. Therefore, basic medical master's education must not only deepen and expand theoretical knowledge but also focus on cultivating interdisciplinary thinking, scientific research competence, and clinical practical skills, enabling students to meet the professional demands of their future careers.

Job competency refers to the comprehensive demonstration of knowledge, abilities, skills, and personal traits necessary for an individual to perform a specific job[3]. Cultivating job competency is of utmost importance for the career development of master's graduate education in basic medical sciences, primarily manifested in: providing essential professional knowledge and skills to address scientific research and clinical challenges; enhancing scientific research innovation and data processing capabilities; improving clinical operation skills and service levels; and helping students maintain learning initiative to continuously upgrade their knowledge base and practical skills in response to increasingly complex job requirements.

The cultivation of job competency is inseparable from a curriculum system that aligns with the professional demands of master' s graduate education in basic medical sciences. An effective curriculum should not only deliver rich theoretical instruction but also provide systematic training in scientific research and data analysis, as well as hands-on practice in laboratory and clinical operations. This enables graduates to strengthen their practical competencies and logical thinking abilities. Therefore, reforming the curriculum system based on job competency is pivotal to advancing the quality of master' s education in basic medical sciences.

2 Problems in the Curriculum System of Master's Graduate Education in Basic Medical Sciences

After years of development, the curriculum system for master' s graduate education in basic medical sciences in China has gradually improved. However, with rapid technological advancements and evolving societal demands, significant deficiencies remain in the cultivation of job competency.

In terms of course content, there is a widespread tendency in universities to prioritize knowledge acquisition over competency development. Curriculum updates often lag behind emerging needs, and the provision of core competency-related courses—such as those in basic medicine, clinical skills, research methods and design, ethics, and medical law—remains inadequate. In addition, interdisciplinary courses in areas such as artificial intelligence and public health are underrepresented, limiting students' exposure to emerging fields.

Regarding teaching methods, traditional teacher-centered instruction still dominates, while student-centered approaches—such as problem-based learning (PBL) and flipped classrooms—are underutilized. The adoption of intelligent teaching platforms by instructors remains low, and personalized learning pathways have yet to be fully implemented. Furthermore, the disconnection between classroom teaching and clinical practice impedes students' ability to translate basic medical knowledge into clinical reasoning, thereby undermining their development of job competency in real-world medical contexts.

3 Approaches to Competency-Based Curriculum System Reform for master's graduate education of basic medical sciences

3.1 Constructing a Curriculum System Centered on job competency

The curriculum system should be guided by clear training objectives and centered on job competency, ensuring alignment between program requirements and course design. Given that most graduates of master's programs in basic medical sciences pursue careers in universities, research institutes, or healthcare settings (e.g., as university instructors, medical professionals, or researchers), our curriculum emphasizes ideological and political education, scientific thinking, academic integrity, foreign language proficiency, international academic communication, and innovation-oriented practical training.

The curriculum structure consists of the following four modules: (1)Basic Courses: Disciplinary foundation courses that provide essential medical knowledge, and general education courses aimed at fostering comprehensive competencies. (2)Professional Courses: Core courses focused on job-related competencies, supplemented by elective courses covering cutting-edge technologies and interdisciplinary fields. (3)Practical Courses: Experimental and training courses designed to offer hands-on experience, as well as project-based courses that cultivate collaboration, problem-solving, and logical thinking. (4)Career Planning Courses: Modules offering career development guidance and support for professional pathway design.

3.2 Strengthening Curriculum Content Updates and Teaching Method Reform

To enhance the job-oriented nature of the curriculum, our school promotes interdisciplinary integration, streamlines redundant content, and fosters connections between basic medicine and fields such as clinical medicine, bioengineering, and computer science. Interdisciplinary courses—such as *Medical Big Data Mining and Intelligent Diagnostic Technology*—have been developed to broaden students' knowledge base, cultivate integrative thinking and interdisciplinary innovation, and stimulate learning motivation.

To advance internationalization, high-quality foreign curricula have been introduced to strengthen students' global perspective and international competitiveness. The proportion of artificial intelligence modules in core courses has been significantly increased, reflecting the deepening integration of AI and medicine. This includes expanded content on data processing and intelligent analysis, such as hands-on training with AI tools like DeepSeek for scientific research applications.

In terms of teaching methods, case-based learning, flipped classrooms, simulation training, and problem-based learning (PBL) have been introduced to foster student initiative, self-directed learning, and innovative thinking. Blended learning approaches combine online pre-class preparation via MOOC/SPOC platforms with offline seminars, aiming to improve instructional effectiveness. Smart teaching platforms—such as China University MOOC, the National Smart Education Platform for Higher Education, and Yutang—are employed to deliver personalized learning resources, monitor progress in real time, and support a pedagogical shift from instructors acting as "knowledge transmitters" to "facilitators of critical thinking."

Furthermore, virtual simulation technology offers risk-free clinical training environments, helping to compensate for the limited availability of hands-on opportunities in traditional medical education

3.3 Enhancing Clinical Practice Competency of master's graduate education of basic medical sciences

Clinical practice ability is a key component and essential evaluation criterion of job competency in master's graduate education in basic medical sciences. Therefore, strengthening the cultivation of clinical practice skills within the curriculum is an urgent priority.

First, efforts have been made to integrate basic and clinical courses, supported by the establishment of interdisciplinary teaching teams that collaboratively foster student development. Second, clinical teaching components have been expanded, and closer collaboration between universities and affiliated hospitals has been promoted to provide students with high-quality practical training platforms. These initiatives help students enhance their clinical skills and problem-solving abilities in real-world medical settings.

Third, specialized courses have been introduced to bridge scientific research with clinical practice. These courses emphasize innovative topic selection driven by actual clinical problems and systematically cover all aspects of clinical research, including design, implementation, data collection, and analysis. The goal is to cultivate students' research innovation capacity and their ability to apply research findings to clinical contexts.

3.4 Innovating Assessment Methods

When evaluating master's graduates, the School of Basic Medicine at our university has strengthened the assessment of fundamental knowledge, innovative thinking, problem-solving abilities, and practical skills. Curriculum assessment emphasizes both the learning process and final outcomes, with increased attention to students' in-class performance, self-directed learning outside the classroom, and overall competency development.

A diversified and multi-level evaluation system has been implemented. The evaluation criteria now incorporate components such as medical humanities, ethics, and professional conduct, highlighting the integration of medical ethics education throughout the curriculum. Master's courses are subject to supervisory teaching inspections, with a particular focus on ideological and political elements, as well as the advancement and innovativeness of course content.

Student performance is evaluated through a combination of formative (process-based) and summative (outcome-based) assessments, aimed at capturing students' comprehensive abilities. Process assessment leverages intelligent teaching platforms to track learning trajectories and assess students' mastery of knowledge and skills in real time. In the outcome assessment, third-party expert blind reviews and dedicated medical ethics scoring criteria are introduced to reinforce the integration of research integrity, academic standards, and ethical professionalism.

4 Cultivation Outcomes

The reform was implemented for 57 master's students admitted in 2023. Questionnaire surveys indicated significant improvements in key competency indicators compared to the pre-reform 2021 cohort (with 2022 as a transition year and thus excluded from analysis). Students' overall quality showed marked enhancement (see Table 1). The updated curriculum emphasized medical humanities, ethics, professional conduct, and research integrity; incorporated physical education as a compulsory component with over 10 specialization options; and ensured 100% participation in international courses. These measures collectively contributed to improvements in students' English proficiency and an increased rate of SCI-indexed publications.

Table 1: Comparison of Core Indicators Before and After Curriculum Reform (2021 vs. 2023)

Indicator	Pre-reform (2021)	Post-reform (2023)	Increase
Student Satisfaction	86.5% (45/52)	100% (57/57)	13.5%
Physical Fitness Improvement Rate	48.1% (25/52)	87.7% (50/57)	39.6%
International Course Participation Rate	48.1% (25/52)	100% (57/57)	51.9%
Annual SCI Publications	3.6 papers	5 papers	38.9%

5 Conclusion

Curriculum reform based on job competency is essential for cultivating high-quality, application-oriented master's graduates in basic medical sciences and for improving the overall quality of education. Optimizing curriculum design, updating teaching content, and strengthening clinical practice can enhance students' innovation capacity, practical skills, and global perspective, thereby contributing to discipline development and national health initiatives.

Although the current reform efforts have demonstrated short-term effectiveness, their long-term impact remains to be assessed through broader pilot programs. As a systematic undertaking, curriculum reform requires coordinated efforts from universities, faculty advisors, students, and society. It should incorporate emerging technologies such as artificial intelligence, deepen international cooperation, and continuously refine implementation strategies. Ultimately, the goal is to build a sustainable educational ecosystem for nurturing high-level medical professionals in alignment with China' s Health Strategy.

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Medical Research

Differential expression gene screening and prognostic biomarkers of skin cutaneous melanoma based on GEPIA database

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Abstract

[Objective] To explore the differential gene expression profiles between skin cutaneous melanoma (SKCM) and normal tissues using bioinformatics methods, and to evaluate their predictive value for patient survival and prognosis. [Methods] Differentially expressed genes (DEGs) between tumor and normal tissues were identified using the GEPIA database. The correlation between key gene expression and overall survival was analyzed.[Results] A total of 6,457 significantly upregulated genes (FDR < 0.05) were identified. The top 10 genes with the highest expression levels included PRAME, RP11-40C6.2, SERPINE2, SDC3, UBE2SP2, ETV5, PLOD3, EIF5AP4, UBE2S, and HNRNPCP2. Survival analysis revealed that the expression levels of EIF5AP4, UBE2S, and SERPINE2 were significantly associated with clinical prognosis. Specifically, high EIF5AP4 expression was significantly associated with shortened disease-free survival (DFS), while high UBE2S expression was significantly associated with reduced overall survival (OS) and DFS. In contrast, high SERPINE2 expression was significantly associated with prolonged OS and DFS.[Conclusion] This study suggests that UBE2S and EIF5AP4 may function as oncogenic factors promoting SKCM progression, whereas SERPINE2 may play a protective role. The combined expression of these three genes may serve as a novel molecular signature for prognostic evaluation in SKCM.

Keywords Skin cutaneous melanoma; GEPIA database; Prognosis

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As a highly invasive cutaneous malignancy, skin cutaneous melanoma (SKCM) has shown a continuously rising global incidence, attracting widespread attention. In addition to severely affecting patients' quality of life, it poses a significant public health burden. Although advances in diagnostic and therapeutic technologies have been made, the five-year survival rate remains suboptimal. Unraveling the molecular mechanisms underlying SKCM has thus become a critical step toward improving therapeutic outcomes.

Abnormal gene regulatory networks play a pivotal role in tumor progression, as the expression of specific genes can significantly influence tumor cell proliferation, metastatic potential, and drug sensitivity.

By comparing the transcriptomic profiles of tumor and normal tissues, researchers can identify molecular markers of clinical relevance. Currently, the rapid advancement of bioinformatics offers new opportunities for such investigations. A prominent example is the Gene Expression Profiling Interactive Analysis (GEPIA) database, which integrates multidimensional genomic data from tumors to facilitate systematic comparative analyses across various cancer types. This study aims to utilize the advanced analytical functions of the GEPIA platform to comprehensively examine the gene expression profile of SKCM and to construct a prognostic gene network, thereby providing a theoretical foundation for the development of personalized diagnostic and therapeutic strategies.

1 Data and Methods

1.1 Differential Gene Screening Process

Data acquisition was conducted using the GEPIA database (http://gepia.cancer.pku.cn/) by accessing the *Differential Gene Expression Analysis* module. The disease type was set to **SKCM**, and the screening thresholds were defined as $|\log_2 \mathrm{FC}| \geq 1.0$ and q-value ≤ 0.01. The ANOVA statistical method was employed, and *Overexpression* was selected in the chromosomal distribution filter.

1.2 Survival Analysis Procedure

For survival analysis, the interface was switched to the *Survival Analysis* module on the GEPIA homepage. The significantly differentially expressed genes identified in the previous step were input individually. Both **Overall Survival (OS)** and **Disease-Free Survival (DFS)** were selected as survival indicators. Grouping was based on the median expression value, with 50% of cases classified into high- and low-expression groups, respectively. The hazard ratio (HR) and 95% confidence interval (CI) were displayed. The SKCM dataset was selected for validation. Finally, the *Build* button was clicked to generate and visualize the survival curves.

2 Results

2.1 Analysis of Differentially Expressed Genes in SKCM

Based on a combined dataset comprising TCGA tumor samples and GTEx normal tissues, a total of 6,457 genes were identified as significantly upregulated in SKCM tissues using the GEPIA platform (461 samples in the tumor group vs. 558 in the normal group). The top 10 genes with the most significant differences in expression were: *PRAME*, *RP11-40C6.2*, *SERPINE2*, *SDC3*, *UBE2SP2*, *ETV5*, *PLOD3*, *EIF5AP4*, *UBE2S*, and *HNRNPCP2*. In the gene expression box plots, SKCM tissues are indicated in red, while normal skin tissues are shown in gray (Figure 1-10).

2.2 Association of gene expression with survival prognosis

Survival analysis of 461 SKCM patients based on the GEPIA platform showed that gene expression levels of EIF5AP4, UBE2S and SERPINE2 showed specific associations with clinical prognosis (Figure 11/18/19). Among them, high expression of EIF5AP4 significantly shortened patients' disease free survival ($P<0.05$) but had no predictive value for overall survival; UBE2S showed a dual risk effect, with its high expression leading to a simultaneous decrease in overall survival and disease free survival($P<0.05$); while high expression of SERPINE2 showed a protective effect, which was associated with a significant prolongation of both overall surviva and disease free survival with a statistical association ($P<0.05$)。

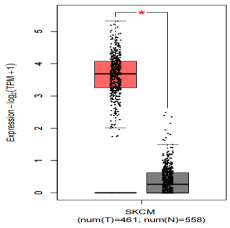

Figure1 Expression of EIF5AP4 in SKCM and normal tissues

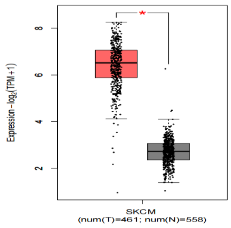

Figure2 Expression of ETV54 in SKCM and normal tissues

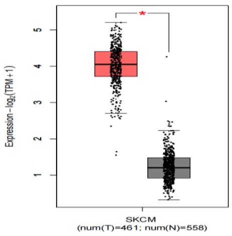

Figure3 Expression of HNRNPCP2 in SKCM and normal tissues

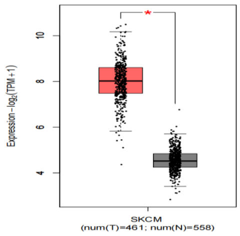

Figure4 Expression of PLOD3 in SKCM and normal tissues

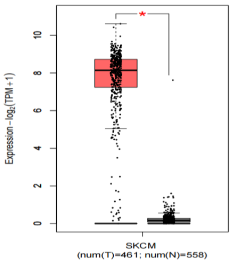

Figure5 Expression of PRAME in SKCM and normal tissues

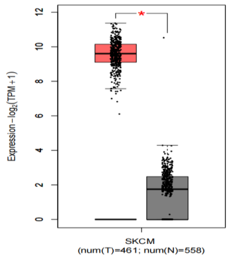

Figure6 Expression of RP11-40C6.2 in SKCM and normal tissues

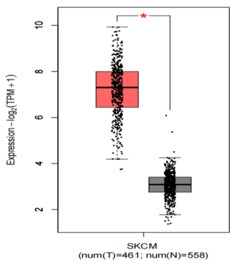

Figure7 Expression of SDC3 in SKCM and normal tissues

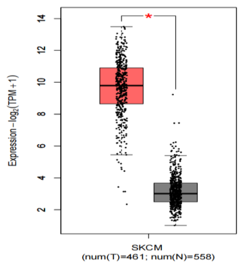

Figure8 Expression of SERPINE2in SKCM and normal tissues

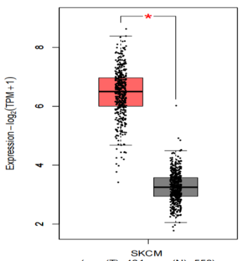

Figure9 Expression of UBE2SPINE2 in SKCM and normal tissues

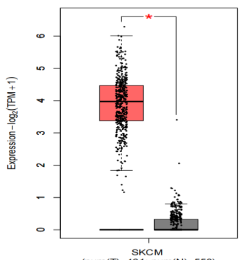

Figure10 Expression of UBE2SP2 in SKCM and normal tissues

Figure 1-10. Analysis of Differentially Expressed Genes in SKCM.

3 Discussion

In this study, we utilized the GEPIA database to elucidate the molecular characteristics of skin cutaneous melanoma (SKCM) and systematically identified 6,457 differentially expressed genes that were significantly upregulated in SKCM tissues. Among them, the top 10 genes with the most significant expression differences were, in order: *PRAME*, *RP11-40C6.2*, *SERPINE2*, *SDC3*, *UBE2SP2*, *ETV5*, *PLOD3*, *EIF5AP4*, *UBE2S*, and *HNRNPCP2*. The identification of these genes provides important clues for understanding the molecular mechanisms underlying SKCM pathogenesis. Functional enrichment analysis revealed that these differentially expressed genes were significantly involved in key biological processes such as cell cycle

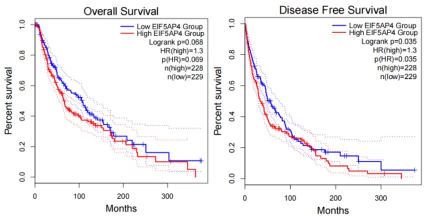

Figure11 Survival analysis of SKCM patients based on EIF5AP4 gene expression

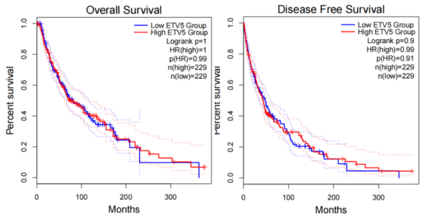

Figure12 Survival analysis of SKCM patients based on ETV5 gene expression

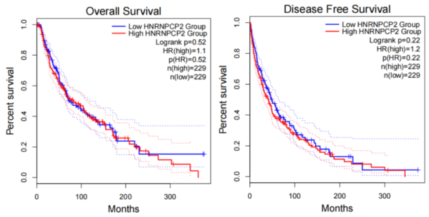

Figure13 Survival analysis of SKCM patients based on HNRNPCP2 gene expression

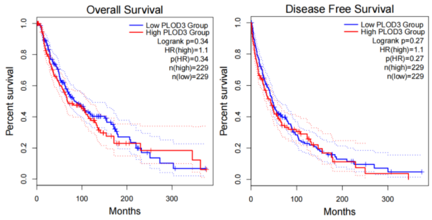

Figure14 Survival analysis of SKCM patients based on PLOD3 gene expression

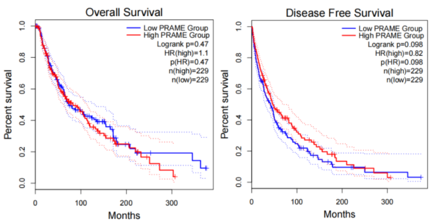

Figure15 Survival analysis of SKCM patients based on PRAME gene expression

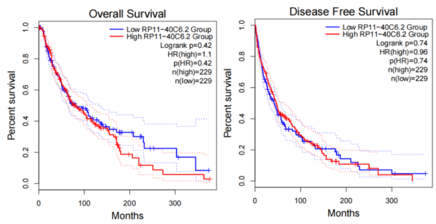

Figure16 Survival analysis of SKCM patients based on RP11-40C6.2 gene expression

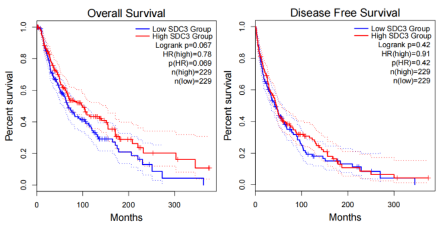

Figure17 Survival analysis of SKCM patients based on SDC3 gene expression

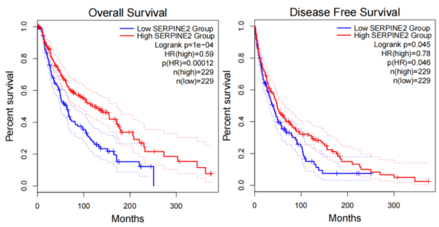

Figure18 Survival analysis of SKCM patients based on SERPINE2 gene expression

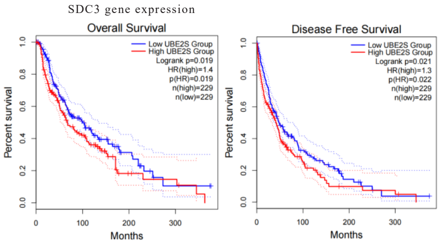

Figure19 Survival analysis of SKCM patients based on UBE2S gene expression

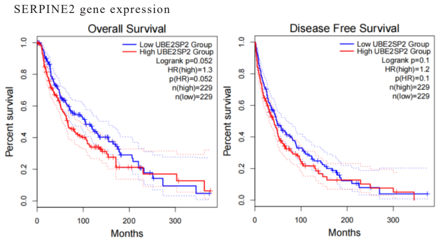

Figure20 Survival analysis of SKCM patients based on UBE2SP2 gene expression

Figure 11-20. Association of gene expression with survival prognosis.

regulation (e.g., *CDK1*, *CCNB1*), MAPK signaling pathways (e.g., *FGF2*, *EGFR*), and apoptosis-related pathways (e.g., *CASP3*, *BCL2*). These pathways are highly consistent with the core mechanisms of tumorigenesis and cancer progression reported in previous studies[1-3], further supporting the reliability and validity of our findings.

In terms of clinical prognosis, the genes *UBE2S* and *EIF5AP4* exhibited clear negative prognostic effects. Patients with high *UBE2S* expression showed shorter overall survival (OS) and significantly reduced disease-free survival (DFS), which aligns with previous findings that *UBE2S* promotes the proliferation of tumors such as hepatocellular carcinoma and breast cancer via the ubiquitin-proteasome system[4,5]. *EIF5AP4* was negatively associated with DFS; however, its dual role in regulating eukaryotic translation initiation may explain the lack of statistical significance in its effect on OS[6].Notably, *SERPINE2* demonstrated a protective effect in this study, with high expression associated with prolonged OS and improved DFS. This contrasts with earlier reports that *SERPINE2* promotes metastasis in gastric and lung cancers[7,8]. Such divergence may result from melanoma-specific microenvironmental regulatory mechanisms. For instance, TGF-β secreted by tumor-associated fibroblasts may inversely regulate *SERPINE2* function through the SMAD signaling pathway[9]. This hypothesis warrants further investigation using experimental approaches such as 3D co-culture models.

Although bioinformatics-based analyses of large datasets have highlighted the clinical relevance of key genes, several limitations must be acknowledged with caution. First, the retrospective nature of the GEPIA database may introduce selection bias, such as the exclusion of unpublished clinical subgroup data. Second, the current analyses have not addressed potential synergistic effects among genes; the construction of protein–protein interaction (PPI) networks and the calculation of combinatorial risk scores are required to enhance predictive power. Third, the biological functions of the identified differentially expressed genes urgently need to be validated at multiple levels using experimental approaches such as CRISPR-Cas9-mediated gene knockdown, organoid models, and patient-derived xenograft (PDX) mouse models. In particular, the specific role of *UBE2S* in melanoma metastasis warrants further in-depth mechanistic investigation.

It should be emphasized that the protective effect of SERPINE2 identified in the present study differs directionally from most previous findings, suggesting a potential gap between bioinformatic predictions and experimental validations. This discrepancy may be attributed to: (1) tumor heterogeneity resulting in tissue-specific gene functions; (2) regulation of protein activity through post-transcriptional modifications not accounted for in the analysis; and (3) confounding factors related to immune cell infiltration within the tumor microenvironment. Therefore, future studies should integrate single-cell sequencing technology with spatial transcriptomics to precisely resolve the expression patterns of this gene across distinct cellular subpopulations [10].

4 Conclusion

In conclusion, this study not only constructed melanoma-specific differential gene expression profiles but also demonstrated the clinical predictive value of UBE2S, EIF5AP4, and SERPINE2 through multidimensional prognostic analysis. These findings provide a theoretical foundation for the development of novel molecular diagnostic markers and targeted therapeutic strategies. Future research should focus on: (1) establishing a dynamic gene expression monitoring system to evaluate therapeutic responses; (2) developing biopsy techniques based on key genes; and (3) exploring the clinical translational potential of small-molecule inhibitors (e.g., UBE2S-specific inhibitors), thereby completing the innovation chain from basic research to clinical application.

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Analysis of the Current Status and Influencing Factors of Postpartum Depression in Hospitalized Parturient Women Under the Three-Child Policy

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Abstract

[Objective] To investigate the current status of postpartum depression (PPD) among women during their hospital stay under the three-child policy and to analyze its influencing factors. [Methods] Women who gave birth in the obstetrics department of a tertiary hospital between December 2024 and March 2025 were selected as research participants. Data were collected using a general information questionnaire, the Edinburgh Postnatal Depression Scale (EPDS), and the Social Support Rating Scale (SSRS). The incidence of PPD during hospitalization was analyzed, and its influencing factors were explored. [Results] A total of 252 women were included in the study, with 37 cases (14.7%) in the PPD group and 215 cases (85.3%) in the non-PPD group. Univariate analysis showed no significant differences between the two groups in mode of delivery, age, parity, marital status, annual family income, presence of a nanny, postpartum care center attendance, or employment status ($P > 0.05$). Significant differences were observed in planned pregnancy, feeding method, history of previous PPD, educational level, sleep quality, and social support ($P < 0.05$). Binary logistic regression analysis identified feeding method, history of previous PPD, educational level, sleep quality, and social support as independent risk factors for PPD ($P < 0.05$). [Conclusion] Under the three-child policy, the occurrence of PPD is influenced by multiple factors. Targeted interventions should be implemented during hospitalization based on these independent factors. Personalized education for high-risk individuals and continuous nursing services are essential to reduce the risk of PPD and ensure the well-being of both mother and child.

Keywords Postpartum Depression; Pregnant Women; Social Support; Risk Factors

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Postpartum depression (PPD) is a common psychological disorder that occurs after childbirth, typically manifesting within six weeks postpartum. It is primarily characterized by persistent low mood, decreased self-esteem, sleep disturbances, anxiety, and even suicidal or infanticidal thoughts[1]. The global incidence of PPD is currently 17.22%, while the incidence in China is as high as 21.4%[2-3].

With the full implementation of the "three-child" policy, postpartum women are facing increased psychological pressure and child-rearing burdens, which in turn have led to a higher incidence of PPD.

Studies have shown that there is a significant negative correlation between PPD and social support, meaning that the higher the level of social support, the lower the risk of PPD[4].

This study investigates the incidence of PPD among postpartum women during their hospital stay at a tertiary hospital and explores the relationship between PPD-related influencing factors and social support, aiming to provide feasible nursing interventions for the early identification and treatment of PPD in postpartum women.

1 Data and Methods

1.1 General Information

A convenience sampling method was used to select pregnant women who gave birth in the obstetrics department of a tertiary hospital from December 2024 to March 2025 as the research subjects.

Inclusion criteria include pregnant women with singleton pregnancies and full-term deliveries, those hospitalized for 2 to 5 days postpartum, individuals with normal comprehension abilities, no communication barriers, who voluntarily participated in the study and were able to cooperate with the survey.

Exclusion criteria include women with mental illness, those with multiple pregnancies, those with pregnancy complications, and those with adverse neonatal outcomes.

1.2 Survey Instruments

1.2.1 General Information Questionnaire

A self-developed questionnaire from the hospital was used, which included 13 items: maternal age, mode of delivery, parity, marital status, annual family income, whether the pregnancy was planned, feeding method, whether a nanny was employed, whether the mother attended a postpartum care center, history of previous postpartum depression, employment status, educational level, and sleep quality.

1.2.2 Edinburgh Postnatal Depression Scale (EPDS)

The EPDS was developed by Cox et al.[5] and translated and revised into a Chinese version by Lee et al.[6]. It is used to assess symptoms of postpartum depression. The scale consists of 10 items, each scored on a 4-point scale ranging from 0 to 3, with a total score ranging from 0 to 30. An EPDS score of $\geq$13 indicates a high risk of postpartum depression, suggesting that the participant may be experiencing postpartum depression and requires further clinical assessment and diagnosis.

1.2.3 Social Support Rating Scale (SSRS)

The SSRS was revised by Xiao Shuiyuan in 1994[7]. It includes 10 items across three dimensions: subjective support, objective support, and utilization of support. The total score is calculated by summing the scores of all items. Generally, a total score of less than 20 indicates low social support; a score of 20 to 30 indicates average social support; and a score of 31 to 40 indicates a satisfactory level of social support.

1.3 Data Collection Methods

The WeChat Questionnaire Star platform survey system was used. A questionnaire was custom-designed within the system, including three sections: the General Information Questionnaire, the Edinburgh Postnatal Depression Scale (EPDS), and the Social Support Rating Scale (SSRS). A QR code was generated for the questionnaire. The responsible nurse guided postpartum women who were hospitalized 2 to 5 days after delivery to scan the QR code on-site and complete the questionnaire on their mobile phones based on their actual situations. The researchers were able to directly view the survey results of each participant in the WeChat environment.

1.4 Statistical Methods

Statistical analysis was performed using SPSS 23.0 software. For continuous data, the mean and standard deviation ($\overline{x} \pm s$) were used for description, and comparisons between groups were conducted using t-tests or analysis of variance (ANOVA). For categorical data, frequency and percentage (n, %) were used for description, and chi-square tests were applied. Multivariate analysis was conducted using binary logistic regression. A p-value less than 0.05 was considered statistically significant.

2 Results

2.1 General Information Questionnaire for Hospitalized Postpartum Women

The WeChat Questionnaire Star platform survey system collected questionnaires from 252 postpartum women who were hospitalized for childbirth. The age of the participants ranged from 20 to 33 years, with an average age of (33.05 ± 5.59) years.

2.2 Postpartum Depression Status and Social Support Levels of Hospitalized Postpartum Women

During the hospital stay, the EPDS scores of postpartum women ranged from 2 to 19, with an average score of (10.00 ± 2.42). A total of 37 cases (14.7%) were identified with postpartum depression. The social support scores ranged from 9 to 40, with an average score of (27.14 ± 6.37). Among the participants, 54 (21.40%) had mild social support, 77 (30.60%) had average social support, and 121 (48.00%) had relatively satisfactory social support.

2.3 Univariate Analysis of Postpartum Depression in Hospitalized Pregnant Women

A total of 252 pregnant women were included in the study, with 37 cases (14.7%) in the PPD group and 215 cases (85.3%) in the non-PPD group. There were no significant differences between the two groups in terms of mode of delivery, age, parity, marital status, annual family income, presence of a nanny, postpartum care center attendance, and employment status ($P > 0.05$).

Significant differences were found between the two groups in planned pregnancy, feeding method, history of previous postpartum depression, educational level, sleep quality, and social support ($P < 0.05$). See Table 1.

2.4 Multivariate Logistic Regression Analysis of Risk Factors for Postpartum Depression in Hospitalized Pregnant Women

To identify independent risk factors for postpartum depression (PPD), a multivariate logistic regression analysis was performed. The model used the occurrence of PPD as the dependent variable and included all variables that were statistically significant in the univariate analysis as independent variables. The analysis revealed that feeding method, a previous history of PPD, educational level, sleep quality, and the level of social support were significant independent predictors of PPD among hospitalized pregnant women (P<0.05). Detailed results are presented in Table 2.

Table 1 Univariate Analysis of Postpartum Depression in Pregnant Women [n(%), $\bar{x}$±s]

Variable	PPD Group (n=37)	Non-PPD Group (n=215)	χ^2/t	P
Mode of Delivery			3.771	0.152
Vaginal Delivery	29（78.4）	138（64.2）		
Cesarean Section	7（18.9）	52（24.2）		
Vaginal Delivery to Cesarean Section	1（2.7）	25（11.6）		
Age	34.27±5.853	32.84±5.527	1.444	0.150
Age				
20 to 25 years old	3（8.1）	17（7.9）	0.203	0.904
26 to 34 years old	18（48.6）	113（52.6）		
≥35 years old	16（43.2）	85（39.5）		
Parity				
First Child	21（56.8）	107（49.8）	1.071	0.784
Second Child	9（24.3）	53（24.7）		
Third Child	5（12.8）	34（15.8）		
More than Three Children	2（8.7）	21（9.8）		
Marital Status				
Unmarried	4（10.8）	19（8.8）	1.823	0.572
Married	29（78.4）	181（84.2）		
Divorced	2（5.4）	9（4.2）		
Widowed	2（5.4）	6（2.8）		
Family Annual Income				
Less than 50,000 yuan	8（21.6）	43（20.0）	1.960	0.581
50,000 - 100,000 yuan	12（32.4）	85（39.5）		
100,000 - 200,000 yuan	9（24.3）	58（27.0）		
200,000 - 500,000 yuan	8（21.6）	29（13.5）		
More than 500,000 yuan	0	0		
Planned Pregnancy				
Yes	16（43.2）	128（59.5）	3.421	0.064
No	21（56.8）	87（40.5）		
Feeding Method				
Breastfeeding	29（78.4）	82（38.1）	21.162	0.000
Bottle Feeding	6（16.2）	76（35.3）		
Mixed Feeding	2（5.4）	57（26.5）		
Presence of a Nanny			0.093	0.761
Yes	20（54.1）	122（56.7）		
No	17（45.9）	93（43.3）		
Attendance at a Postpartum Care Center				
Yes	25（67.6）	139（64.7）	0.118	0.731
No	12（32.4）	76（35.3）		
History of Previous Postpartum Depression			29.000	0.000
Yes	6（16.2）	1（0.5）		
No	31（83.8）	214（99.5）		
Employment Status				
Employed	14（37.8）	91（42.3）	2.686	0.612
Unemployed	5（13.5）	28（13.0）		
Self-employed	5（13.5）	43（20.0）		
Freelancer	10（21.7）	36（16.7）		
Other	3（8.1）	17（7.9）		
Educational Level			19.337	0.000
Primary School	4（10.8）	27（12.6）		
Junior High School	5（13.5）	58（27.0）		
Senior High School/Vocational School	7（18.9）	82（38.1）		
College and Above	21（56.8）	48（22.3）		
Sleep Quality			70.591	0.000
Average	4（10.8）	101（47.0）		
Good	16（43.2）	107（49.8）		
Insomnia	17（45.9）	7（3.3）		
Social Support			23.232	0.000
High	10（17.8）	111（51.6）		
Medium	8（11.3）	69（32.1）		
Low	19（7.9）	35（16.3）		

Table 2 Multivariate Analysis of Risk Factors for Postpartum Depression in Pregnant Women (n=252)

Independent Variables	B	SE	Wald	P	OR	95% CI
Planned Pregnancy	-0.446	0.465	0.923	0.337	0.640	0.257~1.591
Feeding Method	1.052	0.378	7.742	0.005	2.864	1.365~6.010
History of Previous Postpartum Depression	2.704	1.296	4.356	0.037	14.947	1.179~189.442
Educational Level	-0.703	0.256	7.542	0.006	0.495	0.300~0.818
Sleep Quality	-1.611	0.399	16.306	0.000	0.200	0.091~0.437
Social Support	-0.648	0.287	5.097	0.024	0.523	0.298~0.918
Constant	1.886	2.867	0.433	0.511	6.595	

3 Discussion

3.1 Feeding Method

Different feeding methods are associated with postpartum depression to some extent. Breastfeeding is generally considered a protective factor against postpartum depression. Successful breastfeeding can enhance a mother's sense of achievement and self-confidence, thereby reducing depressive symptoms[8]. However, difficulties encountered during breastfeeding, such as nipple pain, mastitis, infant latching problems, and insufficient milk supply, can increase the risk of postpartum depression[9]. Mixed feeding and formula feeding may impose psychological stress on mothers, thereby increasing the risk of postpartum depression. Therefore, providing good social support and breastfeeding guidance to postpartum women can help reduce the incidence of postpartum depression.

3.2 History of Previous Postpartum Depression

A history of previous postpartum depression is one of the important factors affecting the risk of developing postpartum depression. Studies have shown that women with a history of depression or other mental illnesses have a significantly increased risk of developing postpartum depression[10]. In addition, women who experienced depression or anxiety during pregnancy, or those with a family history of mental illness, are also at a higher risk of postpartum depression. These factors may be related to the long-term effects on brain neurofunction, making women more susceptible to emotional problems when facing both physical and psychological stress after childbirth. Therefore, for women with a history of previous mental health issues, more attention and psychological support should be provided to facilitate early identification and intervention of postpartum depression, thereby reducing the risk of its occurrence.

3.3 Educational Level

There is a significant association between educational level and postpartum depression. This study indicates that the higher the educational level, the greater the risk of postpartum depression among hospitalized women. Other research has shown that lower educational level is one of the independent risk factors for postpartum depression. Women with lower educational levels often have limited knowledge of postpartum care and child-rearing, which may lead to feelings of helplessness and anxiety when facing physical and psychological changes after childbirth, thereby increasing the risk of postpartum depression[11]. On the other hand, some studies have pointed out that individuals with higher educational levels may experience more complex emotions due to greater social and psychological pressures, which can also increase the risk of postpartum depression[12]. Therefore, it cannot be simply concluded that higher educational level always leads to a higher risk of postpartum depression. A comprehensive consideration of multiple factors is necessary.

3.4 Sleep Quality

There is a close relationship between sleep quality and postpartum depression. This study shows that poor sleep quality is one of the important risk factors for postpartum depression. Another study has shown that primiparous women with sleep disorders in the mid-to-late stages of pregnancy are 2.504 times more likely to develop postpartum depression[13]. Postpartum depression not only affects the physical and mental health of the mother but can also have a negative impact on the psychological health and growth and development of the infant. Therefore, improving the sleep quality of postpartum women is of great significance for the prevention of postpartum depression. It is recommended that targeted sleep interventions, such as sleep hygiene education and psychological support, be provided to postpartum women to reduce the incidence of postpartum depression.

3.5 Social Support

Social support refers to the emotional, informational, and material assistance that an individual receives from others during social interactions. It is an important resource for coping with life stress. This study shows that there is a significant negative correlation between social support levels and the severity of postpartum depression, meaning that higher levels of social support can significantly reduce the incidence of postpartum depression. This finding is consistent with the research by Hahyeon Cho et al., which showed that women with inadequate social support have a higher risk of postpartum depression. Women with low social support levels are 4.63 times more likely to develop postpartum depression than those with high levels of social support[14]. Therefore, enhancing social support levels is of great significance for the prevention of postpartum depression. Effective improvement of the psychological health of postpartum women can be achieved through support from multiple aspects, including family, community, and healthcare systems.

4 Conclusion

Postpartum depression is a common psychological disorder during the perinatal period, and its occurrence is associated with a variety of factors, such as breastfeeding, history of previous postpartum depression, low educational level, poor sleep quality, and low levels of social support. Prevention of postpartum depression should begin during pregnancy. Community health workers should actively pay attention to high-risk groups from the early stages of pregnancy to the pre-labor period, and disseminate knowledge about physiological and psychological health during pregnancy, childbirth, and the postpartum period to pregnant women and their families through lectures and prenatal examinations, thereby improving their ability to recognize psychological states. At the same time, health education should be provided to family members, informing them to pay attention to the emotional changes of pregnant and postpartum women and to provide good social support. During the pre-labor period, medical staff should create a quiet and comfortable sleep environment for pregnant women to alleviate their nervousness. In addition, medical staff should also take on the important responsibility of educating pregnant women about postpartum knowledge and guiding them in feeding newborns. They should use simple and understandable language to explain based on the women's educational level and comprehension ability. The prevention of postpartum depression also requires the joint participation of families and society. Family members should provide pregnant women with full understanding, care, and support, and help them share the burden of household chores and newborn care. At the social level, support groups for postpartum depression and professional psychological counseling services can be established to provide more support and help for postpartum women. Pregnant women themselves should also actively adjust their mindsets and maintain good living habits, such as a balanced diet and appropriate exercise. Moreover, doctors can conduct depression risk assessments for pregnant women during pregnancy and provide psychological intervention or medication when necessary. After childbirth, timely follow-up by doctors can help detect and manage postpartum depression early. Through these multidimensional interventions, the incidence of postpartum depression can be effectively reduced, and the health outcomes for both mother and baby can be improved.

Article History

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The Transformative Role of Artificial Intelligence in Medical Education: Applications, Benefits, Challenges, and Future Directions

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Abstract

Artificial Intelligence (AI) is rapidly transforming the landscape of medical education, offering new paradigms for teaching, learning, and assessment. This article explores the current global integration of AI in medical education, outlining both its transformative potential and the accompanying challenges. AI-driven tools such as intelligent tutoring systems, virtual patients, and adaptive learning platforms have demonstrated the capacity to personalize education, enhance diagnostic training, and optimize learner performance through real-time feedback and simulation. Furthermore, AI is facilitating a shift in curricular design—from traditional knowledge transmission toward competency-based and data-informed education. However, the adoption of AI also raises critical concerns related to data privacy, algorithmic bias, lack of faculty training, and the risk of over-reliance on automated systems. The article emphasizes the importance of AI literacy, ethical governance, and cross-disciplinary collaboration to ensure responsible implementation. Looking forward, the synergy of AI with other technologies (e.g., VR, big data analytics) and the dynamic redefinition of the physician's role are discussed as key frontiers. This review advocates for a thoughtful, evidence-informed, and human-centered approach to embedding AI in the future of medical education.

Keywords Artificial Intelligence; Medical Education; Intelligent Tutoring; Ethical Oversight; AI literacy
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1 Introduction: The Imperative for Innovation in Medical Pedagogy

1.1 The Evolving Landscape of Medical Knowledge and Practice

The field of medicine is characterized by an unceasing expansion of knowledge and increasing complexity in clinical practice. The volume of available medical information has grown to such an extent that it exceeds the organizing capacity of the human mind, leading to what has been termed an "information overload crisis" among learners and practitioners alike. This exponential growth necessitates a fundamental shift in medical education, moving beyond mere information acquisition towards cultivating skills in information management, critical appraisal, and effective application.

Compounding this challenge is the evolving nature of healthcare delivery. Modern physicians are expected to possess a diverse skill set that extends beyond traditional medical knowledge, encompassing sophisticated collaboration, effective communication, and high levels of technological proficiency. Furthermore, the administrative burden of modern medicine and the prevalence of inefficient technologies can impede patient care and contribute to physician burnout. This context underscores the urgent need for innovative tools and pedagogical approaches to enhance both learning efficiency and the quality of medical practice.

The traditional paradigm of medical education, while foundational, faces significant challenges in preparing physicians for these contemporary demands. The struggle to keep pace with the explosion of medical information, new technologies, and the rapidly changing demands of future practice calls for a re-evaluation of how healthcare professionals are trained. This imperative for change extends beyond incorporating new content—it demands a rethinking of the very processes of learning and skill development.

The limitations of conventional methods in managing the vast and evolving corpus of medical knowledge have catalyzed the search for more advanced solutions. Artificial Intelligence (AI), with its strengths in processing, organizing, and analyzing large datasets, emerges not merely as an enhancement but as a potential necessity for effective learning and competent practice. Consequently, medical curricula must evolve to equip students with the skills to leverage AI for information management, rather than relying solely on memorization.

1.2 Artificial Intelligence: A Paradigm Shift for Medical Education

Artificial Intelligence has emerged as a transformative force capable of addressing many of the pressing challenges in both medical education and clinical practice. No longer a futuristic concept, AI is already making significant inroads across various medical domains. Its development in healthcare dates back to early expert systems such as MYCIN, which assisted in diagnosing bacterial infections in the 1970s, and has since evolved into sophisticated deep learning models capable of analyzing complex medical data.

The integration of AI into medical education represents more than the adoption of new tools—it marks a paradigm shift. While calls for reform have been a recurring theme since Abraham Flexner's 1910 report, the AI revolution introduces qualitatively different challenges and opportunities. Unlike previous reforms that focused on curriculum adjustments within established frameworks, AI necessitates a redefinition of the physician' s role and the nature of medical expertise itself.

Future physicians must not only use AI but also collaborate with and manage AI systems effectively. This requires cultivating new competencies, including advanced data interpretation, a deep understanding of algorithmic limitations, and ethical reasoning in AI-augmented healthcare contexts. This article explores the current applications, benefits, challenges, and ethical considerations of AI in medical education, and advocates for its strategic and ethical integration to prepare future professionals for an increasingly AI-integrated healthcare landscape.

1.3 Thesis Statement

This article explores the current applications, benefits, challenges, and ethical considerations of AI in medical education. It argues for a strategic and ethically grounded integration of AI to adequately prepare future healthcare professionals for an AI-augmented medical landscape.

2 The Shifting Paradigm: From Traditional Methods to AI-Enhanced Learning

2.1 Critical Appraisal of Traditional Medical Education

Traditional medical education, despite its historical successes, is characterized by several inherent limitations that can impede optimal learning and preparation for contemporary medical practice. A dominant feature has been highly lecture-based instruction, which often fosters passive learning environments where students become passive recipients of abundant information. This model tends to impose a scarcely tolerable burden of content, leading to an over-reliance on rote memorization as a survival mechanism to pass content-heavy examinations. Such an approach taxes the memory but not the intellect, with much of the passively acquired knowledge prone to becoming outdated or quickly forgotten. This can result in what has been described as intellectual anaemia, where the emphasis is placed on recall rather than discovery through curiosity and critical thinking.

Another significant challenge is the prevalence of discipline-specific curricula. Historically, medical disciplines have often vied for curriculum time, leading to bloated course contents and a territorial mentality that discourages cross-disciplinary teaching. This results in compartmentalized knowledge, leaving students with diminished ability to integrate, evaluate, and apply concepts across disciplines to solve complex medical problems. The traditional pre-clinical and clinical divide further exacerbates this fragmentation, hindering a holistic understanding of patient care.

Moreover, traditional medical education has often been highly teacher-centred. Educators are frequently positioned as the authoritative source of knowledge, reinforcing a classroom dynamic that discourages student agency. This approach fosters an authority dependency state, in which learners have limited involvement in directing their own education. Essential competencies such as self-directed learning, peer collaboration, and reflective practice are often insufficiently nurtured. Over-mediation by instructors risks deskilling students by preventing them from developing the necessary habits of autonomous learning and knowledge exchange.

Collectively, these limitations illustrate that traditional methods struggle to adequately prepare students for the explosion of medical information, emergent technologies, and the rapidly changing demands of modern healthcare. The deficiencies—passivity, fragmentation, and teacher-centricity—underscore the need for pedagogical transformation. Artificial intelligence offers a suite of tools, such as personalized learning systems and integrated simulations, that are well positioned to address these long-standing challenges and help realign medical education with contemporary professional realities.

2.2 The Imperative for Pedagogical Evolution

The convergence of rapidly advancing medical knowledge and evolving healthcare delivery systems creates a critical imperative for medical schools to revise their teaching methodologies. Contemporary medical learners require educational experiences that cultivate not only factual recall, but also critical thinking, clinical reasoning, effective communication, and collaborative competence. This necessitates a transition from traditional didactic methods toward more interactive, student-focused, and technology-integrated learning environments.

There is growing recognition of the value of student-centred, problem-based, and integrated curricula, as exemplified by models such as SPICES (Student-centred, Problem-based, Integrated, Community-based, Electives, Systematic). These frameworks promote active student participation, contextualized learning, and real-world problem-solving, aligning more closely with the practical demands of clinical medicine.

External pressures have also catalyzed pedagogical innovation. The COVID-19 pandemic, for example, accelerated the adoption of digital technologies due to constraints on physical interaction. This period prompted widespread re-evaluation of traditional teaching formats and spurred innovations such as using platforms like Telegram to deliver bite-sized content in response to the fatigue associated with prolonged virtual lectures. Yet, the transition to digital learning also exposed a critical insight: simply replacing traditional methods with technological surrogates is insufficient. The experience of digital fatigue highlights the necessity for thoughtful design in technology-enhanced learning.

The potential of AI lies in its ability to provide more engaging, adaptive, and pedagogically effective experiences—not merely serving as a new mode of delivery, but transforming the structure and substance of learning itself. If poorly integrated, AI could simply replicate the deficiencies of prior models in digital form. Hence, its implementation must be underpinned by sound instructional design.

Additionally, the territorial mentality and disciplinary silos embedded in many traditional curricula may hinder the successful development and deployment of AI-based educational tools. Effective AI integration requires interdisciplinary collaboration across fields such as medicine, computer science, data science, ethics, and pedagogy. If existing institutional cultures are already resistant to cross-disciplinary education, forging even deeper partnerships for AI innovation presents a considerable challenge. Therefore, the effective integration of AI in medical education is not only a technological challenge—it demands cultural, organizational, and structural reform to support a more collaborative and forward-looking learning ecosystem.

3 Current Frontiers: AI Applications Revolutionizing Medical Teaching

Artificial Intelligence is no longer a theoretical concept in medical education but an active agent of change, with diverse applications already demonstrating their potential to transform how medical knowledge and skills are imparted and acquired. These tools are beginning to address longstanding limitations of traditional pedagogy by offering personalized, interactive, and data-driven learning experiences.

3.1 Personalized and Adaptive Learning Pathways

One of the most significant advancements brought by AI is the ability to tailor educational content and experiences to individual learner needs. Moving beyond the one-size-fits-all approach that has long characterized medical instruction, AI-driven adaptive learning technologies utilize algorithms and machine learning to dynamically adjust content delivery. These systems can assess learner performance in real time, identify areas of strength and weakness, and provide targeted interventions or supplementary resources accordingly. This personalized approach actively counters the passive and uniform nature of traditional lectures, fostering a more engaged and effective learning process.

3.2 Intelligent Tutoring Systems (ITS) for Guided Learning

Intelligent Tutoring Systems (ITS) represent a promising AI application designed to mimic the benefits of one-on-one human tutoring. These systems offer personalized instruction, context-specific feedback, and content that adapts to the evolving competency of each learner. Many ITS platforms integrate Natural Language Processing (NLP), allowing more natural and responsive interaction. For example, systems have been developed to support diagnostic training for conditions like diabetic retinopathy, enabling students to practice classifying case severity and making treatment decisions. ITS promote self-directed learning, offer realistic simulations, and automate assessments—making them highly scalable solutions for individualized instruction, especially where faculty time is limited.

3.3 Virtual Patients and Immersive Simulations (VR/AR)

AI-Powered Virtual Patients (VPs). Virtual Patients are computer-based programs that simulate real-life clinical scenarios, providing a safe environment for students to practice essential skills such as history-taking, physical examination, and clinical decision-making. AI-enhanced VPs—especially those powered by NLP—enable realistic, real-time conversations, encouraging learners to formulate their own questions and responses. This shift from menu-driven interactions toward dynamic dialogue helps improve communication and clinical reasoning. These systems also offer automatic assessment and individualized feedback, enhancing the realism and educational value of simulated patient encounters.

VR/AR Enhanced by AI. Virtual Reality (VR) and Augmented Reality (AR) technologies offer immersive 3D environments ideal for procedural training and complex anatomical visualization. AI augments these technologies by customizing scenarios according to a learner' s skill level, adjusting difficulty in real time, and providing contextual feedback. AI can also enable virtual patients to respond dynamically to user actions, enhancing realism. Additionally, computer vision can track learner performance during simulations, offering detailed feedback on movements and technique—capabilities that previously required direct supervision.

These AI-enhanced simulations address key challenges in clinical training, such as reduced patient contact and limited exposure to rare or high-risk scenarios. They provide opportunities for repeated, safe, and standardized practice, accelerating skill acquisition without compromising patient safety.

3.4 Natural Language Processing (NLP) for Interaction and Analysis

Natural Language Processing empowers AI systems to interpret and respond to human language, playing a central role in enhancing interactivity in medical training. NLP drives conversational agents such as virtual patients, enabling free-text input and more authentic learner engagement. This interactivity fosters active reasoning and mirrors real-life clinical communication.

Beyond virtual dialogue, NLP can automate clinical documentation exercises, analyze educational transcripts to identify learning trends, and support data-driven curriculum development. Chatbots and virtual scribes powered by NLP offer additional platforms for practicing communication and information-gathering skills. Overall, NLP facilitates deeper learner engagement and strengthens critical thinking.

3.5 AI-Driven Automated Assessment and Feedback Mechanisms

Assessment is a cornerstone of medical education, and AI introduces innovative ways to improve both efficiency and objectivity. AI can generate exam questions, design clinical case scripts, and offer real-time formative feedback. A particularly impactful area is surgical skills assessment: using computer vision, AI can evaluate procedural videos to assess technique, procedural flow, and indicators of proficiency. This automation reduces subjectivity and variability inherent in traditional human observation.

Such systems provide immediate, consistent, and actionable feedback—addressing the limitations of delayed or inconsistent faculty evaluation. By enabling objective, data-driven assessment, AI supports competency-based progression models where learner advancement is tied to demonstrated performance rather than time-based criteria.

3.6 Synergistic Applications and Humanistic Considerations

The convergence of multiple AI technologies—NLP with virtual patients, ITS embedded in VR/AR environments, and adaptive feedback via machine learning—creates powerful, integrative learning experiences. These synergistic approaches enable holistic, interactive, and deeply personalized education.

While AI excels at facilitating technical skill development, educators must ensure that these tools also promote humanistic competencies, such as empathy and patient-centered communication. There is a risk that overemphasis on automation may inadvertently neglect the "art of medicine." Some AI systems have begun integrating communication and emotional response features into simulations, signaling a growing recognition of the need to cultivate not just technical expertise, but also interpersonal effectiveness and ethical sensitivity.

To provide a clearer overview of these diverse applications, the following table summarizes key AI tools in medical education:

Table 1: Overview of Key AI Applications in Medical Education

AI Application Category	Core AI Technologies Employed	Primary Educational Objective(s)	Key Benefits Demonstrated/Hypothesized
Personalized Learning Systems	Machine Learning, Algorithms	Adaptive content delivery, Individualized pacing, Addressing specific learner needs	Increased engagement, Improved efficiency, Tailored remediation, Enhanced knowledge retention
Intelligent Tutoring Systems (ITS)	AI (general), NLP, Machine Learning	Guided problem-solving, Personalized instruction, Adaptive feedback, Skill mastery	Improved skill acquisition rate, Self-directed learning, Automated assessment, Scalable individual guidance
AI-Powered Virtual Patients (VPs)	NLP, AI (general), Machine Learning	Clinical reasoning practice, History-taking skills, Decision-making, Communication practice	Realistic interaction, Safe practice environment, Exposure to diverse cases, Objective feedback
VR/AR with AI Integration	VR/AR, AI (Computer Vision, Machine Learning)	Procedural skill acquisition, Anatomical understanding, Immersive learning, Crisis management	Enhanced realism, Adaptive scenarios, Real-time feedback, Risk-free complex procedure practice
NLP-Enhanced Tools (e.g., Chatbots)	Natural Language Processing	Information retrieval, Communication practice, Documentation practice, Learning support	Realistic dialogue, Active thinking, Efficient information access
Automated Assessment Systems	Computer Vision, Machine Learning, AI (general)	Objective skill evaluation, Competency assessment, Exam generation, Immediate feedback	Reduced assessment bias, Consistency, Efficiency, Data-driven insights, Enhanced feedback quality

4 Unlocking Potential: Benefits and Opportunities of AI in Medical Education

The integration of AI into medical education is not merely a matter of technological adoption; it brings with it a spectrum of tangible benefits and opportunities that can significantly enhance the training of future healthcare professionals and, ultimately, the quality of patient care.

4.1 Enhancing Diagnostic Acumen and Clinical Reasoning

One of the most profound contributions of AI in medical education lies in its capacity to sharpen students' diagnostic and clinical reasoning skills. AI-driven tools, including intelligent tutoring systems and virtual patient simulations, provide platforms for repeated practice in differential diagnosis, clinical data interpretation, and treatment planning across diverse scenarios. By engaging with these AI-powered simulations, students are prompted to acquire, synthesize, and apply knowledge in a consequence-free environment—

something that traditional clinical rotations cannot always provide. These experiences help to foster the critical thinking required for accurate decision-making in real-world contexts.

4.2 Improving Learning Efficiency, Knowledge Retention, and Engagement

AI technologies significantly enhance the efficiency, effectiveness, and engagement of the learning process. Personalized learning systems that adapt content and pacing to individual needs can improve both retention and understanding. The interactive nature of AI-powered tools—ranging from simulations to intelligent tutoring systems—helps to boost learner motivation compared to traditional, passive lectures. Immediate and specific feedback enables learners to quickly correct misconceptions, reinforcing learning outcomes. Moreover, the asynchronous availability of AI-enabled learning resources supports continuous study at each student's convenience, a feature especially valuable during demanding clinical phases. These improvements promote confidence, competence, and sustained engagement—driving a self-reinforcing cycle of academic success and skill acquisition.

4.3 Expanding Access to Medical Education and Specialized Training

AI has the potential to democratize medical education by expanding access to quality learning resources. Distance learning platforms enhanced with AI make high-quality education more available to students in underserved regions or remote locations. AI technologies also facilitate the sharing of rare or complex clinical cases, overcoming the limitations of local clinical exposure. The scalability of AI-enabled simulations and tutoring systems allows consistent, high-standard instruction for larger and more diverse cohorts of students, independent of faculty availability. This broader reach can help reduce global disparities in medical training and contribute to the development of a more equitably skilled international healthcare workforce.

4.4 Potential Impacts on Patient Safety Through Improved Training

One of the ultimate goals of medical education is to ensure patient safety, and AI-enhanced training has shown promise in advancing this aim. Simulation-based learning environments, supported by AI, allow learners to practice complex or high-risk procedures in a controlled and safe setting, thus reducing the likelihood of clinical errors. Institutions integrating such training have reported measurable reductions in preventable mistakes and improvements in procedural outcomes. AI-facilitated team simulations also support non-technical skills development, such as communication and crisis resource management—skills critical in emergency care. Furthermore, AI-powered tools for surgical skill evaluation can ensure a certain level of competence before trainees perform procedures independently, further safeguarding patient outcomes.

4.5 Facilitating Active Learning Strategies and Curriculum Enhancement

AI serves as a strong enabler of active learning strategies, shifting the educational model from passive reception to active participation. It effectively supports pedagogical methods such as problem-based learning (PBL), case-based learning (CBL), and team-based learning (TBL), all of which emphasize critical thinking, collaborative problem-solving, and real-world application. In addition to supporting teaching methodology, AI can also enhance curriculum development. Through data analytics, educators can assess the effectiveness of course content, analyze student performance trends, and identify opportunities for improvement. AI can even recommend curriculum updates based on emerging medical knowledge and evolving healthcare demands. These continuous, data-informed adjustments ensure that training remains relevant, rigorous, and aligned with professional expectations.

The benefits of AI in medical education are mutually reinforcing. When expanded access is combined with enhanced diagnostic training and more efficient, personalized learning, the result is a more competent and globally distributed healthcare workforce. This systemic impact has the potential to address structural inequalities in medical education and healthcare delivery, suggesting that strategic investment in AI could be a critical lever in advancing global health equity.

5 Navigating the Complexities: Challenges and Ethical Considerations

While the potential of AI in medical education is vast, its successful and responsible integration entails addressing a range of significant challenges and complex ethical considerations. These challenges span financial, technical, pedagogical, and ethical domains.

5.1 Implementation Hurdles

1. Cost and Resource Allocation. A major barrier to widespread adoption is the substantial financial investment required to develop and implement advanced AI systems. Institutions must also invest in the supporting infrastructure—hardware, software, and secure network environments—to host these technologies. While long-term cost-efficiency may be achievable, particularly through methods like grouped AI processes, initial costs and ongoing maintenance can be prohibitive, especially for smaller or resource-constrained institutions. Furthermore, the most sophisticated AI solution is not necessarily the most cost-effective or scalable in practice.

2. Integration with Existing Curricula and Systems. Seamless integration of AI tools into existing educational frameworks presents logistical and pedagogical challenges. Effective alignment with learning outcomes and curricular goals requires careful planning and coordination. Moreover, the implementation and maintenance of such systems demand technical expertise that may not be readily available across all institutions.

3. Resistance to Change and Faculty Development. Resistance from faculty and students—due to unfamiliarity, skepticism, or concern over implications—is common in the face of disruptive technologies. Overcoming such inertia requires institutional commitment to professional development. Faculty must be equipped not only to use AI tools but also to guide students in understanding their functions, limitations, and ethical dimensions. This transition requires a pedagogical shift from the traditional "sage on the stage" model to that of a facilitator who supports higher-order thinking, ethical inquiry, and reflective learning —roles that AI cannot replace. These hurdles are often interrelated: for example, high costs may limit access to quality training data, thereby exacerbating algorithmic bias; similarly, a lack of faculty training may result in misuse of AI tools, undermining their effectiveness and credibility.

5.2 Algorithmic Bias and Ensuring Equity

A critical ethical concern in AI-based education is the risk of algorithmic bias. AI systems learn from the data they are trained on, and if that data reflects societal inequities or lacks demographic diversity, biased outputs can emerge and reinforce existing disparities.

Sources of such bias include biased training data derived from historical inequities or underrepresentation of certain groups such as ethnic minorities and women; problematic algorithm design, such as the use of proxy variables or ill-defined classification labels; and unconscious developer biases that shape model behavior. If left unaddressed, these biases can lead to unjust disadvantages for specific student groups, affecting their learning outcomes, progression, and even career trajectories. In the broader context, such inequities could translate into disparities in healthcare delivery.

To mitigate these risks, AI systems should be developed with inclusivity in mind, through the construction of diverse training datasets, interdisciplinary development teams that include marginalized voices, and regular fairness audits designed to detect and remediate bias.

5.3 Data Privacy, Security, and Regulatory Compliance

The integration of AI into education often involves processing sensitive student or simulated patient data. This raises significant concerns around data security, ethical usage, and compliance with legal frameworks.

Institutions should adopt robust data protection strategies. These include encrypting data both in transit and at rest; employing secure storage platforms that meet international standards; implementing role-based access controls and multi-factor authentication; de-identifying and anonymizing personal information prior to its use in research or model training; and continuously auditing access patterns and compliance practices. Transparency in how data is collected, analyzed, and used is essential, as is giving students access to their own data and the right to understand how it informs assessment or instructional design.

A balance must be struck between the demand for personalized learning—which depends on extensive data collection—and the imperative to preserve privacy. Emerging technologies such as federated learning or differential privacy offer promising avenues for this equilibrium, though further technical development and policy innovation remain necessary.

5.4 The Evolving Role of Educators and Maintaining Humanistic Medicine

AI's integration inevitably prompts a reassessment of the educator's role. While some fear that automation may erode the relational aspects of teaching, it also creates an opportunity for educators to transition from knowledge transmitters to mentors who foster reflective, ethical, and human-centered learning.

It is vital that AI supports—rather than replaces—the essential human qualities at the core of medical education: empathy, judgment, creativity, and professional identity formation. The art of medicine must not be lost amid technological advancement.

5.5 Reliability, Transparency, and Over-Reliance

Some AI systems operate as "black boxes," generating outputs without clear explanations. This opacity poses risks in educational contexts, where understanding the rationale behind feedback or decisions is vital for critical learning.

There is also a risk of over-reliance. If students treat AI as infallible, they may underdevelop essential skills such as independent reasoning, clinical judgment, and information appraisal. In clinical settings, unquestioning adoption of AI-generated diagnoses or treatment plans without human oversight poses ethical and safety concerns. Thus, AI must be framed as a tool to augment—not replace—critical human insight. Curricula must emphasize transparency, interpretability, and the role of human scrutiny in working with AI outputs.

6 The Horizon Ahead: Future Directions and Preparing for an AI-Integrated Medical Landscape

As artificial intelligence continues its rapid evolution, its role in medical education is poised to expand and deepen, necessitating a forward-looking approach to curriculum design, competency development, and ethical oversight. Preparing future physicians for an AI-integrated healthcare system requires not only leveraging AI as an advanced teaching tool but also fundamentally rethinking how medical knowledge and skills are cultivated.

6.1 Reimagining Medical Curricula for the AI Era

The advent of AI compels a significant transformation in medical curricula, moving beyond traditional models heavily reliant on memorization and passive information acquisition. Future curricula must prioritize teaching competence in integrating and utilizing information derived from diverse sources, including AI-generated insights. This involves incorporating AI itself as a subject of study, ensuring that students gain foundational knowledge of AI principles, capabilities, and limitations, methods for critically evaluating AI outputs, and an understanding of the ethical considerations surrounding its use in healthcare.

Practical skills for utilizing and interpreting AI tools within clinical workflows will become essential. AI also holds the potential to support dynamic, data-driven curricula that adapt rapidly to continuous medical advances and evolving best practices. As AI increasingly handles data retrieval and analysis, educational priorities should shift toward cultivating human-centric competencies—critical thinking, ambiguity navigation, creative problem-solving, empathy, and nuanced communication of AI-generated uncertainties.

This curricular reimagining entails not merely adding content but redefining the very identity of the physician in the 21st century—from knowledge repository to critical thinker, skilled communicator, and ethical co-navigator in an AI-augmented healthcare environment.

6.2 Cultivating AI Literacy and New Competencies in Future Physicians

To practice safely and effectively in an AI-integrated context, physicians must develop robust AI literacy. This includes recognizing that AI systems, however sophisticated, do not reason or intuit like humans. They are tools for pattern recognition and task execution, lacking contextual understanding and holistic judgment.

Clinicians must be trained in how various AI models function, their limitations and biases, and the responsible interpretation of their outputs. Educational initiatives—such as the AMA's "Artificial Intelligence in Health Care Series"—provide foundational knowledge but must be expanded and integrated into formal curricula. Moreover, physicians should actively participate in AI system selection, design, and implementation to ensure these tools are usable, effective, and aligned with clinical realities. Lessons from the limitations of electronic health record (EHR) adoption reinforce the importance of clinician involvement to prevent workflow disruptions and unintended consequences.

6.3 The Synergy of AI with Other Emerging Technologies

AI's impact on medical education will be further amplified through its integration with other emerging technologies. Notably, the convergence of AI with virtual and augmented reality (VR/AR) enables immersive, adaptive, and realistic simulation environments. AI-powered virtual patients within VR/AR platforms can provide personalized, real-time feedback and complex clinical challenges, simulating authentic encounters that traditional didactic methods cannot replicate.

In addition, AI combined with big data analytics allows educators to track learner progress, identify difficulties, and tailor interventions at both individual and cohort levels. Integration with wearable devices may also offer real-time biometric and behavioral feedback during simulations—such as haptic alerts for incorrect procedures—thus enhancing the depth and fidelity of practice environments. Educators will need new capabilities in designing and facilitating such simulations to optimize their pedagogical potential.

6.4 The Ongoing Need for Research, Validation, and Ethical Oversight

Despite growing enthusiasm, AI in medical education is still an evolving field, requiring rigorous research to validate tools, close knowledge gaps, and refine implementation strategies. Continuous, context-sensitive evaluation is vital to ensure that AI applications deliver on their promises without unintended consequences.

Parallel to technical validation, ethical guidelines and regulatory frameworks must evolve to address transparency, explainability, and fairness—especially in high-stakes contexts like clinical decision support or student assessment. Given AI' s rapid development—exemplified by the iterative enhancement of large language models—governance cannot remain static. Instead, ethical norms, research agendas, and educational practices must remain agile and adaptive to technological change.

Medical educators, institutions, and professional bodies must commit to continuous learning and revision of best practices, ensuring that the transformative potential of AI enhances—rather than disrupts—the core mission of medical education.

7 Conclusion: Embracing AI to Shape the Future of Medical Expertise

The integration of Artificial Intelligence into medical education represents a transformative juncture, offering unprecedented opportunities to enhance the training of future healthcare professionals. AI-driven tools have demonstrated the potential to address many long-standing limitations of traditional pedagogical methods by enabling personalized and adaptive learning pathways, facilitating the development of critical clinical skills through immersive simulations and intelligent tutoring systems, and providing objective, data-driven mechanisms for assessment and feedback.

The key benefits are compelling: the cultivation of enhanced diagnostic acumen and clinical reasoning, improvements in learning efficiency and knowledge retention, expanded access to educational resources, and, crucially, the potential for improved patient safety through more effective and comprehensive training.

However, the journey towards fully realizing AI's potential in medical education is complex and laden with challenges. The successful and ethical integration of these powerful technologies requires far more than mere adoption; it demands careful strategic planning, a steadfast commitment to addressing profound ethical concerns such as algorithmic bias and data privacy, substantial investment in faculty development and training, and a willingness to fundamentally redesign curricula to meet the needs of an AI-augmented future.

It is paramount to reinforce the principle that AI should serve to augment human capabilities and support clinical judgment, not to replace the essential human elements of medicine—compassion, critical thinking, ethical deliberation, and the nuanced physician-patient relationship.

The physician of the future will operate in a world where AI is an integral part of the healthcare ecosystem. Consequently, they must be more than just users of technology; they must be adept collaborators with AI, equipped with a high degree of AI literacy, strong critical appraisal skills, and sophisticated ethical reasoning abilities. The imperative for lifelong learning will extend beyond medical knowledge to encompass an ongoing understanding of, and adaptation to, evolving AI technologies and their implications for practice.

The path ahead is both exciting and demanding. It calls for a collective and concerted effort from educators, researchers, policymakers, technology developers, and students themselves. By working collaboratively to harness AI's power responsibly, thoughtfully, and ethically, the medical community can ensure that these advancements serve to elevate the standards of medical education, advance medical knowledge, and ultimately contribute to improving health outcomes for all.

The thoughtful and calculated integration of AI into medical education will indeed have a pivotal impact on shaping the future of healthcare as we navigate this largely unexplored, yet profoundly promising, territory.

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Recombinant Expression of Hypericin Synthase Hyp1 in Escherichia coli and Elucidation of Its Solubility Mechanisms

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Abstract

Hypericin, the principal bioactive naphthodianthrone from Hypericum perforatum, exhibits broad-spectrum antibacterial, antitumor, antidepressant, and antiviral properties; however, its low natural abundance and suboptimal purity hinder large-scale applications. In this study, two hypericin synthase isoforms, Hyp1A and Hyp1B, were recombinantly expressed in Escherichia coli. Following IPTG induction, Hyp1A accumulated to 94.2 $\mu g \cdot g^{-1}$ wet cell mass, which increased to 1.41 $mg \cdot g^{-1}$ upon fusion with a solubility-enhancing tag. In contrast, Hyp1B achieved 7.53 $mg \cdot g^{-1}$ wet cells without modification, highlighting distinct expression phenotypes. Molecular dynamics simulations revealed that Hyp1A harbors a higher proportion of random coils and fewer α-helices relative to Hyp1B, correlating with reduced structural stability. In vitro assays confirmed that Hyp1B catalyzes emodin dimerization to hypericin, albeit with limited activity under current conditions. Collectively, these findings demonstrate the feasibility of emodin-to-hypericin bioconversion and establish a foundation for engineering more efficient biosynthetic processes and the clinical application of hypericin.

Keywords Hypericin; Hypericin Synthase; Recombinant Expression; Enzymatic Catalysis; Molecular Dynamics Simulation; *Hypericum perforatum*

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1 Introduction

Hypericin, the principal active constituent of St. John's Wort (Hypericum perforatum L.), is a naphthodianthrone-type compound[1,2]. It exhibits a broad spectrum of biological activities, including antidepressant, antimicrobial, and antineoplastic effects[3,4]. However, endogenous levels of hypericin in H. perforatum are exceedingly low, yielding only 0.03%-0.09% of dry weight[5]. Such scant accumulation precludes bulk applications, as both yield and purity remain insufficient for industrial demands. Consequently, plant extraction persists as the dominant source of hypericin, despite its limitations.

Chemical approaches have sought to address the low natural abundance of hypericin, yet prevailing synthetic routes typically involve multiple steps and harsh conditions that undermine large-scale feasibility.

For instance, Falk et al. demonstrated a three-step semisynthesis from emodin, achieving an overall yield of approximately 51.6%, but this strategy relies on photochemical coupling in organic media and remains time-intensive[6,7]. Hence, devising streamlined, high-efficiency, and environmentally benign synthetic paradigms continues to represent a formidable challenge.

By contrast, biosynthetic methods offer potential advantages in yield, cost, and sustainability. Nevertheless, the complete *de novo* biosynthetic pathway for hypericin within *H. perforatum* has yet to be fully delineated[8]. In 2003, Bais et al. detected emodin in suspension-cultured *H. perforatum* cells and proposed that emodin serves as a direct precursor to hypericin[9,10]. Subsequent work confirmed that emodin undergoes sequential oxidative coupling events to form hypericin and identified a putative hypericin synthase, Hyp-1, whose gene product catalyzes emodin dimerization[11]. However, expression of Hyp-1 *in planta* does not always correlate with sites of hypericin deposition, and the enzyme' s catalytic parameters under *in vitro* conditions remain under debate.

Given its relative abundance—and its market price (less than 1% that of hypericin, depending on supplier)—*emodin* is an attractive substrate for the biocatalytic production of *hypericin*. In this study, we generated recombinant constructs for two distinct *Hyp-1* isoforms and expressed them in *Escherichia coli*. Both isoforms yielded soluble protein, albeit with markedly different expression levels and solubilities. Through sequence alignment and secondary-structure modeling, we identified molecular features that likely account for their divergent expression phenotypes. *In vitro* enzymatic assays then demonstrated that each isoform can indeed convert *emodin* to *hypericin*. Although the observed catalytic efficiencies warrant optimization, our findings establish the feasibility of *emodin*-to-*hypericin* conversion via recombinant *Hyp-1* and lay the groundwork for future engineering of more robust biocatalysts to enhance *hypericin* biosynthetic throughput.

2 Materials and Methods

2.1 Construction of Recombinant Expression Plasmids

Hyp1A and *Hyp1B* coding sequences were cloned into either *pET-28a* or *pET-28a-SUMO*. Each vector and insert were digested with *BamH I* and *Xho I* (TaKaRa, Beijing) and subsequently ligated using the Ligation Mix kit (TaKaRa, Beijing, China). Ligation products were transformed into *E. coli* DH5α (Tsingke, Beijing, China), and colonies were selected on LB agar containing 50 μg/mL kanamycin (Sangon Biotech, Shanghai, China). Plasmids from kanamycin-resistant clones were sequenced at Tsingke Biotech (Xi' an, China). Only clones confirmed to carry correct inserts were propagated, and plasmid DNA was purified for downstream expression.

2.2 Induction of Recombinant Protein Expression

Recombinant plasmids were introduced into *E. coli* BL21(DE3) (Tsingke, Beijing, China) via the calcium chloride method. Transformants were selected on LB agar containing 50 μg/mL kanamycin. A single colony was inoculated into 10 mL LB medium (kanamycin, 50 μg/mL) and grown overnight at 37 °C to produce seed culture. This culture was diluted into 1 L of fresh LB medium (kanamycin, 50 μg/mL) and incubated at 37 °C with agitation until OD_{600} reached 0.6 0.8. Protein expression was induced by adding IPTG (final concentration as indicated in the figure legend), and cultures were incubated overnight under the specified temperature conditions.

2.3 Purification of Recombinant Histidine-Tagged Protein

Cells were harvested by centrifugation (6,000 rpm, 4 °C, 10 min) and resuspended in TieChui *E. coli* Lysis Buffer (ACE Biotech, Changzhou, China). Cells were lysed, and lysates were clarified by centrifugation

(10,000 rpm, 4 °C, 30 min). The supernatant was loaded onto a Ni-NTA pre-packed column (Smart Lifescience, Changzhou, China). The column was washed sequentially: (1) drain residual 20% ethanol; (2) rinse with five column volumes of deionized water; (3) equilibrate with five column volumes of PBS. Clarified lysate containing His-tagged protein was applied to the column, washed with 20 column volumes of PBS to remove non-specific proteins, and eluted with PBS containing 300 mM imidazole. Eluates were desalted using a PD-10 column (Cytiva, Michigan, USA) to remove imidazole. Glycerol was added to 10% (v/v), and purified protein was stored at –20 °C.

2.4 Enzyme Activity Assay for Hypericin Synthase

Hypericin synthase activity was measured in 15 mL reaction tubes. Each reaction contained 3 mL of enzyme buffer (Tris, 1.211 g/100 mL; KCl, 1.245 g/100 mL; $MgCl_2{\cdot}6H_2O$, 2.033 g/100 mL), 1 mL of purified enzyme solution, and 60 μL of substrate stock (1 mg/mL *emodin*). Reactions were incubated at 4 °C and 200 rpm in the dark for 4 h. Subsequently, 4 mL of *n*-hexane was added for extraction; mixtures were shaken at 30 °C and 200 rpm for 6 h. After centrifugation (11,000 rpm, room temperature, 20 min), the upper *n*-hexane layer was transferred to a new tube. The solvent was evaporated using a rotary evaporator, and the residue was resuspended in 1 mL methanol. Samples were sonicated for 10 min, and absorbance was recorded at 560 nm. Each experimental group (enzyme + substrate) was run in octuplicate. Controls included substrate without enzyme and enzyme without substrate (each also in octuplicate)[1].

2.5 Molecular Dynamics Simulations of Hypericin Synthase

All-atom MD simulations were conducted using GROMACS 2019.6 under periodic boundary conditions. The AMBER99SB-ILDN force field and TIP3P water model were employed. Each *Hyp1* crystal structure was centered in a cubic box with at least 1 nm between the protein surface and the box boundary. Systems were solvated with TIP3P water, and Na^+ ions were added to neutralize charge. Energy minimization was carried out using the steepest descent algorithm until convergence (<1,000 $kJ{\cdot}mol^{-1}{\cdot}nm^{-1}$). The minimized systems were equilibrated in two stages: 100 ps NVT at 300 K, followed by 100 ps NPT at 1 bar, both with positional restraints on protein heavy atoms. Production runs were performed for 30 ns at 300 K and 1 bar with a 2 fs integration time step. All bonds to hydrogen were constrained via the LINCS algorithm, and long-range electrostatics were treated using Particle-Mesh Ewald (PME). Secondary-structure evolution during simulation was analyzed by DSSP. Changes in folding free energy ($\Delta\Delta G$) for point mutations were calculated using the FoldX program.

3 Results

3.1 Recombinant Expression of *Hyp1A* in *E. coli*

To evaluate *Hyp1A* expression, we leveraged the *E. coli* BL21(DE3) *pET-28a* system. The *hyp1A* coding sequence was inserted into *pET-28a* via *BamHI* and *XhoI* (Fig. 1A), and the resulting plasmid was transformed into BL21(DE3) for IPTG induction. SDS-PAGE analysis showed negligible soluble *Hyp1A* (Fig. 1C). As SUMO is known to enhance solubility, we recloned *hyp1A* into *pET-28a-SUMO* (Fig. 1B). Fusion to SUMO improved the soluble yield from 94.2 μg/g to 1.41 mg/g wet cell mass. However, when purified SUMO *Hyp1A* was incubated with *emodin*, no *hypericin* was detected, indicating a loss of enzymatic activity despite improved solubility.

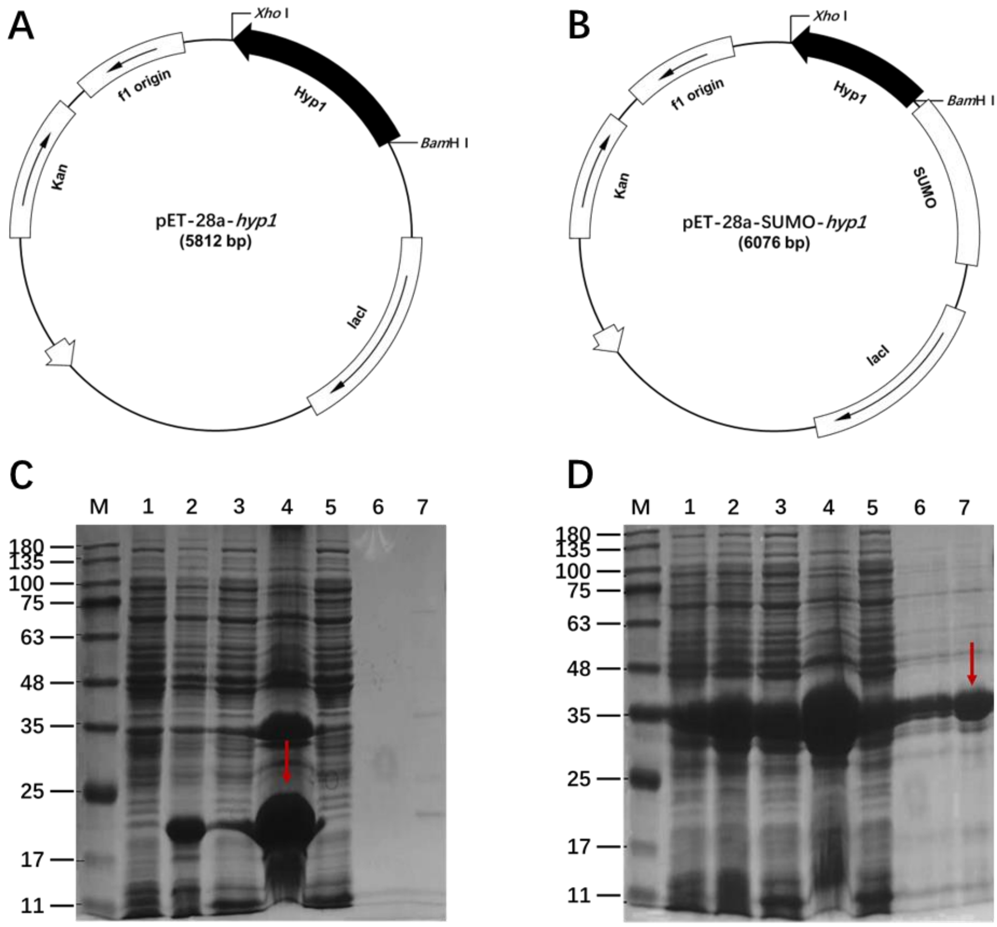

Figure 1. Recombinant expression of hypericin synthase Hyp1A in *Escherichia coli*. (A) Schematic of the Hyp1A expression vector; (B) Schematic of the SUMO-Hyp1A expression vector carrying a solubility tag; (C) Expression of Hyp1A in *E. coli*; (D) Expression of SUMO-Hyp1A in *E. coli*. M: Marker; Lane 1: uninduced cells;Lane 2: induced cells; Lane 3: lysate supernatant (soluble fraction); Lane 4: lysate pellet (insoluble fraction); Lane 5: flow-through 1; Lane 6: flow-through 2; Lane 7: affinity-purified eluate.

3.2 Structural Basis for Differential Solubility of *Hyp1* Isoforms

A second isoform, *Hyp1B*, was identified in the literature as exhibiting robust soluble expression in *E. coli*. Sequence alignment (Fig. 2A) revealed divergence between *Hyp1A* and *Hyp1B* at residues 14, 86, and 119 (Thr $\rightarrow$ Ile, Ile $\rightarrow$ Leu, and Ser $\rightarrow$ Thr, respectively). To investigate how these substitutions affect folding, we performed 30 ns all-atom MD simulations and analyzed secondary-structure dynamics via DSSP. Relative to *Hyp1B*, *Hyp1A* displayed a marked reduction in 3-helix content near residue 86 (replaced by Bend) and an absence of an α-helix near residue 128 (forming Turn instead). Because 3-helix and α-helix elements stabilize protein cores, these alterations suggest that *Hyp1A* is inherently less stable. Indeed, throughout the MD trajectory, the 3-helix fraction of *Hyp1A* declines sharply in later frames, accompanied by an increase in destabilizing Bend segments (Fig. 2D, 2E), whereas *Hyp1B* maintains a consistent secondary-structure profile.

Free-energy calculations using FoldX yielded a ΔG difference of 4.36 kcal/mol (*Hyp1A* vs. *Hyp1B*), corroborating *Hyp1A*'s reduced stability. Structural inspection of the final simulation frames highlighted two key regions: residues 26 36, which adopt an α-helix in *Hyp1B* but remain random coil in *Hyp1A*; and residues 90 95, which form a 3-helix in *Hyp1B* but are also random coil in *Hyp1A*. Michalska et al.[21] noted that *Hyp1B*'s hydrophobic cavity is delineated by a β-sheet concave face and three α-helices;

the three residue substitutions ablate one of these helices in *Hyp1A*, replacing it with an unstable coil (Fig. 2F H), and constrict one entrance to the hydrophobic cavity (Fig. 2I, 2J). Together, these data explain *Hyp1A*'s propensity for misfolding and precipitation during expression and suggest that alterations in the hydrophobic cavity disrupt substrate binding and catalysis.

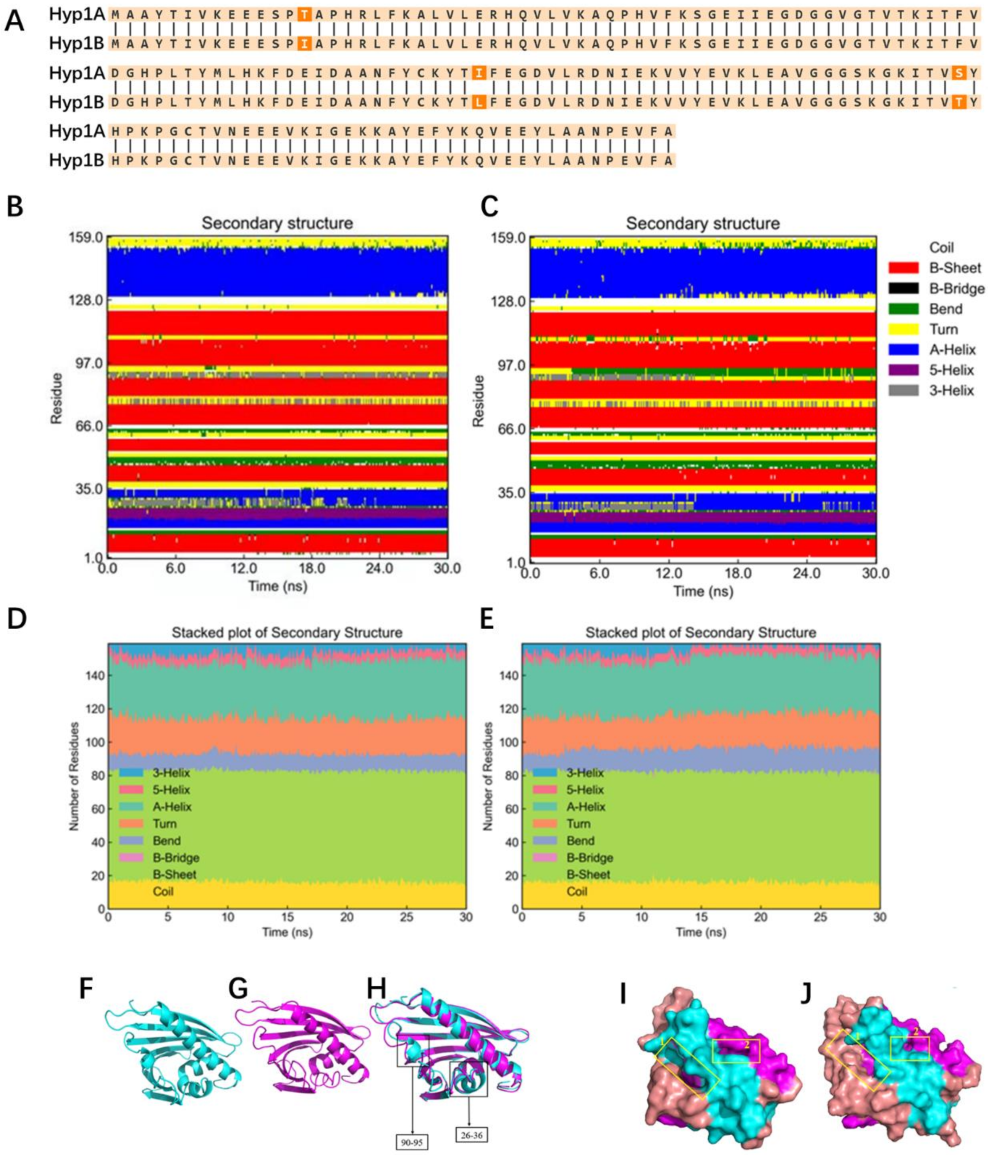

Figure 2. Structure analysis of Hyp1A and Hyp1B. (A) Sequence alignment of Hyp1A and Hyp1B; (B) and (D) Secondary structure analysis of Hyp1A; (C) and (D) Secondary structure analysis of Hyp1B; (F) Tertiary structure of Hyp1A; (G) Tertiary structure of Hyp1B; (I) and (J) Surface models of the two enzymes, respectively.

3.3 Optimization of *Hyp1B* Expression and Storage

Guided by the above insights, we expressed *Hyp1B* in *E. coli* and systematically optimized induction conditions. Maximum soluble yield (7.53 mg/g wet cells, without any solubility tag) was achieved at 25 °C with 0.1 mM IPTG (Fig. 3C). To ensure long-term stability, we evaluated glycerol-mediated cryoprotection. *Hyp1B* remained fully soluble through multiple freeze thaw cycles when formulated in 10% glycerol; lower concentrations led to precipitation (Table 1).

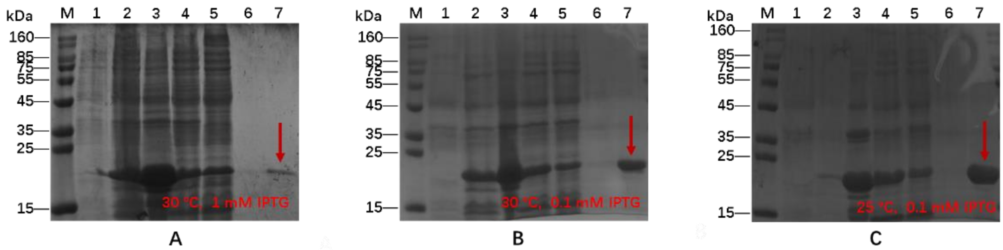

Figure 3. SDS-PAGE of Hyp1B expression under different conditions. M: Marker; Lane 1: uninduced cells;Lane 2: induced cells; Lane 3: lysate supernatant (soluble fraction); Lane 4: lysate pellet (insoluble fraction); Lane 5: flow-through 1; Lane 6: flow-through 2; Lane 7: affinity-purified eluate.

Table 1. Glycerol-Dependent Stability of Hyp1B Solutions

Percent of glycerinum	Precipitability
1%	+++
2%	++
5%	+
10%	-

*"+": precipitation observed (greater "+" indicates greater precipitation); "-": no precipitation.

3.4 Enzymatic Conversion of *Emodin* to *Hypericin* by *Hyp1B*

Emodin and *hypericin* exhibit distinctive absorbance spectra. A UV vis scan (300 700 nm, 10 nm increments) of 0.1 mg/mL standards revealed that *emodin* peaks at 430 nm, whereas *hypericin*'s λ_{max} shifts to 500 600 nm (Fig. 4A). When purified *Hyp1B* was incubated with *emodin*, we detected *hypericin* formation by measuring absorbance at 560 nm. Notably, reactions conducted in the dark yielded approximately 1.9-fold higher *hypericin* levels than those under ambient light, suggesting photolability during enzymatic turnover.

4 Discussion

In this work, we delineated the distinct behaviors of two hypericin synthase isoforms, *Hyp1A* and *Hyp1B*, in *Escherichia coli*, benchmarking our findings against analogous enzyme-engineering studies.

Strikingly, *Hyp1A* yielded negligible soluble protein when expressed from an unmodified *pET-28a* vector; fusing a SUMO tag elevated the soluble yield to 1.41 mg·g^{-1} wet cells, yet SUMO *Hyp1A* remained catalytically inert toward *emodin*. This underscores that solubility enhancement *per se* does not guarantee functional restoration. Indeed, Smith et al. reported that NusA, Trx, or GST fusions improved the solubility of human lysyl oxidase (LOX) but failed to boost—and sometimes abrogated—enzyme activity *in vitro*[12]. Likewise, Xu et al. employed machine-learning designed peptide tags to enhance folding of model enzymes, but did not observe uniform gains in catalytic performance[13]. These precedents mirror our observations: *Hyp1A*'s improved solubility does not translate into enzymatic competence.

By contrast, *Hyp1B* expresses robustly in the absence of any solubility tag, achieving 7.53 mg·g^{-1} wet cells, and remains stable in 10% glycerol. Sequence analysis revealed that three non-conserved residues in *Hyp1A*—positions 14, 86, and 119—induce local conformational perturbations. All-atom molecular dynamics simulations and DSSP analysis demonstrate that *Hyp1A* lacks stabilizing α-helical and 3-helix motifs in critical regions (residues 26 36, ~86, and ~128), replaced instead by disordered coils and Turn/Bend elements. FoldX calculations further quantify *Hyp1A*'s compromised stability ($\Delta\Delta G \approx 4.36$ kcal·mol^{-1}), rationalizing its propensity for aggregation. In contrast, *Hyp1B*'s hydrophobic cavity is sculpted by a β-sheet concave face and three intact α-helices, facilitating substrate accommodation—features absent in *Hyp1A*.

Importantly, purified *Hyp1B* catalyzes *emodin* dimerization to *hypericin*, as evidenced by the characteristic red-shift ($\lambda_{max} \approx 560$ nm). Notably, dark-incubated assays yielded approximately 1.9-fold more *hypericin* than light-exposed controls, echoing Zobayed et al.'s findings that light enhances *hypericin* formation but also accelerates photodegradation[14]. This highlights the necessity of stringent light management during process development.

Although *Hyp1B* exhibits bona fide catalytic activity, turnover remains modest. There are already numerous available methods to enhance the catalytic activity of natural enzymes[15]. We propose that structure-guided mutagenesis of *Hyp1B*'s hydrophobic pocket may improve polarity or geometric complementarity to strengthen substrate binding. Additionally, high-throughput screening or directed evolution could be employed to isolate variants with enhanced substrate affinity and catalytic efficiency. Finally, strategic incorporation of antioxidants (e.g., glutathione), cofactors (e.g., NADPH), or metal ions (e.g., Fe^{2+}, Cu^{2+}), coupled with systematic titration of pH (5.5 7.5) and temperature (20 35 °C), may further maximize *hypericin* yields.

Collectively, our comparative analysis elucidates how subtle sequence variations dictate the solubility, stability, and function of hypericin synthase isoforms. By integrating insights from related enzyme-engineering studies, we lay a roadmap for the rational design of next-generation biocatalysts tailored for scalable *hypericin* production.

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