



# Analysis of the efficacy of Dabuyin pill combined with gonadotropin-releasing hormone analogue in the treatment of central precocious puberty girls based on network pharmacology

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**Background:** Traditional Chinese medicine (TCM) believes that central precocious puberty (CPP) is affected by the imbalance of kidney Yin and Yang. Dabuyin pill is a recipe for nourishing Yin and lowering fire. The network pharmacology method was used to analyze the active components, action targets, and molecular pathways of Dabuyin pill in the treatment of CPP.

**Methods:** The main chemical components of Dabuyin pill were obtained from the Integrative database of Traditional Chinese Medicine enhanced by Symptom Mapping (SymMap) database and Traditional Chinese Medicine Systems Pharmacology (TCMSP), and compound targets were retrieved from SymMap and the Encyclopedia of Traditional Chinese Medicine (ETCM). Disease targets were retrieved from the DisGeNET and Gene Expression Omnibus (GEO) databases, and the intersection of compound targets and disease targets was performed to obtain the prediction targets of Dabuyin pill acting on CPP. The key targets enriched by Database for Annotation, Visualization, and Integrated Discovery (DAVID) were then used for Gene Ontology (GO) functional enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis.

**Results:** GO analysis showed that the biological functions of Dabuyin pill in the treatment of key targets of CPP mainly involved apoptosis, nitric oxide synthesis, estradiol response, angiogenesis, inflammation, and so on. KEGG pathway analysis was mainly enriched in the tumor necrosis factor (TNF) signaling pathway, phosphatidylinositol-3 kinase/protein kinase B (PI3K/Akt) signaling pathway, hypoxia-inducible factor-1 (HIF-1) signaling pathway, and apoptosis. Among them, the regulation effect of Dabuyin pill prescription on apoptosis may both act on TP53 and different signaling pathways of apoptosis, thus playing a synergistic role.

**Conclusions:** Dabuyin pill combined with GnRHa for the prevention and treatment of CPP in girls can effectively intervene CPP, and the effect of Dabuyin pill on sex hormones is one of its protective mechanisms against CPP.

**Keywords:** Dabuyin pill; central precocious puberty (CPP); network pharmacology; bioinformatics analysis

Submitted Dec 11, 2022. Accepted for publication Mar 23, 2023. Published online Mar 30, 2023.

doi: 10.21037/tp-23-111

View this article at: <https://dx.doi.org/10.21037/tp-23-111>

## Introduction

Precocious puberty refers to the onset of puberty characteristics (secondary sexual characteristics) before the age of 8 in girls and 10 in boys, including pseudoprecocious puberty, true precocious puberty, and incomplete precocious puberty (1). Idiopathic precocious puberty is more common in true precocious puberty, accounting for more than 80% of precocious puberty cases in girls, and mostly occurs at the age of 4–8 years (2). Female idiopathic precocious puberty is manifested as breast enlargement and underarm and pubic hair growth before 8 years old. Precocious puberty will accelerate epiphyseal maturation, early bone fusion, short stature after adulthood, may make patients feel inferior, and affect healthy development. The causes and mechanisms of female idiopathic precocious puberty are very complex and have not been fully elucidated, which may be related to excessive nutrition, high hormone food, and other factors (3–5). With the progress of society and the continuous improvement of living standards, the phenomenon of precocious puberty in children has increased, which has become 1 of the 3 major diseases (short stature, obesity, and precocious puberty) that seriously affect the growth and development of children (6). Precocious puberty not only affects children's normal psychological development, but also affects children's lifetime height. Parents are also gradually becoming aware of the dangers of precocious puberty. At present, gonadotropin-releasing hormone analogues (GnRHAs) are the internationally recognized drugs for the treatment of idiopathic true precocious puberty (7). They are effective drugs, but expensive and not readily accepted by the majority of patients. From the

point of view of traditional Chinese medicine, if the sex hormone secretion disorder has a certain relationship with kidney Yin deficiency. From the perspective of traditional Chinese medicine, it is believed that the kidney is the main reproductive function and the kidney is the main sperm storage, so the function of kidney collection is weakened, and the disorder of hormone secretion in the body may occur.

Children's precocious puberty is often triggered by abnormal secretion of gonadotropins in the hypothalamus, so it is also known as central precocious puberty (CPP) (8–10). Affected by a large volume of high hormone foods, excess nutrition, and other factors, the incidence rate of precocious puberty in children is increasing annually, and it has become a common pediatric disease. At present, the internationally recognized drug for the treatment of idiopathic true precocious puberty is GnRHa (11). Although these drugs are effective, they are not accepted by most patients because of their high price. Traditional Chinese medicine (TCM) believes that CPP is affected by the above factors, resulting in imbalance of Yin and Yang of the “kidney”, kidney Yin deficiency, and phase fire, and Dabuyin pill is a recipe for nourishing Yin and reducing fire (12–14).

In recent years, the incidence of precocious puberty has increased significantly, which seriously affects the physical and mental health of children (15). CPP is due to the action of the hypothalamus on the pituitary gland. The premature activation of gonadal function and estrogen secreted by the ovaries cause premature physiological changes in puberty, premature closure of the epiphysis, and involvement of the final adult height, which incurs a range of psychological problems. Early administration of progesterone or anti-androgen drugs treatment, when the dose is sufficiently large, can inhibit the secretion of pituitary gonadotropin and gonadal steroids, which halts the progress of secondary sexual characteristics, and inhibits the onset of menstruation (16). However, significant weight gain and fatigue may occur because of such treatment. Long-term adrenal cortical inhibition may cause liver damage and does not inhibit premature bone maturation, and therefore does not improve the final height of patients (17). With the advent of long-acting formulations of GnRHa, progesterone-based drugs have been gradually abandoned. The indications of GnRHa in the treatment of CPP are as follows: the purpose of drug treatment of CPP is to inhibit the early pubertal development, delay the emergence of secondary sexual characteristics, optimize adult height, and prevent the corresponding social psychological problems. Since the

### Highlight box

#### Key findings

- Dabuyin pill combined with GnRHa for the prevention and treatment of CPP in girls can effectively intervene central precocious puberty.

#### What is known and what is new?

- Dabuyin pill is a recipe for nourishing Yin and lowering fire.
- The effect of Dabuyin pill on sex hormones is one of its protective mechanisms against central precocious puberty.

#### What is the implication, and what should change now?

- Dabuyin pill can inhibit the development of secondary sexual characteristics, reduce the volume of the uterus and ovaries, slow down the speed of bone maturation, and has no adverse reactions. It is safe and reliable, and worthy of clinical application.

clinical progress of CPP varies, whether and when to use GnRHa should be determined according to the specific situation. The expected adult height of slow-progressive precocious puberty is good, and the progression of bone age is small. Even if menstruation occurs, the adult height will not be affected; GnRHa is not necessary, and follow-up observation should be carried out. In fast progressive precocious puberty, sex hormones reach the pubertal level in advance, and the expected height is lower than that of normal adults, which is an indication for GnRHa treatment (18). Central precocious puberty is due to a disease of the central nervous system, or idiopathic precocious puberty, which is the onset of early puberty abnormalities. The phenomenon of secondary sexual characteristics in girls before the age of eight or boys before the age of nine can be divided into central precocious puberty, diseases occurring in the central system, or precocious puberty caused by peripheral gonads called peripheral precocious puberty. Central precocious puberty is due to the early activation of the hypothalamic-pituitary-gonadal axis, resulting in increased secretion of sex hormones, resulting in the early emergence of secondary sex characteristics. Dabuyin pill can treat precocious puberty, but precocious puberty is divided into true precocious puberty and false precocious puberty. If the child belongs to false precocious puberty, often manifested as dry mouth and red lips, red tongue, less tongue coating, night sweats and other Yin deficiency fire Wang symptoms, you can use dabuyin pill to nourish Yin and reduce fire treatment, so as to help the child breast development, menstruation and a series of precocious puberty symptoms have been significantly relieved. If it is true precocious puberty, the use of Dabuyin pills can play a supportive role in the treatment.

In this study, we investigated the TCM ‘greatly tonifying Yin pill’, known as Dabuyin pill for the clinical curative effect of combined therapy with GnRHa female idiopathic precocious puberty through the application of bioinformatics and network pharmacology analysis. We explored the targets location of Dabuyin pill and the related mechanism for the treatment of CPP, with the aim of providing a treatment option for patients with idiopathic precocious puberty with the benefits of a curative effect, moderate price, and minimal side effects. We present the following article in accordance with the STREGA reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-23-111/rc>).

## Methods

### *Chemical constituents and target mining of Dabuyin pill*

The Integrative database of Traditional Chinese Medicine enhanced by Symptom Mapping (SymMap) database combines TCM with modern medicine through internal molecular mechanism and external symptom mapping. The platform provides an abundance of descriptive information about herbs, TCM syndromes, Western medicine symptoms, components, targets, and diseases, and constructs a huge heterogeneous network, which can screen effective compounds and drug targets at the overall level. With the help of the SymMap database (<http://www.symmap.org/>), the chemical components of various TCM ingredients in Dabuyin pill were obtained. Combined with The Traditional Chinese Medicine Systems Pharmacology (TCMSP) platform (<http://tcmispw.com/index.php>), the qualified candidate compounds were screened according to oral bioavailability (OB) and drug-likeness (DL), and then the corresponding targets were retrieved from SymMap and Encyclopedia of Traditional Chinese Medicine (ETCM).

### *Disease target screening*

The databases of DisGeNET ([www.disgenet.org/](http://www.disgenet.org/)) and Gene Expression Omnibus (GEO; [www.ncbi.nlm.nih.gov/geo/](http://www.ncbi.nlm.nih.gov/geo/)) were searched using the terms “Central precocious puberty”, “Sex hormones”, “Immature development”, and “Sexual maturity” for the retrieval of associated disease targets. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Screening of drug targets*

We used Venny (<http://bioinfogp.cnb.csic.es/tools/venny/index.html>) to analyze item 1.1 and 1.2 of the data retrieved for intersection, and obtained the intersection target for the prediction of Dabuyin pill on CPP targets.

### *Target interaction network*

To explore the interaction of Dabuyin pill components on CPP disease targets, the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (<https://string-db.org/>) was used to construct a protein-protein

interaction (PPI) network relationship table. The species parameter was set to *Homo sapiens*, the default settings were retained for other parameters. The downloaded data was imported into Cytoscape 3.6.0 (<https://cytoscape.org/>) for topology analysis and module analysis. The targets with degree and centrality values greater than average node were selected as the key targets.

### **Functional enrichment analysis**

Through Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of the enriched key targets, the main signal pathway of key target parameters was obtained, and the possible mechanism of Dabuyin pill treatment for CPP was studied. Then, the network diagram of TCM-compound-target-pathway was constructed by Cytoscape 3.6.0 to analyze the interaction between the action mechanisms of Dabuyin pill and its herbs.

### **Reverse molecular docking analysis**

To further verify the reliability of predicted targets, the Systems Dock (<http://Systemsdock.unit.oist.jp/>) database was used to conduct molecular docking for the 5 inhibited precocious puberty targets of Rut and degree value. By inputting the Protein Data Bank (PDB) ID of 5 target proteins, the Rut structure was imported, and the dock score of Rut and 5 target proteins was obtained. The matching degree between Rut and target protein was judged.

### **Statistical analysis**

The experimental data were analyzed with SPSS 23.0 software (IBM Corp., Armonk, NY, USA), and statistical analysis was performed for each group by one-way analysis of variance (ANOVA). The data were expressed as  $\bar{x} \pm SD$ , and  $P < 0.05$  indicated that the difference was statistically significant.

## **Results**

### **Screening of drug targets**

In multiple articles,  $OB \geq 30\%$  and  $DL \geq 0.18$  were used as absorption, distribution, metabolism, and excretion (ADME) parameter values to screen TCM active ingredients. Dabuyin pill comprises 4 herbs: shu di huang, gui ban, huang bai and zhi mu. Due to the emphasis on water-

soluble and fat-soluble components of Cortex phellodendri and Rhizoma anemarrhenae components, the ADME parameters of Cortex phellodendri were set as  $OB \geq 30\%$  and  $DL \geq 0.18$  in this paper. The ADME parameters of Rhizoma anemarrhenae were set to  $OB \geq 30\%$  and  $DL \geq 0.36$ .

### **Critical target screening**

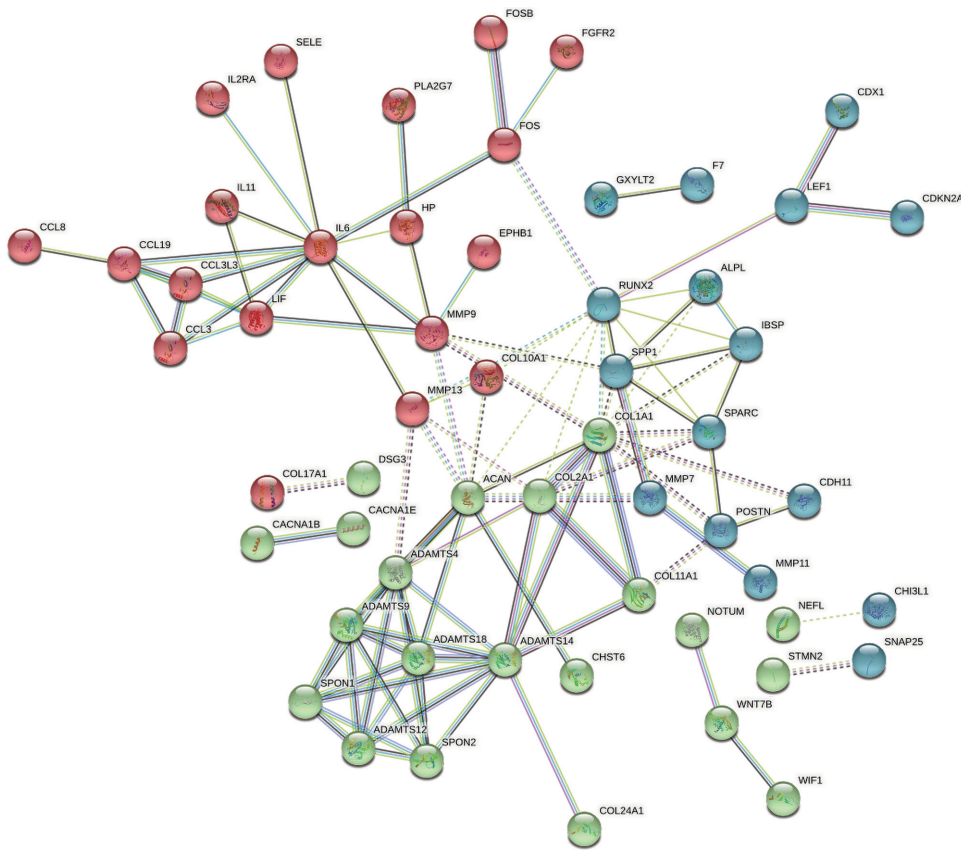
The intersecting target sites were guided into the STRING platform to construct the protein interaction table between disease and drug targets. Cytoscape was used for PPI network analysis, and the Cytoscape module was used for cluster analysis. There were protein interaction targets in the network, and edges represented the interaction between proteins. Degree was selected, and the total greater than the average node was deemed as the key target point. The evenness degree value of all nodes in the network was 15.82 and the average total degree of freedom and centrality was 0.53, and there were 29 targets which were all higher than the average. It is speculated that these targets may be the key targets of CPP treatment in Dabuyin pill. After module analysis, the targets were mainly concentrated into 3 modules: module 1 mainly regulates apoptosis pathway; module 2 mainly affects drug metabolism and plays an oxidative stress role by affecting P450 enzyme, and module 3 mainly plays an anti-inflammatory, inhibition of sexual maturation and development, and other factors role (*Figure 1*).

### **Screening active ingredients of Cortex phellodendri and Rhizoma anemarrhenae and its therapeutic targets for precocious puberty**

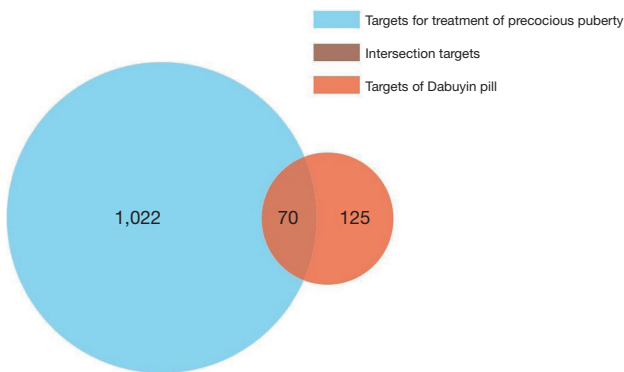
According to  $OB \geq 30\%$  and  $DL \geq 0.18$ , 113 active ingredients in Cortex phellodendri and Rhizoma anemarrhenae were screened. Among them, there were 2 in Radix ribondii, 15 in Poria cocos, 20 in Fructus officinalis, 10 in Rhizoma alismatis, 11 in Cortex moutan, 16 in Dioscorea polystachya, 15 in Anemone, and 37 in Phellodendron phellodendron. We then listed the top 20 active ingredients according to their DL levels. Totals of 125 drug targets of Dabuyin pill and 1,022 disease targets related to sexual premature maturation were obtained by screening, and 70 targets could be obtained by taking the intersection of drug and disease targets, as shown in *Figure 2*.

### **Disease target PPI network**

The target genes related to precocious puberty were



**Figure 1** PPI of CPP. PPI, protein-protein interaction; CPP, central precocious puberty.



**Figure 2** Drug targets and precocious disease targets Venn diagram.

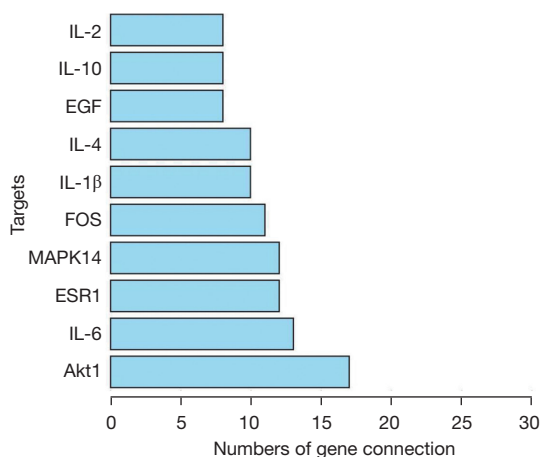
imported into the STRING database to obtain the disease PPI network, which has 61 nodes and 140 edges, and the average number of adjacent nodes in the network was 4.590. The nodes in the network represent the targets, and the edges represent the interaction between the targets. The

larger the number of edges, the more important the target of the node is in the network. The results showed that protein kinase B1 (Akt1), interleukin-6 (IL-6), estrogen receptor 1 (ESR1), mitogen-activated protein kinase 14 (MAPK14), proto-oncogene c-Fos (FOS), IL-1 $\beta$ , IL-4, epidermal growth factor (EGF), IL-10, and IL-2 all had high degree values, which indicated that these proteins play a significant role in the network and are a link to communicate with other proteins (Figure 3).

**GO functional analysis and KEGG pathway enrichment**

Key targets were screened for GO analysis and KEGG pathway enrichment, and the items enriched by biological process (BP) were apoptosis, nitric oxide synthesis, estradiol response, angiogenesis, inflammatory response, oxidative stress, and acute response, among others. Cellular component (CC) was mainly enriched in cytoplasm, nucleus, cytoplasmic matrix, extracellular space, protein complex, steroid hormone receptor activity, heme binding,





**Figure 3** PPI network core protein in precocious disease. IL, interleukin; EGF, epidermal growth factor; FOS, proto-oncogene c-Fos; MAPK14, mitogen-activated protein kinase 14; ESR1, estrogen receptor 1; PPI, protein-protein interaction.

protein kinase, cytokine, superoxide dismutase, nitric oxide synthase activities, and inhibition of sexual maturation and development (Figure 4).

The KEGG pathway information enriched from the KEGG database was histogram prepared by fold enrichment value, which was mainly enriched in the tumor necrosis factor (TNF) signaling pathway and the phosphatidylinositol-3 kinase/protein kinase B (PI3K/Akt) signaling pathway. The hypoxia-inducible factor-1 (HIF-1) signaling pathway, apoptosis, chemokine pathway, vascular endothelial growth factor (VEGF) signaling pathway, prolactin signaling pathway, p53 signaling pathway, adipocytokine signaling pathway, and inhibition of sexual maturation were also enriched (Figure 5).

### Signal pathway transduction analysis

KEGG enrichment analysis of Dabuyin pill inhibition of sexual maturation showed that the target was enriched in pathways including the MAPK pathway, PI3K-Akt pathway, apoptosis pathway, and age-rage pathway.

### Reverse molecular docking verification and spatial structure analysis

A dock score greater than 5.0 indicates that the molecule has good binding activity with the target, whereas a dock score greater than 7.0 indicates that the molecule has

strong binding activity with the target. To further verify the reliability of the predicted results, systems docking was used for molecular docking verification of Rut and key targets in rut-target-Capacitive Voltage Divider (CVD) network (Figure 6).

## Discussion

In recent decades, there has been a rapid development of social economy in China and continuous improvement of people's living standards (19). Influenced by high hormone-containing foods, lifestyle and eating habits, social environment, and other factors, early child sexual development, short stature, precocious puberty, and obesity have become the 3 major diseases of the pediatric endocrinology department (20). The occurrence of idiopathic precocious puberty is related to the premature activation of hypothalamic pituitary-gonadal axis and hyperfunction (21-24). The levels of estradiol (E2), luteinizing hormone (LH), and follicle stimulating hormone (FSH) in the child are significantly increased, the development of secondary sexual characteristics is advanced, the volume of the uterus and ovaries is increased, which is manifested by the growth of pubic and axillary hair, and the enlargement of the mammary glands. The incidence of female CPP accounts for 80–90% of idiopathic precocious puberty, a few cases of which are related to central organic lesions, such as trauma, surgery, infection, tumor, and congenital malformation, among others. Early detection and treatment of idiopathic precocious puberty can inhibit the development of secondary sexual characteristics, slow down the premature closure of epiphysis, and maintain the normal development of the body. For female patients with idiopathic precocious puberty, reducing sex hormone levels and slowing down the maturation rate of sex hormone-dependent structures is the key to successful treatment (25). Dabuyin pills mainly have antibacterial, anti-inflammatory, enhance immune function, reduce blood sugar, strong heart, diuretic and other effects. Enhance immune function: *Phellodendron chinensis* can significantly promote antibody production. Berberine can enhance leukocyte phagocytosis both *in vivo* and *in vitro*.

The use of long-acting GnRH in the treatment of children with true precocious puberty may have a transient excitation response, which can promote the release of gonadotropin, so it can stimulate the desensitization of the pituitary gland and the feedback downregulation effect (26). The comprehensive result is to reduce the

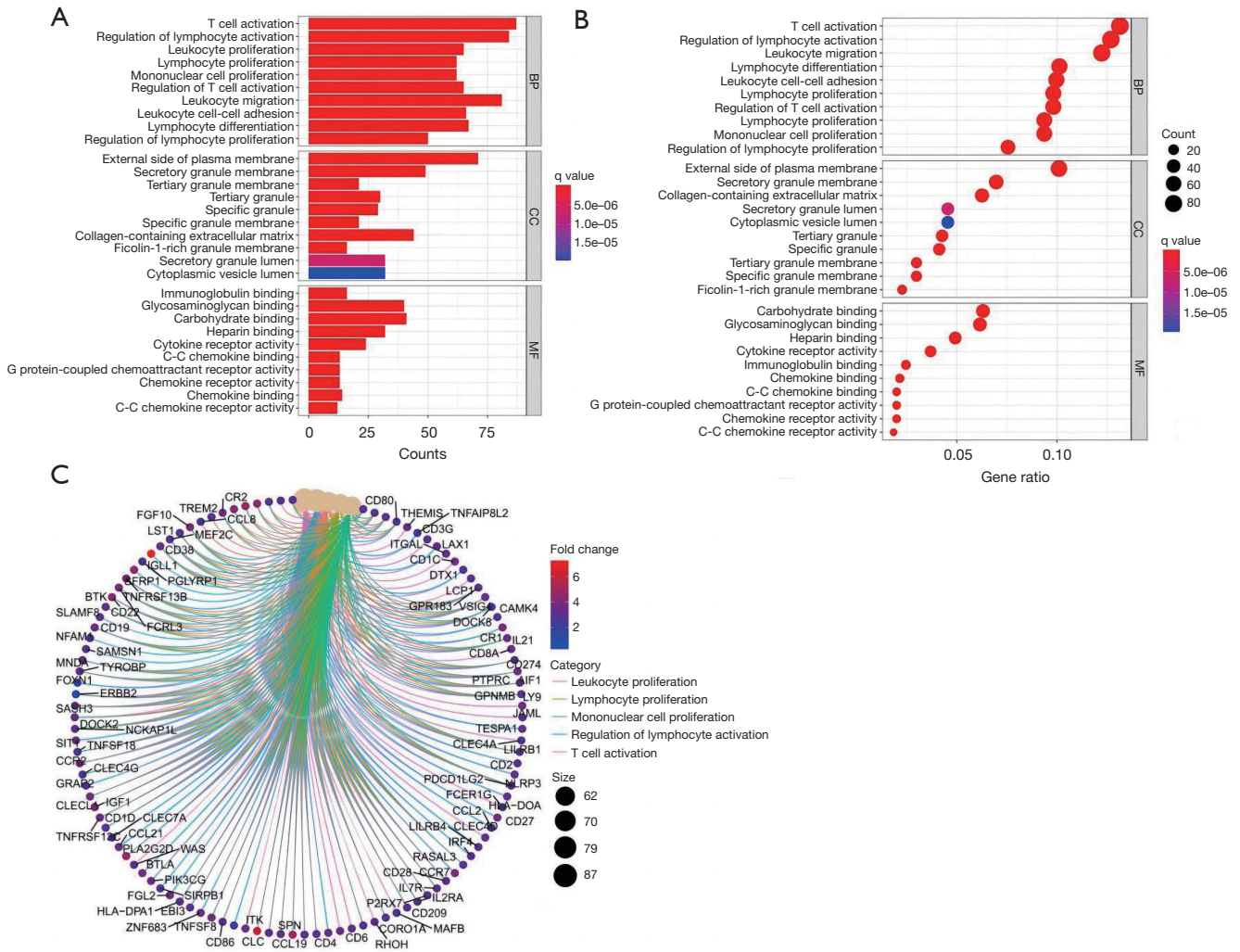


Figure 4 GO functional enrichment analysis. BP, biological process; CC, cellular component; MF, molecular function; GO, Gene Ontology.

level of gonadotropin, and the synthesis and effect of sex hormone. Generally, after 1 year of treatment, the child’s sexual development symptoms will gradually disappear, and the height will gradually return to normal growth rate. Tamiflu is a long-acting Lin GnRHa drug, which in large doses can cause long-term competitive inhibition of pituitary GnRH receptor function, leads to the secretion of pituitary cells reduced susceptibility to long-term GnRH, which downregulates the secretion of gonadotropin and sex hormones, finally having an effect of inhibiting the gonads (27). Dafilin is a GnRHa, which can effectively inhibit the development of secondary sexual characteristics and the increase of bone age, and improve adult height. However, it cannot improve the final height of children with rapidly progressive idiopathic precocious puberty, the

treatment course is long, and the economic applicability is poor, which does not facilitate easy achievement of the expected treatment effect. According to TCM, idiopathic precocious puberty is related to kidney Yin deficiency. Besides sexual characteristics, it is often accompanied by hot flashes, night sweats, heat in the 5 hearts (palms, chest, soles of feet) and other symptoms of Yin deficiency and fire. Dabuyin pill comes from “Danxi xin Law” and is composed of anemone (Zhi Mu), phellodendron bark (Huang Bai), prepared rehmannia (Shu Di Huang), and tortoise plastron (Gui Ban): Zhi Mu, and Huang Bai have the properties of nourishing Yin and tonifying kidney, clearing heat and purging fire; Shu Di Huang tonifies the blood and nourishes Yin, replenishes essence and fills pulp; Gui Ban has the properties of nourishing Yin and subduing

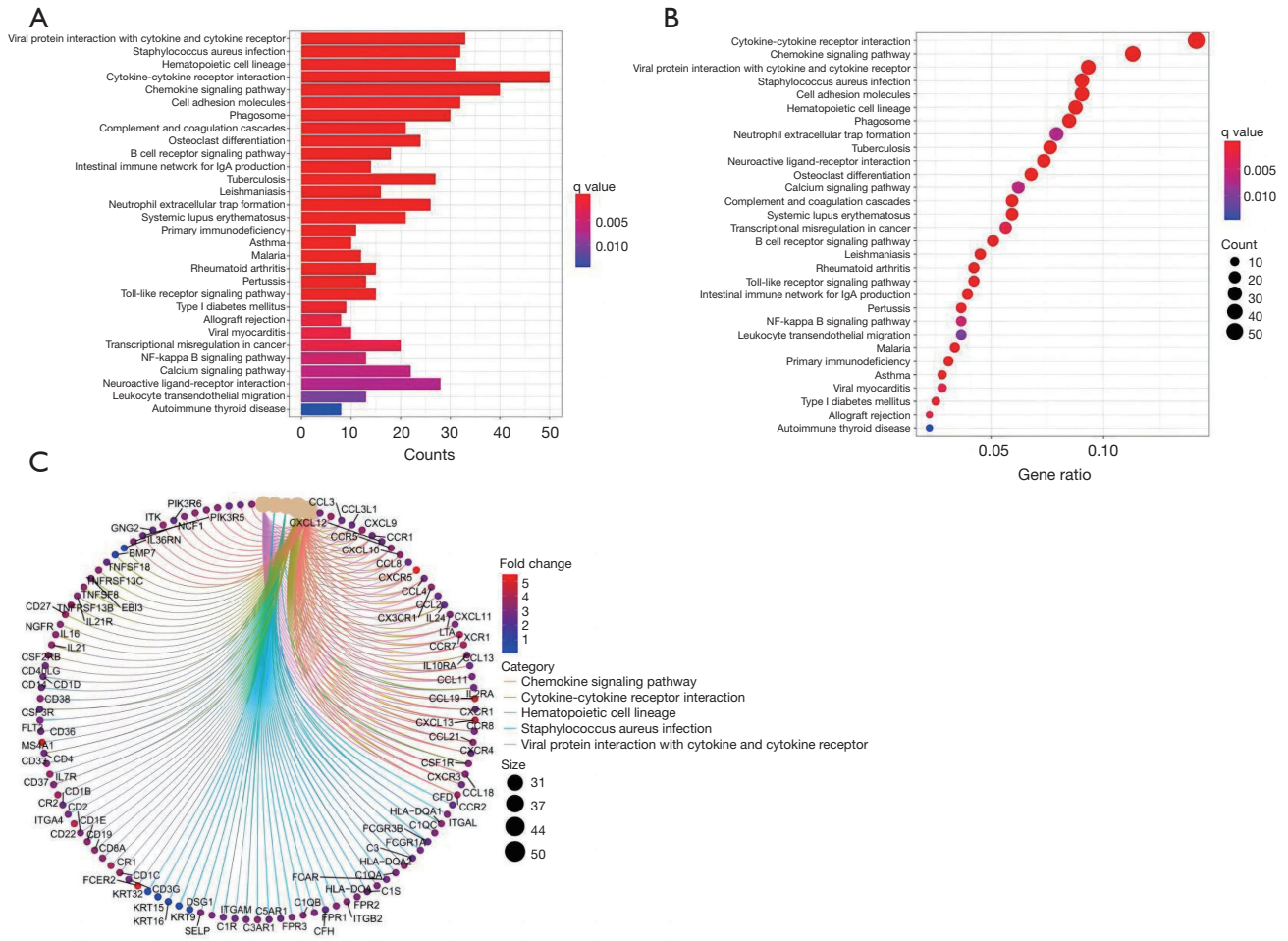


Figure 5 KEGG functional enrichment analysis. IgA, immunoglobulin A; KEGG, Kyoto Encyclopedia of Genes and Genomes.

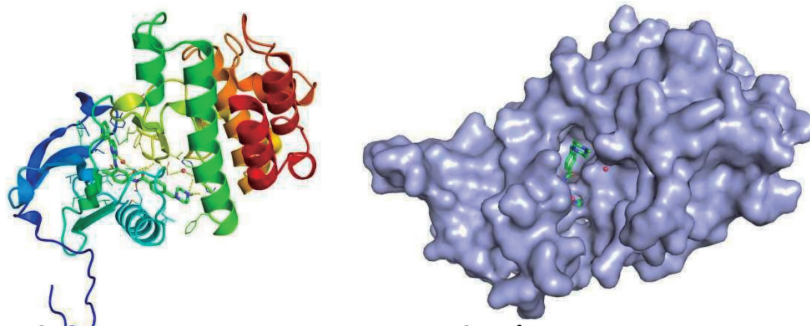


Figure 6 Reverse docking molecular protein model.



Yang, and tonifying kidney and bone (28). Dabuyin pill has the effect of reducing deficiency fire and nourishing kidney Yin. Modern pharmacology has shown that Dabuyin pill can block the release process of central excitatory amino acid transmitter,  $\gamma$ -aminobutyric acid, and  $\beta$ -endorphin, inhibit the synthesis and secretion of GnRH in the hypothalamus, reduce the level of GnRH, and effectively improve the hypothalamic-pituitary-gonadal axis hyperfunction in children with precocious puberty (29-31). The side effects of GnRH-a are low estrogen induced perimenopausal symptoms and osteoporosis. GnRH-a keeps the body in a state of low estrogen and produces menopausal symptoms, such as hot flashes, vaginal dryness, lack of sexual desire, emotional instability, sleep disorders, etc., and long-term application leads to decreased bone density.

The occurrence of idiopathic precocious puberty is due to the premature activation and hyperfunction of the hypothalamic-pituitary-gonadal axis in children. The levels of serum FSH, LH, and E2 were significantly increased, the development of the uterus, ovaries, and sexual characteristics, and bone age were advanced. CPP in women is 80–90% idiopathic precocious puberty, a few cases of which can be caused by central organic lesions: tumors, infections, trauma, surgery, congenital malformations, and so on. In recent years, the incidence of CPP in girls has been increasing year by year, which has become the focus of child growth and development clinics (32). TCM believes that the accelerated growth and development, the early emergence of secondary sexual characteristics is due to the imbalance of Yin and Yang of the kidney, kidney Yin insufficiency, inability to engender Yang, and deficiency fire is made by this hyperactivity (33). Affected children are often accompanied by 5 heart heat, hot flashes, night sweats, a red tongue with no coat or reduced coat, and other Yin deficiency fire flourishing signs. This study showed that the development of reproductive organs was significantly inhibited by oral administration of Dabuyin pill, and the volume of the uterus and ovaries were significantly reduced before and after the treatment of CPP in girls, with significant differences (34). The level of sex hormone also decreased significantly before and after treatment, and the bone age index changed from  $>1$  before treatment to  $<1$  after treatment. These data indicate that Dabuyin pill has definite efficacy in the clinical treatment of CPP in girls. No adverse reactions were observed in the 1-year clinical observation. In the control group, the levels of reproductive organs, sex hormones, and bone age increased significantly during the 1-year clinical observation (35). Therefore, early

detection and early treatment should be carried out for children with precocious puberty.

### Limitation

The present study was a network pharmacology analysis, further clinical studies are still needed.

### Conclusions

The research on the factors related to the prognosis of various diseases is the current research focus (36-39). It is suggested that Dabuyin pill can inhibit the development of secondary sexual characteristics, reduce the volume of the uterus and ovaries, slow down the speed of bone maturation, and has no adverse reactions. It is safe and reliable, and worthy of clinical application.

### Acknowledgments

*Funding:* This study was supported by the Medical Health Science and Technology Project of Zhejiang Province (No. ZJSYXH05).

### Footnote

*Reporting Checklist:* The authors have completed the STREGA reporting checklist. Available at <https://tp.amegroups.com/article/view/10.21037/tp-23-111/rc>

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tp.amegroups.com/article/view/10.21037/tp-23-111/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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- (English Language Editor: J. Jones)

**Cite this article as:** Chen X, Zheng M, Fei X, Ma X. Analysis of the efficacy of Dabuyin pill combined with gonadotropin-releasing hormone analogue in the treatment of central precocious puberty girls based on network pharmacology. *Transl Pediatr* 2023;12(3):364-374. doi: 10.21037/tp-23-111