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# The regulation and mechanism of ZhibaiDihuang on gonadal hormones: A bibliometric and meta-analysis from 2019 to 2023

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## ADMINISTRATIVE INFORMATION

**Support -** None.

**Review Stage at time of this submission -** The review has not yet started.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY2023120016

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 December 2023 and was last updated on 04 December 2023.

## INTRODUCTION

**Review question / Objective** This study analyzes the efficacy and safety of Zhibai Dihuang Pill in regulating gonadal hormone levels and the molecular mechanism of Zhibai Dihuang Pill in regulating gonadal hormone levels. It provides a reference for the rational use of Zhibai Dihuang Pill in clinical practice and provides a new direction for the basic research of Zhibai Dihuang Pill.

**Condition being studied** At present, gonadotropin-releasing hormone analogs (GnRHa) are widely used domestically and internationally to treat CPP, with satisfactory clinical effects. The most commonly used formulations are triptorelin and leuprorelin. Although the efficacy and safety of GnRHa in treating precocious puberty have been widely recognized, its treatment cost is very expensive. Traditional Chinese medicine has unique advantages in treating precocious puberty and has achieved significant clinical efficacy at a low price. Zhi Bai Di Huang Tang is made from Liu Wei Di Huang Wan, Zhi Mu, and Huang Bai. Liu Wei Di Huang Wan the liver and kidneys, and treats three Yin simultaneously, while Zhi Bai Di Huang Tang has a more nourishing and fire-reducing effect. Whether using the classic formula of ZhibaiDihuang Wan alone to treat precocious puberty in girls, or combining it with Western medicine, it can effectively reduce the levels of sex hormones (LH, FSH, E2), slow down the development of the uterus, ovaries, and follicles. The combination of Chinese and Western medicine treatment can significantly shorten the course of treatment. From this, it can be seen that the therapeutic effect of ZhibaiDihuang Tang in the treatment of CPP is worthy of recognition.

## METHODS

**Search strategy** Search((((Child[mh] or Children[tw] or Girls[tw] or Girl[tw] or Boys[tw])) AND ((Puberty, Precocious[mh] or Precocious Puberties[tw] or Puberties, Precocious[tw] or

Pubertas Praecox[tw] or Praecox, Pubertas[tw] or Precocious Puberty[tw] or Precocious Puberty, Central[tw] or Central Precocious Puberties[tw] or Central Precocious Puberty[tw] or Precocious Puberties, Central[tw] or Puberties, Central Precocious[tw] or Puberty, Central Precocious[tw] or exual Precocity[tw] or Precocities, Sexual[tw] or Precocity, Sexual[tw or Sexual Precocities[tw] or Idiopathic Sexual Precocity[tw] or Idiopathic Sexual Precocities[tw] or Precocities, Idiopathic Sexual[tw] or Precocity, Idiopathic Sexual[tw] or Sexual Precocities, Idiopathic[tw] or Sexual Precocity, Idiopathic[tw] or Familial Precocious Puberty[tw] or Familial Precocious Puberties[tw] or Precocious Puberties, Familial[tw] or Precocious Puberty, Familial[tw] or Puberties, Familial Precocious[tw] or Puberty, Familial Precocious[tw] or Precocious Puberty, Male-Limited[tw])))) AND (zhibaidihuang)) AND (Randomized Controlled Trial[mh] or controlled clinical trial[pt] or randomized[tiab] or randomly[tiab] or trial[tiab] or groups[tiab]).

**Participant or population** We will include patients with precocious puberty as the research object, and Gonadal hormone Levels results as the diagnostic criteria.

**Intervention** We will be interested in the effectiveness of Zhibaidihuang in clinical trials, so Dabuyinwan and Gonadotropin-releasing hormone inhibitor treatments as basic Western medicine treatment will be excluded.

**Comparator** The basic treatments (Liangprelin, Triptorelin, and other Gonadotropin-releasing hormone inhibitor treatments) will be compared for this study.

**Study designs to be included** Randomized controlled trials (RCTs).

**Eligibility criteria** Complies with the diagnostic criteria for central precocious puberty in the 2022 edition of the Chinese Journal of Pediatrics and the 2022 Clinical Practice Guidelines for Central Premature puberty in Korean Children and Adolescents published in the Journal of Endocrine Metabolism of Pediatrics.

**Information sources** PubMed, EMBASE, CENTRAL, China Biomedical Literature Database, Chinese National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP will be systematically searched from inception to September 30, 2023. we will Search for the following keywords: TCM constitution, Lung cancer, Systematic review, and meta-analysis. There are no restrictions on languages.

**Main outcome(s)** The primary outcome will be Gonadal hormone Levels, which sensitively reflect important biochemical markers for HPGA initiation. Therefore, it has become an important indicator for screening the initiation of sexual development and has been widely used in clinical diagnosis and drug research.
The second outcome will be identified as Clinical efficacy、Uterine volume、Ovarian volume、Follicle size、bone mineral density). The main basis for clinical efficacy is the improvement of the stimulation test. Healing: Breasts shrink to early adolescence; Vaginal secretions dissolve vaginal bleeding, menstruation disappears, and pubic hair growth stops; B-ultrasound ovarian volume<1mL; FSH＜2.5IU/L; The LH/FSH of the stimulation test is less than 1. Improvement: Significant reduction in breast size; Vaginal secretions and vaginal bleeding disappear, and pubic hair grows slowly; B-ultrasound ovarian volume 1-2Ml; FSH ≤5IU/L, LH＜2.5IU/L; Excitation test LH/FSH≤1. Unhealed: No significant changes in the breasts and external genitalia; The pubic hair continues to grow; B-ultrasound ovarian volume≥2mL; FSH≥5IU/L, LH≥ 2.5IU/L; Challenge test LH/FSH ≥ 1.

**Additional outcome(s)** List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review Supplementary items regarding recommendations related to traditional Chinese medicine (TCM) and integrated Chinese and Western medicine: 1) The search involves ancient classics of traditional Chinese medicine; 2) The recommendations are converted to vernacular style so that the non-TCM practitioners are easy to comprehend; 3) Principle of addition and subtraction is provided according to differentiation of syndromes. 4) Interaction effects between Chinese and Western medicine are specified. 5) For specific clinical circumstances, efficacy and safety of different combinations of integrated Chinese and Western medicine are ranked; 6) Cost-effectiveness information of integrated Chinese and Western medicine is considered. 7) Assessment criteria on prognosis are provided for both diseases (conception of Western medicine) and syndromes (conception of TCM). Timing and effect measures Options are "yes" or "no".

**Data management** Two researchers will independently screen titles, extraction of

information, and cross-check. any disagreement will be resolved through discussion or consultation with a third party. Data extraction will include the following aspects: title of literature, first author, Year of publication, gender, age, cardiac function classification, basic treatment, dose, frequency, and course of treatment of Zhibaidihuang.
Two researchers will independently screen titles, extract information, and cross-check. In case of disagreement, it shall be settled through discussions or negotiation with a third party. After excluding the irrelevant articles, further reading the abstract and full text to determine whether they are included. Data extraction will include the following aspects: 1) basic information of included studies: title, first author, publication time, and study area; 2) baseline and final follow-up data related to outcome indicators. If a study reported multiple follow-up points, only the final follow-up data were extracted; only the first-stage follow-up data were extracted in the crossover trial.

**Quality assessment / Risk of bias analysis** Two researchers independently evaluated the risk of bias included in the study and cross-checked the results. If there are differences, a third party shall negotiate and resolve them. The bias risk assessment was conducted using the RCT bias risk assessment tool and JBI bias risk assessment tool recommended in Cochrane Handbook 5.10. The evaluation tool includes 7 items: 1) Whether the random sequence generation method is appropriate, 2) Whether allocation concealment is correctly implemented, 3) Whether blinding is correctly applied to patients and doctors, 4) Whether blinding is correctly applied to result evaluators and analysts, 5) Whether results are reported without selectivity, 6) Whether the result data is complete, and 7) Whether there is any other risk of bias. If the result is determined to be definitive yes indicating low bias risk and definitively no indicating high bias risk, for items that cannot be determined for bias risk due to lack of direct information, we will infer from other information in the literature that the item is at risk of bias for both probability “yes” and probability “no”.

**Strategy of data synthesis** Two researchers will extract the search results using STAT14.0. The rate and 95% confidence interval (CI) of different TCM Constitution Types in the lung cancer population were calculated, and the main results will be shown by a forest map. If I2 >50%, it is considered that there is statistically significant heterogeneity. The possible sources of heterogeneity should be analyzed again. Finally, a funnel plot, Begg's test, and Egger's test will be used to evaluate the bias.

**Subgroup analysis** Subgroup analysis will be measured for therapeutic medication: ZBDH+GnRH drug vs.GnRH drug, ZBDH vs. GnRH drug.

**Sensitivity analysis** Subgroup analysis will be measured for therapeutic medication: ZBDH+GnRH drug vs.GnRH drug, ZBDH vs. GnRH drug.

**Country(ies) involved** China.

**Keywords** sexual precocity; Zhibaidihuang; Gonadal hormone; molecular mechanism; bibliometrics.

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