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Review article

Herbal formula (Danggui Beimu Kushen Wan) for prostate disorders: a systematic review of classical literature

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ABSTRACT

Background: Danggui Beimu Kushen Wan (DBKW) was initially known for difficult urination in pregnancy and has been widely used for prostate disorders in modern days. This study aimed to comprehensively investigate the implications of DBKW in traditional evidence.

Methods: The Encyclopedia of Traditional Chinese Medicine was searched to identify the ingredients, dosage, etiologies, pathogeneses, actions and indications related to DBKW documented in ancient books. Descriptive summary was provided to their characteristics.

Results: A total of 41 texts in 36 classic books were included. Two etiologies and 10 pathogeneses were investigated. All the identified formulas contain *Angelicae Sinensis Radix*, *Fritillariae Thunbergii Bulbus* and *Sophorae Flavescentis Radix* with the ratio of 1:1:1. The treatment dosage is three to 10 pills each time. The primary indication of DBKW is difficult urination with heat stagnation. Nine included texts specified that this formula could also be used for male.

Conclusion: Included classic literature has provided fundamental evidence for the management of difficult urination in female and male. Further studies should investigate its mechanisms of actions for difficult urination related conditions, such as prostate disorders.

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1. Introduction

The three most commonly seen prostate disorders, including prostatitis, benign prostatic hyperplasia and prostate cancer, affect about 26–50% of men in all ages worldwide.^{1–3} Within all prostate disorders, approximately 1.1 million patients were diagnosed with prostate cancer and around 307,000 deaths were recorded in 2012 globally.⁴ It is worth mentioning that patients with chronic prostatitis had an approximate 30% higher risk to develop prostate cancer than others in the future.⁵ Difficult urination, urogenital pain, frequent micturition, hematuria, urinary incontinence, acute urinary retention or sexual dysfunction may occur when prostate disorders are developed.^{6–8} Conventional management includes active surveillance and observation, surgery, radiation therapy, ablative treatments, hormone treatment, chemotherapy, immunotherapy, physiotherapy and psychotherapy.^{9–11} However, the therapeutic effects are unsatisfactory with inevitable

adverse effects, such as fatigue, depression, postoperative pain, chemotherapy-induced or postoperative nausea and vomiting.⁹

Chinese herbal medicine, such as Danggui Beimu Kushen Wan (Chinese *Angelica*, *Fritillaria* and *Flavescent Sophora* Pill; DBKW), has been used for the management of urination-related disorders for thousands of years.^{12,13} DBKW is also known as Guimu Kushen Wan (GKW; Chinese *Angelica*, *Fritillaria* and *Flavescent Sophora* Pill) or Kushen Wan (KW; *Flavescent Sophora* Pill) in Great Compendium of Chinese Medicinal Formulae.¹⁴ The original record of this formula can be traced back to Jin Gui Yao Lue (Synopsis of Prescriptions of the Golden Chamber; JGYL) written by ZHANG Zhong-jing (150–219 AD) about 1800 years ago.¹⁵ In modern clinical practice, DBKW has been consistently used for a number of diseases involving difficult urination, such as urinary retention in pregnancy,¹⁶ cystitis in pregnancy¹⁷ as well as prostate disorders (prostatitis,¹⁸ benign prostatic hyperplasia¹⁹ and prostate cancer²⁰). Considering unsatisfactory current management of prostate disorders, DBKW may provide a new avenue for prostate disorders. Therefore, it is worth thoroughly investigating the traditional use of DBKW, especially for prostate-related symptoms, and comparing the differences between classic and contemporary applications. This study aimed to comprehensively investigate DBKW's traditional evidence in classic literature that

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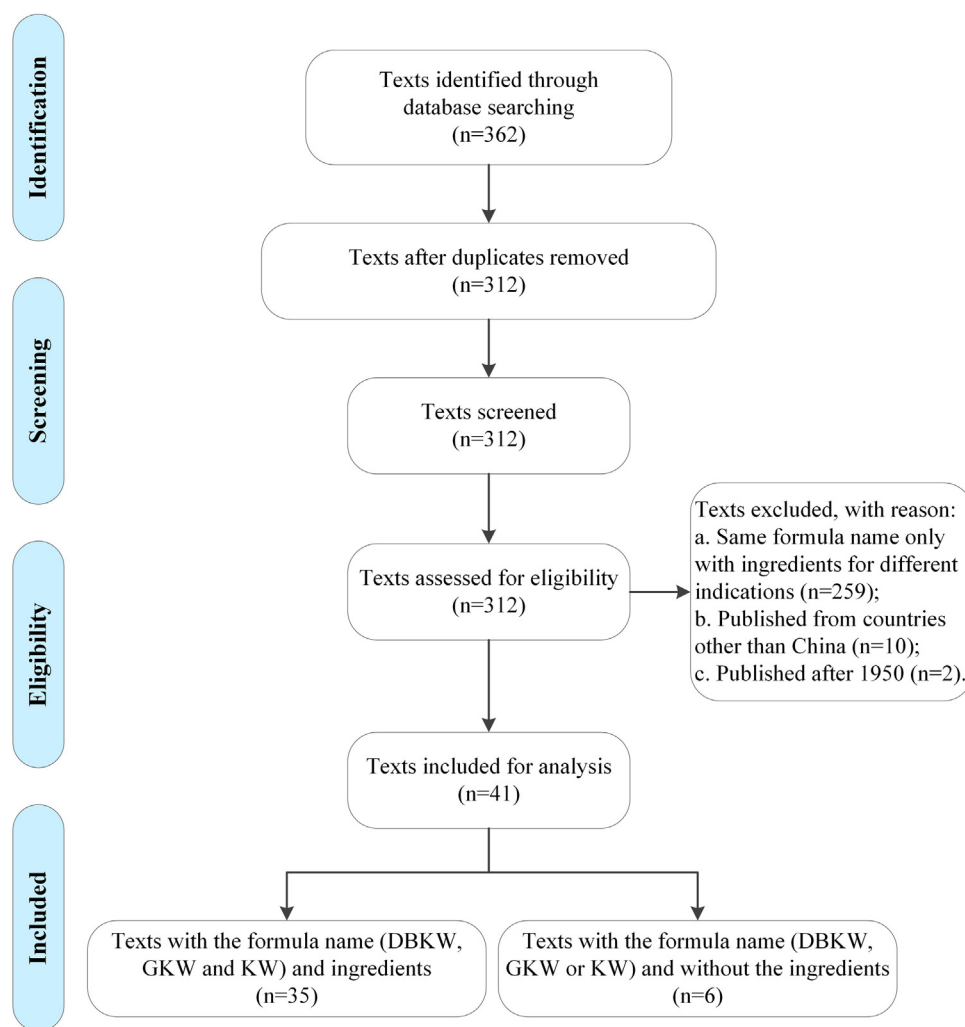


Fig. 1. Selection process of classic texts to be included. DBKW: Danggui Beimu Kushen Wan, Chinese Angelica, Fritillaria and Flavescent Sophora Pill; GKW: Guimu Kushen Wan, Chinese Angelica, Fritillaria and Flavescent Sophora Pill; KW: Kushen Wan, Flavescent Sophora Pill.

may provide modern clinical implications for drug discovery of prostate disorders.

2. Methods

A search of classic literature was conducted in *Zhong Hua Yi Dian* (Encyclopedia of Traditional Chinese Medicine; ZHYD), a CD-ROM containing 1156 ancient books.²¹ Keywords for searching in the CD-ROM included “Danggui Beimu Kushen Wan”, “Guimu Kushen Wan” and “Kushen Wan” in Chinese characters. All the retrieved texts were exported to an Excel file for screening.

The texts were included if they contain the formula name DBKW, GKW or KW, with or without ingredients, and published in China before 1950 since the year 1950 has been identified as the boundary timeline between classic and modern Chinese medicine history.²² The literature was excluded if the formula contains different ingredients from those described in JGYL even though it has the same formula name, or published in countries other than China, or published after 1950.

One reviewer (HL) screened the retrieved texts and extracted the following data to a predesigned Excel file: source of the classic book, author, published dynasty, formula name, ingredients, actions, indications and dosage. The second reviewer (AY) checked the data during the screening and extraction processes. Any discrepancies between two reviewers were resolved through

discussion or the third party (AH). Descriptive summary was provided to the characteristics of extracted data. Dosage of DBKW in ancient units was converted to the international system of units (SI units).

3. Results

A total of 362 texts were identified from ZHYD and 41 of them containing 41 formulas in 36 books were included in this study. Details of identified 41 formulas are listed in Supplement 1. Fig. 1 illustrates the selection process of classic texts in this study.

3.1. Historical development of DBKW

Among 36 classic Chinese medicine (CM) books, 24 texts in 20 books documented the formula as DBKW, 13 texts in 12 books listed as GKW, and four texts in four books recorded as KW. Eleven books mentioned that this formula was cited from JGYL. All included books were published in seven dynasties between year 205 and 1949, including one text in the Eastern Han dynasty (25–220), one text in the Western Jin dynasty (265–316), two texts in the Southern Song dynasty (1127–1279), one text in the Yuan dynasty (1271–1368), nine texts in the Ming dynasty (1368–1644), 26 texts in the Qing dynasty (1644–1912) and one text in the Republic of

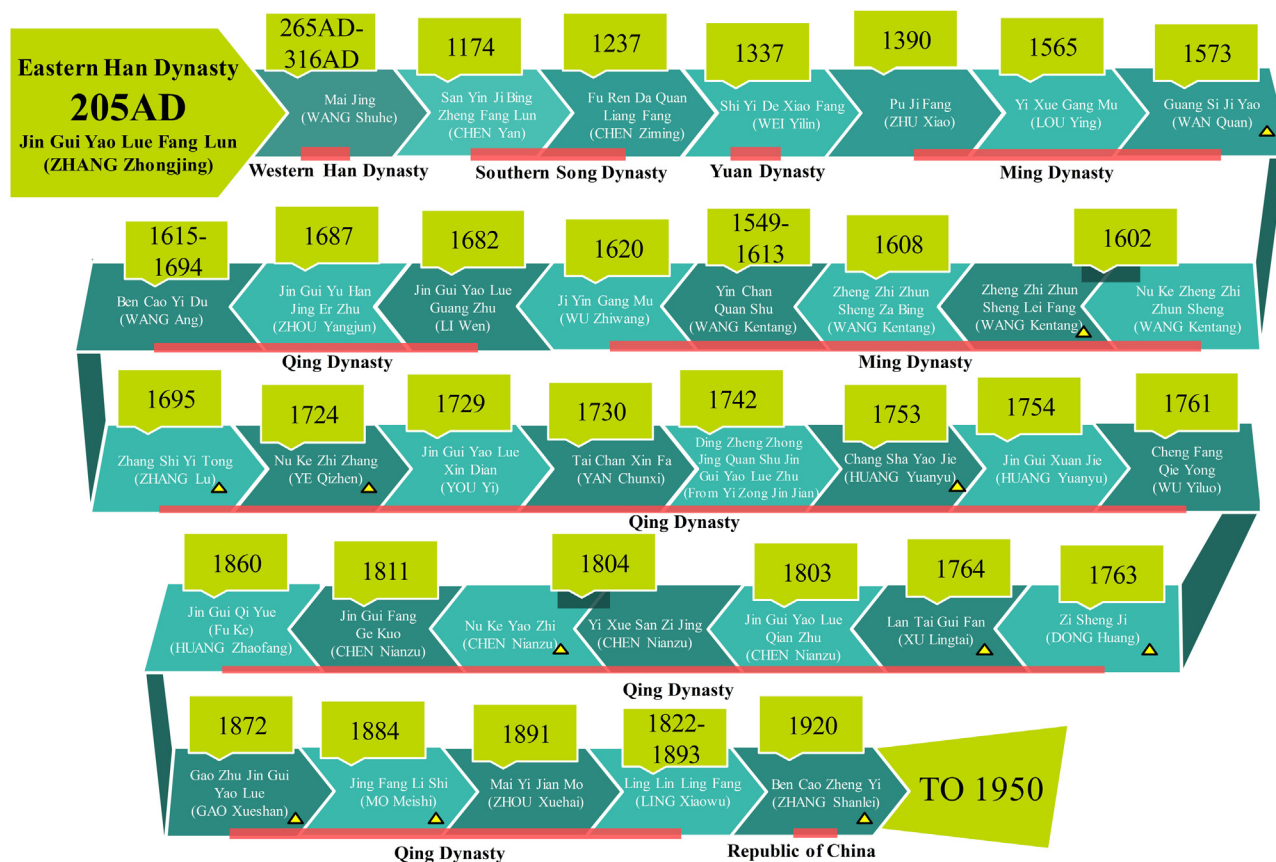


Fig. 2. Historical development of Danggui Beimu Kushen Wan. Δ: Cited formula from Synopsis of Prescriptions of the Golden Chamber. The corresponding English book name referred to Supplement 1.

China (1912–1949). Fig. 2 details the historical development of this formula.

3.2. Etiologies and pathogenesises of DBKW

Twelve books published in the Qing dynasty described the etiologies and pathogenesises of this formula. There are two etiologies and ten pathogenesises mentioned in these books. Fig. 3 shows the primary syndromes treated by DBKW, including Qi stagnation and Blood deficiency due to pregnancy, followed by Qi deficiency due to pregnancy and external wind-cold invasion during pregnancy. With the development of the condition, it aggravates gradually and then may lead to diverse pathogenesises pathways, involving heat stagnation in Lower-Jiao, fetus heat and abdominal distention in pregnancy, and abnormal Bladder Qi-hua. Difficult urination finally occurs when insufficiency of the body fluids or stagnation in water passage is developed.

3.3. Ingredients and dosage of DBKW

Among all the 41 identified formulas, *Angelicae Sinensis Radix* (Dang gui), *Fritillariae Thunbergii Bulbus* (Zhe bei mu) and *Sophorae Flavescentis Radix* (Ku shen) were the three basic ingredients of this formula. The only variation of this formula is that *Talcum* (Hua shi) is contained in 13 formulas (Supplement 1). The original record of this formula clearly indicated that *Talcum* was used for male patients only. Nine formulas specified that *Talcum* was only for male patients. Another four formulas included *Talcum* in its ingredients, however, no gender was specified in their indications. In terms of dosage, 23 formulas disclosed the dosage for each herb (ranging from half to four Liang) and administration of the formulas

(ranging from three pills to 30 pills). Four books demonstrated the administration dosage of this formula without the dosage of each herb whilst two books presented the dosage of each herb, without providing administration dosage for each time. One book provided the herb name only, without a description of dosage. As the size of each pill was only documented as small beans, which is the alternative name of *Vignae Semen* (Chi xiao dou) in Chinese history.²³ One author (HL) measured the weight of each *Vignae Semen* with a digital bench scale (Model: TSDES673, Wedderburn Scales Pty. Ltd.) to examine the administration dosage in the international system of units. The weight of each *Vignae Semen* is approximately 50 mg (Supplement 2).

As summarized in Table 1, the ratio of ingredients (following the herb sequence of *Angelicae Sinensis Radix*, *Fritillariae Thunbergii Bulbus*, *Sophorae Flavescentis Radix* and/or *Talcum*) were identified in three different suggested prescriptions: (1) 1:1:1 for everyone (14 books); (2) 8:8:8:1 for male and 1:1:1 for female (eight books); (3) 6:6:6:1 for everyone (five books). Furthermore, the administration dosage of this formula was recorded in three suggested prescriptions: (1) Three to 10 pills each time (23 books); (2) 20 pills each time (eight books); (3) 30 pills each time (one book).

3.4. Actions and indications of DBKW

All the 41 classic texts claimed the same indication of this formula: difficult urination during pregnancy with normal diet and appetite. Nine of them in three dynasties including Eastern Han dynasty (One text), Ming dynasty (four texts) and Qing dynasty (four texts) specified that this formula could also be used for male patients with difficult urination and normal appetite (Supplement

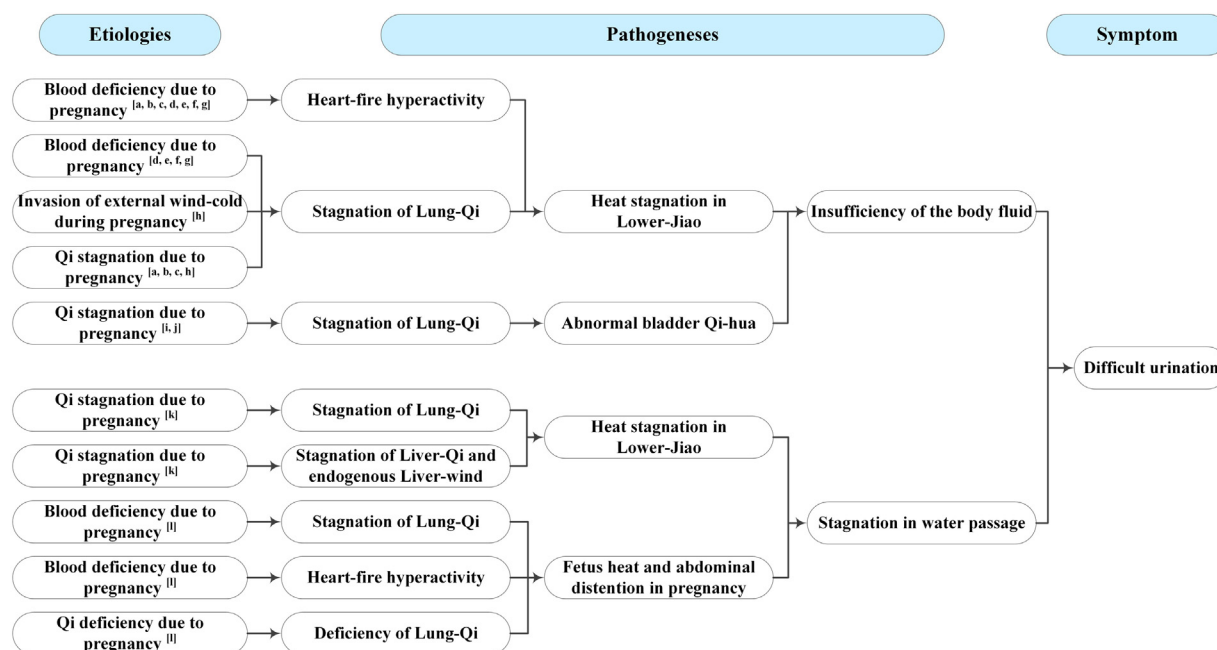


Fig. 3. Etiologies and pathogeneses of Danggui Beimu Kushen Wan. ^[a]Jin Gui Yu Han Jing Er Zhu; ^[b]Zhang Shi Yi Tong; ^[c]Tai Chan Xin Fa; ^[d]Jin Gui Yao Lue Xin Dian; ^[e]Jin Gui Yao lue Qian Zhu; ^[f]Jin Gui Fang Ge Kuo; ^[g]Nu Ke Yao Zhi; ^[h]Cheng Fang Qie Yong; ^[i]Chang Sha Yao Jie; ^[j]Jin Gui Xuan Jie; ^[k]Jin Gui Yao Lue Guang Zhu; ^[l]Gao Zhu Jin Gui Yao Lue. The corresponding English book name referred to Supplement 1.

1). Four texts in three dynasties including Southern Song dynasty (two texts), Yuan dynasty (one text) and Ming dynasty (one text) did not mention whether DBKW could treat male urinary disorders although they included *Talcum* in their prescriptions. Only four texts detailed the possible target diseases of this formula. Specifically, Compendium of Medical Practice (Yi Xue Gang Mu) published in 1565 indicated that the target disease was Zhuan Bao, which is equivalent to urinary retention during pregnancy. Collections of Reproductive and Pediatric Disorders (Guang Si Ji Yao) written in 1573 and Essential Gynecology (Nu Ke Zhi Zhang) written in 1724 claimed that this formula could treat Zi Lin which is similar to urinary tract infections during pregnancy. Encyclopedia of Gynecological Disorders (Yin Chan Quan Shu), documented between 1549–1613, also recorded that this formula could be a treatment for Zhuan Bao as well as Zi Lin.

Although there was no general description for the actions of this formula in CM classic literature, the actions of individual herbs were recorded in 12 books in the Qing dynasty and they are summarized in Supplement 3.

4. Discussion

This study has thoroughly investigated and analyzed DBKW from various aspects, including its ingredients, dosages and indications. Classic literature clearly indicates DBKW can be used for both male and female when they suffer from difficult urination. Three or four ingredients of DBKW were consistently described in the classic texts. However, the use of Bei mu is the concern because there are three main species of Bei mu recorded in CM history, including *Fritillariae Thunbergii* Bulbus (Zhe bei mu), *Fritillariae Cirrhosae* Bulbus (Chuan bei mu) and *Bulbus Bolbostemmati* Rhizoma (Tu bei mu) which ZHANG Zhong-jing did not specify in the original record.²¹ Among the 41 included texts, only Merits of Herbal Medicine (Ben Cao Zheng Yi; 1920, Republic of China) stated that Bei Mu in this formula should be *Fritillariae Thunbergii* Bulbus (Zhe bei mu) which is supported by modern research. Experimental studies have demonstrated that *Fritillariae Thunbergii* Bulbus (Zhe bei mu) could inhibit the abnormal immune response by

relieving the inflammation and over-proliferation of fibroblasts of the prostate as well as reducing the serum level of nitric oxide in the mice model with immunological chronic prostatitis/chronic pelvic pain syndrome.²⁴

4.1. Comparison between classic and contemporary implications

The detailed information of this study assists practitioners and researchers to develop a comprehensive understanding of this formula. DBKW was initially known for managing difficult urination in pregnancy. However, consistent evidence in the included classic literature has indicated that DBKW could also be used for male patients with difficult urination so that the indications of DBKW could be theoretically extended to urinary or reproductive disorders with the similar clinical manifestations in men, such as chronic prostatitis, benign prostatic hyperplasia, or prostate cancer.

A recently published review on clinical and experimental studies of DBKW has revealed that DBKW could be a promising formula with great potential for the management of chronic prostatitis.²⁵ Specifically, four randomized controlled trials (RCTs) applied modified or basic DBKW to treat patients with chronic prostatitis.^{18,26–28} Compared to antibiotic drugs, two RCT involving 170 and 156 patients respectively revealed that the modified DBKW significantly relieved difficult urination, perineal pain and tenderness of prostate after a four-week treatment.^{26,27} However, the review did not synthesize the corresponding data since insufficient details provided in the original studies.²⁵ Another RCT enrolling 100 patients reported that the pH level in the expressed prostatic secretions test was significantly reduced by the modified DBKW decoction after four weeks, compared to ofloxacin (mean difference (MD) -0.17 , 95% confidence interval (CI) -0.33 to -0.01).²⁸ The last study demonstrated adjunct effects of basic DBKW for patients with type III prostatitis on the reduction of NIH-Chronic Prostatitis Symptom Index in addition to terazosin hydrochloride after a six-week intervention (MD -3.08 , 95% CI -5.50 to -0.66).¹⁸ In addition, the modified DBKW has also been reported to treat prostate cancer,²⁰ prostatitis,²⁹ and benign prostatic hyperplasia^{19,30} in non-RCTs, case series and single cases. The outcomes demonstrated

Table 1
Ingredients and dosage of Danggui Beimu Kushen Wan in historical development of Chinese medicine

Dynasty	Per treatment dosage	Weight equivalent to 1 liang (g)	Patient gender (M/F)	Weight of ingredient (Liang)				Weight of ingredient per pill (mg)				Ratio of ingredients	Number of referencing books
				Bei mu	Ku shen	Hua shi	Dang gui	Bei mu	Ku shen	Hua shi	Dang gui		
Eastern Han	0.15–0.5 g 3–10 pills	15.62	M	4	4	4	0.5	16	16	16	2	8:8:8:1	1 book ^[a]
Southern Song	1 g 20 pills	37.3	M & F	3	3	3	0.5	15.79	15.79	15.79	2.63	6:6:6:1	2 books ^[b]
Yuan	1 g 20 pills	37.3	M & F	3	3	3	0.5	15.79	15.79	15.79	2.63	6:6:6:1	1 book ^[c]
Ming	0.15–0.5 g 3–10 pills	37.3	M	4	4	4	0.5	16	16	16	2	8:8:8:1	4 books ^[d]
Ming	0.15–0.5 g 3–10 pills	37.3	F	4	4	4	/	16.67	16.67	16.67	/	1:1:1	2 books ^[e]
Ming	1.5 g 30 pills	37.3	M & F	3	3	3	0.5	15.79	15.79	15.79	2.63	6:6:6:1	1 book ^[f]
Qing	0.15–0.5 g 3–10 pills	37.3	M	3	3	3	0.5	15.79	15.79	15.79	2.63	6:6:6:1	1 book ^[g]
Qing	0.15–0.5 g 3–10 pills	37.3	F	3	3	3	/	15.79	15.79	15.79	/	1:1:1	3 books ^[h]
Qing	0.15–0.5 g 3–10 pills	37.3	M & F	4	4	4	/	16	16	16	2	8:8:8:1	12 books ^[i]
Qing	0.15–0.5 g 3–10 pills	37.3	M & F	4	4	4	/	16.67	16.67	16.67	/	1:1:1	12 books ^[j]

Note: Bei mu, Fritillariae Thunbergii Bulbus; Dang gui, Angelicae Sinensis Radix; F, Female; Hua Shi, Talcum; Ku shen, Sophorae Flavescentis Radix; M, Male.

^[a] One book: Jin Gui Yao Lue; ^[b] Two books: San Yin Ji Bing Zheng Fang Lun, Fu Ren Da Quan Liang Fang; ^[c] One book: Shi Yi De Xiao Liang Fang; ^[d] Four books: Yi Xue Gang Mu, Nu Ke Zheng Zhi Zhun Sheng, Zheng Zhi Zhun Sheng Lei Fang, Ji Yin Gang Mu; ^[e] Two books: Guang Si Ji Yao, Yin Chan Quan Shu; ^[f] One book: Pu Ji Fang; ^[g] One book: Jin Gui Yue (Fu Ke); ^[h] Three books: Nu Ke Yao Zhi, Jin Gui Fang Ge Kuo, Jing Fang Li Shi; ^[i] 12 books: Jin Gui Yao Lue Guang Zhu, Jin Gui Yu Han Jing Er Zhu, Zhang Shi Yi Tong, Jin Gui Yao Lue Xin Dian, Tai Chan Xin Fa, Ding Zheng Zhong Jing Quan Shu Jin Gui Yao Lue Zhu, Chang Sha Yao Jie, Jin Gui Xuan Jie, Lan Tai Gui Fan, Jin Gui Yao Lue Qian Zhu, Gao Zhu Jin Gui Yao Lue, Ling Lin Ling Fang.

The corresponding English book name referred to Supplement 1.

that DBKW could relieve difficult urination and eliminate or offset the adverse effects of chemotherapy. In terms of adverse events, only slight dizziness, fatigue and postural hypertension were complained by the participants in one RCT.¹⁸

Although DBKW has shown promising clinical effects in the recent studies, the recently published CM practice guidelines for prostate disorders did not include DBKW as the intervention.³¹ The treatment effects of this formula on male patients may be overlooked by practitioners and researchers since only nine included classic texts in five dynasties highlighted that this formula could be used for male as well. Nevertheless, we should not deny that DBKW has been consistently used for male along with the development of CM history, evidenced by the included classic texts. Considering the potential therapeutic effects and mild adverse events of this formula, practitioners and researchers should conduct more high quality RCTs to verify its clinical potentials on the prostate disorders in the future.

4.2. Experimental studies of DBKW

A recent review and some experimental studies of DBKW pointed out that DBKW may have multiple actions that could have effects on more than one pathway of prostate disorders at the same time.^{25,32–39} A number of animal studies investigated the mechanisms of actions of DBKW on rats or mice in the treatment of chronic bacterial prostatitis. Researchers believed that DBKW has shown anti-inflammatory, anti-fiber proliferation and bactericidal effects on the prostate gland, evidenced by relieving inflammatory cell infiltration, preventing the damage of epithelial cells during infection period, stimulating the recovery of prostate glandular tissue, restricting interstitial hyperplasia of prostate tissue,³³ and decreasing the density of white blood cell while increasing the density of small particle of lecithin.³⁷ DBKW also stimulated the immune system that reduced the positive expression of intercellular cell adhesion molecule-1,³⁶ Interleukin (IL)-1 β ,³² IL-8³⁴ and tumor necrosis factor- α (TNF- α) mRNA.³⁵ In addition, DBKW may have antagonistic effects on benign prostatic hyperplasia via decreasing the serum level of testosterone propionate and estradiol in the body,³⁸ reducing the expression of proliferating cell nuclear antigen and B-cell lymphoma/leukemia-2 (Bcl-2) as well as increasing the expression of Bcl-2-associated X protein at the genetic level.³⁹

Similar pharmacological effects were reported to the individual herbs contained in this formula.^{40–42} They could support the treatment effects of this formula. Recent laboratory studies reported that all Angelicae Sinensis Radix, Fritillariae Thunbergii Bulbus and Sophorae Flavescentis Radix have anti-inflammatory and immunoregulatory activities evidenced by decreasing the expression of TNF- α ,^{43–47} IL-1 β ,⁴⁸ IL-6,^{45,46} IL-8,⁴⁵ nuclear factor kappa light chain enhancer of activated B cells,⁴⁹ as well as enhancing the expression of Interferon- γ .⁵⁰ The therapeutic effects of DBKW on prostate disorders may be due to the multiple active compounds in DBKW, such as ferulic acid, oxymatrine, oxysophocarpine, matrine, sophocarpine, verticine and verticinone.^{25,40–42,51} However, the actual mechanisms of actions of DBKW for prostate disorders are unknown that should be comprehensively detected in the future. It could be an opportunity for researchers to discover new drugs for the management of prostate disorders, guided by ancient wisdom.⁵²

4.3. Limitations of this study

A few limitations were inevitable in this study. Although this text-mining approach via ZHYD database searching has been considered as a systematical research method for classic literature, its thoroughness and comprehensiveness are subject to the availability of classic books included in the ZHYD.²² The recent review

of modern literature on DBKW highlighted that the quality of its included RCTs is poor and more high quality clinical and experimental studies are recommended to verify its effects for the management of prostate disorders.²⁵ In addition, a doubtful point has been noticed that the dosage recorded in the original text was too low for an adult after being converted to SI units, comparing to the dosage mentioned in the review.²⁵ Thus, the treatment dosage in clinical practice should be further explored in future studies. Even though minor adverse effects were reported in modern clinical studies mentioned above, the safety and toxicity of DBKW should be further investigated.

In conclusion, classic literature has indicated that the primary indication of DBKW was difficult urination with heat stagnation and the treatment dosage of DBKW was three to 10 pills each time. Modern clinical and experimental studies mentioned above agreed that DBKW may have anti-cancer effect, anti-inflammatory effect, anti-proliferation effect and anti-bacterial effect for prostate disorders. Thus, DBKW seems a promising formula for the management of clinical conditions associated with difficult urination involving prostate disorders. However, the exact treatment dosage in modern SI units, adverse effects, toxicity and mechanisms of actions of DBKW for prostate disorders are still unclear. Further study should pay more attention to conduct high quality and well-designed RCTs, in vivo, in vitro and network pharmacological studies so that comprehensive investigation on the efficacy and safety of DBKW for the management of prostate disorders can be performed.

Author contributions

Conceptualization, H.L., A.H. and A.Y.; Methodology, H.L., A.H. and A.Y.; Software, H.L.; Validation, H.L., A.H. and A.Y.; Data Analysis, H.L. and A.Y.; Writing – Original Draft Preparation, H.L.; Writing – Review & Editing, H.L., A.H. and A.Y.; Supervision, A.H. and A.Y.

Conflict of interest

The authors declare no conflict of interest.

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This research received no external funding.

Ethical statement

This study did not involve any human or animal experiment.

Data availability

The data used to support the findings of this study are included within the supplementary information files.

Supplementary material

Details of individual herbs (ingredients) of Danggui Beimu Kushen Wan and measurement of Vignae Semen (Chi xiao dou) weight can be found, in the online version, at doi:<https://doi.org/10.1016/j.imr.2019.08.006>.

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