

# Exploring the Combination Characteristics and Mechanism of Kidney Tonifying Effects of Kidney Qi Pill and Right Return Pill Based on the Theory of "Tonifying and Diarrhea"

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**Abstract:** Kidney Qi Pill is from Zhang Zhongjing's *Jinkui Yaolve* in the Han Dynasty, while Right Return Pill is from Zhang Jingyue's *JingYue QuanShu* in the Ming Dynasty, although the two sides were created in different dynasties, they are both kidney tonic formulas and are still used today. Drugs such as "three tonics" and "three diarrheas" and various drugs such as "less fire and more anger" in kidney qi pills can achieve tonify the kidney qi, while Right Return Pill is based on the Kidney-Qi Pill by deleting the "three tonics" and retaining the "three diarrhoeas". Both of them have the effect of warming the kidney yang, but Kidney Qi Pill aims to warm the kidney yang and transform the kidney qi, while Right Return Pill fills the kidney essence and helps the kidney yang. Its mechanism of action is the same and different, and at the same time, the "three tonics" are used to "seek yang in the yin", and the difference is the "three diarrhea" drugs and filling in the fine matching and trade-offs of the boutique. This paper aims to compare and analyze the characteristics of the combination of kidney qi pill and Right Return pill and modern molecular mechanism. In order to provide reference for the advantages of these two directions to study the drug and compatibility mechanism.

**Keywords:** Kidney Qi Pill; Right Return Pill; Tonics and diarrhoea; Formulation and combination; Mechanism of action

## 1. Introduction

The term "tonifying diarrhoea" originated and was used throughout the *Huangdi Neijing*, and the famous Han Dynasty doctor Zhang Zhongjing applied its theory to the creation of the classic formulas in the *Shanghan Zabing Lun* and *Jinkui Yaolve*. To the Ming dynasty, the medical practitioner Miao Xiyong's book *Shennong Ben Cao Jing Shu* said: "The five organs' bitter desire to tonic and diarrhoea is the first meaning of medicine". The theory of "tonification and diarrhoea" can be applied to adjust both the operational changes of qi and the deficiency and real changes of qi. From ancient times to the present, clinical treatment has been guided by the theory of "tonification and diarrhoea" [1-2]. The Kidney Qi Pill and the Right Return Pill are representatives of the classic formulas that embody the theory of "tonification and diarrhoea". Therefore, this paper intends to compare the similarities and differences between the formulae of Kidney Qi Pill and Right Return Pill in terms of "tonifying diarrhoea" and their modern mechanisms of action, Combined with the modern mechanism of action of its "tonifying and diarrhoea" theory, it provides a theoretical basis for the application of "tonifying and diarrhoea" theory and its clinical prescription medication.

## 2. The historical origin of Kidney Qi Pill and Right Return Pill

Kidney Qi Pill comes from the book "Jinkui Yaolve" by Zhang Zhongjing, a physician of the Eastern Han Dynasty, Development to the Tang Dynasty, the name "eight flavors" was first clearly indicated in the Kidney Qi Pill, and the name was changed to Cui's Eight Flavors Pills in Cuishi Fang, Sun Simiao's book "Thousand Golden Wings" has as many as 6 prescriptions related to kidney qi pill, and calls it Zhang Zhongjing Eight Flavor Kidney Qi Pills. Flowing to the Song Dynasty, The five rules of the volume of the "Taiping Huimin Hejiju Fang" also have its records, named Guifu Eight Flavor Pills;to the Ming dynasty, it was recorded in the "Wanbing Huichun" as a main treatment for

diseases such as the failure of the vital gate fire; to the Qing dynasty, it was clearly recorded in Wu Qian's "Yizong Jinjian" named Eight Flavours of Di Huang Wan. The name "Bawei" was retained in all the above names, and the formula was inherited from Zhang Zhongjing's Jin Kui Kidney Qi Pill, which inspired later generations of doctors to understand kidney deficiency and pioneered the treatment of kidney deficiency [3].

Right Return Pill originated from Zhang Jingyue's "Jingyue Quanshu - Eight New Formulas - Tonic Formulas", a medical practitioner of the Ming Dynasty warm tonic school. Zhang paid special attention to the discussion and research of theories related to the kidney and the vital gate, He believed that clinical treatment theories focused on yin and yang, and that tonifying yin and yang in the human body must start with kidney qi, and he developed the Right Return Pill from the Kidney Qi Pill [6]. As a classic formula for "seeking yang within yin", Right Return Pill fully embodies Zhang Jingyue's principle of tonifying the kidneys by "seeking yang within yin, and having yang assisted by yin will result in infinite biochemistry" [4].

### 3. Characteristics of the formulae of Kidney Qi Pill and Right Return Pill

#### 3.1. *Tonifying and Diarrhea simultaneously and Pure Tonifying without diarrhea*

In the original recipe of "Essentials of Jin Kui", the dosage of kidney qi pill Jun medicine dry ground yellow is eight taels, and the ratio of yam and dogwood medicine that nourishes the liver and kidney in the formula is 1:4. Dry Rehmannia tonifying kidney essence. Cornus officinalis into the liver and kidney two meridians, tonifying liver and kidney, Dioscorea Root is replenishing qi and nourishing yin, Tonifying spleen and kidney, The combination of the three herbs directly or indirectly tonifies the kidney and nourishes the yin of the kidney body. In addition to kidney-tonifying drugs in the compatibility of Kidney Qi Pill, Poria and Alisma can also reduce kidney evil. Danpi is bitter, pungent and slightly cold, which can clear heat and cool the blood, as well as invigorate the blood and disperse blood stasis. The three herbs can dispel water and help the kidneys to be "watery", and they appear in the tonic, aiming to dispel evil and help the righteous, stabilize the righteous, so that the formula is not stagnant [5].

Zhang Jingyue believes that Radix Rehmanniae Praeparata is "the purest and thickest medicine in the essence blood form", and has the effect of "greatly tonifying blood failure, cultivating kidney water, filling bone marrow, and benefiting true yin". Dioscorea Root can help Rehmannia replenishing true yin, Cornus Fruit can nourish yin qi, Goji berries, a medicine that replenishes sperm and blood, can help ripe ground yellow to replenish true yin, and can also treat the disease of true yin deficiency. The antler glue tastes sweet, salty and warm, and functions tonic liver and kidney essence. Dodder and Eucommia strengthen the waist and knees, Angelica nourishes essence and blood. The whole prescription is purely warm tonic, without diarrhea or attacking evil drugs [6,7].

#### 3.2. *Plain tonifying the Kidney Qi and warming the Kidney Yang*

Zhao Xian Ke's "YI Guan" says "Cinnamon and Aconite are pungent and moist, and can nourish fire in water, so they benefit the origin of fire. When water and fire are nourished by them, the kidney energy will be restored." In the formula of Kidney Qi Pill, warming yang medicine ( cassia twig, aconite ) is compatible with nourishing yin medicine ( dried rehmannia, Dioscorea Root, cornus officinalis ), which is the meaning of transforming kidney qi [5,8]. Zhang Zhongjing combined large doses of yin nourishing herbs such as Rehmannia, Dioscorea Root and cornus officinalis with warming yang herbs such as cassia twig and aconite, to make it reach "lessen the fire and make it angry", meaning to tonify kidney qi [9].

Zhang Jingyue created the concept of "essence" on the basis of the doctrine of the vital gate of kidney water proposed by Zhao Xianke. At the same time, he believed that kidney yang is based on kidney yin and kidney essence, therefore, tonifying kidney yang is not only about warming yang and tonic yang, but also about using warming drugs to tonic kidney yang on the basis of tonifying kidney yin, so as to cultivate yuan yang. In this formula, eight taels of raw Dihuang are replaced by eight taels of ripe Dihuang, and the dosage of cassia twig and aconite is increased to two taels. At the same time, a large number of medlar, antler glue, dodder, eucommia, angelica, etc. were added to supplement essence to reduce kidney qi and help yang without damaging yin. The whole formula combines Yin and Yang tonicity, with warmth being the mainstay [5,10,11].

#### **4. Mechanism of action of Kidney Qi Pill and Right Return Pill in tonifying the kidney**

##### ***4.1. Molecular targets and mechanisms of action of the "three tonics" and "three diarrhoea" drugs***

One of the structural similarities between the formulae of Right Return Pill and Kidney Qi Pill is that they both contain the "three tonic" drugs, but the difference is that Kidney Qi Pill also contains the "three diarrhoea" drugs in addition to the "three tonic" drugs. Therefore, the pharmacodynamic basis of the "three tonics" and "three diarrhoea" drugs may be one of the molecular targets and mechanisms of action for the difference in efficacy between the two.

##### ***4.1.1. The mechanism of action of the three tonic drugs***

Wang Jiapeng<sup>[12]</sup> showed that Shu Di Huang could inhibit the p38MAPK signaling pathway and improve 6-OHDA-induced oxidative stress in dopaminergic neuronal cells to a certain extent, thus reducing apoptosis. Wang Jing<sup>[13]</sup> showed that the pharmacological effects of Shu Di Huang in improving energy metabolism and inhibiting hyperactivity and impulsive behaviour in the prefrontal cortex of rats with ADHD may be based on its ability to improve mitochondrial respiratory function, enhance the activity of Na<sup>+</sup>-K<sup>+</sup>-ATPase, Ca<sup>2+</sup>-Mg<sup>2+</sup>-ATPase and mitochondrial respiratory enzymes (SDH and COX), inhibit mPTP opening and increased expression of glucose transporter proteins are related. This molecular mechanism may also be the material basis for the theory of "tonifying the kidney and filling the marrow" in Chinese medicine. Monogam is one of the quality control indicators of *Cornus officinalis*, and experiments in mice with osteoarthritis have shown that monogam injected into the joint cavity of mice can improve cartilage degeneration by promoting chondrocyte proliferation and inhibiting chondrocyte apoptosis<sup>[14]</sup>. Modern studies have shown that Shu Di Huang-Shan Zhu yu can reduce renal cell apoptosis and preserve residual renal units by inhibiting the CASP3 signaling pathway to protect renal function<sup>[15]</sup>. Soysterol, as the active component of the *Dioscorea*-Shu Di Huang pair, not only reduces cholesterol activity, but also resists the IL-1 $\beta$ -induced NF- $\kappa$ B pathway, and has anticancer, antioxidant and immunomodulatory effects<sup>[16]</sup>. Through the study of single drugs or two pairs of drugs, it can be deduced that the "three tonic" drugs may be the pharmacological basis for the simultaneous effects of Kidney Qi Pill and Right Return Pill in tonifying the kidney, anti-aging, regulating the immune and nervous systems, and regulating bone metabolism.

##### ***4.1.2. Mechanism of action of triple diarrhoea drugs***

Liu Ming<sup>[17]</sup> showed that *Poria-Alisma* could improve renal function, lipid metabolism disorders and regulate AQP1 and ADH-AQP2 related pathways to remove dampness and promote water. Modern network pharmacology has shown<sup>[18]</sup> that triterpenoids, as the main chemical components of the *Poria-Alisma* pair, can promote RNA polymerase II promoter transcription initiation, positive and negative regulation, protein serine/threonine kinase activity, modulation of PI3K-Akt, TNK, and MAPK14 through the regulation of TNF, PTGS, NFKB1, MAPK14 and other targets. PI3K-Akt, TNF, HIF-1, Toll-like receptor signaling pathways and other biological repair processes involved in anti-inflammatory and oxidative stress in tissues. Modern network pharmacological analysis<sup>[19]</sup> shows that the active ingredients of peony bark exert anti-inflammatory and antipyretic effects by regulating six pathways: chemokine signalling pathway, Toll-like receptor signalling pathway, T-cell receptor signalling pathway, B-cell receptor signalling pathway, NF- $\kappa$ B signalling pathway and NOD-like receptor signalling pathway. Through the analysis of the molecular mechanism of the "three diarrhoea" drugs, it can be deduced that Kidney Qi Pill can transform Qi and move water, and is also the material basis for the treatment of diseases of the genitourinary and respiratory systems, and is also the basis for the difference in efficacy from that of Right Return Pill

##### ***4.2. Molecular targets and mechanisms of action of "less fire and more heat" and "warming the kidney and filling the essence"***

The difference between the two mechanisms lies mainly in the "flat tonic" and the "warm tonic", as well as the "invisible" and "tangible" benefits of the tonic. The difference between the two mechanisms lies in the "flat tonic" and "warm tonic", as well as the difference between the "invisible" and "tangible" tonic.

##### ***4.2.1. The medicinal mechanism of "less fire and anger"***

Modern medical research into the function of mitochondrial ATP production is highly similar to the interpretation of the function of "less fire and more energy" in Chinese medicine. The process of ATP production is also the material basis for the transformation of refined substances into Qi, and the energy

contained in ATP is the main source of energy for the function of Qi in TCM. Qiu Lin <sup>[20]</sup> and others showed that the combination of kidney qi with "less fire and more energy" could improve the normal physiological operation of ATP in rats with kidney yang deficiency to ensure the normal energy supply of the body. This function is accomplished by increasing the activities of Na<sup>+</sup>-K<sup>+</sup>-ATPase, Ca<sup>2+</sup>-Mg<sup>2+</sup>-ATPase and respiratory chain complexes I, II, III and IV to ensure the normal tricarboxylic acid cycle and oxidative phosphorylation. Li Meihong <sup>[21]</sup> et al. demonstrated through animal experiments that the modern biological basis for the ability of Kidney Qi Pill to treat Yang deficiency in type 2 diabetes may be related to the mitochondrial function of skeletal muscle and energy metabolism of the body in rats, which is in line with the concept of "less fire and more energy" in Chinese medicine. This is consistent with the concept of "less fire and more energy" in Chinese medicine. This also demonstrates the efficacy of Kidney Qi Pill in tonifying the invisible Kidney Qi.

#### 4.2.2. The medicinal mechanism of warming the kidney and filling the essence

Recent medical research has speculated that the material basis of "kidney" function in Chinese medicine may be related to the hypothalamic-pituitary-adrenal, gonadal and thyroid axes as well as the immune system <sup>[22]</sup>. Modern pharmacological studies have shown that flavonoids, as components of *Cuscuta*, can reduce the apoptosis of spermatogenic cells by regulating the hypothalamic-pituitary-gonadal axis. Wang Jisheng <sup>[23]</sup> showed that *Cuscuta sinensis*-*Lycium* could inhibit apoptosis by promoting the expression of PI3K and p-AKT proteins, thus improving testicular pathology. Hu Hailin <sup>[24]</sup> showed that deer horn gum could promote testicular cell repair, increase T levels and provide negative feedback to the hypothalamic-pituitary-testicular endocrine axis, thus improving the spermatogenic environment to treat Yang deficiency and oligospermia. Bi Xiaoying <sup>[25]</sup> et al. showed through animal experiments that total flavonoids of *Eucommia* can inhibit autophagy of ovarian granulosa cells in rats with polycystic ovary syndrome and balance sex hormone secretion by activating PI3K/AKT/mTOR pathway, thus improving the abnormal function of the ovarian axis caused by the hypothalamus acting on the pituitary gland. Modern pharmacological studies of *Eucommia* have shown that it has antioxidant, immunomodulatory, hypoglycemic, hypotensive and hypolipidemic functions. The molecular mechanism of the above drugs can be deduced to suggest that Right Return Pill can tonify the tangible essence, which can also provide support for the material theoretical basis of warming the kidney and filling the essence.

## 5. Summary

The "three diarrhoea" and "warming the kidney and filling the essence" products in the two formulas may be responsible for the difference in efficacy between Kidney Qi Pill and Right Return Pill. However, from the literature, the molecular regulatory mechanisms of the two medicines, such as the multiple pathways, multiple channels and multiple histologies, have not yet been fully penetrated, and need to be further investigated and discovered. The molecular mechanism of action of the two drugs has not yet been fully understood, and further research is needed to discover the molecular mechanism of the difference in drug efficacy.

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