



# The role of collateral disease theory in the prevention and treatment of atherosclerosis in post-menopausal women: a narrative review

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**Abstract:** There was no equivalent term as “atherosclerosis in postmenopausal women” in ancient Chinese medical literature, so there was no precise method to treat this disease. The collateral disease theory is a theoretical system with the characteristics of traditional Chinese medicine, which studies two branches: qi collateral theory and vessel collateral theory. We first analyzed the relationship between qi and vessel collaterals. The collaterals are divided into the qi collaterals of circulating qi and the vessel collaterals of circulating blood. Qi collaterals and vessel collaterals play the role of circulating qi and blood together. We then illustrate that the concept of vessel collateral system in traditional Chinese medicine is like the concept of the vascular system in modern medicine, and atherosclerosis (AS) is a common vessel collateral-vascular system disease. A significant increase in the incidence of AS in postmenopausal women is related to estrogen deficiency, associated with dysfunction of the qi collaterals. AS in postmenopausal women is associated with both qi collaterals and vessel collaterals. *Bazi Bushen capsule* (BZBS) under the guidance of collateral disease theory replenishes kidney essence, coordinates yin and yang, tonifies kidney qi, and circulates blood. Meanwhile, it has 11 unique phytoestrogens (PEs), which resists AS. In this work, for the first time, we combined the vessel collateral theory with qi collateral theory. We explore the potential theoretical mechanism of the prevention and treatment of postmenopausal AS by the BZBS under the guidance of collateral disease theory.

**Keywords:** Collateral disease theory; vessel collateral theory; qi collateral theory; atherosclerosis after menopause (AS after menopause); *Bazi Bushen capsule* (BZBS)

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## Background

Atherosclerosis (AS), a chronic, systemic inflammation manifesting in blood vessels, is the primary origin of coronary artery disease and stroke AS can lead to cardio-cerebrovascular endpoint events in both men and women (1,2). Thanks to the protective effects of estrogen on

the cardiovascular system (3), the incidence of coronary artery disease in women before menopause are 1/10–3/10 of that in men (4); however, the risk increases ten times after menopause (5). Menopause is a key risk factor for developing coronary artery disease in women. It is estimated that there are approximately 1 billion menopausal women

by 2050 (6-8). It is, therefore, of considerable significance to research AS in postmenopausal women.

There was no equivalent term as “atherosclerosis” or “atherosclerosis in postmenopausal women” in ancient Chinese medical literature. It falls under the category of “chest bi-impediment” or “cardiac pain.” The collateral disease theory is a theoretical system with the characteristics of traditional Chinese medicine, which studies two branches: vessel collateral theory and qi collateral theory (9,10). Vessel collateral system and vascular system are similar in structure and function (11), so vessel collateral theory is often used for vessel collateral problems, including AS. Qi collateral theory is often used for qi collateral problems, including disease of endocrine. A significant increase in the incidence of AS in post-menopausal women is related to estrogen deficiency, which is associated with dysfunction of the qi collaterals (3). Both vessel collateral theory and qi collateral theory play essential roles in the prevention and treatment of AS in postmenopausal women. Previous studies have confirmed that Tongxinluo capsule, under the guidance of collateral disease theory, inhibits the progression of AS through a variety of ways, such as regulating blood lipid, preventing plaque rupture, protecting vascular endothelium, inhibiting inflammation and regulating immune response (12-14). This review focuses on the guiding role of collateral disease theory in postmenopausal AS.

We present the following article in accordance with the Narrative Review Checklist (available at <http://dx.doi.org/10.21037/apm-20-1257>).

### **Qi collaterals and vessel collaterals: circulate qi and blood and nourish yin and yang**

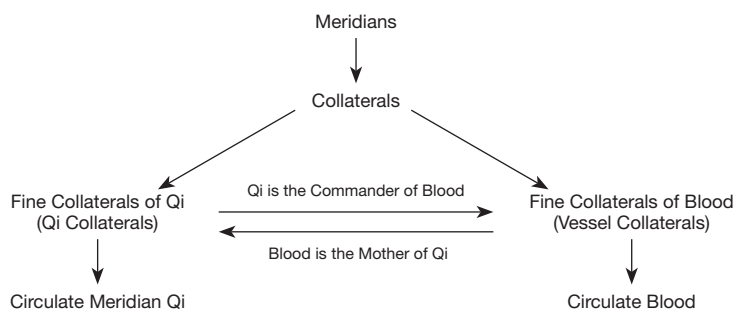
Meridians, the pathways of qi and blood circulation, are an essential structural and functional part of the human body. The *Ling Shu Mai Du* (Chapter 17, Miraculous Pivot) states, “Meridians are in the interior. Their transverse branches are called collaterals. The divergent branches of collateral are called minute collaterals.” Collaterals are like a multi-layer network throughout the body. They act to circulate qi and blood and nourish yin and yang. Zhou Xuehai, a Qing Dynasty physician, proposed the concepts of “fine collaterals of qi” and “fine collaterals of blood.” In a broad sense, collaterals include the “fine collaterals of qi” that circulate meridian qi and “fine collaterals of blood” that circulate blood (15). The two parts are separate but

interconnected. Qi collaterals carry the *Yuan*-primordial qi, *Zong*-pectoral qi, *Wei*-defensive qi, the qi of the zang-fu organs, and the qi of meridians and collaterals. Qi that circulates within meridians is called meridian qi, which becomes collateral qi when it enters collateral. Collateral qi then becomes a structural and functional part of zang-fu organs when it enters the zang-fu organs. These functions are highly correlated with the nerve-endocrine-immune system (NEI system) in modern medicine (16).

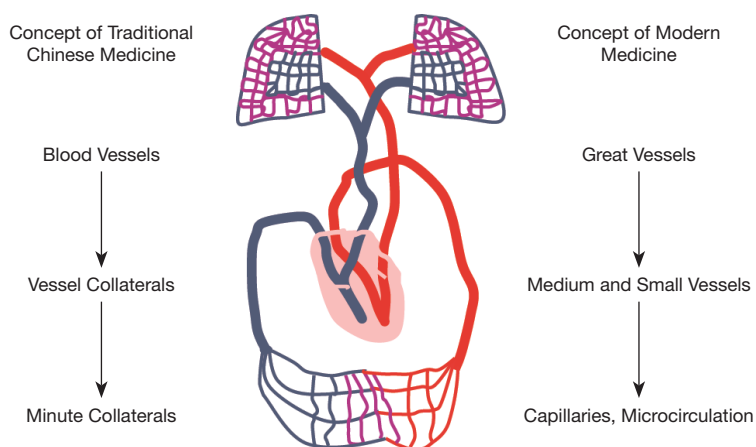
The *Su Wen Mai Yao Jing Wei Lun* (Chapter 17, Basic Questions) states, “Vessel is the house of blood.” Vessel collaterals diverge from blood vessels. The vessel collateral system formed by minute collaterals and their subbranches (17).

The correlation between qi collaterals and vessel collaterals manifests the interactions between qi and blood. Qi and blood are two cornerstone concepts in Chinese medical theory. They both play a significant role in life activities. Qi is yang in nature; it governs moving and warming. Blood is yin in nature; it governs tranquility, moistening, and nourishing. The *Nan Jing* (The Classic of Difficult Issues) states, “Qi governs warming, and blood governs nourishing,” “qi is the commander of blood,” and “blood is the mother of qi.”

In the vessel collateral system, “qi is the commander of blood” that can be understood as qi collaterals, promoting vessel collaterals and keeping blood circulating within the vessels. The *Yuan*-primordial qi is the driving force for the normal functioning of zang-fu organs and the entire body. The *Zong*-pectoral qi governs respiration and distributes clean qi (inhaled through the lungs) all over the body. Qi of the zang-fu organs plays a vital role in regulating blood circulation. “Blood is the mother of qi” can be understood as vessel collaterals, providing nutrients for qi collaterals. The *Xue Zheng Lun* (Treatise on Blood Syndrome) by Tang Rongchuan, a Qing Dynasty physician, has stated that “blood carries qi and qi circulating blood.” The *Sheng Ji Zong Lu* (Comprehensive Recording of Divine Assistance) by Zhao Ji, a Song Dynasty physician, also states, “Qi needs to be carried by the blood, and blood needs to be circulated by qi. The two are inseparable.” The *Huang Di Nei Jing Suwen Ji Zhu* (Annotations to Basic Questions, Yellow Emperor’s Internal Classic) by Zhang Yinan, another Qing Dynasty physician, states, “blood within the vessels permeates through the vessel collaterals, and qi outside the vessels enters the blood through qi collaterals.” Collaterals are essential for the normal functioning of qi and blood (*Figure 1*).



**Figure 1** The correlation between qi collaterals and vessel collaterals. “qi is the commander of blood”: qi collaterals promoting vessel collaterals and keeping blood circulating within the vessels. “Blood is the mother of qi”: vessel collaterals providing nutrients for qi collaterals.



**Figure 2** The concept of “vessel collateral-vascular system disease”.

## AS in postmenopausal women are associated with both vessel collaterals and qi collaterals

### AS: a typical vessel collateral-vascular system disease

The vessel collateral theory further developed the understanding of “blood vessels” in *Huang Di Nei Jing* (Yellow Emperor’s Internal Classic). Blood vessels, vessel collaterals, minute collaterals of the vessel collateral system are anatomically and functionally like arteries, veins, capillaries, and microcirculation in modern medicine (Figure 2). The concept of “vessel collateral-vascular system disease” (11) is on the close correlation between vessel collateral and vascular system. In a narrow sense, vessel collateral-vascular system diseases refer to conditions with functional or structural injury to collaterals. In a broad sense, they include pathogenic factors and later pathological changes of zang-fu organs and tissues (9). The “chest bi-impediment” or

“cardiac pain” was first mentioned in *Huang Di Nei Jing* (Yellow Emperor’s Internal Classic). According to collateral disease theory, this condition is associated with retention of cold, stagnant qi, static blood, and phlegm-fluid in the chest, resulting in collateral obstruction, contracture, or, in severe cases, blockage. The *Su Sen Zhi Zhen Yao Da Lun* (Chapter 74, Basic Questions) states, “Cold may affect the blood and blood vessels..., causing severe cardiac pain”. The *Su Wen Ju Tong Lun* (Chapter 39, Basic Questions) states, “Retained cold qi outside the vessels may cause the vessels to contract and result in sudden pain.” Located in “vessels,” AS is a typical “vessel collateral-vascular system disease”

### Estrogen deficiency after menopause and functional disorder of qi collaterals

As mentioned above, AS is a typical “vessel collateral-

vascular system disease;” however, it is closely associated with “qi.” As the functional and structural carrier of qi, qi collaterals connect, regulate, warm, and nourish the body, defend the body against exogenous pathogens, convey messages, and support homeostasis. AS after menopause is associated with functional disorders of qi collateral in connecting the body and supporting homeostasis.

Collaterals connect zang-fu organs, four limbs, five sense organs, and nine orifices into an organic whole and support homeostasis of the body, known as yin-yang balance in Chinese medicine. They are like the endocrine system that regulates the body through releasing chemical substances, including estrogen.

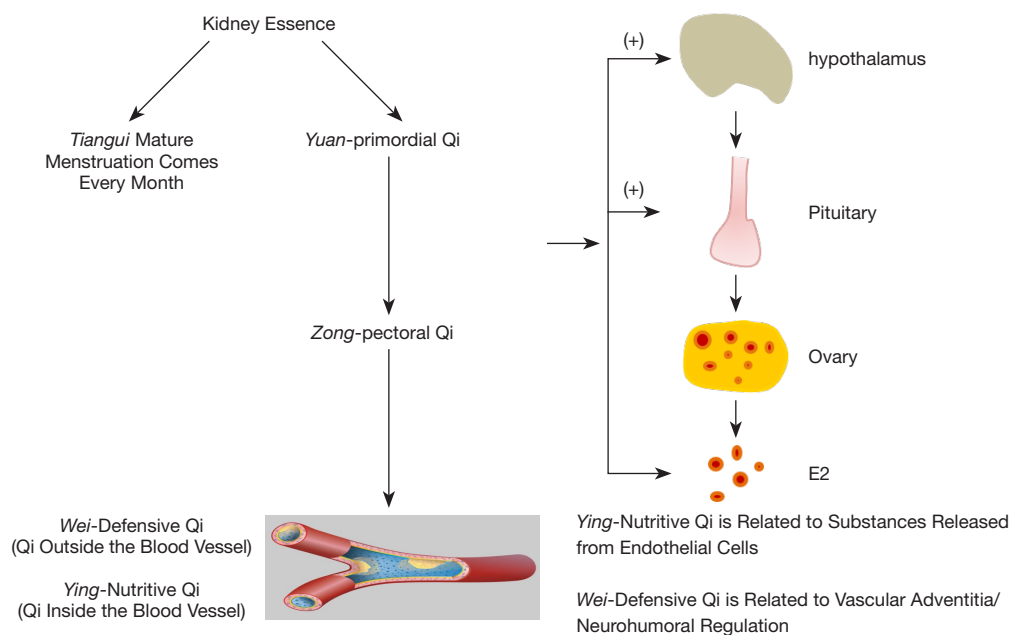
As for the understanding of menstruation in Chinese medicine, the *Su Wen Shang Gu Tian Zhen Lun* (Chapter 1, Basic Questions) clearly states the close association between *Tiangui* and menstruation, “With the abundance of *Tiangui* and flourishing flow of qi and blood in the Ren and Chong meridians, menstruation occurs at the age of 14. Women with menstruation can get pregnant; with *Tiangui* exhaustion and qi decline and blood in the Ren and Chong meridians, menopause occurs at the age of 49. Women cannot get pregnant afterward.” Wu Kun explained in the *Su Wen Wu Zhu* (Wu’s Annotations to Basic Questions), “The *Gui* means kidney water..., which is inborn and endowed by heaven (*Tian*), hence the name “*Tiangui*.” Ma Shi also explained, “*Tiangui* means yin essence, i.e., kidney water. As kidney water is accumulated from pre-natal (*Xian Tian* in Chinese) qi, yin essence is called *Tiangui*.” *Tiangui* is hereditary and transformed from kidney essence and qi (18). Kidney essence governs growth, development, and reproduction. The kidney stores essence and the essence transforms into the blood. With abundant kidney qi and *Tiangui*, women have menstruation and the ability to get pregnant. After experiencing menstruation, pregnancy, childbirth, and lactation, women gradually age. It is said that half of the yin qi become lost at the age of 40, followed by weight gain, reduced hearing, and weak eyesight at the age of 50. Kidney essence is the substantial foundation of menstruation. Abundant kidney essence guarantees normal menstruation, while exhaustion of kidney essence causes a deficiency of the Ren and Chong meridians. The *Fu Qing Zhu Nu Ke* (Fu Qing-Zhu’s Treatise on Gynecology) states, “With kidney qi deficiency, women do not have abundant kidney essence to transform into menstruation.” The *Yi Xue Zheng Zhuan* (Orthodox Introduction to Medicine) states, “Menstrual blood is transformed from kidney water. Exhaustion of kidney water may cause menopause.” These

results match the modern understanding of the role of the hypothalamic-pituitary-gonadal axis in promoting the development and maturity of reproductive organs, ensuring normal growth, development, and reproduction of organs and tissues, and affecting the aging process (16).

During the peri-menopausal period, women are at risk of developing cardio-cerebrovascular diseases, including arterial plaque, atherosclerotic coronary artery disease, or ischemic stroke (19,20). Contributing factors include ovary failure, decrease in estrogen (E2) levels, absence of negative feedback inhibition, functional disorder of hypothalamic-pituitary-gonadal axis, excessive release of gonadotrophin-releasing hormone (GnRH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (21,22), along with functional disturbance of multiple endocrine-regulating centers (especially the hypothalamus and pituitary gland) and cessation of estrogen protection on blood vessels. Consequently, AS in postmenopausal women is closely associated with a disorder of the hypothalamic-pituitary-gonadal axis and dysfunction of qi collateral in regulating the homeostasis (16).

#### *AS in postmenopausal women are associated with both qi collaterals and vessel collaterals*

The *Tiangui* is associated with kidney essence, and its essence transforms into qi. The *Lei Jing* (The Classified Classic) states, its essence transforms into qi. The *Yuan-primordial qi* is transformed from essence.” The *Yuan-primordial qi* is the foundation of all types of qi. The *Nan Jing* (The Classic of Difficult Issues) states, “The origin of *Yuan-primordial qi* is the foundation of the twelve regular meridians, the stirring qi between the kidneys, the source of the five zang and six fu organs, and the root of the twelve regular meridians...” From adolescence to menopause, kidney essence slowly becomes deficient and does not transform into *Yuan-primordial qi*, a crucial component of *Zong-pectoral qi*. The *Yi Xue Zhong Zhong Can Xi Lu* (*Records of Chinese Medicine with Reference to Western Medicine*) states, “the *Zong-pectoral qi* is on *Yuan-primordial qi* and nurtured by qi transformed from water and grains.” The *Zong-pectoral qi* is separated into *Ying-nutritive qi* and *Wei-defensive qi* flowing through the heart vessels. Zhang Jingyue, a well-known Ming Dynasty physician mentioned in the *Lei Jing* (the Classified Classic), “Qi in the exterior (*Wei-defense*) and interior (*Ying-nutrients*) are connected through collateral.” The connection between *Ying-nutrients* and *Wei-defense* provides necessary conditions



**Figure 3** Atherosclerosis in post-menopausal women is associated with both qi collaterals and vessel collaterals.

for metabolism and energy conversion. The *Shang Han Lun* (Treatise on Cold Damage) states, “Incoordination between *Ying*-nutrients and *Wei*-defense causes blood stagnation.” Blood stagnation in AS is caused by age-related kidney essence deficiency, followed by a deficiency of qi and blood, just as the statement in *Chen Su’an Fu Ke Bu Jie* (Supplementary Annotations to Chen Su’an Gynecology), “Stagnant blood contributes to 70–80% of retained menses”. Another major factor is age-related kidney deficiency, followed by collateral qi deficiency and stagnation.

Analysis of patterns in 3,469 AS cases has shown that collateral qi stagnation and deficiency stagnation are the primary pathology and proceed through the whole process of vessel collateral-vascular system diseases (23–25). Laboratory studies have suggested a correlation between *ying*-nutritive qi and vasoactive substances released from endothelial cells and between *Wei*-defensive qi and vascular adventitia/neurohumoral regulation (26). Collateral qi stagnation or deficiency stagnation may disrupt the homeostatic mechanism of NEI network factors and result in endothelial dysfunction and AS (27). AS in postmenopausal women are associated with kidney essence deficiency. As a vessel collateral disease, it is related to the vascular endothelial and mesangial injury. Simultaneously, it is a qi collateral disease and relates to the dysfunctional hypothalamic-pituitary-gonadal axis and

disturbed neurohumoral regulation. Therefore, it is beneficial to understand and treat AS from the collateral disease theory (Figure 3).

### The role of collateral disease theory in AS prevention and treatment

#### *Replenish kidney essence is essential for AS in postmenopausal women*

The *Ji Sheng Fang* (Formula to Aid the Living) states, “*Tiangui* is the essence, and essence is the foundation of life.” The essence is stored in the kidney. Kidney essence insufficiency may cause exhaustion of *tiangui*, which in turn results in menopause. Therefore, the underlying cause of AS in postmenopausal women is kidney essence deficiency, also, AS is directly associated with blood vessels. Collateral qi deficiency and stagnation is the leading cause of AS, a typical vessel collateral-vascular system disease (27). Since collateral deficiency may cause stagnation, it is essential to replenish kidney essence to keep the collateral unobstructed.

The *Lei Jing* (The Classified Classic) states, “To preserve health, one must replenish its essence. An abundance of essence produces an abundance of qi. An abundance of qi creates a sound mind. A sound mind forms a strong body. And a strong body keeps illnesses away.” The *Nan Jing* (The Classic of Difficult Issues) states, “the treatment strategy



for kidney deficiency is to replenish essence.” Most (kidney) essence-replenishing herbs contain phytoestrogens (PEs) and can increase the ovarian response to gonadotropin stimulation, lower FSH levels, and elevate E2 levels (28). Also, they can increase the ovarian weight, induce oocyte maturation and ovulation, and accelerate the functional recovery of the pituitary gland, ovary, and adrenal gland (29). Through analysis of the studies on essence-replenishing herbs, Fan *et al.* produced the idea that “essence” can be understood as a functional state in a microcosmic and systemic network. In this sense, replenishing essence can regulate the NEI network, coordinate the hypothalamic-pituitary-adrenal-gonadal axis, and balance the functional state of the human body (30). What is more, formulas to tonify kidney and replenish essence can regulate the female reproductive axis via multi-targeted organs in multiple levels (31,32).

#### ***Distinctive strengths of Bazi Bushen capsule (BZBS) in AS prevention and treatment***

##### **Replenishes kidney essence, coordinates yin and yang, tonifies kidney qi and circulates blood**

The concept of “tonifying the kidney” was limited to tonify kidney yin and kidney yang before the Ming and Qing Dynasties (1368–1911). Physicians in the Ming and Qing Dynasties started to realize that kidney essence insufficiency is the underlying cause of kidney deficiency, because kidney qi, kidney yin, and kidney yang are all transformed from kidney essence. Consequently, it is vital to replenish kidney essence to tonify the kidney, supplemented by harmonizing kidney yin and kidney yang, and tonifying kidney qi.

As a typical formula to tonify collateral deficiency and unblock stagnation, the BZBS was modified from the *Wuzi Yanzong Wan* (Five-Seed Progeny Pill) in *Yi Xue Ru Men* (Introduction to Medicine) by a Ming dynasty physician Li Chan. The five seeds in this formula are *Gou Qi Zi* (Fructus Lycii), *Tu Si Zi* (Semen Cuscutae), *Fu Peng Zi* (Fructus Rubi) and *Che Qian Zi* (Semen Plantaginis). Our study was the first time a formula to replenish kidney essence using medicinal seeds, or fruits were used. According to the *Ben Cao Zheng Yi* (Orthodox Interpretation of the Materia Medica), “Medicinal seeds/fruits are hard and substantial. They act to tonify the yin of the five zang-organs and replenish their essence and qi. As they are heavy, medicinal seeds/fruits benefit the kidney and strengthen the kidney qi.” Ye Tianshi, a distinguished Qing Dynasty physician, proposed the theory of “replenishing kidney essence with

medicinal animals.” In his *Lin Zheng Zhi Nan Yi An* (Case Records as a Guide to Clinical Practice), Ye Tianshi used *Lu Rong* (Cornu Cervi Pantotrichum), cattle or goat bone marrow, or *Lu Jiao Jiao* (Colla Cornus Cervi) to replenish essence and marrow. Although he had no fixed formula, his idea was an inspiration to the combination of medicinal animals into kidney-tonifying formulas.

The BZBS was developed on the above kidney-tonifying theory. It consists of eight medicinal seeds: *Gou Qi Zi* (Fructus Lycii) and *Tu Si Zi* (Semen Cuscutae) to replenish and benefit kidney essence; *Wu Wei Zi* (Fructus Schisandrae Chinensis), *Fu Peng Zi* (Fructus Rubi) and *Jin Ying Zi* (Fructus Rosae Laevigatae) to replenish and secure kidney essence; *She Chuang Zi* (Fructus Cnidii) and *Jiu Cai Zi* (Semen Allii Tuberosi) to warm yang and benefit essence; and *Chuan Lian Zi* (Fructus Toosendan), the only one to circulate qi, especially qi of the liver and kidney, and help prevent stagnation from essence-replenishing ingredients. Considering from the theory of “using food to replenish essence” in *Huangdi Neijing* (Yellow Emperor’s Internal Classic) and of “using medicinal animals to replenish essence” by Ye Tianshi, the BZBS contains two ingredients from medicinal animals: *Lu Rong* (Cornu Cervi Pantotrichum) to “regenerate essence, replenish the marrow, nourish the blood, warm yang, and strengthen the sinews and bones” (recorded in the *Ben Cao Gang Mu*, i.e., the Compendium of Materia Medica). *Hai Ma* (sea horse) to tonify the kidney, replenish essence, and harmonize between qi and blood.

Also, the BZBS contains *Sheng Di Huang* (Radix Rehmanniae) to nourish kidney yin, *Yin Yang Huo* (Herba Epimedii), *Ba Ji Tian* (Radix Morindae Officinalis) and *Rou Cong Rong* (Herba Cistanches) to warm kidney yang; *Ren Shen* (Radix et Rhizoma Ginseng) to tonify Yuan-primordial qi (recorded in the *Yi Xue Qi Yuan*, i.e., Origins of Medicine) and circulate blood); and *Niu Xi* (Radix Achyranthis Bidentatae) to tonify the liver and kidney, guide the other ingredients downward, and circulate collateral qi. Of the twelve ingredients, *Ren Shen* (Radix et Rhizoma Ginseng) and *Niu Xi* (Radix Achyranthis Bidentatae) supplement qi, tonify the liver and kidney and simultaneously, circulate qi and blood.

##### **Contains PEs and, protects blood vessels**

PEs which is a naturally occurring nonsteroidal plant compound found in plants, fruits, and vegetables. Due to its structural similarity with estradiol, it can cause estrogenic effects but does not cause side effects, including

endometrial hyperplasia (33). Through the mechanism in lowering lipid, anti-inflammation, anti-oxidative stress, protecting the vascular endothelial function, and inhibiting smooth muscle cell proliferation or migration (34,35), PEs exert an anti-AS effect.

Our previous study found that BZBS contains 11 PEs, namely isoquercitrin, hyperoside, verbascoside, epimedin A, icariin, baohuoside I, imperatorin, osthole, catalpol, deoxyschizandrin, schisandrin B (36). BZBS lowered serum lipid levels, and improved fatty acid metabolism in high-fat diet-fed, ovariectomized female ApoE<sup>-/-</sup> mice (36). Disturbance of lipid metabolism is one of the mechanisms of occurrence and development of AS (37,38), and PEs inhibit the progression of AS by improving lipid metabolism (39). These supply an experimental basis for BZBS treatment of postmenopausal AS.

## Conclusions

Vessel collaterals and qi collaterals are the two main branches of collateral disease theory in Chinese medicine. The former is significant in understanding typical vessel collateral—vascular system diseases like AS, while the latter is significant in understanding nerve-endocrine-immune disorders (10). Both take part in AS in postmenopausal women due to the interaction between qi and blood. For postmenopausal AS, the supplementation of exogenous estrogen is controversial (33). The BZBS acts to replenish kidney essence. Its ingredients have PEs and protect blood vessels. An in-depth study on its role in postmenopausal AS using modern laboratory techniques might offer a new perspective on the choice of new medicine for safe, effective interventions.

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