Potential efficacy and mechanism of medicinal plants on chronic kidney disease-associated vascular calcification: a review

Han-Qing Zhang1,2, Shuang Wu1, 2, Xin Chen1, 2, Yi-Xuan Fang1, 2, Qiu-Mei Lan1, 2, Zi-Jun Zhou1, 2, Yan-Heng Qiao1, 2, Jie Li1, 2, Yan-Ru Zhao1, 2, Ming Pei1, 2, Bo Yang1, 2

1Department of Nephrology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300381, China. 2National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin 300381, China.

Correspondence: Bo Yang, Department of Nephrology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, No. 88, Chang Ling Road, Li Qi Zhuang Jie, Xi Qing District, Tianjin 300381, China. E-mail: yb8203@126.com.

Abstract
Vascular calcification is a crucial risk factor that affects the incidence and mortality of cardiovascular disease in chronic kidney disease patients. Modern medicine relies on calcium-phosphorus binding agents, calcium mimetics, active vitamin D, and hemodialysis to prevent and treat vascular calcification, however, their efficacy is unsatisfactory and adverse reactions often occur. Medical plant therapy can act as an integrative regulator in patients with chronic kidney disease-associated vascular calcification, which can significantly improve patients’ symptoms, but its specific mechanism has not been fully elucidated yet. In this paper, we reviewed the domestic and international theoretical studies on the pathogenesis mechanism of chronic kidney disease-associated vascular calcification in recent years, summarized eight active ingredients of medicinal plants as well as four compound formulas for improving chronic kidney disease-associated vascular calcification, and explored the mechanism of action of herbal medicine, which will provide a new strategy for promoting the prevention and treatment of vascular calcification.

Keywords: chronic kidney disease; chronic kidney disease-mineral and bone disorder (CKD-MBD); vascular calcification; medicinal plants; herbal monomers

Author contributions
Zhang HQ designed the project, researched the literature, wrote the original manuscript, and drew the illustrations. Wu S and Chen X participated in searching the literature and editing the manuscript. Fang YX, Lan QM, and Zhou ZJ compiled and supplemented the literature. Qiao YH, Li J, Zhao YR, and Pei M reviewed and revised the manuscript. Yang B guided, supervised, and managed the project. All authors read and approved the final manuscript.

Competing interests
The authors declare no conflicts of interest.

Acknowledgments
The authors would like to thank the members of the Nephrology Department of the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine for their contributions.

Peer review information
Traditional Medicine Research thanks Shi-Jun Yue, Wei Zhou, Ling Chen, Zhen-Wei Wang for their contribution to the peer review of this paper.

Abbreviations
CKD, chronic kidney disease; CKD-MBD, CKD-mineral and bone metabolism abnormalities; CRF, chronic renal failure; CUR, curcumin; CVD, cardiovascular disease; ERS, endoplasmic reticulum stress; FGF23, fibroblast growth factor 23; HD, hemodialysis; Na/PI, sodium-dependent phosphate transporters; NF-κB, nuclear factor κB; PTH, parathyroid hormone; TP, Tripollide; VC, vascular calcification; VSMCs, vascular smooth muscle cells; Wnt, wingless-related integration site.

Citation

Executive editor: Xi Yue Liu.
Received: 23 November 2023; Accepted: 21 March 2024; Available online: 22 March 2024.
© 2024 By Author(s). Published by TMJ Publishing Group Limited. This is an open access article under the CC-BY license. (https://creativecommons.org/licenses/by/4.0/)
In this review, the pathogenesis of vascular calcification associated with chronic kidney disease is discussed. The potential role of medicinal plants and their active ingredients in ameliorating vascular calcification associated with chronic kidney disease and the safety of clinical application are summarized. It has been found that medicinal plants can ameliorate vascular calcification by modulating relevant signaling pathways, such as activating Akt signaling, modulating P/FGF23/αKlotho axis, and inhibiting endoplasmic reticulum stress.

Medical history of objective

The manifestations of vascular calcification are similar to those of “impotence of veins”, a disease recorded in ancient book Yellow Emperor’s Canon of Internal Medicine of the Western Han Dynasty in China (202 B.C.E.–8 C.E.). It states that this is a systemic vascular lesion characterized by deficiency and stasis. Many medicinal plants have the efficacy in improving vascular calcification, such as S railiae Millorrihzae Radix et Rhizoma, which is recorded in the Materia Medica of Ming Dynasty (1368 C.E.–1644 C.E.) as having the ability to invigorate the blood and unclog the blood vessels.

Background

Chronic kidney disease (CKD) has become a public health problem that should not be ignored as the prevalence of CKD is increasing globally. Cardiovascular disease (CVD), a commonly observed complication in individuals with CKD, contributes to 40%-50% of overall mortality in CKD and end-stage kidney disease globally, representing a substantially elevated rate compared to the general population [1].

Kidney Disease Improving Global Outcomes introduced the concept of CKD-mineral and bone metabolism abnormalities (CKD-MBD) in 2005, which is a systemic disorder characterized by hyperphosphatemia, hypercalcemia, skeletal disorders, and vascular calcification (VC), where VC is the hallmark of CKD-MBD [2]. Research has demonstrated a positive correlation between the advancement of CKD and the evolution of VC, therefore, VC is a forceful element of cardiovascular morbidity and mortality in the CKD population [3]. VC occurs as a result of the formation of calcium-phosphate complexes and their ectopic deposition in the vascular wall, endothelial-mesenchymal transdifferentiation induced by endothelial cell injury, modulation of angiogenesis, mechanotransduction, and hemodynamic. Altered pathological processes resulting from endothelial cell injury can occur in the intima and media of almost all arteries, causing calcification of the associated vessels and valves, and have important pathological associations with aging, hypertension, diabetes mellitus, atherosclerosis, and CKD.

CKD-MBD begins in the early stage of CKD, and the causes of its progression to VC have been identified to include hyperphosphatemia, vascular osteoblast transformation, loss of α klotho, increased fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) secretion. Hyperphosphatemia stimulates osteoblast transformation in blood vessels and directly promotes extracellular mineralization. Klotho expression is significantly reduced in the injured kidney, which may directly contribute to uremic vasculopathy; and the absence of klotho also affects the negative feedback of FGF23, which keeps FGF23 secretion elevated [4, 5]. In addition, inflammation and oxidative stress, extracellular vesicles, autophagy, and apoptosis may be involved in the above pathological processes.

The main means of treatment of CKD-MBD in modern medicine include oral administration of calcium-free phosphorus binding agents, such as phosphonate binders, lanthanum, and magnesium carbonate to correct calcium-phosphorus metabolism imbalance; oral administration of active vitamin D (calcitriol) and vitamin D receptor agonists (dioxercalciferol, paricalcitol), calcium-sensitive receptor binders (cinacalcet hydrochloride) or parathyroidectomy to improve the hyperparathyroidism. Dialysis patients can also increase the adequacy of dialysis by prolonging the dialysis time, increasing the number of dialysis sessions, and switching to high-flux dialyzers. However, these drugs are susceptible to various adverse reactions, such as secondary hypercalcemia, gastrointestinal reactions, pruritus, hypertension, which results in unbearable pain for the patient [6, 7].

Moreover, it is reported that the use of active vitamin D, calcium supplements can affect the risk of drug-induced calciphylaxis (NCT02278692) [8]. A multicenter, intra-subject dose-adjustment treatment study of evocalce in Japanese peritoneal dialysis patients reported that the adverse drug reactions occurred in 46.2% (18/39) of patients, with most being of mild-to-moderate severity including gastrointestinal-related events [9]. Cinacalcet, another calcium-sensitive receptor binder, has also been reported to cause cardiogenic shock in a patient with cardiomyopathy and a case of leukocytoclastic vasculitis in an 80-year-old woman on maintenance hemodialysis [10, 11].

The medicinal plants have superior effects in improving the symptoms as well as calcium and phosphorus metabolism and renal function indexes of CKD-MBD patients through overall regulation without obvious adverse reactions.

Pathogenesis of CKD-associated vascular calcification

VC was once thought to be associated with aging and degenerative processes as a passive accumulation of calcium and phosphorus in super-saturated fluids, but later research findings have demonstrated that VC is a dynamic cellular-mediated pathological phenomenon whose regulation involves complex molecular mechanisms [12, 13].

Under physiological circumstances, blood vessels and valves are protected by a variety of active inhibitors, including pyrophosphate, adenosine, matrix Glα protein, osteoblastin, fetuin a, osteoprotegerin, and bone morphogenetic protein-7, which protect blood vessels and valves from supersaturation of serum calcium-phosphorus concentrations and prevent the deposition of aberrant minerals in soft tissues [14, 15]. Once the total volume balance between active inhibitors and inducers is disrupted, VC occurs.

In the population with CKD, the factors leading to calcification cover several aspects. First, hypercalcemia is an important influence, as calcium deposition in the kidney accelerates tubulointerstitial fibrosis and calcification of the renal vasculature due to disturbed calcium metabolism. Secondly, elevated levels of PTH are also thought to be associated with renal calcification, and overproduction of PTH promotes the process of renal fibrosis and calcification. Of which, primarily dyregulation of phosphorus, hyperphosphatemia stimulates the secretion of PTH, which in turn promotes renal fibrosis and calcification [16]. Therefore, the regulation of phosphorus has become an important therapeutic direction in the treatment of CKD. In addition, FGF23 and klotho are all believed to be involved in the process of renal calcification. FGF23 is involved in mineral metabolism, and its function is mostly achieved by klotho and is regulated by the level of klotho. Like osteoblasts, vascular smooth muscle cells (VSMCs) are derived from bone marrow mesenchymal stem cells and undergo contractile phenotype transformation to osteoblast-like phenotype under the action of various factors, such as inflammatory cytokines, up-regulation of osteogenesis-related transcription factors, autophagy, mitochondrial stress, etc. This is a key link in the development of vascular calcification. When a large increase in these calcification-inducing factors is accompanied by a decrease in active inhibitory factors, calcification of the endothelium, mesentery, and valves is induced. These factors interact with each other to promote the process of renal calcification. A brief schematic representation of the mechanisms of CKD-associated VC is shown in Figure 1.

Pi-αKlotho/FGF23 axis

In the progression of CKD-MBD, phosphorus retention plays an initial
**Figure 1 Mechanisms of CKD-associated VC.** CKD-associated VC occurs mainly due to calcification deposited in the vessel wall VSMCs, which cause vascular calcification by apoptosis of VSMCs to form apoptotic vesicles or differentiate into osteoblast-like cells under the regulation of the phosphor-α-Klotho/FGF23 axis, osteogenic transdifferentiation, inflammatory response, endoplasmic reticulum stress, epigenetics, autophagy, and apoptosis. FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; Pi, phosphate; VC, vascular calcification; VSMCs, vascular smooth muscle cells; TLR4, Toll-like receptor 4; LPS, lipopolysaccharide; TNFR, tumor necrosis factor receptor; TNF-α, tumor necrosis factor alpha; Runx2, runt-related transcription factor 2; MSX-2, homology box gene 2; SM22α, smooth muscle 22α; NG-α B, nuclear factor α B; ATF4, activating transcription factor 4; eIF2α, eukaryotic initiation factor 2; DVL, Dishevelled; APC, adenomatous polyposis coli; CKD, chronic kidney disease.
trigging role in VC. Phosphate movement in vivo and in vitro is largely dependent on sodium-dependent phosphate transporters (Na/Pi), which are located in the epithelial cells of the proximal renal tubule and the epithelial cells of the small intestine, and whose primary function is to regulate phosphate excretion and reabsorption in the kidneys, as well as phosphate uptake in the intestinal tract [17]. The role of Na/Pi transporters is critical for the maintenance of blood phosphate homeostasis because they are capable of regulating phosphate uptake and excretion in response to the body’s phosphorus needs. If the function of the Na/Pi transporters is compromised or ineffective, excessive absorption or inadequate excretion of phosphorus from the body can occur, thereby disrupting blood phosphate homeostasis [18].

In addition, phosphorus retention leads to lower blood calcium and 1,25-dihydroxyvitamin D synthesis, which directly promotes PTH synthesis and secretion and causes increased FGF23 content. PTH and 1,25-dihydroxyvitamin D have long been recognized to maintain phosphate homeostasis by controlling Na/Pi, with the progress of research on Na/Pi encoding genes and the phosphate-related molecules, the regulators of α Klotho and FGF23 were also been elucidated [19, 20]. Na/Pi transporter connects the kidney and bone, whereas Klotho expression was also found, which may be a factor driving CKD-MBD. Klotho is a membrane protein participating in the minerals modulation, anti-aging, and anti-inflammatory responses [21]. In addition, the high αKlotho mRNA level in the kidney and the hyperphosphatemia produced by klotho-deficient mice suggest its potential role in the pathological and physiological processes of CKD [22]. Meanwhile, Klotho-deficient mice also exhibited higher levels of FGF23, it may be the result of deregulated downstream caused by Klotho gene silencing, which itself leads to complications associated with CKD, especially CVD [23]. Levels of FGF23 in the serum were increased in patients with advanced CKD and tended to increase as renal function declined, and FGF23 is considered to be associated with the mechanism of pathogenesis of uremic VC. Sakan et al. found a gradual decrease in the level of αKlotho and its mRNA from biopsy specimens in the early stage of CKD and αKlotho expression decreased due to a variety of stresses and ischemia [24]. In the model of ureteral obstruction CKD, increased interstitial fibrosis in αKlotho-knockout mice may be related to impaired TGFβ inhibition, suggesting a mechanism by which αKlotho expression inhibits fibrosis. Those findings suggest that the reduction in αKlotho expression leads not only to dysmetabolism but also to unique pathologic changes.

Osteogenic transdifferentiation
During VC, there is a phenotypic shift of VSMC to osteoblast-like and chondrocyte-like cells. During this process, vascular smooth muscle contraction markers such as smooth muscle 22α and α-SMA levels are down-regulated, while osteogenic markers such as runt-related transcription factor 2 are down-regulated, Msx2 and ALP levels are increased [25]. Studies have shown that signaling pathways involved in osteogenesis include wingless-related integration site (Wnt)/β-catenin, BMP/SMAD, and nuclear factor κ B (NF-κ B) [26, 27].

The Wnt/β-catenin pathway participates in VC similar to that of osteogenesis. A clinical study in dialysis patients showed that Wnt3a inhibitor sclerostin levels correlated with the calcification degree in aortic and coronary artery [28]. Some relevant studies have shown that CKD-associated hyperphosphatasemia drives VC by modifying the Wnt/β-catenin-dependent signaling pathway [29]. Wnt/β-catenin signaling pathway induced by Msx2 via inducing the expression of WNT3A and WNT7A and inhibiting the expression of DKK1, which in turn increases osteogenic transdifferentiation of VSMCs, is an important driver of CKD-associated VC [30]. In addition, as the uric toxic toxins such as indolyl sulfate accumulate in the body, it will increase Wnt protein expression and promote calcification [31].

Inflammation and oxidative stress

Previous works have demonstrated that chronic inflammation and oxidative stress involving p38 MAPK, NF-κ B, ERK, and Akt play an essential role in VC [32, 33]. Inflammatory factors such as TNF-α are involved in NF-κ B pathway activation during high-phosphorus-induced VC, which increases ALP expression by increasing MSX2 and runt-related transcription factor 2 expression, which further induces transdifferentiation in VSMCs [34, 35]. Oxidative stress occurs when oxidative products exceed local antioxidant capacity, leading to increased macromolecule oxidation, which can cause dramatic tissue injury or alteration through a variety of cellular molecular routes [36]. Oxidative stress often occurs in hemodialysis (HD) patients and leads to a variety of complications, such as CVD in HD patients, which may be due to repeated exposure of blood mononuclear cells to dialysis tubing and dialysate membranes, irritation with dialysate and/or dialysate impurities, and renal failure resulting a reduction in the scavenging of oxidative compounds and a rise in water-soluble antioxidants such as vitamin C clearance [37]. Further recent findings have shown that multiple pathways of endoplasmic reticulum stress (ERS) are also a major cause of VC in CKD [38]. For example, the PERK-eIF2α-ATF4-ChOP axis of the TNFα-induced ERS response and the inhibition of the cyclin T1-CDK9-ChOP pathway, which reduces ERS-induced ChOP expression, both inhibit CKD-dependent VC [39, 40].

Epigenetics
During VC, VSMCs are irreversibly transformed into cells with osteoblast-like functions, undergoing up-regulation of genes normally present in osteoblasts, including RUNX2, Msx2, ALP, etc., and a growing body of research suggests that non-coding RNAs have a significant function in this regard [41, 42]. In the CKD population, alterations in downstream noncoding RNA expression in a high-phosphorus-induced environment affect contractility, and responsiveness to stress, and osteogenic transdifferentiation in VSMCs and multiple noncoding RNAs are engaged in the progression of VC, while some others play protective roles [43–47]. In addition, microRNAs can be used as predictors and are involved in risk assessment for the development of VC in CKD patients [48, 49].

Autophagy and apoptosis
Autophagy, a survival mechanism for degradation and recirculation of cellular components prevalent in eukaryotes, is closely associated with a wide range of physiological and pathological states. There are complex interactions between autophagy and VC [50, 51]. Autophagy can reduce VC by suppressing osteogenic differentiation, and the relevant signaling pathways investigated in recent years include HIF-1α/PDK4, miR-30b, mTOR, Klotho, β-catenin, and AMPK, etc [52–54]. However, the exact mechanism of osteogenic differentiation of vascular endothelial cells has not yet been fully elucidated.

Autophagy can also induce osteoblast differentiation and calcification through signaling pathways such as PDK4, miR-32, and AMPK/mTOR [55–58]. In addition, autophagy regulates VC by modulating the expression of bone development-related proteins such as collagen, which are regulated by mTOR, EphrinB2, and RhoA [59]. Apoptosis is a non-inflammatory or silent cell death process under physiological conditions. Apoptotic cells can further coordinate to divide into smaller fragments, so-called apoptotic bodies, which can subsequently be rapidly phagocytized by macrophages. It has been indicated that apoptosis may implicated in the initiation of the VC, and in a model of uremic calcification, apoptosis was positively associated with the calcification of VSMCs, which often occurs before the latter [60]. It has been observed that apoptotic bodies are usually surrounded by highly concentrated calcium, which accumulates on the extracellular matrix and ultimately results in calcification [61].

Active ingredients of medicinal plants improve vascular calcification
Recent studies have also revealed the mechanism of action of many herbal active ingredients (shown in Table 1), which establishes a theoretical basis for the treatment of VC with medicinal plants and
<table>
<thead>
<tr>
<th>Active ingredients</th>
<th>Origin resources</th>
<th>Structural formula</th>
<th>Model/Patient</th>
<th>Related expression</th>
<th>Pathway</th>
<th>Mechanism of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakuchiol</td>
<td>Poriae corylifolia</td>
<td><img src="Image1" alt="Structural formula" /></td>
<td>High-dose vitamin D-treated rats and aorta and VSMCs</td>
<td>LC3-II, BMP2, Runx2↓</td>
<td>Initiating autophagy, suppressing osteogenic transdifferentiation</td>
<td>[64]</td>
<td></td>
</tr>
<tr>
<td>Berberine</td>
<td>Coptis chinensis</td>
<td><img src="Image2" alt="Structural formula" /></td>
<td>High-dose vitamin D-treated rats, β-GP-induced VSMCs in rat aorta</td>
<td>GRP78, CHOP↓, Akt/GSK3</td>
<td>Suppressing ERS</td>
<td>[67]</td>
<td></td>
</tr>
<tr>
<td>Curcumin</td>
<td>Curcuma longa</td>
<td><img src="Image3" alt="Structural formula" /></td>
<td>β-GP induced rat VSMCs</td>
<td>ALP, RUNX2 mRNA↓, miR-92b-3p↓</td>
<td>Suppressing osteogenic transdifferentiation, epigenetic regulation</td>
<td>[71]</td>
<td></td>
</tr>
<tr>
<td>Diosgenin</td>
<td>Dioscorea nipponica</td>
<td><img src="Image4" alt="Structural formula" /></td>
<td>Rat VSMCs</td>
<td>ROS↓, phosphorylation of p38, ERK, JNK and Akt↓</td>
<td>Suppressing inflammatory response</td>
<td>[72]</td>
<td></td>
</tr>
<tr>
<td>Flaxseed oil</td>
<td>Linum usitatissimum</td>
<td><img src="Image5" alt="Structural formula" /></td>
<td>CRF mouse</td>
<td>ALP↓, NO metabolites↓, SOD↓, CAT↓, GPx↓</td>
<td>Reducing oxidative stress</td>
<td>[73]</td>
<td></td>
</tr>
<tr>
<td>Flaxseed oil</td>
<td>Linum usitatissimum</td>
<td><img src="Image6" alt="Structural formula" /></td>
<td>HD patients</td>
<td>hs-CRP↓, sVCAM-1↓</td>
<td>Suppressing inflammatory response</td>
<td>[78]</td>
<td></td>
</tr>
<tr>
<td>Flaxseed oil</td>
<td>Linum usitatissimum</td>
<td><img src="Image7" alt="Structural formula" /></td>
<td>HD patients</td>
<td>Serum N-terminal peptide↓</td>
<td>Inhibiting bone resorption of serum</td>
<td>[79]</td>
<td></td>
</tr>
<tr>
<td>Ginsenoside Rb1</td>
<td>Panax ginseng</td>
<td><img src="Image8" alt="Structural formula" /></td>
<td>Patients with CKD stage 2–3</td>
<td>dR0Mds↓, 8-iso-prostaglandin d2↓, GPx↓, TNF-α↓, PPARγ/Wnt/β-catenin axis</td>
<td>Suppressing inflammatory response and oxidative stress</td>
<td>[82]</td>
<td></td>
</tr>
<tr>
<td>Tanshinone IIA</td>
<td>Salvia miltiorrhiza</td>
<td><img src="Image9" alt="Structural formula" /></td>
<td>CKD-associated VSMCs, β-GP-induced mouse VSMCs</td>
<td>Serum phosphate↓, ALP↓, α-SMA↓, calponin↓, RUNX2↓</td>
<td>Inhibiting osteogenic transdifferentiation</td>
<td>[83]</td>
<td></td>
</tr>
<tr>
<td>Triptolide</td>
<td>Tripterygium wilfordii</td>
<td><img src="Image10" alt="Structural formula" /></td>
<td>High doses of vitamin D3-induced rats, rat VSMCs</td>
<td>MCP-1↓, IL-6↓, TNF-α↓, NO↓, TLRA/TAK1/NF-κB</td>
<td>Suppressing inflammatory response</td>
<td>[84]</td>
<td></td>
</tr>
<tr>
<td>Triptolide</td>
<td>Tripterygium wilfordii</td>
<td><img src="Image11" alt="Structural formula" /></td>
<td>VDN-induced rat aortic</td>
<td>ALP↓, BMP2↓, RUNX2↓, miRNA-204↓</td>
<td>Suppressing osteogenic transdifferentiation, epigenetic regulation</td>
<td>[87]</td>
<td></td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; CRF, chronic renal failure; ERS, endoplasmic reticulum stress; HD, hemodialysis; Runx2, runt-related transcription factor 2; sVCAM-1, circulating vascular cell adhesion molecule-1; VC, vascular calcification; VSMCs, vascular smooth muscle cells; β-GP, β-glycerophosphate; VDN, vitamin D3 plus nicotine.
provides new ideas for future clinical treatment and theoretical studies of CKD-associated VC.

Bakuchiol
Bakuchiol is a class of flavonoids extracted from the leaves and seeds of Poria cocos and, previous pharmacological studies have shown that it has antioxidant and antimicrobial properties [62, 63].

A recent study has confirmed that bakuchiol can inhibit β-glycerophosphate-induced human aortic smooth muscle cell calcification and its related expressions, and initiate autophagy to affect VC occurrence in a mouse aortic media VSMCs calcification model constructed with high vitamin D concentrations [64]. However, the remission or progression of VC caused by autophagy needs to be confirmed by further studies.

Berberine
Berberine is isolated from the medicinal plant Coptis chinensis, which is the major effective ingredient of Coptis chinensis's antimicrobial activity. Modern pharmacology has also confirmed its significant anti-heart failure, cholesterol-lowering, anti-VSMCs proliferation, and anti-inflammatory effects [65, 66].

It was shown that in vivo and in vitro berberine treatment significantly ameliorated VC in high-dose vitamin D-treated rats and the β-glycerophosphate-induced calcification model of rat aortic vascular endothelial cells, which may be achieved through stimulation of Akt signaling and inhibition of ERK, which provides a new drug candidate for VC prevention and treatment [67].

Curcumin (CUR)
Curcumin (CUR) is a natural polyphenolic compound extracted from the plant Curcuma longa, and current studies have shown its anti-inflammatory, antioxidant, and lipid-lowering effects [68, 69].

Earlier investigations have revealed that CUR may be engaged in the modulation of vascular endothelial cell apoptosis by suppressing the JNK/Bax signaling pathway [70]. A recent study has shown CUR represses VSMC calcification by enhancing the expression of miR-92b-3p in exosomes, which in turn regulates the expression of KLF4/RUNX2 axis, thereby regulating VC [71].

Diosgenin
Diosgenin is a steroidal saponin found in the plant Trigonella foenum-graecum. Previous studies have shown that diosgenin inhibits TNF-α-induced intracellular ROS production and phosphorylation of p38, ERK, and Akt, and inhibits TNF-α-induced NF-κB activation [72]. The high-phosphorus environment of chronic renal failure (CRF) predisposes to calcium accumulation, elevated ALP activity, and transdifferentiation of VSMCs. Studies have shown that in a rat model of CRF-induced hyperphosphatemia, there is a large amount of calcium accumulation in the mesangial layer of the blood vessels of CRF rats and that diosgenin reduces aortic ALP activity (131.74 ± 8.11 vs. 88.17 ± 7.14, P < 0.05) and enhances NO metabolism through antioxidant function and restoring enzymatic antioxidant activity in the aorta, significantly inhibiting plasma lipid peroxidation level, and having significant preventive effects on aortic calcification in CRF rats [73].

Flaxseed oil
Linum usitatissimum is a traditional herbal plant, Compendium of Materia Medica, “Eating flax for 100 days, can get rid of all chronic diseases; eating flax for a year, the body and face clean and not disease; eating flax for two years, white hair back to black; eating flax for three years, the teeth are more born”. Research has also found that it can also improve kidney function.

Inflammatory response and oxidative stress are important risk factors for CVD in HD patients [74, 75]. Previous research has demonstrated that flaxseed oil or alpha-linolenic acid reduces serum concentrations of systemic and vascular markers of inflammation, Mirfatahi et al. also found that a daily intake of 6 g of flaxseed oil reduced serum hs-CRP and circulating vascular cell adhesion molecule-1 (VCAM-1) levels in HD patients, both are strongly associated with cardiovascular events [76–78]. In addition, a randomized controlled trial in HD patients found that a daily intake of 6 g of flaxseed oil significantly reduced serum N-terminal peptide concentrations, a marker of bone resorption, suggesting that flaxseed oil inhibits serum bone resorption and thus delays VC [79]. Therefore, the flaxseed oil diet can be regarded as a daily strategy to reduce CVD risk factors in HD patients by lowering vascular inflammatory markers (e.g., VCAM-1) by preventing the activation of the NF-κB pathway [80].

Ginsenoside Rb1
Modern studies of the herbal medicine ginseng have shown that ginseng strengthens the heart, lowers blood pressure, resists hypoxia and protects the myocardium, improves blood rheology, and has antiinflammatory effects. Ginsenoside is the main component of the traditional medicinal plant Panax ginseng, which can be categorized into panaxa-diols (PPD) and panaxat-triols (PPT) according to its chemical structure, and ginsenoside Rb1 is the most abundant component of PPT.

Many studies in recent years have revealed that ginsenoside Rb1 exerts an effective function in protecting the kidneys and slowing down the progression of VC, mainly through various pathways such as enhancing circulating klotho levels, reducing serum creatine and inflammatory cytokine levels in patients with chronic kidney disease, and down-regulating the Wnt/β-catenin pathway to improve osteogenic transdifferentiation [81–83].

Tanshinone IIA
Tanshinone IIA is the richest fat-soluble component isolated from the medicinal plant Salvia miltiorrhiza. For the past few years, it has been found that tanshinone IIA plays a cardiovascular protective role through various mechanisms, including anti-cell proliferation, anti-inflammation, and anti-oxidation.

Tanshinone IIA inhibits the NF-κB signaling pathway and ameliorates lipopolysaccharide-induced inflammatory response in vascular endothelial cells [84]. Furthermore, Zhong et al. found that the protein expression levels of osteoblast-like differentiation marker genes RUNX2 and MSX2 were significantly inhibited in tanshinone IIA-treated VSMCs, suggesting that tanshinone IIA may inhibit the transdifferentiation of VSMCs to osteoblast-like cells by suppressing the NF-κB and β-catenin signaling pathways, thus delaying VC [85].

Triptolide
Tripterygium glycosides is an anti-inflammatory and immunomodulatory herbal medicine, which is widely used in the treatment of rheumatic joints, glomerulonephritis, nephrotic syndrome, lupus erythematosus, etc. Triptolide (TP) is an active ingredient extracted from Tripterygium wilfordii, a traditional medicinal plant, which can have an inhibitory effect on inflammation, tumors, etc., and has the function of regulating the immune system. TP appears to have a dual effect on the regulation of bone metabolism. According to previous studies, TP was able to reverse the state of osteoblast differentiation inhibited by TNF-α and positively regulate osteoblast remodeling, thus promoting osteogenesis. However, recent studies have shown that TP significantly attenuates vitamin D3 plus nicotine-induced VC and reduces ALP activity; moreover, TP inhibits BMP2 and RUNX2 expression by upregulating miRNA-204 levels, suggesting that TP could be a potential drug for the treatment of VC [86, 87].

**Herbal medicine compounds improve vascular calcification**

Baoshen Decoction is established from Synopsis of the Golden Chamber, it includes Astragali Radix, Atractyloids Macrocephala Rhizoma, Salviae Miltiorrhizae radix et Rhizoma, Angelicae Sinensis Radix, Smilacis Glabrae Rhizoma, Alliatis Rhizoma, Descaruniae Semen Lepidii Semen, Poria, Rhe Radix et Rhizoma, Bambusae Caulis in Taenias, which can strengthen the kidney and remove blood stasis (improve blood flow).

Submit a manuscript: https://www.tmrjournals.com/tmr
Clinical experiments have proved that it has good therapeutic effects on uremic patients with high-flux HD, the TCM syndrome score of the observation group was significantly lower than that of the control group (P < 0.05). After treatment, the Baoshen Decoction group decreased serum creatinine, blood urea nitrogen, β2-MG, Pi, and calcium-phosphorus product levels compared with the control group (P < 0.05), at the same time it reduced the expression of VC factors BMP-2 and osteoprotegerin (OPG) (P < 0.05), and effectively prevent the VC of uremic patients with an overall effective rate of 86.57% vs 70.15% (P < 0.05) [88]. Adverse reactions in both groups were relieved after symptomatic management, and the incidence of adverse reactions was comparable.

In a clinical trial of non-dialysis patients with stage 3 to 5 CKD, Zhang et al. found that the self-defined prescription Jianpibushentongluo Decoction (includes Astragali Radix, Polygonati Rhizoma, Eucommiae Cortex, Angelicae Sinensis Radix, Salviae Miltiorrhizae Radix et Rhizoma, Puerariae Lobatae Radix, Chuanxiong Rhizoma, Prunellae Spica, Tribuli Fructus, Sinapis Semen, Rhei Radix et Rhizoma) combined with calcitriol treating for 24 weeks can effectively decrease patients’ syndrome score, iPTH, hs-CRP, IL-6, TNF-α, serum creatine, β2-MG, blood urea nitrogen levels (P < 0.05), and up-regulate klotho protein (P < 0.05). The combination group reduced the incidence of VC with an overall clinical effectiveness rate of 97.5%, which is significantly higher than that of the TCM group (70.0%) and Western medicine group (77.5%) (P < 0.05) [89]. In the course of treatment, gastrointestinal reactions occurred in 2, 3, and 4 patients in the TCM group, western medicine group, and combination group, respectively, which were significantly improved after drug withdrawal or symptomatic treatment, and no other treatment-related adverse reactions were observed. The mechanism may be related to the inhibition of ERS and the improvement of apoptosis by the PERK/ATF4/CHOP pathway [90].

Hu and other scholars have found that Ronghuang Yishen Jiedu Decoction (Cistanches Herba, Rhei Radix et Rhizoma, Achyranthis Bidentatae Radix, Taraxaci Herba, Serissa Japonica, Bambusae Caulis in Taenias, Poria, Persicae Semen, Glycyrrhizae Radix et Rhizoma) has the efficacy of improving symptoms in patients with CKD-MBD. After treatment for 12 weeks, the result showed that the levels of serum creatine, eGFR, P, PTH, hs-CRP, and homocysteine in the treatment group were significantly lower than those in the control group (P < 0.05) [91]. This demonstrates that Ronghuang Yishen Jiedu Decoction improves inflammation and calcium and phosphorus metabolism in patients while at the same time playing a down-regulating role for high homocysteine levels, reflecting to a certain extent its interventional role in VC and bone metabolism.

Xiong et al. through clinical research found that the self-designed Gu Ben Qu Zhuo Fang (Rehmanniae Radix, Codonopsis Radix, Astragali Radix, Poria, Atractylodis Macrocephalae Rhizoma, Cibotii Rhizoma, Eucommiae Cortex) which was designed by activating blood circulation to eliminate blood stasis and lowering turbidities to consolidate kidneys (reduce uremic toxins and improve kidney function), had shown promising efficacy in the adjunctive treatment of hypophosphatemia of patients undergoing HD after 3 months. It reduced blood calcium, blood phosphorus, iPTH, serum urea nitrogen, serum creatinine, FGF23, and Nox4 levels, and increased Klotho protein and fetuin-A levels compared with the control group (P < 0.05), which can reduce VC and oxidative stress. No serious adverse reactions were observed, and the incidence of adverse reactions was not different between the two groups [92].

The above four compounds can significantly improve various symptoms and indicators of patients through different mechanisms, and achieve good clinical results (shown in Table 2).

**Table 2 Clinical effect and possible mechanism of herbal medicine compounds to improve CKD-associated VCs**

<table>
<thead>
<tr>
<th>Herbal medicine compounds</th>
<th>Drug composition</th>
<th>Patients</th>
<th>Clinical effect</th>
<th>Possible mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baoshen decoction</td>
<td>Astragali Radix, Atractylodis Macrocephalae Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Angelicae Sinensis Radix, Smilacis Glabrae Rhizoma, Alismatis Rhizoma, Descaruriatae Semen Lepidii Semen, Portia, Rhei Radix et Rhizoma, Bambusae Caulis in Taenias</td>
<td>High-flux hemodialysis uremia patients</td>
<td>Reducing BMP-2, OPG, blood phosphorus, and calcium-phosphorus product levels</td>
<td>Suppressing osteogenic transdifferentiation</td>
<td>[88]</td>
</tr>
<tr>
<td>Jianpibushentongluo decoction</td>
<td>Cistanches Herba, Rhei Radix et Rhizoma, Achyranthis Bidentatae Radix, Taraxaci Herba, Serissa Japonica, Bambusae Caulis in Taenias, Poria, Persicae Semen, Glycyrrhizae Radix et Rhizoma</td>
<td>Non-dialysis patients with stage 3 to 5 CKD</td>
<td>Reducing iPTH, hs-CRP, IL-6, TNF-α, SCr, β2-MG, BUN levels, and increasing klotho levels</td>
<td>Inhibiting inflammation and ER stress</td>
<td>[89]</td>
</tr>
<tr>
<td>Ronghuang Yishen Jiedu decoction</td>
<td>Rehmanniae Radix, Codonopsis Radix, Astragali Radix, Poria, Atractylodis Macrocephalae Rhizoma, Cibotii Rhizoma, Eucommiae Cortex</td>
<td>Non-dialysis patients with stage 3 to 5 CKD</td>
<td>Reducing Pi, iPTH, hs-CRP, Hcy levels</td>
<td>Inhibiting inflammation</td>
<td>[91]</td>
</tr>
<tr>
<td>Gu Ben Qu Zhuo Fang</td>
<td>Maintenance hemodialysis</td>
<td>Reducing Pi, iPTH, FGF23, Nox4, fetuin A levels, and increasing klotho level</td>
<td>Inhibiting oxidative stress</td>
<td>[92]</td>
<td></td>
</tr>
</tbody>
</table>

BUN, blood urea nitrogen; CKD, chronic kidney disease; FGF23, fibroblast growth factor 23; Hcy, homocysteine; PTH, parathyroid hormone; VC, vascular calcification.
Conclusion

In summary, the occurrence of CKD-associated VC mainly involves the integrated regulation of the phospho-αKlotho/FGF23 axis, osteogenic transdifferentiation, inflammatory response, endoplasmic reticulum stress, epigenetics, autophagy and apoptosis, etc. This suggests that we can improve the therapeutic effect by using the active ingredients of these medicinal plants as adjuvant therapy on the basis of conventional therapy, such as Damshen injection combined with conventional therapy, which is clinically effective and safe [93]. However, the current literature shows that many of the exact molecular mechanisms are currently unclear. In the future, more molecular and pharmacological studies are needed to confirm its specific mechanism of action. In addition, whether the active ingredients of the compounds are a superposition of herbal components, and whether they interact with each other to produce new compounds can be further explored.

References


57. Liu Y, Li J, Han Y, et al. Advanced glycation end-products suppress autophagy by AMPK/mTOR signaling pathway to

Submit a manuscript: https://www.tmrjournals.com/tmr

9


91. Hu Q, Zhang Y, Yu Y. Effect of Ronghuang Yishen Jiedu Decoction on the Level of High Sensitive C-reactive Protein and Homocysteine for CKD-MBD Patients with Kidney Deficiency and Damp Heat Syndrome. *J Sichuan Tradit Chin Med*. 2021;39(05):126–129. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=w1Je9LIFm5AiMHCDkJrd4xQ2X9x46-xloR6Sil0O9DvyyVL57znNSPj0BwHyl-WWbOOf86rCbof5XioNZTnaP84q5ShLy1dPLR2t1PLZCt4BGC-Dx7gsc0sW2574J0J_nFfe8 = &uniplatform = NZKPT&flag = copy

92. Xiong JH, Yang Q, Li N. Effects of self-designed Gu Ben Qu Zhuo Fang in adjuvant treatment of hyperphosphatemia in patients with maintenance hemodialysis. *Guangxi Med J*. 2022;44(05):521–525+538. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=w1Je9LIFm58Q6X26q_7TKzhtvdcD59oLCku8R6Xr1xsj6QOBzgS0izeRBDU0rCqlL72Kj1I1I1MgGkmddyZ8qDevFH8GjuYtw3qZDVh_1ppptm74SdB-fq1bcFI3SABQjoGj_C3A = &uniplatform = NZKPT&flag = copy