Medicine Insights

Review

Synergistic Multi-Target Mechanisms of the Astragalus-Salvia Herb Pair in Chronic Kidney Disease

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Abstract: Chronic kidney disease (CKD) is a progressive condition associated with persistent inflammation, oxidative stress, and renal fibrosis. This review aims to summarize the therapeutic potential and molecular mechanisms of the Astragalus membranaceus--Salvia miltiorrhiza herb pair in CKD. Relevant studies on astragaloside IV and salvianolic acid B were analyzed to explore their effects on renal protection and related signaling pathways. Current evidence indicates that these compounds can alleviate renal injury by regulating inflammatory responses through the NF-κB pathway, enhancing antioxidant defense via the Nrf2/HO-1 pathway, and suppressing fibrotic progression through the TGF-β/Smad pathway. The findings suggest that the Astragalus membranaceus--Salvia miltiorrhiza herb pair may delay CKD progression through coordinated regulation of multiple pathological processes. This review provides a theoretical basis for further investigation of TCM-based approaches in CKD prevention and treatment.

Keywords: chronic kidney disease; astragalus membranaceus; salvia miltiorrhiza; herb pair; network pharmacology

1. Introduction

Chronic kidney disease (CKD) has become a major global health problem, affecting about 10% of the world's population, bringing a heavy medical and economic burden to individuals and medical systems. CKD is manifested as a gradual decline in renal function, and in most cases it cannot be reversed. It may eventually develop into end-stage kidney disease, while increasing the risk of heart disease, vascular disease and death [1-3]. At present, the treatment methods we use, such as ACE inhibitors, ARB drugs, SGLT2 inhibitors and drugs that block mineralising hormone receptors, have significantly enhanced kidney protection and slowed down the progression of the disease in many patients [4]. However, these therapies mainly target specific pathways that regulate blood flow and metabolism, but there are still a large number of patients who continue to lose kidney function, which shows that CKD has complex characteristics - a variety of different disease processes promote the development of the disease at the same time [5].

More and more evidence shows that inflammation, oxidative stress and kidney scars are the main drivers of chronic kidney disease (CKD); these factors are interrelated and affect each other in the progression of the disease. For example, inflammatory activation may lead to oxidative stress imbalance, and additional oxidative stress will further exacerbate inflammatory reactions and fibrotic changes; if these pathways continue to be active, the kidney tissue will be gradually damaged and the function will continue to deteriorate [6-10]. Therefore, treatment methods that can regulate the course of multiple diseases at the same time may bring additional benefits to the treatment of CKD.

Traditional Chinese medicine (TCM) has attracted increasing attention in chronic disease research because of its multi-component and multi-pathway characteristics. In TCM practice, herb pairs represent a commonly used therapeutic approach in which two

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medicinal substances are combined based on traditional principles to enhance therapeutic effects. The Astragalus membranaceus--Salvia miltiorrhiza herb pair is widely applied in clinical practice for kidney-related disorders [11]. According to TCM theory, Astragalus membranaceus (Huangqi) tonifies qi, whereas Salvia miltiorrhiza (Danshen) promotes blood circulation and removes blood stasis. The combination of these two herbs is considered to regulate both deficiency and blood circulation disorders associated with chronic renal diseases. Astragaloside IV, the core active ingredient extracted from Astragalus membranaceus, has attracted extensive research attention for its renal protective functions [12, 13]. Salvia miltiorrhiza (Danshen), another classic herbal medicine for activating blood circulation, exerts anti-inflammatory and anti-fibrotic effects via multiple signaling pathways against renal fibrosis damage [14-16]. This paper systematically summarizes the mechanism of CKD pathological damage and the pharmacological mechanism of astragaloside IV and salvianolic acid B based on network pharmacology.

This review summarises the latest research progress on the pathogenesis of chronic kidney disease (CKD), and explores the possible protective effect of the combination of astragalus and ginseng herbs, paying special attention to the role of astragalus IV and ginseng phenolic acid B. In addition, the article also discusses how these compounds regulate inflammation, oxidative stress and fibrosis-related pathways, such as NF-κB, Nrf2/HO-1 and TGF-β/Smad signalling pathways. By integrating the research results of traditional medicine and modern pharmacology, this article aims to clarify more clearly the possible role of this herbal combination in the prevention and treatment of chronic kidney disease.

2. Major Pathological Processes Involved in CKD Progression

The worsening of CKD does not come from just one disease event, instead it involves several biological processes interacting with each other; among these, ongoing inflammation, oxidative stress, and kidney scarring are seen as big reasons for kidney injury and function loss; these processes link closely together and take part in disease advancement through shared molecular routes and back-and-forth control.

2.1. Inflammatory Responses in CKD

Persistent inflammation has been confirmed to be a key feature of the worsening of chronic kidney disease (CKD); acute inflammation can usually effectively remove harmful factors and initiate the repair process, but chronic kidney disease is accompanied by mild but persistent inflammation, which cannot be completely subsided. When the inflammatory signal continues to be activated, it will damage kidney cells, change the internal environment of the kidney, and accelerate the changes in the internal structure of the kidney. More and more evidence shows that inflammation is involved in various stages of chronic kidney disease from early tissue damage to late scar formation and renal loss.

Among the multiple signalling pathways associated with inflammation in chronic kidney disease (CKD), the NF-κB pathway is one of the most researched regulatory mechanisms. NF-κB is responsible for activating many genes related to immune responses, producing signalling molecules, and participating in cellular stress responses. Under normal circumstances, inhibitory proteins such as IκBα can keep the NF-κB protein complex (mainly composed of p65 and p50) in the cytoplasm, thus preventing NF-κB from entering the nucleus and maintaining a low level of inflammation signalling.

When chronic kidney disease (CKD) occurs, many harmful factors can disrupt this balance and activate the NF-κB signalling pathway. These factors include oxidative stress, late glycose end products (AGEs), accumulation of angiotensin II, inflammatory cytokines, mechanical stress caused by abnormal renal blood flow and metabolic problems. Once stimulated, the IKK complex is activated, and IKKβ adds a phosphate group to IκBα at a specific location; then, the phosphorylated IκBα is labelled by ubiquitin and degraded by proteasomes, thus releasing the NF-κB protein complex. The released NF-κB enters the

nucleus and binds to specific DNA regions to regulate the expression of inflammation-related genes.

When NF-κB is turned on in kidney tissues, it leads to the making of several inflammation-driving substances, such as TNF-α, IL-1β, IL-6, MCP-1 (a protein that draws monocytes), and ICAM-1; these molecules help pull circulating immune cells, mainly monocytes and lymphocytes, into the kidney's interstitial spaces; the buildup and activation of these immune cells further boost local inflammation [17], causing added harm to tubule lining cells, endothelial cells, and glomerular structures; so, keeping NF-κB active for a long time acts as a key link between first kidney injury and later disease progress [18, 19].

Besides the inflammatory signals that happen inside the kidney's own cells, how immune cells are controlled also matters a lot in CKD-related inflammation; among the immune cells that move into the kidney, macrophages stand out, because they are highly flexible in function and can react to shifts in the kidney's local environment; when faced with different triggers, macrophages can switch into different active forms, which have long been grouped into M1 and M2 types.

M1 macrophages activated by substances such as interferon-γ (IFN-γ) and lipopolysaccharides (LPS) show strong pro-inflammatory properties, which will release a large number of inflammation-related signal molecules, chemokines and reactive oxygen (ROS), thus aggravating oxidative damage and tissue damage. Researchers found that the number of M1 macrophages increased significantly in a variety of experimental renal injury models, and it was closely related to the aggravation of kidney inflammation.

On the other hand, M2 macrophages are generally considered to be involved in the process of inhibiting inflammation, repairing tissues and remodelling tissues; they are often activated by signalling proteins such as interleukin-4 (IL-4) and interleukin-13 (IL-13). However, in chronic kidney disease (CKD), the role of M2 macrophages is more complex than simple protection: in the case of long-term kidney damage, when M2 macrophages continue to be active for too long, they may promote TGF-β1, PDGF, galactose agglutin-3 and other extracellular matrix-related The release of the substance exacerbates the formation of scars. These observations show that the response of macrophages depends to a large extent on the stage of the disease and the local environment.

Inflammation is also closely related to other major disease processes that drive the progression of chronic kidney disease (CKD); activated inflammatory pathways will increase the production of reactive oxygen (ROS) by stimulating oxidase, resulting in impaired mitochondrial function and cell damage; at the same time, oxidative stress can further activate NF-κB Signal, forming a cycle that continuously causes inflammation. In addition, signalling proteins related to inflammation, such as IL-6 and TNF-α, can promote fibroblasts to become active and promote the accumulation of extracellular matrix by regulating TGF-β-related pathways. This interaction between inflammation, oxidative stress and scar formation exacerbates the continuous deterioration of kidney structure and function.

Since inflammation plays a key role in the deterioration of chronic kidney disease (CKD), the study of inflammatory signalling pathways has become an important direction for treatment. However, since inflammation is involved in damage and repair in a complex way, adopting a strategy of balanced immune regulation rather than extensive immune suppression may bring greater treatment prospects. Natural substances, such as ingredients derived from traditional Chinese medicine plants, have attracted attention because they can regulate multiple inflammatory pathways at the same time. The following part will introduce how the key compounds in the two types of astragalus IV and astragalus B play an anti-inflammatory role.

2.2. Oxidative Stress and Impaired Antioxidant Defense

Oxidative stress is a key factor in promoting the development of the disease in chronic kidney disease (CKD). Its cause is an imbalance: on the one hand, it produces too

much reactive oxygen (ROS), and on the other hand, it produces insufficient antioxidant Defence. In the normal physiological state, ROS is always produced as a by-product of cell metabolism and is strictly regulated by the body's own antioxidant system. However, in the case of long-term kidney damage, excessive ROS continues to accumulate, exceeding the ability of kidney cells to maintain redox balance, resulting in further deterioration of cell function. And tissue damage.

The kidney is particularly susceptible to oxidative damage, because its renal tubular epithelial cells need a lot of energy to complete the function of ion transport and filtration; this high demand for energy is accompanied by the high-intensity work of mitochondria, resulting in the accumulation of active oxygen (ROS) in kidney cells in mitochondria. In chronic kidney disease (CKD), the increase in oxidative stress is mainly related to mitochondrial disfunction, increased activity of NADPH oxidase (especially NOX4) and decreased activity of endothelial nitric oxide synthase (eNOS); these factors together lead to superoxide anions.

Excessive reactive oxygen (ROS) will directly damage the key components of cells, such as fat and protein in the cell membrane and DNA in the nucleus and mitochondria; lipid peroxidation will destroy the integrity of the cell membrane, and the oxidation changes of proteins will affect the function and signal transduction of normal enzymes in cells; in addition, the damage of mitochondrial DNA will further worsen the function of mitochondria, resulting in a decrease in ATP production and an increase in ROS production, thus forming a continuous cycle of oxidative damage [20].

In addition to directly damaging cells, reactive oxygen (ROS) is also a key signal molecule involved in regulating inflammation and scar formation; for example, higher ROS levels can activate red ox sensitive gene regulatory proteins, such as NF-κB, thus promoting the generation of inflammation-related signal molecules and chemokines; oxidative stress It can also enhance the activation of fibroblasts and the generation of extracellular matrix by regulating pathways related to fibrosis. Therefore, oxidative stress imbalance is not only the result of kidney damage, but also actively accelerates the development of chronic kidney disease.

Nrf2 pathway (nuclear red blood cell 2 related factor 2) is one of the main endogenous Defence systems for maintaining the antioxidant ability of cells. Under normal circumstances, Nrf2 is always regulated by a protein called Keap1, which is labelled Nrf2 through ubiquitin and degraded by the Cullin 3-dependent E3 ubiquitin relationase complex. When cells face oxidative stress, some cysteine sites on Keap1 change, thus weakening the binding to Nrf2, allowing Nrf2 to accumulate and enter the nucleus. Once it enters the nucleus, the activated Nrf2 will bind to the antioxidant response element (AREs) to activate a series of gene expressions that protect cells. The proteins produced downstream include HO-1, superoxide dismutase (SOD), hydrogen peroxidase, glutathione peroxidase and enzymes involved in the synthesis of glutathione. By regulating these antioxidant systems, Nrf2 helps to maintain the redox balance in cells and protects kidney cells from oxidative damage.

Still, long-lasting oxidative stress in CKD can weaken the Nrf2 pathway's protective job; being exposed to ROS all the time can throw off antioxidant responses, lower the cell's repair ability, and make cells easier to hurt further; so, bringing back the Nrf2-driven antioxidant defense has been looked at as a possible treatment plan to cut down oxidative damage and slow CKD advancement [21-23].

2.3. Renal Fibrosis and Interaction with Other Pathological Processes

Renal fibrosis is the main disease consequence caused by long-term kidney damage, which is closely related to the permanent decline of renal function. No matter what the cause of chronic kidney disease (CKD) is caused, as long as the activation of the fibrosis pathway is maintained, it will eventually lead to excessive accumulation of extracellular matrix (ECM) components, destroying the normal kidney structure and gradually losing function of renal tubules. Typical characteristics of renal fibrosis include the activation of

fibroblasts, conversion into myofibroblasts, and the accumulation of proteins such as collagen, fibrin and layered adhesion protein.

TGF-β1 is widely regarded as a key intermediate molecule in kidney scar reaction; once activated, TGF-β1 will bind to the corresponding receptor and initiate signal conduction in cells by adding phosphate groups to receptor-regulated Smad proteins (mainly Smad2 and Smad3); activated Smad2/3 cooperates with Smad4 and enters the nucleus, thus regulating the opening of scar-related genes; this signalling pathway promotes the generation of collagen I, collagen III, fibrobin and α-SMA, which in turn contributes to the activation of fibroblasts and the accumulation of extracellular matrix.

In addition to promoting matrix generation, TGF-β1 also affects the degradation of the matrix; it can reduce the activity of MMPs and increase the level of TIMPs, thus slowing down the renewal rate of extracellular matrix and leading to the continuous accumulation of scar tissue. Therefore, when the TGF-β1 signal is continuously activated for a long time, it plays a key role in transforming kidney damage into a continuous scarring process.

Although the TGF-β/Smad pathway is regarded as the main signalling pathway for the formation of kidney scars, there are also many pathways unrelated to Smad; the Wnt/β-catenin pathway promotes the expression of fibrotic genes by regulating the stability and activity of β-catenin in the nucleus; in addition, the MAPK pathway (such as ERK, JNK and p38 MAPK) responds to different stress signals and synergises with the TGF-β signalling pathway to regulate the activation of fibroblasts; the PI3K/Akt pathway also participates in scar formation, affecting cell survival, metabolism and synthesis of matrix collagen.

It should be noted that with the progression of chronic kidney disease (CKD), inflammation, oxidative stress and scar formation are not independent disease events, but affect each other and work together on the whole disease process. Signalling proteins associated with inflammation, such as TNF-α and IL-6, can stimulate the production of TGF-β1 and promote fibrosis; at the same time, TGF-β1 can also increase oxidative stress by regulating enzymes that produce reactive oxygen (ROS) (such as NOX4); excessive ROS further activate inflammation Pathway, and accelerate the deposition of matrix metalloprotein (ECM). This continuous mutual feedback not only aggravates kidney damage, but also explains why treatment for a single pathway may have limited long-term effect.

Therefore, methods that can control inflammation, oxidative stress and scar formation at the same time may help delay the deterioration of chronic nephropathy (CKD); while natural compounds such as astragalus IV and dan ginseng phenolic acid B in the combination of astragalus-dan ginseng are attracting more and more research attention because they may affect these interrelated disease processes.

3. Potential Multi-Target Mechanisms of the Astragalus Membranaceus--Salvia Miltiorrhiza Herb Pair in CKD

The progression of chronic kidney disease (CKD) involves a variety of mechanisms such as inflammation, oxidative stress and scar formation. Therefore, treatments that can regulate these related pathways may be more advantageous than those for a single mechanism alone. The combination of astragalus and ginseng contains a variety of active ingredients, among which astragalus IV and danphenol B are considered to play an important role in kidney protection. Current studies show that these compounds may regulate a variety of signalling pathways associated with the progression of CKD, such as NF-κB-mediated inflammatory responses, Nrf2/HO-1-related oxidative stress reactions, and TGF-β/Smad-dependent scar formation.

3.1. Regulation of Inflammatory Responses

Inflammation turning on is an early and lasting event as CKD moves forward; both astragaloside IV and salvianolic acid B have been reported to hold down inflammation

responses by managing NF-κB signaling, though the ways they work at the molecular level might differ.

Astragaloside IV has been proven to block the activation of IKK complexes and reduce the degradation of IκBα, thus limiting the entry of NF-κB p65 into the nucleus and the subsequent activation of inflammatory genes. In addition, astragaloside IV may also regulate early inflammatory signals, such as TLR4/MyD88 signalling pathways, to further promote NF-κB activation when the kidneys are damaged. Through these effects, astragaloside IV can reduce the production of inflammatory substances such as TNF-α, IL-1β, IL-6 and MCP-1.

Salvianolic acid B also shows inflammation-fighting activity by controlling NF-κB-linked signaling; earlier studies have pointed out that salvianolic acid B can stop NF-κB from turning on and cut down the production of inflammation-linked signaling proteins; what's more, its impact on other inflammation routes, like JAK/STAT signaling, might further help in keeping inflammation under control; when these compounds manage several inflammation routes at the same time, it may help bring down the long-lasting immune activation seen as CKD advances.

Regulating macrophages is another possible mechanism for this herbal combination to fight inflammation; research shows that astragaloside IV can promote macrophages to polarise in a direction more conducive to repair by reducing the activation of inflammation associated with M1; at the same time, salvianol Ic acid B may inhibit the scar reaction caused by macrophages by reducing the production of factors related to scar formation (such as TGF-β1). These findings show that astragalus-dan ginseng can not only play a role by inhibiting inflammation, but also regulate the immune response by maintaining a more balanced macrophage type.

3.2. Regulation of Oxidative Stress through the Nrf2/HO-1 Pathway

Oxidative imbalance is closely related to renal cell damage and the deterioration of chronic kidney disease (CKD); the Nrf2/HO-1 pathway is a key endogenous Defence mechanism against oxidative stress, and the activation of this pathway has been widely studied as a possible way to protect the kidney.

It is reported that Astragaloside IV can enhance Nrf2 activation and increase the level of downstream antioxidant enzymes. By helping Nrf2 accumulate in the nucleus, Astragaloside IV can make cells resist oxidative damage more effectively and reduce the accumulation of reactive oxygen (ROS). These effects help protect kidney cells from oxidative damage caused by mitochondrial disfunction and inflammatory activation.

Salianic acid B also shows strong antioxidant ability; studies show that salianic acid B can activate the Nrf2 pathway by regulating key factors in early signalling pathways such as PI3K/Akt; activating this pathway can promote the generation of HO-1, SOD and glutathione-related enzymes; in addition, salic acid The ability of Acid B to remove free radicals also helps to directly reduce oxidative damage.

When astragaloside IV and salviaolic acid B act on the antioxidant Defence system at the same time, it may provide additional protection for the body against oxidative damage. By reducing the production of excessive reactive oxygen (ROS) and enhancing the body's own antioxidant response, these compounds can indirectly inhibit the activation of inflammation caused by ROS and the formation of scars caused by it.

3.3. Inhibition of Renal Fibrosis

Renal scars are an important factor leading to the permanent decline of renal function; the TGF-β/Smad pathway is regarded as a key signalling pathway related to fibroblast activation and extra-matrmal matrix deposition; by regulating scar-related pathways, both astragloside IV and hydroquine B both show anti-scar properties.

Astragaloside IV has been reported to hold back TGF-β1 production and lower the phosphorylation of Smad2/3, which then suppresses the switching on of downstream scarring genes [24]; furthermore, astragaloside IV may boost the expression of Smad7, a brake on TGF-β signaling, which helps reduce scarring [25].

Salvianolic acid B also shows a blocking effect on kidney scarring; earlier studies have suggested it can control TGF-β/Smad signaling and cut down the expression of proteins tied to scarring, like collagen and fibronectin; in addition, salvianolic acid B may affect other scarring routes, like Wnt/β-catenin and MAPK signaling, which are involved in making ECM and turning on myofibroblasts.

By managing several scarring-linked routes, astragaloside IV and salvianolic acid B may tone down myofibroblast activation, hold back too much ECM deposit, and keep kidney tissue structure intact [26]; these findings give a possible reason why the Astragalus--Salvia miltiorrhiza pair shows protective effects in experimental models of kidney scarring.

3.4. Integrated Effects of the Astragalus Membranaceus--Salvia Miltiorrhiza Herb Pair in CKD

The progression of chronic kidney disease involves the continuous interaction between inflammation activation, oxidative stress and scar formation; the therapeutic effect of astragalus and ginseng may come from the overall regulation of these related processes, not just the individual regulation of one of the pathways. Intravenous injection of astragalus polysaccharide and ginseng phenolic acid B jointly control inflammation, oxidative stress and scar formation through partially overlapping but not exactly the same mechanism of action: inhibiting inflammation activation can reduce oxidative damage and fibrosis signals, and enhancing antioxidant ability can help to further prevent inflammation-related kidney damage; at the same time, blocking The broken scar formation pathway also helps to maintain the integrity of kidney tissue and avoid further loss of function.

Even though current experimental proof backs the possible kidney-protective effects of this herb pair, more studies are needed to pin down the exact interactions between single parts and to find out if giving them together adds extra benefit over treatment with just one compound; future studies that use well-planned clinical trials and lab models will help nail down the treatment value of the Astragalus--Salvia miltiorrhiza pair in managing CKD.

4. Conclusion

Chronic kidney disease (CKD) is still a major clinical problem because it continues to worsen and involves a variety of disease processes; current studies show that inflammation, oxidative stress and scar formation play an important role in kidney injury and disease progression. The combination of astragalus and ginseng often used in traditional Chinese medicine has been proven to have a potential kidney protection effect by regulating these key pathological processes..

As the main active ingredients in the pair, Astragaloside IV and hydramine B are reported to be able to regulate a variety of signalling pathways associated with the progression of chronic kidney disease, such as inflammatory reactions activated by NF-κB, oxidative stress reactions associated with Nrf2/HO-1 and TGF-β/Smad-dependent scar formation. By regulating inflammation activation, antioxidant Defence and matrix metalloproteinase deposition, these compounds may play a synergistic role in protecting kidney structure and function.

Although the current laboratory research supports the potential application of astragalus-dan ginseng in the treatment of chronic kidney disease (CKD), there are still some problems to be clarified; it is necessary to carry out more research to understand the interaction between the components in a deeper way, determine the best treatment combination and dosage, and through carefully designed Clinical trials to verify its efficacy. Future research that combines laboratory research with clinical evidence will help to better understand the role of this herbal combination in the treatment of CKD and promote the development of evidence-based traditional Chinese medicine therapy.

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