Clinical Effect of Zhongyao Decoction on Chronic Kidney Disease Complicated with Insomnia

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Abstract
The purpose of this study was to investigate the clinical efficacy of Chinese ointment prescription in patients with chronic kidney disease complicated with insomnia. Through careful observation of the patients and data analysis, we found that Zhongyao formula has a significant effect on improving the symptoms of chronic kidney disease complicated with insomnia. After receiving the treatment of TCM ointment, the severity of insomnia was significantly reduced, and the time to fall asleep and the quality of sleep were significantly improved. In addition, the Chinese ointment formula also played a certain protective role in the kidney function of the patients, helping to alleviate the condition of chronic kidney disease. The results of this study provide a practical basis for the application of traditional Chinese medicine in the treatment of chronic kidney disease complicated with insomnia. As a safe and effective treatment, Chinese herbal ointment prescription can not only improve insomnia symptoms, but also maintain kidney health. However, further in-depth research and clinical validation are needed to fully understand the specific treatment mechanism and long-term efficacy of the TCM ointment formula. It is believed that with the development of more studies, Chinese medicine will be more widely used in the treatment of chronic kidney disease complicated with insomnia, and bring more benefits to the health of patients.

Keywords
Chinese Herbal Ointment Prescription; Chronic Kidney Disease; Insomnia; Clinical Efficacy.

1. Introduction:
As a common clinical condition, chronic kidney disease combined with insomnia has a significant impact on patients' health and quality of life. Insomnia not only worsens the patient's physical discomfort, but may also accelerate the progression of kidney disease. As one of the traditional Chinese medicine treatment methods, TCM ointment formula has unique advantages in regulating the balance of qi and blood, Yin and Yang, etc. The purpose of this study was to investigate the clinical efficacy of TCM ointment prescription in patients with chronic kidney disease complicated with insomnia, and to provide scientific basis for clinical practice.

2. Application Background and Significance of Chinese Medicinal Ointment Formula
2.1. Clinical Characteristics of Chronic Kidney Disease Complicated with Insomnia
Chronic kidney disease, as a common metabolic disease, has become a global health problem. Its incidence is increasing year by year, which has a serious impact on the quality of life and health status of patients. Patients are often accompanied by a variety of symptoms, such as
abnormal urine volume, hypertension, proteinuria and so on. However, one of them, insomnia, as one of the common complications of chronic kidney disease, has brought patients physical and mental troubles that can not be ignored. Insomnia is not only a simple sleep problem, but more likely to cause serious physiological and psychological consequences, affecting the overall health of patients.

In clinical practice, the manifestations of chronic kidney disease combined with insomnia are varied, and often present complexity and diversity. Patients may experience difficulty falling asleep, multiple awakenings during the night, and early awakenings, resulting in reduced quality of rest throughout the night. At the same time, insomnia may also trigger daytime fatigue, lack of energy, poor concentration and other problems in the patient, and even exacerbate the patient’s mood disorders and anxiety symptoms in severe cases. This situation of kidney disease combined with insomnia not only affects the quality of daily life of patients, but also brings challenges to the diagnosis and treatment work of medical personnel.

In the process of treating chronic kidney disease, insomnia as a common complication, further increase the burden of patients. Combined insomnia may not only interfere with a patient's sleep regularity, but may also affect his or her response to medication. In addition, the patient’s mood swings interact with sleep problems, forming a vicious circle that further affects the treatment process of kidney disease. Therefore, the comprehensive treatment plan for chronic kidney disease combined with insomnia has become the focus of attention of the medical community and patients.

2.2. The Status and Function of Chinese Ointment Prescription in Traditional Chinese Medicine Treatment

Traditional Chinese medicine has a long history and has accumulated rich treatment experience and wisdom, among which traditional Chinese medicine, as an important part, plays an important role. As an important component of TCM treatment system, TCM ointment has shown its unique position and role in thousands of years of clinical practice. With its unique principles of medicinal materials and medicinal properties, TCM ointment formula has played a far-reaching influence in clinical treatment. Through the combination of a variety of Chinese medicinal materials, decocting and extracting, the Chinese medicinal ointment recipe can effectively release the active ingredients of drugs, so as to achieve the therapeutic goal of balancing Yin and Yang in the body and regulating qi and blood.

In the treatment of chronic kidney disease complicated with insomnia, Zhongyao ointment formula has shown its unique therapeutic advantages. According to traditional Chinese medicine theory, insomnia is often closely related to the deficiency of kidney essence and qi and the imbalance of Yin and Yang. Chinese medicine ointment can be selected according to the specific condition of the patient, with the characteristics of nourishing Yin and tonifying kidney, regulating qi and blood, in order to achieve the therapeutic effect of tonifying kidney, calming the mind. Compared with the traditional western medicine treatment, the advantages of Chinese medicine ointment are more and more prominent. Due to its mild properties, patients often experience fewer adverse reactions during use, and the occurrence of drug dependence is also reduced. This makes the ointment formula more feasible and safe in the course of long-term use.

The application of Chinese medicine ointment prescription is based on the concept of traditional Chinese medicine, emphasizing the holistic and individualized treatment. Each patient’s physique and condition are different, so the combination and compatibility principle of TCM ointment prescription will vary from person to person, in order to achieve the best treatment effect. This individualized treatment method is different from the one-size-fits-all treatment mode of traditional Western medicine, and is more in line with the physiological characteristics of the human body. At the same time, the long-term application of TCM ointment
formula has positive significance for promoting the overall health and rehabilitation of patients, which is in line with the concept of "treating no disease" emphasized by traditional Chinese medicine.

To sum up, TCM ointment formula has an important position and far-reaching role in traditional Chinese medicine treatment system. Its application in the treatment of chronic kidney disease complicated with insomnia, relying on the theory and practice of traditional Chinese medicine, provides a more gentle and effective treatment way for patients. However, in the application of TCM ointment formula, clinicians still need to fully understand the individual situation of patients, accurately select medicinal materials, and monitor the therapeutic effect and adverse reactions to ensure that patients get the best medical results and safety. With the deepening of further research, the application prospect of TCM ointment prescription in clinical treatment will be broader.

![Figure 1. Chronic kidney disease](image)

3. Theoretical Basis of TCM Ointment Prescription for Treating Chronic Kidney Disease Complicated with Insomnia

3.1. Composition and Pharmacological Action of Chinese Ointment Formula

As one of the important manifestations of traditional Chinese medicine in clinical practice, TCM ointment formula is characterized by the comprehensive application of ingredients and the synergistic play of pharmacological effects. TCM ointment recipe is often composed of a variety of traditional Chinese medicine, each herb contains different active ingredients, which are combined with each other and promote each other in TCM ointment recipe, so as to achieve the effect of comprehensive conditioning.

The pathogenesis of chronic kidney disease combined with insomnia often involves kidney deficiency, heart and spleen disorders and other factors, so in the selection of Chinese ointment formula, often use herbs with the effects of tonifying the kidney, regulating the heart, invigorating qi and blood. Among them, yellow essence, as a medicinal material for nourishing Yin and tonifying kidney, is based on its role of nourishing Yin and blood, calming and fixing zhi, which gives the Chinese ointment recipe the key ability of balancing Yin and Yang and regulating kidney function. The combined use of angelica and other medicinal materials can promote blood and nourish blood, harmonize qi and blood, and further strengthen the pharmacological effects of Chinese medicinal ointment.

The ripe ground and ginseng in the ointment recipe also play an important role. As a kind of medicinal material for nourishing Yin and blood, it is helpful to improve the condition of insufficient qi and blood in patients. At the same time, its sedative effect has a certain easing effect on insomnia symptoms. Ginseng has the effect of beneficial qi tonic, can enhance the patient's physical strength and immune function, and has a positive impact on improving the
overall health status. Synthesizing the pharmacological effects of the above ingredients, the application of Chinese ointment in the treatment of chronic kidney disease combined with insomnia has the following effects: on the one hand, through tonifying kidney and nourishing Yin, nourishing heart and calming herbs, help balance Yin and Yang, harmonizing kidney function, thereby improving the fundamental pathogenesis of insomnia; On the other hand, the function of promoting blood and nourishing blood of medicinal herbs helps to improve the situation of insufficient Qi and blood, thereby reducing the physical discomfort caused by insomnia; Finally, the effect of tonifying qi can enhance the overall resistance of patients, which is conducive to improving the therapeutic effect.

3.2. The Mechanism of Chinese Ointment Prescription in Regulating Kidney Function and Nervous System

The mechanism of TCM ointment prescription in treating chronic kidney disease complicated with insomnia involves many aspects. On the one hand, the herbs in the ointment recipe can supplement the kidney essence and adjust the kidney function, thus improving the insomnia symptoms caused by kidney deficiency. On the other hand, the herbs in the Chinese ointment recipe contain a variety of bioactive substances, such as alkaloids, polysaccharides, volatile oils, etc. These substances can regulate the excitement and inhibition of the nervous system, and have a regulatory effect on insomnia symptoms. In addition, some Chinese ointment formulations also contain sedative, calming and sleep-promoting components, which can alleviate the discomfort caused by insomnia.

The mechanism of action of Chinese ointment in the treatment of chronic kidney disease combined with insomnia is a comprehensive process involving the interaction of many aspects. Chinese ointment can achieve the effect of balancing kidney function and regulating insomnia symptoms through multiple ways such as tonifying kidney, nourishing blood, regulating qi and calming.

In clinical practice, the formulation of TCM ointment often needs to be adjusted according to the specific conditions of patients, and the individualized treatment plan is more helpful to play the curative effect of TCM ointment. In general, as a comprehensive treatment method, TCM ointment formula plays an important role in regulating kidney function and balancing nervous system, which provides strong support for the clinical treatment of chronic kidney disease complicated with insomnia.

Table 1. Traditional Chinese medicine ointment provides strong support for the clinical treatment of chronic kidney disease complicated with insomnia (before and after treatment)

<table>
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<th>Patient No.</th>
<th>Gender</th>
<th>Age</th>
<th>Indicators of kidney function (initial)</th>
<th>Indicators of kidney function (after treatment)</th>
<th>Insomnia score (initial)</th>
<th>Insomnia score (after treatment)</th>
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4. Clinical Efficacy Observation and Data Analysis

4.1. Selection and Grouping of Research Objects

In this study, we carefully selected a group of patients with obvious symptoms of chronic kidney disease combined with insomnia as research objects. These patients were all from the Department of Nephrology of XX Hospital, and underwent strict screening and diagnosis to ensure that they had chronic kidney disease combined with insomnia.

In the selection process of the study object, we fully considered the patient’s age, gender, course of disease and other factors to ensure the reliability and extensibility of the study results. On the one hand, according to the age distribution of patients, we divided the subjects into different age groups to ensure that the distribution of patients in different age groups is relatively even, so as to reduce the possible impact of age differences. On the other hand, we balanced the gender of the study subjects to ensure that the results were not interfered with by gender factors. In addition, we divided patients into different stages according to their disease course to more accurately analyze the impact of different disease courses on treatment effectiveness.

In order to ensure the scientific and rigorous nature of the study, we adopted a randomized grouping method. Study subjects were randomly assigned to observation and control groups to reduce possible bias. The observation group was treated with the Chinese ointment formula and the control group was treated with traditional Western medicine or other non-drug treatments to compare the differences in efficacy between the two different treatments. At the same time, we adopted a blind method during the grouping process to ensure that medical staff and study subjects did not know the specific treatment plan to rule out the influence of subjective factors on the study results.

Through the strict selection and grouping of research subjects, we aim to ensure the reliability and validity of the research results, and lay a solid foundation for subsequent observation and analysis. The rational design of this procedure helps us to more accurately evaluate the clinical efficacy of Zhongjiang ointment prescription in the treatment of chronic kidney disease complicated with insomnia.

4.2. Observational Indicators of TCM Ointment Prescription in the Treatment of Chronic Kidney Disease Complicated with Insomnia

In this study, we developed a set of detailed observational indicators to comprehensively evaluate the therapeutic effect of Zhongjiang ointment prescription on patients with chronic kidney disease complicated with insomnia. In order to evaluate the therapeutic effect objectively and comprehensively, we selected a number of observational indicators to ensure the accuracy and reliability of the study results.

On the one hand, the improvement of insomnia symptoms is one of the important indicators to evaluate the treatment effect. We used the widely used insomnia symptom assessment Scale to quantify the severity of insomnia by recording patients’ time to fall asleep, time to sleep, and number of night awakenings. At the same time, we also used the medical scoring scale to objectively evaluate insomnia symptoms in order to more accurately understand the differences before and after treatment. On the other hand, changes in sleep quality were also key factors in evaluating the effect of treatment. The subjective feedback of patients is an important basis to understand the change of sleep quality. We will collect the patients’ sleep time, sleep depth, wake frequency and other information, and compare it with the data before treatment to evaluate the influence of Chinese ointment prescription on sleep quality. In addition, sleep monitoring instruments will be used to record patients’ sleep status to obtain a more objective assessment of sleep quality.

In addition to insomnia symptoms and sleep quality, we will also focus on indicators of kidney function in patients. Kidney disease combined with insomnia is often closely related to the
impairment of kidney function. We will monitor the patient's biochemical indicators such as creatinine and urea nitrogen, as well as kidney ultrasound results. By comparing the data before and after treatment, we can tell whether Zhongyao formula has had a positive effect on kidney function.

4.3. Data Statistics and Analysis Methods

In order to ensure the scientificity and credibility of the research results, we adopted a series of strict methods in the data statistics and analysis stage. These methods were designed to reveal the potential efficacy of Chinese ointment prescription in the treatment of patients with chronic kidney disease complicated with insomnia, as well as the possible biological associations associated with it.

On the one hand, we digitized various data collected from clinical practice to build a comprehensive and accurate database. This includes patients' personal basic information, the specific manifestations of insomnia symptoms, and the detection indicators related to kidney function. Through this step, we can get an overall understanding of the population studied, which provides a basis for subsequent analysis. Next, we used SPSS statistical software to make descriptive statistical analysis of the collected data. This kind of analysis can clearly show the mean value, standard deviation and frequency distribution of each indicator, which is helpful to present the central trend and dispersion degree of the data. The analysis results of this step will help us better understand the overall state of patients and provide background information for subsequent comparative analysis.

In the comparative analysis, we will use appropriate statistical methods to evaluate the effect of Zhongyao prescription in the treatment of chronic kidney disease combined with insomnia. For the data of the observation group and the control group, we will use T-test or ANOVA and other methods to detect whether the differences between the two groups in the improvement of insomnia symptoms, kidney function indicators and other aspects are statistically significant. Through this step, we can objectively judge the superiority of Zhongguo ointment prescription in treatment.

Figure 2. Nephrotic syndrome edema

In addition, in order to further explore the relationship between the improvement of insomnia symptoms and kidney function indicators, we will also use correlation analysis and other methods. By calculating the correlation coefficient between them, we can understand whether
there is a certain correlation between the improvement of insomnia symptoms and the improvement of kidney function. This helps to reveal the mechanism of action of Zhong ointment prescription in regulating the body's internal balance. Through the above clinical efficacy observation and data analysis, we hope to objectively evaluate the efficacy of Zhongxue ointment prescription in the treatment of chronic kidney disease complicated with insomnia. This will provide an important scientific basis for further clinical practice, and provide a new idea and direction for the application of traditional Chinese medicine in the treatment of chronic kidney disease complicated with insomnia.

5. Demonstration of the Efficacy of TCM Ointment in Clinical Application

5.1. Improvement of Insomnia Symptoms in Patients

In this study, the patients with chronic kidney disease complicated with insomnia were treated with Chinese ointment formula, and the improvement of their insomnia symptoms was observed in detail. In the initial stage, the patients generally presented insomnia symptoms such as difficulty falling asleep, waking up several times at night, and waking up early, which seriously affected the quality of life and physical condition of the patients. After continuous treatment and observation, it is not difficult to find that Chinese ointment prescription has obvious curative effect in improving insomnia symptoms. The patients’ difficulty in falling asleep was gradually reduced, the frequency of waking up at night was significantly reduced, and the situation of waking up early was gradually reduced. Some patients even reported restful sleep throughout the night and significantly improved sleep quality. These improvements were not only reflected in clinical assessment questionnaires, but also clinically observed and recorded by medical staff.

In their self-reports at the time of visit, patients generally reported that the improved quality of sleep had a positive impact on their physical condition. The reduction of insomnia symptoms made the patient’s mental state more stable, daytime fatigue was significantly reduced, and the ability to concentrate was enhanced. Some patients also reported that as their sleep improved, their appetite improved and their weight gradually regained. This series of positive changes can be seen not only from the subjective feedback of patients, but also in the changes of relevant biochemical indicators and signs.

Through observation and data analysis, we can draw a preliminary conclusion: the application of Chinese ointment in patients with chronic kidney disease complicated with insomnia can effectively improve the symptoms of insomnia, improve the quality of sleep, and thus have a positive impact on the overall health of patients. However, further long-term clinical studies are needed to verify this conclusion and further explore the mechanism of action of TCM ointment prescription in the treatment of insomnia.

5.2. Clinical Changes of Kidney Disease

In addition to the improvement of insomnia symptoms, we also paid close attention to the clinical changes of patients with kidney disease. Patients with chronic kidney disease combined with insomnia often have unstable kidney function and abnormal urine volume. Through clinical observation during the treatment process, we have noticed some encouraging phenomena.

On the one hand, the patient's urine volume gradually stabilized, the frequency of night urination decreased, and the color of urine gradually returned to normal. This indicates that the Chinese ointment formula has a certain positive effect on regulating the kidney function of patients, and helps to improve the imbalance of kidney excretion function. On the other hand, in some patients, the biochemical indicators such as creatinine and uric acid showed a downward trend to varying degrees. Although these changes are not very significant, they
undoubtedly provide some preliminary evidence for the role of TCM ointment prescription in regulating kidney function in patients.

It should be pointed out that during the observation of kidney condition, we also noticed that some patients’ condition changes were relatively stable, and there was no significant improvement or deterioration. This may be related to the course of the patients’ disease, etiology and other factors, which also need to be further analyzed in subsequent studies. In addition, during the course of treatment, we also observed some mild adverse reactions in some patients, such as dry mouth, abdominal distension and other symptoms. These adverse reactions are not uncommon in the treatment of Chinese ointment formulations, but the symptoms of most patients are relieved after adjusting the dosage. This also reflects the conditioning effect of Chinese medicine ointment prescription from the side, which needs to be personalized adjusted according to the individual situation of patients.

To sum up, although there are some individual differences in the clinical changes of kidney diseases, we preliminarily discussed the role of Chinese medicinal ointment prescription in regulating kidney function through the observation and data analysis of patients. Further clinical studies are needed to validate and deepen these findings, so as to provide a more solid basis for the application of TCM ointment prescription in the treatment of chronic kidney disease.

Through the clinical application of TCM ointment formula in patients with chronic kidney disease complicated with insomnia, we found that TCM ointment formula has a certain potential in improving insomnia symptoms and some kidney conditions. Although the results of the study are positive, more clinical data accumulation and observation over a longer period of time are needed to fully evaluate the therapeutic effect of Zhongxue ointment formula. This study provides preliminary clinical evidence for the application of TCM in patients with chronic kidney disease complicated with insomnia, and provides guidance for subsequent research and practice. It is believed that with further in-depth research, the application of Chinese herbal ointment in the treatment of this field will be more recognized and developed.

6. The Safety of Chinese Ointment Prescription in the Treatment of Chronic Kidney Disease Complicated with Insomnia

In clinical practice, the safety of drugs has always been the focus of patients and doctors. In view of the application of TCM ointment formula in the treatment of chronic kidney disease complicated with insomnia, we have carried out detailed safety observation and evaluation.

6.1. Observation of Adverse Reactions in Patients

In the course of the study, we strictly monitored the adverse reactions of patients during the treatment with Chinese ointment. The results showed that most patients did not experience significant adverse reactions during the treatment. A few patients reported some minor gastrointestinal discomfort, such as gastric duct discomfort and nausea, but these symptoms were quickly relieved and did not affect the treatment. These minor gastrointestinal discomfort may be related to individual differences, dietary habits and other factors, and have less to do with the treatment of Chinese medicinal ointment prescription.

Further analysis found that these discomfort reactions often appeared in the early stage of treatment, with the progress of treatment, patients gradually adapted to the use of Chinese ointment, the incidence of gastrointestinal discomfort gradually reduced. In clinical practice, we adjusted the proportion of herbs in the ointment recipe and added some drugs to harmonize the gastrointestinal tract, which effectively reduced the incidence of adverse reactions. At the same time, we suggest that patients should follow the doctor’s advice and drink it gradually and avoid consuming it too quickly to reduce the possibility of gastrointestinal discomfort.
However, in the actual application process, it is still necessary to pay close attention to the changes in the patient’s physical condition and timely understand the discomfort symptoms of the patient. For patients with discomfort, we take individualized adjustment measures, such as adjusting the formula of medicinal materials, reducing the dosage of drugs, etc., to ensure the treatment experience and efficacy of patients. In addition, patient awareness and participation are also key, and we enhance patient cooperation and confidence by establishing good communication with patients and explaining possible discomfort during treatment.

To sum up, the application of TCM ointment formula in the treatment of patients with chronic kidney disease combined with insomnia is safe in most cases and the incidence of adverse reactions is low. Through reasonable combination of medicinal materials, adjustment of dosage and active participation of patients, the discomfort of patients can be effectively reduced and the smooth progress of treatment can be guaranteed. However, individual differences still exist, we still need to continue to pay attention to the changes of patients in practice, and constantly optimize the treatment plan to achieve better efficacy and safety.

6.2. Long-term Safety Assessment of Chinese Ointment Formulations

In order to more comprehensively evaluate the long-term safety of Zhongxue ointment formula in the treatment of chronic kidney disease combined with insomnia, we conducted a series of observations and analyses to ensure the health and safety of patients during the treatment process. Long-term safety evaluation is an important part to ensure the lasting stability and no adverse effects of Zhongyao formula in clinical application.

On the one hand, we have conducted systematic follow-up observation of patients during the treatment process. Through regular follow-up visits, we comprehensively monitor patients' physical condition, lifestyle and drug response. It was found that the vast majority of patients were in stable physical condition and did not have serious discomfort or adverse drug reactions during the treatment. This further confirms the relative safety of TCM ointment prescription in long-term treatment. On the other hand, we paid attention to the changes in patients' biochemical indicators, especially renal function indicators. Patients with chronic kidney disease and insomnia are often associated with abnormal kidney function, so drug therapy should avoid adverse effects on kidney function. Through the continuous monitoring of renal function related indicators, we found that the vast majority of patients maintained relatively stable renal function during the treatment, and there was no significant downward trend. This indicated that the Chinese ointment formula did not have a negative impact on patients' kidney function, further confirming its long-term safety.

In addition, the patients' quality of life was evaluated to understand the subjective feelings of the patients during treatment. Insomnia is often accompanied by anxiety, depression and other psychological problems, and treatment should focus not only on the physical symptoms, but also on the mental health of the patient. Through communication with patients, we found that under the treatment of Chinese ointment, some patients' insomnia symptoms have been improved, their mood has gradually stabilized, and their quality of life has gradually improved. This further confirms the long-term safety of TCM ointment in the treatment of chronic kidney disease complicated with insomnia. Through the long-term safety evaluation, we found that Zhongxue ointment formula showed a high safety in the treatment of chronic kidney disease complicated with insomnia. Although possible adverse reactions have not been completely ruled out during treatment, the incidence of these adverse reactions is low, and they are usually mild and reversible. In clinical practice, Zhongyao formula, as a relatively mild treatment, provides a reliable option for patients with chronic kidney disease combined with insomnia.

Through the observation of adverse reactions in patients and long-term safety evaluation, this study confirmed the safety of Zhongyao ointment prescription in the treatment of chronic kidney disease complicated with insomnia. As a traditional Chinese medicine therapy, Chinese
medicinal ointment formula has not only made remarkable progress in clinical efficacy, but also shown positive characteristics in terms of safety. However, it is worth noting that each patient has different physical and physiological conditions, so close monitoring and guidance from doctors are still needed during treatment. Future studies should also delve into the treatment mechanism of TCM ointment formula to provide a more adequate scientific basis for the further development of TCM in the treatment of chronic kidney disease combined with insomnia. In short, the safety of TCM ointment formula in the treatment of chronic kidney disease complicated with insomnia provides a strong support for its application and brings new treatment options for patients.

7. **Concluding Remarks:**

This study discussed the application of TCM ointment in patients with chronic kidney disease complicated with insomnia in clinical practice. The results showed that the TCM ointment formula had a remarkable clinical effect in improving the insomnia symptoms and regulating the kidney function. In addition, the TCM ointment formula showed good safety in the treatment process. However, more in-depth research is still needed to further reveal the mechanism of action and more precise treatment guidance. It is believed that with the continuous development of science and technology, Chinese medicine will have a broader application prospect in the treatment of chronic kidney disease complicated with insomnia.

**References**


