Review

Chinese herbal enema therapy for the treatment of chronic kidney disease

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Abstract: Chronic kidney disease (CKD) has emerged as a pressing public health issue characterized by increasing incidence and mortality rates. The imperative for effective treatments to halt its progression cannot be overstated. Central to the concept of the "gut-kidney axis" is the belief that as CKD advances, uremic toxins (UTs) gradually build up, undermining the integrity of the intestinal barrier and resulting in an imbalanced gut microbiota. This dysbiosis in the gut microbiota, coupled with the compromised intestinal barriers, intensifies renal damage by furthering UT accumulation and inducing systemic inflammation. Grounded in this understanding, the use of Chinese herbal enemas has shown promising outcomes in CKD management. This review consolidates both domestic and international studies related to the "gut-kidney axis" and delves into the combination of Chinese herbal enemas with standard therapy, colon dialysis, and traditional oral Chinese medicine practices. Our aim is to shed light on novel perspectives and pinpoint emerging avenues for the evolving therapeutic landscape of CKD.

Keywords: Gut-kidney axis; Chinese herbal enema; Chronic kidney disease; Research progress

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Contents

1. Introduction

Chronic kidney disease (CKD) emerges as a complex pathological condition resulting from a range of primary or secondary diseases that impair the kidney's structure and function. It is defined by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2, evidence of kidney damage, or both, persisting for over 3 months[1]. Emerging as a critical public health challenge[2], CKD has a global footprint affecting a staggering number of individuals, with over 750 000 cases reported worldwide[3,4]. The global incidence stands at 13.4%[5], while China witnesses an incidence of approximately 10.8%[6]. The nation's in-hospital mortality rate hovers

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around 4.3%[7]. Notably, the incidence of patients requiring dialysis (per million population) in China surged from 51.7 in 2008 to 92.3 in 2009[8–10]. Surveys from 1988 to 1994 have unveiled that 11% (or 19.2 million) of adult participants are grappling with CKD[10]. A subsequent survey spanning 1999 to 2004 has flagged an even higher prevalence at 13%[11]. Alarmingly, CKD is on track to emerge as the fifth primary contributor to global mortality and morbidity by 2040[12]. Hence, the urgency to unearth effective interventions to stall CKD's progression is palpable.

The concept of the "entero-renal axis" first surfaced during the International Dialysis Conference in 2011, as presented by Meijers[13]. At its core, the concept posits that with the steady decline of renal function in CKD patients, uremic toxins (UTs) begin to amass, hastening the transition from CKD to end-stage kidney disease (ESKD). The primary culprits in producing UTs are intestinal microorganisms, which metabolize proteins. The ensuing build-up of UTs causes a breakdown in the intestinal barrier's integrity, heightening the permeability of intestinal epithelial cells. Consequently, toxins permeate the bloodstream, triggering the intestinal mucosal immune system and instigating a systemic inflammatory response. This chain of events cultivates a microinflammatory environment in the kidneys, further propelling CKD's progression[14].

The theory illuminates the intricate link between the progression of kidney disease and shifts in intestinal microenvironment equilibrium[14]. In optimal health, the host and its microbial community coexist symbiotically[15]. However, this harmonious balance is perturbed in CKD patients, leading to microbial disequilibrium[16,17]. Furthermore, metabolic waste and toxins, typically earmarked for renal excretion, can inadvertently compromise the intestinal flora and barrier functionality.

Under the guiding principle of the "gut-kidney axis", Chinese medicine enemas have made encouraging strides in CKD treatment. Thus, this review aims to shed light on the "gut-kidney axis" framework, examining the potential of Chinese medicine enemas combined with foundational therapies, colon dialysis, and traditional oral Chinese remedies. Our goal is to highlight new directions and therapeutic targets for researchers specializing in CKD treatment.

2. The intestine and CKD

The concept of the "chronic kidney disease-colon axis" was first proposed by Pahl[18], who underscores the cyclical relationship wherein diminished kidney functionality precipitates disruptions in the intestinal barrier and imbalances in the intestinal flora. Conversely, these disturbances in the intestinal barrier and microbial equilibrium can trigger chronic inflammation, further exacerbating renal impairment. This insight paints a comprehensive picture of the intertwined dynamics between intestinal dysbiosis, compromised intestinal barrier integrity, and the pathophysiological underpinnings of CKD.

2.1. Impaired intestinal barrier function

In healthy individuals, the intestinal mucosal barrier consists of a layer of intact epithelial cells connected by tight junctions (TJs). These junctions act as a primary defense mechanism against the infiltration of pathogens, exogenous antigens, and toxins. By sealing the intercellular space, TJs prevent unwanted substances from entering the peritoneal cavity or the circulatory system. This maintains the body's internal environment in a state of relative equilibrium[19]. The integrity of the intestinal mucosal barrier is vital for overall health, and its preservation is crucial in averting various diseases. Any disruption or damage can lead to heightened intestinal permeability, inflammation, and a compromised immune response.

The effect of UTs on the intestinal barrier is primarily reflected in the depletion of essential protein structures. Research by Vaziri et al.[20–23] shows a notable reduction in the expression of key colonic TJ proteins, such as claudin-1, occludin, and ZO-1, in patients with CKD. This diminished protein expression correlates with the increased intestinal permeability observed in renal disease, facilitating the escape of bacterial endotoxins and other detrimental products from the intestinal lumen. Besides the evident decrease in TJ proteins, there's also a concurrent reduction in trans-epithelial resistance. This suggests a rise in permeability and a decrease in epithelial barrier function. Notably, this research provides the inaugural evidence that CKD can deplete vital protein components of colonic TJs, elucidating the mechanisms that underpin the impaired intestinal barrier function and subsequent systemic inflammation in CKD.

Xie et al.[24] have provided evidence pointing to a strong link between UTs and damage to the intestinal barrier. UTs can be grouped into three categories based on their biochemical properties: water-soluble UTs, medium-molecular UTs, and protein-bound UTs. Notably, protein-bound UTs[25–27], derived from dietary sources and produced by intestinal flora, specifically indoxyl sulfate (IS) and trimethylamine N-oxide (TMAO), are termed enterogenic UTs. Their high toxicity is well-documented. Multiple studies highlight that these enterically derived UTs not only amplify the decline of renal function in CKD patients but are also challenging to remove through hemodialysis. This difficulty results in an elevated risk of cardiovascular complications[26,27].

Further supporting this, Huang et al.[28] have reported that the intestinal tissues of CKD-afflicted mice display a reduced density of TJs, wider cell gaps, and a significant downregulation in genes related to TJs (ZO-1, occludin, claudin-1, and claudin-2). These observations point to a compromised intestinal barrier in these mice. Moreover, when these mice were subjected to IS injections, there was a noticeable degradation in TJs and a surge in serum inflammatory markers. These collective results suggest that IS substantially reduces the expression of genes vital for TJs, accelerating damage to the intestinal epithelial cells. As CKD advances and IS levels rise, the severity of damage to the intestinal barrier intensifies. One major consequence of this compromised barrier function is the onset of systemic inflammation in both uremic animals and humans[29]. Furthermore, weakened intestinal epithelial TJs can permit the migration of bacteria and endotoxins through the intestinal wall into surrounding tissues. This breach can activate the innate immune response, setting off an inflammatory chain reaction consistent with sustained damage to the intestinal barrier[30,31].

2.2. Dysbiosis of gut microbiota

The gut microbiota forms a symbiotic ecosystem, delivering both protective and nutritional benefits to the host[32]. However, the onset of CKD disrupts this harmonious relationship between the host organs and gut microbiota. This disturbance results in a state of dysbiosis within the gut, which further exacerbates the progression of CKD[33]. This dynamic underscores a bidirectional interplay between gut flora dysbiosis and CKD pathogenesis[34–36].

As CKD develops, the once-symbiotic nature of the intestinal environment deteriorates, leaning more toward a dysbiotic state[37]. This shift manifests as heightened colonic protein fermentation, an escalation in UTs originating from the microbiota, diminished carbohydrate fermentation, and a decline in the production of beneficial metabolites like short-chain fatty acids (SCFAs)[38]. It's pivotal to highlight that SCFAs, as essential byproducts of intestinal flora metabolism, play an indispensable role in preserving the integrity of the intestinal barrier.

As an integral part of host biology, gut microbiota participates in a variety of essential processes[39]. As CKD progresses, the accumulated UTs and elevated levels

of urea, uric acid (UA), and oxalate in the colon perturb the intestinal biochemistry and microbial composition. Impaired renal function results in the accumulation of various endogenous substances and exogenous drugs and their metabolites. Therefore, avoiding secondary kidney damage is necessary[40]. The gut microbiota can influence the onset and progression of CKD through inflammatory, endocrine, and neurological pathways[41]. Additionally, it metabolizes dietary components, producing biologically active molecules (including vitamin precursors, SCFAs, and UTs), which, upon absorption into the bloodstream, can impact CKD progression[42].

CKD itself can reshape the gut microbiome, promoting the proliferation of UT-producing microbiota and suppressing those generating beneficial products[43]. Research has indicated a decline in bifidobacteria and a surge in anaerobic bacteria in patients on maintenance hemodialysis, underscoring CKD's role in altering the gut microbial balance[44]. These shifts elevate toxin production and absorption, igniting a systemic inflammatory response that propels CKD progression[38,41]. In CKD patients, 12 out of 19 microbial families are identified to contain urease, five families exhibit uricase, and several colonies produce indole and *p*-toluene-forming enzymes[38]. While certain studies have noted no significant difference in total microbial count, aerobic bacteria are supplanted by anaerobic bacteria, lactobacilli, and bifidobacteria. This change promotes the degradation of nitrogen compounds, amplifying the uremic state's deteriorative effects[21,45]. UTs induce inflammation throughout the gastrointestinal tract, altering the structure, composition, and function of the gut microbiota. This leads to the production of pro-inflammatory byproducts while suppressing the beneficial effects typically offered by commensal flora, potentially inducing gut dysbiosis[46]. Increased colonization in the duodenal and jejunal regions is more prevalent in CKD patients compared to their healthy counterparts[46].

The intertwined relationship between impaired intestinal barrier function, gut-kidney interaction, gut flora dysbiosis, and CKD collectively exacerbate patient health, posing a serious threat to survival. This intricate connection has paved the way for CKD treatments rooted in the "intestine-kidney axis" theory[43].

3. Research progress of Chinese medicine enema in the treatment of CKD

3.1. Chinese herbal enema combined with basic therapy for CKD

Recent research by Zou et al.[47] has unveiled promising findings regarding the therapeutic potential of Da Huang for CKD. When introduced into the intestine, Da Huang is observed to enhance intestinal kinetics, mend the intestinal barrier function, modulate the intestinal microbiota, and diminish the build-up of UTs like IS. This culminates in reduced renal fibrosis, suggesting a slower progression of CKD. Such findings accentuate the prospective benefits of rhubarb in CKD management and emphasize the worthiness of further exploration in this domain.

In a related study, Zeng et al.[48] have employed a 5/6 nephrectomy CKD rat model to delve deeper into this potential. They have observed that administering an enema of Da Huang, combined with a 0.4% sodium carboxymethyl cellulose aqueous solution, considerably decreases levels of UTs, including urea and IS. Notably, this treatment alters the intestinal microbiota composition. There is a reduction in detrimental bacteria, such as Clostridium perfringens, while beneficial bacteria, like Lactobacillus spp., show a marked increase. Moreover, Da Huang enema also notably improves creatinine clearance (CCr) and serum urea nitrogen (BUN) levels in the subjects. The collective findings from these studies underscore the potential therapeutic value of Da Huang enema in CKD management. Further investigations into the exact mechanisms behind these observed effects can pave the way for innovative treatments for CKD patients.

In a study by Ji et al.[49], a 5/6 nephrectomized rat model is utilized to explore the effects of Da Huang enema on CKD. Their findings reveal that the enema leads to a rise in the levels of SCFAs in the rats. This increase is associated with improved intestinal barrier health, diminished inflammation, reduced blood creatinine (Scr) levels, and regulation of the intestinal flora's composition and abundance. Importantly, the study has identified that the positive effect of Da Huang on the progression of CKD in the model rats can be linked to the modulation of SCFA production by seven specific strains of intestinal flora. These insights underscore the potential of Da Huang in CKD management, emphasizing its capability to refine the intestinal flora composition and bolster the intestinal barrier's health. Future research in this domain is certainly warranted to delve deeper into these findings.

In another study, Zou et al.[50] have delved into the benefits of traditional Chinese proprietary colon cleansers in managing CKD. Their research points out that retained enemas composed of cleansers, notably including Da Huang, Mu Li, and Pu Gong Ying, have a significant positive effect on CKD patients. Notably, there is a marked reduction in Scr, BUN, and IS levels. This leads to evident improvement in clinical symptoms and plays a role in decelerating the progression of CKD. These results highlight the potential benefits of traditional Chinese medicine, particularly the use of proprietary colon cleansers, in the management of CKD. As the search for effective treatments in renal medicine continues, further exploration into the underlying mechanisms of these traditional remedies seems both timely and essential.

In a study conducted by Ji et al.[51] using a 5/6 nephrectomy rat model, it has been found that the administration of Da Huang enemas has a significant impact on 5/6 nephrectomy-induced CKD rats. Notably, these enemas reduce serum TMAO and TMA levels, curb the expression of inflammatory markers, and mitigate renal issues, including tubular atrophy, monocyte infiltration, and interstitial fibrosis. Additionally, the enema promotes the proliferation of beneficial commensal and probiotic bacteria and curtails the abundance of potential pathogenic bacteria at the genus level. These observations posit that Da Huang enemas can be a valuable intervention for CKD management, particularly in terms of gut microbiota regulation and renal function enhancement. The compelling nature of these results emphasizes the need for further research to unpack the underlying mechanisms and refine the clinical utility of this treatment strategy.

Lei et al.[52] have embarked on an exploratory study, employing a specially concocted herbal enema formula comprised of Hung Qi, Tao Ren, Ji Xue Cao, Hong Hua, Mu Li, Da Huang, and Zhi Qiao to assess its efficacy in CKD patients. Their results reveal that patients who undergo treatment with these herbal retention enemas experience lowered SCr and BUN levels, an enhanced estimated glomerular filtration rate (eGFR), and a notable decline in inflammatory indicators, such as TNF-α, high-sensitivity C-reactive protein (hs-CRP), and IL-6. These findings underscore the potential of herbal enemas in moderating inflammatory levels, thus ameliorating the inflammatory state of the body and decelerating CKD progression. The insights gleaned from this study accentuate the importance of additional research to understand the mechanisms driving the therapeutic outcomes of herbal enemas and to explore their broader implications for renal medicine.

Chen et al.[53] have investigated the therapeutic potential of anhydride-lowering agents in enema treatments, incorporating traditional Chinese medicine components such as Da Huang, Tu Fu Ling, Wu Yao, Tao Ren, Zao Jiao Ci, Fu Zi, and Wang Bu Liu Xing. The results demonstrate that patients treated with these Chinese medicine enemas experience improved renal function and a mitigated inflammatory response. Key indicators like SCr, BUN, UA, cystatin C (CysC), monocyte chemotactic protein-1 (MCP-1), TNF-α, and IL-6 are

notably lower in the treatment group compared to controls. These findings highlight the promise of Chinese medicine enemas as a treatment avenue for CKD, underscoring the need for deeper exploration into the mechanisms behind their therapeutic benefits. The possibility of tailoring these treatments to individual CKD patients also warrants further attention.

In a separate study, Ji et al.[54] have employed a 5/6 nephrectomy rat model to delve into the therapeutic benefits of Da Huang enemas on CKD. The results revealed that Da Huang enemas not only thwart the proliferation of potentially harmful bacteria but also modulate the intestinal flora, strengthen intestinal barrier metrics, and diminish the inflammatory response *via* the TLR4-MyD88-NF-kappaB pathway. Consequently, systemic inflammation is curtailed, and renal fibrosis is alleviated. This evidence supports the premise that Da Huang enemas can rejuvenate the intestinal barrier's integrity, recalibrate gut microbial imbalances, stifle systemic inflammation, and enhance renal health. The mechanisms underpinning the therapeutic attributes of Da Huang enemas and their broader clinical applications in CKD management remain essential areas for future research.

3.2. Chinese herbal enema combined with colonic dialysis for CKD

Zhang et al.[55] have explored the effectiveness of colonic dialysis combined with a renal failure enema formula, which includes Da Huang, Mu Li, Chi Shao, and Dan Shen, in treating patients with CKD. When compared to colonic dialysis alone, patients receiving the Chinese medicine enema in conjunction with colonic dialysis demonstrate notably decreased levels of SCr, BUN, IS, serum endotoxin, and D-lactic acid. Additionally, these patients display an elevated eGFR and reduced levels of Escherichia coli. These results indicate that herbal enemas are efficient in diminishing UTs and enhancing intestinal microecology in CKD patients, potentially slowing CKD progression. Further investigations are required to better understand the therapeutic mechanisms of herbal enemas and their potential clinical applications in CKD management.

Similarly, Ding et al.[56] have assessed the clinical benefits of preserved enemas combined with colonic dialysis for CKD patients. The enema formula in this study, named "He Luo and Lowering Turbidity Soup", comprises Chinese herbs such as Sheng Di Huang, Da Huang, Huang Qi, Xu Duan, Shan Zhu Yu, Bai Zhu, Fu Ling, Chuan Xiong, Mu Li, Dan Shen, and Che Qian Zi. The results reveal that the combined treatment significantly decreases levels of hs-CRP, TNF-α, IL-6 and BUN. Moreover, there are improvements in CCr and serum ferritin levels when compared to patients undergoing only colonic dialysis. This underscores the potential of Chinese medicine enemas to significantly mitigate the micro-inflammatory state in CKD patients, a key factor in preserving renal function. Further studies are essential to evaluate the long-term implications and any potential side effects of utilizing Chinese medicine enemas in CKD treatment.

3.3. Herbal enema combined with oral Chinese medicine for CKD

Zhou et al.[57] have assessed the effectiveness of a combined treatment using a Chinese herbal enema containing Da Huang and oysters, along with Ban Xia Xie Xin Soup. This soup is a blend of several Chinese herbs, including Ban Xia, Gan Jiang, Huang Lian, Huang Qin, Zhi Gan Cao, Da Zao, and Ren Shen. The results reveal notable reductions in levels of SCr, BUN, and blood phosphorus, highlighting improvements in renal function and symptom alleviation for CKD patients. These findings suggest that pairing a Chinese herbal enema with Ban Xia Xie Xin Soup may serve as a potent strategy for CKD treatment. There's a need for additional research to delve into the therapeutic mechanisms of this combined treatment, fine-tuning dosage and administration timings to maximize efficacy and minimize potential side effects.

In a parallel study, Guo et al.[58] have explored the efficacy of a dual treatment method: oral Chinese herbal medicine containing ingredients such as Huang Qi, Tu Fu Ling, Liu Yue Xue, Ji Xue Cao, and more, coupled with a Chinese herbal enema formula that includes herbs like Huang Qi, Mu Li, and Da Huang, among others. Their findings indicate substantial improvements in both overall efficiency and renal function indicators post-treatment. This combined approach of oral Chinese herbal medicine and herbal enema demonstrates its potential in safeguarding renal function, enhancing clinical symptoms, and decreasing urinary protein levels, hinting at its promise for CKD treatment. Further inquiries are essential to pinpoint the ideal dosage and treatment duration, as well as to understand its long-term implications and possible side effects.

In conclusion, treating CKD with herbal enemas, whether used alone, in combination with oral herbal medicine, or alongside colonic dialysis, has demonstrated notable efficacy. This success may be attributed to the reduction of UTs and the amelioration of the microinflammatory condition.

4. Summary and outlook

In summary, the "intestine-kidney axis" theory posits that as CKD develops, UTs accumulate in the body, causing disruptions in the composition and environment of the intestinal microbiota, impairing intestinal barrier function, and leading to dysregulation of intestinal flora. Consequently, this initiates a systemic inflammatory response due to the production and absorption of UTs, resulting in kidney damage and the progressive advancement of CKD. These processes are interconnected, suggesting the potential for treating kidney diseases through interventions focused on the intestine. Therapeutic methods and drug interventions aimed at regulating the intestinal microbiota have garnered significant attention from scholars worldwide. Despite the progress made in treating CKD using Chinese herbal enemas guided by the "intestine-kidney axis" theory, several key issues still require further elucidation.

Firstly, although impaired intestinal barrier function and dysbiosis of intestinal flora have been identified as factors contributing to CKD progression, the precise mechanisms by which they influence this process remain unclear. Nonetheless, studies have shown that compromised TJs in the intestinal mucosal immune system can induce systemic inflammatory responses, underscoring their importance as a critical factor in the "intestinal-renal axis". Thus, targeting pathological factors such as TJ proteins holds promise as a potential avenue for future CKD treatment research.

Secondly, despite the link between CKD progression and dysbiosis of intestinal flora, it remains uncertain which specific pathogenic bacteria are directly responsible for renal function deterioration in CKD patients or how to identify suitable targets for treatment.

Lastly, the composition of drugs in the enema formulas used for treatment varies, necessitating further research to determine which drugs target specific mechanisms and the extent of their effectiveness.

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中药灌肠治疗慢性肾脏病的研究进展

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摘要: 慢性肾脏病(CKD)作为一个公共卫生问题, 发病率高, 死亡率高, 寻找有效控制发展的治疗手段是亟待解决的难题。“肠-肾轴”理论的核心观点认为, 随着CKD的进展, 尿毒症毒素(UTs)逐渐蓄积, 肠道屏障功能受损, 肠道菌群失调; 反过来, 失调的肠道菌群和受损的肠道屏障通过加剧UTs的蓄积和诱导全身炎症反应等途径加重肾脏的损伤。基于此理论指导下的中药灌肠在治疗CKD上取得了一定的进展, 本文结合国内外相关文献对“肠-肾轴”理论和运用中药灌肠联合基础治疗、中药灌肠联合结肠透析和中药灌肠联合口服中药等进行综述, 以期为后续CKD的治疗提供新思路、新靶点。

关键词: 肠肾轴; 中药灌肠; 慢性肾脏病; 研究进展