



Ameliorating impact of berberine on gut microbiota in chronic kidney disease

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Abstract

Chronic kidney disease is a global health concern, with a growing frequency, significant economic burden, and raised morbidity and mortality. In this disease, alterations in the gut microbiome's integrity led to renal failure's progression. Berberine is a natural substance that balances the efficacy of gut microbiota, which could be beneficial in chronic kidney disease.

Keywords: Berberine, Chronic kidney disease, Dysbiosis, Microbiota

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Introduction

Chronic kidney disease is a significant world wide health issue, with a growing frequency, and a high economic load, with raised morbidity and death (1). Several studies have detected that the gut microbiome is central to the gut-kidney axis. The microbiome products, like advanced glycation products, indoles, and phenols, are absorbed into the circulation; however, these substances are effectively eliminated from the body through the renal excretion process (2).

In renal failure, these toxic substances are responsible for progression toward chronic renal failure.

The gut microbiome comprises all bacteria existing in the gut. In physiological circumstances, gut microbiota has a substantial effect on health consistency. Numerous functions, like protection against various pathogens, augmentation, and regulation of host immunity, constitute the role of the gut microbiome in the body (3). Additionally, the synthesis of some vitamins, such as vitamins B and K, has been identified as another function of the gut microbiome (4). Alterations in the qualitative and quantitative integrity of the gut microbiome due to any cause will lead to the initiation of various diseases. Some of these conditions are the associations between the gut microbiome and cardiovascular diseases, diabetes mellitus, and obesity. Previous studies showed that, in chronic kidney failure, some uremic substances like trimethylamine n-oxide, indole, and p-cresol are produced by the gut microbiome, which is connected with the

progression of both kidney and cardiovascular diseases (5). In advanced stages of renal failure, the dysbiotic gut micro-flora has been detected with a strengthening of pathogenic micro-flora compared to symbiotic flora. This condition is accompanied by increased intestinal barrier permeability, which allows various endotoxins to enter the blood (6).

Following the fermentation of undigested compounds in the colon, the micro-flora of this organ generates amines, phenols, and indoles that are absorbable by the host. These products then accumulate in persons suffering from chronic renal disease, resulting in harmful impacts on the body. The gut-originated uremic substances and the augmented permeability of the intestinal barrier in renal failure conditions have been concomitant with enhanced micro-inflammation and oxidative stress that results in the complications of chronic kidney disease (7). The micro-inflammation and oxidative stress are alongside the progression of heart disease, mineral metabolism abnormalities, anemia, and even the evolution of chronic kidney disease toward end-stage renal disease. Likewise, a bidirectional renal-gut axis was designated in this population. First, gut dysbiosis may stimulate chronic kidney disease development. Secondly, a specific gut microbiota disturbance associated with chronic kidney disease was suggested (8).

Alternatively, a heart-gut axis was also defined, linked to atherosclerosis and cardiovascular disease. Previous investigations have indicated that gut dysbiosis in

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■ Implication for health policy/practice/research/medical education

Berberine can diminish the concentration of *p*-cresol sulfate in plasma, principally by inhibiting the tyrosine-*p*-cresol pathway within the gut microbiota, which leads to modulating the intestinal microbiome.

Individuals suffering from chronic renal failure could explain this population's strengthened rate of heart disease mortality. Therefore, gut dysbiosis could be considered as a potential cardiac disease risk factor in cases with chronic renal failure across other established risk factors. Consequently, the interaction among the heart, kidney, and gut is of great clinical magnitude, as gut microbiota constituents could be moderated by physical activity, diet, prebiotics, and probiotics (8). Luo et al collected fecal samples and followed the clinical outcomes of 73 end-stage renal disease cases, comprising 33 pre-dialysis end-stage renal disease, 19 peritoneal dialysis cases, and 21 hemodialysis individuals. The researchers conducted an analysis on the disparities in gut microbiota composition between pre-dialysis and dialysis end-stage renal disease cases. This study demonstrated that gut bacteria affect a patient's prognosis (9).

Systemic effects of gut microbiota

Regardless of local consequences contributed to the gut microbiota, it also has systemic impacts throughout elaborating various active substances, containing short-chain fatty acids like propionate, butyrate, and acetate, as well as the neurotransmitters like noradrenaline, serotonin, dopamine, and some other substances like bile acids, trimethylamine, cortisol, and finally gastrointestinal hormones such as leptin, peptide YY, and glucagon-like peptide-1. Meanwhile, gut microbiota could also be considered a genuine endocrine organ that adjusts drug metabolism, antimicrobial protection, immune response and nutrients, consequently leading to the stability of the gastrointestinal tract (8). It is noteworthy to remember that the loss of residual renal function is tightly connected with a high plasma uremic toxin concentration. Further, gut microbiota products will be an additional risk that worsens the plasma accumulation of uremic toxins. In this condition, a vicious circle will be ensued. Accordingly, conserving the residual renal function and normalizing the gut microbiota are practical approaches to alleviate the worse outcomes of dysbiosis (10).

Balancing the gut microbiota constitution is a promising treatment modality to diminish the hazards of uremic toxins. Since a principal part of abnormal gut microbiota is caused by daily diet, dietary modification is the safest strategy to modify the microbiota. The diet modification includes more fibers, bioactive substances, and an abridged animal protein intake through changing toward a plant-based dietary regimen. Despite several

controversies, administering symbiotics, prebiotics, and probiotics might be considered a reasonable choice (10).

According to several studies, natural substances could diminish the creation of some uremic toxins. Recently, much consideration has been targeted toward using Berberine as a potential treatment for chronic kidney disease. As a natural substance with low oral availability, Berberine considerably improved chronic renal failure by adjusting the gut microbiota composition and preventing the construction of gut-originated uremic toxins comprising *p*-cresol.

This natural medicine is an active constituent of phellodendri cortex, with anti-inflammatory and kidney protective efficacy. However, the therapeutic efficacy of Berberine on hyperuricemia has not been explored. Li et al performed an experimental study to demonstrate the anti-hyperuricemic and reno-protective effects of Berberine in rat kidneys (11). Berberine diminished the content of *p*-cresol sulfate in plasma principally by reducing the quantity of some bacteria and hampering the gut flora's tyrosine-*p*-cresol pathway. In addition, Berberine enhanced the butyric acid-generating bacteria with increasing fecal butyric acid content, associated with decreased kidney toxic trimethylamine *N*-oxide (12). The result of these studies propose that Berberine could be a promising agent capable of improving chronic renal failure across the gut–renal axis.

Conclusion

The gut microbiota is an environmental parameter that cross-talks with its host and participates in the emergence and progression of several diseases. Berberine can balance the main metabolic index by recovering the balance of the gut microbiome, subsiding the quantity of harmful microbiota and lipopolysaccharide concentrations, and strengthening the production of short-chain fatty acids, principally butyrate, in animal models. Nevertheless, further investigation is required to elucidate all aspects of this medicine on gut flora through experimental studies and clinical trials.

Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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