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Current Status of Research on Probiotics and Their Metabolites for the Treatment of Drug-Induced Nephropathy

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Abstract: Probiotics have shown potential in the prevention and treatment of drug-induced nephropathy, a common cause of kidney injury. This paper mainly reviews probiotics and their metabolites for the treatment of drug-induced nephropathy. Experimental studies, particularly those involving cisplatin-induced acute kidney injury, have demonstrated that various probiotic strains, such as lactobacillus rhamnosus and clostridium species, can alleviate kidney damage by modulating the gut microbiota, reducing oxidative stress, and enhancing anti-inflammatory responses. These probiotics work by improving gut dysbiosis, lowering uremic toxin levels, and protecting renal tubular cells. Additionally, the production of short-chain fatty acids (SCFAs), such as butyrate, plays a key role in their protective effects. Probiotic therapy may be further enhanced by combining it with prebiotics, which support the growth of beneficial bacteria, or synbiotics, which combine both. While these findings are promising, the clinical application of probiotics in drug-induced nephropathy remains limited, and further research is needed to identify the most effective strains, optimize dosages, and evaluate their safety and efficacy in large-scale clinical trials. This paper highlights the potential of probiotics as a therapeutic strategy for drug-induced nephropathy and outlines the challenges that need to be addressed for their clinical implementation.

Keywords: Pharmacological nephropathy, Probiotics, Inflammatory response, Oxidative response, Gut-kidney axis

1. Introduction

Drug-induced kidney injury (DKI) is a common adverse drug reaction, particularly associated with the use of aminoglycoside antibiotics, platinum-based chemotherapy agents, and nonsteroidal anti-inflammatory drugs (NSAIDs). These medications frequently lead to acute or chronic kidney injury. Current treatment strategies primarily include drug discontinuation or dosage adjustment, symptomatic supportive therapy, and antioxidant and anti-inflammatory treatments. Patients may suffer from severe kidney function impairment, posing significant health risks and adding pressure to modern healthcare systems. This condition can exacerbate doctor-patient conflicts due to the challenges it presents in clinical management. Clinically, drug-induced kidney injury often manifests as acute kidney failure, posing substantial therapeutic challenges and even life-threatening risks to patients.

At present, the treatment of drug-induced nephropathy faces several difficulties, including the challenge of early diagnosis, significant individual variability in drug response, limited preventive

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measures, and a lack of effective therapeutic options. Probiotics are commonly used to improve gut microbiota and gastrointestinal health, yet their role in drug-induced kidney injury remains relatively underexplored. If probiotics could be employed as a non-invasive therapeutic approach in combination with potentially nephrotoxic drugs, they might reduce the incidence of drug-induced kidney injury without compromising the therapeutic effects of these drugs. This, in turn, could improve patients' quality of life and enhance their treatment adherence.

As a key regulator of gut microbiota, probiotics help maintain gut microbial balance, suppress the overgrowth of harmful bacteria, and inhibit the translocation of harmful substances (such as endotoxins) into the body. Through these mechanisms, they can modulate immune and inflammatory responses, thereby reducing the risk of kidney damage. The metabolic byproducts of probiotics, particularly short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, exhibit strong antioxidant properties. These compounds alleviate oxidative stress in renal tubular cells, mitigating drug-induced kidney injury. Given their non-invasive nature, low cost, and minimal side effects, probiotics offer a promising strategy for improving gut microbiota while also serving as an adjunctive therapy to slow the progression of kidney dysfunction and chronic kidney disease (CKD). Clinically, they could help optimize pharmacological treatment plans and reduce the incidence of drug-induced kidney injury. Among them, lactic acid bacteria have been extensively studied and have demonstrated significant potential in alleviating drug-induced kidney damage.

This review explores the mechanisms, research progress, and future prospects of probiotics and their metabolites in treating drug-induced nephropathy, providing a theoretical basis for their clinical application. Current treatments rely on drug withdrawal and supportive therapy but lack targeted, low-risk interventions. Probiotics offer a promising approach by modulating gut microbiota, reducing uremic toxins, and alleviating inflammation and oxidative stress, though their precise mechanisms remain unclear. While animal studies support their potential, clinical research is limited. This review summarizes existing studies, evaluates feasibility and challenges, and aims to optimize probiotic-based therapies for clinical translation, ultimately advancing personalized treatment strategies for drug-induced nephropathy.

2. Pathogenesis of Drug-induced Nephropathy

The pathogenesis of drug-induced kidney injury (DKI) is highly complex, typically involving multiple factors, such as the direct toxicity of drugs, the inherent susceptibility of the kidneys, and the body's immune response.

Taking cisplatin and NSAIDs as examples, their primary pathogenic mechanisms differ, with cisplatin exerting direct cytotoxic effects, while NSAIDs primarily cause hemodynamic alterations.

Cisplatin, a platinum-based chemotherapeutic agent widely used in the treatment of various solid tumors, is well known for its pronounced nephrotoxicity in clinical settings. Once cisplatin enters renal tubular epithelial cells, it induces a substantial production of reactive oxygen species (ROS), leading to mitochondrial damage, DNA damage, and endoplasmic reticulum stress. These events collectively trigger apoptosis and necrosis of renal tubular cells. Moreover, cisplatin activates inflammatory pathways, such as the NF-κB and TLR4 signaling pathways, which promote the release of pro-inflammatory cytokines (e.g., TNF-α, IL-1β), thereby exacerbating tubulointerstitial injury. Additionally, cisplatin suppresses the Nrf2/ARE signaling pathway, impairing the body's antioxidant defense mechanisms and further aggravating kidney damage [1].

In contrast, NSAIDs (such as ibuprofen and indomethacin) primarily exert nephrotoxic effects by inhibiting cyclooxygenase (COX-1/COX-2), leading to reduced prostaglandin (PG) synthesis [2]. Prostaglandins play a crucial role in maintaining renal hemodynamics, particularly under conditions of reduced blood volume or decreased renal perfusion pressure. Under such circumstances, PGs mediate the dilation of afferent arterioles to sustain the glomerular filtration rate (GFR). However,

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NSAID-induced inhibition of PG synthesis leads to afferent arteriole constriction, reducing renal blood flow and subsequently causing glomerular ischemia and acute kidney injury (AKI). Furthermore, NSAIDs may also contribute to kidney damage by inducing tubulointerstitial inflammation and oxidative stress responses [3].

Despite differences in their pathogenic mechanisms, both cisplatin and NSAIDs share common pathways in inducing nephrotoxicity, including oxidative stress, inflammatory responses, and apoptosis, ultimately leading to structural and functional kidney impairment.

3. Mechanisms of Probiotics in the Treatment of Drug-induced Nephropathy

In recent years, the relationship between gut microbiota and kidney health has gained increasing attention, with probiotics emerging as a potential therapeutic strategy for drug-induced nephropathy through modulation of the gut-kidney axis. By regulating the gut microbiota and restoring microbial homeostasis, probiotics help reduce gut-derived toxins (such as p-Cresol sulfate, Indoxyl sulfate, and Trimethylamine-N-oxide), thereby lowering systemic inflammation and protecting kidney function. Additionally, probiotics promote the growth of beneficial bacteria (e.g., Bifidobacteria and Lactobacilli) while suppressing harmful bacteria (e.g., toxin-producing Escherichia coli and Clostridium perfringens), ultimately reducing the production of uremic toxins [4].

Probiotics can also modulate the NF-κB pathway, leading to a decreased expression of pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-6), thereby alleviating inflammation and offering renal protection. Furthermore, the metabolic byproducts of probiotics, particularly short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, play a crucial role in regulating Treg cells, thereby mitigating kidney inflammation and fibrosis. Additionally, probiotics can reduce endotoxin (LPS, lipopolysaccharide) release, thereby lowering endotoxemia and inhibiting tubulointerstitial inflammation.

Regarding cisplatin-induced nephrotoxicity, the protective effects of probiotics are primarily attributed to their ability to enhance antioxidant capacity by activating the Nrf2/ARE signaling pathway and increasing the levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH). The SCFAs produced by probiotics help regulate the gut-kidney axis, alleviating oxidative stress and inflammatory responses, strengthening intestinal barrier function, and reducing the absorption of gut-derived uremic toxins (such as indoxyl sulfate and p-cresol sulfate (p-CS)), thereby minimizing their nephrotoxic effects.

Beyond cisplatin-induced nephropathy, probiotics also exhibit protective effects against NSAID-induced kidney injury by influencing uric acid metabolism, thereby mitigating hyperuricemia-induced renal damage associated with NSAID use.

4. Existing Studies

Currently, some experimental studies have explored the role of probiotics in the treatment of drug-induced nephropathy, with particular focus on their protective effects against cisplatin-induced acute kidney injury. Research utilizing a mouse model of cisplatin-induced acute kidney injury has screened probiotic strains with kidney-protective effects. One study found that Lactobacillus rhamnosus GKLC1 could mitigate the increase in serum urea nitrogen (BUN) and creatinine (CRE) levels caused by cisplatin, suggesting its protective role in kidney function [5]. Additionally, probiotics isolated from traditional pickles have shown protective effects on kidney function in a hyperuricemia rat model. Specifically, in the probiotic intervention group, the serum levels of uric acid (UA), creatinine (Scr), and urea nitrogen (BUN) were lower than those in the model group, indicating that probiotics may have a therapeutic effect on kidney damage caused by hyperuricemia.

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Furthermore, Clostridium species play a role as mediators of the gut-kidney axis in cisplatin-induced nephrotoxicity by restoring the composition of the gut microbiota, inhibiting the production of uremic toxins, and enhancing the production of butyrate. The renal protective effect of butyrate is partially mediated by increased anti-inflammatory actions and the maintenance of gut barrier integrity [6]. Research by Wen-Jung Chen further demonstrates that butyrate, through the modulation of the gut microbiome and anti-inflammatory responses, alleviates kidney damage caused by cisplatin [7]. Butyrate administration significantly improves renal function in a dose-dependent manner, reducing kidney fibrosis. Moreover, butyrate intervention ameliorates cisplatin-induced gut microbiota dysbiosis, preserving the structure and diversity of healthy microbial communities. These findings suggest that butyrate, a metabolite from the gut microbiota, can protect against cisplatin-induced kidney damage by restoring microbiota balance and exerting anti-inflammatory effects.

Current research indicates that probiotics may alleviate drug-induced kidney damage through multiple mechanisms, including regulating the gut microbiota to improve gut dysbiosis and reduce the proliferation of harmful bacteria; lowering uremic toxin levels and decreasing the production of gut-derived uremic toxins such as indoxyl sulfate (IS), p-hydroxyphenylacetic acid (p-HPA), and p-hydroxybenzoic acid (p-HB); exerting antioxidant effects to reduce oxidative stress caused by drugs like cisplatin and nonsteroidal anti-inflammatory drugs (NSAIDs); modulating immune-inflammatory responses to reduce levels of inflammatory cytokines such as TNF-α, IL-6, and IL-1β [8]; and protecting renal tubular cells by reducing apoptosis and promoting tissue repair. Future research should aim to further clarify the specific targets of probiotics in different types of drug-induced nephropathy and explore the differences in renal protection among various probiotic strains.

The effects of different probiotic strains may vary considerably. Commonly studied strains include those from the genera Lactobacillus and Bifidobacterium. For instance, Lactobacillus rhamnosus GG (LGG) has shown good anti-inflammatory and antioxidant effects in cisplatin-induced kidney injury models, while Bifidobacterium breve can improve kidney function by modulating short-chain fatty acid (SCFA) levels [9]. However, there is still a lack of systematic studies comparing the therapeutic efficacy of different strains. Future research should focus on strain selection, optimizing probiotic combinations, and exploring their applicability in different models of drug-induced nephropathy.

The effectiveness of probiotics when used alone may be influenced by factors such as microbial colonization capacity and individual host differences. Therefore, the combined use of prebiotics and synbiotics may become a key area for future research. Prebiotics, which are substrates that can be utilized by probiotics, such as inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), can promote the growth of beneficial bacteria and enhance the stability of the gut microbiota. Some studies have shown that prebiotics can amplify the beneficial effects of probiotics on kidney function, such as by increasing SCFA levels, which in turn suppress inflammation and oxidative stress [10]. Furthermore, synbiotics, which combine probiotics and prebiotics, may further enhance kidney protection. Future studies should investigate the optimal ratio and mechanisms of action of these combinations.

Currently, research on probiotics in drug-induced nephropathy is still largely in the animal model phase, with limited clinical studies available. Some clinical research, mainly focused on chronic kidney disease (CKD) patients, suggests that probiotics may delay disease progression by lowering uremic toxin levels and improving gut permeability [11]. However, large-scale clinical trials targeting acute or chronic kidney injury induced by drugs such as cisplatin and NSAIDs are still lacking.

5. Issues and challenges

Although the potential of probiotics in the treatment of drug-induced nephropathy has been preliminarily demonstrated, challenges remain, including insufficient research, unclear mechanisms, and individual variability. Future studies should focus on enhancing basic research to uncover the

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precise mechanisms by which probiotics protect the kidneys, as this knowledge is crucial for the clinical application of probiotics. Additionally, the development of corresponding therapeutic agents and their evaluation in clinical trials will be essential to assess their safety and efficacy. Furthermore, clinical research should explore precision medicine strategies, optimizing probiotic interventions tailored to different patient populations.

6. Conclusion

Drug-induced nephropathy is a common form of renal injury in clinical practice, with a complex pathogenesis involving oxidative stress, inflammation, mitochondrial damage, and tubular cell apoptosis. Currently, the treatment of drug-induced nephropathy mainly relies on discontinuing or reducing the dosage of nephrotoxic drugs, providing symptomatic support (such as fluid resuscitation and antioxidants), and avoiding other risk factors that may exacerbate kidney damage. However, these measures have limited therapeutic effectiveness, and some drug-induced renal injuries may be irreversible. Therefore, exploring new therapeutic strategies is of significant importance for improving the prognosis of patients with drug-induced nephropathy.

In recent years, with the deeper exploration of the gut-kidney axis, the role of the gut microbiota in kidney diseases has attracted increasing attention. Probiotics, as an important means of regulating the gut microbiota, are considered to have potential therapeutic value in various kidney diseases. Studies have shown that probiotics can improve kidney injury caused by drugs like cisplatin and nonsteroidal anti-inflammatory drugs (NSAIDs) by regulating the gut microbiota, lowering uremic toxin levels, improving oxidative stress and inflammatory responses, and enhancing intestinal barrier function. Additionally, certain probiotic strains can promote the production of beneficial metabolites, such as short-chain fatty acids (SCFAs), which further exert protective effects on the kidneys.

Although animal experiments have initially confirmed the potential of probiotics in the prevention and treatment of drug-induced nephropathy, several challenges remain. Firstly, the effects of different probiotic strains on improving kidney damage may vary significantly, and future research needs to further identify the most suitable strains for kidney protection and optimize their dosage and administration methods. Secondly, the effects of probiotics are often influenced by individual host factors, including genetic background, dietary habits, and underlying diseases. Therefore, before clinical application, in-depth research is needed for different patient populations to develop personalized treatment strategies. Moreover, the combined use of probiotics with prebiotics and synbiotics may further enhance their efficacy. Future research could also explore the combined application of probiotics with other drugs, such as SGLT2 inhibitors and antioxidants, to achieve synergistic protective effects.

Currently, research on probiotics in drug-induced nephropathy is still primarily focused on animal experiments, with limited clinical studies that often have small sample sizes and short follow-up periods. Therefore, large-scale, multicenter, randomized controlled trials (RCTs) are needed to systematically evaluate the safety and efficacy of probiotics in the treatment of drug-induced nephropathy. Furthermore, advances in synthetic biology offer the possibility of genetically engineering probiotics to enhance their antioxidant and anti-inflammatory capabilities, or to enable them to secrete specific protective metabolites, providing new hope for the treatment of drug-induced nephropathy.

In conclusion, probiotics, as a safe, economical, and feasible intervention strategy, show promising potential for the prevention and treatment of drug-induced nephropathy. As research progresses, probiotics are expected to become an adjunctive therapy for drug-induced nephropathy, offering new treatment options to improve kidney function and the quality of life of patients. However, further basic and clinical research is necessary to ensure their efficacy and safety and to explore the optimal treatment protocols before widespread clinical application.

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