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Probiotics and chronic kidney disease

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Probiotics are the focus of a thorough investigation as a natural biotreatment due to their various health-promoting effects and inherent ability to fight specific diseases including chronic kidney disease (CKD). Indeed, intestinal microbiota has recently emerged as an important player in the progression and complications of CKD. Because many of the multifactorial physiological functions of probiotics are highly strain specific, preselection of appropriate probiotic strains based on their expression of functional biomarkers is critical. The interest in developing new research initiatives on probiotics in CKD have increased over the last decade with the goal of fully exploring their therapeutic potentials. The efficacy of probiotics to decrease uremic toxin production and to improve renal function has been investigated in *in vitro* models and in various animal and human CKD studies. However to date, the quality of intervention trials investigating this novel CKD therapy is still lacking. This review outlines potential mechanisms of action and efficacy of probiotics as a new CKD management tool, with a particular emphasis on uremic toxin production and inflammation.

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KEYWORDS: chronic kidney disease; gut; inflammation; microbiota; probiotic

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Chronic kidney disease (CKD) is emerging as a major risk factor of cardiovascular disease (CVD). Uremic illness is considered to be due to the accumulation of organic waste products, so-called uremic retention solutes (URSs) that are normally cleared by the kidneys. URS such as phenols and indoles are generated along the gastrointestinal tract (GIT), where the gut microbiota has a significant role in their production[1] and have been shown to have deleterious effects on the cardiovascular system. A number of treatments targeting URS have been proposed, such as reducing substrates (dietary protein restriction), decreasing absorption (oral adsorbents such as AST-120), increasing clearance by renal replacement therapies (long and/or more efficient dialysis, absorbent membranes, kidney transplantation), and modulating cellular pathways (organic anion transporters and antioxidants).[2] Unfortunately, most of these treatments display inherent disadvantages (side effects, high cost, unavailability in patients with moderate CKD) and remain limited to experimental studies.

The gut microbiota is essential for regulating the normal function of the intestinal barrier: it promotes immunological tolerance to antigens from nutrients or organisms, controls nutrient uptake and metabolism, and prevents propagation of pathogenic organisms.[3] Hence, the concept has emerged that dysregulation of intestinal microbiota may have a significant role in cancer and metabolic and inflammatory digestive disease. Recently, it has been demonstrated that CKD is associated with dysbiotic gut microbiotia.[4]

During CKD, the potential utilization of therapies modulating the gut microbiota such as probiotics has emerged as an attractive strategy to reduce URS and improve CVD. Probiotics, a word derived from Greek meaning 'for life', is defined by the World Health Organization[5] as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host'. Probiotics are being increasingly used for various pathologic conditions.[6] However, not all probiotics strains are beneficial in all circumstances and the careful selection of specific organisms based on desired clinical outcome is crucial. Over the past 15 years, considerable experimental and clinical data reinforced the hypothesis that probiotics have a therapeutic role in maintaining a metabolically balanced GIT, reducing the progression of CKD and the generation of URS. For the purpose of this review, we will define the mechanisms of the action of probiotics and we will focus on recent

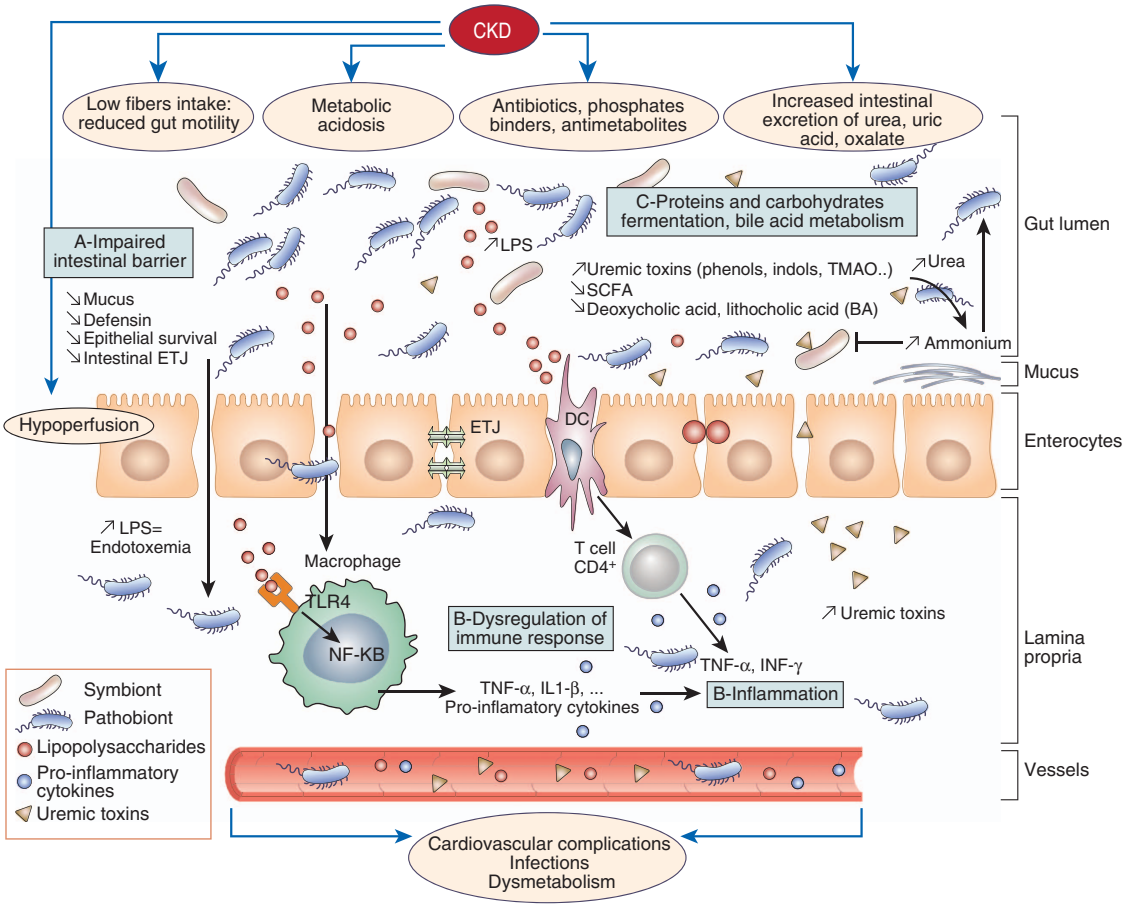

Figure 1 | Dysbiosis and chronic kidney disease (CKD). CKD impairs the balance between symbionts and pathobionts in a way that favors pathobionts overgrowth. Consequences are as follows: (A) impairment of intestinal barrier by disrupting the colonic epithelial tight junction (ETJ) and decreasing epithelial survival. Loss of integrity increase in intestinal permeability allows translocation of bacteria and lipopolysaccharide (LPS). (B) Dysregulation of immune response and inflammation. LPS could activate innate immune cells through a Toll-like receptor 4 (TLR4)-dependent and nuclear factor-kappa B (NF-κB) pathways. Pathobionts stimulate dendritic cells (DCs) that activate a Th17/Th1 T-cell response and enhance production of inflammatory cytokines. (C) Modification of carbohydrates, protein, and bile acid (BA) fermentation. Proteins are fermented by intestinal pathobionts, which are then converted preferentially into indoxyl-sulfate (IS), p-cresyl sulfate (PCS), and trimethylamine n-oxide (TMAO). The reduction in symbionts, specifically *Bifidobacterium,* induces a decrease in short-chain fatty acids (SCFAs). Dysbiosis modifies BA levels and composition. INF-γ, interferon γ; IL-1, interleukin-1; TNF-α, tumor necrosis factor-α.

developments in probiotics in the field of CKD from both *in vitro* and *in vivo* studies.

DYSBIOSIS AND CKD

Recent data highlight that uremia is associated with abnormalities in the gastrointestinal mucosa[7] and a disequilibrium in the intestinal ecosystem.[4] Specifically, these studies demonstrate the presence of aerobic bacteria, such as *Firmicutes*, *Actinobacteria,* and *Proteobacteria,* and fewer anaerobic bacteria, such as *Sutterellaceae*, *Bacteroidaceae*, and *Lactobacillaceae.*[4] The intestinal dysbiosis may be due to iatrogenic causes or uremia *per se* as shown in Figure 1. If the consequences of intestinal microbiota dysregulation in the progression and complications of CKD are currently largely unknown, recent studies give new insights.

First, besides the passive accumulation of URS due to a reduction in kidney clearance, the modification of the intestinal microbiota in CKD strongly increases transformation of amino acids into URS, e.g., indoxyl-sulfate (IS), p-cresyl sulfate (PCS), and trimethylamine n-oxide (TMAO)[1] among others. Increased intestinal concentration of uremic toxins may lead to microbial dysbiosis and pathobionts overgrowth. For example, a modification of the GIT biochemical milieu in the presence of locally accumulated uric acid and urea could perturb symbionts overgrowth.[8] Second, the dysbiosis could participate in immune dysregulation and inflammation in CKD.[9] Pathobionts trigger the intestinal immune system toward a proinflammatory response by preferentially activating Th17-Th7 cells and increasing the production of lipopolysaccharides (LPSs), a major component of the outer membrane of Gram-negative bacteria. Third, dysbiosis also contributes to an increase in intestinal permeability by disrupting the colonic epithelial tight junction,[7] which may subsequently lead to translocation of LPS and bacteria into the host's internal environment. Finally, metagenomic analyses of the microbiota performed in

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