



# The Promise of Synbiotic in Gut-Kidney Axis

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## ABSTRACT

Human microbiota plays a role in protecting human health. Change in the microbial composition will lead to an imbalance between the beneficial and potentially harmful bacteria, leading to “dysbiosis”. The pathogenic interconnection between gut microbiota and kidney diseases is called the gut–kidney axis, which is implicated in a wide range of clinical manifestations such as CKD (chronic kidney disease), AKI (acute kidney injury), hypertension, nephrolithiasis, IgA nephropathy, hemodialysis, and peritoneal dialysis. Synbiotic, a mixture of probiotics and prebiotics are reported to be beneficial in human health via the gut-kidney axis.

**Keywords:** Dysbiosis, gut-kidney axis, microbiota, synbiotic.

## ABSTRAK

Mikrobiota manusia berperan menjaga kesehatan manusia pada kondisi seimbang. Perubahan komposisi mikroba akan menyebabkan ketidakseimbangan antara bakteri menguntungkan dan bakteri yang berpotensi merugikan, menyebabkan “disbiosis”. Hubungan patogenik antara mikrobiota usus dan penyakit ginjal disebut *gut–kidney axis*, yang berimplikasi pada berbagai manifestasi klinis seperti PGK (penyakit ginjal kronik), AKI (*acute kidney injury*), hipertensi, nefrolitiasis, nefropati IgA, hemodialisis, dan dialisis peritoneal. Sinbiotik, campuran probiotik dan prebiotik dilaporkan bermanfaat bagi kesehatan manusia melalui *gut–kidney axis*. **Josephine Herwita Atepela. Manfaat Sinbiotik pada Gut-kidney Axis.**

**Kata Kunci:** Disbiosis, *gut-kidney axis*, mikrobiota, sinbiotik.



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## INTRODUCTION

Humans have various microbiota in their bodies, especially in the gut, vagina, and skin. The adult gut contains around  $10^{14}$  bacterial cells with more than 1,000 varieties of bacterial species.<sup>1</sup> The role of those bacteria is to protect human health. The gut bacteria will protect humans from potentially harmful bacteria.<sup>1</sup> In healthy individuals, there is crosstalk and cross-regulation between the host and the microbiota, which makes a homeostatic balance of bacteria in the gut. Balanced bacteria will ensure a healthy gastrointestinal tract by preventing the overgrowth of potentially pathogenic or harmful bacteria.<sup>1</sup>

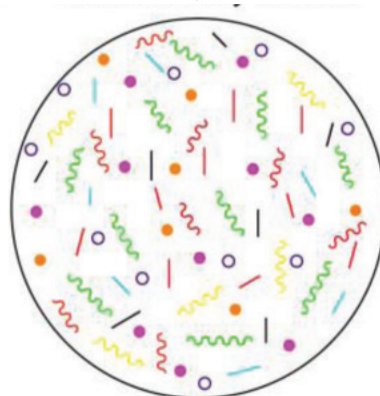
### Human Microbiota, Dysbiosis, and Gut-kidney Axis

In normal conditions, microbiota interacts with the host immune system through the intestine’s mucosa surface. This process allows the host to have normal immune regulatory functions.<sup>1</sup> This protection is known as the “barrier effect” or colonization resistance.<sup>1</sup>

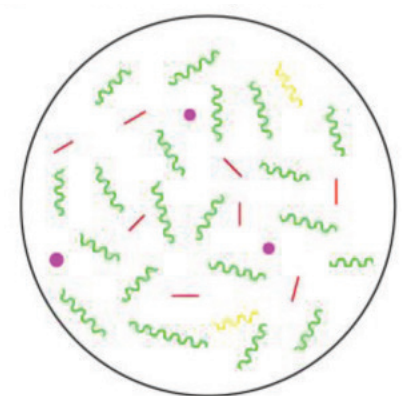
A change in the microbial composition will lead to an imbalance between the beneficial and the potentially harmful bacteria. This imbalance is called “dysbiosis”, defined as an altered gut microbiota.<sup>1</sup> This may be caused by three main causes: an imbalance in the flora itself, changes in the functional composition and metabolic activities of the bacteria, or

changes in the local distribution.<sup>1</sup> Gut is the largest immune organ in the human body with a complex of the mucosal immune system on the inner surface and exposed to the lumen.<sup>2</sup> This mucosal immunity is characterized by individually compartmentalized gut-associated lymphoid tissues (GALTs) that form an interface between the intestinal

A Normal healthy intestine



B Intestinal Dysbiosis



**Figure 1.** Normal and dysbiotic intestinal microbiota.<sup>1</sup>

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lymph and the blood. In normal conditions, these immune responses are in harmony within the physiological range to ensure homeostasis between intestinal microbiota and systemic immune response. Therefore, the gut microbiota has an important role not only in local immune outcomes but also in maintaining systemic physiology.<sup>2</sup>

Dysbiosis is categorized into three types: (1) Loss of beneficial organisms, (2) Excessive growth of potentially harmful organisms, and (3) Loss of overall microbial diversity.<sup>1</sup> Several types of dysbiosis usually occur at the same time.<sup>1</sup> Besides the importance of bacteria count, the variety and diversity of the bacteria are also essential.

Dysbiosis has been discussed to be the root of many human diseases.<sup>1</sup> Gut dysbiosis leads to high intestinal permeability which allows intestinal bacteria and their products to translocate into the host blood circulation.<sup>3</sup> This translocation allows microbiota to interact with distant organs, such as the brain, heart, kidney, and other organs.<sup>1,3</sup> Dysbiosis is considered the root cause of many diseases, such as Alzheimer's disease, inflammatory bowel disease (IBD), obesity, allergic disorders, diabetes mellitus, cancer, obesity, and also systemic disease such as kidney disease.<sup>1,3</sup>

The pathogenic interconnection between gut microbiota and kidney diseases is called the gut-kidney axis.<sup>2,4</sup> It is implicated in a wide range of clinical manifestations such as CKD (chronic kidney disease), AKI (acute kidney injury), hypertension, nephrolithiasis, IgA nephropathy, hemodialysis (HD), and peritoneal dialysis.<sup>4</sup> The gut-kidney axis can be divided into two mechanism pathways, which are the metabolism-dependent and immune pathways.<sup>2</sup> The metabolism-dependent pathway is primarily mediated by the metabolites produced by microbiota and can regulate the physiological function of the host.<sup>2</sup> In the metabolism-dependent pathway, an imbalanced diet plays an important role in disrupting of the gut barrier and increasing gut permeability which induces an influx of endotoxins and uraemic toxins into the kidney and contributes to renal inflammation. In the immune pathway, inflammatory cells, such as lymphocytes, monocytes, and cytokines have a role in communication between the gut and the kidney by activating receptors and

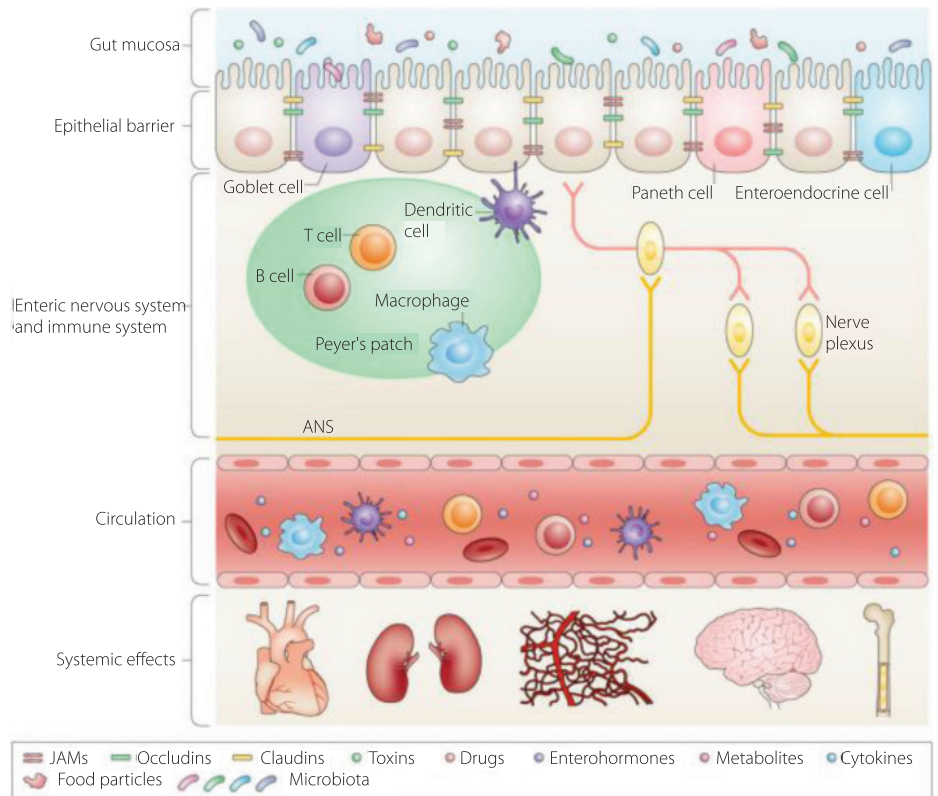


Figure 2. The anatomy of the gut and its interactions with multiple systems.<sup>3</sup>

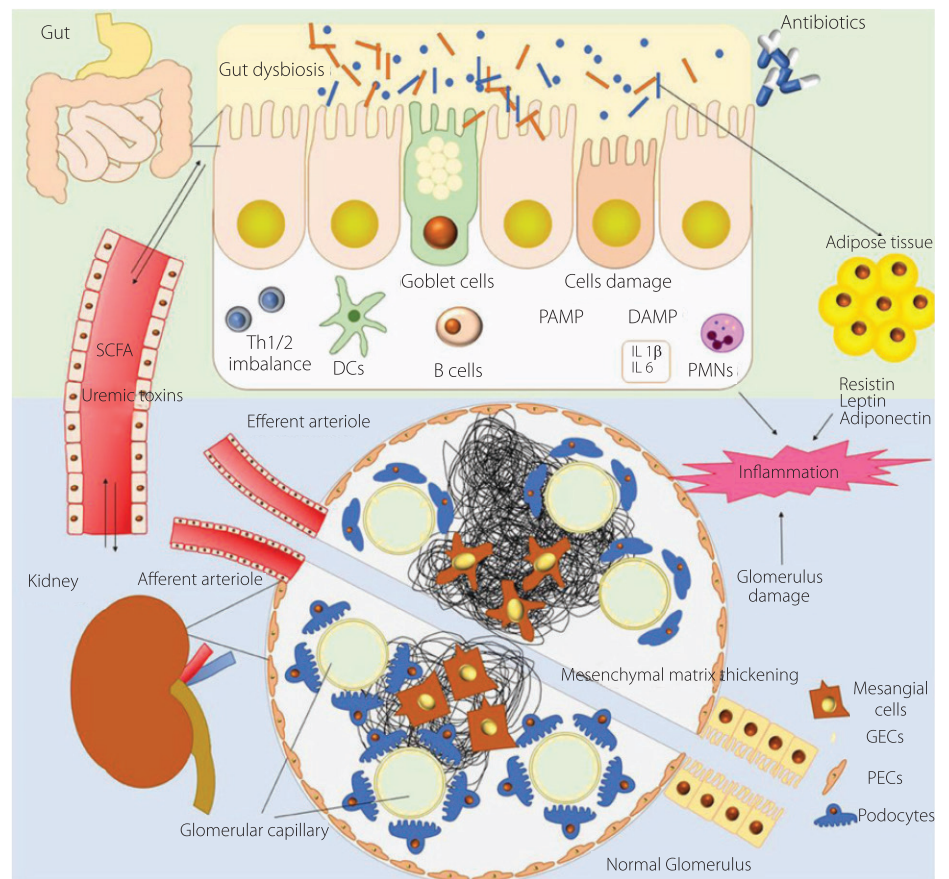


Figure 3. The gut-kidney axis.<sup>4</sup>



inducing renal inflammation.<sup>2</sup> The crosstalk between these two mechanism pathways also has an important role in maintaining the balance of the gut-kidney axis.<sup>2</sup>

**Role of Probiotics, Prebiotics, and Synbiotics in Kidney Diseases**

The homeostasis of the gut microbiota is influenced by many factors; diet is one of the most important factors.<sup>1</sup> Early intervention of gut microbiota is breastfeeding, indicated by different gut microbial compositions between breast-fed and formula-fed babies.<sup>1</sup>

The synbiotic intervention has been used for years as a diet intervention to restore gut microbiota by introducing exogenous bacteria to manipulate and improve endogenous gut flora in the host.<sup>1</sup> Synbiotic is a combination of prebiotic and probiotic intervention.<sup>3</sup> Probiotics are live, mostly gram-positive bacteria that benefit the host by promoting intestinal barrier integrity, preventing bacterial translocation in the gut, and reducing the inflammatory response.<sup>1</sup> The most commonly used bacteria are *Bifidobacterium* and *Lactobacillus*.<sup>1,3</sup> Prebiotics are non-digestible fibers, such as complex carbohydrates, oligosaccharides, fructans, galactans, starch, and polyphenols.<sup>3,4</sup> Prebiotics stimulate the growth of beneficial bacteria by producing short-chain fatty acids (SCFAs), improve the intestinal barrier integrity, regulate inflammation and immune system dysfunction, and modulate the metabolism of glucose and lipid.<sup>4</sup> A combination of both, which is known as synbiotic, possesses both activity.<sup>4</sup>

Chronic kidney disease (CKD) is one of the risk factors for dysbiosis due to low fiber diet, uremia, prolonged colonic transit time, impaired protein assimilation, use of antibiotics, phosphate-binding agents, iron supplementation, decreased physical activity, and other comorbidities.<sup>5</sup> Dysbiosis in CKD patients can increase the production of uremic toxins, one of which is indoxyl sulphate (IS). In addition to the increase in uremic toxins, gastrointestinal symptoms, such as constipation, are also very common in patients undergoing HD.<sup>5</sup> Digestive motility disorders in CKD patients are caused by inflammation, increased uremic toxins, and decreased butyric acid. Inadequate management results in persistent constipation, which can affect

the mental health and quality of life of CKD patients.<sup>5</sup> Studies show that CKD patients undergoing HD have a poorer quality of life and mental health when they are constipated.<sup>5</sup>

Lydia, *et al*, (2022)<sup>5</sup> conducted a randomized double-blind study with a parallel design on CKD patients undergoing HD and experiencing constipation at Dr. Cipto Mangunkusumo Hospital Jakarta with synbiotics compared with a placebo. The synbiotic group (n=27) was given a supplement containing probiotics (*Lactobacillus acidophilus* and *Bifidobacterium longum*) 5x10<sup>9</sup> colony forming unit (CFU) and fructooligosaccharides (FOS) 60 mg 2 capsules a day for 60 days. The results of the study showed that synbiotic supplementation after 60 days had not shown a significant decrease in IS uremic toxin levels (p=0.438). This is thought to occur due to the short duration of therapy.<sup>5</sup> But, synbiotic is effective in improving abdominal (p=0.023), rectal (p=0.025), stool (p=0.047), and overall constipation symptoms (p=0.006) based on the patient assessment of constipation symptoms (PAC-SYM) questionnaire. There was also a significant improvement in the overall quality of life of participants who received synbiotics (p=0.001), which are in improving physical discomfort (p=0.007), psychosocial (p=0.000), and worries/concerns (p=0.001) based on the patient assessment of constipation quality of life (PAC-QoL) questionnaire.<sup>5</sup> Based on this study, it can be concluded that there are significant symptoms and QoL improvement after 60 days of synbiotic supplementation.<sup>5</sup>

A meta-analysis study by Yu, *et al*, (2022)<sup>6</sup> aimed to assess the efficacy of probiotics, prebiotics, and synbiotics on inflammatory factors, uremic toxins, and gastrointestinal (GI) symptoms in end-stage renal disease (ESRD) patients undergoing HD. The result showed that synbiotic was the best intervention in the reduction of CRP (C-reactive protein) and endotoxin, synbiotic was an effective supplement for the alteration of malondialdehyde (MDA) level, and synbiotic was a better treatment in alleviating GI symptoms than placebo.<sup>6</sup> Other meta-analysis and systematic review by Zheng, *et al*, (2020)<sup>7</sup> of 13 RCT studies evaluate the effectiveness of probiotic, prebiotic, or synbiotic supplementation on metabolic parameters in CKD patients. This study focused on metabolic changes and oxidative stress

parameters because CKD is also characterized by those two parameters.<sup>7</sup> The most widely used species in the studies involved were *Lactobacillus* (8/13) and *Bifidobacterium* (7/13). The result showed that there is a significant improvement in C-reactive protein (CRP) level (p=0), total antioxidant capacity (TAC) (p=0.027), glutathione (GSH) level (p=0.000), MDA level (p=0.000), cholesterol level (p=0.003), high-density lipoprotein (HDL) level (p=0.034), triglyceride level (p=0.033), low-density lipoprotein (LDL) level (p=0.042), and that single-strain probiotics did not show a significant reduction of CRP compared to controls.<sup>7</sup>

One of the main goals in CKD patients is to diminish the accumulation of uremic toxins and to slow the progression of renal failure.<sup>8</sup> A prospective observation study<sup>8</sup> with a randomized control and open-label design with a total of 24 stable CKD stage III to V patients, who are not on renal replacement therapy, were enrolled and randomly assigned to 2 groups: (1) Low protein diet and synbiotic supplementation, receiving 3 tablets of synbiotic supplementation daily for 6 months and (2) Control group receiving low protein diet only.<sup>8</sup> The supplement used was a combination of *Streptococcus thermophilus* (15 billion cells/CFU), *Lactobacillus acidophilus* (15 billion cells/CFU), *Bifidobacterium longum* (15 billion cells/CFU), and FOS (100 mg). The result showed that the declining glomerular filtration rate (GFR) during synbiotic supplementation was significantly lower (-11.6±8.6 vs. -3.4±4.6 mL/min per 1.73 m<sup>2</sup> per year, 95% CI -6.45 - -9.86, p<0.001) than those with low protein diet alone.<sup>8</sup> There was no change in serum albumin and body mass index (BMI) reported, which indicated that a low protein diet along with synbiotic supplementation does not lead to severe malnutrition.<sup>8</sup> This study concluded that synbiotic supplementation along with low protein diet delayed the progression of CKD.<sup>8</sup>

One of the major causes of ESRD is diabetic kidney disease (DKD), which is one of the most frequent complications of diabetes. DKD is characterized by abnormal glucose and lipid metabolism, renal hemodynamic changes, oxidative stress, and immune-inflammatory responses.<sup>9</sup> A systematic review and meta-analysis included 10 RCTs to evaluate the impact of using probiotic



supplementation on patients with DKD.<sup>9</sup> Compared to controls, probiotics significantly decreased serum creatinine ( $p=0.004$ ), blood urea nitrogen (BUN) ( $p=0.001$ ), cystatin C ( $p<0.00001$ ), urinary albumin/creatinine ratio (UACR) ( $p=0.004$ ), and sodium (Na) ( $p=0.04$ ) in patients with DKD.<sup>9</sup> Probiotic supplementation has also been shown to improve glycemic control, including reduced levels of fasting plasma glucose (FPG,  $p<0.0001$ ), hemoglobin A1c (HbA1c,  $p=0.002$ ), homeostasis model of assessment-estimated insulin resistance (HOMA-IR,  $p<0.0001$ ), and increased quantitative insulin sensitivity check index (QUICKI,  $p=0.01$ ).<sup>9</sup> Lipid profile was also shown to be better in the probiotics group, including decreased total cholesterol ( $p=0.004$ ) and LDL

( $p=0.0003$ ) levels compared to the control group.<sup>9</sup> Probiotics have also been shown to improve inflammation and oxidative stress parameter by decreasing high-sensitivity CRP ( $p<0.00001$ ), MDA ( $p=0.01$ ), TAC ( $p<0.00001$ ), and GSH ( $p=0.003$ ) levels.<sup>9</sup> This study supports that probiotic supplementation could delay the progression of renal function injury by improving glucose and lipid metabolism and also reducing inflammation and oxidative stress in patients with DKD.<sup>9</sup>

#### Conclusion

The adult gut contains around  $10^{14}$  bacterial cells with more than 1,000 varieties of bacterial species to protect human health. Dysbiosis or imbalance in gut microbiota is the cause

of many diseases, including kidney disease. The pathogenic interconnection between gut microbiota and kidney diseases is called the gut–kidney axis which is implicated in a wide range of clinical manifestations in renal disease. Synbiotic intervention, which is a combination of probiotic and prebiotic, has been used for years as a diet intervention to restore gut microbiota by introducing exogenous bacteria to manipulate and improve endogenous gut flora in the host. Supplementation of prebiotics, probiotics, and/or synbiotics was proven to help improve symptoms, metabolic parameters, and quality of life in patients with kidney disease. The supplementations were also proved to delay the progression of CKD.

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