Escola Superior
de Tecnologia
da Saúde
Politécnico de Coimbra

Sara Rodrigues Martins

FLAVONOIDS-AHR PHARMACODYNAMICS IN THE GUT-IMMUNE-KIDNEY AXIS: THERAPEUTIC INSIGHTS IN CHRONIC KIDNEY DISEASE

Dissertação no âmbito do Mestrado em Farmácia – Especialização em Farmacoterapia Aplicada orientada pela Professora Doutora Sofia Andreia Domingues Viana, pelo Doutor Flávio Nelson Fernandes Reis e pelo Mestre Pedro Miguel Dias Vieira e apresentada na Escola Superior de Tecnologia da Saúde do Politécnico de Coimbra para obtenção do grau de Mestre.

Setembro de 2024

Escola Superior de Tecnologia da Saúde
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This work was performed at the Institute of Pharmacology and Experimental Therapeutics and at the Coimbra Institute for Clinical and Biomedical Research (iCBR), from the Faculty of Medicine of the University of Coimbra.

This work was supported by the European Regional Development Fund (ERDF) through the Operational Program for Competitiveness Factors (COMPETE) and by National funds via Portuguese Science and Technology Foundation (FCT) through strategic projects UIDB/04539/2020 and UIDP/04539/2020.

Agradecimentos

A conclusão desta tese representa o encerrar de um ciclo importante na minha vida profissional e pessoal, e por isso, tenho várias pessoas a quem devo agradecer.

Gostaria de expressar a mais profunda gratidão aos meus orientadores, Professora Doutora Sofia Andreia Domingues Viana, Doutor Flávio Nelson Fernandes Reis e ao Mestre Pedro Miguel Dias Vieira, pela paciência, pelos conhecimentos e pelo apoio incondicional. Foram fundamentais para o desenvolvimento deste projeto e para o meu crescimento individual. Acrescento ainda, um agradecimento especial ao Pedro que foi incansável durante todo este processo, sem a tua paciência, a tua pró-atividade e as tuas palavras de conforto nos momentos mais complicados nada disto tinha sido possível!

Aos meus colegas de trabalho, que me ajudaram sempre que precisei de me ausentar ou de trocar de turno, o meu sincero agradecimento, sem vocês, esta jornada teria sido muito mais difícil.

À minha família, especialmente aos meus pais, Joaquim e Maria de Fátima, e irmã Dina, que sempre acreditaram em mim e me incentivaram a seguir os meus sonhos. A paciência, o amor e o suporte incondicional foram essenciais para a conclusão deste objetivo.

Aos meus amigos, que compreenderam as minhas ausências e ainda assim ofereceram apoio nos momentos mais difíceis. Obrigado por estarem sempre presentes!

Gostaria de agradecer também a todos os professores do mestrado que de alguma forma contribuíram com o conhecimento transmitido durante o ano letivo e pelo papel importante na minha formação ao longo destes anos.

A todos, o meu mais sincero obriga!

Resumo

Contexto: A doença renal crónica (DRC) é atualmente considerada uma condição imuno-mediada com estreita relação com a composição e função da microbiota intestinal (MI). As toxinas urémicas produzidas pela MI, agonistas do receptor AhR, demonstraram agravar a disbiose intestinal, aumentar a hiper-reatividade do sistema imunológico e agravar o dano renal. Por este motivo, o eixo intestino-sistema imune-rim tem ganho destaque devido ao seu papel central na progressão da DRC.

O crescente uso de suplementos alimentares e alimentos à base de plantas medicinais, enriquecidos com flavonoides, deve-se às respetivas propriedades antioxidantes e anti-inflamatórias, bem documentadas na DRC. Apesar da sua natureza pleiotrópica, foi demonstrado que os flavonoides contrariam os efeitos deletérios das toxinas urémicas no rim, mediados por AhR. No entanto, os flavonoides exibem uma atividade dual enquanto agonistas e antagonistas na sinalização via AhR, atuando tanto como indutores quanto inibidores das enzimas metabolizadoras de fármacos reguladas por AhR. A complexidade da sinalização dos flavonoids-AhR é ampliada pelo facto dos recetores pertencerem a um sistema conservado de destoxificação que regula processos-chave do metabolismo de fármacos, em particular os que envolvem as enzimas CYP. Além disso, a atividade flavonoide-AhR parece depender do tecido envolvido, o que dificulta a tradução de modelos preditivos *in silico* e de ensaios *in vitro*, comprometendo com frequência a validade externa dos resultados. Este estudo, focado na disfunção do eixo intestino-imune-rim na DRC, tem dois principais objetivos: 1) caracterizar a atividade dual agonista/antagonista que subsiste às interações flavonoide-AhR; e 2) correlacionar a atividade flavonoide-AhR com os resultados funcionais específicos de cada tecido.

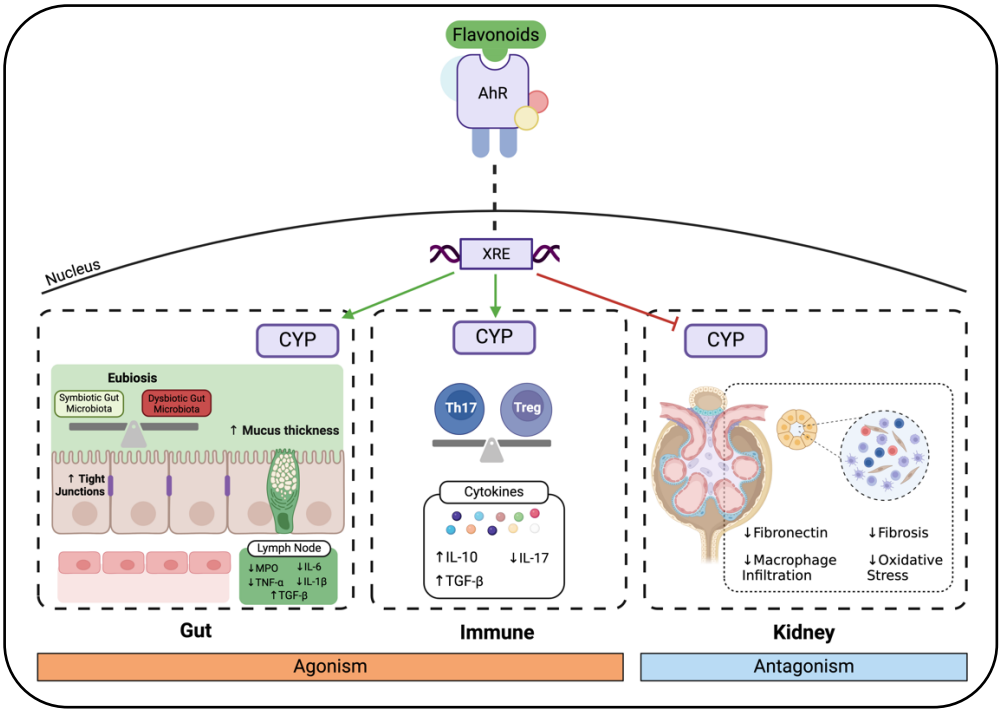
Métodos: Foi realizada uma revisão *scoping* seguindo as diretrizes do PRISMA-ScR, com a seleção dos estudos baseada no framework Participantes-Conceito-Contexto (PCC). Os estudos relevantes foram identificados em bases de dados como a PubMed, Scopus e Web of Science.

Resultados: Dos 154 registos identificados, foram incluídos 23 na análise. Estes estudos avaliaram a sinalização de AhR utilizando 19 flavonoides distintos: 11 avaliados no intestino (por exemplo, Baicalina, Quercetina, Alpinetina), 5 no sistema imunológico (por exemplo, Quercetina, Cinnamtannin D1, Alpinetina, Naringenina) e 6 no rim (por exemplo, Barlerisídeo A, Flavanona Pentahidroxi, Aminoflavona). No intestino, as interações flavonoide-AhR reforçaram o equilíbrio da microbiota intestinal, a barreira de muco e a permeabilidade intestinal, criando um ambiente anti-inflamatório. No sistema imunológico, a sinalização flavonoide-AhR promoveu um equilíbrio favorável entre as células T reguladoras (Treg) e Th17, além de reduzir a inflamação. No rim, os flavonoides mediaram o antagonismo de AhR, levando a efeitos renoprotetores significativos.

Conclusões: Este estudo destaca a natureza dupla dos flavonoides, atuando como agonistas de AhR no intestino e no sistema imunológico, enquanto exercem um papel antagonista no rim. Esses efeitos parecem ser independentes do flavonoide em particular, dado a diversidade de moléculas testadas. Independentemente de atividade agonista ou antagonista subjacente ao tipo de tecidos, as interações flavonoide-AhR conduziram a resultados benéficos de forma consistente. São necessários estudos futuros que melhorem o conhecimento de como as interações flavonoide-AhR podem ser exploradas terapeuticamente no eixo intestino-imune-rim para retardar a progressão da DRC e controlar a inflamação intestinal.

Palavras-chave: Flavonóides; Recetor dos Aril Hidrocarbonetos (AhR); Farmacodinâmica; Intestino-Sistema Imune-Rim; Doença Renal Crónica

Resumo Gráfico



Abstract

Context: The scientific community increasingly recognizes chronic kidney disease (CKD) as an immune-mediated condition, closely associated with disruptions in gut microbiota composition and function. Uremic metabolites produced by the gut microbiota, well-known AhR agonists, have been shown to worsen gut dysbiosis, heighten immune system hyperreactivity, and exacerbate renal damage. Accordingly, the gut-immune axis has gained attention for its potential central role in CKD pathophysiology.

The growing use of dietary supplements and medicinal plant-based foods enriched with flavonoids reflects their well-documented antioxidant and anti-inflammatory properties in CKD. Regardless their pleiotropic nature, flavonoids were found to counteract AhR-dependent uremic toxin deleterious role in the kidney. Still, flavonoids are known to exhibit dual agonistic and antagonistic activity in AhR signaling, functioning as both inducers and inhibitors of AhR-regulated drug-metabolizing enzymes. The complexity of flavonoid-AhR signaling is heightened by its role in a conserved detoxification system that regulates key drug metabolism processes, particularly those involving CYP enzymes. Furthermore, the tissue-specific nature of flavonoid-AhR activity complicates the translation of predictive *in silico* models and *in vitro* experiments, often undermining the external validity of the results. This study, focusing the dysfunction of the gut-immune-kidney axis in CKD, has two main goals: 1) to characterize the dual agonistic/antagonistic activity of flavonoid-AhR interactions; 2) to correlate flavonoid-AhR activity with tissue-specific functional outcomes.

Methods: A scoping review was conducted following the PRISMA-ScR guidelines, with studies selected based on the Participants-Concept-Context (PCC) framework. Relevant studies were identified through comprehensive screening of databases such as PubMed, Scopus, and Web of Science.

Results: Of the 154 records identified, 23 were included in the analysis. These studies assessed AhR signaling using 19 distinct flavonoids: 11 evaluated in the gut (e.g., Baicalein, Quercetin, Alpinetin), 5 in the immune system (e.g., Quercetin, Cinnamtannin D1, Alpinetin, Naringenin), and 6 in the kidney (e.g.,

Barleriside A, Pentahydroxy Flavanone, Aminoflavone). In the gut, flavonoid-AhR interactions were found to reinforce gut microbiota balance, enhance the mucus barrier, and improve intestinal permeability, creating a predominantly anti-inflammatory environment. In the immune system, flavonoid-AhR signaling exhibited significant immunomodulatory effects, promoting a favorable Treg/Th17 balance and reducing inflammation. In the kidney, flavonoids mediated AhR antagonism, leading to significant renoprotective effects.

Conclusions: This study highlights the dual nature of flavonoids, acting as AhR agonists in the gut and immune system, while serving as antagonists in the kidney. These tissue-specific effects appear to be independent of the particular flavonoid, given the diversity of molecules tested. Regardless of their tissue-specific agonist or antagonist activity, flavonoid-AhR interactions consistently produced beneficial outcomes. Further research is needed to better understand how these interactions can be therapeutically harnessed in the gut-immune-kidney axis to slow CKD progression and manage gut inflammation.

Keywords: Flavonoids; Aryl Hydrocarbon Receptor (AhR); Pharmacodynamics; Gut-Immune System-Kidney; Chronic Kidney Disease

Graphical Abstract

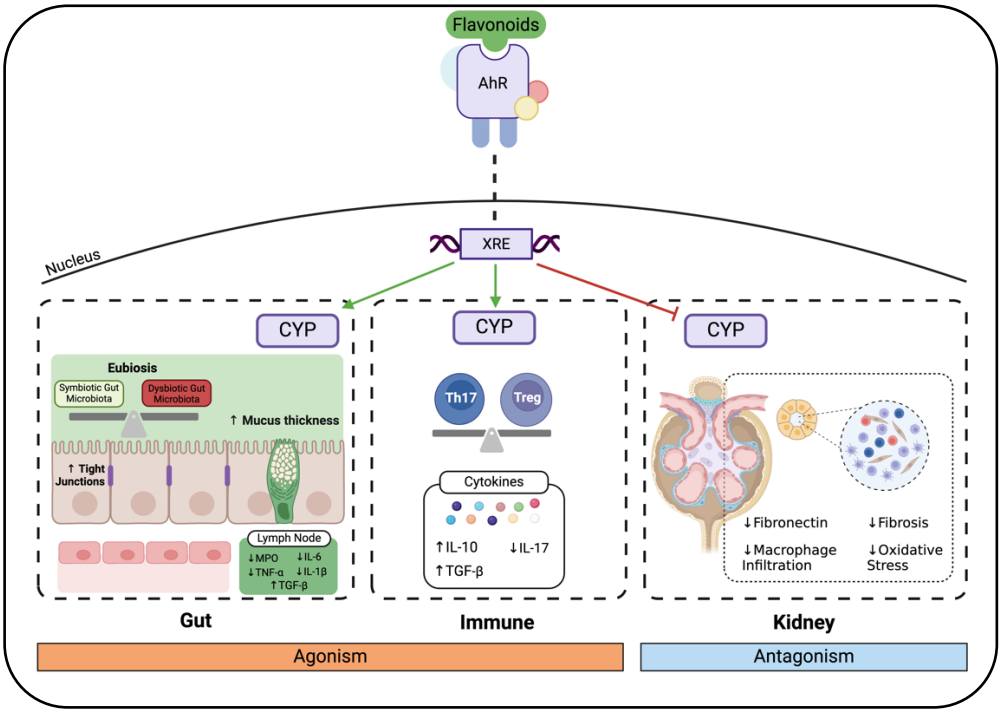


Table of Abbreviations

ACE	Angiotensin-Converting Enzyme
AhR	Aryl hydrocarbon Receptor
ARNT	Aryl hydrocarbon Receptor Nuclear Translocator
AhRR	Aryl hydrocarbon Transcriptional Repressor
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DC	Dendritic Cells
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
GALT	Gut-associated Lymphoid Tissue
GI	Gastrointestinal
GBM	Glomerular Basement Membrane
GFR	Glomerular Filtration Rate
GM	Gut Microbiota
HD	Hemodialysis
HFHS	High fat/High Sugar Diet
HIE	High-Intensity Exercise
IBD	Inflammatory Bowel Disease
IEC	Intestinal Epithelial Cell
IS	Indoxyl Sulphate
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KRT	Kidney Replacement Therapy
KTR	Kidney Transplant Recipients
LBD	Ligand Binding Domain
LBP	LPS-binding Protein
LPS	Liposaccharides
NASH	Non-alcoholic Steatohepatitis
OSF	Open Science Framework
PAG	Phenylacetylglutamine
PD	Peritoneal Dialysis
PKD	Polycystic Kidney Disease

pCS	p-Cresyl Sulfate
PTH	Parathyroid Hormone
RRT	Renal Replacement Therapy
SCFA	Short-Chain Fatty Acids
TJ	Tight Junctions
TLR	Toll-like Receptors
TMAO	Trimethylamine N-oxide
XRE	Xenobiotic Response Elements

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Chapter I – Introduction

1.1 Chronic Kidney Disease (CKD): An Overview

1.1.1 Renal physiology: Principles, structure and function

Kidneys are fundamental components of the excretory system and are involved in several physiologic functions via regulatory, excretory, and endocrine activities (Imenez Silva & Mohebbi, 2022; Reddi, 2020). For example, the renal system is responsible for the balance of composition and volume of body fluids, regulates acid-base equilibrium, and is also involved in the control of blood pressure. Additionally, kidneys also participate in the elimination of several metabolic waste products by urine excretion. Finally, they produce vital hormones such as renin, erythropoietin, and active vitamin D3 (calcitriol). All these diverse functions are closely connected with their macro and microscopic structure.

The kidney structure is complex and divided into three main regions: the pelvis, cortex, and medulla (**Figure 1a**). Therefore, they comprise over 1 million nephrons, the basic unit of renal filtration (**Figure 1b**), composed of a renal corpuscle and renal tubules (Gopalan & Kirk, 2022). The renal corpuscle contains the glomerulus and the Bowman's capsule that surrounds and collects the filtrate from blood (**Figure 1c and 1d**)(Murray & Paolini, 2023).

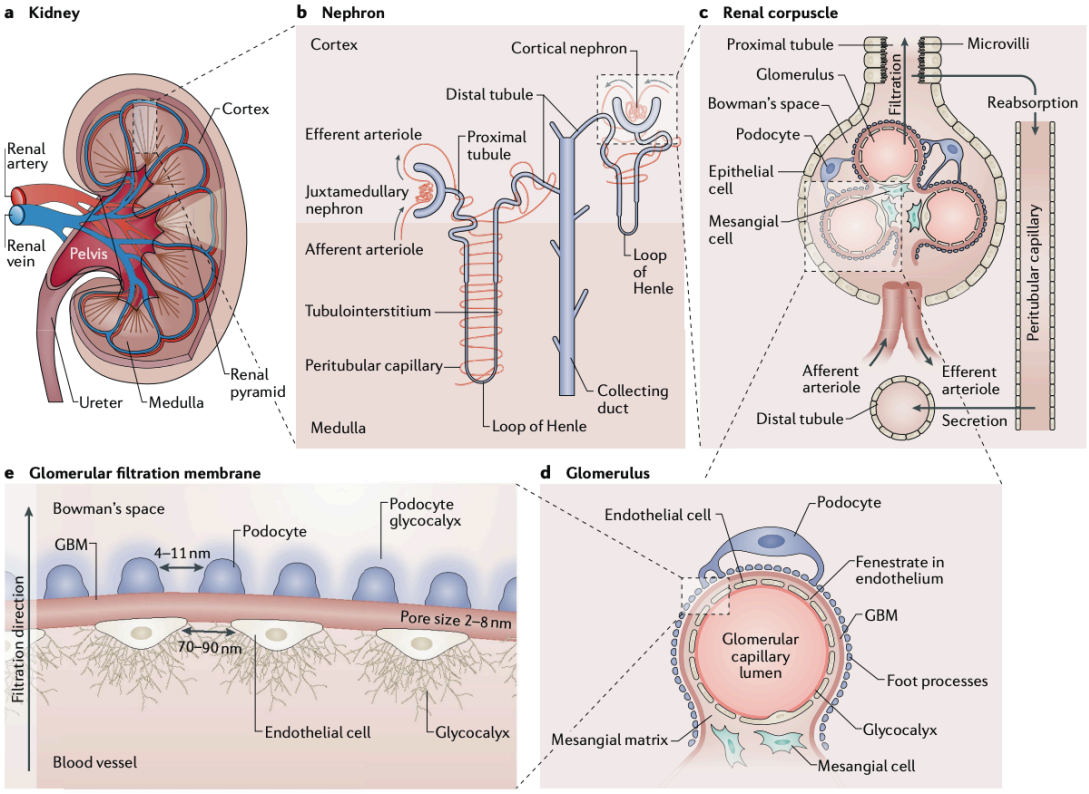


Figure 1. Kidney physiology and glomerular filtration barriers (Taken from Du et al., 2018).

The glomerulus is surrounded by podocytes and mesangial cells (Akilesh, 2014). The capillary's permeable endothelium permits acellular blood filtrate to pass, while podocytes cover the vessel with foot processes, contributing to the formation of the glomerular basement membrane (GBM) in conjunction with the endothelium.

Consequently, the filtrate that permeates the endothelial pores passes through the glomerular membrane and is collected in Bowman's space, an initial reservoir where primary filtrate is conducted down to the tubular nephron (Preuss, 1993).

The epithelial tubule of the nephron is divided into four segments: proximal tubules, loop of Henle, distal convoluted, and the connecting tubule. The proximal tubule is involved in multiple functions, including the reabsorption of important solutes such as glucose, protein, and amino acids that are filtered against through a damaged glomerular filter. On the other hand, the loop of Henle and distal portions of the tubular nephron primarily focus on regulating water resorption and electrolyte balance (Akilesh, 2014).

Any disturbance of these fundamental principles, structures, and functions can lead to diverse renal disorders and/or CKD (**Table 1**).

Table 1: Primary functions of the kidney and consequences of impaired function. (Taken from Chan, 2014)

Renal Function	Normal	Impaired
Excretory	Metabolic waste products, especially protein waste (e.g., creatinine, urea, ammonia, uric acid), other metabolites and toxins	**- Accumulation:** Uremia, buildup of fluids, electrolytes, metabolites, toxins
Regulation	• Acid-base balance • Homeostasis • Fluid and electrolyte balance • Blood pressure (nitric oxide, renin-angiotensin system) • Metabolism (glucose and lipids)	**- Uncontrolled:** • Acidosis • Hypertension • Glucose and lipid abnormalities
Endocrine (hormonal balance)	• Parathyroid hormone (PTH), vitamin D, calcium and phosphate metabolism • Erythropoietin/hemoglobin synthesis • Degradation of hormones, e.g., insulin, glucagon, PTH	**- Hormonal imbalance:** • Osteodystrophy • Anemia • Glucose intolerance

1.1.2 CKD: Epidemiology

CKD is known as a progressive, complex, and multifactorial disorder characterized by a gradual decline in kidney function. (Kovesdy, 2022) It is recognized as one of the most severe health problems, with a significant influence on morbidity, mortality, and healthcare expenses (Luyckx et al., 2020).

Recent estimations show a worldwide estimated prevalence of 10%, which represents more than 850 million people with this condition **(Figure 2)** (Kovesdy, 2022).

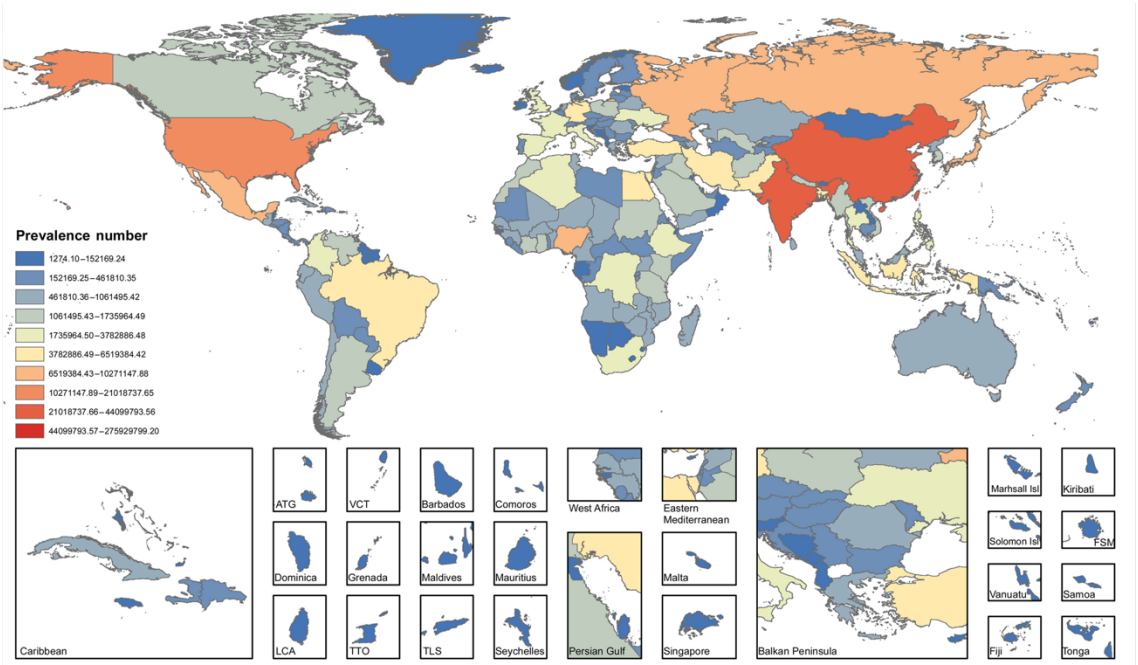


Figure 2. Global prevalence of CKD. (Taken from Xie et al., 2018)

It is important to point out that CKD prevalence also differs across countries and is influenced by specific socio-demographic characteristics such as age, gender, and ethnicity (Khan et al., 2018). The CKD incidence also increases with age, but this condition can also occur across all age groups, even in children and adolescents (Nitta et al., 2014; Warady et al., 2015).The CKD burden is also more prevalent in developed countries like the US, Europe, and parts of Asia because of the impact of lifestyle, health care, and environmental exposure (Hill et al., 2016).

CKD currently occupies the 12th position in causes of death, but it is believed to ascend to the 5th position by 2040 (Kovesdy, 2022). CKD-related deaths account for approximately 1.2 million annually, equating to 15 deaths every minute, reflecting the disease's impact on global mortality rates (Bikbov et al., 2020).

CKD can lead to the requirement of renal replacement therapy like dialysis or kidney transplantation. Recent data shows that over 2 million individuals are dependent on dialysis or kidney transplants for survival, but this is just a fraction of those who need treatment **(Figure 3)** (Himmelfarb et al., 2020). Kidney transplantation is considered the most effective intervention for end-stage renal disease (ESRD), the severe form of CKD (Eckardt et al., 2009). However, organ shortages, financial limitations, and logistical complexities difficult this alternative. Therefore, despite 100,000 kidney transplants being performed per year, there are

still long waiting periods and disparities in access (Garcia et al., 2012) (Mudiayi et al., 2022).

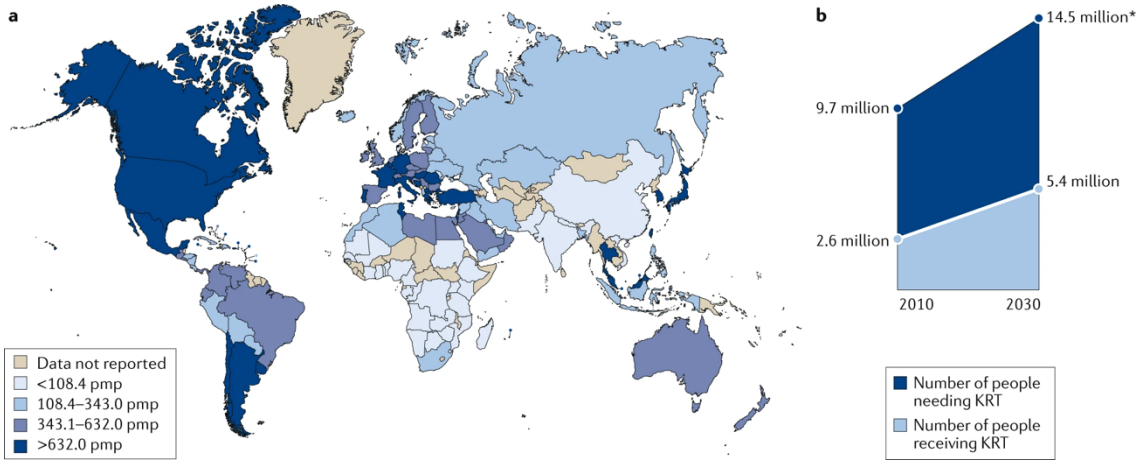


Figure 3. Current and projected prevalence of kidney failure requiring kidney replacement therapy (KRT). **a**) Global prevalence of chronic dialysis. **b**) Estimated worldwide need and projected capacity for KRT by 2030. pmp, per million population. (Taken from Himmelfarb et al., 2020)

Furthermore, the economic impact of CKD is substantial, with healthcare expenditures escalating rapidly to manage the disease and its complications. These costs involve expenses related to diagnostic tests, medications, hospitalizations, and renal replacement therapy (Wing-Shing Fung et al., 2024). Moreover, CKD is involved in a considerable societal burden, resulting in lost productivity, disability, and diminished quality of life for affected individuals and their families (Bello et al., 2023).

In Portugal, CKD presents a significant healthcare challenge, mirroring global trends. Studies like CaReMe, PREVADIAB, and RENA offer valuable insights into CKD prevalence and impact within the Portuguese population (Gardete-Correia et al., 2010; Sundström et al., 2022; Vinhas et al., 2020). For instance, the RENA study revealed that approximately 20% of adults over the age of 65 in Portugal have some degree of kidney impairment, emphasizing the urgency of proactive management strategies (Vinhas et al., 2020).

These epidemiological insights highlight the pressing need for proactive management approaches to mitigate global CKD's escalating burden.

1.1.3 CKD: Clinical Presentations and Pathophysiology

The Kidney Disease: Improving Global Outcomes (KDIGO) international guidelines define CKD as defects in kidney structure or function persistent for more than 3 months (Eckardt et al., 2009). Specifically, these are defined with a glomerular filtration rate (GFR) below 60 mL/min per 1.73 m^2, and/or other markers for kidney damage.

Recently updated, these guidelines divide the refined classification of CKD into different stages based on (G1, G2, G3a, G3b, and G5) and albuminuria levels (A1, A2, A3), which are recognized markers of renal excretory function and glomerular barrier integrity **(Figure 4)** (Eckardt et al., 2009).

				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30-300 mg/g 3-30 mg/mmol	> 300 mg/g > 30 mg/mmol
GFR categories (ml/min/1.73m²) Description and range	**G1**	Normal or high	≥ 90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	< 15			

Figure 4. The KDIGO classification of CKD by GFR and albuminuria categories. Green, low risk; yellow, moderately increased risk; orange, high risk; red, very high risk. (Taken from KDIGO work group 2024 Eckardt et al., 2009)

The clinical manifestations of CKD are variable and dependent on the many stages of the disease, varying from asymptomatic to pronounced symptoms across the different stages **(Figure 5)** (Collins et al., 2020; Webster et al., 2017).

Figure 5. Schematic diagram showing the association between CKD progression and clinical and economic burden.(Taken from Evans et al., 2022).

Many studies have shown that CKD often presents with minimal symptoms in its early stages. In many cases, are only detected by routine screening tests or when investigating other health problems. However, in advanced stages, CKD patients present several symptoms indicative of defective kidney function (Chen et al., 2019). The most common of these symptoms are alterations in urinary patterns, which include increased urination frequency, especially nocturia, hematuria, and foamy urine, which is indicative of albuminuria (Girgin & Arici, 2023). These urinary symptoms often prompt further evaluation to determine the underlying cause of renal dysfunction.

In addition, advanced stages of CKD are also characterized by systemic symptoms, which include fatigue, weakness, poor appetite, nausea, vomiting, and unintentional weight loss that can affect several organ systems (Collins et al., 2020; Girgin & Arici, 2023; Webster et al., 2017)

CKD patients are also more susceptible to developing cardiovascular complications such as hypertension, which can lead to symptoms such as headaches, chest pain, or shortness of breath (Jankowski et al., 2021; Kalantar-Zadeh et al., 2022). Nevertheless, CKD patients are also more susceptible to other cardiovascular diseases such as heart failure, coronary artery disease, and stroke (Subbiah et al., 2016; Warrens et al., 2022).

Metabolic disorders are also characteristic features of CKD and can occur as electrolyte imbalances, such as high potassium levels (hyperkalemia) or metabolic acidosis (Cook et al., 2021; Lin et al., 2022).

Neurological symptoms may also occur in CKD, which can include peripheral neuropathy, or other cognitive impairments (Arnold et al., 2016).

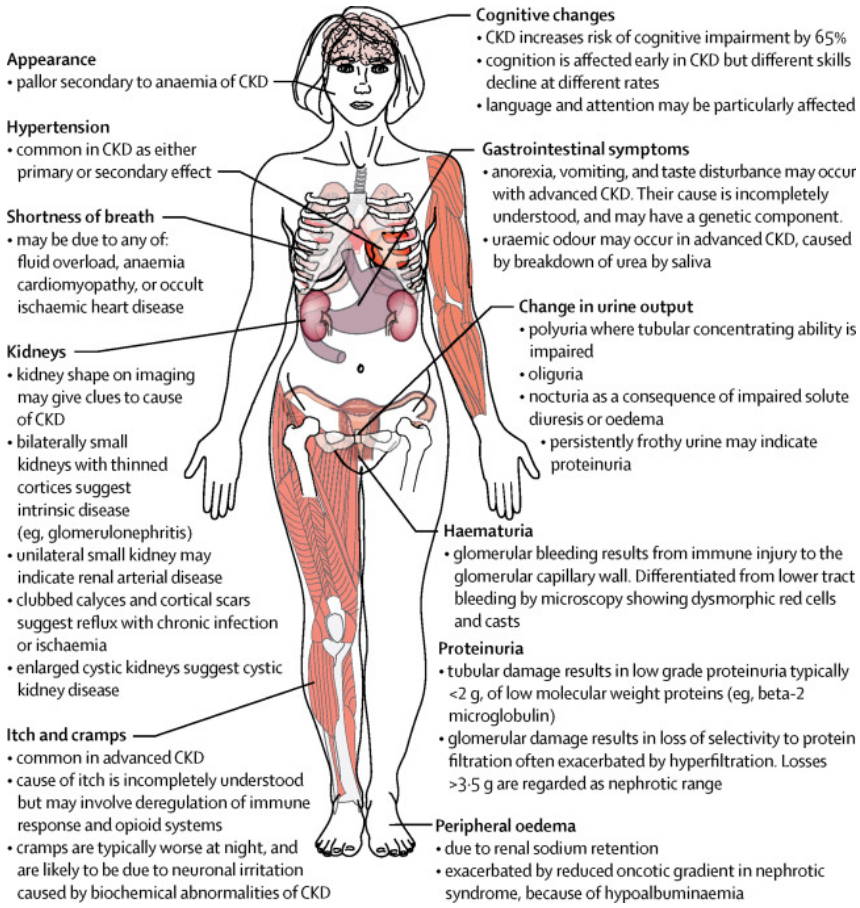


Figure 6. Symptoms and signs of CKD. (Taken from Webster et al., 2017)

The clinical symptoms of CKD directly mirror the underlying pathophysiological changes. The CKD pathophysiology is composed of a variety of complex processes and mechanisms involved in structural and functional alterations of the kidney. The pathological hallmark manifestation is renal fibrosis, which is involved in diverse structural alterations, including glomerulosclerosis, tubular atrophy, and interstitial fibrosis **(Figure 7)** (Webster et al., 2017).

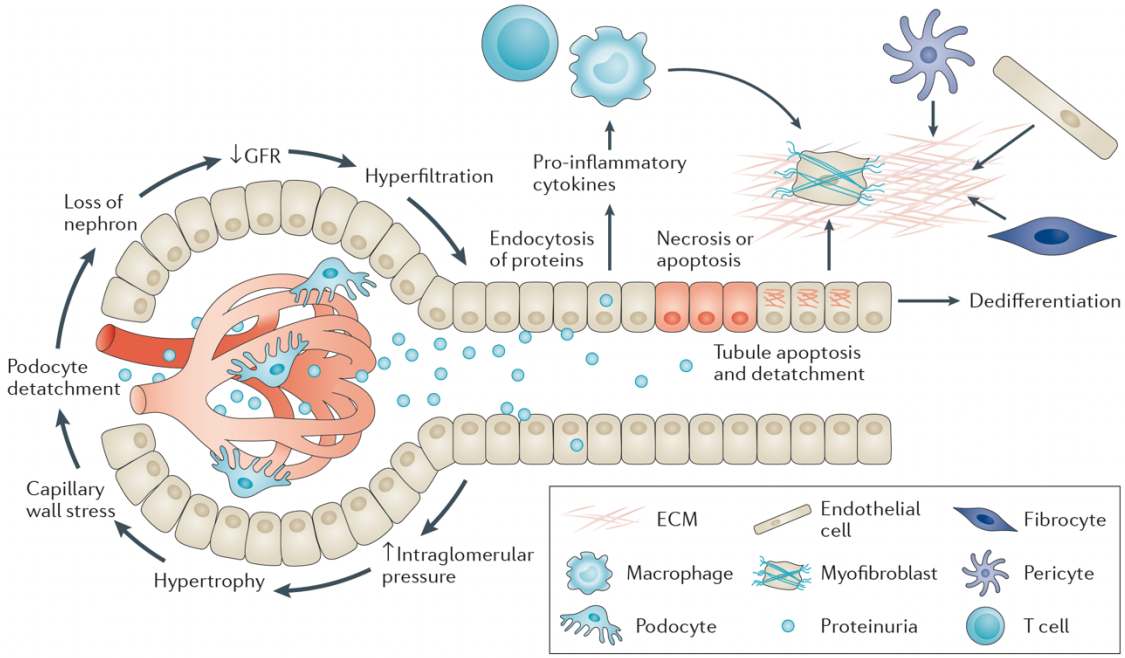


Figure 7. Development of renal fibrosis (Taken from Edeling et al., 2016).

Glomerulosclerosis is caused by the damage and dysfunction of the endothelium, proliferation of smooth-muscle cells and mesangial cells, ultimately leading to podocyte loss (Hu et al., 2024; Webster et al., 2017). These will later trigger several pathological alterations that include the activation of endothelial cells and the invasion of inflammatory peripheral cells such as macrophages and foam cells (Ameer, 2022).

Tubular atrophy and interstitial fibrosis are intimately linked to GFR and proteinuria. Unfiltered urinary proteins, including complement, cytokines, and albumin, stimulate tubular epithelial cells to produce inflammatory mediators like reactive oxygen species and chemokines (Li et al., 2021). This induces the infiltration of inflammatory cells into the renal interstitium and activates the interactions between interstitial myofibroblasts (Sheng & Zhuang, 2020). Moreover, as fibrosis progresses, the cells of epithelium will lose regenerative ability, leading to tubular atrophy and non-functional glomerulus.

Furthermore, CKD affects the function of cells involved in collagen degradation namely collagen I and II, basement membrane proteins, proteoglycans, and glycoproteins (Miguel & Rojo, 2023).

1.1.4 CKD: Comorbidities and complications

CKD patients often exhibit several comorbidities and complications that are closely connected with the negative impact of the disease (Bello et al., 2017). The most common complications are cardiovascular diseases (CVD) which greatly affects most of the patients. Some reports show that CKD patients present a five- to ten-fold increased risk of developing CKD, responsible for 40% to 50% of all deaths in CKD (Vondenhoff et al., 2024). The second most common complication among CKD patients is hypertension, whose prevalence varies from 60 to 90% depending on the stage and etiology of CKD (Ku et al., 2019). Besides, hypertension among CKD patients is also modulated by additional factors such as volume overload, salt retention, endothelial dysfunction, and hormonal changes that contribute to kidney damage and CKD progression (Ku et al., 2019).

Anemia is a frequent complication of CKD and occurs due to a lack of erythropoietin factor produced by the kidneys together with iron deficiency and inflammation (Hain et al., 2023). The prevalence of anemia in CKD patients is estimated at 15.4% and increases in the more advanced stages of CKD (Hain et al., 2023). This complication contributes to fatigue, reduced quality of life, and even increased cardiovascular risk.

Furthermore, mineral bone disorder is also recognized as a serious complication and is provoked due to metabolic changes in calcium, phosphate, PTH, and vitamin D metabolism (Bello et al., 2017). Eventually, the decreased endocrine function by the kidney can also lead to calcitriol deficiency and result in hypocalcemia. This condition is also provoked by reduced calcium absorption by the gut due to insufficient levels of active vitamin D and leads to calcium release by the bone, which could result in bone pain, fractures, and vascular calcification (Bello et al., 2017).

Neurologic complications also occur in CKD and can include cognitive dysfunction, stroke, peripheral and autonomic neuropathy (Arnold et al., 2016). Metabolic complications are other comorbidities that can be observed in CKD patients (Moranne et al., 2009). Metabolic acidosis is a prevalent complication of CKD that leads to a low pH level of the blood and is often involved in the severity of bone diseases (Moranne et al., 2009).

Importantly, CKD patients often have gastrointestinal complications, such as constipation and diarrhea, which involves increased uremic toxins levels and alterations in the intestinal microbiota (detailed in section 1.2.2) (Lew & Radhakrishnan, 2020).

1.1.5 CKD: Causes and Risk Factors

CKD comprises several risk factors that interact with each other and contribute to both disease onset and progression. Here, behavioral choices, cardiovascular health, and metabolic factors, among others are examples of CKD's multifactorial nature (**Figure 8**) (Hannan et al., 2021).

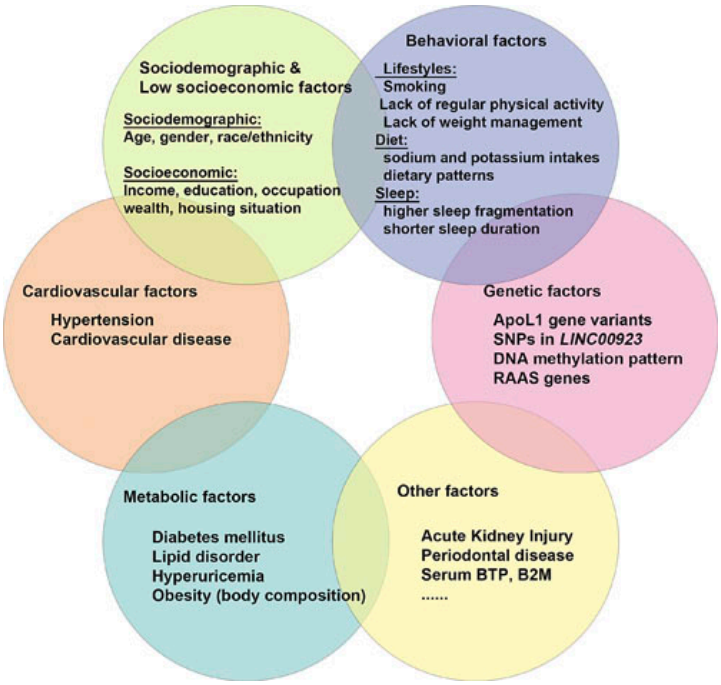


Figure 8. Risk factors associated with CKD. Risk factors associated with CKD are summarised into the following categories: (1) socio-demographic and economic, (2) behavioral, (3) cardiovascular, (4) metabolic, (5) genetic, and (6) newly defined factors. Details of each category were listed in each circle. (Taken from Liu et al., 2023).

As previously mentioned, a significant aspect of CKD's complexity is its relationship with hypertension and diabetes. These conditions are both causes and consequences of CKD, affecting almost two-thirds of CKD patients. Notably,

diabetic kidney disease is among the most common complications of diabetes, affecting approximately 40% of patients with Type 2 Diabetes Mellitus.

Socio-demographic factors such as age, gender, race/ethnicity, and education are also strongly connected to CKD development (Hannan et al., 2021). Age is one of the main risk factors of this group, particularly over 65 years old. Despite being more prevalent in women, men are more prone to progress to advanced CKD stages (Hill et al., 2016). Race and ethnicity are also important risk factors, where African American, Hispanic, and Indigenous communities are more affected due to social and genetic factors, as well as lack of healthcare access (Norton et al., 2016).

Economic factors, including income, employment status, and healthcare access, further exacerbate CKD outcomes due to limited access to preventive care and healthcare resources (Garcia-Garcia et al., 2015).

Genetic factors are also important risk factors. For example, autosomal dominant polycystic kidney disease (PKD) is caused by mutations in the PKD1 or PKD2 genes, and Alport syndrome is associated with mutations in type IV collagen genes (COL4A3, COL4A4, and COL4A5), which affects the filtration systems of the kidney (Cosgrove & Liu, 2017; Harris & Torres, 2022).

Behavioral factors are also recognized to drive the onset and progression of CKD. For instance, tobacco use is associated with an increased risk of CKD development through several mechanisms as pro-inflammatory state, oxidative stress, endothelial dysfunction, and glomerulosclerosis. In addition, a high intake diet of sugars, salts, and fats from red meats and protein alters several of the body's metabolic processes which predisposes to CKD development (Odermatt, 2011). Therefore, lifestyle modifications and public health interventions are key components in CKD management and improve disease outcomes.

1.1.6 CKD: Therapeutic management

The therapeutic options for CKD are still limited and without a definitive cure, which enhances the importance of early diagnosis and appropriate management approaches (Stevens et al., 2024). CKD therapeutic management is focused on the

treatment of the underlying cause and the implementation of secondary preventive measures that are fundamental to alleviate symptoms, delay disease progression, and reduce the risk of developing associated complications (Yan et al., 2021).

The treatment of CKD is determined by the stage of CKD and varies according to the use of pharmacological, and non-pharmacological approaches (**Figure 9**), among which non-pharmacological approaches like lifestyle and dietary modifications are in the first line because they improve cardiometabolic health and have favourable long-term effects on the kidney (*Guideline on Nutrition in CKD*, 2019; Ndumele et al., 2023).

After progression to advanced CKD, renal replacement therapy consisting of dialysis or kidney transplantation is required. In this case, incremental transition to peritoneal or hemodialysis therapy might be a preferred approach to preserve residual kidney function while reducing the frequency of dialysis, although clinical trials are needed to examine this and other alternative dialysis transition strategies (Obi et al., 2016).

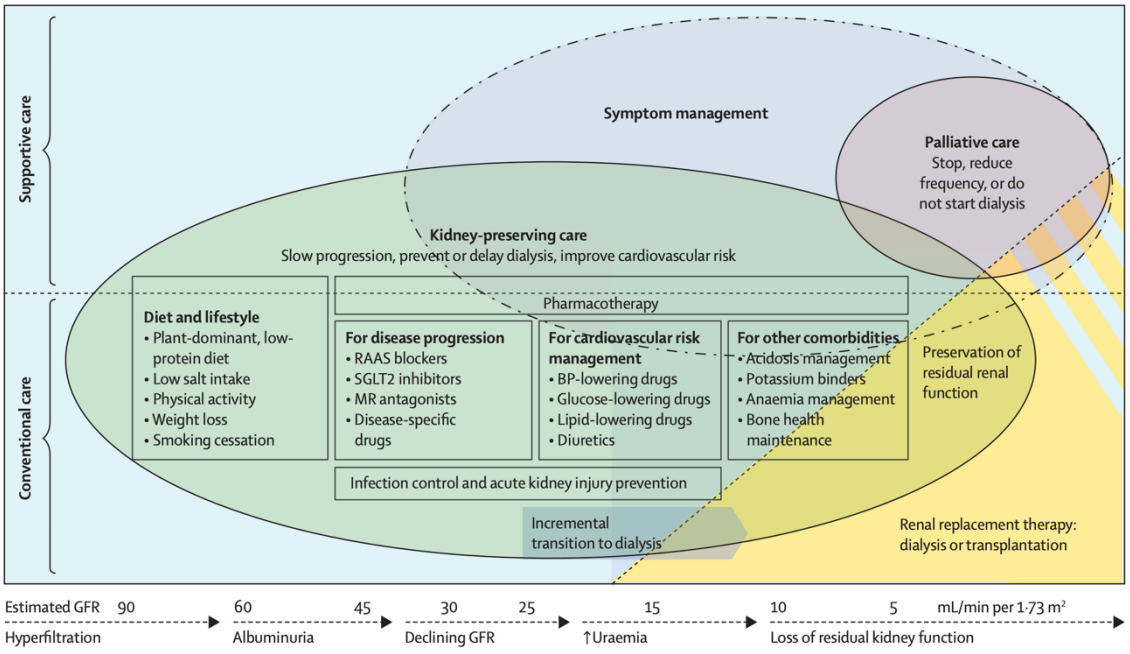


Figure 9. Conservative and preservative management of chronic kidney disease without dialysis or renal transplantation. (Taken from Kalantar-Zadeh et al., 2021).

1.1.6.1 Dietary interventions (Renal diet)

Dietary interventions are a key factor in the long-term control of CKD. In the early stages of CKD, the targets of dietary management are primarily aimed at slowing the advancement of kidney disease and the lowering of cardiovascular risk. In contrast for those patients who are on dialysis, the attention turns to the management of electrolyte imbalances and the treatment of or the avoidance of protein-calorie imbalances (Rhee et al., 2023).

Consequently, dietary restrictions and international guidelines claim for modifications in the macro- and micro-nutrient intake, namely, protein, sodium, potassium, and phosphorous, as well as other specific macronutrients such as fatty acids and sugars (**Table 2**) (Ikizler et al., 2020).

Table 2: Nutritional requirements for patients with non-dialysis CKD according to 2020 Kidney Disease Outcomes Quality Initiative (KDOQI Guidelines) (Ikizler et al., 2020).

	ND-CKD stage 3-5	Transplantation
Energy (kcal/kg ideal weight/day)[a]	25-35	25–35 in maintenance KTR 25 (obesity) 35–40 for the first 4 weeks after transplantation
Protein (g/kg/day)[a,b]	0.55–0.60 or 0.28–0.43 plus keto/amino acid supplementation 0.80–0.90 (diabetes) 1.0 (illness)	0.8
Sodium (g/day)	<2.3	<2.3
Potassium[c]	Adjust dietary potassium intake to maintain serum potassium within the normal range	Adjust dietary potassium intake to maintain serum potassium within the normal range
Calcium (mg/day)	800–1,000d	Adjust dietary potassium intake to maintain serum potassium within the normal range
Phosphorus	Adjust dietary phosphorus intake to maintain serum phosphate levels in the normal range	Adjust dietary phosphorus intake to maintain serum phosphate levels in the normal range
Fiber (g/day)	25–38	25–38
Vitamin D (IU/day)	600–800	600–800
Vitamin B12 (µg/day)[f]	2.4	2.4
Folic acid (µg/day)[f]	400	400
Vitamin C (mg/day)[f]	90 (M), 75 (W)	90 (M), 75 (W)
Vitamin E (mg/day)[f]	15	15
Vitamin K (µg/day)[f]	120 (M), 90 (W)	120 (M), 90 (W)
Selenium (µg/day)[f]	55	55
Zinc (mg/day)[f]	11 (M), 8 (W)	11 (M), 8 (W)

ND-CKD, non-dialysis chronic kidney disease; KTR, kidney transplant recipients; M, men; W, women.
[a] Energy and protein intake should be adapted to age, gender, level of physical activity, body composition, weight status goals, CKD stage, and concurrent illness or presence of inflammation to maintain normal nutritional status. If present, priority should be given to the correction of protein-energy wasting.
[b] Not enough evidence to make a statement on protein sources.
[c] Guidelines do not suggest specific dietary K range (restriction per se may favour other nutrient deficiencies). Before restricting healthy foods, other causes of hyperkalemia (acidosis, constipation…) should be corrected.
[d] Including dietary calcium, calcium supplementation, and calcium-based phosphate/potassium binders.
[e] When making decisions about phosphorus restriction treatment, consider the bioavailability of phosphorus sources (e.g., animal, vegetable, additives).
[f] No specific recommendations are provided by KDOQI guidelines. In the absence of evidence specific to persons with CKD, recommended Dietary Allowances for Adult General Population should apply.

Traditionally, renal diets recommend a protein intake of 0.55–0.60 g/kg/day for stable patients with non-dialysis CKD 3–5 dialysis, which can be lowered to 0.28–0.43 g/kg/day with supplementation of 7–15 g/day of keto analogs and essential amino acids (Ikizler et al., 2020). It has also been advised to take a caloric maintenance of 25–35 kcal/kg/day to maintain a neutral or positive nitrogen balance resulting from inflammation and CKD comorbidities. However, these adjustments are individualized according to the patient's characteristics such as age, lean body mass, exercise, and the cause of kidney disease (Kovesdy et al., 2013).

For recipients of kidney transplantation, the nutritional management is individualized time-dependently. Within the perioperative period, KTRs, (kidney transplant recipients) must control their energy intake not below 35-40 kcal/kg and protein not lower than 1.4 g/kg for not less than 4 weeks after kidney transplantation to compensate for the increase in protein catabolism following steroid use and surgical stress (Ikizler et al., 2020).

Sodium restriction (<2.3 g/day) is recommended for the management of CKD to achieve better volume control, blood pressure reduction, and proteinuria in synergy with pharmacologic interventions. Similarly, CKD patients may benefit from a daily fiber intake of 25–30 g/day or more, aligning with general population recommendations (Ikizler et al., 2020).

Calcium is limited to an intake of 800–1,000 mg/day in adults with CKD 3–4 who do not are supplemented with active vitamin D analogs and phosphate binders (Ikizler et al., 2020).

The consumption of an adequate fiber intake is also a challenge in the context of CKD due to potassium and phosphorus restrictions. Thus, these dietary restrictions are hard to implement in clinical practice and are associated with lower patient adherence (Nielsen et al., 2018).

1.1.6.2 Pharmacological Approaches

Pharmacological approaches in CKD tend to be focused on the control of the risk factors. Consequently, these interventions, accompanied by lifestyle modifications are mainly focused on the control of blood pressure, albuminuria, and blood sugar and lipid levels (Ruggenenti et al., 2012).

Usually, the first line in treatment for blood pressure accommodates the usage of renin-angiotensin system drugs like ACE inhibitors and angiotensin receptor blockers (Brenner et al., 2001; Lambers Heerspink et al., 2013). Besides, these therapeutic agents may be used for albumin-lowering effect in combination with non-steroidal anti-inflammatory drugs and corticosteroids (Qin et al., 2020).

Lipid-lowering drugs are recommended for all patients from stage 3 of CKD and are frequently associated with improved outcomes in the context of CKD. For example, among patients with stages 1-4 CKD, simvastatin administration showed a reduction in cardiovascular events and all-cause mortality (Pontremoli et al., 2020). In general, statin therapy is recommended for pre-dialysis CKD patients and possibly for renal transplant recipients. However, initiation of treatment is not recommended for individuals undergoing hemodialysis or peritoneal dialysis (Jung et al., 2020).

While several oral antidiabetic agents are available, it is important to highlight that CKD may alter the pharmacokinetics of all therapeutic classes for various reasons. Yet, there are conflicts as to the most appropriate method of glycemic control among patients who developed chronic renal failure, while even more lacking is specific evidence regarding insulin doses as well as insulin profiles in this group of patients (Arnouts et al., 2014).

SGLT2 inhibitors have been approved by the FDA to reduce blood sugar levels in patients with T2DM and have become useful in the management of CKD. They maintain renal function by mediating glomerular pressure decrease via tubuloglomerular feedback independent of glucose control (Yau et al., 2022).

Also, due to frequent vitamin D deficiency in CKD patients, it is recommended their supplements on patients in stages 3 and 4 (Kandula et al., 2011).

1.1.6.3 Renal replacement therapy

Renal replacement therapy (RRT) is the last option in CKD management and several factors must be considered, including the balance of the risks and benefits associated with the procedure. RRT incorporates any procedure replacement of the kidney's blood filtration function. It includes dialysis, a

mechanical procedure to remove salts and other waste products from the circulation, which is divided into two main categories: hemodialysis (HD) and Peritoneal dialysis (PD). On the other hand, kidney transplantation involves the placement of a healthy kidney from the donor into the patient's body thus replacing the damaged kidneys therefore providing renal function (Bello et al., 2022).

HD is the most common form of RRT representing approximately 69% of all kidney replacement therapy and 89% of all dialysis (Bello et al., 2022).

The principle of hemodialysis is consistent with other dialysis methods, where solute diffusion occurs across a semipermeable membrane within the dialyzer. This is performed by applying the concept of counter-current flow, where the dialysate flows in opposition to the blood flow within the extracorporeal circuit. Usually, this procedure is done approximately 3 times a week a session of about 4 hours each session in a hospital setting for HD (Phadke & Khanna, 2011).

PD serves as an alternative modality for renal replacement therapy, offering patients flexibility and independence in managing their kidney failure (Andreoli & Totoli, 2020). Unlike HD, PD leverages the body's peritoneal membrane as a natural filter. The procedure entails the introduction of a sterile dialysis solution into the peritoneal cavity via a surgically implanted catheter in the abdomen. This solution, enriched with dextrose or glucose, facilitates the osmotic removal of waste products and excess fluid from the bloodstream across the peritoneal membrane. Subsequently, after a dwell period typically spanning several hours, the utilized dialysis solution is drained from the abdomen, effectively expelling accumulated toxins and surplus fluid (Andreoli & Totoli, 2020).

PD offers a multitude of advantages, notably including the capacity for home-based administration, thus circumventing the necessity for frequent healthcare facility visits (François & Bargman, 2014). Moreover, PD's continuous and gentle blood filtration mechanism holds promise for the preservation of residual kidney function, potentially surpassing the efficacy of conventional hemodialysis. Additionally, the inherent flexibility of PD appeals to certain patient demographics, owing to lifestyle preferences, travel adaptability, or challenges associated with vascular access (Andreoli & Totoli, 2020). However, peritoneal dialysis also

presents risks like peritonitis, hernias, and complications related to the catheter (Khan, 2023).

Kidney transplantation has been shown to have superior outcomes among patients in terms of survival and quality of life as compared to the other option of RRT (Righini et al., 2022). However, the limited availability of organs, the possibility of rejection, and the risk of postoperative complications are still challenging (Alasfar et al., 2023).

1.2 CKD: The Gut-Immune-Kidney axis

1.2.1 Gut Physiology: Principles, Structure, and Function

The gut is an anatomical structure of the gastrointestinal (GI) tract that displays several physiologic activities that include digestion, accrual of nutrients, and the immune balance. Its thin-walled design allows for more absorption of nutrients as well as hosting the highest density of immune cells (Mason, Huffnagle, Noverr, & Kao, 2008).

The small intestine, the primary site for digestion and nutrient absorption, is anatomically segmented into three distinct regions: the duodenum, jejunum, and ileum, whose wall encompasses four essential layers: mucosa, submucosa, muscularis externa, and serosa (**Figure 10**). The lining of the mucosa is filled with closely packed, finger-like projections, serving to significantly amplify the absorptive surface area (Bass & Wershil, 2015).

The large intestine extends between the caecum and the rectum and receives unabsorbed components. Within this segment, mucosal activities encompass water absorption, the solidification of colonic contents into feces, and the subsequent retention of fecal matter before expulsion (Collins et al., 2024; Greenwood-Van Meerveld et al., 2017).

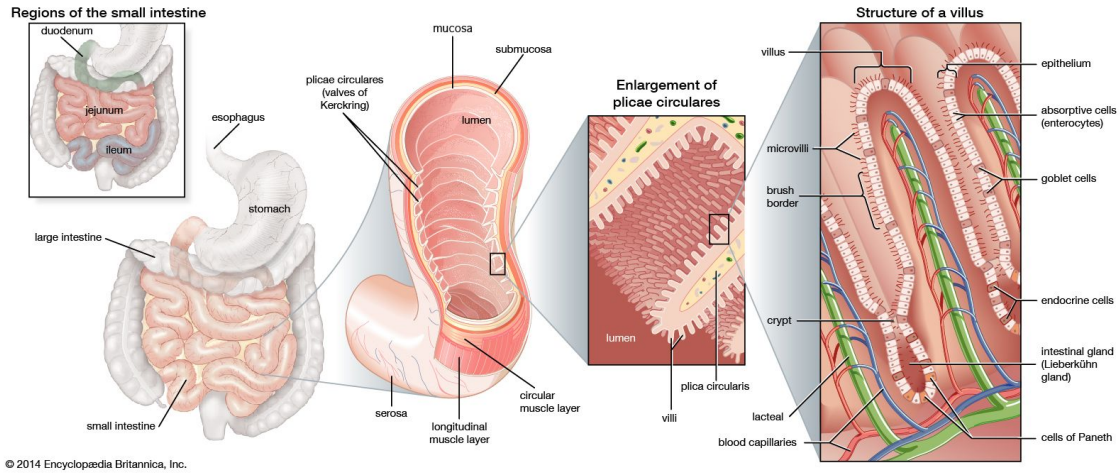


Figure 10. Gut physiology and regions. (T.Editors of Encyclopaedia, 2024).

The gut barrier function contains three primary lines of defense. The first line of defense is the biological barrier which includes gut flora also known as gut microbiota (GM). Second, an immune barrier composed of several components as gut-associated lymphoid tissue (GALT), effector and regulatory T cells, IgA-producing B (plasma) cells, group 3 innate lymphoid cells, as well as resident macrophages and dendritic cells in the lamina propria. Third, a mechanical barrier that closed the lining of intestinal epithelial cells (IEC) and capillary endothelial cells (König et al., 2016).

GM refers to the collection of microorganisms that reside in the GI tract including bacteria, yeast, and viruses. Generally, the GM is composed of more than 2000 bacterial species residing in the human gut, with four dominant phyla (Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria) accounting for 90% of the GM. Their composition is unique for each individual and develops early in life with composition, diversity, and function shaped by both intra-individual and inter-individual variations (Manos, 2022). This group of bacteria participates in the food's fermentation processes and protects against pathogens, enhances the immune system, and produces vitamins, as well as other processes that enhance one's immune and metabolic functions (Manos, 2022).

Based on their metabolism, GM bacteria can be categorized into saccharolytic and proteolytic bacteria (Aguirre et al., 2016). Saccharolytic bacteria primarily ferment carbohydrates to produce beneficial short-chain fatty acids (SCFAs), which play a crucial role in maintaining gut health by providing energy to colonocytes, regulating inflammation, and preserving the integrity of the gut barrier

(Silva et al., 2020). On the other hand, proteolytic bacterial species predominantly metabolize diet-derived and exogenous-derived proteins and peptides via extracellular proteases and peptidases into various metabolites with potential toxic effects, such as phenols, indoles, amines, and ammonia (Rowland et al., 2018).

In a healthy condition, a symbiotic relationship is thought to be established between the host and its GM. The balanced microbial products and activities in symbiosis are considered beneficial to health (Manos, 2022). However, when these microbial products and activities are imbalanced by a shift in the GM composition and function, a dysbiotic condition occurs which is thought to result in the generation of toxins and other deleterious effects in the host. Dysbiosis of GM has been suggested to be associated with a variety of different diseases such as inflammatory bowel disease (IBD), obesity, neurological disorders, diabetes, CVD, and CKD (Degruttola et al., 2016).

1.2.2 CKD: Crosstalk between the gut and the kidney

The gut and kidney share a bidirectional, dynamic relationship as GM composition affects kidney health and function while kidney disease can also interfere with GM composition or function (**Figure 11**) (Colombo et al., 2021). This communication occurs not only through direct contact between the host and microbiota but also through indirect communication via microbiota-derived metabolites. On one hand, GM metabolites particularly, SCFAs are generally proven to promote kidney function (Li et al., 2019). On the other hand, uremic toxins, including indoles, ammonia, and trimethylamine N-oxide, produced by the gut microbiota enhance the development and progression of CKD (Colombo et al., 2021).

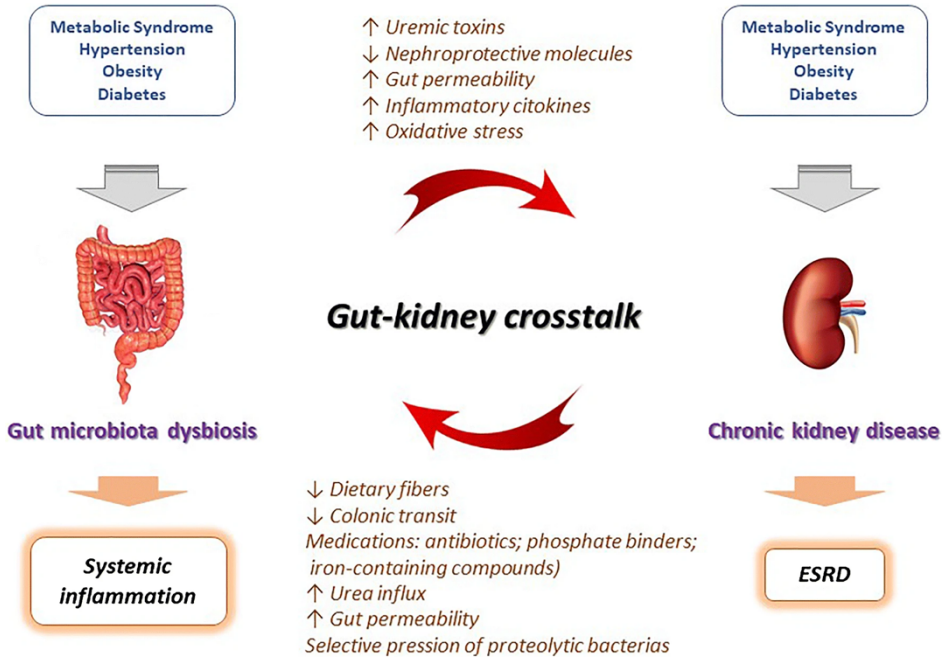


Figure 11. Mechanisms involved in the relationship between gut dysbiosis and CKD. (Taken from Rukavina Mikusic et al., 2020).

1.2.2.1 Bidirectional relationship between uremia and gut dysbiosis

As previously noted, CKD is widely acknowledged to cause GM dysbiosis, which is evident in the early stages of CKD and progresses with structural and functional alterations. Additionally, dietary restrictions aimed at preventing or managing hyperkalemia and hyperphosphatemia often lead CKD patients to consume fewer fiber-rich foods such as fruits, vegetables, and legumes (Ikizler et al., 2020). This dietary shift favours proteolytic over saccharolytic bacterial fermentation, which results in elevated urea and decreased SCFA synthesis, which contributes further to dysbiosis (Colombo et al., 2021).

As renal function declines, compounds that usually were eliminated or metabolized by the kidney tend to accumulate leading to increased blood concentration of numerous molecules and resulting in uremic syndrome. Urea enters the intestinal lumen through the entero-hepatic cycle, where it is converted to ammonia and ammonium hydroxide by gut microbiota, which is enhanced by an increased abundance of urease-producing bacteria (Lauriola et al., 2023).

Elevated ammonia levels deplete colonic tight junction proteins, disrupting the gut epithelial barrier (known as 'leaky gut'), which worsens endotoxemia and promotes microbial translocation into the bloodstream, contributing to systemic

inflammation (Vaziri et al., 2013). Additionally, increased ammonia levels raise colonic pH, a shift that can further aggravate microbial dysbiosis.

1.2.2.2 Uremic toxins: role in health and disease

Uremic toxins are solutes that accumulate in the blood and tissues of patients with CKD and adversely affect physiological systems, notably the cardiovascular and kidney systems (Rosner et al., 2021). The accumulation of such toxins can in themselves contribute to CKD progression as a consequence of inflammation and oxidative stress. Thus, uremic toxins are considered both a cause and a consequence of CKD.

Two classification systems to stratify uraemic toxins have been described in the literature. Conventionally, and as proposed by the European Uremic Toxin Work group (EUTox), these uremic retention solutes are classified according to molecular weight and plasma-protein binding characteristics, both of which influence their removal during dialysis in kidney failure (**Figure 12**) (Depner, 2001; Rosner et al., 2021).

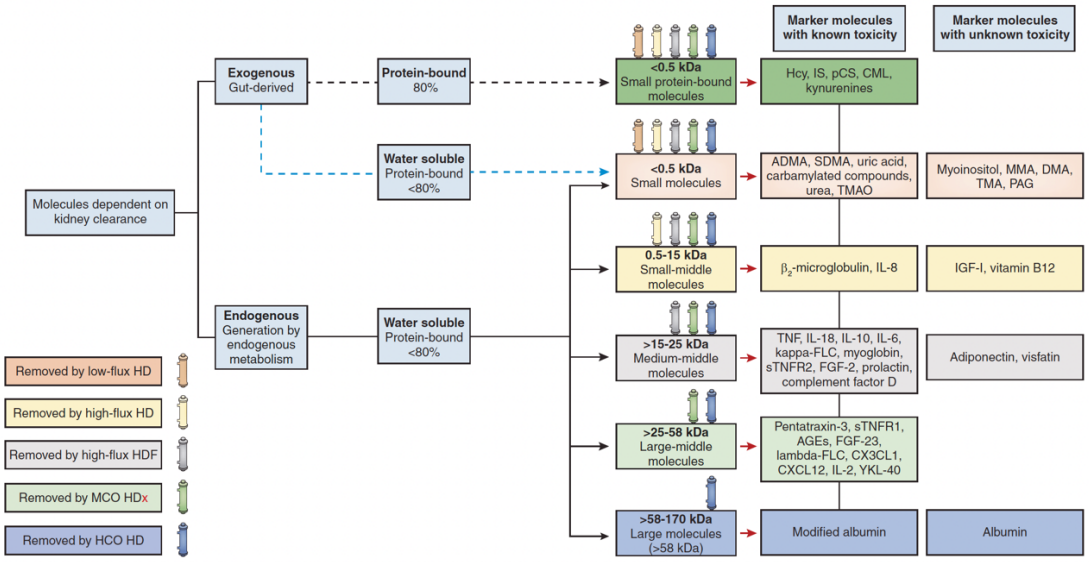


Figure 12. New definition and classification of uremic toxins (Taken from Rosner et al., 2021). The black broken line indicates that many compounds with protein binding >80% are intestinally generated; the blue broken line indicates that some small water-soluble compounds may be intestinally generated.

Low molecular weight (<500 Da) compounds that are unbound to protein are readily removed by conventional dialysis (Rosner et al., 2021). Middle molecular

weight molecules (>500 Da) require large pore membranes for efficient removal (Kawanishi, 2024). Highly protein-bound molecules are poorly cleared by dialysis due to their tight protein-binding properties. Many of the uraemic toxins belonging to the middle and protein-bound classes are toxic to multiple organs, primarily the cardiovascular and kidney systems (Krieter et al., 2010).

The alternative classification system clusters uraemic toxins according to their site of origin; ingested from an exogenous source or produced by either endogenous or microbial metabolism. Endogenous metabolism produces the majority of uraemic toxins, however, exogenous dietary toxins, such as oxalate and advanced glycation end products, also contribute to uremia (Xu et al., 2023).

Uremic toxins produced via gut microbial metabolism, such as p-cresyl sulfate (pCS) indoxyl sulfate (IS), trimethylamine N-oxide (TMAO), and phenylacetylglutamine (PAG) have been associated with increased risk of kidney disease progression, cardiovascular disease, and mortality. Both IS and PCS remain protein-bound in circulation, while TMAO and PAG are water-soluble toxins (Rysz et al., 2021).

IS and pCS are protein metabolites produced from the microbial metabolism of aromatic amino acids tryptophan, tyrosine, and phenylalanine. Thus, GM degrades tryptophan into indole, while 4-hydroxyphenylacetate decarboxylase degrades tyrosine and phenylalanine into 4-hydroxyphenylacetic acid, which is, in turn, decarboxylated to p-cresyl. Once absorbed from the colon into the circulatory system, further metabolism takes place in the liver to produce IS and pCS, respectively (Rysz et al., 2021).

IS and pCS strongly bind to albumin, but in CKD patients, this binding becomes saturated, resulting in high levels of their free fractions. Normally, these compounds are excreted in urine through organic anion and cation transporters in kidney tubular cells (tubular secretion). However, in CKD patients, this elimination is reduced, leading to their systemic accumulation. Additionally, these compounds are not efficiently removed by dialysis, further contributing to their buildup and CKD progression (Rosner et al., 2021).

As for the two above-mentioned water-soluble toxins, TMAO is a compound produced from the degradation of quaternary amines like betaine, l-carnitine, and phosphatidylcholine. First, trimethylamine is converted to TMAO through the enzymatic action of flavin monooxygenase in the liver. Second, PAG is a

nitrogenous compound produced during the fermentation of phenylalanine and is also known to present elevated concentrations in patients with ESRD (Rosner et al., 2021).

1.2.2.3 Impaired intestinal environment, leaky gut and endotoxemia

There have been several observations confirming the dysfunction of the intestinal barrier and significant changes in the composition of colon bacteria in patients suffering from advanced CKD. Such evidence includes the presence of endotoxemia among uremic patients. This condition is known as leaky gut and is characterized by increased permeability and low levels of epithelial tight junction proteins (TJ) (Vaziri et al., 2016). A leaky gut leads to damages in the intestinal lining and allows entrance of pathogens, toxins, or undigested food particles to the blood circulation, affecting several systems such as the endocrine, immune, and renal (Vaziri, Yuan, Nazertehrani, et al., 2013).

One of the mechanisms by which TJs are disrupted in CKD is due to the accumulation of urea (**Figure 13**) (Lau & Vaziri, 2017; Vaziri, 2012).

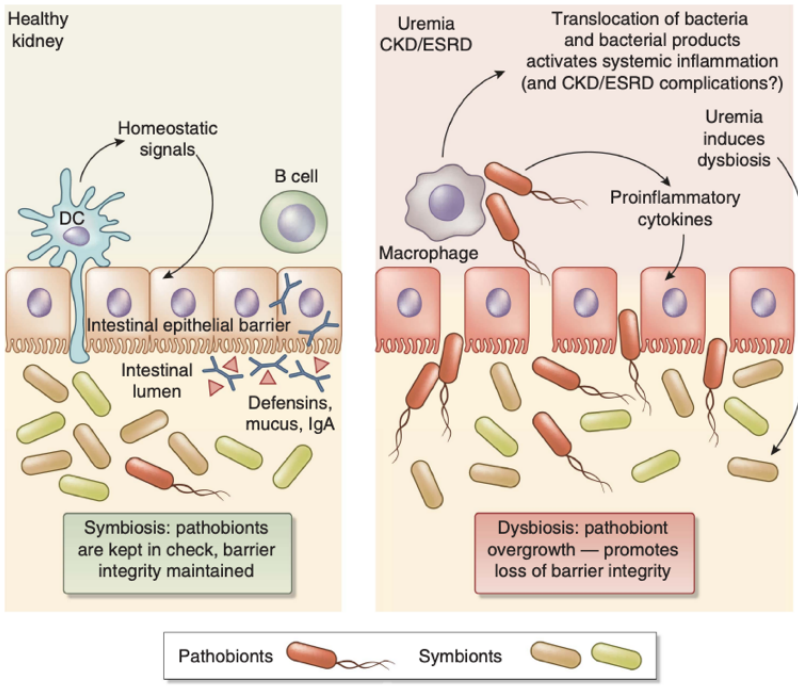


Figure 13. Hypothetical concept about how a failing kidney and the intestinal microbiota affect each other. (Taken from Anders et al., 2013)

Endotoxins, such as liposaccharides (LPS), are the major glycolipid component of the outer membrane of gram-negative bacteria, which compose 70%

of the total bacteria in the healthy human gut. Usually, LPS is released upon bacterial cell lysis mediated by the immune response, originating from fragments of their membrane containing these endotoxins, which then enter the bloodstream, causing endotoxemia (McIntyre et al., 2011).

Levels of circulating endotoxin increase with the severity of the CKD stage and are most elevated in ESRD patients undergoing maintenance dialysis, typically due to volume overload in these patients. Endotoxin contamination of dialysis water has long been recognized as a cause of cardiovascular instability during dialysis. Circulating endotoxin can potentially lead to increased production of pro-inflammatory cytokines (Mohammad & Thiemermann, 2020). LPS can bind to lipoprotein or the LPS-binding protein (LBP) in the circulation, but only the LPS-LBP complex can activate membrane receptors (toll-like receptors; TLRs) in immune system cells, cardiomyocytes, and endothelial cells. This cellular response is mediated by CD14 and leads to the activation of nuclear factor-κB, which in turn plays a key role in the activation and transcription of genes involved in the innate immune response. Repeated ischemic injury to this vulnerable vascular bed results in acute cardiac injury, long-term myocardial damage, and increased mortality (Gonçalves et al., 2006).

1.2.3 CKD: An immune-mediated condition

CKD is increasingly recognized as an immuno-mediated condition, where immune system dysregulation plays a crucial role in its development and progression. The kidneys, as immunologically active organs, interact closely with various immune system components. In fact, CKD involves the dysregulation of both innate and adaptive immune responses, which exacerbate inflammation and contribute to disease progression, alongside alteration in gut microbiota that will impact systemic immunity (**Figure 14**) (Espi et al., 2020).

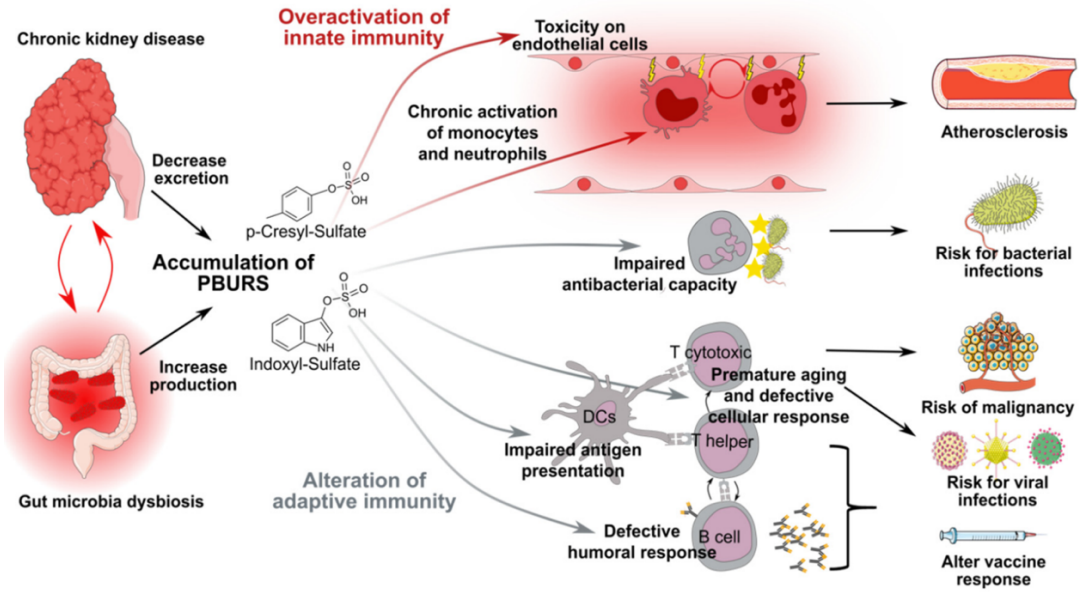


Figure 14. Schematic representation of CKD-associated immune dysfunctions. (Taken from (Espi et al., 2020).

1.2.3.1 Intestinal immunity and systemic inflammation

Several factors (e.g. uremic toxins, dietary changes) are responsible for profound changes in the intestinal immunity of CKD patients, as explored earlier in this thesis. In addition, some kidney diseases can coexist in IBD patients highlighting the interconnected nature between intestinal and renal systems (Vajravelu et al., 2020).

Intestinal epithelial damage, increased gut permeability, and endotoxemia trigger systemic immune responses, which contribute to the chronic inflammatory state observed in CKD patients (Lau et al., 2015). In addition, CKD-related dysbiosis is another factor that supports chronic inflammation and impaired intestinal immunity caused by low levels of SCFA production, which are crucial for maintaining intestinal barrier function and regulating immune responses, alongside increased uremic toxins production (Magliocca et al., 2022).

Furthermore, CKD also results in GALT dysfunction, limited response against pathogens, and impaired mucosal barrier integrity (Lau et al., 2021). These factors usually result in more susceptibility to infections and perpetuation of the inflammatory state. This chronic inflammatory state is marked by an increase in pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6

(IL-6), and C-reactive protein, factors that aggravate not just kidney damage but also causes cardiovascular disease, anemia and other complications (Lau et al., 2021).

1.2.3.2 Innate and Adaptive Immune Dysfunction

As the body's first line of defense, the innate immune system includes various types of cells and components of the complement system that provide a rapid and non-specific response to pathogens (Marshall et al., 2018). This response is classically activated through pattern recognition receptors, particularly the TLRs which target molecular patterns present in foreign pathogens or endogenous molecules released after cell stress or injury conditions. The process of activation of the innate immune cells is accompanied by the secretion of pro-inflammatory cytokines, which have beneficial actions in the short term but can have adverse effects in the cases of prolonged exposure (Ochando et al., 2022).

CKD is characterized by increased levels of pro-inflammatory cytokines, particularly TNF-α and IL-6, which are correlated with the decline in GFR (Amdur et al., 2016). Neutrophils and monocytes from patients with CKD show hyperreactivity upon LPS-based stimulation, possibly due to increased expression of TLR2 and TLR4 induced by the uremic environment (Espi et al., 2020). This chronic activation of monocytes may be further exacerbated by gut-derived uremic toxins. Indeed, experimental studies support the role of gut-derived uremic toxins in triggering innate immune responses in CKD. For example, IS activates the aryl hydrocarbon receptor (AhR) on monocytes, promoting the generation of pro-inflammatory cytokines, which can lead to endothelial damage and increased cardiovascular risk (Kim et al., 2017). Another example was the administration of IS and pCS in rats that induced leukocyte adhesion and extravasation, addressing the impact of these toxins on the innate immune response (Pletinck et al., 2013).

Additionally, dendritic cells (DC) are found in reduced number in the circulation of CKD patients, with less expression of major histocompatibility complex class I and II, resulting in decreased T cell activation (Espi et al., 2020b). Similarly, high concentrations of pCS significantly altered DC functions, including reduced phagocytosis and impaired antigen processing and presentation (Azevedo et al., 2016). Moreover, IS exposure decreased DC proliferation and the expression of costimulatory molecules, potential through AhR activation (Espi et al., 2020b;

Ghimire et al., 2018). In line with this, synthetic AhR agonists showed a reduction in DC proliferation and the promotion of a tolerogenic profile (Platzer et al., 2009).

The adaptive immune system, responsible for the generation of immunological memory, is also significantly affected in CKD. Indeed, in CKD occurs a notable shift in T cell subsets, with a decrease in naïve and regulatory T cells and an increase in memory T cells. For instance, a study reported a 50% reduction in naïve CD4+ T cells and a 34% rise in central memory CD4+ T cells in CKD stage 5 patients compared to healthy individuals (Litjens et al., 2006). Additionally, CKD presents a positive correlation with percentages of Th17 and Treg cells, reflected an increased Th17/Treg ratio (Zhu et al., 2018). Consistently, CKD stage was positively correlated with IL-17 concentrations and negatively with IL-10 levels (Zhu et al., 2018).

Uremic status not only alters lymphocyte phenotypes but also affects inflammatory cytokine patterns. Notably, CKD patients exhibit elevated serum levels of pro-inflammatory cytokines such as IFN-γ, TNF-α, GM-CSF, IL-4, IL-8, MCP-1, and MIP-1β (Hartzell et al., 2020). Additionally, experimental evidence also linked the accumulation of uremic toxins with defective T cell responses. For example, increased pCS levels in mice correlate with decreased IFN-γ production by Th1 cells (Cano-Romero et al., 2019).

Furthermore, CD4+ T cells are also sensitive targets for AhR regulation. Activation of AhR by exogenous ligands promoted the development of regulatory T cells while suppressing effector T cell responses. Interestingly, treatment with AhR ligands has also been shown to ameliorate the development of several T-cell-dependent auto-immune diseases in animal models (Espi et al., 2020b).

1.3 Aryl Hydrocarbon Receptor (AhR): an intricate player of the Gut-Immune-Kidney axis

1.3.1 AhR biochemistry

The AhR is a ligand-activated member of the basic-helix-loop-helix Per-ARNT-Sim (bHLH/PAS) family of transcriptional regulators, playing a crucial role in sensing and integrating environmental and external stimuli into cellular adaptive responses. First discovered in hepatocytes in 1976 as a modulator of the toxic response to dioxins, AhR is highly conserved across vertebrate species and its functions extend beyond xenobiotic metabolism (Larigot et al., 2018) (discussed in section 1.3.2).

Over the past decades, several studies have demonstrated that AhR signaling influences nearly every cell type and organ in vertebrates and many invertebrates. Notably, the highest levels of AhR can be found in the liver, kidney, gut, thymus, lung, spleen, and placenta (Jiang et al., 2010).

Structurally, AhR comprises several distinct domains (**Figure 15**). The N-terminal region contains a bHLH domain, which is essential for binding specific DNA sequences and facilitates the receptor's dimerization with the aryl hydrocarbon receptor nuclear translocator (ARNT) upon ligand binding (Larigot et al., 2018).

AhR also contains two PAS domains, named A and B. The PAS A domain is required for the formation of a stable AhR:ARNT heterodimer, while PAS B together with bHLH domains is the primary site of AHR dimerization for both the cytoplasmic chaperone 90kDa heat shock protein (HSP90) and ARNT(Shivanna et al., 2022). Additionally, PAS B contains the ligand binding domain (LBD), which is crucial for the receptor's ability to bind various ligands, enabling the activation of AhR and subsequent transcriptional responses. The C-terminal region of AhR contains the transactivation domain, which is vital for inducing target gene expression. Here, the Q-rich (glutamine-rich) subdomain is particularly important for the transcriptional activation of xenobiotic response elements (XRE) (Larigot et al., 2018).

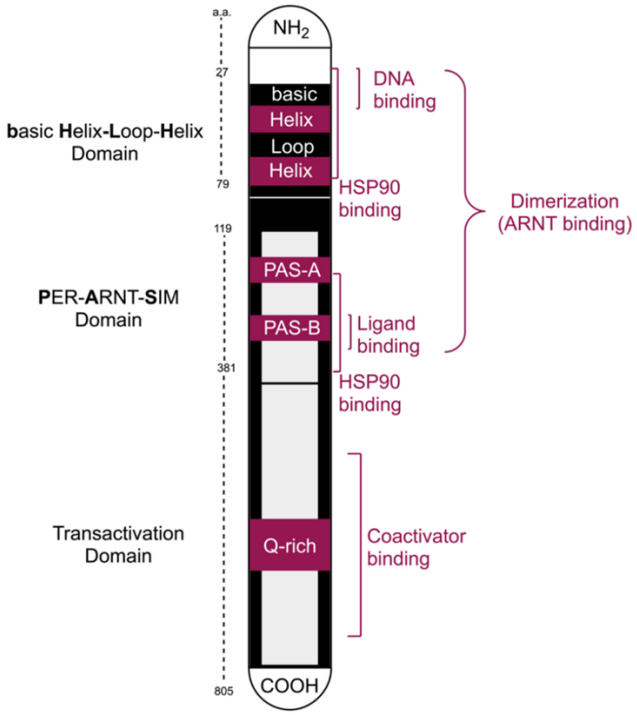


Figure 15. Schematic domain organization of the aryl hydrocarbon receptor (AhR) and its binding sites (Goya-Jorge et al., 2021).

In the absence of ligands, the AhR (monomer) resides in the cytoplasm in a transcriptionally inactive form as part of a complex with two molecules of the HSP90 chaperone, a co-chaperone p23, an X-associated protein 2 (XAP2), and a protein kinase SRC (**Figure 16**). The HSP90 is responsible for stabilizing AhR and assisted by co-chaperone p23 to maintain the complex's conformation (Goya-Jorge et al., 2021). The HSP90 is a protein folding tool responsible for AhR stabilization. The co-chaperone p23 contributes to the ligand binding and to the release from HSP90 chaperone machinery. Meanwhile, XAP2 presents a discrete domain organization with a tetratricopeptide repeat motif whose carboxyl-terminal domain is responsible for the interaction with AhR protein (Beischlag et al., 2008). In addition, XAP2 modulates the receptor's sensitivity to ligands and transcriptional responses. The SRC tyrosine kinase contributes to ligand recognition and indirectly ensures the transcriptional process (Larigot et al., 2018).

The AhR pathway starts once the ligand binds to the LBD, causing conformational changes in the PAS A domains that trigger the release of SRC from the complex and facilitate translocation to the nucleus. Once in the nucleus, AhR dissociates from the chaperone complex and heterodimerizes with ARNT, losing the

chaperone proteins in the process and forming the AhR/ARNT complex (Larigot et al., 2018).

Depending on the target genes involved in the subsequent transcriptional activity triggered by the AhR/ARNT complex (discussed in section 1.3.4), the genomic signaling is classified as canonical when it is mediated by XRE or as non-canonical XRE.

The canonical signaling begins when the AhR/ARNT complex binds to the XRE identified by the DNA consensus motif sequence 5'-TNGCGTG-3'. The non-canonical XREs, sometimes referred to as AhR-Responsive Elements-II, are recognized by the consensus promoter region 5'-CATG{N6}C[T|A]TG-3' (Wright et al., 2017). The AhR-ARNT complex also interacts with other transcriptional regulators to control the expression of multiple target genes (Hankinson, 2005).

Similar to other PAS proteins involved in critical signaling functions, AhR expression is controlled by a transcriptional repressor (AhRR) with a similar N-terminal region sequence. The AhRR competes with AhR by forming the heterodimeric AhRR/ARNT complex, which binds to the XRE and consequently represses transcription (Sakurai et al., 2017).

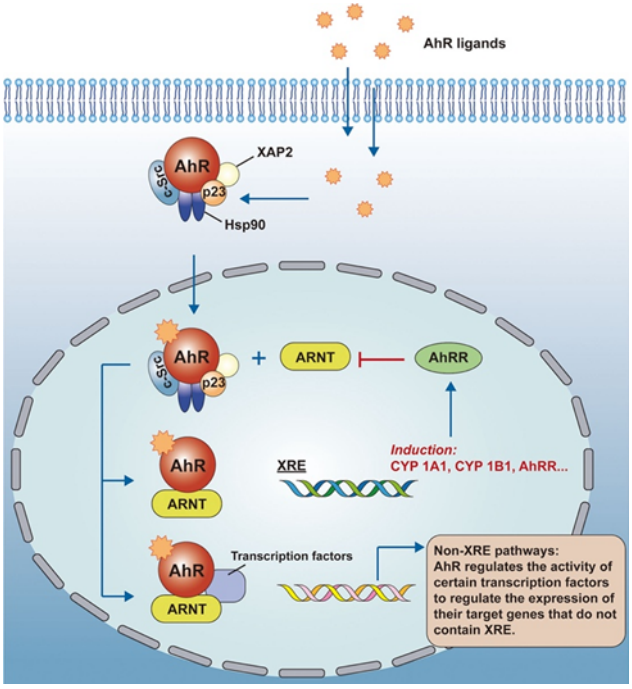


Figure 16. AhR signalling pathway. (Taken from Wu et al., 2022)

1.3.2 AhR in health and disease

Identified as a xenobiotic receptor, AhR is part of the organism's detoxification system, playing an important role in the metabolism of environmental pollutants and other exogenous compounds by controlling the expression of a battery of genes. Since its discovery, AhR has been the focus of extensive toxicological research, revealing its role in the up-regulation of phase I and phase II biotransformation enzymes (Omiecinski et al., 2011).

Besides their detoxification functions, AhR has other important physiological roles not yet fully understood. These include observation of the AhR crucial role in proper liver and vascular development, immune system function, and cell growth differentiation (Larigot et al., 2018). For example, AhR knockout studies have shown that AhR deficiency leads to microvesicular steatosis, prolonged extramedullary hematopoiesis, and reduced liver size. Similarly, $AhR^{-/-}$ mice also exhibit failure to close the ductus venosus, cardiac hypertrophy, and hypertension (Bunger et al., 2008).

Additionally, changes in AhR expression have been observed in many chronic inflammatory diseases. For instance, in multiple sclerosis patients, recognized as a chronic immune-mediated demyelinating disease of the central nervous system, there were lower circulating AhR levels compared to healthy controls. Similarly, in IBD as Crohn's disease and ulcerative colitis, AhR levels are significantly lower in the inflamed mucosa of Crohn´s disease patients and markedly reduced in some ulcerate colitis samples compared to controls (Cannon et al., 2021, Neavin et al., 2018).

On the other hand, AhR overexpression is observed in various neoplastic diseases including actinic keratosis and cutaneous squamous cell carcinoma, lung adenocarcinoma, small cell lung carcinoma, and gastric cancer (Griffith & Frankel, 2024). In CKD, multiple studies indicate that AhR activation is involved in CKD progression by inflammation, fibrosis, and oxidative stress. Furthermore, uremic toxins activate AhR and cause detrimental effects on renal function and structure (Mo et al., 2020). For these reasons, AhR is being targeted in CKD treatment, with AhR antagonists being investigated for their ability to mitigate CKD-related complications.

Despite being tightly regulated, literature has shown that the mode of action and responses mediated by AhR might be ligand-specific, cell-specific, and context-specific (Denison et al., 2011). This means that similar ligands can cause different (physiological or pathogenic) responses in different cell types. Therefore, it is important to know and understand the variety of substances that can act as AhR ligands and their effects in cell-specific contexts.

1.3.3 AhR signaling pathways in intestinal, immune, and renal cells

The intestinal epithelial barrier is the primary site of contact with AHR ligands derived from diet or microbial metabolism (Stockinger et al., 2021). Here, under homeostatic conditions, AhR signaling via dietary or microbiota-derived ligands is essential for maintaining intestinal barrier integrity and function, achieved through IL-22 secretion, IL-10 induction, strengthening of tight junctions, and effects on colonic neurons (Han et al., 2021).

Additionally, considering the specific role of AhR in immune responses, increasing evidence highlights its intersections with other critical immunological pathways such as NF-κB, transforming growth factor β mediator SMAD 3 (TGFβ/SMAD3), and TLRs (Wajda et al., 2020). Notably, AhR regulates innate inflammatory signaling by directly binding to RELA and RELB, members of the NF-κB family. Besides, AhR interacts with estrogen receptor α and directly binds estradiol, with significant crosstalk between this receptor and NF-κB (Matthews & Gustafsson, 2006; Øvrevik et al., 2014).

AhR ligands exhibit both oxidative and antioxidative properties, which further impact in T cell immune response. In particular, oxidative AhR ligands influence the differentiation of naïve CD4+T cells into Th22 cells, promoting the expression of the signature cytokines and transcription factors of Th1, Th2, and Th17 cells, while antioxidant AhR ligands can induce Tregs and suppress Th17 cells (Santana & Esquivel-Guadarrama, 2006; Singh et al., 2020).

Furthermore, the expression of AhR by many other immune cells, including macrophages, mast cells, eosinophils, DCs, and B cells, suggests that AhR signaling is essential for their regulation and survival. For example, AhR deficiency disrupts ILC balance, increases eosinophils and neutrophils, and decreases ILC3s

and IELs, leading to reduced IL-22, higher pro-inflammatory cytokines (TNF, IL-6, IL-17, IFNγ), vascular leakage, a thinner mucus layer, and impaired tight junction (S. Li et al., 2018; Schanz et al., 2020).

AhR activity is strongly implicated during CKD. Evidence has demonstrated a positive correlation between renal AhR expression and CKD severity. Compared with healthy controls, CKD patients and 5/6 nephrectomy mice exhibited increased serum AhR-activating potential, which was strongly correlated with GFR (Dou et al., 2018). Furthermore, AhR activation induces podocyte injury, progressive glomerular damage, and a pro-inflammatory phenotype *in vitro* and *in vivo* (Ichii et al., 2014).

1.3.4 AhR target genes

AhR is responsible for inducing the transcriptional activation of a battery of physiologically important genes. The most extensively recognized targets of AhR gene battery include xenobiotic-metabolizing phase I enzymes, such as CYP1A1, CYP1A2, CYP1B1, and phase II enzymes, including NADPH:quinone oxidoreductase (NQO1), and UDP-glucuronosyltransferase (UGT) 1A1 and UGT1A6. In addition to this canonical signaling pathway, AHR frequently interacts with other signaling pathways, such as nuclear factor-κB (NF-κB), nuclear factor erythroid 2-related factor 2 (NRF2), and estrogen receptor signaling (Grishanova & Perepechaeva, 2022).

Another important AhR target is the AhRR, which acts as a feedback inhibitor of AhR signaling. AhRR competes with AhR for binding to ARNT and for binding to DNA at AhR-responsive elements, thereby attenuating AhR activity. This feedback loop is crucial for maintaining the balance and preventing excessive activation of AhR, which could lead to deleterious effects (Kimura et al., 2017).

1.3.5 Dietary AhR ligands

AhR ligands can be divided into exogenous and endogenous, and into agonists and antagonists. Environmental pollutants like polycyclic aryl hydrocarbons

as well as their halogen derivatives have been the most extensively studied classes of AhR ligands. However, diet and GM are tremendous sources of AhR modulators that trigger complex and fundamental processes in health and diseases (Gao et al., 2018; Lamas et al., 2018).

1.3.5.1 Tryptophan-Derived Uremic Toxins

Tryptophan is an essential aromatic amino acid obtained from dietary intake, and its metabolites have emerged as significant endogenous AhR ligands. The metabolism of tryptophan occurs via the indolic, serotonin, and kynurenine pathways, resulting in the production of various metabolites with significant health implications, whose mechanism remains poorly understood (Xue et al., 2023). It has been reported that changes in tryptophan metabolites have been associated with alterations on the intestinal homeostasis, as well as other gastrointestinal, metabolic, and neurological disorders (Gao et al., 2018; Taleb, 2019; Xue et al., 2023)

In the context of CKD, these metabolites that would normally be eliminated by the kidneys are retained due to the decrease of renal function. Among these, indolic metabolites have emerged in the AhR activation. For instance, at typical concentrations in uremic patients, IS and indole-3-acetic acid induce the nuclear translocation of AhR, particularly in hepatic and endothelial cells, can upregulate AhR-regulated genes such as CYP1A1 and CYP1B1 (Gondouin et al., 2013).

In addition to the indolic pathway, the kynurenine pathway also produces metabolites that act as AhR ligands. Kynurenine has been shown to activate AhR and upregulate genes involved in the immune response in glioma cells (Opitz et al., 2011). Additionally, kynurenic acid, another metabolite from the kynurenine pathway, acts as an AhR agonist and is associated with inflammation in CKD (DiNatale et al., 2010).

1.3.5.2 Short-chain Fatty acids

SCFAs are key metabolites produced by the fermentation of dietary fibers by GM, playing crucial roles in maintaining intestinal health and systemic metabolic functions. They have been recognized not only for their role as energy sources and signaling molecules but recently also for their potential as ligands for AhR.

In the intestine, for example, SCFAs can regulate AhR and its target genes promoting anti-inflammatory activity and enhanced barrier function. For example, SCFAs upregulate IL-22 production by enhancing the expression of AhR and hypoxia-inducible factor 1α to maintain intestinal homeostasis (Yang et al., 2020).

Korecka et al. demonstrated that SCFA exposure increased AhR signaling and its target gene expression in mouse intestine and liver (Korecka et al., 2016). Accordingly, another study revealed that SCFAs enhance the expression of AhR target genes, such as CYP1A1, both in mouse colonocytes and on the human Caco-2 cells, in an AHR-dependent manner (Jin et al., 2017). Additionally, butyrate via AhR activation can promote 5-HT release from neural enterochromaffin cells to regulate intestinal homeostasis and peristalsis (Reigstad et al., 2015).

However, research on the specific interactions between SCFAs and AhR in different cell types is still limited, and further investigations are needed to fully understand their implications.

1.3.5.3 Plant-derived Flavonoids

Polyphenols are a diverse group of plant-derived secondary metabolites characterized by multiple phenol structural units and widely recognized for health benefits. Among these, flavonoids, a major subclass of polyphenols, are particularly prevalent in a wide array of fruits, vegetables, and plant-derived beverages like tea and wine (Panche et al., 2016). Notably, these phytochemicals are among the primary natural dietary ligands of the AhR, with flavones, flavonols, and flavanones being the main subclasses of flavonoids reported as AhR modulators (Goya-Jorge et al., 2021; Xue et al., 2017). However, like other AhR modulators, flavonoids exhibit host, cell type, and context-specific activities on AhR that are still puzzling and poorly understood (Goya-Jorge et al., 2021). For instance, quercetin has shown

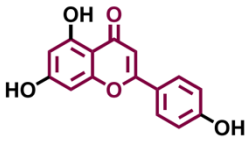
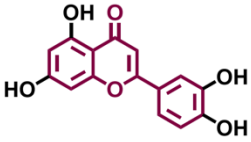
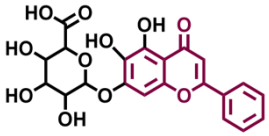
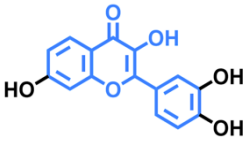
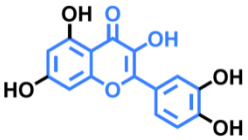
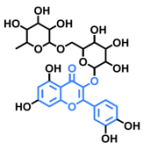
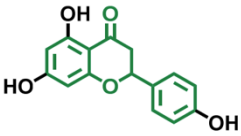
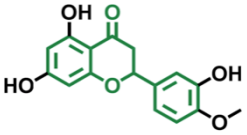
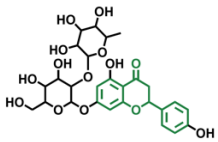
both agonist and antagonist activities on AhR transcriptional activation, depending on the cellular context (CIOLINO et al., 1999).This complexity, combined with the intricate role of AhR in both physiological and pathological conditions, contributes to discrepancies in the reported positive or negative molecular effects of flavonoids.

1.3.5.3.1 Chemistry and Structure-Activity Relationships

Flavonoids share a common chemical structure comprising 15 carbon atoms arranged in a C6-C3-C6 configuration, forming two benzene rings, designated as A and B (Dias et al., 2021).The A-ring and B-ring are connected by a three-carbon bridge, typically forming an oxygenated heterocyclic ring known as the C-ring. Based on the degree of saturation, oxidation level of the C-ring, and the specific connections between the B-ring and C-ring, flavonoids are further classified into various subgroups (Dias et al., 2021).

Although certain chemical structure features and substitution patterns of flavonoids have been suggested to contribute to their activity as AhR modulators, generalizations regarding structure-activity relationships are limited. Consisted with this, **Table 3** shows both AhR agonism and antagonist responses across different flavones, flavonols, and flavanones subgroups.

Table 3. Structures and AhR activity reported from the flavone, flavonol, and flavanone class of compounds (Adapted from Goya-Jorge et al., 2021)

Flavones		
Apigenin  Agonist (Kaur & Badhan, 2017) Antagonist (Ashida, 2008)	Luteolin  Agonist (Jin et al., 2018) Antagonist (Ashida et al., 2015)	Baicalin  Agonist (Kaur & Badhan, 2017) Antagonist (Xue et al., 2015)
Flavonols		
Fisetin  Agonist (Kaur & Badhan, 2017) Antagonist (Ashida et al., 2000)	Quercetin  Agonist (Kaur & Badhan, 2017) Antagonist (Ashida et al., 2000)	Rutin  Agonist (Kaur & Badhan, 2017) Antagonist (Ashida et al., 2000)
Flavanones		
Naringenin  Agonist Antagonist (Ashida, 2008)	Hesperetin  Agonist (Kaur & Badhan, 2017) Antagonist (Tan et al., 2018)	Naringin  Agonist (Kaur & Badhan, 2017) Antagonist (Ashida et al., 2000)

The complexity of these interactions indicates that deeper investigations focusing on flavonoids' specific agonist or antagonist responses could significantly contribute to their clinical applications.

Chapter II – Aims

2. Aims

The scientific community increasingly recognizes CKD as an immune-mediated condition, closely associated with disruptions in gut microbiota composition and function (Mertowska, et al., 2021) . Uremic metabolites produced by the gut microbiota, well-known AhR agonists, have been shown to worsen gut dysbiosis, heighten immune system hyperreactivity, and exacerbate renal damage (Mertowska, et al., 2021). Accordingly, the gut-immune axis has gained attention for its potential central role in CKD pathophysiology (Behrens, Bartolomaeus, Wilck, & Holle, 2024).

The growing use of dietary supplements and medicinal plant-based foods enriched with flavonoids reflects their well-documented antioxidant and anti-inflammatory properties in CKD. Regardless their pleiotropic nature, flavonoids were found to counteract AhR-dependent uremic toxin deleterious role in the kidney (Iwashima, et al., 2024). Still, flavonoids are known to exhibit dual agonistic and antagonistic activity in AhR signaling, functioning as both inducers and inhibitors of AhR-regulated drug-metabolizing enzymes (Park, et al., 2022). The complexity of flavonoid-AhR signaling is heightened by its role in a conserved detoxification system that regulates key drug metabolism processes, particularly those involving CYP enzymes. Furthermore, the tissue-specific nature of flavonoid-AhR activity complicates the translation of predictive *in silico* models and *in vitro* experiments, often undermining the external validity of the results.

This study, focusing the dysfunction of the gut-immune-kidney axis in CKD, has two main goals:

1) to characterize the dual agonistic/antagonistic activity of flavonoid-AhR interactions;

2) to correlate flavonoid-AhR activity with tissue-specific functional outcomes.

Chapter III- Methods

3. Methods

This scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) and guided by the PRISMA-ScR checklist (Tricco et al., 2018). The protocol for this review was registered with the Open Science Framework (https://doi.org/10.17605/OSF.IO/FSR5N)

3.1. Research Question

The research question for this scoping review was: **"What are the pharmacodynamic outcomes arising from flavonoids-Aryl Hydrocarbon Receptor (AhR) agonism/antagonism within the gut-immune-kidney axis?"**.

3.2 Search Strategy

The search strategy was developed using the Participants-Concept-Context framework as recommended by the Joanna Briggs Institute. This strategy targeted studies on Flavonoids (participants) and their pharmacodynamic interactions with AhR (concept) within the gut-immune-kidney axis (context), combined with boolean operators using the following syntax: **((Flavonoids) AND (AhR)) AND (Gut OR intestine OR immune OR kidney)**. The literature search was conducted from 1999 to 2023 in the PubMed, Scopus, Web of Science databases.

3.3 Eligibility criteria

Only quasi-experimental and experimental studies published in English were considered were considered, limited to those utilizing *in vitro* models or animal models to explore the mechanistic pathways involved.

Studies that did not address the interaction between flavonoids and AhR or were unrelated to the gut, immune, or kidney components were excluded. Additionally, non-original research articles, such as systematic reviews, meta-analyses, and other review articles, were not included in the analysis.

3.4 Study Selection

The screening process was managed using Covidence software (https://www.covidence.org/). All retrieved records were imported into Covidence, where duplicate entries were automatically removed. Title and abstract screenings were conducted independently by two reviewers, with any disagreements resolved through discussion with a third reviewer. Articles that passed the initial screening were subjected a full-text review based on the inclusion criteria detailed above. The results of the search and reasons for exclusion at the full-text review stage are presented in **Figure 17**.

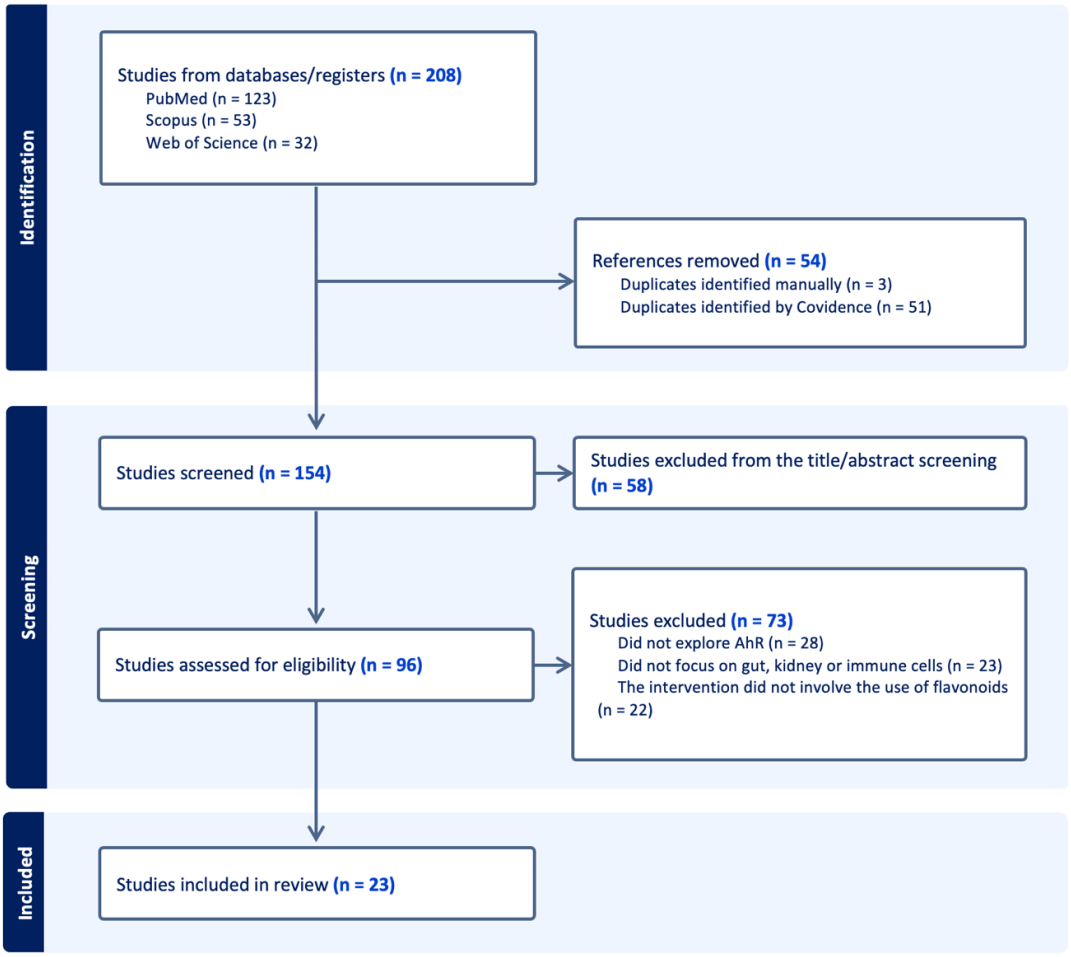


Figure 17. PRISMA flowchart of the study selection process.

3.5 Synthesis of results

Key findings from the included studies were analyzed to evaluate Flavonoid-AhR interactions, focusing on agonistic and antagonistic effects within the gut-immune-kidney axis. Pharmacodynamic outcomes, along with relevant general outcomes, were synthesized and organized into three separate evidence tables, each corresponding to the gut, kidney, and immune cell contexts.

Chapter IV- Results

4.1. Flavonoid-AhR Activity and Pharmacodynamic Outcomes

The 23 studies included in this review utilized 19 distinct flavonoids: 11 evaluated in the gut (Wogonin, Isovitexin, Baicalein, Quercetin, Alpinetin, β-Naphthoflavone, Kurarinone, Chinese medicinal herb decoction QRZSLXF, Methylated Pelargonidin, Cranberry polyphenol extract, Dihydromyricetin), 5 evaluated in the immune system (Baicalein, Quercetin, Cinnamtannin D1, Alpinetin, Naringenin), and 6 evaluated in the kidney (Taurisolo®, Fisetin, Barleriside A, Pentahydroxy flavanone, Barleriside A, Aminoflavone).

4.1.1. Flavonoid-AhR activity in the gut

Table 4 outlines the gut-dependent flavonoid-AhR agonistic/antagonistic activity with the resulting pharmacodynamic effects on key gut health parameters. A total of 13 studies were included in this section describing 17 conditions in both *in vivo* and *in vitro* models: 11 studies focused on IBD, 2 on non-alcoholic steatohepatitis (NASH), 1 on high fat/high sugar diet (HFHS), 1 on high-intensity exercise (HIE), and 2 other used *in vitro* models of intestinal epithelial and intraepithelial cell lines.

Table 4. Flavonoid-AhR modulation in the gut: ligand-receptor activity and functional readouts

Study characterization	Flavonoid	Flavonoid-AhR Activity	CYP Density & Activation	GM Modulation	Gut Barrier Integrity	Colonic Immunologic & Inflammatory Regulation	Ref.
- Male C57BL/6 mice (DSS-induced colitis)	- Wogonin (20 mg/kg/d) by gavage (24 days)	Agonism	ND	✓	✓	✓	(Ye et al., 2024)
- Male C57BL/6 (DSS-induced colitis)	- Isovitexin (25, 50, 100 mg/kg/d) orally (14 days)	Agonism	+	ND	✓	✓	(Mu et al., 2023)
- Rat IECs stimulated with TNF-α	- Isovitexin (20, 40, 80 μg/ml)	Agonism	ND	ND	✓	✓	
- Male C57BL/6 (DSS-induced colitis)	- Baicalein (10, 20, 40 mg/kg/d) orally (10 days)	Agonism	+	ND	✓	✓	(Yang Li et al., 2022)
- Male C57BL/6 (DSS-induced colitis)	- Baicalein (10, 20, and 40 mg/kg/d) orally (10 days)	Agonism	+	ND	✓	✓	(Liu et al., 2020)
- Female C57BL/6 WT and AhR-/- mice (DSS-induced colitis)	- Quercetin (50 mg/kg/d) (15 days) by gavage	Agonism	ND	ND	✓	✓	(Riemschneider et al., 2021)
- Female C57BL/6 (DSS-induced colitis)	- Alpinetin (7.5, 15, 30 mg/kg) orally (10 days)	Agonism	ND	ND	✓	✓	(Lv et al., 2018)
- Female C57BL/6J mice (DSS-induced colitis)	- β-naphtoflavone (1 mg/mice/d) by gavage (5 days)	Agonism	+	ND	✓	✓	(Furumatsu et al., 2011)
- SW480 human epithelial colon cancer cell line	- β-naphtoflavone (10 uM) in vitro	Agonism	+	ND	ND	✓	
- Male C57BL/6 mice (TNBS-induced IBD)	- Kurarinone (100 mg/kg/d) i.p. injection (10 days)	Agonism	ND	ND	✓	✓	(Xu et al., 2021)
- male BALB/c mice (TNBS-induced colitis)	- Chinese medicinal herb decoction QRZSLXF (20 mg/kg/d) intragastric injection (7 days)	Antagonism	ND	ND	✓	✓	(Zhang et al., 2020
- male Balb/C mice (TNBS-induced colitis)	- Methylated Pelargonidin (5 mg/kg/d) by gavage (4 days)	Agonism	+	ND	✓	✓	(Biagioli et al., 2021)
- male C57BL6 WT and AhR −/− mice (NASH model)	- Methylated Pelargonidin (5 mg/kg/d) by gavage (5 weeks)	Agonism	+	ND	✓	✓	

+ Increased; ✓ Observed; ND - Not Determined; CYP - Cytochrome; GM - Gut microbiota

Table 4. Flavonoid-AhR modulation in the gut: ligand-receptor activity and functional readouts – Cont.

Study characterization	Flavonoid	Flavonoid-AhR Activity	CYP Density & Activation	GM Modulation	Gut Barrier Integrity	Colonic Immunologic & Inflammatory Regulation	Ref.
- male Balb/C mice (TNBS-induced colitis)	- Methylated Pelargonidin (5 mg/kg/d) by gavage (4 days)	Agonism	+	ND	✓	✓	(Biagioli et al., 2019)
- male C57BL6 mice (NASH model)	- Methylated Pelargonidin (5 mg/kg/d) by gavage (5 weeks)	Agonism	+	ND	✓	✓	
- Male C57BL6 mice (HFHS diet)	- Cranberry polyphenol extract (200 mg/kg/d) by gavage (9 weeks)	Agonism	ND	✓	✓	✓	(Medina-Larqué et al., 2022)
- Male C57BL/6 mice (HIE-induced intestinal barrier dysfunction)	- Dihydromyricetin (100mg/kg/d) by gavage (14 days)	Agonism	+	ND	✓	✓	(Hou et al., 2022)

+ Increased; ✓ Observed; ND - Not Determined; CYP - Cytochrome; GM - Gut microbiota

Wogonin, a natural flavonoid commonly used in Chinese medicine, induced AhR activation in a mouse model of DSS-induced colitis. In this study, it was observed an AhR-dependent gut barrier protection, evidenced by increased colonic expression of Muc-2 and the TJ proteins ZO-1, occludin, and claudin-1. Additionally, the AhR upregulation was associated with a reduction in colonic inflammatory markers TNF-α, IL-1β, and IL-6, restoration of the spleen index, and decreased ILC3/ILC1 plasticity (Ye et al., 2024). In a similar model, the oral consumption of isovitexin, a glycosylated flavonoid isolated from Asian rice, ameliorated the colonic histopathological lesions, enhanced tight junction integrity (ZO-1 and occludin) and decreased inflammatory cytokines (IL-1β and TNF-α) through the AhR pathway (Mu et al., 2023).

Two studies of the same group evaluated the effects of baicalein, the major active flavone derived from *Scutellaria baicalensis Georgi*, on DSS-induced colitis (Yang Li et al., 2022; Liu et al., 2020). In these studies, baicalein demonstrated AhR agonistic effects with increased CYP1A1 expression. Both studies demonstrated that this pharmacodynamic action on colonic AhR participated in the reduction of histopathological lesions and body weight loss recovery. Importantly, baicalein also restored Th17/Treg balance in an AhR-dependent manner.

On another case of DSS-induced colitis, quercetin was studied in WT and AhR knockout mice. This treatment increased claudin levels, promoted the Th17/Treg balance, and provoked a significant reduction in macrophage infiltration and MPO levels, through AhR-mediated anti-inflammatory mechanisms (Riemschneider et al., 2021). Similarly, alpinetin and β-naphtoflavone, displayed AhR agonistic properties and CYP1A1 induction. Notably, both treatments reduced body weight loss, improved histological lesions, and decreased TNF-α and IL-1β in the colon (Lv et al., 2018; Furumatsu et al., 2011). In the case of alpinetin, there was an AhR-dependent regulation of Th17/Treg balance (Lv et al., 2018).

Kurinone is a flavonoid derived from Sophora flavescens that has been reported to be effective in many inflammatory conditions. In a TNBS-induced mice model and mediated by AhR agonism it showed reduced plasma LPS levels and decreased FITC permeability. The immunological profile showed a reduction in macrophage infiltration and IL6, TNF-α, and IL-1β markers, accompanied by an increase in the anti-inflammatory cytokine IL-10 (Xu et al., 2021).

QRZSLXF is a Chinese medicinal herb recipe that is commonly prescribed for the treatment of UC. In a mice model of TNBS-induced colitis, QRZSLXF decreased AhR levels among with reduced body weight loss, reduced FITC permeability, and restored Treg/Th17 balance, contrasting with the predominant agonistic effects previously observed in the gut, highlighting the complexity of these interactions (Zhang et al., 2020).

Methylated pelargonidin, tested in both colitis and NASH models, consistently activated AhR and induced CYP expression. In colitis models, methylated pelargonidin reduced histological damage and weight loss while decreasing inflammatory mediators like IL-1β, TNF-α, and IFN-γ. Notably, in both colitis and NASH models, it improved barrier integrity featured by reduced FITC permeability and increased occludin levels. In colitis models, it also prevented body weight loss while in NASH models, it decreased body weight gain, improved glucose tolerance, and reduced liver steatosis (Biagioli et al., 2021; Biagioli et al., 2019).

Medina-Larqué et al., 2022 studied the effects of cranberry polyphenol extract, which is rich in flavonoids, in a mice model a model of HFHS diet-induced gut dysfunction. Notably, this supplementation, beyond the reduction of weight gain

and improved glucose tolerance, also increased the colonic mucus production, goblet cell number, and GM modulation (e.g. increased *Akkermansia muciniphila*) along with decreased IL-13 and TNF-α proinflammatory cytokines and the modulation of Tyk2, Rorc, and Irf7 immune markers.

Dihydromyricetin, tested in a mice model of exercise-induced intestinal dysfunction, induced colonic AhR activation, increased CYP1A1 levels accompanied with increased TJ proteins (ZO-1, occluding, and claudin), decreased endotoxemia markers (serum LPS) and reduced levels of pro-inflammatory cytokines (IFN-γ, TNF-α, and IL-10) (Hou et al., 2022).

Lastly, two in vitro studies were conducted using isovitexin on IEC lines and β-naphtoflavone on a colonic epithelial cell line. Both studies demonstrated AhR activation and tight junction regulation, further supporting the beneficial effects of these flavonoids in an *in vitro* setting (Mu et al., 2023; Furumatsu et al., 2011).

In summary: Sixteen of the seventeen studies analyzed demonstrated the AhR agonistic activity of flavonoids in the gut. Accordingly, 10 studies reported altered CYP expression and activity, the most extensively recognized target of AhR gene battery. The effects of flavonoids mediated by AhR receptors consistently align with improvements in several parameters of gut health. Of the 17 conditions evaluated, all demonstrated positive impacts on regulating the intestinal immune response and reducing inflammatory load. Likewise, 16 studies reported enhanced intestinal barrier integrity. These molecular and cellular outcomes appear to correlate with the pathophysiological and clinical parameters of the conditions analyzed. In IBD, improvements in histopathological scores were noted, while in NASH, enhanced glucose tolerance was observed. Taken together, our results strongly suggest that **flavonoid-AhR agonism plays a beneficial role** in IBD and other gut-related disorders.

4.1.2. Flavonoid-AhR activity in the immune system

The effects of flavonoid-AhR activity strictly on immune cells, regardless the intestinal or renal environments, are represented in **Table 5**. The search strategy used in this work resulted in 6 *in vitro* studies focusing on naïve CD4+ T cells and DCs.

Table 5. Flavonoid-AhR modulation in the immune system: ligand-receptor activity and functional readouts.

	Flavonoid	Flavonoid-AhR Activity	CYP Density & Activation	Immunomodulation		Inflammation	Ref.
				Treg	Th17		
- Naïve CD4+ T cells	- Baicalein (5μM and 10 μM)	Agonism	ND	+	-	-	(Liu et al., 2020)
- LPS-matured DCs (LPS-DCs)	- Quercetin (10 uM)	Agonism	+	+	ND	-	(Michalski et al., 2020)
- Naïve CD4 cells were isolated from BALB/c mice	- Cinnamtannin D1 (40 μM)	Antagonism	ND	+	-	-	(Shi et al., 2020)
- Naïve CD4+ T cells from MLNs of C57BL/6 mice	- Alpinetin (30 μM)	Agonism	+	+	=	-	(Lv et al., 2018)
- Naïve CD4+ T cells (isolated from BALB/c mice)	- Baicalein (30 μmol/mL)	Agonism	ND	+	ND	ND	(Bae et al., 2016)
- CD4+ T cells isolated from female BALB/c mice splenocytes	- Naringenin (50 μM)	Agonism	ND	+	ND	ND	(Wang et al., 2012)

+ Increased; **-** Decreased; ND - Not Determined; CYP - cytochrome; Treg – Regulatory CD4-T cells; Th17 – T helper CD4-T cells expressing IL-17

Baicalein is a flavonoid derived from *Scutellaria baicalensis* that has been shown to act as an AhR agonist and promote Treg differentiation (Liu et al., 2020; Bae et al., 2016). Liu et al., 2020 also demonstrated a cumulative reduction in Th17 cell levels, associated downregulation of IL-17, and increased IL-10 cytokine.

Quercetin, in monocyte-derived DCs, displayed AhR agonistic activity with increased CYP1A1 levels. Furthermore, quercetin-treated DCs co-cultured in allogenic T cells enhanced Treg differentiation along with increased TGF-β1 and decreased IL-17p70 levels (Michalski et al., 2020).

In contrast, cinnamtannin D1, a biflavonoid extracted from Cinnamomum tamala, performed an antagonistic interaction with AhR in naïve CD4+ T cells. In this work, cinnamtannin D1 increased Treg differentiation and IL-10 levels while reducing Th17 cells and the levels of IL-17A cytokine (Shi et al., 2020).

Alpinetin is the major flavonoid of Alpinia katsumadai Hayata, which seed has been used in traditional Chinese medicine on digestive system-related diseases. In naïve CD4+ T cells, alpinetin increased both AhR and CYP expression. Despite no changes in Th17 levels, this flavonoid increased Treg and IL-10 levels (Lv et al., 2018).

Lastly, naringenin, a flavonoid present in citrus fruits, similarly acted as an AhR agonist in CD4+ T cells, promoting Treg differentiation (Wang et al., 2012).

Overall, these studies reveal that flavonoid-AhR interactions in the immune context predominantly promote Treg differentiation while suppressing pro-inflammatory Th17 cells. However, despite the general association of AhR agonism with immune modulation in the literature, cinnamtannin D1's antagonistic action also demonstrated beneficial immunoregulatory outcomes, indicating a more complex and context-dependent activities that need further investigation.

In summary: Five of the six studies analyzed demonstrated the AhR agonistic activity of flavonoids in both dendritic and T-cells. Four studies confirmed this agonism activity by assessing CYP expression/activity. The effects of flavonoids mediated by AhR receptors consistently align with immunomodulatory and anti-inflammatory effects. Of the 6 conditions evaluated, all demonstrated increased levels of Treg cells upon flavonoid-AhR signaling. Th17 cells were found decreased in 2 studies and the inflammatory status was found downregulated in 4 studies. Collectively, these results suggest a **favorable Treg/Th17 balance driven by flavonoid-AhR agonism** contributing to significant anti-inflammatory effects.

4.1.3. Flavonoid-AhR activity in kidney

Table 6 presents the kidney-dependent flavonoid-AhR agonistic/antagonistic activity with the resulting pharmacodynamic effects on key hallmarks of renal pathology. A total of 6 studies were included in this section describing 7 conditions in both *in vivo* (CKD animal models, n=3) and *in vitro* models (n=4).

Table 6. Flavonoid-AhR modulation in kidney: ligand-receptor activity and functional readouts.

	Flavonoid	Flavonoid-AhR Activity	CYP Density & Activation	Renal Parameters				Ref.
				Fibronectin	Fibrosis	Macrophage Infiltration	Inflammatory and OS biomarkers	
- MDBK cells infected with BoAHV-1	- Taurisolo® (0.5 mg/ml)	Agonism	ND	ND	ND	ND	ND	(Cerracchio et al., 2023)
- male C57BL/6 mice (Hyperuricemia-Induced CKD)	- Fisetin (50 and 100 mg/kg/d) (4 weeks)	Antagonism	ND	-	-	ND	ND	(Ren et al., 2021)
- male Sprague–Dawley rats (5/6 nephrectomy)	- Barleriside A (10 mg/kg/d) i.p. (4 weeks) - PHF (10 mg/kg/d) i.p. (4 weeks)	Antagonism	-	-	-	ND	ND	(Miao et al., 2020)
- Normal rat kidney proximal tubular epithelial cells NRK-52E	- Barleriside A (10 µM)	Antagonism	-	-	-	ND	ND	
- male C57BL/6 mice (STZ-induced diabetic nephropathy)	- Aminoflavone (5 mg/kg) i.p. 8 weeks	Antagonism	ND	-	-	-	-	(Lee et al., 2016)
- RMC - MMC - HK2 cells	- Aminoflavone (5 µM)	Antagonism	ND	-	-	ND	-	
- Human renal cancer cell lines (TK-10, SN12-C, Caki-1, A498 and ACHN)	- Aminoflavone 1 µM	Agonism	ND	ND	ND	ND	ND	(Callero et al., 2012)

+ Increased; **-** Decreased; ND - Not Determined; CYP - Cytochrome; OS - Oxidative stress

Some studies demonstrate that flavonoids may contribute to CKD management by targeting the gut-kidney crosstalk through AhR modulation. For example, fisetin, a flavonol found in edible plants was studied in a model of hyperuricemia-induced CKD. Notably, fisetin acted as an AhR antagonist and regulated the GM's tryptophan metabolism accompanied by reduced fibronectin and fibrosis markers (α-SMA and collagen I) (Ren et al., 2021). Similarly, barleriside A and 5,7,30,40,50-pentahydroxy flavanone, tested in a nephrectomy-induced fibrosis model, also presented antagonistic effects on AhR with a reduction on CYP1A1,

CYP1A2 and CYP1B1 levels. These approaches individually reduced the IS levels in the kidney among with decreased fibronectin, collagen I, and α-SMA levels (Miao et al., 2020). Consistently, barleriside A also reduced collagen I and α-SMA levels in normal rat kidney proximal tubular epithelial cells (NRK-52E) (Miao et al., 2020).

In addition, aminoflavone acted as an AhR agonist in a diabetic nephropathy model. It reduced the expression of fibronectin, collagen IV and α-SMA and decreased the infiltration of F4/80 positive cells. Moreover, this compound was also associated with a significant reduction in oxidative stress markers (4-HNE, MDA) and pro-inflammatory mediators (COX-2 and PGE2) (Lee et al., 2016).

In summary: Five of the seven conditions assessed demonstrated the AhR antagonistic activity of flavonoids in both *in vitro* and *in vivo* models. The only 2 studies observing flavonoid-AhR antagonistic activity were performed *in vitro*. Flavonoid-mediated AhR antagonism was linked to CYP inhibition in 2 studies and resulted in overall improvements in kidney parenchyma by reducing fibrosis (5 studies), macrophage infiltration (1 study) and improving both inflammatory status and oxidative stress (2 studies). Collectively, these findings suggest a **renoprotective role for flavonoid-AhR antagonism**.

Chapter V-Discussion and Concluding Remarks

5. Discussion and Concluding Remarks

This comprehensive scoping review systematically examines the agonistic and antagonistic activity of flavonoid-AhR interactions, linking them with tissue-specific functional outcomes within the gut, the immune system and the kidney. **Figure 18** provides a summary of the key conclusions drawn, based on the most frequent observations for each parameter analyzed:

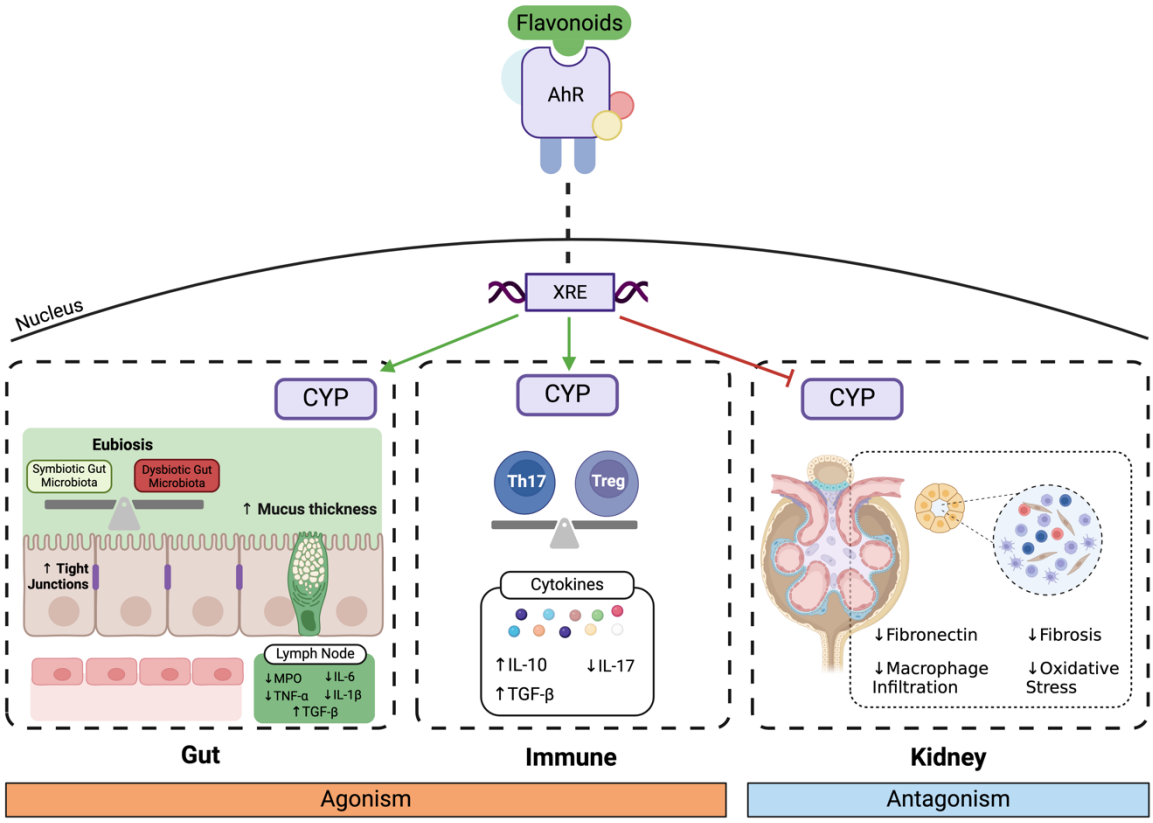


Figure 18. Agonistic and antagonistic activity of flavonoid-AhR interactions and gut-, immune- and kidney-specific effects (Created in Biorender®).

In the gut, flavonoids act as **AhR agonists**, reinforcing the balance of the gut microbiota, enhancing the mucus barrier, and improving intestinal permeability, ultimately creating a predominantly anti-inflammatory environment. These findings align with the observations of Han and colleagues, who noted that under homeostatic conditions, AhR signaling through dietary or microbiota-derived ligands is crucial for maintaining intestinal barrier integrity and function, facilitated by IL-22 secretion, IL-10 induction, strengthening of tight junctions, and modulation of colonic neurons (Han et al., 2021).

In the immune system, flavonoids also act as **AhR agonists**, exerting significant immunomodulatory effects. The expression of AhR in various immune cells, including macrophages, mast cells, eosinophils, dendritic cells, and B cells, underscores the importance of AhR signaling in their regulation and survival (Han et al., 2021). Our study further supports the beneficial impact of flavonoid-AhR signaling by promoting a favorable Treg/Th17 balance and exerting anti-inflammatory effects.

In the kidney, flavonoids mediate **AhR antagonism**. Notably, AhR signaling is associated with podocyte injury, progressive glomerular damage, and the promotion of a pro-inflammatory phenotype (Ichii et al., 2014). In the context of chronic kidney disease (CKD), flavonoid-AhR antagonism demonstrates renoprotective effects by reducing fibrosis, decreasing macrophage infiltration, and improving both inflammatory status and oxidative stress. Collectively, these findings indicate that flavonoid-AhR antagonism plays a significant renoprotective role.

The first limitation of this study is the lack of experimental research evaluating flavonoid-AhR-dependent signaling in both the gut and immune system in the context of CKD. As a result, it is not possible to draw conclusions about the modulation of AhR by flavonoids across the gut-immune-kidney axis simultaneously in the context of CKD. Furthermore, since flavonoids are substrates for intestinal PAZyme-producing bacteria, it is possible that the beneficial effects observed in AhR signaling *in vivo* may also result from interactions with microbiota-derived metabolites that possess AhR agonistic activity.

Nevertheless, despite these limitations, this study offers an important update on flavonoid-AhR signaling, providing valuable information on this topic. It underscores the dual nature of flavonoids, which act as AhR agonists in the gut and immune system, in contrast to their antagonistic role in the kidney. This effect appears to be independent of the specific flavonoid, given the diversity of molecules (19) used. Similar to other diseases like IBD, it is plausible that flavonoid-AhR agonism in the gut and immune system enhances intestinal barrier function, thereby mitigating the harmful effects of uremic toxins in CKD, as proposed by Mo and colleagues (Mo et al., 2020). These working hypotheses, once addressed in future studies, may further our understanding of how flavonoid-AhR interactions can be therapeutically manipulated to slow CKD progression and manage gut inflammation.

Chapter VI – References

6. References

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