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Exploring the Role of the Endocannabinoid System in Chronic Kidney Disease: Implications for Therapeutic Interventions

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Authors' contributions

This work was carried out in collaboration among all authors. All authors contributed to the study conception, preparation and analysis of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Assess alterations in circulating endocannabinoid levels and their potential correlation with the progression of chronic kidney disease. Additionally, the study aims to consider potential implications for the clinical use of these compounds.
Study Design: Descriptive, qualitative, and retrospective observational approach, utilizing a methodological framework grounded in a bibliographic examination of publications featured in indexed journals.
Methodology: An exploration was conducted on the academic search platform PubMed, using the search terms "endocannabinoid system" and "kidney disease," with a chronological filter spanning

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the last 10 years. This search yielded 60 articles, which then underwent a screening and sorting process using the platform's tools to categorize documents based on their thematic relevance.
Results: The exhaustive examination of cannabinoid signaling in chronic kidney disease unveils a nuanced and intricate landscape where the distinctive functions of CB1 and CB2 receptors become apparent. The manipulation of the endocannabinoid system arises as a potentially efficacious therapeutic approach for mitigating kidney disease and injury, substantiated by evidence highlighting its pivotal role in homeostasis and normal kidney function. Nevertheless, the intricate interplays with renal physiology demand a circumspect methodology in the formulation of therapeutic interventions, considering the varied effects observed in different contexts of the endocannabinoid system and renal function.
Conclusion: The exploration of the interaction between the endocannabinoid system and kidney function presents a promising avenue, offering valuable insights for the development of innovative therapeutic approaches in the treatment of kidney diseases.

Keywords: Endocannabinoids; cannabidiol; renal physiology; therapeutics.

1. INTRODUCTION

Chronic kidney disease (CKD) is a progressive condition marked by a gradual decline in kidney function. It is estimated that around 10% of the worldwide population is impacted by CKD, and its advancement may ultimately culminate in end-stage renal disease. This advanced stage often necessitates renal replacement therapies, including dialysis or kidney transplantation [1]. The global prevalence of chronic kidney disease (CKD) is on the rise, parallel to the increasing incidence of key contributing factors and consequences, including diabetes, obesity, hypertension, and autoimmune diseases. Moreover, a comprehensive understanding of the underlying mechanisms contributing to kidney disease is imperative for informing and implementing effective public health initiatives [2-5].

The endocannabinoid system (ECS) constitutes a significant signaling pathway wherein lipid ligands, referred to as cannabinoids, bind to cannabinoid receptors, which also encompass endocannabinoid metabolic enzymes ARCERI et al., [2,6]. This system contributes to various cellular processes, with its components playing crucial roles in a range of physiological and pathological processes, including but not limited to energy metabolism and inflammation (PERMYAKOVA et al., 2023; SUZUKI; FLEIG; PENNER, [7] ZHOU et al., [8]

The ECS signaling pathway comprises two principal receptors, namely the cannabinoid receptor type 1 (CB1) and the cannabinoid receptor type 2 (CB2). Specifically, this pathway involves endogenous cannabinoid ligands, commonly referred to as endocannabinoids (ARCERI et al., [2]. PERMYAKOVA et al., 2023; SUZUKI; FLEIG; PENNER, [7]. The best characterized endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which are lipid-derived molecules generated on demand by the metabolism of membrane phospholipids in response to various stimuli (PERMYAKOVA et al., 2023; KLAWITTER et al., 2022; PRESSLY et al., 2019; BARUTTA et al., 2018).

Currently, ECS has gained attention in the therapeutic context [6,4] being suggested as an alternative to anti-inflammatories, antiemetics, antipsychotics and antiepileptics, in a wide range of conditions [9] Although initial research primarily concentrated on the role of the endocannabinoid system (ECS) in the central nervous system, more recent investigations have identified significant concentrations of endocannabinoids, the requisite machinery for their biosynthesis and degradation, as well as cannabinoid receptors, in various organs, including kidney tissue [6,10,11].

Kidney diseases are instigated and perpetuated through an intricate interplay of various mechanisms, encompassing inflammation, oxidative stress, epithelial-mesenchymal transition, cytokine activation, growth factors, and genetic factors. Profound comprehension of these implicated mechanisms is imperative for the formulation of efficacious treatments for renal diseases [7]. Furthermore, recent data have demonstrated that alterations in the ECS and subsequent pathways may contribute to the pathogenesis of kidney diseases, both acute and chronic [10,4].

Beyond its conventional role in energy metabolism and inflammation, the ECS exerts a profound influence on CKD through intricate

connections with oxidative stress, inflammatory cascades, renal injury, and vascular alterations. Oxidative stress, a hallmark of CKD, involves an imbalance between reactive oxygen species (ROS) production and the antioxidant defense system [12]. The ECS, particularly cannabinoid receptors CB1 and CB2, has been implicated in modulating oxidative stress in renal tissue, influencing redox-sensitive pathways and exacerbating renal injury [13]. Another aspect to be highlighted is that CKD, encompassing renal fibrosis and diabetic kidney disease, has been associated with cannabinoid signaling, particularly involving CB1. Although CB2 has been identified in the human kidney, its activity in the kidney remains contradictory and not as thoroughly characterized. However, CB2 is currently emerging as a subject of study in the context of kidney diseases [2,8].

Additionally, the ECS intertwines with the inflammatory milieu characteristic of CKD, contributing to the perpetuation of cytokine activation, growth factor dysregulation, and the intricate network of inflammatory mediators [14]. This interplay extends to renal injury, where cannabinoid receptor activation, notably CB1, has been linked to the fostering of inflammation and the promotion of fibrosis within the kidney [2]. Furthermore, alterations in the ECS have been associated with vascular changes, emphasizing its role in modulating blood flow dynamics within the renal microenvironment. By delving into these interconnected facets, a more comprehensive understanding of the ECS's influence on CKD can be elucidated, providing a nuanced framework for subsequent discussions on potential therapeutic interventions (KWIATKOWSKA et al., 2023).

Given the significance of the subject matter, its comprehension is contemporaneous and imperative. In this context, the current investigation seeks to assess the potential correlation between alterations in circulating endocannabinoids and the progression of CKD. Additionally, the study aims to contemplate prospective implications for the clinical utilization of these substances.

2. METHODOLOGY

This investigation constitutes a descriptive, qualitative, and retrospective observational study employing a methodological framework rooted in a bibliographic survey of publications featured in indexed journals. The research was conducted on the academic search platform PubMed, utilizing the search terms "endocannabinoid system" and "kidney disease" with a chronological filter spanning the past 10 years. The search yielded 60 articles, subsequently subjected to a screening and categorization process utilizing the platform's available tool for classifying documents based on thematic relevance. Through a critical analysis of these works, those demonstrating significance within the context of this narrative review were singled out. Conversely, publications deemed devoid of a direct connection to the thematic proposal, as per the interpretative analysis conducted by the authors of this review, were intentionally excluded from the study's purview (Fig. 1).

This investigation employed stringent inclusion and exclusion criteria to ensure the relevance and specificity of the selected literature. Articles included in the study were required to focus explicitly on the relationship between the endocannabinoid system and kidney disease,

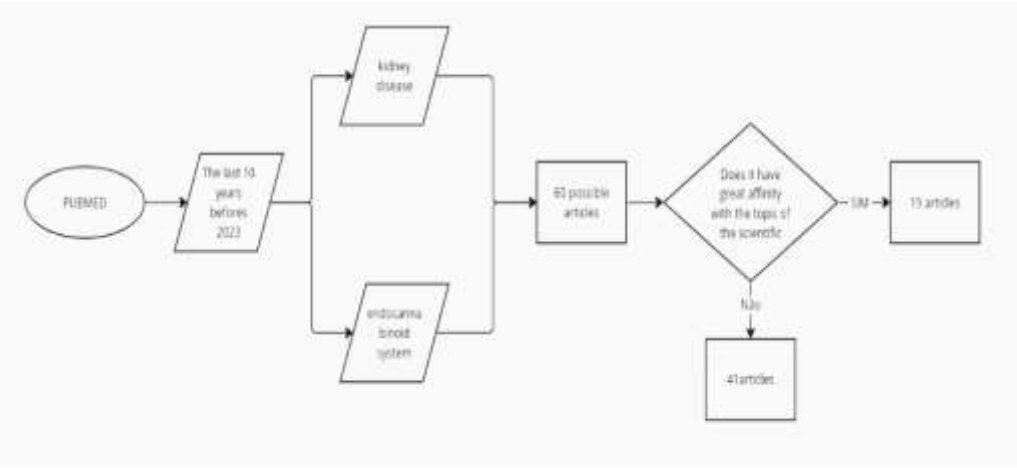

Fig. 1. Flowchart detailing the methodology

providing insights into the molecular mechanisms, signaling pathways, and potential therapeutic implications. The chronological filter spanned the past 10 years to ensure the incorporation of recent advancements in the field. Exclusion criteria involved a meticulous screening process, with articles deemed irrelevant to the thematic proposal intentionally omitted. Specifically, publications lacking a direct connection to the endocannabinoid system's impact on kidney disease, as determined through interpretative analysis by the authors, were excluded. This methodological approach aimed to maintain the precision and relevance of the literature surveyed, aligning with the study's narrative review design.

3. RESULTS AND DISCUSSION

The examination of the ECS has surfaced as a research area of considerable significance owing to its pervasive impact on various physiological and pathological processes within the body [2]. The main results of the selected studies relating to the endocannabinoid system and its relationship with kidney disease can be seen in Table 1.

The natural products present in Cannabis fall into two primary classes: cannabinoid and terpenoid compounds, both possessing anti-inflammatory and analgesic properties. Cannabinoids operate through diverse mechanisms, impacting various biological targets, including G protein-coupled receptors, notably CB1 and CB2 receptors, as well as 5-HT1A and 5-HT2A serotonin receptors. Additionally, cannabinoids influence various ion channels, such as TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, and TRPM8 REIN et al., [16] SUZUKI; FLEIG; PENNER, [7] BARUTTA et al.,[4].

CB1 receptors exhibit activation by both cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC). However, only THC induces psychoactive effects, while CBD mitigates inflammatory processes through mechanisms that remain unknown (SUZUKI; FLEIG; PENNER, 2023; GOLOSOVA et al., [6] BARUTTA et al.,[4] A third cannabinoid, cannabigerol (CBG), shares a pharmacological profile with THC and CBD. The acidic form of CBG (CBGA) is noted for its neuroprotective properties; however, further elucidation is required to understand its properties and pharmacological effects fully. According to Suzuki, Fleig, and Penner [7] CBGA stands out as the most potent cannabinoid inhibitor of store-operated calcium entry and IL-2 production in T cells. This characteristic positions it as a promising candidate molecule for modulating calcium signaling and inflammatory mechanisms in various pro-inflammatory immune cells, potentially influencing kidney inflammation.

The ECS has recently gained prominence as a significant contributor to the pathogenesis of progressive chronic kidney disease, diabetic nephropathy, and drug-induced nephrotoxicity, as cannabinoid receptors appear to contribute to kidney disease and promote kidney damage to varying degrees [16,7].). CB1 activation is implicated in fostering inflammation and kidney injury, while also acting as a crucial mediator in promoting fibrosis not only within the kidney but also in the liver [6,15].). Conversely, CB2 activation may exert anti-inflammatory and renoprotective effects, although existing literature presents conflicting data on this aspect [16,7].

Lecru et al. (2015) conducted a comparative analysis of gene expression in fibrotic and normal murine kidneys. Notably, the CB1 receptor emerged as one of the most prominently upregulated genes, accompanied by a significant elevation of 2-AG levels in mice exhibiting fibrosis. Additionally, the study observed a reduction in renal fibrosis upon CB1 receptor blockade, attributing this effect to a direct influence on myofibroblasts, resulting in decreased collagen expression in vitro. Furthermore, the research revealed a substantial increase in CB1 protein expression in kidney biopsies obtained from patients diagnosed with IgA nephropathy, diabetes, and acute interstitial nephritis. Rimonabant, a discerning antagonist targeting the endocannabinoid CB1 receptor, exerted modulation on the macrophage infiltrate implicated in renal fibrosis. This indicates that CB1 may represent a novel therapeutic target for addressing chronic kidney disease. Similarly, Zhao et al. (2021) assert that rimonabant possesses the capacity to mitigate kidney damage by inhibiting dysregulated mitochondrial dynamics within the renal milieu.

As per Golosova et al. [6], in contrast to CB1 receptors, the deletion of CB2 receptors intensifies tissue damage, amplifying inflammatory, oxidative, and fibrotic processes. This effect is not limited to the kidneys but extends to the liver and skin as well. Additionally, the pharmacological inhibition or blockade of CB2 has been observed to enhance cardiac, hepatic, and cutaneous fibrosis. Conversely, CB2 agonists exhibit a mitigating effect on fibrogenesis.

Table 1. Scientific articles analyzed and their main results

Article title	Authors / Year	Results
Genetic and Genomics Investigation of Structure and Function of the Kidney	Pressly et al.,[15]	SMM-95 (selective CB2 agonist) showed the ability to increase renal cortical blood flow and promote direct vasodilation of isolated perfused afferent arterioles.
CB1 receptor antagonist rimonabant protects against chronic intermittent hypoxia-induced renal injury in rats	Zhao et al., [8]	In tests carried out on patients with obstructive sleep apnea, it was possible to verify that the use of Rimonabant reduced the expression of CB1 receptors, which are responsible for promoting renal function.
Cannabinoid receptor 2 plays a central role in renal tubular mitochondrial dysfunction and kidney ageing	Zhou et al.,[8]	It is concluded that CB2 is an important mediator in renal aging and that it promotes mitochondrial dysfunction in renal tubular cells through the activation of ß-catenin.
Acute and long-term effects of cannabinoids on hypertension and kidney injury	Golosova et al., [6]	Tests on healthy and hypertensive mice demonstrated that the use of Anandamide (cannabinoid receptor ligand) affected hypertensive mice, resulting in increased renal interstitial fibrosis and glomerular damage in the late phase of hypertension. Healthy rats showed no physiological changes.
Endocannabinoid system in polycystic kidney disease	Klawitter et al., [10]	This study aimed to relate the endocannabinoid system to autosomal dominant polycystic kidney disease. Their results showed reduced plasma levels of anandamide and 2-arachidonoylglycerol in patients with this pathology.
Cannabinoid receptor 1 is a major mediator of renal fibrosis	Dao & François, 2021	In a comparison involving healthy mice and mice with diseased and fibrotic kidneys from the experimental model of unilateral urethral obstruction (UUO), it was possible to verify increased expression of CNr1 and 2-arachidonoylglycerol during the UUO process.
Renal Endocannabinoid Dysregulation in Obesity-Induced Chronic Kidney Disease In Humans	Permyakova et al., 2023	A comparison involving lean and obese men using a blood sample and a kidney biopsy revealed morphological changes, kidney damage and fibroblastic markers. Serum endocannabinoid levels are similar between the two groups, however there were elevated levels of anandamide in obese patients. The expression of cannabinoid receptor-1 is reduced in the group of obese individuals, but there was an increase in the activity of endocannabinoid synthesizing and degrading enzymes.
A Retrospective Cohort Study That Examined the Impact of Cannabis	Rein et al., [16]	The study compared hospitalized adult patients with and without chronic kidney disease (CKD) who used cannabis before hospitalization. It was

Article title	**Authors / Year**	**Results**
Consumption on Long-Term Kidney Outcomes		concluded that Cannabis did not negatively affect the renal function of patients without CKD, but in patients who presented this pathology there was a faster annual decline in the estimated glomerular filtration rate.
CBGA ameliorates inflammation and fibrosis in nephropathy	Suzuki; Fleig; Penner, [7]	In a comparative study involving healthy mice and acute and chronic nephropathic patients, it was possible to observe that the use of cannabidiol and cannabigerols reduced and prevented kidney damage in mice presenting such pathology.

Pressly et al. [15] conducted an inquiry into the impact of a CB2 receptor agonist, specifically SMM-295, on renal vasculature, employing the evaluation of cortical perfusion as a metric. The agonist has demonstrated the ability to induce renal vasodilation through the activation of both vascular and non-vascular CB2 receptors. This suggests a potential avenue for therapeutic intervention in renal injuries affecting blood flow dynamics within the kidneys. Conversely, Zhou et al. [11] underscored the pivotal role of CB2 in kidney aging, elucidating its potential to instigate mitochondrial dysfunction in renal tubular cells. The study cautions that prolonged CB2 receptor activation, particularly in recreational users of exocannabinoids, may expedite the aging process in the kidneys.

Chua et al. [17] assert that manipulation of ECS could serve as an efficacious therapeutic approach for addressing kidney diseases and injuries. This proposition is grounded in the observed significance of the SeCB system in maintaining homeostasis and facilitating normal kidney function. Nonetheless, the authors emphasize the imperative for more comprehensive studies to elucidate the precise role of the SeCB system and delineate the individual contributions of its constituent components.

A nuanced examination of the selected articles unveils a complex interplay within the endocannabinoid system (ECS) and its impact on chronic kidney disease (CKD). Across the literature, CB1 receptor activation consistently emerges as a pivotal factor exacerbating inflammation and fostering renal damage. As reported, Lecru et al. [18] and Golosova et al. [6] provide converging evidence, demonstrating upregulated CB1 expression in fibrotic kidneys and highlighting the detrimental effects of CB1 activation. Notably, therapeutic interventions targeting CB1, such as Rimonabant, exhibit promising results in mitigating macrophage infiltration and renal fibrosis. This consistency underscores the potential of CB1 as a viable therapeutic target in the context of CKD.

In contrast, the role of CB2 receptors exhibits more variability, with conflicting data on their anti-inflammatory and renoprotective effects. Golosova et al. [6] present evidence of intensified tissue damage upon CB2 receptor deletion, extending beyond the kidneys to impact the liver and skin. Conversely, Pressly et al. [15] and Zhou et al. [8] suggest potential renoprotective effects of CB2 activation, demonstrating its ability to induce renal vasodilation and influence mitochondrial dysfunction in renal tubular cells. These divergent findings highlight the contextual sensitivity of CB2's effects, dependent on factors such as experimental conditions and specific cellular contexts. This comparative analysis underscores the need for a nuanced understanding of the ECS in CKD and emphasizes the importance of considering diverse experimental contexts when interpreting results, pointing toward avenues for future research to reconcile these discrepancies and refine the therapeutic potential of ECS modulation in CKD.

As the ECS assumes a pivotal role in the pathogenesis of kidney diseases, ongoing research uncovers intricate nuances, prompting the exploration of personalized therapeutic strategies and selective modulation of cannabinoid receptors. This endeavor aims to maximize therapeutic benefits while mitigating potential adverse effects (MORADI et al., 2020; UDI et al., 2020). Nevertheless, the intricate interplay with renal physiology underscores the necessity for a judicious approach in developing therapeutic interventions, given the diverse effects observed across distinct experimental contexts CHUA et al., [17,18]

While the present investigation contributes valuable insights into the intricate interplay between the ECS and CKD, certain limitations should be acknowledged. The included studies themselves contribute to the study's limitations, as the existing literature on the ECS and CKD exhibits variability in experimental designs, methodologies, and reported outcomes. This heterogeneity poses challenges in drawing definitive conclusions and necessitates cautious interpretation of the findings. Additionally, while the study delves into the potential therapeutic implications of alterations in circulating endocannabinoids, it does not provide direct clinical evidence or outcomes from interventions, warranting future research to bridge this gap between preclinical observations and clinical applicability [19,20].

4. CONCLUSION

Investigating the ECS, its receptors, and ligands may offer enhanced understanding leading to novel treatment modalities for various kidney diseases. Its discernible presence and functionality have been identified in multiple organs and systems, encompassing the central

nervous system, the immune system, and notably, the kidneys. This intricate system, comprising receptors, endogenous ligands, and associated enzymes, assumes a pivotal role in the regulation of homeostatic balance. Appreciating the intricacies of the ECS becomes imperative not only for advancing physiological knowledge but also for exploring potential therapeutic applications in both health and disease conditions. Within this framework, delving into the interplay of this complex system with kidney function emerges as a promising avenue, providing valuable insights for the development of innovative therapeutic approaches in the treatment of kidney diseases.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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