BBA - Molecular and Cell Biology of Lipids 1870 (2025) 159668

Contents lists available at ScienceDirect

BBA - Molecular and Cell Biology of Lipids

journal homepage: www.elsevier.com/locate/bbalip

Review article

Polyunsaturated fatty acids in kidney diseases: Navigating the fine line between healing and damage

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ARTICLE INFO

Keywords:
Polyunsaturated fatty acids
Inflammation
Lipid mediators
Cyclooxygenase
Lipoxygenase
Kidney diseases

ABSTRACT

Polyunsaturated fatty acids (PUFAs) regulate renal inflammation through metabolites generated by COX, LOX, and CYP pathways. While prostaglandins, leukotrienes, and 20-hydroxyeicosatetraenoic acid (20-HETE) exacerbate kidney injury, epoxyeicosatrienoic acids (EETs), lipoxins, and other specialized pro-resolving mediators (SPMs) counteract inflammation and promote tissue repair. These lipid mediators also modulate nuclear receptors such as peroxisome proliferator-activated receptors (PPARs) and fibrotic pathways like TGF-β signaling. Disease-specific imbalances in PUFA metabolism have been implicated in nephrotic syndrome, glomerulonephritis, kidney transplantation, and renal cancer. This review integrates mechanistic insights with experimental and clinical data, highlighting therapeutic strategies including dietary ω-3 PUFA supplementation, synthetic SPM analogs, selective enzyme inhibitors, and nanocarrier-based delivery systems. We also address limitations, such as short half-life, off-target effects, and immunoregulatory risks. Lipidomic profiling may aid in patient stratification and treatment personalization. Collectively, targeting PUFA-derived lipid mediators offers a promising adjunct to conventional therapies for inflammatory and immune-mediated kidney diseases.

1. Introduction

Polyunsaturated fatty acids (PUFAs), characterized by multiple double bonds within their structure, are essential for various physiological functions, including neural activity, coagulation, and muscle health [1]. Beyond their fundamental biological roles, PUFAs and their metabolites, collectively termed oxylipins, are intricately involved in inflammatory processes, which are central to the pathogenesis of a range of kidney diseases [2]. The enzymes responsible for PUFA metabolism, namely cyclooxygenases (COXs), lipoxygenases (LOXs), and cytochromes P450 (CYPs), play pivotal roles in regulating the production of lipid mediators such as prostaglandins (PGs), leukotrienes (LTs), and lipoxins (LXs). These lipid mediators modulate inflammation and fibrosis, key processes in kidney pathology [3].

COXs are the primary enzymes involved in converting arachidonic acid (AA) into PGs, thromboxanes (TXs), and prostacyclins, all of which are critical in regulating inflammatory responses and maintaining vascular homeostasis [4]. In the context of kidney injury, metabolites derived from COX contribute significantly to inflammation and fibrosis, the hallmarks of chronic kidney diseases (CKDs) [5]. The use of COX inhibitors, including non-steroidal anti-inflammatory drugs (NSAIDs), is known to reduce inflammation and mitigate renal damage, underscoring the importance of COX-derived metabolites in the progression of kidney diseases [6].

LOXs, a family of dioxygenase enzymes, catalyze the oxidation of PUFAs such as AA, linoleic acid (LA), and alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), dihomo-γ-linolenic acid (DGLA), as well as less frequently discussed but biologically relevant PUFAs such as 18:3 ω-6, 22:4 ω-6, 22:5 ω-6, 18:4 ω-3, and 22:5 ω-3 [7]. The enzymatic activity of LOXs on these substrates gives rise to hydroxylated fatty acids and specialized pro-resolving mediators involved in immune modulation and inflammation resolution [8]. In renal injury, LOXs play a critical role in driving inflammation and fibrosis [9]. LTs enhance inflammation by increasing vascular permeability and recruiting immune cells, contributing to the pathogenesis of conditions such as glomerulonephritis (GN) and diabetic nephropathy (DN) [10]. In contrast, LXs, produced by 15-LOX, facilitate the resolution of inflammation and promote tissue repair, highlighting the dual role of LOXs in both initiating and resolving inflammation [11,12]. Specifically, 15-LOX-1 has been implicated in kidney damage,

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https://doi.org/10.1016/j.bbalip.2025.159668
Received 15 March 2025; Received in revised form 18 July 2025; Accepted 20 July 2025
Available online 23 July 2025

particularly in chronic conditions like diabetic nephropathy, by driving both inflammation and fibrosis [9]. Among LOX isoforms, 15-LOX exists in two distinct variants. 15-LOX-1 displays a dual role in inflammation, it can generate anti-inflammatory mediators such as 15-hydroxyeicosatetraenoic acid (15-HETE) from AA and 15-hydroxyeicosapentaenoic acid (15-HEPE) from EPA, which are precursors of LXs and resolvins. Moreover, it produces pro-inflammatory metabolites, such as 13-hydroxyoctadecadienoic acid (13-HODE) from LA, which may contribute to oxidative stress and vascular dysfunction [13]. In contrast, 15-LOX-2 primarily oxygenates esterified fatty acids within membrane phospholipids and is more associated with tissue remodeling and epithelial differentiation [13,14]. Other LOX isoforms, such as 5-LOX and 12-LOX, also influence renal inflammation.

CYP enzymes are integral to the metabolism of PUFAs, particularly in the production of epoxyeicosatrienoic acids (EETs) [15]. These metabolites regulate key processes such as vascular tone, inflammation, and renal blood flow, all of which are essential for maintaining kidney homeostasis. Disruption in the activity of CYP450 enzymes can lead to kidney dysfunction, exacerbating conditions like acute kidney injury (AKI) and CKD [16]. Specifically, CYP450-derived EETs have protective effects by promoting vasodilation and reducing inflammation. However, an imbalance in the production of these metabolites can also contribute to kidney damage, fibrosis, and the progression of renal diseases. Furthermore, CYP450 enzymes interact with various endogenous and exogenous compounds, influencing drug metabolism and potentially contributing to nephrotoxicity in renal pathways [17].

This review endeavors to clarify the dual roles of PUFAs within these pathological processes, detailing the complex mechanisms by which PUFAs and their metabolites regulate inflammatory and fibrotic responses. Furthermore, it aims to provide a comprehensive understanding of their contributions to renal damage and to explore potential therapeutic implications in the context of kidney diseases.

2. Dyslipidemia in kidney disease progression

Growing experimental and clinical evidence underscores the strong association between lipid abnormalities and the onset and progression of CKD. Dyslipidemia is a major factor in accelerating CKD, with large-scale clinical trials and meta-analyses indicating that statin therapy may help to slow down this process [18]. Elevated low-density lipoprotein (LDL) cholesterol levels have been linked to a more rapid decline in estimated glomerular filtration rate (eGFR) in patients with CKD [19]. Furthermore, observational studies correlate lipid imbalances, including high triglycerides, low high-density lipoprotein (HDL), and an increased LDL/HDL ratio, with an increased risk of CKD onset and faster GFR decline over time [19].

Dyslipidemia promotes renal dysfunction through mechanisms similar to lipid-mediated vascular injury in atherosclerosis [20]. These include mesangial cell activation, glomerular lipid accumulation, podocyte injury, monocyte infiltration, and tubular lipid deposition [20]. LDL binds to specific receptors on mesangial cells, triggering matrix protein synthesis and the release of proinflammatory cytokines, leading to macrophage infiltration and sustained inflammation [21]. Excess lipoprotein accumulation within the glomerular mesangium enhances extracellular matrix production, fostering glomerulosclerosis [21]. Podocytes, essential for maintaining glomerular integrity, are highly susceptible to damage from elevated triglycerides and cholesterol, while oxidized LDL intensifies renal inflammation by promoting monocyte infiltration into renal tissues [22]. Additionally, lipid reabsorption *via* the megalin–cubilin complex, along with increased nephron glucose uptake, accelerates lipid accumulation in renal tubules and interstitium, further aggravating kidney injury [20].

Disruption of lipid metabolism is a critical factor in the pathogenesis of both glomerular and interstitial damage, driving the progression of CKD [23]. Conditions such as focal segmental glomerulosclerosis (FSGS) and tubulointerstitial fibrosis worsen with excessive dietary cholesterol intake, which alters fatty acid composition in renal tissues, promotes macrophage infiltration, induces mesangial expansion, and enhances lipid accumulation and foam cell formation [24]. Patients with CKD are at a heightened risk of cardiovascular diseases (CVDs), with dyslipidemia being a modifiable yet significant contributor [25]. While lipid-lowering therapies have shown limited benefits in kidney disease, controlled trials and meta-analyses suggest that lipid reduction decreases proteinuria and helps preserve GFR [25]. Changes in lipid profiles during different CKD stages negatively impact renal function and substantially elevate the risk of CVDs [26].

Statins exert pleiotropic effects beyond LDL reduction, improving renal outcome by mitigating inflammation, reducing oxidative stress, and stabilizing atherosclerotic plaques [27]. As inhibitors of hydroxymethylglutaryl-CoA (HMG-CoA) reductase, statins decrease isoprenoid production, thereby limiting mesangial cell proliferation, leukocyte adhesion, and monocyte activation [28]. In experimental models, statins have been shown to protect glomeruli by reducing macrophage infiltration, inhibiting mesangial cell proliferation, and suppressing NF-κB activation in response to inflammatory stimuli [29].

An emerging aspect of statin therapy is its interaction with PUFAs. Statins and PUFAs share overlapping cellular pathways, suggesting that PUFA metabolites might act as secondary messengers in statin-mediated renal protection [30]. Research consistently indicates that ω-3 PUFAs lower serum lipid levels, even in individuals not undergoing statin therapy, reinforcing their therapeutic potential in preventing glomerular injury [31]. Understanding the interplay between statins and PUFAs could provide novel insights into cardiovascular and renal protection, warranting further exploration of their combined effects in CKD management.

3. PUFAs and the progression of renal diseases

3.1. Overview: mechanistic links between PUFAs and kidney injury

PUFAs are categorized into two main groups: ω-6 and ω-3. Their primary dietary precursors, LA (18:2 ω-6) and ALA (18:3 ω-3), are metabolized into AA (20:4 ω-6), eicosapentaenoic acid (EPA, 20:5 ω-3) and docosahexaenoic acid (DHA, 22:6 ω-3), respectively. The balance between these PUFAs plays a crucial role in regulating inflammation, as they influence the production of eicosanoids, which mediate pro-inflammatory and anti-inflammatory responses [32]. A diet rich in PUFAs has been shown to regulate leukocyte chemotaxis, improve endothelial function, and modulate cytokine synthesis, demonstrating significant therapeutic potential in inflammatory conditions [33]. Clinical and experimental studies highlight the impact of dietary PUFAs on renal inflammation and fibrosis, two key processes in CKD progression. Lin et al. reported that diabetic patients consuming ω-3 PUFAs and high-quality proteins exhibited a lower risk of developing DN [34]. Similarly, increased intake of marine fish, shellfish, and low-fat dairy products has been associated with a decreased risk of DN [34]. These findings emphasize the role of dietary PUFA composition in modifying phospholipid profiles, thereby influencing inflammatory pathways in the kidneys. In addition to inflammation, renal fibrosis significantly contributes to CKD progression. Dietary interventions modifying PUFA composition have been shown to impact fibrotic pathways, potentially mitigating nephropathy [35]. In a study on polycystic kidney disease, Ogborn et al. demonstrated that a diet rich in conjugated LA significantly improved chronic interstitial nephritis (CIN) [36]. Additionally, Khan et al. found that fish oil and flaxseed oil, both abundant in ω-3 PUFAs, effectively reduced nephrotoxicity and oxidative stress in male Wistar rats exposed to sodium nitroprusside [37].

The beneficial effects of fish oil on blood pressure and proteinuria in both human and animal models of hypertension are attributed to its vasodilatory properties and its ability to regulate transforming growth factor-beta (TGF-β), renin, fibronectin, and nitric oxide (NO) synthesis [38]. Ng et al. demonstrated that fish oil supplementation improved

renal function in patients with IgA nephropathy following transplantation [39]. Furthermore, Tsipas and Morphake observed that a balanced intake of ω-6 and ω-3 PUFAs mitigated cyclosporine-induced nephrotoxicity [40]. These findings underscore the therapeutic promise of PUFAs in managing various kidney disorders. The mechanisms underlying the nephroprotective effects of PUFAs are still being investigated. Studies suggest that renal injury occurs primarily through two pathways: inflammatory responses involving TGF-β, tumor necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1); and hemodynamic changes mediated by NO, angiotensin II (Ang II), and PGs [41,42]. These factors drive renal fibrosis, ultimately contributing to end stage renal disease (ESRD). The early phase of renal damage involves the activation of cellular mediators, with TGF-β playing a pivotal role. This leads to cell proliferation, extracellular matrix (ECM) expansion, and progressive fibrosis. Ang II, a major pro-inflammatory mediator, influences macrophage activity, fibroblast proliferation, and renal cell hypertrophy. It enhances tubular epithelial cell activation and upregulates profibrotic cytokines *via* TGF-β-dependent pathways [43]. Moreover, PUFAs have been shown to modulate renal fibrosis by affecting apoptosis, inflammation, migration, proliferation, and differentiation [44]. This highlights the complexity of kidney fibrosis and the potential for targeting these mechanisms to slow down the progression of CKD (Fig. 1).

EPA, a major ω-3 PUFA from fish oil, has been found to suppress mesangial cell proliferation in response to platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) [45]. This occurs through the inhibition of PDGF receptor autophosphorylation, suppression of extracellular signal-regulated kinase (ERK) activation, and downregulation of cyclin-dependent kinase 4 (CDK4) and cyclin D1 expression [46]. Additionally, in anti-Thy 1.1 GN models, fish oil supplementation significantly reduced mesangial cell activation and proliferation, leading to lower proteinuria and improved renal histology.

PUFAs also regulate key pathways such as the renin-angiotensin system (RAS) and NO metabolism, both of which are central in CKD and hypertension. Evidence suggests that PUFAs inhibit angiotensin-converting enzyme (ACE) activity, reduce Ang II production, enhance endothelial NO synthesis, and downregulate TGF-β expression [47]. AA, an ω-6 PUFA, enhances the response of mesangial Ca^{2+}-activated K^{+} channels to Ang II, which is crucial for regulation of glomerular filtration [48].

DHA, another key ω-3 PUFA, has shown protective effects in murine models of ischemic AKI by reducing serum creatinine levels and suppressing TNF-α and inducible nitric oxide synthase (iNOS) expression post-reperfusion [49]. Furthermore, long-term supplementation with EPA-DHA in patients with prior myocardial infarction significantly slowed kidney function decline, particularly in those with pre-existing CKD [50].

Emerging research indicates that PUFAs influence peroxisome proliferator-activated receptor (PPAR) activity in renal tissues, affecting lipid metabolism, inflammation, and glomerulosclerosis progression [51]. Targeting PPARs through dietary or pharmacological interventions presents a promising strategy for slowing CKD progression.

Although the general roles of PUFA-derived mediators in kidney inflammation and fibrosis have been broadly delineated, growing evidence underscores the heterogeneity of their impact across distinct renal disorders. The pathophysiological landscapes of nephrotic syndrome (NS), GN, transplantation-related nephropathy, autoimmune kidney diseases and renal cancer differ markedly in terms of cellular targets, inflammatory cascades, and lipid mediator profiles [52]. Consequently, a deeper understanding of PUFA metabolism requires disease-specific analysis. Indeed, although PUFAs and their metabolites participate in the pathogenesis of nearly all kidney diseases, their patterns of

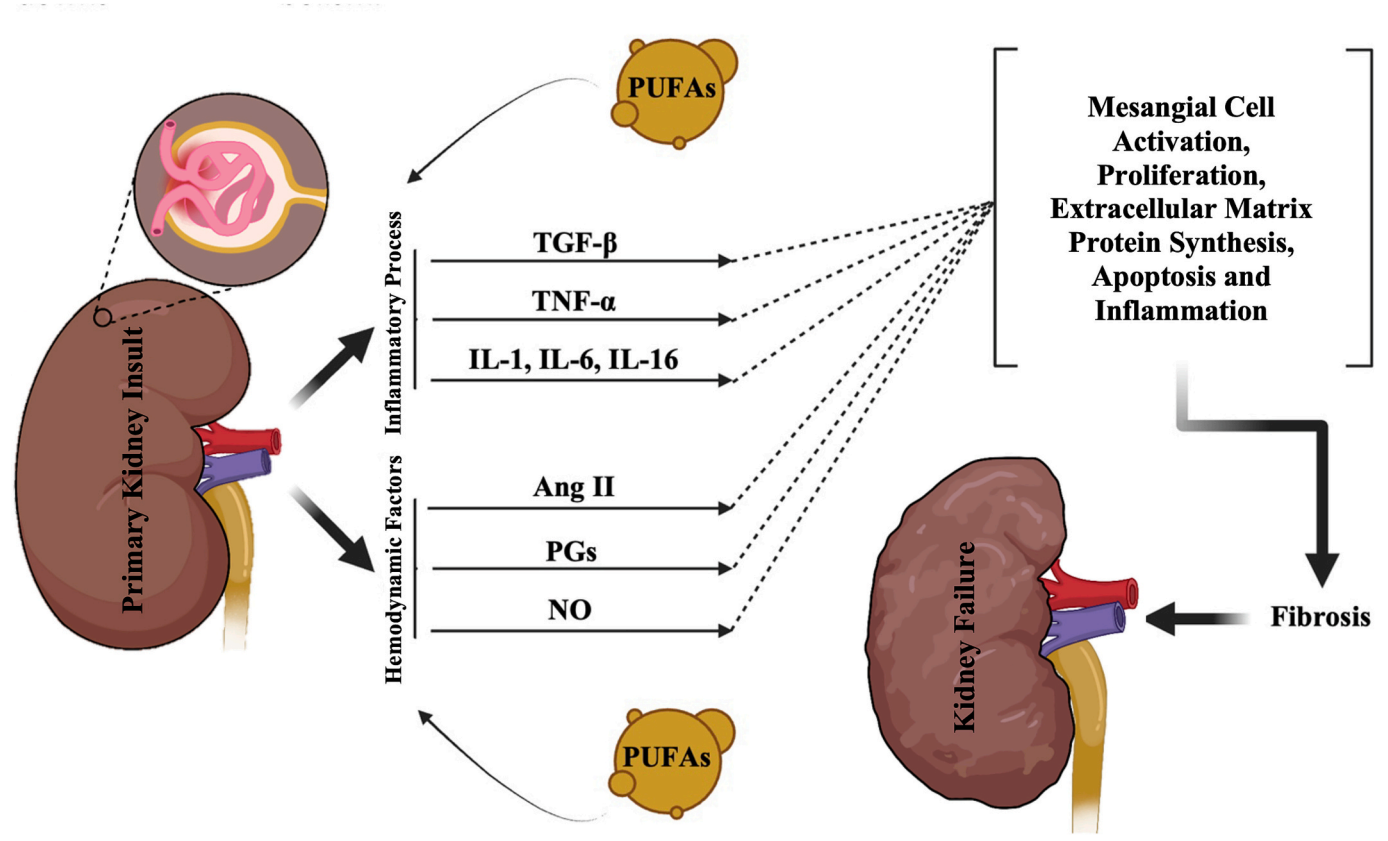

Fig. 1. Potential targets of PUFAs in renal fibrosis process. PUFAs play their pro-inflammatory or anti-inflammatory role by regulating several main factors in the two groups of inflammatory and hemodynamic factors. PUFAs interfere with the processes involved in kidney fibrosis, such as the activation and proliferation of mesangial cells and the synthesis of ECM proteins, as well as apoptosis, proliferation, differentiation and migration of renal cells.

involvement vary substantially depending on the specific disease context. The dominance of particular oxylipins, such as LTB4 in GN [53], PGE2 in NS [54], 20-HETE in ischemia/reperfusion injury (IRI) [55], and LXA4 in autoimmune nephritis [56], reflects the distinct inflammatory and hemodynamic environments of each condition. These distinctions are critical for elucidating both shared and divergent mechanisms and informing tailored therapeutic strategies.

Thus, while the metabolic pathways are conserved, the balance, downstream targets, and clinical implications of each mediator differ significantly across disease types. This concept underpins the disease-specific organization as presented in the following subsections.

3.2. Nephrotic syndrome

NS, defined by massive proteinuria, hypoalbuminemia, hyperlipidemia, and peripheral edema, is increasingly recognized as an immunoinflammatory disorder with substantial glomerular involvement. A growing body of evidence implicates PUFA-derived eicosanoids, particularly LTs and LXs, in modulating both the initiation and resolution of glomerular inflammation [10]. Several clinical studies have reported elevated urinary and plasma concentrations of LTB4, cysteinyl leukotrienes (LTC4, LTD4), as well as increased levels of thromboxane B2 (TXB2), the stable metabolite of TXA2 in pediatric patients with active NS, particularly during relapses and in steroid-resistant cases [57,58].

These eicosanoids promote mesangial proliferation, cytokine production, and leukocyte recruitment, contributing to glomerular permeability and podocyte injury. In contrast, LXA4, an endogenous pro-resolving mediator generated through the lipoxygenase pathway, has demonstrated anti-inflammatory and cytoprotective effects in nephrotic models. LXA4 exerts its action *via* inhibition of NF-κB signaling and suppression of pro-inflammatory cytokines such as TNF-α and IL-1β [11]. While direct evidence from adriamycin-induced nephrosis is limited, studies in DN and other inflammatory kidney conditions suggest that LXA4 analogs reduce proteinuria, inhibit NF-κB signaling, and suppress pro-fibrotic responses [59]. LXA4 has also been reported to influence macrophage polarization, promoting a shift toward the M2 reparative phenotype and reducing fibronectin expression, mechanisms that may help mitigate mesangial expansion and interstitial fibrosis [60].

From a clinical perspective, ω-3 PUFAs, namely EPA and DHA, have been evaluated as adjunctive therapy in NS due to their anti-inflammatory and lipid-lowering properties. ω-3 PUFAs, particularly EPA and DHA, reduce inflammation by competing with AA for enzymatic metabolism, thereby lowering the production of pro-inflammatory eicosanoids [61]. Clinical trials have shown that supplementation with 3 g/day of ω-3 fatty acids can reduce serum triglycerides and modestly lower proteinuria in patients with glomerular diseases such as membranous nephropathy and focal segmental glomerulosclerosis [29]. A meta-analysis of randomized trials further supports a small but significant reduction in proteinuria with ω-3 supplementation, though no clear effect on eGFR was observed [29]. Furthermore, adherence to a Mediterranean diet, rich in ω-3 fatty acids, was associated with a more favorable plasma PUFA profile and reduced ω-6 to ω-3 ratio in children with idiopathic nephrotic syndrome (INS), potentially contributing to improved inflammatory status [62].

These studies support the potential adjunctive role of ω-3 PUFAs in managing lipid abnormalities and proteinuria in NS, though further large-scale studies are needed to confirm their efficacy and define optimal dosing strategies. However, evidence for improved glomerular filtration or enhanced steroid responsiveness remains limited. While ω-3 PUFAs show promise in managing NS comorbidities, their inability to consistently preserve renal function or demonstrate universal proteinuria reduction across glomerulopathies underscores the need for personalized dosing strategies and subtype-specific clinical guidelines [63].

Importantly, ω-3 PUFAs exhibit a favorable safety profile, with gastrointestinal discomfort being the most commonly reported side effect. Their inclusion as part of individualized dietary strategies offers a low-risk option for managing hyperlipidemia and inflammatory burden in NS [64]. Meanwhile, the therapeutic potential of LXA4 remains confined to preclinical research due to metabolic instability and lack of approved formulations. Emerging delivery technologies, including nanoparticle-based encapsulation, may facilitate renal targeting and enhance bioactivity of such lipid mediators in future interventions [65].

3.3. Glomerulonephritis

GN encompasses a diverse group of immune-mediated glomerular diseases, including IgA nephropathy, lupus nephritis (LN), which is discussed in greater detail in Section 3.5 due to its systemic autoimmune features, membranoproliferative GN, and rapidly progressive GN. Despite etiologic heterogeneity, these conditions share a common pathophysiological theme: immune cell infiltration, cytokine activation, and disruption of the glomerular filtration barrier. PUFA metabolites play an increasingly recognized role in amplifying or resolving these immune responses.

Among the AA-derived eicosanoids, LTB4 is a potent chemoattractant that recruits neutrophils and monocytes to glomerular tissue. Elevated renal and systemic levels of LTB4 have been demonstrated in both animal models and human biopsies of IgA nephropathy [66,67]. Its receptor BLT1 is overexpressed in glomerular endothelial and infiltrating immune cells, and pharmacological inhibition of LTB4 signaling significantly reduces glomerular injury in murine models [68].

On the anti-inflammatory axis, LXA4 has emerged as a critical modulator of immune resolution in GN. LXA4 levels are reported to be diminished in active LN, as further detailed in Section 3.5. Exogenous administration of LXA4 or its stable analogs has been shown to suppress NF-κB signaling, reduce the expression of adhesion molecules such as ICAM-1 and VCAM-1, and facilitate the clearance of activated leukocytes [69]. These actions collectively help preserve glomerular integrity and limit proteinuria.

In GN subtypes such as IgA nephropathy and LN, ω-3 PUFAs may attenuate glomerular inflammation by downregulating LTB4 and TXA2 production through competitive inhibition of AA metabolism. This shift favors the biosynthesis of specialized pro-resolving mediators like resolvins, which suppress mesangial proliferation and immune activation in experimental models. EPA-derived RvE1 has also been shown to suppress mesangial proliferation and macrophage activation in experimental GN models [70,71].

Collectively, the evidence highlights that PUFA-derived lipid mediators act as active regulators of glomerular inflammation in GN rather than inert byproducts. These mediators, ranging from pro-inflammatory leukotrienes to pro-resolving agents like resolvins and lipoxins, exert bidirectional effects on immune activation and resolution dynamics within the glomerular microenvironment. As such, therapeutic strategies that seek to recalibrate this lipid mediator balance offer promise as adjunctive approaches in GN management. This may be particularly relevant for treatment-resistant or relapsing cases where conventional immunosuppressive regimens are insufficient to achieve durable disease control.

3.4. Kidney transplantation

Kidney transplantation offers the most definitive treatment for patients with ESRD. Yet, despite advances in surgical techniques and immunosuppressive therapy, long-term graft survival remains limited by immune-mediated injury and persistent low-grade inflammation [72]. Within this context, PUFAs and their bioactive derivatives have garnered attention for their potential to modulate immune responses and promote graft homeostasis.

While direct studies on ω-3 PUFA supplementation in murine models

of renal transplantation are limited, related animal studies have demonstrated that ω-3 PUFAs can attenuate inflammatory responses. For instance, in a controlled mouse model of fat grafting, fish oil supplementation reduced serum CRP levels, decreased expression of pro-inflammatory cytokines, and diminished infiltration of inflammatory cells in graft tissues, indicating enhanced resolution of inflammation and improved graft survival [73].

Clinical trials investigating ω-3 PUFA supplementation in kidney transplant recipients have yielded mixed results. Some studies have reported benefits such as reduced triglyceride levels and improved endothelial function. For instance, a randomized controlled trial found that supplementation with 2.6 g/day of EPA and DHA for 44 weeks led to significant reductions in plasma triglycerides and improvements in endothelial function, although no significant changes in GFR were observed [74]. Another study reported that fish oil supplementation at a dose of 6 g/day during the first postoperative year improved renal hemodynamics and reduced blood pressure in kidney transplant recipients [75].

3.5. Autoimmune-associated renal diseases

Autoimmune nephropathies, including systemic lupus erythematosus (SLE)-associated nephritis and ANCA-associated vasculitis, are driven by a breakdown in immune tolerance, characterized by immune complex deposition, complement activation, and chronic glomerular inflammation [76]. In these contexts, lipid mediators derived from PUFAs have emerged as key regulators of immune responses, bridging metabolic and immunologic dysfunction. In LN, as discussed in Section 3.3, renal expression of COX-2 and 5-LOX is elevated, leading to increased production of pro-inflammatory eicosanoids including PGE2 and LTB4, which contribute to immune-mediated tissue injury. Inhibition of LTB4 signaling in murine LN models reduces proteinuria and improves histological outcomes. Similarly, in ANCA-associated vasculitis, increased circulating and renal levels of LTB4 have been correlated with neutrophil extracellular trap (NET) formation and crescentic GN. This suggests a conserved pathogenic axis across autoimmune renal disorders [77].

In LN, LXA4 is significantly diminished during active disease phases, as demonstrated in both patient samples and lupus-prone animal models [78,79]. These mechanisms, detailed at the glomerular level in Section 3.2, include the suppression of NF-κB activity, downregulation of pro-inflammatory cytokines such as IL-6 and TNF-α, and inhibition of early growth response protein 1 (EGR-1)-mediated TGF-β signaling, which is central to fibrosis [80]. Additionally, LXA4 promotes macrophage-mediated clearance of apoptotic cells (efferocytosis), contributing to the resolution of inflammation without compromising antimicrobial defense [81]. These multifaceted effects position LXA4 not only as a biomarker of disease activity but also as a potential therapeutic candidate in autoimmune renal disorders.

Dietary supplementation with ω-3 PUFAs has demonstrated immunomodulatory effects in autoimmune nephritis models. In lupus-prone MRL/lpr mice, ω-3 PUFA intake significantly reduced circulating anti-dsDNA antibody levels, glomerular IgG deposition, and histological evidence of renal inflammation. These effects were associated with lowered IL-6 expression and inhibition of mesangial cell proliferation, indicating a protective role in modulating autoantibody-driven renal injury [82].

PPARγ agonists, particularly pioglitazone, have shown nephroprotective properties in experimental models of lupus and diabetic nephropathy, where they reduce mesangial expansion, enhance podocyte survival, and inhibit SMAD (Small mothers against decapentaplegic)-mediated fibrogenesis [51]. Additionally, ω-3 PUFA derivatives such as 17-hydroxydocosahexaenoic acid (17-HDHA) can function as endogenous PPARγ ligands, further amplifying these anti-inflammatory and antifibrotic effects [83]. However, clinical evidence in LN remains limited, with small trials suggesting improvements in proteinuria but raising concerns regarding fluid retention, especially in patients with advanced renal impairment [51].

In autoimmune kidney diseases, targeting lipid mediator pathways may offer therapeutic benefits. Targeting these pathways through combined COX/LOX inhibition and ω-3 PUFA supplementation has shown promise in modulating systemic inflammation in autoimmune renal diseases [84]. Urinary lipidomic profiling may serve as a noninvasive tool for stratifying patients based on inflammatory mediator signatures. For instance, elevated urinary LTB4 is associated with heightened glomerular inflammation and may identify candidates for 5-LOX inhibitor therapy [66], whereas reduced urinary LXA4 levels in active autoimmune nephritis suggest a potential role for specialized pro-resolving mediators (SPMs)-based interventions in selected individuals [85].

3.6. PUFAs metabolism in kidney cancer

PUFAs, particularly ω-6 and ω-3, exhibit various anticancer properties, including the ability to induce apoptosis and inhibit tumor growth [86]. These fatty acids influence cancer progression by modifying gene and protein expression, interfering with cell cycle regulation, and triggering apoptotic pathways. PUFAs facilitate the release of cytochrome C from mitochondria, which alters mitochondrial metabolism and enhances Caspase 3 activity, a key enzyme in apoptosis [87]. For instance, gamma-linolenic acid (GLA), an ω-6 PUFA, has been shown to induce cytochrome C release in rat carcinosarcoma cells (LLC-WRC256), leading to apoptosis [87]. LOXs, a crucial group of enzymes in PUFA metabolism, are involved in apoptosis, metastasis, and carcinogenesis [88]. These enzymes exhibit both tumor-promoting and tumor-suppressing functions, making their role in cancer complex [89]. Notably, 15-LOX-2 expression and activity are significantly elevated in macrophages infiltrating human renal cell carcinoma (RCC), where they enhance tumor-associated inflammation and immune suppression [90]. Tumor-associated macrophages (TAMs) expressing high levels of 15-LOX-2 produce 15(*S*)-HETE, a lipid mediator that fosters an immunosuppressive tumor microenvironment by increasing CCL2 and IL-10 while downregulating IFN-γ and TNF-α [90]. This environment facilitates angiogenesis and tumor cell proliferation [91]. Targeting 15-LOX-2 may reduce these immunosuppressive effects, restore antitumor immunity, and enhance immunotherapeutic responses [91].

In RCC, 15-LOX-1 primarily functions as a tumor suppressor [92]. This isoform facilitates apoptosis through metabolites such as 13(*S*)-HpODE, derived from LA [93]. Additionally, epigenetic modifications, including DNA methylation and histone modifications, regulate 15-LOX-1 expression, and disruptions in these processes may impair its tumor-suppressive function [92]. Moreover, 15-LOX-1 plays a role in ferroptosis, a form of regulated cell death driven by iron-dependent lipid peroxidation, suggesting an additional mechanism by which it promotes tumor cell death [94]. However, immunohistochemical analyses of RCC and normal kidney tissues have revealed dynamic changes in LOX enzyme expression during cancer progression, highlighting a complex lipid metabolism landscape [89]. At early cancer stages, 15-LOX-1 expression may increase, potentially influencing lipid signaling pathways that support tumor adaptation [95]. In contrast, 5-LOX and 12-LOX expression initially decreases but rises as the disease advances, contributing to tumor progression [96]. This shifting pattern underscores the intricate role of LOX enzymes in RCC pathophysiology (Fig. 2) [89].

Additionally, 12-LOX can modulate the effects of tyrosine kinase inhibitors (TKIs), which target VEGF receptors to inhibit tumor angiogenesis [97]. While TKIs disrupt tumor blood supply, they may also induce hypertension by altering vascular tone. One mechanism involves increased 12-LOX activity and elevated levels of 12S-HETE following VEGF inhibition, which affects endothelial function and blood pressure regulation [98]. 5-HETE and 12-HETE contribute to intermediate-grade RCC progression by promoting angiogenesis and endothelial

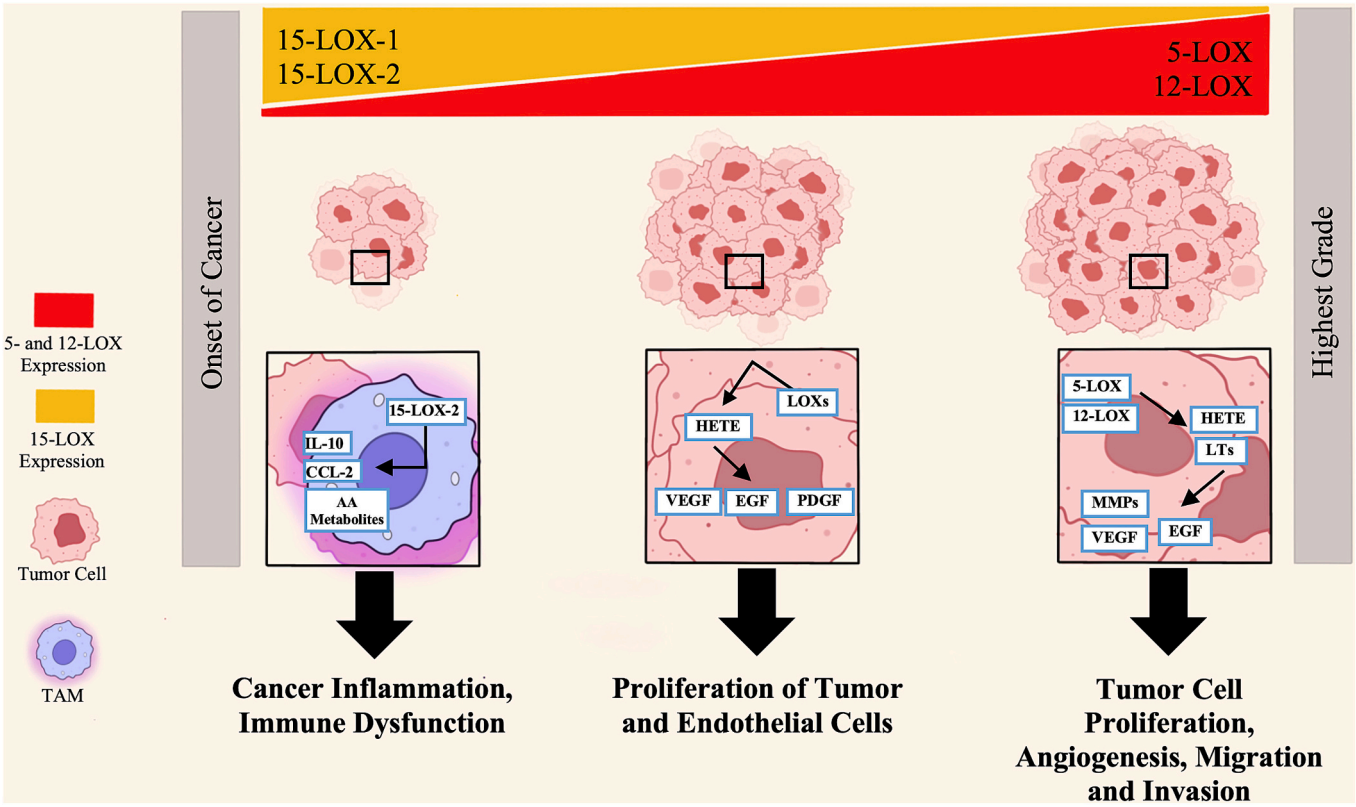

Fig. 2. Multiple roles of LOX enzymes in the process of tumor progression in the kidney.
At any stage of kidney cancer, the different distribution of 5-LOX, 12-LOX, 15-LOX-1 and 15-LOX-2 triggers the expression and activation of various pathways, which contribute to tumor progression.

proliferation, essential for tumor expansion and metastasis [99]. Moreover, LTs derived from 5-LOX facilitate immune cell recruitment to the tumor microenvironment, further supporting tumor growth by modulating VEGF and PDGF signaling [96]. Similarly, 20-HETE, a CYP metabolite, enhances endothelial and tumor cell proliferation by interacting with vascular endothelial growth factor (VEGF), EGF, PDGF, and Fibroblast growth factor (FGF), which drive tumor progression [100]. Studies have shown that 20-HETE also stimulates angiogenesis, and its inhibition significantly reduces tumor growth, suggesting a potential therapeutic strategy in RCC.

The CYP4:20-HETE pathway has been identified as a key regulatory mechanism in cancer biology, with its modulation influencing tumor size in animal models of RCC and other malignancies [101]. Moreover, CYP epoxygenase-derived EETs have been implicated in tumor metastasis, independent of their effects on tumor growth [102]. Abnormal CYP activity enhances EET synthesis, leading to the suppression of c-Jun N-terminal kinase (JNK), which accelerates tumor cell proliferation [103]. Inactivation of JNK increases Cyclin D1 expression, driving tumor growth through mitogen-activated protein kinase phosphatase-1 (MKP-1)-mediated signaling [104]. COX-2 has also been shown to play a significant role in RCC progression. Studies on RCC cell lines, such as OS-RC-2, indicate that COX-2 is overexpressed in malignant cells both *in vitro* and *in vivo*, where it enhances angiogenesis, proliferation, and invasion by upregulating VEGF [105]. This has led to the exploration of COX-2 inhibitors as potential therapeutic agents for RCC, particularly when combined with VEGF-targeting therapies [106].

PPARγ is highly expressed in RCC, and its ligands exhibit stronger anticancer effects compared to 5-LOX inhibitors [107]. PPARα, PPARδ, and PPARγ are found in RCC tissues, particularly in epithelial cells and blood vessels, but their expression does not significantly vary across different tumor grades [107,108]. While PPARγ activation has been linked to apoptosis and suppressed cell proliferation in RCC, its role in cancer remains multifaceted, depending on the tumor microenvironment [107,108]. The differential expression of PPARs in malignant *versus* normal tissues underscores their importance in RCC development and highlights the need for further research into their therapeutic potential [109].

4. Regulation of arachidonic acid metabolism in the kidney

AA (20:4 ω-6) and its precursor, LA (18:2 ω-6), are major ω-6 PUFAs in cellular membranes. During inflammatory responses, phospholipids undergo hydrolysis by phospholipase A2 (PLA2) and phospholipase C (PLC), leading to AA release [110]. AA is then metabolized into bioactive compounds that influence inflammatory cascades and renal function.

AA metabolism follows three primary enzymatic pathways: COXs (COX-1 and COX-2, also known as prostaglandin H synthase-1 and -2 [PGHS-1 and PGHS-2]), LOXs (5-LOX, 15-LOX and 12-LOX), and CYP enzymes, including CYP2 epoxygenases and CYP4 ω-hydroxylases [111]. Each pathway produces distinct classes of oxylipins, collectively termed eicosanoids, which include prostanoids (PGs, prostacyclins, TXs), LTs, LXs, EETs, and HETEs [111]. These bioactive lipids play critical roles in modulating renal blood flow, inflammation, and fibrosis, thereby influencing kidney function and disease progression (Fig. 3).

4.1. COX pathway

COX-1 and COX-2 (PGHS-1 and PGHS-2) are critical enzymes in the metabolism of AA. These enzymes catalyze the conversion of AA into prostaglandin G2 (PGG2) and subsequently into prostaglandin H2 (PGH2), which acts as a precursor for further metabolism by specific PGs and TX synthases [112]. COX-1 is constitutively expressed and regulates the production of prostaglandin E2 (PGE2), which plays a role in renal

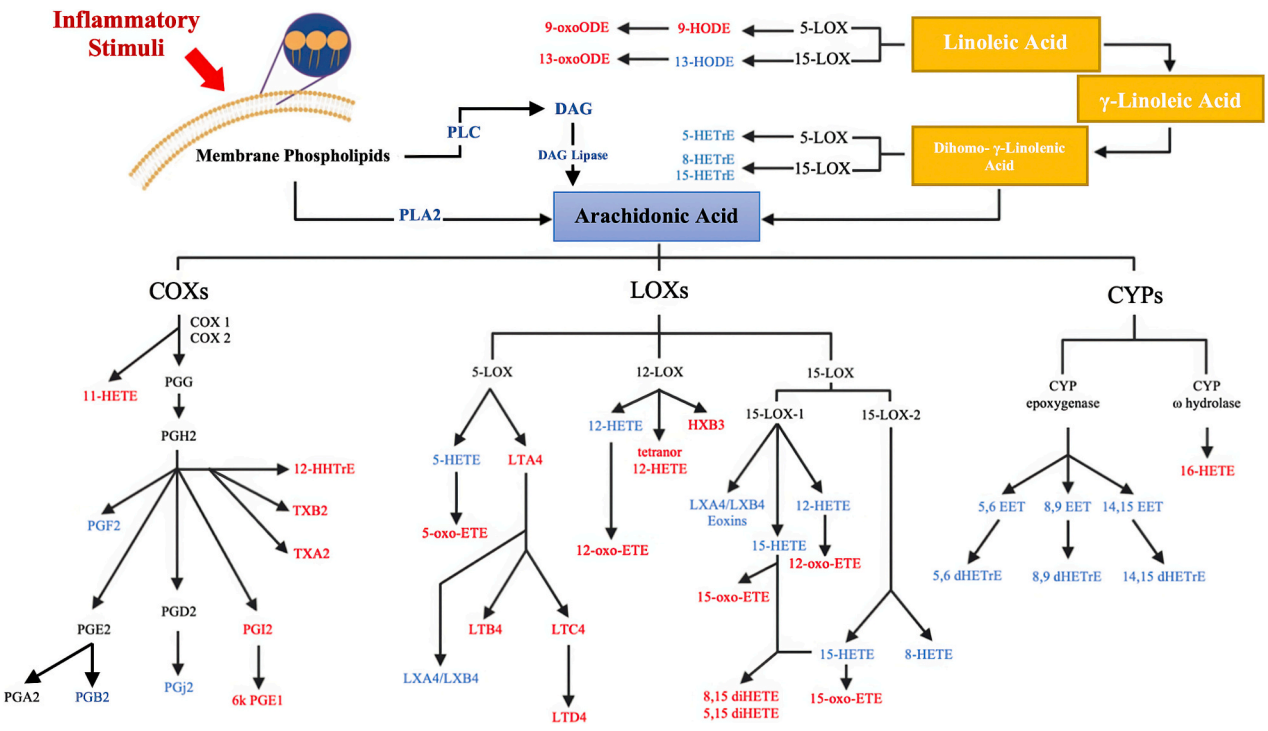

Fig. 3. Overview of eicosanoid biosynthesis pathways from PUFAs in mammals. This figure summarizes the three primary biosynthetic pathways associated with AA and its metabolites. Pro-inflammatory oxylipins are indicated in red, while anti-inflammatory oxylipins are denoted in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

perfusion and electrolyte balance [111]. In contrast, COX-2 is typically inducible and becomes activated during inflammation, kidney injury, and sodium depletion. Both PGHS-1 and PGHS-2 are enzymes that metabolize AA following its release [113]. They have complementary activities: the COX site converts AA to PGG2, while the peroxidase site reduces PGG2 to PGH2 [111]. This dual functionality highlights the crucial role of COXs in prostanoid biosynthesis, which mediates various physiological and pathological processes. PGH2, a reactive intermediate, is converted into bioactive PGs like PGD2, PGE2, PGF2α, PGI2, and TXs by specific synthases [114]. Additionally, TX synthase can decompose PGH2 into malonaldehyde (MDA) and 12 L-hydroxy-5,8,10-heptadecatrienoic acid (HHT) [115]. TX synthase converts PGH2 into TXA2, a potent vasoconstrictor and platelet aggregator, which rapidly hydrolyzes into TXB2 [116]. Conversely, PGI2, predominantly produced by endothelial cells, functions as a vasodilator and inhibits platelet aggregation [117]. Microsomal PGE2 synthase (mPGES) plays a critical role in PGH2 metabolism, influencing inflammation through E-type prostanoid (EP) receptors [118]. PGE2, abundantly synthesized in the renal cortex and medulla, modulates kidney function by affecting vasodilation, sodium excretion, and immune responses. A distinct COX enzyme, COX-3, originates from the *COX-1* gene but retains intron 1 in its mRNA. In humans, COX-3 is predominantly expressed in the brain's cerebral cortex and the heart, and it is notably inhibited by specific NSAIDs [119]. Impaired regulation of COX pathways plays a crucial role in the development of renal inflammation and fibrosis, positioning them as key targets for therapeutic intervention in kidney disease management.

4.2. LOX pathway

The conversion of AA into hydroperoxyeicosatetraenoic acid (HpETE) occurs at the 5-, 12-, and 15-positions, mediated by 5-LOX, 12-LOX, and 15-LOX, respectively [120]. The process begins with the release of AA from membrane phospholipids, catalyzed by cytosolic phospholipase A2 (cPLA2), after which 5-LOX converts AA into 5-HpETE. Most 5-HpETE (95 %) is reduced 5-HETE, with the remainder (5 %) converted to 8-HETE [121]. These steps initiate the production of pro-inflammatory LTs. In human polymorphonuclear leukocytes (PMNLs), oxo-eicosatetraenoic acid (oxo-ETE) is formed from HETEs by microsomal dehydrogenase, acting as a secondary product of the 5-LOX pathway [122]. Oxo-ETEs are potent bioactive mediators in eosinophils. Metabolism continues through the 5-LOX activating protein (FLAP) and dehydrase, leading to leukotriene A4 (LTA4) and LXs [123]. 5-LOX catalyzes two major phases: incorporation of molecular oxygen and epoxide formation *via* LTA4 synthase [120]. LTA4, an unstable intermediate, can undergo hydrolysis, conjugation with glutathione, or transcellular transfer, yielding bioactive eicosanoids. In neutrophils and other inflammatory kidney cells, epoxide hydrolase converts LTA4 into LTB4 [124]. The production of cysteinyl LTs, such as LTC4, LTD4, and LTE4, from LTA4 is crucial in conditions like asthma and other inflammatory disorders, as they promote bronchoconstriction and vascular permeability. LTC4 is synthesized through the action of glutathione S-transferase (GST) and γ-glutamyl transferase, which further converts it into LTD4 and LTE4. LTE4 can then be metabolized into leukotriene F4 (LTF4) [125]. The 12-LOX pathway is responsible for producing 12-HETE and its precursor, 12-HpETE. Additionally, 12-LOX can metabolize 15(*S*)-HETE into 14(*R*),15(*S*)-dihydroxyeicosatetraenoic acid (diHETE) and 5(*S*)-HETE into 5(*S*),12(*S*)-diHETE, which contribute to the production of LTA4 outside the platelets [126,127]. A cooperative interaction between 5-LOX in neutrophils and 12-LOX in platelets facilitates the synthesis of LXs, where LTA4 generated by neutrophils is transferred to platelets for conversion into LXA4 and LXB4 [128]. This transcellular biosynthesis demonstrates the complex interplay of lipoxygenase enzymes in inflammatory processes [123]. The 15-LOX pathway, with its isoforms 15-LOX-1 and 15-LOX-2, plays a key role in AA metabolism. 15-LOX-1 converts AA into LXA4, LXB4, and 15-oxo-ETE, while 15-LOX-2 primarily generates 15-oxo-ETE and 8S-HETE [129,130]. Both 12-LOX and 15-LOX-1 produce LXB4 from 5,15-diHpETE, with 15-LOX-1 being more efficient [123]. These enzymes, through their distinct metabolic roles, contribute to the synthesis of bioactive lipid mediators, including HETEs, LXs, and eicosatrienoic

acids (ETEs), which are critical regulators in kidney injury and other inflammatory conditions [131].

4.3. CYP pathway

The CYP pathway serves as a pivotal metabolic route for AA in the kidney, complementing the functions of COX and LOX pathways, with its highest enzyme expression observed in proximal tubules, glomeruli, and endothelial cells. These enzymes are distributed across cellular compartments, including the endoplasmic reticulum, mitochondria, and nuclear membrane [132]. Within the CYP pathway, AA is metabolized primarily through three mechanisms [133]. The kidney exhibits significant epoxygenase activity, producing enantioselective EETs, with 14,15-EET being the predominant product. The CYP2C and CYP2J families are the primary enzymes responsible for EET formation in human renal tissues, with CYP2C8 being the most notable isoform, particularly in the production of 14,15-EET [134,135]. After their synthesis, EETs can be metabolized by soluble epoxide hydrolase (sEH) to form dihydroxyeicosatrienoic acids (DHETs), which exhibit less biological activity than their epoxide precursors. The sEH-mediated conversion of EETs to DHETs represents an important inactivation pathway, and sEH inhibition has been proposed as a strategy to increase EET levels and amplify their beneficial effects *in vivo* [136]. Furthermore, AA can be converted into HpETEs by LOX or COX, which are then metabolized by CYP isozymes to yield HETEs. The CYP4 family, including isoforms CYP4A11, CYP4F11, and CYP4F2, plays a central role in the production of HETEs in the kidney [10]. Additionally, studies on CYP2C epoxygenases have identified isoforms responsible for generating specific EET regioisomers in the kidney. CYP2C29 and CYP2C39 are involved in the production of 14,15-EET, while CYP2C38 is linked to the formation of 11,12-EET [137]. Additionally, the CYP2J family plays a crucial role in EET production in both human and mouse kidneys [138]. Human CYP2J2 isoforms exhibit high efficiency in epoxidizing AA at the 14,15-position [139]. In the mouse kidney, CYP2J5, an epoxygenase enzyme localized in tubular cells, metabolizes AA to 8,9-EET, 11,12-EET, and 14,15-EET.

4.4. Balancing ω-3 and ω-6 PUFA-derived mediators in renal inflammation

PUFA-mediated immunometabolism in renal diseases depends on the fine-tuned balance between pro-inflammatory and anti-inflammatory lipid mediators derived from both ω-6 (*e.g.*, AA) and ω-3 (*e.g.*, EPA, DHA) pathways. While AA can be metabolized into both pro-inflammatory (*e.g.*, LTB4, PGE2) and pro-resolving mediators (*e.g.*, LXA4), the balance of its metabolic fate is context-dependent and influenced by disease-specific enzymatic cascades. Under certain pathological conditions, this balance shifts toward a pro-inflammatory dominance, contributing to immune cell recruitment and renal damage, whereas in resolution phases or under regulatory cues, AA-derived lipoxins may facilitate inflammation resolution and tissue repair [10]. In contrast, ω-3 PUFAs such as EPA and DHA are enzymatically converted to SPMs, including resolvins, protectins, and maresins [70]. These mediators actively promote resolution of inflammation, enhance efferocytosis, and support tissue regeneration. Moreover, by influencing enzymatic substrate preference EPA and DHA ω-3 PUFAs, indirectly modulate the output of COX, LOX, and CYP450 pathways, shifting lipid mediator production away from AA-derived pro-inflammatory species. Differences in receptor affinities and downstream signaling pathways between n-3 and n-6–derived mediators further modulate the renal immune microenvironment [81,82,140].

Disturbances in the ω-3/ω-6 PUFA ratio have been correlated with distinct lipid mediator profiles in LN and IgA nephropathy, indicating that intrinsic metabolic dysregulation contributes to disease pathogenesis independently of dietary influences [84]. Therapeutic restoration of PUFA balance has demonstrated efficacy in reducing proteinuria, attenuating glomerular structural damage, and ameliorating systemic inflammatory responses in these conditions [76,82,141]. It is important to recognize that the immunological effects of ω-3 and ω-6 PUFAs are complex and context-dependent, involving overlapping pro-inflammatory and pro-resolving pathways rather than a simple dichotomy. Although ω-3–derived mediators predominantly favor resolution, AA also participates in anti-inflammatory processes *via* its conversion to SPMs such as LXA4 [80]. The emphasis on AA within this review reflects its dualistic and context-dependent role in renal immunopathology, rather than a hierarchical assumption regarding its therapeutic superiority over EPA or DHA. Collectively, these observations highlight the importance of lipid mediator balance and support further exploration of both n-3 and n-6–derived pathways as therapeutic targets in kidney diseases.

4.5. Strategies to restore PUFA metabolite balance in renal diseases

A central therapeutic objective in renal disease management is restoring the balance between pro-inflammatory and pro-resolving lipid mediators derived from PUFAs, particularly AA. Pathological conditions often skew AA metabolism toward excessive generation of LTs, PGs, and 20-HETE, while suppressing the production of specialized SPMs such as lipoxins, resolvins, and protectins. This imbalance sustains chronic inflammation, promotes immune cell recruitment, and drives progressive tissue injury and fibrosis across multiple renal disease contexts [142].

One strategy to counteract this dysregulation involves the use of metabolically stable analogs of LXA4. Compounds such as 15-epi-LXA4 methyl ester and benzo-LXA4 resist rapid enzymatic degradation and have demonstrated renoprotective efficacy in models of LN, ischemia-reperfusion injury, and adriamycin-induced nephropathy [143,144]. These analogs reduce neutrophil infiltration, suppress NF-κB activity, and enhance apoptotic cell clearance, collectively contributing to the resolution of renal inflammation and preservation of glomerular structure [143,144].

A second approach focuses on inhibiting deleterious AA-derived metabolites. 20-HETE, a vasoconstrictive and pro-inflammatory eicosanoid produced by CYP enzymes, has been implicated in oxidative stress, endothelial dysfunction, and tubulointerstitial fibrosis [145]. Selective inhibitors such as HET0016 and 20-SOLA have been shown to improve renal perfusion and reduce fibrogenic signaling in hypertensive and DN models [146,147].

Another promising axis of intervention involves modulating nuclear receptors responsive to PUFA-derived ligands, particularly PPARα and PPARγ. Agonists such as fenofibrate and pioglitazone have demonstrated anti-inflammatory and antifibrotic effects in models of chronic kidney disease, in part through modulation of COX-2 expression and attenuation of pro-inflammatory eicosanoid signaling [148]. Moreover, ω-3 PUFA metabolites such as 17-HDHA function as endogenous ligands of PPARγ, thereby potentially enhancing these renoprotective pathways [149].

Collectively, these strategies illustrate a shift away from non-specific lipid supplementation toward precision modulation of lipid mediator biosynthesis. Rather than administering AA, which may inadvertently exacerbate inflammation, therapeutic efforts now aim to selectively guide its metabolism using enzyme inhibitors or competitive substrate supplementation with EPA and DHA. Such metabolic reprogramming favors the endogenous production of anti-inflammatory and pro-resolving lipid mediators and may enhance the efficacy of standard immunosuppressive or antifibrotic therapies in patients with glomerulopathies or tubulointerstitial diseases marked by persistent inflammation [150].

Future clinical trials should prioritize defining optimal therapeutic combinations, assessing long-term safety, and identifying patient subgroups based on lipidomic and immunologic profiling to tailor PUFA-based interventions more effectively.

5. The role of HETEs in kidney inflammation

HETEs are key regulators of platelet function, acting through autocrine and paracrine mechanisms, and play a crucial role in renal inflammation [151]. In renal vascular diseases, HETEs exhibit dual functionality, displaying both anti-thrombotic and pro-thrombotic properties, depending on the physiological context [152]. In type 2 diabetes, the 12-LOX pathway is implicated in various complications, producing pro-inflammatory lipid mediators like 12-HpETE and 12(*S*)-hydroxyeicosatetraenoic acid (12(*S*)-HETE), which activate inflammatory cascades through P38 mitogen-activated protein kinase (P38-MAPK) and related pathways [153]. Exogenous administration of 12-HpETE stimulates P38-MAPK signaling, leading to enhanced platelet activation under oxidative stress. The reduction in glutathione peroxidase activity further aggravates this process, promoting 12-HpETE accumulation and intensifying platelet activation, contributing to renal damage and complications associated with diabetes [154].

These findings highlight the central role of the 12-LOX pathway in the interaction between inflammation, oxidative stress, and the progression of both diabetic and renal pathologies. Studies also show that 5-HETE, 12-HETE, and 15-HETE inhibit PLA2 activity in platelets, potentially affecting their functional responses [151]. In addition, platelets with disrupted 12-LOX activity exhibit increased sensitivity to adenosine diphosphate (ADP)-induced aggregation, indicating the importance of 12-LOX in regulation of platelet function in renal diseases. These observations suggest that HETE-induced renal inflammation is significantly mediated by platelet activity, underlining the complex interplay between eicosanoid signaling and platelet function in renal disease pathophysiology [155]. 20-HETE, a potent vasoconstrictor, plays a vital role in regulating renal blood flow, GFR, and urinary sodium excretion. Both 20-HETE and 20-carboxy-arachidonic acid (20-COOH-AA) mimic furosemide-like effects by reducing intracellular sodium (Na^+) and potassium (K^+) levels in the medullary thick ascending limb of Henle (mTALH) cells, highlighting their role in renal function modulation [156]. Moreover, 20-HETE is essential in maintaining renal vascular tone, with its inhibition linked to salt-sensitive hypertension, emphasizing its role in blood pressure regulation. It suppresses Na^+/K^+-ATPase activity in renal microvessels, and its increased production in renal microcirculation correlates with reduced GFR and glomerular capillary pressure, contributing to the development of hypertension [157]. However, the rise in renal vascular resistance due to 20-HETE helps prevent hypertension-induced glomerular damage by reducing strain on the glomeruli during circulation [158]. The synthesis of 20-HETE is crucial for self-regulating renal blood flow and the tubuloglomerular feedback mechanism. Disruption in 20-HETE synthesis leads to significant physiological consequences, such as impaired ion transport, altered blood pressure regulation, and worsening the renal pathologies like GN and renal tubulointerstitial nephritis [158]. Furthermore, the role of 20-HETE in IRI is evident, as its altered regulation leads to prolonged vasoconstriction, intensifying injury severity. Renal ischemia, a major cause of AKI, increases 20-HETE production after IRI, reinforcing its critical role in maintaining renal function and blood pressure homeostasis [100]. The imbalance in 20-HETE synthesis contributes to hypertension and renal complications, emphasizing its importance in renal physiology. Additionally, 20-HETE is involved in AKI pathogenesis and is emerging as a therapeutic target. Studies have shown that 20-HETE analogs can lower elevated plasma creatinine levels after IRI with preconditioning, significantly reducing tubular epithelial necrosis [159]. The protective mechanisms of 20-HETE include enhanced medullary blood flow, inhibition of renal tubular sodium transport, and improved oxygen delivery. However, excessive 20-HETE expression can exacerbate cell damage during IRI by activating Caspase-3 and generating free radicals *via* CYP4A pathway [145]. The link between 20-HETE and AKI is further elucidated through its role in apoptosis and renal inflammation. In diabetic models, such as OVE26 mice, increased CYP4A and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase activity correlates with elevated 20-HETE production [160]. Hyperglycemia exacerbates 20-HETE-dependent reactive oxygen species (ROS) production, contributing to podocyte and tubular epithelial cell apoptosis. Blocking 20-HETE reduces ROS, improves apoptosis, and alleviates albuminuria [161]. Additionally, 20-HETE enhances TRPC6 activity in podocytes, leading to foot process effacement and preventing podocyte detachment, highlighting its dual effects on podocyte integrity [162].

6. LTs/LXs and their cellular roles in renal inflammation

6.1. LTs/LXs: dual regulators of renal inflammation

Both LTs and LXs, principal metabolites of the LOX pathway, play essential but contrasting roles in the inflammatory landscape of the kidney. LTs, especially LTB4, act as potent chemotactic agents that promote the migration and activation of leukocytes toward inflamed renal tissue, exacerbating injury [163]. Renal epithelial and mesangial cells can produce LTs independently of infiltrating immune cells through the expression of enzymes such as 5-LOX and leukotriene C4 synthase (LTC4S) [164]. Following IRI, LTB4 is rapidly synthesized and recruits polymorphonuclear neutrophils (PMNs), which contribute to endothelial injury, impair vasodilation, and worsen tubulointerstitial damage [165]. This inhibition reduces albumin absorption, leading to tubulo interstitial damage in renal IRI models [166]. In these models, LTA4 is rapidly converted to LTB4 following the reperfusion phase, which coincides with the recruitment of PMNs. LTB4 acts as a chemotactic agent, directing PMNs toward ischemic renal tissue. This accumulation exacerbates immune-mediated renal damage and further impairs renal function, perpetuating a harmful cycle of tissue injury contributing to the pathophysiology of IRI [167].

The involvement of LTB4 in glomerular injury is well-documented, particularly in nephrotoxic serum-induced glomerular injury models. These studies show a marked increase in the recruitment and activation of PMNs, accompanied by elevated renal production of LTB4. This inflammatory response is strongly associated with a significant decline in GFR [54]. Additionally, elevated levels of LTB4, along with other LTs such as LTC4, LTD4, and LTE4, have been found in patients with NS. These increased leukotriene concentrations are correlated with reductions in serum creatinine, diastolic blood pressure, and protein-to-creatinine ratios, highlighting their potential role in the clinical and pathological manifestations of the disease [168].

In contrast, LXs, particularly LXA4, are endogenous anti-inflammatory mediators that modulate immune responses in various cell types, including neutrophils, mononuclear macrophages, and mesangial cells [169]. LXs are essential in regulating inflammatory responses and promoting tissue repair. LXA4, for example, has been shown to reduce leukocyte infiltration in GN, a kidney disorder marked by glomerular inflammation [11]. During the acute phase of post-streptococcal glomerulonephritis (APSGN), neutrophil and monocyte infiltration into the glomeruli exacerbates tissue damage [170]. In this context, LXA4 helps control the inflammatory response by inhibiting leukotriene production and reducing neutrophil recruitment, which is vital for limiting tissue damage and facilitating recovery [171].

LXA4 has been extensively studied for its ability to suppress pro-inflammatory cytokines such as TNF-α and IL-1β. It has been shown to downregulate these cytokines by targeting essential pathways involved in inflammation [172]. LXA4 inhibits TNF-α-induced expression of VCAM-1 in salivary epithelial cells, showcasing its ability to modulate inflammatory signaling and prevent cytokine-driven effects [173]. At nanomolar concentrations, LXA4 reduces NF-κB activation, a key regulator of inflammation. Furthermore, LXA4 suppresses IL-1β-induced ICAM-1 expression in human astrocytoma cells by interfering with NF-κB activation [174]. Experimental data also demonstrate that LXA4 and its stable analogs inhibit TNF-α-induced IL-1β production in neutrophils in a time- and dose-dependent manner, reinforcing its role as a potent

anti-inflammatory agent [175].

Emerging research has revealed the interaction between LXA4 and EGR-1, a transcription factor involved in inflammatory pathways in kidney diseases. TNF-α exposure increases EGR-1 expression in renal epithelial cells, intensifying the inflammatory response. However, LXA4 treatment significantly attenuates this TNF-induced EGR-1 activation, suggesting that LXs protect against kidney inflammation [176]. EGR-1 plays a critical role in kidney diseases, particularly through its involvement in TGF-β signaling, which regulates immune cell infiltration and amplifies renal inflammation [177]. The modulation of EGR-1 by LXs provides a potential mechanism for mitigating kidney injury, highlighting their therapeutic potential in inflammation-associated renal disorders.

While the precise mechanisms behind the renoprotective effects of LXs are not fully understood, they are believed to alleviate inflammation and oxidative stress, two central factors in the progression of diabetic nephropathy. By targeting these pathogenic processes, LXs could offer a therapeutic avenue to halt or even reverse renal damage in diabetic patients, underscoring their potential as promising candidates for managing kidney disorders related to inflammation.

While LXA4 is widely recognized for its anti-inflammatory and pro-resolving effects, its actions are not universally beneficial. In the early phases of infection, excessive or premature LXA4 signaling may suppress essential leukocyte recruitment, thereby impairing host defense and increasing susceptibility to secondary infections, as observed in sepsis and immunosuppression models [178]. Similarly, PGE2 exerts highly context-dependent effects. Depending on receptor subtype engagement (EP1–EP4) and cytokine milieu, PGE2 may amplify pro-inflammatory pathways, such as TH17 cell polarization *via* IL-23, or alternatively, promote anti-inflammatory responses by enhancing IL-10 production [179]. These dual roles underscore the importance of dosage, timing, and tissue-specific context in the potential therapeutic use of PUFA-derived lipid mediators.

6.2. *Interactions of PUFA-derived lipid mediators with immune and inflammatory cells*

PUFA-derived mediators, particularly those generated from AA, EPA, and DHA, play critical roles in regulating immune cell behavior in renal inflammation. These bioactive lipids, including eicosanoids, LXs, resolvins, and HETEs, affect cytokine expression, immune cell recruitment, and resolution mechanisms across various kidney diseases [142]. LXA4, derived from AA *via* the 15-LOX pathway, attenuates inflammatory signaling by inhibiting NF-κB activation and downregulating TNF-α, IL-1β, and TGF-β expression in renal tissues [60,80]. In GN models, reduced neutrophil infiltration and lower expression of adhesion molecules such as ICAM-1 and VCAM-1 have been observed following LXA4 treatment [57].

Macrophage polarization is also influenced by PUFA metabolites. Both LXA4 and DHA can promote the transition from M1 to M2 phenotypes, fostering tissue repair in conditions like LN and DN [60]. In contrast, LTB4, a potent pro-inflammatory product of the AA–5-LOX axis, facilitates neutrophil and monocyte recruitment, contributing to glomerular injury in IRI and autoimmune nephritis [57,66]. EPA- and DHA-derived resolvins and protectins mitigate this damage by limiting neutrophil transmigration and enhancing their clearance from inflamed sites [65,70,142]. HETE derivatives also modulate platelet behavior and redox signaling. In hyperglycemic states, 12-HETE and 20-HETE activate P38-MAPK signaling, enhancing platelet aggregation and contributing to microvascular injury in diabetic kidney disease. Moreover, they can influence TXA2 secretion and ADP responses, linking PUFA metabolism to thrombogenic processes in hypertensive nephropathy [180].

Beyond their effects on innate immunity, PUFA-derived lipid mediators, especially LXA4, resolvins, and PGE2, also exert regulatory functions in adaptive immune responses relevant to renal inflammation. LXA4, acting through the ALX/FPR2 receptor expressed on T cells, has been shown to inhibit differentiation and effector function of TH17 cells, reduce production of pro-inflammatory cytokines (*e.g.*, IL-17, IFN-γ), and enhance Treg stability and activity in both murine models and human cell cultures [181,182]. D-series resolvins, including resolvin D1 and D2, have been shown to suppress TH17 cell differentiation and IL-17 production, while promoting regulatory T cell function, *via* pathways that converge on STAT3 signaling in both murine and human models [183]. While direct evidence in renal tissue remains limited, these findings support a nuanced role for SPMs in fine-tuning immune balance, potentially influencing resolution pathways in chronic kidney disease and glomerulonephritis.

These findings highlight how PUFA-derived mediators differentially regulate leukocyte function, cytokine signaling, and vascular responses in kidney inflammation. Targeting these pathways could support the development of adjunctive therapies aimed at resolving chronic renal inflammation.

7. The interplay between PPARs, TGF-β, and PUFA metabolism

PPARs are nuclear receptors that regulate various physiological processes, including lipid metabolism, inflammation, and cellular development [184]. Among the three PPAR isotypes, PPARα, PPARδ, and PPARγ, research has highlighted their involvement in the pathogenesis of kidney diseases, as well as their regulatory role in lipid metabolism, including pathways associated with PUFAs and their bioactive derivatives [185]. PPARα, primarily expressed in the kidney, regulates genes involved in fatty acid oxidation and energy metabolism [185]. Activation of PPARα has been shown to reduce inflammation in mesangial cells and decrease inflammatory cytokine secretion in adipocytes [186]. PPARδ, also expressed in renal tissue, regulates the expression of CD36, which contributes to tubule-interstitial cell apoptosis and subsequent renal inflammation and fibrosis [187]. PPARγ plays a crucial role in kidney health by protecting podocytes from injury, with therapeutic potential in various kidney diseases, including AKI, diabetic nephropathy, obesity-induced nephropathy, hypertensive nephropathy, and IgA nephropathy [188]. It exerts protective effects through anti-inflammatory, antifibrotic, and antioxidant actions, as well as regulating lipid metabolism and apoptosis, making it a promising target for kidney disease treatment (Fig. 4).

PUFA-derived oxylipins, including PGs, LTs, LXs, and HETEs, can modulate renal inflammation and fibrosis through their interaction with PPARs. Notably, 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), an endogenous ligand of PPARγ, induces apoptosis in renal proximal tubular and cancer cells, including renal cell carcinoma, through mechanisms involving covalent receptor binding, ROS generation, and NF-κB inhibition [189,190]. Other oxylipins, such as 13-HODE and 17-HDHA, have also been identified as natural PPAR ligands with anti-inflammatory and renoprotective properties in various pathological contexts [191,192].

Synthetic PPARγ agonists, particularly thiazolidinediones (TZDs), have demonstrated antifibrotic and anti-inflammatory effects in both diabetic and non-diabetic kidney disease models by enhancing PPARγ activity in podocytes and tubular epithelial cells [193]. However, their clinical application is limited by adverse metabolic effects [194]. Studies in leptin- and PPARγ-deficient mice have shown exacerbated renal hypertrophy, dyslipidemia, and increased TGF-β expression, underscoring the role of PPARγ in maintaining renal homeostasis [195]. Furthermore, PPARγ activation in tubular epithelial cells has been shown to preserve metabolic balance and prevent fibrogenesis, whereas pharmacological inhibition with antagonists like GW9662 leads to tubular dysfunction and progression of injury [196].

The impact of fatty acid treatment on PPARγ expression in podocytes is also significant in lipotoxicity research. Studies have shown that administering fatty acids to podocytes reduces PPARγ expression, resulting in inflammation and apoptosis [197]. PPARγ activation decreases profibrotic TGF-β expression, inhibits apoptosis, and improves

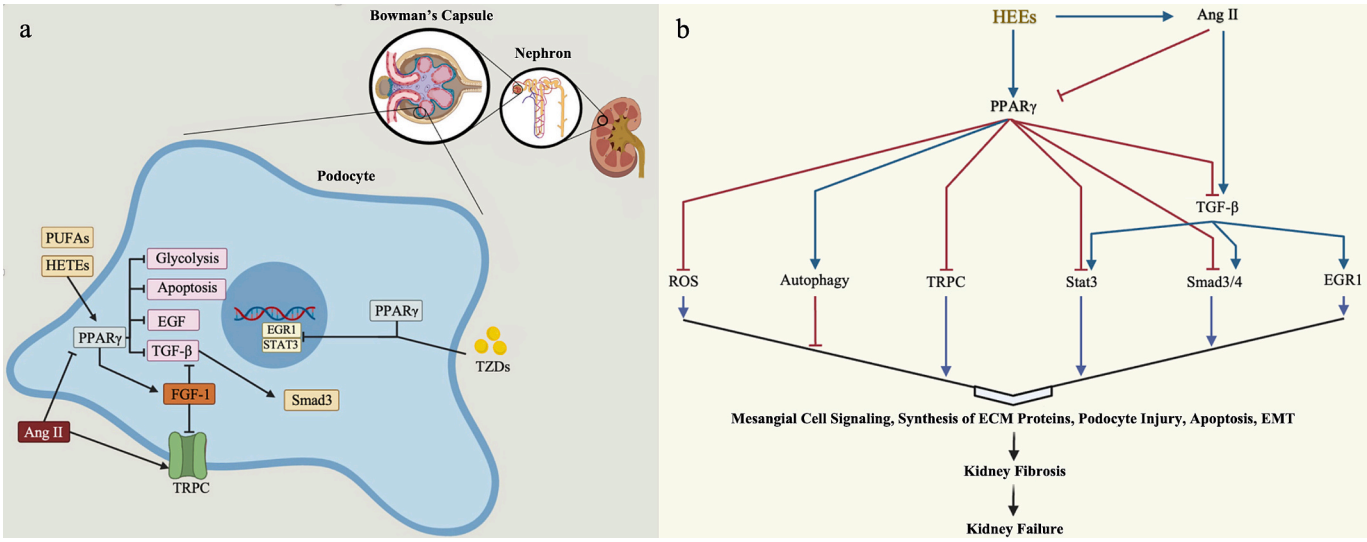

Fig. 4. The role of PUFAs and their metabolites in activating PPARγ pathways in kidney tissue.
a. PUFAs and eicosanoids lead to the activation of PPARγ in podocytes, which ultimately play a protective role in kidney damage by affecting multiple signaling pathways. b. Activation of Ang II and PPARγ by PUFAs, with opposite effects on downstream signaling pathways, indirectly controls fibrosis and eventually kidney failure.

podocyte foot process effacement, highlighting its role in protecting podocytes and reducing kidney injury. FGF-1 has also been shown to play a role in maintaining glomerular function and preventing fibrosis by lowering TGF-β expression through PPARγ induction [198]. FGF-1 inhibits mesangial cell proliferation, a feature of glomerulosclerosis, by reducing transient receptor potential canonical (TRPC) channels. Additionally, PPARγ activation inhibits mesangial cell proliferation and prevents glomerulosclerosis by reducing calcium influx induced by Ang II [199].

PPARγ agonists, particularly thiazolidinediones, have shown therapeutic efficacy in managing DN by decreasing albuminuria and renal inflammation [200]. Experimental models of aging with PPARγ deletion exhibit features of type 2 diabetes mellitus (T2DM) and progressive renal fibrosis, underscoring the role of receptor in maintaining renal metabolic homeostasis [201]. Mechanistically, PPARγ activation suppresses TGF-β signaling and downregulates pro-fibrotic mediators such as STAT3 and EGR1, leading to attenuation of tubulointerstitial fibrosis [202]. Additionally, Ang II, a potent mediator of renal fibrosis, downregulates PPARγ expression in the kidney, whereas treatment with the Ang II receptor blocker losartan restores PPARγ activity, highlighting a therapeutic interplay between renin- angiotensin system inhibition and PPARγ preservation in fibrotic kidney injury [203].

Renal IRI is a multifactorial pathophysiological condition characterized by overproduction of ROS during reperfusion, a major contributor to AKI [204]. PPARγ activation has been shown to reduce ROS generation in renal epithelial cells under hypoxic condition and modulate renal IRI [205]. Pretreatment with pioglitazone prior to renal ischemia-reperfusion reduces AKI, with PPARγ activation linked to increased uncoupling protein-1 (UCP1) expression in renal epithelium [206]. PPARγ also inhibits *N*-methyl-D-aspartate (NMDA) receptors during renal IRI, potentially mitigating excitotoxicity and apoptosis [207]. Autophagy, playing a dual role in renal IRI, can both protect cells from injury and contribute to cell death [208]. Understanding autophagy interaction with renal IRI is crucial for developing targeted interventions.

PPARγ has also been identified as essential for kidney function in transplant settings, particularly in chronic allograft nephropathy (CAN) [209]. CAN is characterized by fibrosis and loss of kidney function, with elevated PAI-1 expression correlating with fibrosis severity [209]. PPARγ activation reduces PAI-1 levels and improves kidney fibrosis in models of glomerulosclerosis [210]. Moreover, PPARγ activation inhibits fibroblast and macrophage migration, crucial drivers of fibrosis and inflammation in kidney diseases [211]. These findings underline the potential of PPARγ as a therapeutic target in the management of chronic kidney injury and fibrosis in renal transplants.

8. Utilizing PUFAs for treatment of kidney diseases

8.1. Clinical and pharmacological applications of PUFA pathway modulation in kidney diseases

Numerous treatments aimed at addressing kidney inflammation, which are based on the metabolic pathways of PUFAs, are currently in different stages of development for control of human kidney diseases. The complexity of treating renal diseases based on PUFAs, which encompasses numerous variables, is the reason why we have only addressed a selection of methods applicable to humans in Table 1.

Research on PUFA metabolism in kidney disease suggests a complex interplay between therapeutic benefits and potential risks. While corticosteroids, often combined with rituximab for PLA2R-targeted therapy, have shown efficacy in nephropathy [230], their use in acute interstitial nephritis (AIN) has been linked to worsening tubulointerstitial fibrosis [231]. Similarly, while PLA2R-Ab therapy is promising for idiopathic membranous nephropathy (IMN) [232], concerns persist regarding its potential to increase the recurrence of tubulointerstitial nephritis (TIN), necessitating further investigation into the interaction between corticosteroids and PUFA metabolites in renal pathology [233].

The impact of acetylsalicylic acid (ASA; aspirin) on AKI remains controversial. Some studies indicate a protective effect [234], while others associate its use with an increased risk of hemorrhage-induced AKI due to its rapid conversion to salicylate, which has minimal COX inhibitory activity [235]. NSAIDs such as nimesulide and carprofen also exhibit mixed effects. Nimesulide, despite its COX-inhibitory properties, appears to have limited efficacy in preventing AKI at therapeutic doses. In contrast, carprofen modulates solute absorption in the thick ascending limb (TAL) of the loop of Henle, potentially improving GFR, though its clinical significance requires further validation [218]. Selective COX-2 inhibitors pose additional concerns. Rofecoxib has been linked to an increased risk of severe cardiovascular events, while naproxen and celecoxib have been associated with AKI, NS, and AIN [236,237]. Traditional NSAIDs, such as indomethacin, may further impair renal function by promoting sodium retention and reducing GFR,

Table 1
Therapeutic approaches targeting PUFA metabolism in kidney diseases.

Study	Targets	Kidney disease	Outcome	Reference
Examining the relationship between anti-PLA2R Abs and the effectiveness of combined cyclophosphamide and mycophenolate mofetil therapy	Glucocorticoid receptors	Idiopathic membranous nephropathy (IMN)/IgA nephritis	ALB ↑ GFR ↑ ICI ↓ PLA2R Ab ↓ Proteinuria ↓	[212]
Investigating the role of rituximab in relation to anti-PLA2R Ab levels in membranous nephropathy	Anti-CD20 monoclonal Ab	Idiopathic membranous nephropathy (IMN)	ICI ↓ PLA2R Ab ↓ Proteinuria ↓	[213]
Studying the effect of ibuprofen and kidney inflammation in children	COX1/COX2/ CYP2C8	AKI	Pain ↓	[214]
Investigating the anti-inflammatory effect of licofelone on human mesangial cells (HMC)	5-LOX/ COX2	Glomerulonephritis	Proliferation of HMC ↓ IL-18 pro-inflammatory cytokine ↓	[215]
Assessing the impact of nimesulide on renal hemodynamics and electrolyte excretion	COX1/COX2	Acute renal failure	Indices of renal hemodynamics ↓ Urinary excretion of PGE2 ↓ Aldosterone levels ↓	[216]
Examining the link between AKI and aspirin (ASA) use in patients undergoing cardiac surgery	COX1/COX2	AKI	74 % lower incidence of renal failure was observed with the use of preoperative ASA	[217]
The effect of ketorolac and diclofenac on metastasis risk of kidney cancer	COX mediated PGE2	Kidney cancer	GFR ↑ Resorption of solute ↓ Sodium and chlorine excretion ↓	[218]
Anti-inflammatory effects of ω-6, and ω-3 FAs, AA and EETs on renal indices and inflammation	COX/ LOX/ PGs/ Ang II	Kidney inflammation	ACE-2 ↑ Renal markers of inflammation ↓	[219]
Exploring the positive effects of RASI inhibitors and EPA on IgA nephropathy (IgAN)	–	IgAN	GFR ↑ Proteinuria ↓	[220]
The analysis of 15-LOX activity and eicosanoid production in the renal TME	15-LOX-2	RCC	IL-10 and CCL2 ↑ IS in RCC TME	[221]
The role of ASA and NSAIDs on patients with metastatic RCC (mRCC)	COX1/COX2	mRCC	No survival advantage was observed in mRCC patients after using ASA and NSAIDs	[222]
The combination therapy of interferon-α, cimetidine, candesartan and meloxicam in patients with advanced RCC	COX2/RAS	mRCC	Symptom relief	[223]
Use of 5-LOX inhibitors as apoptosis inducers in RCC4	5-LOX	VHL-negative RCC	Apoptosis ↑ Proliferation ↓ LC3B and P62 ↑	[224]
Caffeic acid derivatives as potent 12-LOX inhibitors	12-LOX	Renal cancer cells	Apoptosis ↑ Proliferation ↓	[225]
Studying the impact of thiazolidinedione PPARγ ligands on proliferation and apoptosis in hRC cell lines	PPARγ	Renal cancer cells	Apoptosis ↑ Proliferation ↓	[226]
Examining the effect of baicalein as 12-LOX inhibitor on RCC cells	12-LOX	Renal cell carcinoma	Apoptosis ↑	[227]
The use of CYsLTR antagonists (LTRAs) and kidney cancer risk reduction in asthma patients	LTB4/LTC4/LTD4/ LTE4	–	Risk of cancer ↓	[228]
Investigating the role of zafirlukast in cell death mechanisms in clear cell renal cell carcinoma (ccRCC)	CysLTR1	ccRCC	Induction of oxidative cell death in ccRCC ↑	[229]

particularly in individuals with preexisting kidney dysfunction [238]. Given the inconsistencies in current findings and the limited number of clinical trials, further research is essential to clarify the renal effects of PUFA-targeting therapies, NSAIDs, and corticosteroids. Understanding their precise mechanisms of action will be critical for optimizing treatment strategies while minimizing adverse outcomes.

8.2. Overcoming pharmacokinetic and biosynthetic challenges in PUFA-based therapies

Despite the therapeutic promise of PUFA-derived lipid mediators such as LXA4, their clinical translation faces major hurdles, particularly related to metabolic stability and targeted delivery. LXA4 has a plasma half-life of less than 4 min due to rapid enzymatic degradation, primarily related to enzymatic inactivation by 15-hydroxyprostaglandin dehydrogenase and oxidation at its omega-end, which limits its therapeutic potential [239]. To address this limitation, researchers have developed synthetic and metabolically stable LXA4 analogs, such as 15-epi-LXA4 methyl ester and benzo-LXA4, that preserve biological activity while resisting inactivation. These analogs have demonstrated renoprotective effects in preclinical models of LN and IRI [143,144]. Moreover, advances in nanotechnology have enabled targeted renal delivery of LXA4 through encapsulation in PEGylated nanoparticles or mesoporous silica-based carriers.

Another key consideration in PUFA-based therapy, particularly with AA, is its metabolic bifurcation into both pro-inflammatory and pro-resolving eicosanoids. While AA is classically associated with the generation of inflammatory mediators such as PGE2 and LTB4, foundational studies have demonstrated that its metabolic fate is context-dependent. Under resolution-phase condition, characterized by upregulation of 15-LOX and a shift in enzymatic milieu, AA is increasingly converted to LXA4, rather than PGE2. This phenomenon, referred to as an “eicosanoid class switch,” illustrates that AA metabolism can be therapeutically redirected toward resolution-promoting pathways rather than indiscriminately suppressed [240].

8.3. Risks and limitations of PUFA-derived therapeutics in renal diseases

While the therapeutic modulation of PUFA pathways offers promising anti-inflammatory and antifibrotic effects in kidney diseases, several biological risks and translational challenges must be carefully addressed. These limitations arise from the pleiotropic nature of PUFA metabolites, their interactions with immune signaling, and pharmacological unpredictability across diverse renal pathologies [241].

8.3.1. Immunomodulatory risks of specialized pro-resolving mediators

SPMs, including LXA4, resolvins, and protectins, exert anti-inflammatory effects by suppressing leukocyte infiltration, cytokine production, and antigen-presenting cell activation. However, excessive or untargeted enhancement of these pathways may impair host defense mechanisms. Preclinical studies have shown that heightened LXA4 signaling can suppress neutrophil recruitment and phagocytic activity, increasing susceptibility to opportunistic infections in immunocompromised settings, such as sepsis [11].

8.3.2. Pro-inflammatory potential of arachidonic acid, LTB4, and 20-HETE

Although AA is a substrate for both pro-resolving and pro-inflammatory eicosanoids, its administration may inadvertently promote inflammatory cascades. LTB4 and 20-HETE have been implicated in glomerular leukocyte infiltration, oxidative stress, endothelial dysfunction, and tubulointerstitial fibrosis in LN, DN, and IRI [57,68,242]. These metabolites also influence vascular tone and platelet aggregation, further contributing to renal injury in patients with metabolic or hypertensive comorbidities [38].

8.3.3. Context-dependent effects of COX-derived mediators

Prostaglandins such as PGE2, PGI2, and TXA2 display dual roles in renal physiology. At physiological levels, PGE2 and PGI2 maintain glomerular filtration and mediate antifibrotic actions [53]. However, overexpression or receptor imbalance may result in mesangial proliferation, enhanced angiogenesis, and accelerated progression of renal cell carcinoma [53,243]. TXA2 has been associated with glomerular vasoconstriction and thrombosis, particularly in diabetic and hypertensive nephropathy [243].

8.3.4. Translational barriers and off-target effects

Despite promising preclinical data, several PUFA-derived mediators face limitations in clinical translation. Many SPMs, such as resolvins and protectins, exhibit rapid metabolic degradation and poor receptor characterization in humans [70]. Systemic delivery may lead to unintended off-target effects, including hemodynamic instability or immunosuppression. Moreover, the lack of standardized formulations and validated biomarkers for therapeutic monitoring further complicates their use in nephrology trials [70,244].

8.3.5. Strategies to mitigate therapeutic risks

To enhance therapeutic precision while minimizing adverse effects, several forward-looking strategies can be considered. These include the design of structurally modified pro-resolving mediators with enhanced metabolic stability and receptor selectivity [245]; targeted renal delivery approaches employing advanced carriers such as liposomes, nanoparticles, or biodegradable polymers [246]; and personalized treatment regimens guided by patient-specific variables, including immune profile, disease subtype, and eicosanoid signatures [247]. Additionally, combination therapies may be developed to favorably shift arachidonic acid metabolism toward resolution-phase mediators, thereby limiting pro-inflammatory amplification [247].

Altogether, these approaches emphasize the importance of precision medicine in PUFA-based therapies. A thorough understanding of the metabolic, immunologic, and pharmacodynamic context is critical to harness the therapeutic benefits of these lipid mediators while minimizing unintended harm.

8.4. Route of administration, dosing, and formulation of PUFAs in renal therapy

The therapeutic efficacy of PUFAs in renal diseases is significantly influenced by their administration route, dosing regimen, and formulation. These factors affect bioavailability, tissue distribution, metabolic stability, and patient adherence, which are particularly critical in CKD due to altered pharmacokinetics and systemic inflammation.

Oral supplementation of ω-3 PUFAs, primarily in the form of fish oil containing EPA and DHA, remains the most common approach in clinical nephrology. Clinical trials involving patients with IgA nephropathy have utilized daily doses ranging from 1.8 g EPA and 1.2 g DHA to higher doses, with treatment durations varying from 12 months to 2 years [248]. These studies have reported benefits including reductions in proteinuria, improvements in eGFR, and decreased systemic inflammation [248,249]. For diabetic nephropathy, studies have explored daily doses of ω-3 PUFAs up to 4 g/day over periods ranging from 6 to 12 weeks. While some trials did not observe significant changes in urinary albumin excretion, others reported improvements in serum renal damage markers, suggesting potential benefits of ω-3 PUFA supplementation in renal function [250]. Moreover, findings from Guillot et al. demonstrated that daily DHA supplementation at 1.6 g over 6 weeks increased lipid peroxidation markers in healthy men, underscoring the need for cautious dose optimization, particularly in patients with impaired redox buffering capacity such as those with CKD [251].

Various formulations of PUFAs have been developed to enhance gastrointestinal tolerability and absorption efficiency. These include triglyceride forms, ethyl esters, and free fatty acid preparations. Studies indicate that re-esterified triglyceride forms exhibit superior bioavailability compared to ethyl esters, with free fatty acid forms demonstrating intermediate absorption efficiency. For instance, a study comparing these formulations found that the bioavailability of EPA and DHA from re-esterified triglycerides was approximately 124 % relative to natural fish oil, whereas ethyl esters exhibited about 73 % bioavailability, and free fatty acids showed around 91 % [252].

In critically ill or dialysis-dependent patients, where oral intake is limited, intravenous administration of ω-3-enriched lipid emulsions has been explored. A pilot study involving hemodialysis patients demonstrated that intradialytic intravenous administration of ω-3 PUFAs was safe and well-tolerated, with potential to attenuate the inflammatory response associated with hemodialysis sessions [253]. However, large-scale, nephrology-specific clinical trials are still lacking to conclusively determine the efficacy and safety of this intervention.

Emerging delivery platforms, including liposomes, polymeric nanoparticles, and PUFA-loaded micelles, are being investigated in preclinical models to improve renal tissue targeting, reduce systemic exposure, and enable co-delivery with immunomodulatory agents. These technologies have demonstrated improved pharmacokinetics in preclinical models, but translation into human trials is still in early stages [254]. Moreover, establishing reference concentration ranges for PUFA-derived lipid mediators and validating urinary assays of their stable metabolites could support the development of non-invasive biomarkers for renal inflammation, although these translational objectives remain largely unmet.

While oral PUFA therapy remains the prevailing approach in nephrology, future strategies are expected to shift toward precision-based interventions. These would optimize dosing, formulation, and delivery based on patient-specific variables such as renal function, comorbidities, and individual lipid mediator profiles [255]. The emerging field of lipidomics offers promising tools for monitoring therapeutic response and guiding personalized PUFA regimens. However, significant gaps persist in the standardization of PUFA administration, including variability in EPA/DHA content, formulation type (triglyceride *vs.* ethyl ester), and dose-response relationships, hindering the integration of lipid-based therapies into routine nephrology practice.

9. Conclusion

The intricate interplay between PUFAs, their metabolizing enzymes, and kidney pathophysiology highlights a dynamic balance between protective and deleterious effects. The diverse roles of LOX, COX, and CYP pathways in renal inflammation and tumorigenesis underscore the complexity of lipid metabolism in kidney diseases. While inconsistencies

in current findings reflect the multifaceted nature of these bioactive lipids, accumulating evidence suggests that PUFAs profoundly influence renal function, warranting a more refined analysis of their metabolic impact. A fundamental challenge lies in deciphering whether PUFA metabolites serve as mediators of renal protection or contributors to disease progression. This ambiguity stems from the diverse nature of their derivatives, context-dependent enzyme activity, and the heterogeneity of kidney disorders. Future research should shift from broad pathway analyses toward a mechanistic dissection of enzyme-specific actions, providing deeper insights into their role in kidney injury. As highlighted in this review, targeting PUFA metabolism offers a compelling therapeutic avenue for mitigating renal inflammation, preserving kidney function, and potentially transforming the management of kidney diseases.

CRediT authorship contribution statement

Mehrdad Aghasizadeh: Writing – original draft, Methodology, Investigation. **Ahmad Reza Bahrami:** Methodology. **Maryam M. Matin:** Writing – review & editing, Methodology, Investigation.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors would like to thank Miss Azar M. Bazzaz for her valuable contributions during the preparation of this paper.

References

[1] A.P. Simopoulos, Genetic variants in the metabolism of omega-6 and omega-3 fatty acids: their role in the determination of nutritional requirements and chronic disease risk, Exp. Biol. Med. (Maywood) 235 (7) (Jul. 2010) 785–795, https://doi.org/10.1258/EBM.2010.009298.
[2] C.N. Serhan, N. Chiang, Resolution phase lipid mediators of inflammation: agonists of resolution, Curr. Opin. Pharmacol. 13 (4) (Aug. 2013) 632–640, https://doi.org/10.1016/J.COPH.2013.05.012.
[3] S. Melissa Gabbs, J.G. Leng, M. Monirujjaman Devassy, H.M. Aukema, Advances in our understanding of oxylipins derived from dietary PUFAs, Adv. Nutr. 6 (5) (Sep. 2015) 513–540, https://doi.org/10.3945/AN.114.007732.
[4] R. Li, C. Hu Medchemcomm, S. Ma, Recent development of lipoxygenase inhibitors as anti-inflammatory agents, Medchemcomm 9 (2) (Nov. 2017) 212, https://doi.org/10.1039/C7MD00390K.
[5] R. Wang, et al., Dysregulated palmitic acid metabolism promotes the formation of renal calcium-oxalate stones through ferroptosis induced by polyunsaturated fatty acids/phosphatidic acid, Cell. Mol. Life Sci. 81 (1) (Dec. 2024), https://doi.org/10.1007/S00018-024-05145-Y.
[6] E. Michael August, T. Nguyen, N.M. Malinowski, R.L. Cysyk, Non-steroidal anti-inflammatory drugs and tumor progression: inhibition of fibroblast hyaluronic acid production by indomethacin and mefenamic acid, Cancer Lett. 82 (1) (Jul. 1994) 49–54, https://doi.org/10.1016/0304-3835(94)90145-7.
[7] I. Wood, A. Trostchansky, H. Rubbo, Structural considerations on lipoxygenase function, inhibition and crosstalk with nitric oxide pathways, Biochimie 178 (Nov. 2020) 170–180, https://doi.org/10.1016/J.BIOCHI.2020.09.021.
[8] I. Ivanov, et al., Molecular enzymology of lipoxygenases, Arch. Biochem. Biophys. 503 (2) (Nov. 2010) 161–174, https://doi.org/10.1016/J.ABB.2010.08.016.
[9] J.R. Montford, et al., 15-Lipoxygenase worsens renal fibrosis, inflammation, and metabolism in a murine model of ureteral obstruction, Am. J. Physiol. Ren. Physiol. 322 (1) (Jan. 2021) F105, https://doi.org/10.1152/AJPRENAL.00214.2021.
[10] T. Wang, et al., Arachidonic acid metabolism and kidney inflammation, Int. J. Mol. Sci. 20 (15) (Aug. 2019) 3683, https://doi.org/10.3390/IJMS20153683.
[11] A. Singh, et al., Lipoxin A4, a 5-lipoxygenase pathway metabolite, modulates immune response during acute respiratory tularemia, J. Leukoc. Biol. 101 (2) (Feb. 2017) 531–542, https://doi.org/10.1189/JLB.4A0815-365RR.
[12] M. Aghasizadeh, T. Moghaddam, A.R. Bahrami, H. Sadeghian, S.J. Alavi, M. M. Matin, 8-Geranyloxycarbostyril as a potent 15-LOX-1 inhibitor showed great anti-tumor effects against prostate cancer, Life Sci. 293 (Mar. 2022), https://doi.org/10.1016/j.lfs.2021.120272.
[13] R.G. Snodgrass, B. Brüne, Regulation and functions of 15-lipoxygenases in human macrophages, Front. Pharmacol. 10 (Jul. 2019) 465434, https://doi.org/10.3389/FPHAR.2019.00719.
[14] M. Aghasizadeh, et al., Evaluation of several farnesyloxycarbostyril derivatives as potential 15-LOX-1 inhibitors for prostate cancer treatment, Toxicol. Appl. Pharmacol. 498 (May 2025), https://doi.org/10.1016/J.TAAP.2025.117293.
[15] F. Fan, R.J. Roman, Effect of cytochrome P450 metabolites of arachidonic acid in nephrology, J. Am. Soc. Nephrol. 28 (10) (Oct. 2017) 2845–2855, https://doi.org/10.1681/ASN.2017030252.
[16] M.A. Ladda, K.B. Goralski, The effects of CKD on cytochrome P450-mediated drug metabolism, Adv. Chronic Kidney Dis. 23 (2) (Mar. 2016) 67–75, https://doi.org/10.1053/J.ACKD.2015.10.002.
[17] M.L. Schwartzman, N.G. Abraham, M.A. Carroll, R.D. Levere, J.C. McGiff, Regulation of arachidonic acid metabolism by cytochrome P-450 in rabbit kidney, Biochem. J. 238 (1) (Aug. 1986) 283–290, https://doi.org/10.1042/BJ2380283.
[18] A. Cases, E. Coll, Dyslipidemia and the progression of renal disease in chronic renal failure patients, Kidney Int. Suppl. 68 (99) (Dec. 2005), https://doi.org/10.1111/J.1523-1755.2005.09916.X.
[19] S.H. Suh, S.W. Kim, Dyslipidemia in patients with chronic kidney disease: an updated overview, Diabetes Metab. J. 47 (5) (Sep. 2023) 612–629, https://doi.org/10.4093/DMJ.2023.0067.
[20] Z. Gai, T. Wang, M. Visentin, G.A. Kullak-Ublick, X. Fu, Z. Wang, Lipid accumulation and chronic kidney disease, Nutrients 11 (4) (Apr. 2019), https://doi.org/10.3390/NU11040722.
[21] J. Mesquita, A. Varela, J.L. Medina, Dyslipidemia in renal disease: causes, consequences and treatment, Endocrinol. Nutr. 57 (9) (Nov. 2010) 440–448, https://doi.org/10.1016/J.ENDONU.2010.06.003.
[22] Y. Nishida, H. Oda, N. Yorioka, Effect of lipoproteins on mesangial cell proliferation, Kidney Int. Suppl. 71 (Jul. 1999) S51–S53, https://doi.org/10.1046/J.1523-1755.1999.07113.X.
[23] D.T. Chan, et al., Chronic kidney disease delays VLDL-apoB-100 particle catabolism: potential role of apolipoprotein C-III, J. Lipid Res. 50 (12) (Dec. 2009) 2524–2531, https://doi.org/10.1194/JLR.P900003-JLR200.
[24] A. Mitrofanova, S. Merscher, A. Fornoni, Kidney lipid dysmetabolism and lipid droplet accumulation in chronic kidney disease, Nat. Rev. Nephrol. 19 (10) (Oct. 2023) 629–645, https://doi.org/10.1038/S41581-023-00741-W.
[25] Z.A. Ceja-Galicia, et al., The development of dyslipidemia in chronic kidney disease and associated cardiovascular damage, and the protective effects of curcuminoids, Foods 12 (5) (Mar. 2023), https://doi.org/10.3390/FOODS12050921.
[26] M. Moafi, et al., Impact of dyslipidemia on estimated glomerular filtration rate in apparently healthy children and adolescents: the CASPIAN-V study, World J. Pediatr. 15 (5) (Oct. 2019) 471–475, https://doi.org/10.1007/S12519-019-00270-2.
[27] K. Esmeijer, O.M. Dekkers, J.W. de Fijter, F.W. Dekker, E.K. Hoogeveen, Effect of different types of statins on kidney function decline and proteinuria: a network meta-analysis, Sci. Rep. 9 (1) (Dec. 2019), https://doi.org/10.1038/S41598-019-53064-X.
[28] J. Davis, K.K. Pula, K.B. Alton, R.E. Burrier, R.W. Watkins, The synergistic hypocholesterolemic activity of the potent cholesterol absorption inhibitor, ezetimibe, in combination with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in dogs, Metabolism 50 (10) (Oct. 2001) 1234–1241, https://doi.org/10.1053/meta.2001.26737.
[29] J. Hu, Z. Liu, H. Zhang, Omega-3 fatty acid supplementation as an adjunctive therapy in the treatment of chronic kidney disease: a meta-analysis, Clinics 72 (1) (Jan. 2017) 58, https://doi.org/10.6061/CLINICS/2017(01)10.
[30] J.K. Bird, P.C. Calder, M. Eggersdorfer, The role of n-3 long chain polyunsaturated fatty acids in cardiovascular disease prevention, and interactions with statins, Nutrients 10 (6) (Jun. 2018), https://doi.org/10.3390/NU10060775.
[31] H.E. Theobald, P.J. Chowienczyk, R. Whittall, S.E. Humphries, T.A.B. Sanders, LDL cholesterol-raising effect of low-dose docosahexaenoic acid in middle-aged men and women, Am. J. Clin. Nutr. 79 (4) (Apr. 2004) 558–563, https://doi.org/10.1093/AJCN/79.4.558.
[32] A. Balić, D. Vlašić, K. Žužul, B. Marinović, Z.B. Mokos, Omega-3 versus omega-6 polyunsaturated fatty acids in the prevention and treatment of inflammatory skin diseases, Int. J. Mol. Sci. 21 (3) (Feb. 2020), https://doi.org/10.3390/IJMS21030741.
[33] W. Raphael, L.M. Sordillo, Dietary polyunsaturated fatty acids and inflammation: the role of phospholipid biosynthesis, Int. J. Mol. Sci. 14 (10) (Oct. 2013) 21167–21188, https://doi.org/10.3390/IJMS141021167.
[34] S.P. Lin, C.M. Chen, K.L. Wang, K.L. Wu, S.C. Li, Association of dietary fish and n-3 unsaturated fatty acid consumption with diabetic nephropathy from a district hospital in northern Taiwan, Nutrients 14 (10) (May 2022), https://doi.org/10.3390/NU14102148.
[35] J. Zhou, N. Franceschini, W.H.D. Townley-Tilson, N. Maeda-Smithies, Nutritional strategies against diabetic nephropathy: insights from animal studies and human trials, Nutrients 16 (12) (Jun. 2024), https://doi.org/10.3390/NU16121918.
[36] M.R. Ogborn, E. Nitschmann, N. Bankovic-Calic, H.A. Weiler, S. Fitzpatrick-Wong, H.M. Aukema, Dietary conjugated linoleic acid reduces PGE2 release and interstitial injury in rat polycystic kidney disease, Kidney Int. 64 (4) (Oct. 2003) 1214–1221, https://doi.org/10.1046/J.1523-1755.2003.00215.X.

[37] M.W. Khan, S. Priyamvada, S.A. Khan, S. Khan, A. Naqshbandi, A.N.K. Yusufi, Protective effect of ω-3 polyunsaturated fatty acids (PUFAs) on sodium nitroprusside-induced nephrotoxicity and oxidative damage in rat kidney, Hum. Exp. Toxicol. 31 (10) (Oct. 2012) 1035–1049, https://doi.org/10.1177/0960327112444475.
[38] U.N. Das, Long-chain polyunsaturated fatty acids interact with nitric oxide, superoxide anion, and transforming growth factor-β to prevent human essential hypertension, Eur. J. Clin. Nutr. 58 (2) (Feb. 2004) 195–203, https://doi.org/10.1038/SJ.EJCN.1601766;KWRD=MEDICINE.
[39] R. Ng, Fish oil therapy in recurrent IgA nephropathy, Ann. Intern. Med. 138 (12) (Jun. 2003) 1011–1012, https://doi.org/10.7326/0003-4819-138-12-200306170-00029.
[40] G. Tsipas, P. Morphake, Beneficial effects of a diet rich in a mixture of n - 6/n - 3 essential fatty acids and of their metabolites on cyclosporine - nephrotoxicity, J. Nutr. Biochem. 14 (8) (Aug. 2003) 480–486, https://doi.org/10.1016/S0955-2863(03)00102-5.
[41] Z. Zeng, H. Yang, Y. Wang, J. Ren, Y. Dai, C. Dai, Omega-3 polyunsaturated fatty acids attenuate fibroblast activation and kidney fibrosis involving MTORC2 signaling suppression, Sci. Rep. 7 (Apr. 2017), https://doi.org/10.1038/SREP46146.
[42] W. Liu, S. Liu, Q. Ren, R. Yang, S. Su, X. Jiang, Association between polyunsaturated fatty acids and progression among patients with diabetic kidney disease, Prim. Care Diabetes 18 (2) (Apr. 2024) 177–182, https://doi.org/10.1016/J.PCD.2024.01.002.
[43] M. Rupérez, Ó. Lorenzo, L.M. Blanco-Colio, V. Esteban, J. Egido, M. Ruiz-Ortega, Connective tissue growth factor is a mediator of angiotensin II-induced fibrosis, Circulation 108 (12) (Sep. 2003) 1499–1505, https://doi.org/10.1161/01.CIR.0000089129.51288.BA.
[44] Z. Deng, et al., TGF-β signaling in health, disease and therapeutics, Signal Transduct. Target. Ther. 9 (1) (Mar. 2024) 1–40, https://doi.org/10.1038/s41392-024-01764-w.
[45] M. Hida, H. Fujita, K. Ishikura, S. Omori, M. Hoshiya, M. Awazu, Eicosapentaenoic acid inhibits PDGF-induced mitogenesis and cyclin D1 expression via TGF-beta in mesangial cells, J. Cell. Physiol. 196 (2) (Aug. 2003) 293–300, https://doi.org/10.1002/JCP.10298.
[46] K. Nitta, et al., Eicosapentaenoic acid inhibits mitogen-induced endothelin-1 production and DNA synthesis in cultured bovine mesangial cells, Am. J. Nephrol. 18 (2) (Mar. 1998) 164–170, https://doi.org/10.1159/000013328.
[47] M.M. Diaz Encarnacion, G.M. Warner, J. Cheng, C.E. Gray, K.A. Nath, J. P. Grande, n-3 fatty acids block TNF-α-stimulated MCP-1 expression in rat mesangial cells, Am. J. Physiol. Ren. Physiol. 300 (5) (May 2011) 1142–1151, https://doi.org/10.1152/AJPRENAL.00064.2011.
[48] J.D. Stockand, M. Silverman, D. Hall, T. Derr, B. Kubacak, S.C. Sansom, Arachidonic acid potentiates the feedback response of mesangial BKCa channels to angiotensin II, Am. J. Phys. 274 (4) (Apr. 1998), https://doi.org/10.1152/AJPRENAL.1998.274.4.F658.
[49] M.L. Kielar, D.R. Jeyarajah, X.J. Zhou, C.Y. Lu, Docosahexaenoic acid ameliorates murine ischemic acute renal failure and prevents increases in mRNA abundance for both TNF-alpha and inducible nitric oxide synthase, J. Am. Soc. Nephrol. 14 (2) (Feb. 2003) 389–396, https://doi.org/10.1097/01.ASN.0000045047.44107.0B.
[50] E.K. Hoogeveen, et al., Effect of omega-3 fatty acids on kidney function after myocardial infarction: the Alpha Omega Trial, Clin. J. Am. Soc. Nephrol. 9 (10) (Aug. 2014) 1676–1683, https://doi.org/10.2215/CJN.10441013.
[51] V. Sharma, V. Patial, Peroxisome proliferator-activated receptor gamma and its natural agonists in the treatment of kidney diseases, Front. Pharmacol. 13 (Oct. 2022) 991059, https://doi.org/10.3389/FPHAR.2022.991059.
[52] J.L. Harwood, Polyunsaturated fatty acids: Conversion to lipid mediators, roles in inflammatory diseases and dietary sources, Int. J. Mol. Sci. 24 (10) (May 2023) 8838, https://doi.org/10.3390/IJMS24108838.
[53] Y. Li, et al., Prostaglandins in the pathogenesis of kidney diseases, Oncotarget 9 (41) (May 2018) 26586–26602, https://doi.org/10.18632/ONCOTARGET.25005.
[54] A. Yared, C. Albrightson-Winslow, D. Griswold, K. Takahashi, A. Fogo, K.F. Badr, Functional significance of leukotriene B4 in normal and glomerulonephritic kidneys, J. Am. Soc. Nephrol. 2 (1) (Jul. 1991) 45–56, https://doi.org/10.1681/ASN.V2145.
[55] U. Hoff, et al., Inhibition of 20-HETE synthesis and action protects the kidney from ischemia/reperfusion injury, Kidney Int. 79 (1) (Jan. 2011) 57–65, https://doi.org/10.1038/KI.2010.377.
[56] U.N. Das, Lipoxins as biomarkers of lupus and other inflammatory conditions, Lipids Health Dis. 10 (May 2011) 76, https://doi.org/10.1186/1476-511X-10-76.
[57] A. Bakr, S. Hawas, S. Slem, A.A. Moniem, T. Ghatab, M. Tawfik, 5-lipoxygenase and leukotriene A4 hydrolase expression in primary nephrotic syndrome, Pediatr. Nephrol. 19 (4) (Apr. 2004) 396–399, https://doi.org/10.1007/S00467-003-1399-3.
[58] S. Sadeghi-Bojd, et al., Platelet indices in children with nephrotic syndrome, Nephro-Urol. Mon. 16 (2) (May 2024), https://doi.org/10.5812/NUMONTHLY-139841.
[59] C. Chen, et al., Lipoxin A4 restores septic renal function via blocking crosstalk between inflammation and premature senescence, Front. Immunol. 12 (Apr. 2021) 637753, https://doi.org/10.3389/FIMMU.2021.637753/BIBTEX.
[60] J. Yuan, et al., Lipoxin A4 regulates M1/M2 macrophage polarization via FPR2–IRF pathway, Inflammopharmacology 30 (2) (Apr. 2022) 487–498, https://doi.org/10.1007/S10787-022-00942-Y.
[61] P.C. Calder, Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? Br. J. Clin. Pharmacol. 75 (3) (Mar. 2013) 645–662, https://doi.org/10.1111/j.1365-2125.2012.04374.x.
[62] T. Stefano, et al., Adherence to the mediterranean diet improves fatty acids profile in pediatric patients with idiopathic nephrotic syndrome, Nutrients 13 (11) (Nov. 2021), https://doi.org/10.3390/NU13114110.
[63] J. Duan, Y. Song, X. Zhang, C. Wang, Effect of ω-3 polyunsaturated fatty acids-derived bioactive lipids on metabolic disorders, Front. Physiol. 12 (May 2021) 646491, https://doi.org/10.3389/FPHYS.2021.646491.
[64] P.C. Calder, Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance, BBA Mol. Cell. Biol. Lipids 1851 (4) (Apr. 2015) 469–484, https://doi.org/10.1016/J.BBALIP.2014.08.010.
[65] J. Li, X. Liu, Q. Xiang, T. Xia, H. Meng, Design of nanoformulation of specialized pro-resolving mediators to facilitate inflammation resolution and disease treatment, Nano Today 52 (Oct. 2023) 101978, https://doi.org/10.1016/J.NANTOD.2023.101978.
[66] R. Shioda, et al., The leukotriene B4/BLT1-dependent neutrophil accumulation exacerbates immune complex-mediated glomerulonephritis, FASEB J. 37 (2) (Feb. 2023) e22789, https://doi.org/10.1096/FJ.202201936R.
[67] L. Hongyan, Z. Yi, D. Bao, L. Yuewu, M. Juan, A study on clinical and pathologic features in lupus nephritis with mainly IgA deposits and a literature review, Clin. Dev. Immunol. 2013 (Sep. 2013) 289316, https://doi.org/10.1155/2013/289316.
[68] M. Kamata, et al., Role of the high-affinity leukotriene B4 receptor signaling in fibrosis after unilateral ureteral obstruction in mice, PLoS One 14 (2) (Feb. 2019) e0202842, https://doi.org/10.1371/JOURNAL.PONE.0202842.
[69] K.Y.C. Yu, et al., Clinico-pathological associations of serum VCAM-1 and ICAM-1 levels in patients with lupus nephritis, Lupus 30 (7) (Jun. 2021) 1039–1050, https://doi.org/10.1177/09612033211004727.
[70] M.C. Basil, B.D. Levy, Specialized pro-resolving mediators: endogenous regulators of infection and inflammation, Nat. Rev. Immunol. 16 (1) (Jan. 2015) 51, https://doi.org/10.1038/NRI.2015.4.
[71] S. Hong, Y. Lu, Omega-3 fatty acid-derived resolvins and protectins in inflammation resolution and leukocyte functions: targeting novel lipid mediator pathways in mitigation of acute kidney injury, Front. Immunol. 4 (Jan. 2013) 13, https://doi.org/10.3389/FIMMU.2013.00013.
[72] H.U. Meier-Kriesche, J.D. Schold, B. Kaplan, Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? Am. J. Transplant. 4 (8) (Aug. 2004) 1289–1295, https://doi.org/10.1111/j.1600-6143.2004.00515.x.
[73] M. Li, F. Li, Effects of omega-3 polyunsaturated fatty acids on inflammation resolution and angiogenesis in fat grafts in a controlled mouse model, Plast. Reconstr. Surg. (Jan. 2025), https://doi.org/10.1097/PRS.0000000000011997.
[74] I.A. Eide, et al., Effects of marine n-3 fatty acid supplementation in renal transplantation: a randomized controlled trial, Am. J. Transplant. 19 (3) (Mar. 2019) 790–800, https://doi.org/10.1111/AJT.15080.
[75] J.J.H. van der Heide, H. Bilo, J.M. Donker, J.M. Wilmink, A.M. Tegzess, Effect of dietary fish oil on renal function and rejection in cyclosporine-treated recipients of renal transplants, N. Engl. J. Med. 329 (11) (Sep. 1993) 769–773, https://doi.org/10.1056/NEJM199411033311804.
[76] J.J. Pestka, N-3 polyunsaturated fatty acids and autoimmune-mediated glomerulonephritis, Prostaglandins Leukot. Essent. Fat. Acids 82 (4–6) (Apr. 2010) 251, https://doi.org/10.1016/J.PLEFA.2010.02.013.
[77] V. Ivković, et al., ANCA-associated glomerulonephritis: diagnosis and therapy proceedings of the henry shavelle lectureship, Glomerular Dis. 5 (1) (Jan. 2025) 26–47, https://doi.org/10.1159/000542925.
[78] T.L. McGaha, M.P. Madaio, Lupus nephritis: animal modeling of a complex disease syndrome pathology, Drug Discov. Today Dis. Model. 11 (Feb. 2014) 13, https://doi.org/10.1016/J.DDMOD.2014.08.002.
[79] M.M. Sedky Abdou, D.A. Effat, L.A. Mansour, N.M. Abd El Baky, M.M. Abdul Salam, Urinary lipoxin A4 as a biomarker for systemic lupus erythematosus, Egypt. Rheumatol. Rehabil. 42 (2) (May 2015) 55–61, https://doi.org/10.4103/1110-161X.157861.
[80] H. Liu, et al., Lipoxin A4 suppresses angiotensin II type 1 receptor autoantibody in preeclampsia via modulating caspase-1, Cell Death Dis. 11 (1) (Jan. 2020) 1–17, https://doi.org/10.1038/s41419-020-2281-y.
[81] Y. Ge, M. Huang, Y.M. Yao, Efferocytosis and its role in inflammatory disorders, Front. Cell Dev. Biol. 10 (Feb. 2022) 839248, https://doi.org/10.3389/FCELL.2022.839248/XML/NLM.
[82] A. Liu, et al., ω-3 polyunsaturated fatty acid alleviates systemic lupus erythematosus by suppressing autoimmunity in a murine model, Int. Immunopharmacol. 126 (Jan. 2024) 111299, https://doi.org/10.1016/J.INTIMP.2023.111299.
[83] R. Rodriguez-Echevarria, J. Macias-Barragan, M. Parra-Vargas, J.R. Davila-Rodriguez, E. Amezcua-Galvez, J. Armendariz-Borunda, Diet switch and omega-3 hydroxy-fatty acids display differential hepatoprotective effects in an obesity/nonalcoholic fatty liver disease model in mice, World J. Gastroenterol. 24 (4) (Jan. 2018) 461, https://doi.org/10.3748/WJG.V24.I4.461.
[84] P.C. Calder, Omega-3 fatty acids and inflammatory processes: from molecules to man, Biochem. Soc. Trans. 45 (5) (Oct. 2017) 1105–1115, https://doi.org/10.1042/BST20160474.
[85] M.H. Omer, A. Shafqat, O. Ahmad, J. Nadri, K. AlKattan, A. Yaqinuddin, Urinary biomarkers for lupus nephritis: a systems biology approach, J. Clin. Med. 13 (8) (Apr. 2024) 2339, https://doi.org/10.3390/JCM13082339.

[86] I.M. Berquin, et al., Modulation of prostate cancer genetic risk by omega-3 and omega-6 fatty acids, J. Clin. Invest. 117 (7) (Jul. 2007) 1866, https://doi.org/10.1172/JCI31494.
[87] A. Colquhoun, R.I. Schumacher, γ-Linolenic acid and eicosapentaenoic acid induce modifications in mitochondrial metabolism, reactive oxygen species generation, lipid peroxidation and apoptosis in Walker 256 rat carcinosarcoma cells, Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1533 (3) (Oct. 2001) 207–219, https://doi.org/10.1016/S1388-1981(01)00136-6.
[88] L. Oguh-Olayinka, et al., The investigation of lipoxygenases as therapeutic targets in malignant pleural mesothelioma, Pathol. Oncol. Res. 26 (2) (Apr. 2020) 985–995, https://doi.org/10.1007/S12253-019-00652-X.
[89] A. Gohara, et al., Human 5-, 12- and 15-lipoxygenase-1 coexist in kidney but show opposite trends and their balance changes in cancer, Oncol. Rep. 28 (4) (Jul. 2012) 1275–1282, https://doi.org/10.3892/OR.2012.1924.
[90] I. Daurkin, et al., Tumor-associated macrophages mediate immunosuppression in the renal cancer microenvironment by activating the 15-lipoxygenase-2 pathway, Cancer Res. 71 (20) (Oct. 2011) 6400–6409, https://doi.org/10.1158/0008-5472.CAN-11-1261.
[91] A.L. Gonzalez, R.L. Roberts, P.P. Massion, S.J. Olson, Y. Shyr, S.B. Shappell, 15-lipoxygenase-2 expression in benign and neoplastic lung: an immunohistochemical study and correlation with tumor grade and proliferation, Hum. Pathol. 35 (7) (Jul. 2004) 840–849, https://doi.org/10.1016/J.HUMPATH.2004.04.001.
[92] Y. Wu, et al., 15-LOX-1 suppression of hypoxia-induced metastatic phenotype and HIF-1α expression in human colon cancer cells, Cancer Med. 3 (3) (Jun. 2014) 472–484, https://doi.org/10.1002/CAM4.222.
[93] M.A. Vaezi, et al., 15-Lipoxygenase and its metabolites in the pathogenesis of breast cancer: a double-edged sword, Lipids Health Dis. 20 (1) (Dec. 2021), https://doi.org/10.1186/S12944-021-01599-2.
[94] X. Tian, X. Li, M. Pan, L.Z. Yang, Y. Li, W. Fang, Progress of ferroptosis in ischemic stroke and therapeutic targets, Cell. Mol. Neurobiol. 44 (1) (Feb. 2024) 1–15, https://doi.org/10.1007/S10571-024-01457-6.
[95] Y.J. Na, et al., Deficiency of 15-LOX-1 induces radioresistance through downregulation of macroH2A2 in colorectal cancer, Cancers 11 (11) (Nov. 2019) 1776, https://doi.org/10.3390/CANCERS11111776.
[96] A.S. Kahnt, A.K. Häfner, D. Steinhilber, The role of human 5-lipoxygenase (5-LO) in carcinogenesis - a question of canonical and non-canonical functions, Oncogene 43 (18) (Apr. 2024) 1319–1327, https://doi.org/10.1038/s41388-024-03016-1.
[97] S. Shyam Sunder, U.C. Sharma, S. Pokharel, Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management, Signal Transduct. Target. Ther. 8 (1) (Jul. 2023) 1–27, https://doi.org/10.1038/s41392-023-01469-6.
[98] B.I. Rini, et al., Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib, J. Natl. Cancer Inst. 103 (9) (May 2011) 763–773, https://doi.org/10.1093/JNCI/DJR128.
[99] M. Matsuyama, R. Yoshimura, Relationship between arachidonic acid pathway and human renal cell carcinoma, Onco. Targets Ther. 1 (Oct. 2008) 41, https://doi.org/10.2147/OTT.S3973.
[100] F. Fan, et al., Molecular mechanisms and cell signaling of 20-hydroxyeicosatetraenoic acid in vascular pathophysiology, Front. Biosci. (Landmark Ed.) 21 (7) (Jun. 2016) 1427, https://doi.org/10.2741/4465.
[101] A.M. Guo, et al., Expression of CYP4A1 in U251 human glioma cell induces hyperproliferative phenotype in vitro and rapidly growing tumors in vivo, J. Pharmacol. Exp. Ther. 327 (1) (Oct. 2008) 10–19, https://doi.org/10.1124/JPET.108.140889.
[102] R.N. Gomes, F. da C. Souza, A. Colquhoun, Eicosanoids and cancer, Clinics (Sao Paulo) 73 (Suppl. 1) (Aug. 2018), https://doi.org/10.6061/CLINICS/2018/E530S.
[103] C. Cecilia, et al., Cytochrome 450 metabolites of arachidonic acid (20-HETE, 11,12-EET and 14,15-EET) promote pheochromocytoma cell growth and tumor associated angiogenesis, Biochimie 171–172 (Apr. 2020) 147–157, https://doi.org/10.1016/J.BIOCHI.2020.02.014.
[104] M. Potente, U.R. Michaelis, B. Fisslthaler, R. Busse, I. Fleming, Cytochrome P450 2C9-induced endothelial cell proliferation involves induction of mitogen-activated protein (MAP) kinase phosphatase-1, inhibition of the c-Jun N-terminal kinase, and up-regulation of cyclin D1, J. Biol. Chem. 277 (18) (May 2002) 15671–15676, https://doi.org/10.1074/JBC.M110806200.
[105] B.I. Rini, et al., Maximal COX-2 immunostaining and clinical response to celecoxib and interferon alpha therapy in metastatic renal cell carcinoma, Cancer 106 (3) (Feb. 2006) 566–575, https://doi.org/10.1002/CNCR.21661.
[106] X. Wang, et al., Cox-2 inhibition enhances the activity of sunitinib in human renal cell carcinoma xenografts, Br. J. Cancer 108 (2) (Feb. 2013) 319–326, https://doi.org/10.1038/BJC.2012.591.
[107] D.J. Sanchez, D.J. Steger, N. Skuli, A. Bansal, M.C. Simon, PPARγ is dispensable for clear cell renal cell carcinoma progression, Mol. Metab. 14 (Aug. 2018) 139–149, https://doi.org/10.1016/J.MOLMET.2018.05.013.
[108] F.G. Yang, et al., Peroxisome proliferator-activated receptor gamma ligands induce cell cycle arrest and apoptosis in human renal carcinoma cell lines, Acta Pharmacol. Sin. 26 (6) (Jun. 2005) 753–761, https://doi.org/10.1111/j.1745-7254.2005.00753.x.
[109] J. Sun, L. Yu, X. Qu, T. Huang, The role of peroxisome proliferator-activated receptors in the tumor microenvironment, tumor cell metabolism, and anticancer therapy, Front. Pharmacol. 14 (May 2023) 1184794, https://doi.org/10.3389/FPHAR.2023.1184794/BIBTEX.
[110] L. Zhu, C. Jones, G. Zhang, The role of phospholipase C signaling in macrophage-mediated inflammatory response, J. Immunol. Res. (Feb. 2018) 5201759, https://doi.org/10.1155/2018/5201759.
[111] B. Wang, et al., Metabolism pathways of arachidonic acids: mechanisms and potential therapeutic targets, Signal Transduct. Target. Ther. 6 (1) (Feb. 2021) 1–30, https://doi.org/10.1038/s41392-020-00443-w.
[112] R. Nørregaard, T.H. Kwon, J. Frøkiær, Physiology and pathophysiology of cyclooxygenase-2 and prostaglandin E2 in the kidney, Kidney Res. Clin. Pract. 34 (4) (Dec. 2015) 194–200, https://doi.org/10.1016/J.KRCP.2015.10.004.
[113] C. Yang, et al., Mechanism for the reactivation of the peroxidase activity of human cyclooxygenases: investigation using phenol as a reducing cosubstrate, Sci. Rep. 10 (1) (Dec. 2020), https://doi.org/10.1038/S41598-020-71237-X.
[114] K. Kawahara, H. Hohjoh, T. Inazumi, S. Tsuchiya, Y. Sugimoto, Prostaglandin E2-induced inflammation: relevance of prostaglandin E receptors, Biochim. Biophys. Acta 1851 (4) (Apr. 2015) 414–421, https://doi.org/10.1016/J.BBALIP.2014.07.008.
[115] J.U. Scher, M.H. Pillinger, 15d-PGJ2: the anti-inflammatory prostaglandin? Clin. Immunol. 114 (2) (Feb. 2005) 100–109, https://doi.org/10.1016/J.CLIM.2004.09.008.
[116] Z. Zhou, C. Sun, S.L. Tilley, S.J. Mustafa, Mechanisms underlying uridine adenosine tetraphosphate-induced vascular contraction in mouse aorta: role of thromboxane and purinergic receptors, Vasc. Pharmacol. 73 (Oct. 2015) 78–85, https://doi.org/10.1016/J.VPH.2015.04.009.
[117] M. Alhouayek, G.G. Muccioli, COX-2-derived endocannabinoid metabolites as novel inflammatory mediators, Trends Pharmacol. Sci. 35 (6) (Jun. 2014) 284–292, https://doi.org/10.1016/J.TIPS.2014.03.001.
[118] C. Pierre, et al., Invalidation of microsomal prostaglandin E synthase-1 (mPGES-1) reduces diet-induced low-grade inflammation and adiposity, Front. Physiol. 9 (Oct. 2018) 1358, https://doi.org/10.3389/FPHYS.2018.01358.
[119] N.V. Chandrasekharan, et al., COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression, Proc. Natl. Acad. Sci. USA 99 (21) (Oct. 2002) 13926–13931, https://doi.org/10.1073/PNAS.162468699.
[120] O. Rådmark, O. Werz, D. Steinhilber, B. Samuelsson, 5-Lipoxygenase, a key enzyme for leukotriene biosynthesis in health and disease, Biochim. Biophys. Acta 1851 (4) (Apr. 2015) 331–339, https://doi.org/10.1016/J.BBALIP.2014.08.012.
[121] M. Mittal, et al., Kinetic investigation of human 5-lipoxygenase with arachidonic acid, Bioorg. Med. Chem. Lett. 26 (15) (Aug. 2016) 3547–3551, https://doi.org/10.1016/J.BMCL.2016.06.025.
[122] W.S. Powell, F. Gravelle, S. Gravel, Metabolism of 5(S)-hydroxy-6,8,11,14-eicosatetraenoic acid and other 5(S)-hydroxyeicosanoids by a specific dehydrogenase in human polymorphonuclear leukocytes, J. Biol. Chem. 267 (27) (Sep. 1992) 19233–19241, https://doi.org/10.1016/S0021-9258(18)41766-8.
[123] W.S. Powell, J. Rokach, Biosynthesis, biological effects, and receptors of hydroxyeicosatetraenoic acids (HETEs) and oxoeicosatetraenoic acids (oxo-ETEs) derived from arachidonic acid, Biochim. Biophys. Acta 1851 (4) (Apr. 2015) 340–355, https://doi.org/10.1016/J.BBALIP.2014.10.008.
[124] A.R. Green, et al., 5 S,15 S-Dihydroperoxyeicosatetraenoic acid (5,15-diHpETE) as a lipoxin intermediate: reactivity and kinetics with human leukocyte 5-lipoxygenase, platelet 12-lipoxygenase, and reticulocyte 15-lipoxygenase-1, Biochemistry 57 (48) (Dec. 2018) 6726–6734, https://doi.org/10.1021/ACS.BIOCHEM.8B00889.
[125] C.J. Smyrniotis, S.R. Barbour, Z. Xia, M.S. Hixon, T.R. Holman, ATP allosterically activates the human 5-lipoxygenase molecular mechanism of arachidonic acid and 5(S)-Hydroperoxy-6(E),8(Z),11(Z),14(Z)-eicosatetraenoic acid, Biochemistry 53 (27) (Jul. 2014) 4407, https://doi.org/10.1021/BI401621D.
[126] D.D. Sears, et al., 12/15-lipoxygenase is required for the early onset of high fat diet-induced adipose tissue inflammation and insulin resistance in mice, PLoS One 4 (9) (Sep. 2009) e7250, https://doi.org/10.1371/JOURNAL.PONE.0007250.
[127] J.A. Giménez-Bastida, A. González-Sarrías, J.M. Laparra-Llopis, C. Schneider, J. C. Espín, Targeting mammalian 5-lipoxygenase by dietary phenolics as an anti-inflammatory mechanism: a systematic review, Int. J. Mol. Sci. 22 (15) (Aug. 2021) 7937, https://doi.org/10.3390/IJMS22157937/S1.
[128] A. Kulkarni, J.L. Nadler, R.G. Mirmira, I. Casimiro, Regulation of tissue inflammation by 12-lipoxygenases, Biomolecules 11 (5) (May 2021) 717, https://doi.org/10.3390/BIOM11050717.
[129] J.J. Moreno, New aspects of the role of hydroxyeicosatetraenoic acids in cell growth and cancer development, Biochem. Pharmacol. 77 (1) (Jan. 2009) 1–10, https://doi.org/10.1016/J.BCP.2008.07.033.
[130] H. Kühn, S. Banthiya, K. van Leyen, Mammalian lipoxygenases and their biological relevance, Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1851 (4) (Apr. 2015) 308–330, https://doi.org/10.1016/j.bbalip.2014.10.002.
[131] J. Chi, J. Cheng, S. Wang, C. Li, M. Chen, Promising anti-inflammatory tools: biomedical efficacy of lipoxins and their synthetic pathways, Int. J. Mol. Sci. 24 (17) (Sep. 2023) 13282, https://doi.org/10.3390/IJMS241713282.
[132] J.-F. Wang, C.-C. Zhang, K.-C. Chou, D.-Q. Wei, Structure of cytochrome p450s and personalized drug, Curr. Med. Chem. 16 (2) (Dec. 2009) 232–244, https://doi.org/10.2174/092986709787002727.
[133] S. Tacconelli, P. Patrignani, Inside epoxyeicosatrienoic acids and cardiovascular disease, Front. Pharmacol. 5 (Nov. 2014), https://doi.org/10.3389/FPHAR.2014.00239.
[134] A.E. Enayetallah, R.A. French, M.S. Thibodeau, D.F. Grant, Distribution of soluble epoxide hydrolase and of cytochrome P450 2C8, 2C9, and 2J2 in human tissues, J. Histochem. Cytochem. 52 (4) (Apr. 2004) 447–454, https://doi.org/10.1177/002215540405200403.

[135] L. Kiss, J. Bier, Y. Röder, N. Weissmann, F. Grimminger, W. Seeger, Direct and simultaneous profiling of epoxyeicosatrienoic acid enantiomers by capillary tandem column chiral-phase liquid chromatography with dual online photodiode array and tandem mass spectrometric detection, Anal. Bioanal. Chem. 392 (4) (Oct. 2008) 717–726, https://doi.org/10.1007/S00216-008-2308-1.
[136] C. Morisseau, B.D. Hammock, Impact of soluble epoxide hydrolase and epoxyeicosanoids on human health, Annu. Rev. Pharmacol. Toxicol. 53 (Jan. 2012) 37, https://doi.org/10.1146/ANNUREV-PHARMTOX-011112-140244.
[137] Z. Yu, et al., Soluble epoxide hydrolase regulates hydrolysis of vasoactive epoxyeicosatrienoic acids, Circ. Res. 87 (11) (Nov. 2000) 992–998, https://doi.org/10.1161/01.RES.87.11.992.
[138] G. Luo, D.C. Zeldin, J.A. Blaisdell, E. Hodgson, J.A. Goldstein, Cloning and expression of murine CYP2Cs and their ability to metabolize arachidonic acid, Arch. Biochem. Biophys. 357 (1) (Sep. 1998) 45–57, https://doi.org/10.1006/ABBI.1998.0806.
[139] S. Wu, C.R. Moomaw, K.B. Tomer, J.R. Falck, D.C. Zeldin, Molecular cloning and expression of CYP2J2, a human cytochrome P450 arachidonic acid epoxygenase highly expressed in heart, J. Biol. Chem. 271 (7) (Feb. 1996) 3460–3468, https://doi.org/10.1074/JBC.271.7.3460.
[140] C.N. Serhan, Pro-resolving lipid mediators are leads for resolution physiology, Nature 510 (7503) (Jun. 2014) 92–101, https://doi.org/10.1038/nature13479.
[141] W.F. Clark, A. Parbtani, Omega-3 fatty acid supplementation in clinical and experimental lupus nephritis, Am. J. Kidney Dis. 23 (5) (May 1994) 644–647, https://doi.org/10.1016/S0272-6386(12)70273-1.
[142] C.N. Serhan, N. Chiang, T.E. Van Dyke, Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators, Nat. Rev. Immunol. 8 (5) (May 2008) 349–361, https://doi.org/10.1038/nri2294.
[143] Y.P. Sun, et al., Anti-inflammatory and pro-resolving properties of benzo-lipoxin A4 analogs, Prostaglandins Leukot. Essent. Fat. Acids 81 (5–6) (Nov. 2009) 357, https://doi.org/10.1016/J.PLEFA.2009.09.004.
[144] M.O. Leonard, et al., 15-Epi-16-(para-fluorophenoxy)-lipoxin A4-methyl ester, a synthetic analogue of 15-epi-lipoxin A4, is protective in experimental ischemic acute renal failure, J. Am. Soc. Nephrol. 13 (6) (Jun. 2002) 1657–1662, https://doi.org/10.1097/01.ASN.0000015795.74094.91.
[145] S. Eid, et al., 20-HETE and EETs in diabetic nephropathy: a novel mechanistic pathway, PLoS One 8 (8) (Aug. 2013) e70029, https://doi.org/10.1371/JOURNAL.PONE.0070029.
[146] J.V. Pascale, et al., 20-Hydroxyeicosatetraenoic acid (20-HETE): bioactions, receptors, vascular function, cardiometabolic disease and beyond, Adv. Pharmacol. 97 (Jan. 2023) 229–255, https://doi.org/10.1016/bs.apha.2023.01.002.
[147] M. Haddad, et al., Activation of 20-HETE synthase triggers oxidative injury and peripheral nerve damage in type 2 diabetic mice, J. Pain 23 (8) (Aug. 2022) 1371–1388, https://doi.org/10.1016/J.JPAIN.2022.02.011.
[148] A. Manzéger, G. Garmaa, M.M. Mózes, G. Hansmann, G. Kökény, Pioglitazone protects tubular epithelial cells during kidney fibrosis by attenuating miRNA dysregulation and autophagy dysfunction induced by TGF-β, Int. J. Mol. Sci. 24 (21) (Nov. 2023) 15520, https://doi.org/10.3390/IJMS242115520/S1.
[149] M. Arita, et al., Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2,4,6-trinitrobenzene sulfonic acid-induced colitis, Proc. Natl. Acad. Sci. USA 102 (21) (May 2005) 7671–7676, https://doi.org/10.1073/PNAS.0409271102.
[150] L. Feng, X. Chen, Y. Huang, X. Zhang, S. Zheng, N. Xie, Immunometabolism changes in fibrosis: from mechanisms to therapeutic strategies, Front. Pharmacol. 14 (Jul. 2023) 1243675, https://doi.org/10.3389/FPHAR.2023.1243675.
[151] T. Lisman, Platelet-neutrophil interactions as drivers of inflammatory and thrombotic disease, Cell Tissue Res. 371 (3) (Mar. 2018) 567–576, https://doi.org/10.1007/S00441-017-2727-4.
[152] R. Zhang, et al., A new perspective on proteinuria and drug therapy for diabetic kidney disease, Front. Pharmacol. 15 (Jul. 2024) 1349022, https://doi.org/10.3389/FPHAR.2024.1349022/BIBTEX.
[153] L. Coulon, C. Calzada, P. Moulin, E. Véricel, M. Lagarde, Activation of p38 mitogen-activated protein kinase/cytosolic phospholipase A2 cascade in hydroperoxide-stressed platelets, Free Radic. Biol. Med. 35 (6) (Sep. 2003) 616–625, https://doi.org/10.1016/S0891-5849(03)00386-1.
[154] A.D. Dobrian, et al., Role of the 12-lipoxygenase pathway in diabetes pathogenesis and complications, Pharmacol. Ther. 195 (Mar. 2019) 100–110, https://doi.org/10.1016/J.PHARMTHERA.2018.10.010.
[155] A. Yamaguchi, et al., Fatty acids negatively regulate platelet function through formation of noncanonical 15-lipoxygenase-derived eicosanoids, Pharmacol. Res. Perspect. 11 (1) (Feb. 2023), https://doi.org/10.1002/PRP2.1056.
[156] B. Escalante, D. Erlij, J.R. Falck, J.C. McGiff, Effect of cytochrome P450 arachidonate metabolites on ion transport in rabbit kidney loop of Henle, Science 251 (4995) (Feb. 1991) 799–802, https://doi.org/10.1126/SCIENCE.1846705.
[157] J.M. Williams, A. Sarkis, B. Lopez, R.P. Ryan, A.K. Flasch, R.J. Roman, Elevations in renal interstitial hydrostatic pressure and 20-hydroxyeicosatetraenoic acid contribute to pressure natriuresis, Hypertension 49 (3) (Mar. 2007) 687–694, https://doi.org/10.1161/01.HYP.0000255753.89363.47.
[158] O.H. Elshenawy, S.M. Shoieb, A. Mohamed, A.O.S. El-Kadi, Clinical implications of 20-hydroxyeicosatetraenoic acid in the kidney, liver, lung and brain: an emerging therapeutic target, Pharmaceutics 9 (1) (Feb. 2017) 9, https://doi.org/10.3390/PHARMACEUTICS9010009.
[159] K.R. Regner, et al., Protective effect of 20-HETE analogues in experimental renal ischemia reperfusion injury, Kidney Int. 75 (5) (Mar. 2009) 511–517, https://doi.org/10.1038/KI.2008.600.
[160] A.A. Eid, et al., Mechanisms of podocyte injury in diabetes: role of cytochrome P450 and NADPH oxidases, Diabetes 58 (5) (May 2009) 1201–1211, https://doi.org/10.2337/DB08-1536.
[161] P. Houeiss, et al., Urinary 20-HETE: a prospective non-invasive prognostic and diagnostic marker for diabetic kidney disease, J. Adv. Res. 44 (Feb. 2023) 109–117, https://doi.org/10.1016/J.JARE.2022.04.013.
[162] D.V. Ilatovskaya, A. Staruschenko, TRPC6 channel as an emerging determinant of the podocyte injury susceptibility in kidney diseases, Am. J. Physiol. Ren. Physiol. 309 (5) (Sep. 2015) F393–F397, https://doi.org/10.1152/AJPRENAL.00186.2015.
[163] J.M. Klausner, et al., Postischemic renal injury is mediated by neutrophils and leukotrienes, Am. J. Phys. 256 (5 Pt 2) (May 1989), https://doi.org/10.1152/AJPRENAL.1989.256.5.F794.
[164] J.R. Montford, et al., Inhibition of 5-lipoxygenase decreases renal fibrosis and progression of chronic kidney disease, Am. J. Physiol. Ren. Physiol. 316 (4) (Apr. 2019) F732, https://doi.org/10.1152/AJPRENAL.00262.2018.
[165] E. Noiri, et al., An in vivo approach showing the chemotactic activity of leukotriene B4 in acute renal ischemic-reperfusion injury, Proc. Natl. Acad. Sci. USA 97 (2) (Jan. 2000) 823–828, https://doi.org/10.1073/PNAS.97.2.823.
[166] G.A. Zimmerman, T.M. McIntyre, Neutrophil adherence to human endothelium in vitro occurs by CDw18 (Mo1, MAC-1/LFA-1/GP 150,95) glycoprotein-dependent and -independent mechanisms, J. Clin. Invest. 81 (2) (Feb. 1988) 531–537, https://doi.org/10.1172/JCI113351.
[167] L. Li, M.D. Okusa, Macrophages, dendritic cells, and kidney ischemia-reperfusion injury, Semin. Nephrol. 30 (3) (May 2010) 268–277, https://doi.org/10.1016/J.SEMNEPHROL.2010.03.005.
[168] M.M. Zedan, et al., Montelukast as an add-on treatment in steroid dependant nephrotic syndrome, randomised-controlled trial, J. Nephrol. 29 (4) (Aug. 2016) 585–592, https://doi.org/10.1007/S40620-016-0297-2.
[169] N.E. Kieran, P. Maderna, C. Godson, Lipoxins: potential anti-inflammatory, proresolution, and antifibrotic mediators in renal disease, Kidney Int. 65 (4) (Apr. 2004) 1145–1154, https://doi.org/10.1111/j.1523-1755.2004.00487.x.
[170] P. Prieto, J. Cuenca, P.G. Través, M. Fernández-Velasco, P. Martín-Sanz, L. Boscá, Lipoxin A4 impairment of apoptotic signaling in macrophages: implication of the PI3K/Akt and the ERK/Nrf-2 defense pathways, Cell Death Differ. 17 (7) (Jan. 2010) 1179–1188, https://doi.org/10.1038/cdd.2009.220.
[171] S.H. Wu, P.Y. Liao, P.L. Yin, Y.M. Zhang, L. Dong, Elevated expressions of 15-lipoxygenase and lipoxin A4 in children with acute poststreptococcal glomerulonephritis, Am. J. Pathol. 174 (1) (Jan. 2009) 115–122, https://doi.org/10.2353/AJPATH.2009.080671.
[172] K. Rodgers, B. McMahon, D. Mitchell, D. Sadlier, C. Godson, Lipoxin A4 modifies platelet-derived growth factor-induced pro-fibrotic gene expression in human renal mesangial cells, Am. J. Pathol. 167 (3) (Sep. 2005) 683–694, https://doi.org/10.1016/S0002-9440(10)62043-3.
[173] H.X. Mei, et al., LXA4 inhibits lipopolysaccharide-induced inflammatory cell accumulation by resident macrophages in mice, J. Inflamm. Res. 14 (Apr. 2021) 1375–1385, https://doi.org/10.2147/JIR.S301292.
[174] A. Gaudin, M. Tolar, O.A. Peters, Lipoxin A4 attenuates the inflammatory response in stem cells of the apical papilla via ALX/FPR2, Sci. Rep. 8 (1) (Dec. 2018), https://doi.org/10.1038/S41598-018-27194-7.
[175] E.P. Brennan, et al., Lipoxins regulate the early growth response-1 network and reverse diabetic kidney disease, J. Am. Soc. Nephrol. 29 (5) (May 2018) 1437–1448, https://doi.org/10.1681/ASN.2017101112.
[176] N. Zhang, et al., Calycosin attenuates renal ischemia/reperfusion injury by suppressing NF-κB mediated inflammation via PPARγ/EGR1 pathway, Front. Pharmacol. 13 (Oct. 2022) 970616, https://doi.org/10.3389/FPHAR.2022.970616/BIBTEX.
[177] L.C. Ho, et al., Egr-1 deficiency protects from renal inflammation and fibrosis, J. Mol. Med. (Berl.) 94 (8) (Aug. 2016) 933–942, https://doi.org/10.1007/S00109-016-1403-6.
[178] N. Chiang, et al., Infection regulates pro-resolving mediators that lower antibiotic requirements, Nature 484 (7395) (Apr. 2012) 524–528, https://doi.org/10.1038/NATURE11042.
[179] P. Kalinski, Regulation of immune responses by prostaglandin E2, J. Immunol. 188 (1) (Jan. 2012) 21, https://doi.org/10.4049/JIMMUNOL.1101029.
[180] M.H. Gangadhariah, et al., Hypertension is a major contributor to 20-hydroxyeicosatetraenoic acid-mediated kidney injury in diabetic nephropathy, J. Am. Soc. Nephrol. 26 (3) (Mar. 2015) 597–610, https://doi.org/10.1681/ASN.2013090980.
[181] T. Saraiva-Santos, et al., Therapeutic activity of lipoxin A4 in TiO2-induced arthritis in mice: NF-κB and Nrf2 in synovial fluid leukocytes and neuronal TRPV1 mechanisms, Front. Immunol. 14 (Jun. 2023) 949407, https://doi.org/10.3389/FIMMU.2023.949407/XML.
[182] J. Perez-Hernandez, V. Chiurchiù, S. Perruche, S. You, Regulation of T-cell immune responses by pro-resolving lipid mediators, Front. Immunol. 12 (Nov. 2021) 768133, https://doi.org/10.3389/FIMMU.2021.768133.
[183] A. Mázló, V. Jenei, S. Burai, T. Molnár, A. Bácsi, G. Koncz, Types of necroinflammation, the effect of cell death modalities on sterile inflammation, Cell Death Dis. 13 (5) (May 2022) 1–12, https://doi.org/10.1038/s41419-022-04883-w.
[184] L. Michalik, W. Wahli, Peroxisome proliferator-activated receptors: three isotypes for a multitude of functions, Curr. Opin. Biotechnol. 10 (6) (Dec. 1999) 564–570, https://doi.org/10.1016/S0958-1669(99)00030-0.
[185] A. Christofides, E. Konstantinidou, C. Jani, V.A. Boussiotis, The role of peroxisome proliferator-activated receptors (PPAR) in immune responses,

Metabolism 114 (Jan. 2021), https://doi.org/10.1016/J.METABOL.2020.154338.
[186] Y.Y. Qiu, J. Zhang, F.Y. Zeng, Y.Z. Zhu, Roles of the peroxisome proliferator-activated receptors (PPARs) in the pathogenesis of nonalcoholic fatty liver disease (NAFLD), Pharmacol. Res. 192 (Jun. 2023), https://doi.org/10.1016/J.PHRS.2023.106786.
[187] N. Wagner, K.-D. Wagner, Recent insights into the role of PPARs in disease, Cells 12 (12) (Jun. 2023) 1572, https://doi.org/10.3390/CELLS12121572.
[188] P.A. Sarafidis, P.C. Stafylas, P.I. Georgianos, A.N. Saratzis, A.N. Lasaridis, Effect of thiazolidinediones on albuminuria and proteinuria in diabetes: a meta-analysis, Am. J. Kidney Dis. 55 (5) (May 2010) 835–847, https://doi.org/10.1053/J.AJKD.2009.11.013.
[189] D.S. Straus, et al., 15-Deoxy-Δ12,14-prostaglandin J2 inhibits multiple steps in the NF-κB signaling pathway, Proc. Natl. Acad. Sci. USA 97 (9) (Apr. 2000) 4844–4849, https://doi.org/10.1073/PNAS.97.9.4844.
[190] A.F. Soares, et al., Covalent binding of 15-deoxy-delta12,14-prostaglandin J 2 to PPARγ, Biochem. Biophys. Res. Commun. 337 (2) (Nov. 2005) 521–525, https://doi.org/10.1016/j.bbrc.2005.09.085.
[191] V. Vangaveti, B.T. Baune, R.L. Kennedy, Hydroxyoctadecadienoic acids: novel regulators of macrophage differentiation and atherogenesis, Ther. Adv. Endocrinol. Metab. 1 (2) (Apr. 2010) 51, https://doi.org/10.1177/2042018810375656.
[192] G. Li, et al., NLRP3 inflammasome as a novel target for docosahexaenoic acid metabolites to abrogate glomerular injury, J. Lipid Res. 58 (6) (Jun. 2017) 1080, https://doi.org/10.1194/JLR.M072587.
[193] N. Thangavel, M. Al Bratty, S. Akhtar Javed, W. Ahsan, H.A. Alhazmi, Targeting peroxisome proliferator-activated receptors using thiazolidinediones: strategy for design of novel antidiabetic drugs, Int. J. Med. Chem. 2017 (Jun. 2017) 1069718, https://doi.org/10.1155/2017/1069718.
[194] M.L. Riess, R. Elorbany, D. Weihrauch, D.F. Stowe, A.K.S. Camara, PPARγ-independent side effects of thiazolidinediones on mitochondrial redox state in rat isolated hearts, Cells 9 (1) (Jan. 2020) 252, https://doi.org/10.3390/CELLS9010252.
[195] C. Martínez-García, et al., Accelerated renal disease is associated with the development of metabolic syndrome in a glucolipotoxic mouse model, MM Dis. Models Mech. 5 (5) (Sep. 2012) 636–648, https://doi.org/10.1242/DMM.009266.
[196] M. Zhao, et al., Renal tubular epithelium-targeted peroxisome proliferatoractivated receptor-γ maintains the epithelial phenotype and antagonizes renal fibrogenesis, Oncotarget 7 (40) (Oct. 2016) 64690–64701, https://doi.org/10.18632/ONCOTARGET.11811.
[197] C. Martínez-García, et al., Renal lipotoxicity-associated inflammation and insulin resistance affects actin cytoskeleton organization in podocytes, PLoS One 10 (11) (Nov. 2015), https://doi.org/10.1371/JOURNAL.PONE.0142291.
[198] D. Wang, et al., PPARγ mediates the anti-epithelial-mesenchymal transition effects of FGF1ΔHBS in chronic kidney diseases via inhibition of TGF-β1/SMAD3 signaling, Front. Pharmacol. 12 (Jun. 2021) 690535, https://doi.org/10.3389/FPHAR.2021.690535/BIBTEX.
[199] L. Wei, et al., Rosiglitazone inhibits angiotensin II-induced proliferation of glomerular mesangial cells via the Gαq/Plcβ4/TRPC signaling pathway, Cell. Physiol. Biochem. 44 (6) (Jan. 2017) 2228–2242, https://doi.org/10.1159/000486056.
[200] F. Pistrosch, J. Passauer, K. Herbrig, U. Schwanebeck, P. Gross, S.R. Bornstein, Effect of thiazolidinedione treatment on proteinuria and renal hemodynamic in type 2 diabetic patients with overt nephropathy, Horm. Metab. Res. 44 (12) (Jun. 2012) 914–918, https://doi.org/10.1055/S-0032-1314836.
[201] B. Toffoli, et al., Nephropathy in Pparg-null mice highlights PPARγ systemic activities in metabolism and in the immune system, PLoS One 12 (2) (Feb. 2017) e0171474, https://doi.org/10.1371/JOURNAL.PONE.0171474.
[202] S.H. Attia, S.F. Saadawy, S.M. El-Mahroky, M.M. Nageeb, Alleviation of pulmonary fibrosis by the dual PPAR agonist saroglitazar and breast milk mesenchymal stem cells via modulating TGFß/SMAD pathway, Naunyn Schmiedeberg's Arch. Pharmacol. 397 (8) (Aug. 2024) 5953–5974, https://doi.org/10.1007/S00210-024-03004-Y.
[203] E. Maquigussa, et al., Klotho and PPAR gamma activation mediate the renoprotective effect of losartan in the 5/6 nephrectomy model, Front. Physiol. 9 (Aug. 2018) 1033, https://doi.org/10.3389/fphys.2018.01033.
[204] P. Jia, X. Wu, T. Pan, S. Xu, J. Hu, X. Ding, Uncoupling protein 1 inhibits mitochondrial reactive oxygen species generation and alleviates acute kidney injury, EBioMedicine 49 (Nov. 2019) 331–340, https://doi.org/10.1016/J.EBIOM.2019.10.023.
[205] S. Granata, et al., Oxidative stress and ischemia/reperfusion injury in kidney transplantation: focus on ferroptosis, mitophagy and new antioxidants, Antioxidants (Basel) 11 (4) (Apr. 2022), https://doi.org/10.3390/ANTIOX11040769.
[206] W.B. El Gazzar, M.M. Allam, S.A. Shaltout, L.A. Mohammed, A.M. Sadek, H. E. Nasr, Pioglitazone modulates immune activation and ameliorates inflammation induced by injured renal tubular epithelial cells via PPARγ/miRNA-124/STAT3 signaling, Biomed. Rep. 18 (1) (Jan. 2022), https://doi.org/10.3892/BR.2022.1584.
[207] A.P. Singh, N. Singh, P.M.S. Bedi, Pioglitazone ameliorates renal ischemia reperfusion injury through NMDA receptor antagonism in rats, Mol. Cell. Biochem. 417 (1–2) (Jun. 2016) 111–118, https://doi.org/10.1007/S11010-016-2718-X.
[208] X. Xi, C. Zou, Z. Ye, Y. Huang, T. Chen, H. Hu, Pioglitazone protects tubular cells against hypoxia/reoxygenation injury through enhancing autophagy via AMPK-mTOR signaling pathway, Eur. J. Pharmacol. 863 (Nov. 2019), https://doi.org/10.1016/J.EJPHAR.2019.172695.
[209] M.P. Revelo, C.C. Federspiel, H. Helderman, A.B. Fogo, Chronic allograft nephropathy: expression and localization of PAI-1 and PPAR-gamma, Nephrol. Dial. Transplant. 20 (12) (Dec. 2005) 2812–2819, https://doi.org/10.1093/NDT/GFI172.
[210] L.J. Ma, C. Marcantoni, M.F. Linton, S. Fazio, A.B. Fogo, Peroxisome proliferator-activated receptor-gamma agonist troglitazone protects against nondiabetic glomerulosclerosis in rats, Kidney Int. 59 (5) (May 2001) 1899–1910, https://doi.org/10.1046/J.1523-1755.2001.0590051899.X.
[211] W. Wang, F. Liu, N. Chen, Peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists attenuate the profibrotic response induced by TGF-β1 in renal interstitial fibroblasts, Mediat. Inflamm. 2007 (Dec. 2007), https://doi.org/10.1155/2007/62641.
[212] A.P. Bech, J.M. Hofstra, P.E. Brenchley, J.F.M. Wetzels, Association of anti-PLA₂R antibodies with outcomes after immunosuppressive therapy in idiopathic membranous nephropathy, Clin. J. Am. Soc. Nephrol. 9 (8) (Aug. 2014) 1386–1392, https://doi.org/10.2215/CJN.10471013.
[213] L.H. Beck, et al., Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy, J. Am. Soc. Nephrol. 22 (8) (Aug. 2011) 1543–1550, https://doi.org/10.1681/ASN.2010111125.
[214] M. de Martino, A. Chiarugi, A. Boner, G. Montini, G.L. de Angelis, Working towards an appropriate use of ibuprofen in children: an evidence-based appraisal, Drugs 77 (12) (Aug. 2017) 1295–1311, https://doi.org/10.1007/S40265-017-0751-Z.
[215] Y.J. Wu, M. Xue, H. Chen, Licofelone inhibits interleukin-18-induced pro-inflammatory cytokine release and cellular proliferation in human mesangial cells, Basic Clin. Pharmacol. Toxicol. 111 (3) (Sep. 2012) 166–172, https://doi.org/10.1111/J.1742-7843.2012.00882.X.
[216] F. Steinhäuslin, A. Munafo, T. Buclin, A. Macciocchi, J. Biollaz, Renal effects of nimesulide in furosemide-treated subjects, Drugs 46 Suppl 1 (1) (1993) 257–262, https://doi.org/10.2165/00003495-199300461-00066.
[217] D.T. Mangano, Aspirin and mortality from coronary bypass surgery, N. Engl. J. Med. 347 (17) (Oct. 2002) 1309–1317, https://doi.org/10.1056/NEJMOA020798.
[218] P. Forget, et al., Neutrophil: lymphocyte ratio and intraoperative use of ketorolac or diclofenac are prognostic factors in different cohorts of patients undergoing breast, lung, and kidney cancer surgery, Ann. Surg. Oncol. 20 (3) (Dec. 2013), https://doi.org/10.1245/S10434-013-3136-X. SUPPL.
[219] A. Ulu, et al., Anti-inflammatory effects of ω-3 polyunsaturated fatty acids and soluble epoxide hydrolase inhibitors in angiotensin-II-dependent hypertension, J. Cardiovasc. Pharmacol. 62 (3) (Sep. 2013) 285–297, https://doi.org/10.1097/FJC.0B013E318298E460.
[220] T. Moriyama, et al., Effects of combination therapy with renin-angiotensin system inhibitors and eicosapentaenoic acid on IgA nephropathy, Intern. Med. 52 (2) (Jan. 2013) 193–199, https://doi.org/10.2169/INTERNALMEDICINE.52.8323.
[221] S. Kusmartsev, Enhanced 15-lipoxygenase activity and elevated eicosanoid production in kidney tumor microenvironment contribute to the inflammation and immune suppression, Oncoimmunology 1 (2) (Mar. 2012) 249–251, https://doi.org/10.4161/ONCI.1.2.18502.
[222] L. Hamieh, R.B. Moreira, X. Lin, R. Simantov, T.K. Choueiri, R.R. McKay, Impact of aspirin and non-aspirin nonsteroidal anti-inflammatory drugs on outcomes in patients with metastatic renal cell carcinoma, Kidney Cancer 2 (1) (Mar. 2018) 37–46, https://doi.org/10.3233/KCA-180027.
[223] M. Tatokoro, et al., Phase-II trial of combination treatment of interferon-α, cimetidine, cyclooxygenase-2 inhibitor and renin-angiotensin-system inhibitor (I-CCA therapy) for advanced renal cell carcinoma, Cancer Sci. 102 (1) (Jan. 2011) 137–143, https://doi.org/10.1111/J.1349-7006.2010.01756.X.
[224] A. Selka, et al., Discovery of a novel 2,5-dihydroxycinnamic acid-based 5-lipoxygenase inhibitor that induces apoptosis and may impair autophagic flux in RCC4 renal cancer cells, Eur. J. Med. Chem. 179 (Oct. 2019) 347–357, https://doi.org/10.1016/J.EJMECH.2019.06.060.
[225] H. Cho, et al., Novel caffeic acid derivatives: extremely potent inhibitors of 12-lipoxygenase, J. Med. Chem. 34 (4) (Apr. 1991) 1503–1505, https://doi.org/10.1021/JM00108A039.
[226] F.G. Yang, et al., Peroxisome proliferator-activated receptor gamma ligands induce cell cycle arrest and apoptosis in human renal carcinoma cell lines, Acta Pharmacol. Sin. 26 (6) (Jun. 2005) 753–761, https://doi.org/10.1111/J.1745-7254.2005.00753.X.
[227] R. Yoshimura, et al., Expression of 12-lipoxygenase in human renal cell carcinoma and growth prevention by its inhibitor, Int. J. Mol. Med. 13 (1) (Jan. 2004) 41–46, https://doi.org/10.3892/IJMM.13.1.41/HTML.
[228] M.J. Tsai, et al., Cysteinyl leukotriene receptor antagonists decrease cancer risk in asthma patients, Sci. Rep. 6 (Apr. 2016), https://doi.org/10.1038/SREP23979.
[229] C. Wolf, S. Smith, S.J.L. van Wijk, Zafirlukast induces VHL- and HIF-2α-dependent oxidative cell death in 786-O clear cell renal carcinoma cells, Int. J. Mol. Sci. 23 (7) (Apr. 2022), https://doi.org/10.3390/IJMS23073567.
[230] F. Pourcine, et al., Prognostic value of PLA2R autoimmunity detected by measurement of anti-PLA2R antibodies combined with detection of PLA2R antigen in membranous nephropathy: a single-centre study over 14 years, PLoS One 12 (3) (Mar. 2017), https://doi.org/10.1371/JOURNAL.PONE.0173201.
[231] F.H. Mose, H. Birn, N. Hoffmann-Petersen, J.N. Bech, Prednisolone treatment in acute interstitial nephritis (PRAISE) - protocol for the randomized controlled trial, BMC Nephrol. 22 (1) (Dec. 2021), https://doi.org/10.1186/S12882-021-02372-4.

[232] A.A. Eddy, Drug-induced tubulointerstitial nephritis: hypersensitivity and necroinflammatory pathways, Pediatr. Nephrol. 35 (4) (Apr. 2020) 547–554, https://doi.org/10.1007/S00467-019-04207-9.
[233] Y. Sun, et al., Analysis of glomerular PLA2R efficacy in evaluating the prognosis of idiopathic membranous nephropathy in the background of different serum anti-PLA2R levels, Ren. Fail. 44 (1) (Dec. 2022) 731–740, https://doi.org/10.1080/0886022X.2022.2068442.
[234] F.J. Abelha, M. Botelho, V. Fernandes, H. Barros, Determinants of postoperative acute kidney injury, Crit. Care 13 (3) (May 2009), https://doi.org/10.1186/CC7894.
[235] Y. Huang, H. Xu, F. Xiang, W. Feng, Y. Ma, L. Jin, Aspirin increases the risk of acute kidney injury in critical patients with chest trauma: a retrospective cohort study, Int. J. Emerg. Med. 18 (1) (Dec. 2025) 1–10, https://doi.org/10.1186/S12245-025-00835-1/FIGURES/5.
[236] P. Ungprasert, W. Cheungpasitporn, C.S. Crowson, E.L. Matteson, Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: a systematic review and meta-analysis of observational studies, Eur. J. Intern. Med. 26 (4) (May 2015) 285–291, https://doi.org/10.1016/J.EJIM.2015.03.008.
[237] A.N. Colebatch, J.L. Marks, D.M. Van Der Heijde, C.J. Edwards, Safety of nonsteroidal antiinflammatory drugs and/or paracetamol in people receiving methotrexate for inflammatory arthritis: a Cochrane systematic review, J. Rheumatol. Suppl (Suppl. 90) (Sep. 2012) 62–73, https://doi.org/10.3899/JRHEUM.120345.
[238] F.A. Nawaz, C.P. Larsen, M.L. Troxell, Membranous nephropathy and nonsteroidal anti-inflammatory agents, Am. J. Kidney Dis. 62 (5) (Nov. 2013) 1012–1017, https://doi.org/10.1053/J.AJKD.2013.03.045.
[239] A. Koudelka, et al., Lipoxin A4 yields an electrophilic 15-oxo metabolite that mediates FPR2 receptor-independent anti-inflammatory signaling, bioRxiv (Feb. 2024), https://doi.org/10.1101/2024.02.06.579101, p. 2024.02.06.579101.
[240] B.D. Levy, C.B. Clish, B. Schmidt, K. Gronert, C.N. Serhan, Lipid mediator class switching during acute inflammation: signals in resolution, Nat. Immunol. 2 (7) (Jul. 2001) 612–619, https://doi.org/10.1038/89759.
[241] S. Han, et al., Omega-3 fatty acids attenuate renal fibrosis via AMPK-mediated autophagy flux activation, Biomedicines 11 (9) (Sep. 2023), https://doi.org/10.3390/BIOMEDICINES11092553.
[242] C. Zhang, G.W. Booz, Q. Yu, X. He, S. Wang, F. Fan, Conflicting roles of 20-HETE in hypertension and renal end organ damage, Eur. J. Pharmacol. 833 (Aug. 2018) 190–200, https://doi.org/10.1016/j.ejphar.2018.06.010.
[243] M. Okumura, et al., Role for thromboxane A2 from glomerular thrombi in nephropathy with type 2 diabetic rats, Life Sci. 72 (24) (May 2003) 2695–2705, https://doi.org/10.1016/S0024-3205(03)00180-2.
[244] T.T. van Duijl, D. Soonawala, J.W. de Fijter, L.R. Ruhaak, C.M. Cobbaert, Rational selection of a biomarker panel targeting unmet clinical needs in kidney injury, Clin. Proteomics 18 (1) (Feb. 2021) 1–14, https://doi.org/10.1186/S12014-021-09315-Z.
[245] C.N. Serhan, N. Chiang, J. Dalli, New pro-resolving n-3 mediators bridge resolution of infectious inflammation to tissue regeneration, Mol. Asp. Med. 64 (Dec. 2018) 1–17, https://doi.org/10.1016/j.mam.2017.08.002.
[246] X. Huang, Y. Ma, Y. Li, F. Han, W. Lin, Targeted drug delivery systems for kidney diseases, Front. Bioeng. Biotechnol. 9 (May 2021) 683247, https://doi.org/10.3389/FBIOE.2021.683247/XML/NLM.
[247] E. Brennan, P. Kantharidis, M.E. Cooper, C. Godson, Pro-resolving lipid mediators: regulators of inflammation, metabolism and kidney function, Nat. Rev. Nephrol. 17 (11) (Jul. 2021) 725–739, https://doi.org/10.1038/s41581-021-00454-y.
[248] J.V. Donadio, J.P. Grande, The role of fish oil/omega-3 fatty acids in the treatment of IgA nephropathy, Semin. Nephrol. 24 (3) (May 2004) 225–243, https://doi.org/10.1016/J.SEMNEPHROL.2004.01.004.
[249] J. Donadio, T.S. Larson, E.J. Bergstralh, J.P. Grande, A randomized trial of high-dose compared with low-dose omega-3 fatty acids in severe IgA nephropathy, J. Am. Soc. Nephrol. 12 (4) (Apr. 2001) 791–799, https://doi.org/10.1681/ASN.V124791.
[250] E. Han, et al., Effects of omega-3 fatty acid supplementation on diabetic nephropathy progression in patients with diabetes and hypertriglyceridemia, PLoS One 11 (5) (May 2016) e0154683, https://doi.org/10.1371/JOURNAL.PONE.0154683.
[251] N. Guillot, E. Caillet, M. Laville, C. Calzada, M. Lagarde, E. Véricel, Increasing intakes of the long-chain ω-3 docosahexaenoic acid: effects on platelet functions and redox status in healthy men, FASEB J. 23 (9) (Sep. 2009) 2909–2916, https://doi.org/10.1096/FJ.09-133421.
[252] J. Dyerberg, P. Madsen, J.M. Møller, I. Aardestrup, E.B. Schmidt, Bioavailability of marine n-3 fatty acid formulations, Prostaglandins Leukot. Essent. Fat. Acids 83 (3) (Sep. 2010) 137–141, https://doi.org/10.1016/j.plefa.2010.06.007.
[253] M. Szklarek-Kubicka, J. Fijałkowska-Morawska, D. Zaremba-Drobnik, A. Uciński, S. Czekalski, M. Nowicki, Effect of intradialytic intravenous administration of ω-3 fatty acids on nutritional status and inflammatory response in hemodialysis patients: a pilot study, J. Ren. Nutr. 19 (6) (Nov. 2009) 487–493, https://doi.org/10.1053/J.JRN.2009.05.007.
[254] H. Yu, D. Liu, G. Shu, F. Jin, Y. Du, Recent advances in nanotherapeutics for the treatment and prevention of acute kidney injury, Asian J. Pharm. Sci. 16 (4) (Jul. 2020) 432, https://doi.org/10.1016/J.AJPS.2020.11.001.
[255] V.M. Saglimbene, et al., Effects of omega-3 polyunsaturated fatty acid intake in patients with chronic kidney disease: systematic review and meta-analysis of randomized controlled trials, Clin. Nutr. 39 (2) (Feb. 2020) 358–368, https://doi.org/10.1016/J.CLNU.2019.02.041.