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RESOLUTION PHARMACOLOGY IN CHRONIC KIDNEY DISEASE: ROLE OF LIPID MEDIATORS IN TISSUE REPAIR

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ABSTRACT

About 10-15% of people worldwide are affected by chronic kidney disease (CKD), a progressive disorder that causes chronic inflammation, oxidative stress, tubular injury, and fibrosis. RAAS inhibitors and $sglt_2$ inhibitor drugs slow down disease progression but don't actively promote tissue regeneration. Why? In contrast, resolution pharmacology presents another therapeutic option where endogenous mechanisms that resolve inflammation and restore tissue homeostasis are enhanced to improve healing. Lipoxins, resolving and lipid mediators (masins) are examples of bioactive fatty acid molecules that act as "pro-resolution mediator"(spm), suppressing inflammation, increasing efferocytosis, decreasing fibrositis, and encouraging renal repair. Preclinical studies reveal that spms decrease renal inflammation, prevent kidney damage, and minimize fibrotic development in many models of CKD. The review summarizes the biosynthesis, receptor pharmacology, and nephroprotective mechanisms of spms, as well as the current translational obstacles and future opportunities.[1,4,20,27]

KEYWORDS: Chronic kidney disease, Resolution pharmacology, Lipid mediators, Specialized pro- resolving mediators, Resolvins, Lipoxins, Protectins, Maresins, Renal inflammation, Tissue repair, Renal regeneration.

INTRODUCTION

A significant global health issue, chronic kidney disease (CKD), affects around 10–15% of the population and is a major factor in end-stage renal disease (ESRD), cardiovascular complications, and premature death. Diabetes, hypertension, obesity, and age have all played a role in contributing to the increasing burden of CKD. Why? Although current treatments, such as RAAS and sglt2 inhibitors, do not completely reverse disease progression or correct established fibrosis, they do provide partial protection against damage to renal tissue's pathogenesis is marked by prolonged inflammation, immune dysfunction, podocyte injury, tubular cell damage and progressive fibrosis. [α 2: Primary lymphoma anal]/Antagonist response [ATP]. Inflammation resolution has been identified as an active biological process, regulated by specific molecular pathways in immunology. Chronic inflammation and maladaptive tissue remodelling in CKD are caused by the failure of endogenous resolution mechanisms, making it an essential therapeutic target. However, conventional anti-inflammatory treatments have not been effective. A new therapeutic approach, resolution pharmacology, has been developed to encourage the active inhibition of inflammation and tissue regeneration. This concept revolves around the use of specialized pro-resolving mediators (spms), including lipoxins, resolutants and protectins from omega-3 and omega-6 polyunsaturated fatty acids. These lipid mediators regulate immune responses by inhibiting neutrophil infiltration, improving macrophage-mediated clearance of cellular debris, Promoting reparative macrophaphae phenotypes, and suppressing pro-inflammatory and profibrotic signaling pathways. In models of obstructive nephropathy, diabetic glomeruli or kidneys that were subjected to preclinical studies, spms have been shown in reduce renal inflammation and attenuate renal fibrination, preserve structural integrity of the organ, and improve renal function.[1–14] Despite these promising findings, clinical translation is still hindered by limitations such as limited stability, bioavailability, and the lack of validated clinical biomarkers. The biosynthesis, receptor pharmacology, and Reno protective mechanisms of spms in CKD are briefly discussed in this review. The article evaluates the current preclinical evidence, discusses translational obstacles, and identifies potential therapeutic options for incorporating resolution pharmacology into CKD management.

CHRONIC KIDNEY DISEASE: OVERVIEW AND GLOBAL BURDEN

CKD CLASSIFICATION CHART

Prognosis of CKD by GFR and Albuminuria Categories (KDIGO 2024)

GFR Category (G1–G5)	GFR (mL/min/1.73 m²) Description	Albuminuria Category (uACR) A1 < 30 mg/g (Normal to mildly increased)	A2 30 – 300 mg/g (Moderately increased)	A3 > 300 mg/g (Severely increased)
G1	≥ 90 Normal or high	LOW RISK	MODERATELY INCREASED RISK	HIGH RISK
G2	60 – 89 Mildly decreased	LOW RISK	MODERATELY INCREASED RISK	HIGH RISK
G3a	45 – 59 Mildly to moderately decreased	MODERATELY INCREASED RISK	HIGH RISK	VERY HIGH RISK
G3b	30 – 44 Moderately to severely decreased	HIGH RISK	VERY HIGH RISK	VERY HIGH RISK
G4	15 – 29 Severely decreased	VERY HIGH RISK	VERY HIGH RISK	VERY HIGH RISK
G5	< 15 Kidney failure	VERY HIGH RISK	VERY HIGH RISK	VERY HIGH RISK

ABBREVIATIONS
GFR: Glomerular Filtration Rate
uACR: Urine Albumin-to-Creatinine Ratio

RISK CATEGORIES
- **LOW RISK** — If no other markers of kidney disease, no CKD
- **MODERATELY INCREASED RISK** — Monitor CKD progression
- **HIGH RISK** — Monitor closely and manage complications
- **VERY HIGH RISK** — High risk of CKD progression, cardiovascular events and mortality

Note: Prognosis is based on persistent abnormalities ≥ 3 months. Source: KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.

Fig. No. 1: Chronic Kidney Disease Classification.

Chronic kidney disease (CKD) is characterized by the Improving Global Outcomes report, which defines any abnormalities of kidney structure or function that persist for at least three months and have implications for health. This duration sets apart CKD from acute kidney injury (AKI).. The diagnosis is based on a persistent eGFR below 60 mL/min/1.73 mm and/or markers of kidney damage, such as albuminuria, abnormalities in urine sediments, electrolyte disturbances from tubular dysfunction, structural abnormality or histopathological changes on kidney biopsy. The KDIGO CGA is used to classify CKD according to Cause, with the GFR and Albuminuria categories. G1 (moisture of less than 90 mL/min/1.73 mm2) to G5 (mean: 0.78 g per volume equivalent, or GFR) range.[30,33]

INFLAMMATION AND FIBROSIS IN CHRONIC KIDNEY DISEASE

- **Mechanisms of promoting innate immunity and enhancing inflammatory response:** The onset of renal inflammation is a significant factor in the progression of CKD, and it is often caused by immune-mediated injury, nephrotoxins, or other insults. The release of damage-associated molecular patterns (DAMPs) is triggered by injury to other renal cells, such as tubular epithelial cells. They trigger the activation of pattern-recognition receptors, including Toll-like receptor 4 (TLR4) and the NLRP3 inflammasome, which in turn activate NF-B and MAPK signaling pathways. Following this, the kidney is energized by the release of pro-inflammatory cytokines and chemokines like TNF-, IL-1/3, il-6, and MCP-1, which facilitate the recruitment of macrophages, neutrophils und lymphocytes.'". While inflammation is initially a protective measure, chronic injury and inadequate response cause tissue damage, podocyte loss (remove of protons) and progressive renal function (detection of pod cells to the brain).[5,6,18,32]
- **Causes of oxidative stress, mitochondrial dysfunction and immune dysregulation:** CKD development is significantly associated with oxidative stress.? The production of reactive oxygen species (ROS) by NADPH oxidases, dysfunctional mitochondria, and uncoupled endothelial nitric oxide synthase is observed. The destruction of lipids, proteins, and DNA by these ROS leads to tuberculotomy, cell death, as well as the activation of immune responses. The Nrf2/HO-1 pathway is suppressed in CKD, leading to ongoing oxidative damage by inhibiting the antioxidant defence system. The progression of the disease is aggravated by immune dysregulation. Pro-inflammatory M1 phenotype is more prevalent in macrophages, while reparative and M2 macrophages are less common. Additionally, prolonged survival of neutrophils and increased Th1/Th17 immune responses maintain inflammation and promote renal fibrosis, which hinders the proper repair of tissues.[5,7,32,33]

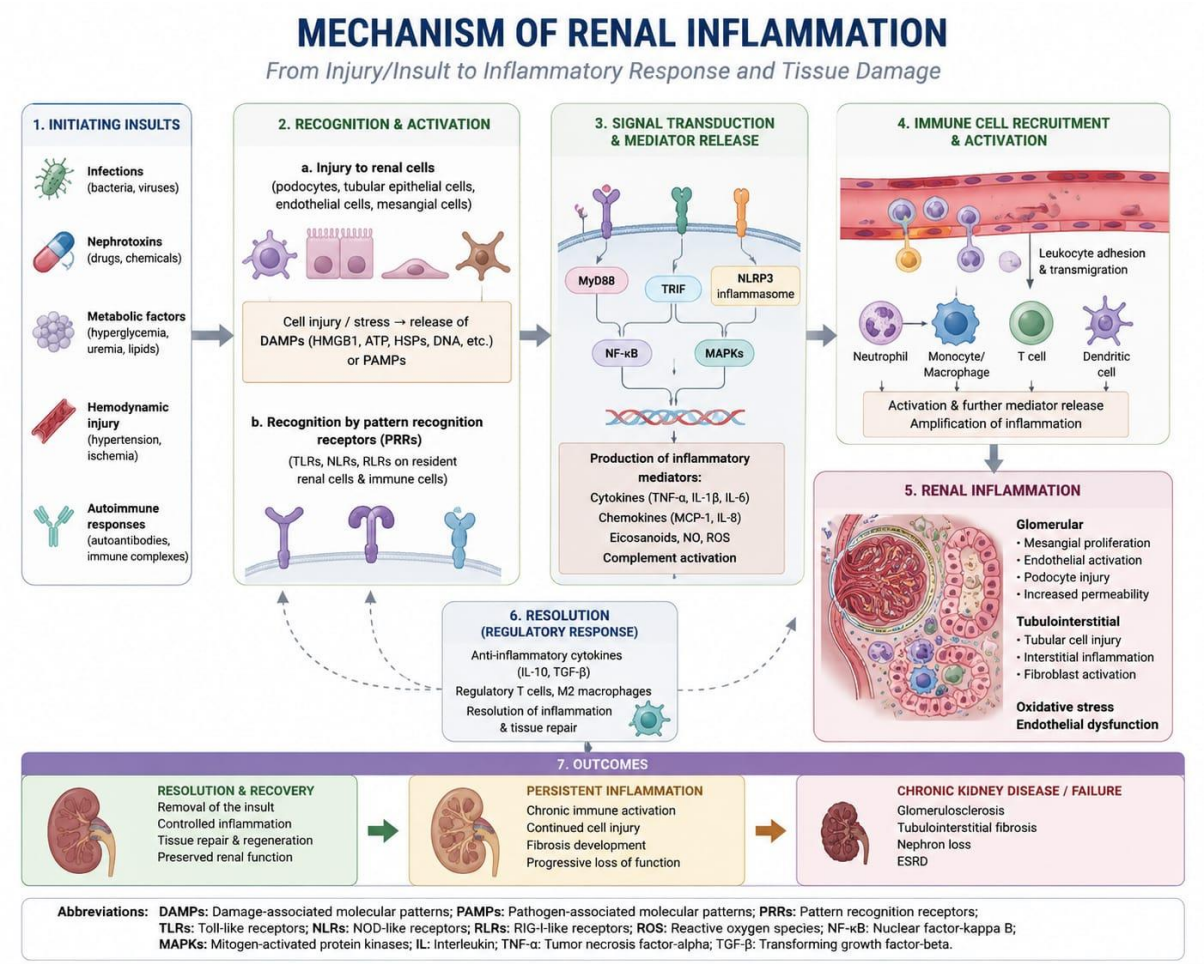

Fig. No. 2: Mechanism of Renal Inflammation.

- **Extracellular matrix accumulation, Renal Fibrosis & irreversible GFR decline the signs of aging:** The most reliable predictor of kidney failure is renal fibrosis, which is the final common pathway in CKD. Fibroblasts are stimulated to differentiate into myofibroblast, which produces excessive ECM proteins, through chronic inflammation. Why? The Smad2/3 signaling pathway is responsible for the upregulation of collagen, fibronectin, and other matrix components, making TGF-1 the primary profibrotic mediator. This process involves growth factors. The accumulation of ECM disrupts the normal nephron architecture, leading to tubular atrophy, glomerulosclerosis, and the loss of peritubular capillaries. What are these conditions? Tissue injury and fibrotic signaling are enhanced by chronic hypoxia, which is caused by a lack of blood supply. Eventually, the replacement of functional nephrons by scar tissue will lead to irreversible decline in the glomerular blood flow rate (GFR), which ultimately causes end-stage kidney disease (ESKD). The strong association between fibrosis and chronic inflammation highlights the potential for pro-resolving lipid mediators to be effective as therapeutic agents. By resolving inflammation, improving macrophage-mediated clearance of cellular debris, and inhibiting profibrotic signaling pathways, these mediators may aid in slowing down CKD progression and tissue repair.[5,6,17]

CONCEPT OF RESOLUTION PHARMACOLOGY

It has been acknowledged that inflammation resolution is not a passive modulation of signal integrity, but rather an active biological process. Lipoxins, resolvins and protectin also occur in the resolution phase; other PUFAs such as arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosacceridol (DHA) form specialising pro-resolution

mediator[M]1sPMs. These polyunsaturated fatty acids are called poly. Lipid mediator class switching is the term used to describe the redirection of inflammatory pathways towards tissue repair and restoration of homeostasis. SPMs play a crucial role in slowing down neutrophil recruitment, encouraging neutropenicty, elevating macrophage-mediated efferocytosis, and stimulating macrophages to switch from the pro-inflammatory M1 phenotype to the reparative M2. Furthermore, they facilitate tissue regeneration and remodelling to restore the normal state of an organ's structure and function.[1,2,3,4,11,28]

In chronic kidney disease, the resolution mechanisms responsible for SPM production and pro-inflammatory mediators are impaired, leading to a "resolution deficit." This causes persistent leukocyte infiltration, defective clearance of Apoptotic cells, sustained M1 macrophage activation, and progressive fibrogenesis. Thus, restoring resolution pathways has become a promising therapeutic option for CKD.[5,6,7,17]

- **Principles of Resolution Pharmacology**: Another emerging approach is resolution pharmacology, which promotes inflammation-resolution pathways by using the body's natural processes through the use of agents or specialized pro- Resolving mediator (SPM) drugs. This is not just about suppressing inflammation; it's about actively restoring tissue homeostasis.[1,2,4,28]
- **Difference from Conventional Anti-inflammatory Therapy**: Inflammation can be reduced by anti-inflammatory drugs like NSAIDs, corticosteroids and cytokine inhibitors which block pro-inflammatory mediators. ". Despite their effectiveness in managing symptoms, they can still delay SPM synthesis and prolong resolution defects. In contradistinction, resolution pharmacology stimulates endogenous mechanisms of resolution by receptor-mediated activation, which promotes the repair of tissue without significant immunosuppression.[4,29]

Receptor Pharmacology of SPMs

- **SPMs function by means of specific G-protein-coupled receptors (GPCRs):** ALX/FPR2 is a receptor that can handle Lipoxin A4 and specific Resolvin D-series mediators, inhibiting neutrophil migration and promoting efferocytosis.[M].Resolvin D-series compounds exhibit anti-inflammatory effects due to their GPR32 (DRV1) activity.ChemR23 (CMKLR1), a receptor for Resolvin E1, inhibits neutrophil recruitment and enhances macrophage clearance functions. Anti-inflammatory signalling is influenced by GPR18 (DRV2), which functions as a receptor for Resolvin D2.Among the activators of Mastin’s, LGR6 serves as a mediator for tissue protection and regeneration.[2,14,15,16,27]
- **Core Principles:** Among the key elements of resolution pharmacology are: Inflammation resolution is the time when SPMs are most effective. Their control of neutrophils, macrophages and epithelial cells, as well as fibroblasts is multi-target action. Without Immunosuppression, inflammation is terminated but host defence mechanisms remain intact. The anti-fibrotic impact of SPMs is to decrease the amount of myofibroblast activation, collagen deposition, and tissue fibrosis.
- **Therapeutic value in chronic diseases:** Chronic diseases such as CKD, atherosclerosis, COPD, Alzheimer's disease, rheumatoid arthritis, non-alcoholic steatohepatitis, and type 2 diabetes are increasingly believed to be linked to persistent unresolved inflammation. This is particularly notable. The presence of defective resolution mechanisms and excessive inflammation are common symptoms of these conditions.[20,21,29]
- **A common approach to address the deficit resolution:** Inadequate SPM production and signalling levels result in impaired efferocytosis, persistent macrophage activation, excessive tissue fibrositis, and progressive tissue

damage. Renal function and fibrosis are associated with decreased lipoxins and other resolvins, 15-lipoxygenase expression, and impaired macrophage function in CKD. These factors are linked to these disorders.[15,17,20]

- **Preclinical Evidence in CKD:** Several experimental models of CKD have been shown to reduce renal inflammation, decrease cytokine production, limit fibrosis, preserve podocyte integrity, and improve kidney function with Lipoxin A4, Resolvin D1, maresins, and protectin. These results imply that therapeutic interventions based on resolution have the potential to be effective.[17,20]
- **Paradigm Shift: From Suppression to Restoration:** Resolution pharmacology seeks to restore physiological repair mechanisms, unlike traditional anti-inflammatory therapies that suppress inflammatory signalling. It has the potential to work alongside RAAS inhibitors and SGLT2 inhibitors in treating chronic inflammation and tissue damage in CKD.
- **Future Directions:** While preliminary studies are promising, clinical translation remains problematic due to the limited delivery options, short half-life of natural SPMs, and absence of validated biomarkers. Currently, research is concentrated on creating analogues of SPM that are stable, exploring nanoparticle-based delivery methods and supplementing PUFA, as well as improving the process itself. CKD and other chronic inflammation diseases may benefit from resolution pharmacology as a new therapeutic approach.[14,20,28]

LIPID MEDIATORS IN INFLAMMATION RESOLUTION

Biosynthesis of Specialized Pro-Resolving Mediator

- **Polyunsaturated Fatty Acids: Overview and Precursor Carrier:** Inflammation is resolved by the production of specialized pro-resolving mediators (SPMs), which are endogenous lipid molecules. Unlike pro-inflammatory eicosanoids, SPMs are generated from membrane proteins via the enzyme phospholipase A2 and converted to monophosphates dimers. SPM precursors include three major polyunsaturated fatty acids: arachidonic acid (AA) that produces lipoxins; eicosapentaenoic acid (EPA) which creates E-series resolvins and docosahexaenoic acid (3HA), which produce D- series reagent, protectine, and Mursalin. Lipoxygenases (5-LOX, 12-LOx, and 15-LCX), cyclooxigenogenase-2 (COX-2), and related enzymes are involved in their coordinated biosynthesis. The major metabolic pathways.[1,2,14,27]
- **Lipid Mediator Class Switching:** Lipinoid mediator class switching regulates the transition from inflammation to resolution. Arachidonic acid is predominantly converted into prostaglandins and leukotriene (B12) during acute inflammation, which leads to increased vasodilation, vascular permeability, and recruitment of leukocytes. Lipoxins, resolvins and protectins/ massives are produced by various enzymes as inflammation progresses. The inflammatory environment is altered by the presence of pro-inflammatory mediators, leading to active restoration of homeostasis and tissue repair.[11,23,27]
- **Aspirin-Triggered SPM Pathways:** In particular, aspirin plays an important role in biosynthesis of SPM by aqueously binding to COX-2 and thus diverting its activity towards the production of precursors to SMP rather than toward prostaglandins. Afterward, these intermediates are converted into lipoxins and resolvins that act as triggers for the release of aspirin. The aspirin-triggered SPMs are more resistant to enzyme degradation and exhibit longer biological activity. The reduction of prostaglandin synthesis by low-dose aspirin is not the only mechanism that contributes to anti-inflammatory and tissue-protective effects.[2,27]
- **Transcellular Biosynthesis:** Transcellular biosynthesis, which involves interdependence between different cell types, is a common method for producing SPM. Lipopoxins are produced by platelets after neutrophils produce

intermediate metabolites. The synthesis of resolvins, protectinS, and maremins takes place in the same manner as endothelial cells, macrophages (see section below), and leukocytes. This coordinated mechanism produces SPMs precisely where inflammation is required for resolution.[1,2,27]

- **The role of SPM biosynthetic in chronic kidney disease:** Reduced lipoxygenase expression, oxidative stress, accumulation of uremic toxin and reduced omega-3 fatty acid availability are all associated with the impairment of SPM biosynthesis in CKD. The outcome is a marked decrease in lipoxins, resolvins and other SPMs in patients with CKD.[M].This deficit is responsible for persistent inflammation, macrophage dysfunction, and progressive fibrosis. Meanwhile, the eicosanoids' levels remain high due to their anti-inflammatory properties, creating an imbalance that favors chronic renal damage and disease progression.[15,17,20]

Classification of Specialized Pro-Resolving Mediators

- **Lipoxins:** Arachidonic acid is the source of lipoxins, which are the first known SPM family members. Lipoxin A4 (LXA4) and Lipoxygenase (LD) are the primary components that arise from interactions between these pathways in leukocytes and platelets. Lipoxins function mainly via the ALX/FPR2 receptor, inhibiting neutrophil recruitment, suppressing inflammatory cytokine production, improving macrophage efferocytosis, and decreasing oxidative stress. Experimental evidence indicates that lipoxins can be effective in reducing proteinuria, glomerular injury, and renal fibrosis as a potential therapy for CKD.[15,20]
- **Resolvin:** Resolvins can be categorized into two groups: E-series (derived from EPA) and D-Series, which is derived from DHA. Consequently, these mediators restrict neutrophil infiltration, inhibit inflammatory signalling, enhance macrophage-mediated apoptotic cell clearance, and facilitate tissue repair. The use of resolvins in models for kidney disease involves reducing albuminuria, maintaining renal function, inhibiting NLRP3 inflammasome activation, and attenuating fibrotic remodelling. They are also potent anti-inflammatory and pro-repair effects, making them ideal therapeutic candidates for CKD.[2,21,27]
- **Protectins:** DHA-based mediators known as protectins have potent anti-inflammatory and cytoprotective effects. The best-characterized member, Protectin D1 (PD1), has protective effects such as reducing leukocyte infiltration, inhibiting oxidative stress, and preventing renal cell apoptosis. The role of protectins in renal protection has been supported by experimental evidence, which suggests that they can reduce proteinuria and glomerular damage while maintaining kidney function.[3,27]
- **Maresins:** DHA-derived mediators known as maeses are predominantly produced by macrophages. Maresin 1 (MaR1) plays a role in resolving inflammation by increasing efferocytosis, encouraging tissue repair, and driving macrophage polarization towards the anti-inflammatory M2 phenotype. In CKD experimental models, maresins reduce inflammatory cytokine production, inhibit fibrosis, and promote tissue regeneration. These effects are demonstrated by animal studies of the mouse model. Their pro-resolution and regenerative actions make them an effective preventative measure against progressive renal damage.[16,24]

- **Integrated SPM Network for Renal Resolution**

The coordination of inflammation and tissue repair is facilitated by the four major SPM families, including lipoxins, resolvins (anti-inflammatory mediators), protectin's groups, and maresin(s) that function as an integrated network. The families do not function as isolated entities, but rather participate in different phases of the resolution process. Early resolution results in the formation of lipoxins, which limit the recruitment of neutrophils and facilitate the clearance of inflammatory cells by macrophages. The resolution of these processes is further enhanced by the addition of molecules

called "resolvins" which suppress inflammatory signaling, regulate immune responses and improve mitochondrial function. Protectins have cytoprotective effects, protecting renal cells (including podocytes) and reducing tissue damage. El biofilms. In the latter phases of resolution, Maresins participate by reprogramming macrophages, regeneration of tissue and inhibition or stimulation of fibrosis. Low omega-3 fatty acids and insufficient SPM biosynthesis are the hallmarks of CKD. The endogenous resolution program fails due to the impaired receptor signalling and PUFA availability. This insufficient amount leads to persistent inflammation, progressive fibrosis, nephron loss, and reduced kidney function. Thus, the reactivation of this network is one of the most promising therapeutic approaches for slowing down CKD progression and aiding renal regeneration.[1,2,3,27]

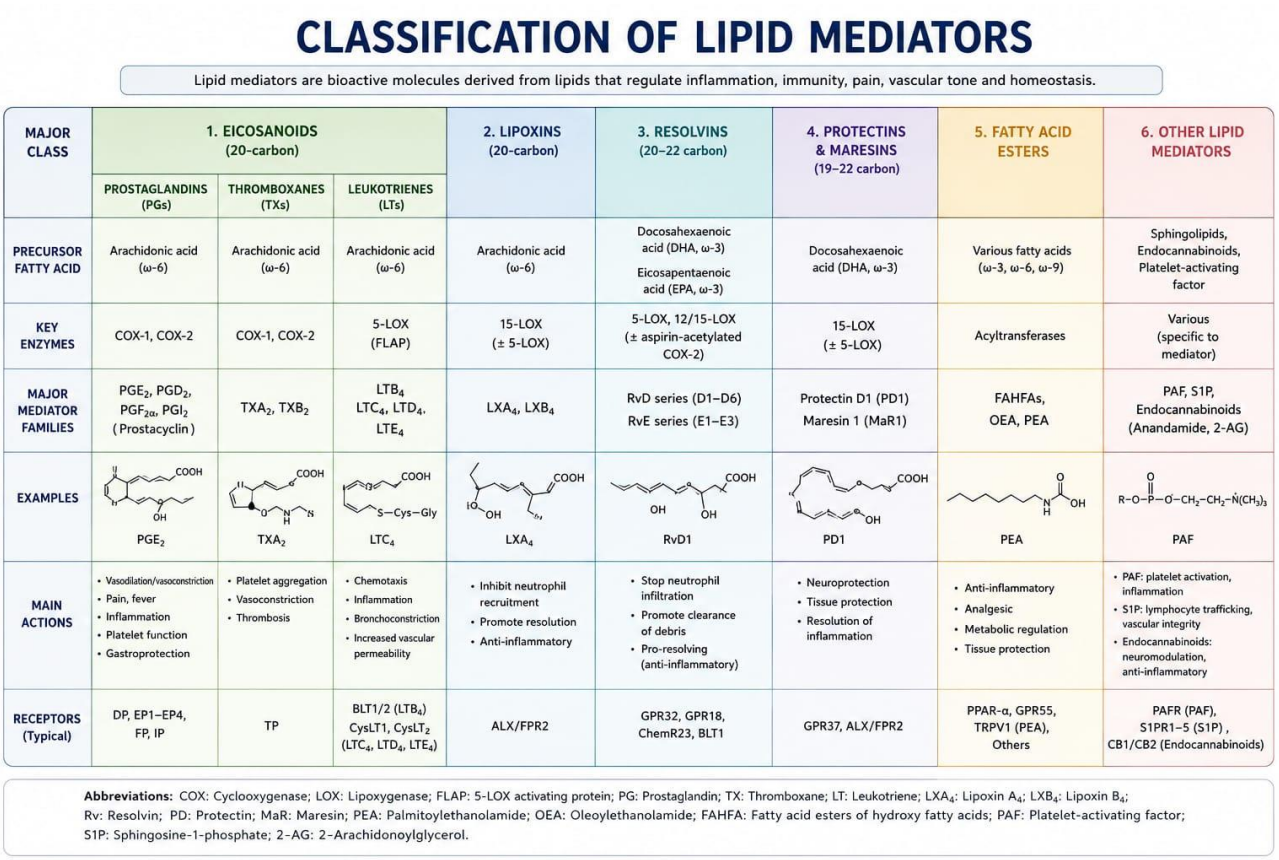

Fig. No. 3: Classification of Lipid Mediators.

- **Mechanisms of action for liposomes:** Liptonitins, resolvinphins and protectinides, as well as maresin-like substances that act as pro-resolution mediators (SPMs) actively reduce inflammation rather than suppress it. By utilizing receptors like ALX/FPR2, GPR32, and ChemR23, they limit excessive inflammation while maintaining normal immune defence and tissue repair.
- **Regulation of Immune Cells:** Innate and adaptive immune responses are also regulated by SPMs, which help to maintain tissue homeostasis. Their actions inhibit the migration of neutrophils, decrease the production of oxidative burst and ROS, and curtail more leukocyte recruitment to damaged tissues. In parallel, they stimulate macrophage polarization from the pro-inflammatory M1 phenotype to the reparative M2 encephalopathy, leading to improved debris clearance and tissue remodelling. SPMs inhibit dendritic cell activation, suppress Th1 andTh17 responses to environmental factors, and boost regulatory T-cell activity. The disruption of chronic inflammatory cycles and resolution can be achieved through these actions in CKD.[2,3,22]

- **Suppression of Pro-inflammatory Cytokines:** Inhibition of inflammatory signaling by SPMs can hinder the activity of transcription factors, including non-coding for genes. The outcome is a decline in the expression of essential pro-inflammatory chemicals, such as TNF-, IL-1+/IL-6, MCP-1, and IC-17. They also inhibit the synthesis of inflammatory prostaglandins and suppress COX-2 expression. SPMs are unlike immunosuppressive drugs because they selectively target and control harmful inflammation, while maintaining the balance of immune function in CKD patients.[2,20,29]
- **Promotion of Tissue Regeneration:** Besides resolving inflammation, SPMs also actively promote tissue repair. ". Resolvins and maresin lipid targets stimulate the proliferation of renal tubular cells, protect podocytes from apoptosis, and activate antioxidant pathways like Nrf2/HO-1. Lipoxins prevent collagen deposition and fibrosis by inhibiting TGF-/Smad3 signaling. By promoting angiogenesis, extracellular matrix remodeling, and wound healing, these mediators help to maintain the structure and function of the kidney.[17,25]
- **Enhancement of Efferocytosis:** Macrophages play a significant role in the inhibition of inflammation through efferocytosis, which is achieved by macrophages. By enhancing the expulsion of apoptotic neutrophils and cellular debris, they prevent secondary necrosis and further damage to the body.[Note 4]. Efferocytosis promotes the release of anti-inflammatory mediators such as IL-10 and TGF, creating a pro-repair environment.[3,22,24]

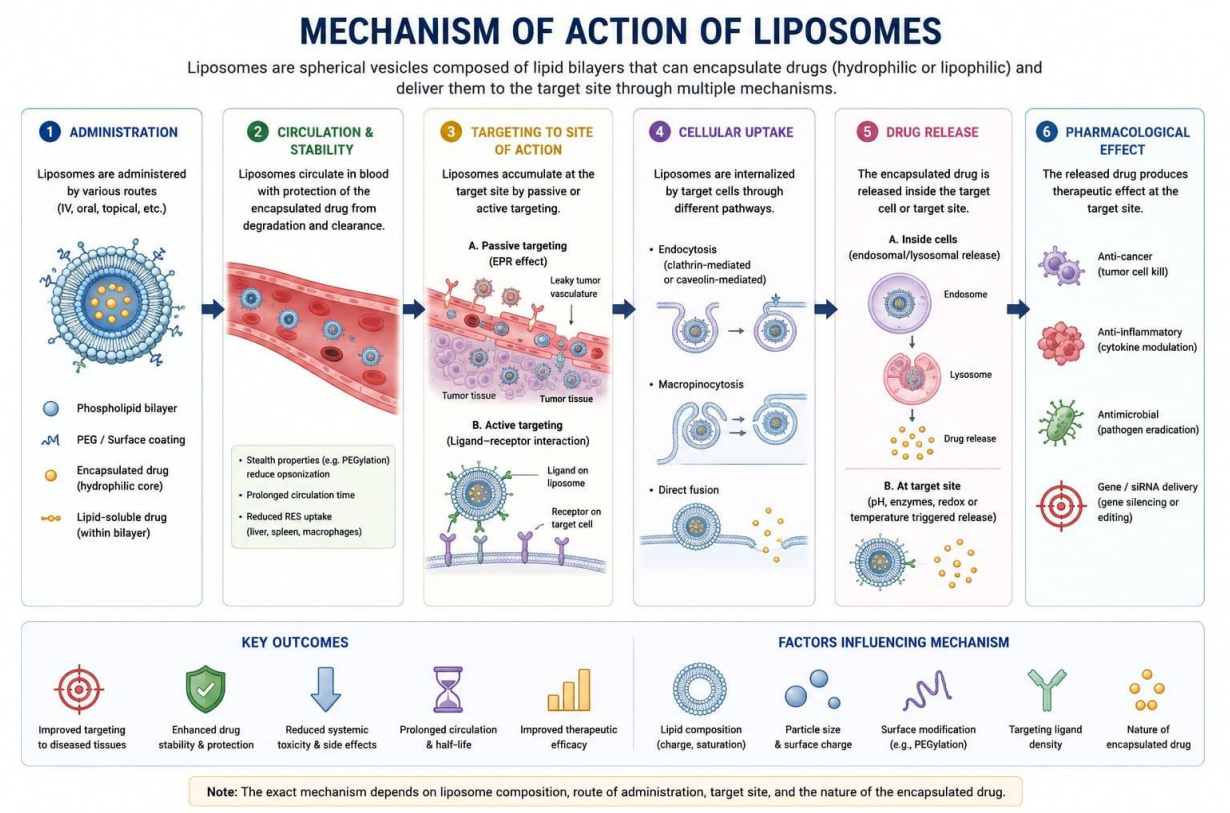

Fig. No. 4: Mechanism Action of Liposomes.

ROLE OF LIPID MEDIATORS IN CHRONIC KIDNEY DISEASE

- **In chronic kidney disease, what is the function of lipid mediators:** Among patients with CKD, lipoxins, resolvins/protectin and maresin also play an important role in controlling renal inflammation and encouraging tissue repair (SPM). They help regulate the pH of blood plasma and balance electrolytes within the cells. In contrast to traditional anti-inflammatory drugs that primarily suppress immune responses, SPMs actively restore

the resolution phase of inflammation by targeting the persistent inflammatory state that drives CKD progression. Consequently, they can decrease inflammation while protecting the integrity of renal cells, regulate inflammation and reduce the risk of fibrosis, and maintain optimal kidney function.[17,20]

- **Effects on Renal Inflammation:** Progression of the disease is largely due to chronic inflammation. SPMs decrease the amount of inflammatory cell infiltration and inhibit the production of pro-inflammatory cytokines such as TNF-, IL-1 und IMP. Lipoxin A4, Resolvin D1, and Resolin E1 (RvE1) inhibit NF-B signaling, while Maresin 1 promotes macrophage polarization towards the anti-inflammatory M2 phenotype. Research has demonstrated that SPMs have the ability to decrease renal inflammation without causing generalized immunosuppression.[15,17,20]
- **Protection Against Kidney Injury:** SPMs have a direct protective effect on podocytes and tubular epithelial cells. RvD1 activates various survival pathways, including PI3K/Akt, while LXA4 targets Nrf2/HO-1 and reduces oxidative stress. Apoptosis is reduced and the nephron is kept healthy with Protectin D1. The use of SPM treatment in models of acute and chronic kidney injury reduces structural damage and improves markers of renal function, indicating the importance of these markers in preventing progressive nephron loss.[17,20]
- **Prevention of Renal Fibrosis:** CKD typically advances through renal fibrosis, which is the most prevalent stage of its development. The inhibition of fibrogenic signaling by SPMs is due to the suppression of TGF-/Smad pathways, which results in a decrease in myofibroblast activation and extracellular matrix accumulation. They also impede the epithelial-mesenchymal transition and encourage degradation of the matrix.e. According to animal studies, SPM treatment leads to significant reductions in collagen deposition and tubulointerstitial fibrosis.[5,6,17]
- **Improvement of Renal Function:** Increased kidney function can be attributed to the combined anti-inflammatory, cytoprotective, and antifibrotic effects of SPMs. Research conducted on animals shows declines in albuminuria, serum creatinine, and blood urea nitrogen, along with preservation of the normal (GFR) glomerular filtration rate. Lower SPM levels are associated with faster CKD progression, according to recent clinical evidence. As a result, new treatments for renal protection are being developed using SPM-based approaches and stable SAM analogues.[17,20,26]

PRECLINICAL AND CLINICAL EVIDENCE

Evidence from both experimental and clinical studies indicates that specialized pro-resolving mediators (SPM) may be effective in treating CKD. The findings suggest that disease progression is influenced by impaired resolution pathways, while the restoration of SPM signaling results in a decrease in inflammation, fibrosis, and renal dysfunction.

- **Experimental Studies:** Through specific receptor-mediated pathways, SPMs have been shown to exert direct renoprotective effects in cell-based studies. Lipoxin A4 (LXA4) suppresses TGF-1 induced collagen production and fibrotic signaling, while Resolvin D1 (RvD1) safeguards tubular epithelial cells from oxidative stress by activating the Nrf2/HO-1 pathway. Maresin 1 enhance macrophage-mediated efferocytosis and IL-10 production, while Protectin D1 inhibits podocyte apoptosity. SPMs exhibit anti-inflammatory, anti–fibrotic, and cytoprotective effects at physiologically relevant concentrations, as evidenced by these findings.[17,20]

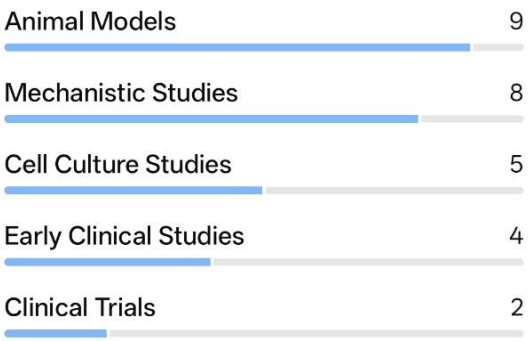

Fig. No. 5: Preclinical and Clinical evidence.

- **Animal Models of CKD:** The positive effects of SPMs are consistently observed in animal studies across different CKD models. Albuminuria, glomerular injury, and interstitial fibrosis are reduced in diabetic nephropathy by SPMs. Why? Sale function models for both ischemia-reperfusion and nephrotoxic injury maintain a high glomerular filtration rate (GFR), minimize tubular damage, and improve renal function.[M]. Investigations in models of unilateral ureteral obstruction and 5/6 nephrectomy reveal decreased collagen deposition, reduced fibrosis, and reduced functional decline. SPMs have the ability to mitigate these impacts without affecting host defence.[17,20]
- **Human Clinical Studies:** Although there is limited clinical evidence, the future is bright. In patients with CKD, there is evidence of lower circulating levels of LXA4, RvD1, and MaR1, which is associated with increased proteinuria, lower expression of eGFR, and faster disease progression. Endogenous SPM production may be stimulated by increasing endogenously produced SMP, as indicated by indirect clinical studies utilizing omega-3 fatty acid supplementation. Although there are no studies on kidney-specific SPM analogues, early research on other inflammatory diseases has revealed relatively favourable safety profiles.[26,33]

THERAPEUTIC POTENTIAL OF RESOLUTION PHARMACOLOGY IN CHRONIC KIDNEY DISEASE

- **CKD: Therapeutic potential of resolution pharmaceuticals:** Resolution pharmacology is another new approach to treating CKD, as it activates endogenous pathways that terminate inflammation and aid in the healing of tissue. In contrast to more aggressive approaches that primarily target inflammation, resolution-based therapies restore immune homeostasis by decreasing fibrosity and maintaining renal function.[1,4,20]
- **Novel Drug Targets:** Several pathways that involve specialized pro-resolving mediators (SPM) have become potential targets for drug candidates. Receptors such as ALX/FPR2, GPR32, ChemR23, and LGR6 can act as mediators between lipoxins, resolvins or maresin proteins and directly stimulate resolution. These receptors are also used by the mouse to regulate cell division. Therapeutic targets may also include enzymes involved in the biosynthesis of SPM, such as 5-lipoxygenase and 12/15-lipoxin. MerTK and CD36, two efferocytosis-related receptors, could aid in the clearance of apoptotic cells and facilitate their repair. Targets that are not typical immunosuppressive pathways may have safer safety profiles. However, these targets are unique.[2,14,16]
- **Lipid Mediator-Based Therapies:** Direct administration of SPMs or their synthetic analog counterparts is the most advanced approach to resolution. Anti-inflammatory, anti-fibrotic, and cytoprotective effects have been observed in stable analogs of LXA4, RvD1, RVE1, or MaR1, which also overcome the rapid degradation of native mediators. Enhanced bioavailability and renal targeting are achieved through the use of nanoparticles and

liposomal delivery systems. Supplementation with omega-3 fatty acids may boost endogenous SPM production, but direct analogs are likely to deliver more predictable therapeutic effects.[14,20,26]

- **Combination Therapy Approaches:** It is anticipated that resolution pharmacology will complement existing CKD therapies, not replace them. In addition to hemodynamic control, SPMs may reduce inflammation and fibrosis, which could enhance the benefits of RAAS inhibitors. It is possible to enhance mitochondrial function and reduce oxidative stress by using SGLT2 inhibitors in combination with other drugs. SPMs may interact with anti-fibrotic agents that specifically target TGF- or CTGF pathways. Moreover, biomarker-based approaches that utilize circulating SPM levels may be applicable to identify the patients most likely to benefit from resolution-driven therapies.[17,20]

CHALLENGES AND LIMITATIONS

While specialized pro-resolving mediators (SPMs) are highly effective therapeutically in CKD, there remain several challenges to successfully translating these findings into clinical practice. These include metabolic instability of native mediators, difficulties in effective delivery of drugs, limited clinical evidence and the need for comprehensive safety assessment.

- **The stability and delivery of lipid mediators:** The rapid degradation of native SPMs leads to short biological half-lives and reduced therapeutic efficacy. A new class of analogues has been developed that is both inactivating and retaining biological activity, while also remaining stable due to the lack of inactivity. Moreover, the hydrophobic character of SPMs restricts their distribution and bioavailability in tissue-specific settings. To enhance stability, circulation time and kidney targeting, more advanced delivery systems like nanoparticles or liposomes (e.g. Increasing therapeutic effectiveness and decreasing systemic exposure are potential outcomes of these approaches.[14,20]
- **Clinical Translation:** The renoprotective effects have been consistently demonstrated in preclinical studies, but it is still challenging to translate this into human CKD. Currently, there are no established biomarkers that can be used to identify patients with impaired resolution capacity or assess treatment responses. Furthermore, the nature of CKD is varied and the function of resolution pathways may differ among the different diseases. The development of clinical trials poses challenges. Because SPMs promote homeostasis restoration rather than direct immunosuppression, conventional inflammatory endpoint may not capture the therapeutic benefit. It will also require long-term studies of other renal outcomes, such as GFR decline and the progression to kidney failure.[28,29]
- **Safety Considerations:** Evidence suggests that SPMs have a positive safety profile because they enhance endogenous resolution mechanisms without suppressing immune function. This is supported by current studies. They are less likely to affect the likelihood of infection or host defense, unlike traditional immunosuppressive therapies.But there are still few long-term data on human safety.'... Possible concerns involve off-target receptor effects, interactions with frequently used CKD drugs and questions about the appropriate dosing of medications. Before broad clinical applications, thorough studies of pharmacokinetics, chemistry, and toxicology are indispensable.[3,28,29]

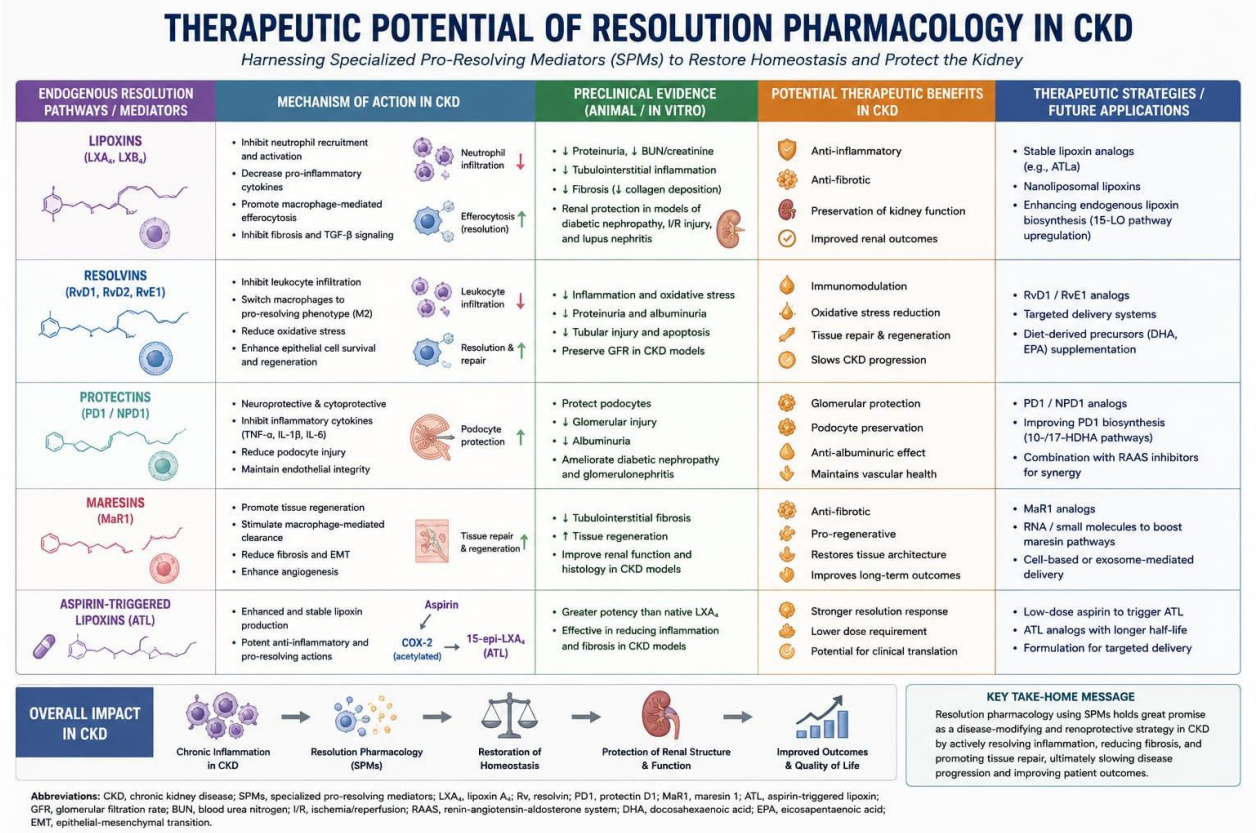

Fig. No. 6: Therapeutic Potential of Resolution Pharmacology In CKD.

- **Clinical Translation**: The renoprotective effects have been consistently demonstrated in preclinical studies, but it is still challenging to translate this into human CKD. Currently, there are no established biomarkers that can be used to identify patients with impaired resolution capacity or assess treatment responses. Furthermore, the nature of CKD is varied and the function of resolution pathways may differ among the different diseases.The development of clinical trials poses challenges. Because SPMs promote homeostasis restoration rather than direct immunosuppression, conventional inflammatory endpoint may not capture the therapeutic benefit. It will also require long-term studies of other renal outcomes, such as GFR decline and the progression to kidney failure.[28,29]
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FUTURE PERSPECTIVES

The progress of resolution pharmacology in CKD will be determined by developments in precision medicine, biomarker development, drug-delivery technologies, and clinical translation. Combined, they seek to address existing barriers and facilitate the application of clinical applications for these specialized pro-resolving mediators (SPMs).

- **Precision Medicine Approaches:** High intra-individual variability in SPM biosynthesis and signaling makes resolution pharmacology a useful tool for precision medicine. The resolution capacity of endogenous organisms can be influenced by genetic factors, dietary omega-3 content, microbiome composition, and disease stage. Patients with impaired pro-resolving responses may be the most susceptible to SPM-based therapies due to comprehensive lipid mediator profiling. This could aid in identifying these patients. Lipidomic, inflammatory and genomic data could be used to develop tailored treatment plans for the pathogenic factors that drive progression in CKD.[14,20]
- **Biomarker Development:** Hence, clinical translation depends on reliable biomarkers of resolution activity.eu. The development of lipidomics has enabled the measurement of SPMs and other relatedmetabolites in plasma, urine, and renal tissue. Among the candidate biomarkers are LXA4, RvD1, and MaR1 circulating levels, and SPM-to pro-inflammatory mediator ratios. Regulatory approval of biomarker-guided interventions, patient stratification, and therapeutic monitoring will all require the use of standard analytical methods.[14,26]
- **Nanotechnology-Based Delivery Systems:** Despite the limitations of native SPMs, nanotechnology presents opportunities for improving their pharmacokinetic capabilities. The use of liposomes, lipolisinates or polymeric carriers can improve stability, increase circulation time, and enhance renal targeting. Inflamed renal tissue may be infused with stimuli-responsive delivery systems that can release therapeutic agents, which could result in increased efficacy and reduced systemic exposure. Early trials demonstrate positive outcomes for these technologies, which are a significant focus for future advancements.[14,20]
- **Future Research Directions:** In the future, research should be conducted to establish the safety and effectiveness of SPM-based treatments in CKD in the long run. Other priorities include understanding the mechanisms of SPM resistance, developing metabolically stable SMP mimetics, and exploring combination therapies with known renoprotective agents. These agents may include SGLT2 inhibitors, finerenone, or GLP-1 receptor agonists. The success of regulatory approval and the determination of therapeutic efficacy will depend on large-scale, biomarker-guided clinical trials. The impact of lifestyle factors, such as diet and the gut microbiome, on endogenous resolution pathways is also a topic of interest.[17,20,28]

CONCLUSION

The occurrence of chronic kidney disease (CKD) is increasingly acknowledged as a condition marked by prolonged inflammation and impaired resolution. Lipoxins, resolvin and other pro-resolution mediators (SPMs) act as active antidotes to address the above-mentioned resolution deficit by restoring immune homeostasis through reduced tissue injury and reduction of fibrotic remodeling, rather than simply suppressing inflammation.In various CKD models, preclinical studies have consistently shown that SPMs decrease renal inflammation, protect nephron structure, reduce and prevent fibrosis while also maintaining kidney function. This is contradictory. The relationship between decreased SPM levels and disease progression is supported by new clinical evidence, which supports their role as both therapeutic targets and potential biomarkers. Resolution pharmacology's translational potential has been expanded by improvements in stable SPM analogs, targeted delivery systems, and combination strategies with established renoprotective therapies.Despite the challenges of pharmacokinetic limitations, biomarker validation, and the need for long-term clinical studies, advancements in medicinal chemistry, nanotechnology, lipidomics, or precision medicine are gradually dissipating these hindrances. These developments highlight the potential of resolution pharmacology as an effective therapeutic approach that can complement existing therapies for CKD by encouraging active tissue repair and restoring renal homeostasis. Advocates.[1,2,3,4,17,20,28]

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