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Role of Antioxidants in The Management of Chronic Kidney Disease

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ABSTRACT

Chronic kidney disease (CKD) is a chronic disease that is characterized by the gradual impairment of renal activity, which is mostly caused by oxidative stress, inflammation, and fibrosis. The accumulation of reactive oxygen species (ROS) adds to the endothelial dysfunction, tubular damage, and extracellular deposition, and enhances the development of the disease. Nrf2 activators, natural (curcumin and resveratrol) and synthetic (bardoxol methyl) are all antioxidant therapies that have demonstrated the potential to reduce oxidative damage, regulate inflammatory and fibrotic responses, and conserve renal function in preclinical models. The natural antioxidants have anti-inflammatory and antifibrotic effects, whereas synthetic antioxidants have multidirector effects of high activity. Although mechanistic understanding is being encouraged, bioavailability, variation in dosing, and species-specific differences are some of the challenges, which limit clinical translation. To prove the effectiveness of antioxidant-based interventions, future studies need to concentrate on rigorous clinical studies, optimal delivery methods, and patient stratification. Altogether, antioxidants are an attractive adjunctive management option to enhance the traditional CKD treatment and reduce the rate of the disease.

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Key Words:

Keywords: Chronic Kidney Disease, Oxidative Stress, Antioxidants, Nrf2 Activators, Curcumin, Resveratrol, Renal Fibrosis, Bardoxolone Methyl

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1. INTRODUCTION

Chronic kidney disease (CKD) is an irreversible and progressive disorder, which is marked by gradual kidney failure, resulting in metabolic waste product accumulation, fluid imbalance, and electrolyte imbalance. In the world, CKD is estimated to impact between 10 and 15 percent or the population and has been known to cause high morbidity and mortality mainly through cardiovascular events and end-stage renal disease (ESRD)[1]. CKD pathogenesis is multifactorial, which means hypertension, diabetes, glomerulonephritis, and other systemic diseases. Oxidative stress, which is an imbalance between the generation of reactive oxygen species (ROS) and the body antioxidant defenses, is a critical attribute in the evolution of CKD.

The high level of ROS enhances endothelial dysfunction, inflammation, and apoptosis, as well as fibrosis in renal tissues, promoting the development of the disease and decreasing the effectiveness of the traditional therapy. With these limitations, a renewed focus is on strategies to address oxidative stress to inhibit CKD progression and outcomes as a complement to reducing the rate of renal failure.

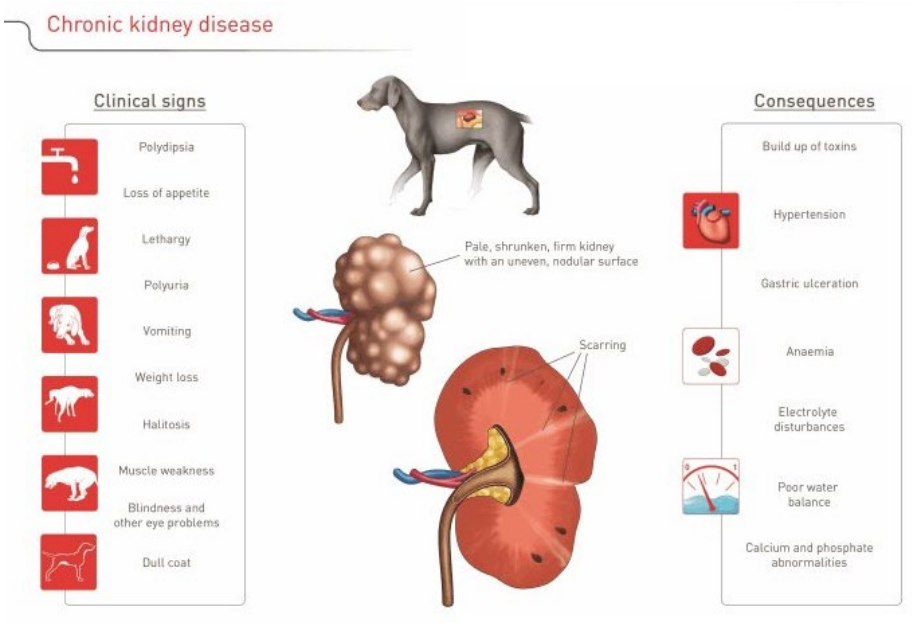

Figure 1: Chronic Kidney Disease[2].

Endogenous and exogenous antioxidants are crucial in counteracting ROS and replacing the redox balance to avoid oxidative damage of the renal cells. Recent studies have also shown the promise of antioxidant therapy, including natural and synthetic antioxidants (curcumin and resveratrol, respectively, and bardoxolone methyl) to alleviate oxidative stress, inflammation, and fibrosis in CKD models. The combination of antioxidant interventions in CKD management provides a potential source of research growth to supplement traditional treatment and possibly delay disease development[3]. This review will serve to conduct a critical synthesis of existing data on the topic of antioxidant use in CKD, covering mechanistic understanding, preclinical and clinical research, and therapeutic considerations. It is hoped that this review will inform the future of research on antioxidant interventions and assist in creating more effective and focused treatments to treat CKD patients by critically evaluating the efficacy, mechanisms, and challenges of these interventions.

1.1 Background Information and Context

The emergence of chronic kidney disease as a major public health issue of concern across the globe is increasing because of its high prevalence rate, tremendous economic investment, and the quality of life. Conventional approaches to management, such as blood pressure management, glycemic regulation, and inhibition of the renin-angiotensin-aldosterone system, are mainly meant to reduce the rate of disease, and not reverse renal damage[4]. Nevertheless,

oxidative stress has proved to be a major pathophysiologic player in CKD, which connects hyperglycemia, inflammation, mitochondrial pathology, and endothelial damage to structural and functional renal dysfunction.

1.2 Objectives of the Review

The primary objective of this review is to:

- To evaluate the role of oxidative stress in the pathogenesis and progression of chronic kidney disease.
- To analyze the therapeutic potential of Nrf2 activators, natural antioxidants, and synthetic antioxidants in mitigating oxidative damage and renal fibrosis.
- To critically assess preclinical evidence on antioxidant interventions, including methodologies, efficacy, and limitations in CKD models.
- To explore the mechanistic pathways through which antioxidants modulate inflammation, fibrosis, and cellular injury in CKD.
- To identify gaps in current research and propose future directions for translating antioxidant therapy into clinical practice.

1.3 Importance of the Topic

Considering the prevalence of CKD and its progressive course, a clinical concern related to the adjunctive interventions aimed at the oxidative stress reduction would be of value. The antioxidant interventions can be helpful to supplement the current therapies, decrease the kidney damage, and enhance the outcome of patients[5]. In addition, knowledge of the molecular processes that drive antioxidant activities has the potential to inform the creation of new, specific treatments that can help slow down the progression of disease, cut down healthcare expenses, and improve the quality of life of a person with CKD.

2. ANTIOXIDANT THERAPIES IN CHRONIC KIDNEY DISEASE: PRECLINICAL EVIDENCE, METHODOLOGIES, AND CRITICAL INSIGHTS

Studies on antioxidant therapy in CKD have shown that Nrf2 activation and NRF2 synthetic or natural antioxidants decrease oxidative stress, inflammation, and fibrosis and improves renal function and structure in animal models. Research uses a variety of CKD models, including diabetic nephropathy, ischemia-reperfusion injury, and unilateral ureteral obstruction, to determine the antioxidant activity by using biochemical (ROS, MDA, antioxidant enzymes) and histological (serum creatinine, BUN, GFR) measures[6]. Although the benefits of such controlled animal studies are important mechanistic understanding, dose responds, and comprehensive molecular and histological support, species differences, simplified disease models, and inconsistencies of treatment regimens limit the application of such studies, thus requiring caution in their interpretation and validation in human clinical trials.

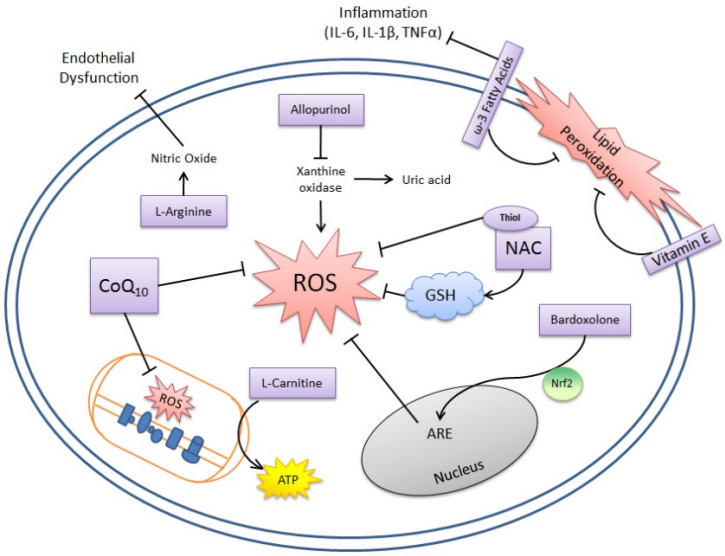

Figure 2: Antioxidant Therapies in Chronic Kidney Disease[7].

2.1 Key Research Studies

Nrf2 activation and natural (e.g., curcumin, resveratrol) or synthetic antioxidant (e.g., bardoxolone) use lowers oxidative stress and inflammation and fibrosis in CKD models. These treatments enhance kidney functioning and structural integrity, which underscores their therapeutic capability.

- **Nrf2 Activation:** In many studies, nuclear factor erythroid 2 related factor 2 (Nrf2) has been brought to fore as an important mediator of cellular redox homeostasis. Nrf2 pathway can induce a wide array of antioxidant and cytoprotective genes to counteract oxidative stress. Pharmacological activation of Nrf2 in rodent models of CKD has been demonstrated to lower the accumulation of reactive oxygen species (ROS), inhibit lipid peroxidation and limit the progression of renal injury[8]. An example is that interventions causing Nrf2 nuclear translocation led to better renal activity and inhibition of glomerulosclerosis and tubulointerstitial fibrosis in these models providing evidence of a possible therapeutic approach to the management of CKD (MDPI).
- **Natural Antioxidants:** Natural antioxidants including curcumin, resveratrol, quercetin and green tea polyphenols have shown reno protective activity in preclinical models of CKD. Other effects of these agents include scavenging free radicals, regulating inflammatory, apoptotic, and fibrotic signaling pathways[9]. It is demonstrated in animal studies that curcumin treatment reduces the oxidative stress indicators such as malondialdehyde (MDA) and the improvement of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase. Equally, resveratrol therapy has been linked with reduced inflammation in the renal tract and elevated structural and functional integrity of the kidney meaning that dietary or pharmacological natural antioxidants might also provide additional approaches in CKD treatment (MDPI).
- **Synthetic Antioxidants:** Synthetic antioxidants have also been considered in addition to the naturally occurring compounds in CKD. There are promising agents like bardoxolone methyl, which is the potent Nrf2 activator, which have shown promising results in preclinical studies[10]. These substances enhance the renal hemodynamics,

lower the pro-fibrotic markers and mitigate cellular injury caused by oxidative stress in CKD models. Indicatively, treatment of diabetic nephropathy models with bardoxolone methyl increased the glomerular filtration rate and reduced the fibrosis progression, highlighting the therapeutic value of specific synthetic antioxidants in delaying the development of CKD progression (MDPI).

2.2 Methodologies and Findings

Antioxidant therapy studies on CKD have employed different animal models to simulate the different pathological characteristics of the disease. In general, diabetic nephropathy, ischemia-reperfusion injury, and unilateral ureteral obstruction are frequently used as models, which are associated with particular mechanisms of CKD development[11]. The efficacy of antioxidants is normally evaluated through a combination of biochemical, histological and functional tests. The measure of the oxidative stress markers includes MDA, ROS, and antioxidant enzyme activity using biochemical analyses; glomerular and tubular structural integrity, fibrosis, and inflammatory cell infiltration using renal histology. The following are quantitative indicators of the kidney functioning; functional assays, such as serum creatinine, blood urea nitrogen (BUN), and glomerular filtration rate. Overall, these works all indicate that antioxidant interventions can decrease oxidative damage, lower the production of inflammatory cytokines, and reduce renal fibrosis and is therefore protective in CKD models.

2.3 Critical Evaluation

The studies on CKD and antioxidant action in animals offer an appropriate controlled environment to examine these processes, which can be useful in terms of molecular and histological background. Nonetheless, the restriction of direct translation to human clinical outcome is constrained by differences between species and simplified models.

- **Strengths:** Animal studies have a high level of control and in this case, researchers are able to study the pathophysiology of CKD and the mechanistic action of antioxidant interventions in a systematic manner[12]. They allow assessing both preventive and therapeutic approaches, which gives insightful information about dose-response connections, molecular pathways, and long-term outcomes. The fact that histological and biochemical studies can be performed in detail in vivo only enhances the reliability of the results.
- **Weaknesses:** In spite of these benefits, there are a number of limitations in regard to the direct application of animal model research to clinical practice. Metabolic, immune, and renal physiological species-specific differences may have effects on the safety and efficacy of antioxidants[13]. The cross-study comparisons are difficult due to the varying dosages, duration of treatment and the selection of CKD models. Furthermore, the multifaceted multifactorial nature of human CKD, which can be accompanied by comorbidities, cannot be accurately recreated in the experimental models, which makes it necessary to interpret it carefully and then confirm it in the human clinical trials.

3. OXIDATIVE STRESS AND ANTIOXIDANT-BASED THERAPEUTIC STRATEGIES IN CHRONIC KIDNEY DISEASE

The primary cause of CKD progression is oxidative stress induced by overproduction of ROS, antioxidant deficiency, endothelial dysfunction, tubular injury, inflammation, and fibrosis. Reno protective effects were demonstrated using therapeutic agents to combat oxidative stress, such as Nrf2 activators, natural antioxidants (e.g., curcumin, resveratrol), and synthetic antioxidants (e.g., bardoxolone) in reducing ROS, regulating inflammatory and fibrotic processes, and maintaining renal function in preclinical models[14]. Nrf2 stimulators are more effective in promoting the endogenous antioxidant gene expression and in the inhibition of NF-KB-mediated inflammation whereas natural compounds also offer anti-inflammatory and antifibrotic effects. Synthetic antioxidants are very potent and selective, regulating a variety of signal pathways to suppress oxidative damage. With a good prospect of good preclinical results, there are issues like bioavailability, safety and clinical translation, which make further research a prerequisite to successful human usage.

3.1 Oxidative Stress Mechanisms in CKD

Oxidative stress has a key role in the pathogenesis and progression of chronic kidney disease (CKD). It is caused by the uncoordinated formation of excess reactive oxygen species (ROS) and the reduction of the ability of endogenous antioxidant systems in counteracting the reactive molecules. Hyperglycemia, uremic toxins, and chronic inflammation are some of the factors that increase ROS production in the renal tissues of CKD. High ROS concentrations cause cellular damage of lipids, proteins, and nucleic acids, which result in endothelial dysfunction, tubular damage, and glomerulosclerosis[15]. The resulting oxidative damages are the buildup of oxidative stress, which is associated with a pro-inflammatory microenvironment (enhanced cytokine release, leukocyte infiltration, and stimulation of pro-fibrotic signaling pathways) that increases the severity of renal injury and disease progression (BioMed Central).

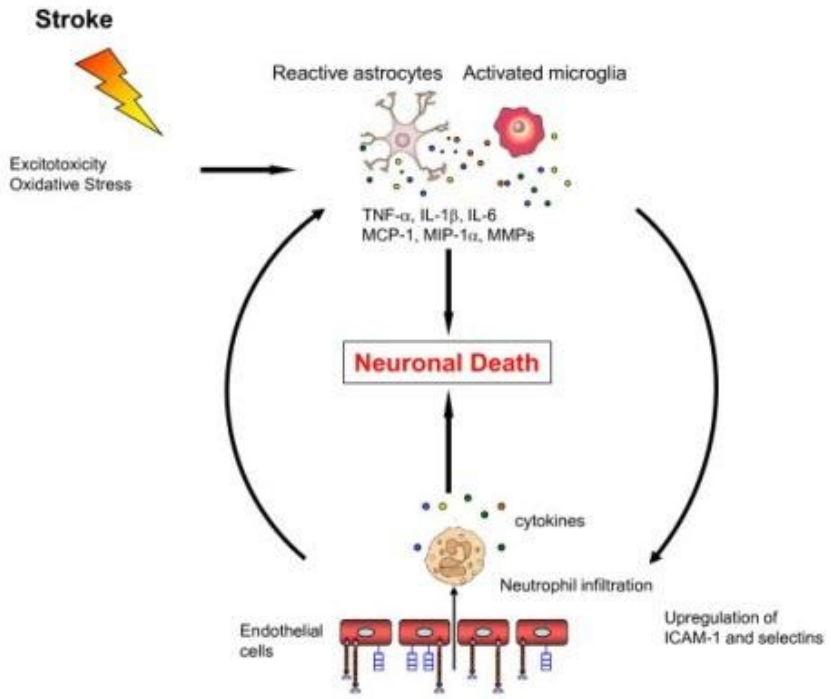

Figure 3: Oxidative Stress Mechanisms[16].

Moreover, the oxidative stress of CKD is strictly connected with the disruption of the main signaling pathways of redox homeostasis. As an example, the reduced activity of antioxidant enzymes like superoxide dismutase (SOD), catalase and glutathione peroxidase reduce the capacity of the kidney to neutralize ROS. Mitochondrial impairment, which is one of the major symptoms of CKD, increases the production of ROS and activates the apoptotic cascades, which also lead to the depletion of functional nephron mass[17]. The continuous loop of ROS generation, antioxidant loss, and inflammatory response is a strong point provoking therapeutic intervention that can integrate redox homeostasis and avoid the subsequent impact of oxidative stress on CKD.

3.2 Antioxidant Interventions

Natural (e.g. curcumin, resveratrol) and synthetic (e.g. bardoxolone) antioxidants, like Nrf2 activators, decrease oxidative stress, inflammation, and fibrosis, and improve kidney functioning in CKD models[18]. These agents work via antioxidant, anti-inflammatory and anti-fibrotic, which underscores the therapeutic potentials but needs additional research to translate to clinical implementation.

- **Nrf2 Activators**

The promotion of the Nrf2 (nuclear factor erythroid 2related factor 2) pathway is one of the possible ways to reverse the oxidative stress in CKD. Nrf2 is a transcription factor which controls the expression of a wide array of antioxidant and cytoprotective genes, such as heme oxygenase-1 (HO-1), NAD (P)H quinone oxidoreductase 1 (NQO1) and glutathione S-transferase (GST)[19]. Nrf2 pharmacological activation in preclinical CKD models has been demonstrated to lead to a decrease in the levels of ROS accumulation, lower levels of inflammatory cytokines and prevention of renal cells against apoptosis. Nrf2 activators can alleviate glomerular and tubular damage, mitigate fibrosis, and improve the overall organ renal function, which indicates their relevance as disease-modifying agent (MDPI).

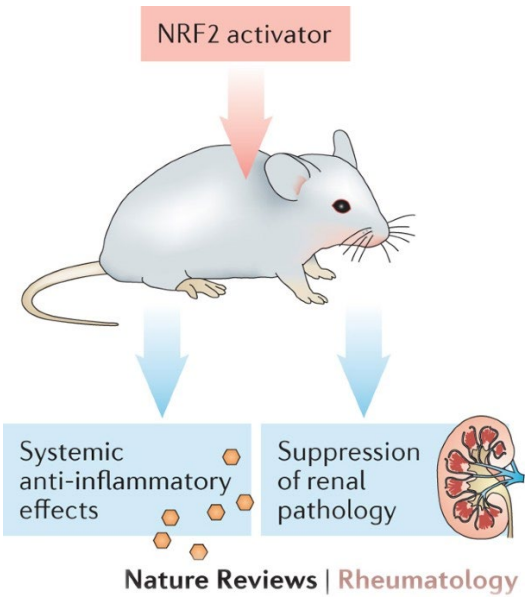

Figure 4: Nrf2 Activators[20].

In addition, Nrf 2 activation not only suppresses the effects of oxidative stress but also regulates several other inflammatory and fibrotic pathways. Research has also shown that Nrf2 activators have the ability to inhibit the NF-kB pathway thus inhibiting the expression of pro-inflammatory cytokines like TNF-alpha, IL-6, and MCP- 1. This bifunctional effect of the antioxidant and anti-inflammatory effect of Nrf2, makes the Nrf2-targeted therapies especially useful in multifaceted CKD pathology, wherein oxidative stress and inflammation are interconnected[21]. Long-term preclinical findings have also indicated that sustained Nrf2 activation can delay the onset of diseases and conserve renal architecture, but the results need to be carefully applied to clinical management in terms of dosing, safety, and specifics of patients.

Natural Compounds

Polyphenols and flavonoids, which have been included as natural antioxidants, such as curcumin, resveratrol, quercetin, and green tea catechins have attracted considerable attention with regard to their therapeutic value in CKD. The compounds have Reno protective effects related to direct scavenging of ROS, the ability to increase endogenous anti-oxidant enzyme activity, and the regulation of inflammatory and fibrotic processes[22]. Individually, curcumin, has been reported to suppress the lipid peroxidation, replenish glutathione levels, and suppress the expression of pro-fibrotic markers including transforming growth factor-beta (TGF-b) in diabetic nephropathic animal models. Resveratrol, in its turn, triggers sirtuin-1 (SIRT1) signaling, which enhances mitochondrial activity and mitigates oxidative stress, which also speaks in its favor as a CKD remedial (MDPI).

The antioxidant effects, natural compounds have anti-inflammatory and antifibrotic effects, which complement their Reno protective effects. They may block major signaling pathways, including NF- 0 B, MAPK and TGF- 0 B/Smad, which suppress cytokine release, macrophage infiltration and extracellular matrix deposition in the kidney[23]. Notably, several of these agents are usually well-tolerated, and may be offered in oral form, which makes them good choices as a long-term adjunct agent. Nevertheless, some issues, including low bioavailability, metabolic unpredictability and inconsistent efficacy on CKD models, require additional research to streamline formulation, dosing and combinatorial approaches to clinical translation.

Synthetic Antioxidants

Antioxidants produced synthetically, offering more specific and effective effects, have been reported to be effective in preclinical CKD models. The potent Nrf2 activators like bardoxolone methyl have been proved to enhance renal function by lowering oxidative stress, inflammation, and fibrosis. Bardoxolone methyl improves glomerular filtration and reduces serum creatinine and histopathological injury in diabetic nephropathy and another CKD models[24]. The combination of antioxidant, anti-inflammatory, and antifibrotic effects achieves these effects and ensures the ability of synthetic antioxidants to serve as promising agents of therapeutic development (MDPI).

In addition to bardoxolone methyl, various other artificial molecules have been considered in CKD treatment such as new redox modulators, small molecule ROS scavengers. These agents

have benefits over natural compounds, including increased stability, higher potency, and control of molecular targets[25]. The preclinical research shows that synthetic antioxidants can simultaneously regulate various signaling pathways, such as Nrf2, NF- 0 B, and TGF -0 B, covering the full range of protection against oxidative stress and fibrosis. However, a close consideration of safety, off-target effects, and long-term efficacy is essential in clinical translation since the ratio between the therapeutic effects and the undesired effects continues to be a serious issue when it comes to managing CKD.

4. RENAL FIBROSIS AND ANTIOXIDANT THERAPY IN CKD

Renal fibrosis is a symptomatic feature of chronic kidney disease (CKD) and the ultimate similar pathway to progressive renal dysfunction. It is a condition of excessive deposition of extracellular matrix (ECM) elements (collagen and fibronectin) in the glomeruli and interstitial spaces[26]. It is precipitated by the continuous oxidative stress, chronic inflammation and stimulation of pro-fibrotic pathways, such as transforming growth factor-beta (TGF-B)/Smad, connective tissue growth factor (CTGF) and platelet-derived growth factor (PDGF). The role of reactive oxygen species (ROS) in this process is to trigger epithelial-to-mesenchymal transition (EMT) in tubular cells, activate fibroblasts and induce myofibroblast differentiation. Accordingly, chronic oxidative stress not only harms renal parenchyma by itself, but also increases the output of fibrotic signals to cause permanent structural and functional destruction of the kidney.

Antioxidant treatment has been a promising approach to alleviate renal fibrosis in CKD through attacking the ROS-related processes[27]. The natural and synthetic antioxidants have been demonstrated to decrease the ECM deposition, suppress fibroblast activation, and suppress pro-fibrotic signaling in preclinical models. As an example, Nrf2 stimulators strengthen the native antioxidant responses, and consequently, the oxidative stress decreases, and TGF-B-regulated fibrogenesis is inhibited. To support the conclusion, natural compounds anti-fibrotics include curcumin and resveratrol, which inhibit EMT, reduce the concentration of inflammatory cytokines, and depress the synthesis of collagen. In a similar manner, synthetic antioxidants such as bardoxolone methyl are also able to decrease the ROS levels, enhance renal hemodynamics, and inhibit the development of fibrosis, which also indicates their promising clinical use.

Antioxidants have a mechanistic effect in reversing renal fibrosis along complex mechanisms. Antioxidants inhibit oxidative stress on tubular and glomerular cells by preventing the elimination of cellular apoptosis and the ultimate recruitment of fibroblasts[28]. They also prevent activation of nuclear factor-kappa B (NF-x-B) and other pro-inflammatory transcription factors which are major mediators of chronic inflammatory and fibrosis. Also, antioxidant treatments control signaling pathways (TGF- 2/Smad and MAPK), which mediate ECM synthesis and fibroblast differentiation. In these mechanisms, antioxidants do not only delay the course of development of renal fibrosis but also maintain the remaining level of renal functions, which delay the development of end-stage renal disease.

Nevertheless, even after encouraging preclinical research, it is difficult to transfer antioxidant therapy to clinical practice in the case of renal fibrosis[29]. Bioavailability variability, dosage, and treatment duration variability, species-specific differences in antioxidant response make

animal research interpretation difficult. Additionally, diabetic, hypertensive, and cardiovascular disease comorbidities are frequent renal fibrosis determinants of human CKD that can affect treatment outcomes[30]. Thus, although antioxidant therapy has great potential in reducing the renal fibrosis, clinical trials should be continued to provide the best measures, long term results and safe and effective methods of using the therapy in patients with CKD.

Table 1: Summary of Key Studies on Oxidative Stress and Antioxidant Interventions in Chronic Kidney Disease

Author(s) & Year	Study	Focus Area	Methodology	Key Findings
Tang et al., 2021[31]	Mitochondrial quality control in kidney injury and repair	Role of mitochondrial dysfunction in CKD progression	Literature review of mitochondrial dynamics, mitophagy, and biogenesis in renal injury models	Mitochondrial dysfunction increased oxidative stress and apoptosis, impairing renal repair; targeting mitochondrial quality control could prevent further renal injury
Tirichen et al., 2021[32]	Mitochondrial ROS contribution in CKD progression	Effect of mitochondrial ROS on CKD pathophysiology	Review of studies assessing ROS production, inflammation, and fibrosis in CKD	Excess mitochondrial ROS caused oxidative damage, inflammation, and fibrosis; interventions reducing mitochondrial ROS may slow CKD progression
Uddin et al., 2021[33]	Pharmacotherapy against oxidative stress in CKD	Small molecule natural products targeting Nrf2-HO-1 signaling	Literature review of preclinical studies using curcumin, resveratrol, quercetin	Nrf2 activators enhanced antioxidant defenses, reduced ROS, inflammation, and fibrosis; suggested potential as adjunct CKD therapy
Vera-Aviles et al., 2018[34]	Protective role of histidine supplementation in CKD anemia	Nutrient-based antioxidant therapy in CKD-associated anemia	Preclinical and clinical review of histidine supplementation effects	Histidine reduced oxidative damage, improved erythropoietic function, and mitigated oxidative stress; showed therapeutic potential of amino acid supplementation
Verma et al., 2021[35]	Implications of oxidative stress in CKD	Current concepts and therapies targeting oxidative stress	Review of preclinical and clinical studies on natural and synthetic antioxidants	Elevated ROS caused endothelial dysfunction, inflammation, and fibrosis; antioxidant interventions were effective in preclinical models, but clinical translation

				requires attention to bioavailability, dosing, and safety

5. DISCUSSION

The findings of the preclinical research highlighting the importance of oxidative stress in chronic kidney disease (CKD) development, the therapeutic value of antioxidant interventions in reducing kidney damage and fibroblasts, is critical[36]. It has been shown that approaches based on ROS inhibition, like Nrf2 activation, natural products such as curcumin or resveratrol, or artificial antioxidants, e.g. bardoxolone methyl, are effective in attenuating oxidative damage, regulating inflammatory and fibrotic responses, and maintaining kidney function in a variety of animal models. These findings offer mechanistic information on the process through which antioxidants can disrupt the vicious cycle of ROS generation, inflammation and deposition of extra-cellular matrix that contributes to CKD development.

5.1 Interpretation and Analysis of Findings

In preclinical research, the Nrf2 activators have a permanent advantage of stimulating the endogenous antioxidant correlates and inhibiting the pro-inflammatory signal pathway, providing two-fold advantage in alleviating oxidative stress and fibrosis[37]. Besides neutralizing the free radicals, natural antioxidants modulate major signaling pathways including NF-kB, MAPK, and TGF- 0/ Smad which indicate that natural antioxidants exhibit pleiotropic actions beyond simply neutralizing the ROS. Synthetic antioxidants deliver precise, high-intensity interventions that have the potential to coordinate several pathways and it only serves to highlight the plausibility of pharmacologically managing oxidative stress in CKD. Together, these results can support the idea that antioxidant treatment may be used as an adjunctive measure along with the standard CKD therapies, which may be able to delay the disease and maintain the remaining renal activities.

5.2 Implications and Significance

The importance of the findings is in its potential clinical implication: addressing the problem of oxidative stress is one of the key pathological processes of CKD that is not completely regulated with the existing standard treatment. High-quality patient outcomes and improved quality of life may be achieved through antioxidant interventions, which can decrease the outbreak of CKD-related complications, including cardiovascular disease and ESRD[38]. Moreover, knowledge of the molecular pathways of antioxidant action can guide the creation of new, specific therapies that could be shaped to the conditions of the individual patient and provide a personalized intervention to CKD.

5.3 Gaps and Future Research Directions

Although the evidence on antioxidant therapy is encouraging at preclinical ology there are a number of gaps, which prevent the application of antioxidant therapy in clinical practice[39]. The differences in the bioavailability, pharmacokinetics, dosage, and length of treatment of antioxidant agents do not allow a direct extrapolation to the human population. Also, not all species respond to oxidative stresses and CKD pathophysiology in a similar way, which reduces the predictive capability of animal models. Human CKD can be comorbid with other

diseases, including diabetes, hypertension, cardiovascular disease, and this factor can affect the effectiveness of antioxidant interventions[40]. Research that is more rigorous such as clinical trials to determine safety, optimum dosing, and durability of antioxidants in various CKD groups should be conducted in the future. Continuing to study combination treatments, high-performance delivery methods to enhance bioavailability and stratified patient treatment depending on oxidative stress biomarkers can also increase the clinical relevance of antioxidant-based approaches.

6. CONCLUSION

The oxidative stress is a key factor in the pathogenesis and progression of chronic kidney disease, which initiates inflammation, tubular injury, and renal fibrosis. Preclinical data reveal that antioxidant interventions, such as Nrf2 activators, natural antioxidants (curcumin and resveratrol) and synthetic agents (bardoxolone methyl) are effective in reducing the effects of oxidative injury, preventing pro-inflammatory and pro-fibrotic signalling, and maintaining renal function in various CKD models. These results reveal the possibilities of antioxidant therapy as an addition to traditional therapies that provide mechanistic and therapeutic advantages and that focus on basic disease pathways. Nevertheless, limitations in bioavailability, species-specific variations, and inconsistencies in dosing and duration of treatment support the necessity of properly designed clinical trials to confirm efficacy, optimize regimens, and provide safe translation into clinical CKD management in the human population. In general, antioxidants are a promising adjunctive treatment that can delay CKD development, overcome renal fibrosis, and enhance patient outcomes, which is why the importance of further studies in this field should not be ignored.

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