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Renoprotective bioactives; evaluating the efficacy of nutraceuticals in mitigating inflammation and oxidative stress in chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) characterizes one of the most pressing public health challenges of the 21th century. This disease characterized by a progressive and often irreversible loss of kidney function and structure that terminates in end-stage renal disease (ESRD), that requiring dialysis or transplantation. The global prevalence of chronic renal failure continues to rise, driven largely by the epidemics of diabetes mellitus and hypertension, since the present standard of care remains primarily conducted on slowing progression rather than reversing damage. Although pharmacological interventions like renin-angiotensin-aldosterone system (RAAS) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors have demonstrated significant efficiency in maintaining glomerular filtration rate, a substantial residual risk remains for many patients. This therapeutic gap has prompted intense scientific interest in adjunctive therapies, particularly directing on the underlying molecular drivers of kidney injury. Amongst these drivers, chronic low-grade inflammation and oxidative stress stand out as central pathological mechanisms that stimulate the vicious cycle of nephron loss and fibrosis. Consequently, the exploration of kidney protective bioactives, generally categorized under the group of nutraceuticals that has identified as a hopeful frontier in nephrology. Additionally, these bioactive complexes, derived from food sources or herbal medicinal, present the capability to alter the intricate signaling pathways accompanying by kidney inflammation and redox imbalance, providing a complementary modality to standard pharmacotherapy.

Implication for health policy/practice/research/medical education:
Nutraceuticals, described as compounds that are frequently considered as the food or an active part of food, which provide medical or health benefits. These substances comprising disease prevention and treatment. Recently, these compounds have achieved substantial interest due to their potential physiological benefits and perceived safety. A balanced diet and supplementation can provide general health, counting the protection of renal function, and help to manage the main risk factors for kidney injury. In recent years, various naturally substances, have been proposed as therapeutic tools for chronic kidney disease patients, which also needs substantial consideration regarding their safety.

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Introduction

Chronic kidney disease (CKD) characterizes as a noteworthy global health challenge, considered by a progressive deterioration in renal function. This situation is principally driven by chronic illnesses like diabetes mellitus and high blood pressure (1). Previous authors found that, in developed countries diabetes, hypertension, and obesity are the main risk factors for CKD. The pathogenesis of CKD is complex, comprising oxidative stress, endoplasmic reticulum stress, metabolic disturbances, chronic inflammation and ferroptosis, all attributing to the irreversible loss of renal function (2). Despite optimal therapies, many patients eventually progress to end-stage renal disease (ESRD), necessitating

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dialysis or transplantation. Thereby, the development of novel CKD therapies is urgently needed due to the current treatments' ineffectiveness in improving kidney function for all patients (3). Nutraceuticals, as the bioactive compounds from food sources, show promise in countering these mechanisms through antioxidant and anti-inflammatory actions, potentially slowing CKD advancement without the side effects of pharmaceuticals. Nutraceuticals target core pathologies in CKD (4). Oxidative stress arises from excess reactive oxygen species (ROS) overwhelming antioxidants, damaging renal cells and promoting fibrosis. Recent studies demonstrated that, inflammation, fueled by some cytokines like tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), aggravates tubular damage and glomerular sclerosis (5). Accordingly, bioactives substances like polyphenols and CoQ10 (coenzyme Q10) neutralize ROS; inhibit nuclear factor-kappa B (NF-κB) pathways, across with boosting nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated defenses, which lead to preservation of glomerular filtration rate, along with reducing proteinuria (4). This review sought to discuss on the efficacy of nutraceuticals in mitigating inflammation and oxidative stress in chronic renal failure.

Search strategy

To identify relevant literature for this narrative review, we searched multiple databases, including PubMed, Scopus, Embase, Web of Science, EBSCO, DOAJ, and Google Scholar, using terms such as "nutraceuticals," "chronic kidney disease," "chronic inflammation," "oxidative stress," "end-stage renal disease," "glomerular filtration rate," "reactive oxygen species," and "antioxidants."

Role of oxidative stress in CKD

The renal system is a metabolic organ with significant oxygen utilization, affecting it inherently vulnerable to oxidative injury (6). In a healthy state, there is a fragile balance among the creation of ROS and the capacity of endogenous antioxidant systems, like glutathione peroxidase, superoxide dismutase and catalase to neutralize them. Conversely, in the state of chronic renal failure, this balance is overwhelmingly disturbed (7). In addition, the accumulation of uremic toxins, chronic activation of the immune system and metabolic acidosis direct to an overproduction of ROS. It should remember that, oxidative burden is not simply a byproduct of kidney injury but is an active participant in disease evolution (8). More recent studies detected that, ROS damage DNA, proteins and cellular lipids leading to podocyte damage, activation of profibrotic pathways and endothelial dysfunction (9). In parallel, oxidative stress acts as a strong stimulator for inflammation. In the next step, oxidative stress activates the NF-κB pathway, that acts as a master switch for the transcription of pro-inflammatory cytokines like TNF-α, IL-6 and IL-1 beta (IL-1β). These cytokines recruit immune cells to the kidney interstitium, provoking more tissue injury and scarring (10). Current studies have detected the impact of the NLRP3 (NOD-like receptor family pyrin domain-containing 3) inflammasome, as a multi-protein complex which acts as a sensor for cellular stress (11). In CKD, the activation of the NLRP3 inflammasome leads to the maturation of IL-1 beta and IL-18, driving pyroptosis, a form of inflammatory cell death that exacerbates renal injury (12). Therefore, any therapeutic agent capable of interrupting this nexus between oxidative stress, inflammasome activation, and inflammation holds significant renoprotective potential (13). Another key molecular target for mitigating oxidative stress in CKD is the nuclear factor erythroid-2 related factor 2 (NRF2) pathway (14). Previous studies confirmed that, NRF2 is a predominant transcription factor that regulates the expression of a wide array of genes responsible for encoding antioxidant proteins, thiol molecules and their generating enzymes, detoxifying enzymes, and stress response proteins. These proteins collectively counteract inflammatory and oxidative damage (15). Experimental evidence suggests that NRF2 signaling plays a protective role in renal injuries caused by various pathological conditions. Impaired NRF2 activity and subsequent repression of target genes have been observed in CKD animal models (16). Therefore, pharmacological intervention that activates NRF2 signaling can be beneficial in protecting against kidney dysfunction in CKD (16). Naturally occurring NRF2 activators, such as sulforaphane, resveratrol, curcumin, and cinnamic aldehyde, have shown renoprotective effects. These experimental results, coupled with clinical experiences with synthetic triterpenoids like bardoxolone methyl, offer hope for ameliorating CKD progression by preventing oxidative stress and maintaining cellular redox homeostasis (16). Therefore, nutraceuticals, with their diverse chemical structures and pleiotropic effects, are uniquely positioned to target these specific molecular nodes (16).

Administration of nutraceuticals in CKD

Among the various classes of nutraceuticals, polyphenols have gathered the most consideration for their potent antioxidant and anti-inflammatory capabilities (17). Curcumin, the primary bioactive compound found in the rhizome of Curcuma longa, or turmeric, serves as an example of a kidney protective bioactive with extensive preclinical validation (18). Previous investigations found that, curcumin acts by various mechanisms, most remarkably by activating the Nrf2 pathway. This pathway is responsible for upregulating the expression of endogenous antioxidant enzymes, thereby bolstering the kidney's intrinsic defense system against oxidative assault (19). In addition, curcumin inhibits the NF-κB signaling cascade, effectively reducing the production of inflammatory cytokines that drive kidney fibrosis. It also

suppresses the Transforming growth factor β (TGF-β)/ Smad signaling pathway, which is the crucial mediator of extracellular matrix accumulation and scarring in the kidney (20). Recent animal models of diabetic nephropathy and cisplatin-induced acute kidney injury have constantly discovered that curcumin supplementation can abolish proteinuria, lower serum creatinine concentration, and reduce pathological signs of glomerular sclerosis (18). Even so, the translation of these findings to human clinical trials are with several challenges. While previous studies indicated a decline in proteinuria and inflammatory markers in cases with lupus nephritis or diabetic kidney disease; importantly, the clinical effectiveness is often impeded by the compound's poor bioavailability (18). Besides, curcumin is rapidly metabolized and removed, which necessitates the use of specialized formulations, like those combined with piperine or encapsulated in liposomes, to achieve therapeutic concentrations in kidney tissue (21). In spite of these pharmacokinetic tasks, the safety profile of curcumin remains favorable, suggesting this compound as a valuable candidate for long-term adjunctive management (18). Similarly, resveratrol as a stilbenoid found in the skin of grapes, peanuts and berries represents another polyphenol with noteworthy capacity in the management of chronic renal failure (22). Like curcumin, resveratrol exerts its effects by the modulation of sirtuin 1, as a protein deacetylase implicated in cellular stress resistance and mitochondrial function (17). Following the activation of sirtuin 1, resveratrol strengthen mitochondrial biogenesis and effectiveness, diminishing the leakage of electrons that leads to superoxide formation. This mechanism is particularly relevant in diabetic nephropathy, where mitochondrial dysfunction is a hallmark of early damage (23). More recent preclinical investigations implies that resveratrol ameliorates glomerular hypertrophy and mesangial expansion, as the main aspects of diabetic kidney disease (24). The human investigations, clearly demonstrated that supplementation has been accompanied by amendments in parameters of oxidative stress, like malondialdehyde across with diminutions in systemic inflammation (17). Similar to curcumin, resveratrol suffers from low oral bioavailability and rapid glucuronidation (18). It is also imperative to note that high doses of resveratrol may interact with CYP (cytochrome P450) enzymes, potentially altering the metabolism of concomitant drugs commonly administered to CKD cases, like statins or calcium channel blockers (25). Though the mechanistic rationale of resveratrol is strong, clinical implementation necessitates exact dosing and monitoring. Moving beyond polyphenols, vitamins and essential fatty acids constitute another critical category of nutraceuticals evaluated for kidney protection (22). On the other hand, vitamin D, specifically its active form calcitriol, is well-known for its role in calcium and phosphate homeostasis, but it also possesses potent immunomodulatory properties (26). In the state of chronic renal failure, the conversion of vitamin D to its active form is disturbed due to the loss of renal 1-alpha-hydroxylase activity, directing to the state of deficiency that exacerbates inflammation and fibrosis (27). Accordingly, supplementation with nutritional vitamin D, either as ergocalciferol or cholecalciferol, or its analogs has been indicated to suppress the renin-angiotensin system and decrease the expression of TGF-β, as a main mediator of kidney scarring (28). Clinical trials have demonstrated that correcting vitamin D deficiency in CKD patients can lead to a reduction in proteinuria and a stabilization of glomerular filtration rate (29). However, the therapeutic window is narrow, and excessive supplementation carries the risk of hypercalcemia and vascular calcification, which are already heightened risks in the CKD population (30). Therefore, the administration of vitamin D as a nutraceutical must be strictly guided by serum levels and mineral metabolism parameters (31). Similarly, vitamin E, a fat-soluble antioxidant, has been investigated for its ability to protect cell membranes from lipid peroxidation (32). Given that, early studies suggested benefits in reducing oxidative stress markers, however large-scale randomized controlled trials have yielded mixed results regarding hard renal outcomes (33). Some studies suggest a modest benefit in slowing the progression of diabetic nephropathy, particularly when combined with other antioxidants, nevertheless it is not universally recommended as a standalone therapy for all CKD patients (34). Numerous studies demonstrated that, omega-3 polyunsaturated fatty acids, primarily eicosapentaenoic acid and docosahexaenoic acid which are found in fish oil, offer a distinct mechanism of action focused on lipid mediation and inflammation resolution (35). Chronic renal failure is often associated with a pro-inflammatory lipid profile, and omega-3 fatty acids serve as precursors to specialized pro-resolving mediators that actively terminate the inflammatory response rather than merely suppressing it (36). By incorporating into cell membranes, omega-3s alter the production of eicosanoids, shifting the balance from pro-inflammatory prostaglandins to less inflammatory variants (37). Clinical evidence supports the administration of omega-3 supplementation in reducing triglyceride levels and potentially slowing the decline of renal function in patients with IgA nephropathy, a specific type of glomerulonephritis. In this context, omega-3s have been shown to reduce proteinuria and preserve kidney function over several years (38,39). Though, in broader CKD populations, like those with diabetic nephropathy, the results are less consistent. Since, cardiovascular benefits of this compound are well-established, the direct kidney protective effects appear to be disease-specific (39). Notably, high doses of fish oil can increase the risk of bleeding, which is a consideration for CKD patients who may already have platelet dysfunction or are on antiplatelet therapy (40). Despite these caveats,

the favorable safety profile and cardiovascular benefits make omega-3 fatty acids a reasonable consideration in the nutritional management of CKD, predominantly for individuals with concurrent hypertriglyceridemia (41). In addition to isolated compounds, medicinal plants and traditional botanicals have been utilized for centuries to support renal health, though their integration into modern nephrology requires rigorous scrutiny (42). In this regard, Astragalus membranaceus, a staple in traditional Chinese medicine, contains bioactive saponins and polysaccharides that have established immunomodulatory and antifibrotic effectivity (43). Previous studies implied that Astragalus diminishes proteinuria and ameliorated serum albumin levels in patients with chronic glomerulonephritis. The proposed mechanisms include the inhibition of podocyte apoptosis and the suppression of collagen deposition in the renal interstitium (44). Likewise, *Cordyceps sinensis*, as a medicinal fungus, is another botanical that has detected hopeful in improving energy metabolism and decreasing kidney fibrosis in animal models (45). Human trials suggest potential benefits in stabilizing creatinine levels and improving anemia in renal failure cases, possibly through the stimulation of erythropoietin production (45,46). However, the use of herbal nutraceuticals carries inherent risks that cannot be overlooked. The lack of standardization in herbal preparations implies that the concentration of active bioactives can vary widely between batches. More critically, some medicinal plants contain nephrotoxic compounds, like aristolochic acid, which can cause rapid and irreversible renal failure (47,48). Even benign-appearing herbs can interact with prescription medications; for instance, St. John's Wort induces CYP enzymes and can decrease the efficacy of immunosuppressants in transplant recipients (49). Hence, the evaluation of herbal bioactives must prioritize safety and standardization, ensuring that products are free from contaminants and heavy metals, which CKD individuals are less able to excrete (50,51).

Focus on gut-kidney axis

A relatively newer and substantially encouraging line in the field of nutraceuticals consist of modulation of the gut-kidney axis (52). The intestinal microbiome plays a pivotal role in the generation of uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, which are protein-bound solutes that accumulate in CKD and contribute significantly to oxidative stress and endothelial damage. These toxins are produced by gut bacteria from the fermentation of dietary proteins (53). Nutraceuticals in the form of prebiotics, probiotics, and synbiotics aim to alter the composition of the gut microbiota to reduce the production of these harmful metabolites (54). Prebiotics, such as resistant starch and inulin, serve as fuel for beneficial bacteria, promoting the growth of species that produce short-chain fatty acids like butyrate, which have anti-inflammatory properties and strengthen the gut barrier (55). Probiotics introduce live beneficial bacteria, with strains such as Lactobacillus and Bifidobacterium being the most commonly studied, that can compete with toxin-producing strains (56). Clinical trials investigating synbiotic supplementation in CKD patients have shown reductions in serum levels of indoxyl sulfate and p-cresyl sulfate, accompanied by improvements in markers of inflammation and oxidative stress (57). Recent studies also report a modest improvement in glomerular filtration rate and quality of life. This approach is particularly attractive because it addresses the source of the toxins rather than just attempting to filter them out by dialysis (57).

Nevertheless, this topic is still young, and issues exist about the particular strains of bacteria that are most effectual, the optimal dosage, and the long-term sustainability of microbiome changes (58). Furthermore, in advanced CKD, the dysbiotic gut environment may impair probiotic colonization, suggesting that dietary interventions to support microbial ecology may be equally critical as direct probiotic supplementation (59).

Concerns on the bioavailability, standardization and safety

In spite of the compelling mechanistic evidence and promising initial clinical data, the widespread adoption of nutraceuticals in CKD management features substantial difficulties, primarily concerning bioavailability, standardization, and safety (4). In fact, numerous bioactive compounds have poor absorption rates and are rapidly metabolized by the liver and gut, which limiting the quantity that actually reaches the renal tissue (60). In this regard, nanotechnology and innovative delivery systems are being progressed to improve bioavailability. However, these technologies add to the cost and complexity of the supplements. Standardization is another critical issue (61). Unlike pharmaceutical drugs, which are synthesized to exact specifications, nutraceuticals derived from herbs can alter in effectiveness based on soil conditions, harvest time, and processing methods. This variability makes it difficult to reproduce clinical trial results in practical settings (50). Safety is perhaps the most important concern. It should remember that, the renal system is the primary organ for excreting waste products, since in chronic renal failure, this excretory function is disturbed. Accordingly, molecules which are harmless to healthy individuals can accumulate to toxic levels in individuals with diminished glomerular filtration (62). As an example, some herbal supplements are high in potassium, posing a risk of life-threatening hyperkalemia in chronic renal failure cases (63). Moreover, the possibility for drug-nutrient interactions is elevated, as many renal failure cases are on complex medication regimens containing antihypertensive medications, anticoagulants, and phosphate binder agents (64). Indeed, a nutraceutical that induces or inhibits drug-metabolizing enzymes may modify the therapeutic levels of these critical medications,

directing to treatment failure or toxicity (65). Regulatory oversight of nutraceuticals also lags behind that of pharmaceuticals (66). Thereby, for nephrologist and patients, this situation makes a background of uncertainty. Hence, rigorous, large-scale, randomized controlled trials are crucial to verify definitive dosing guidelines, and to recognize which patient subgroups benefit most, and confirm long-term safety (67). Most existing studies are small, short-term, or conducted in animal models, which limits the strength of the recommendations that can be made. Consequently, next investigations should emphasis on personalized nutrition, identifying that the effectiveness of a nutraceutical may depend on the patient's genetic makeup, the stage of their renal disease, and their specific underlying etiology (68). Remarkably, an individual with diabetic kidney disease driven by oxidative stress might benefit more from a polyphenol-rich regimen, while a patient with inflammation driven by gut dysbiosis might respond better to synbiotics. Thus, integrating nutrigenomics into CKD management could permit for tailored nutraceutical prescriptions that maximize efficiency while minimizing risk (69).

Conclusion

Taken together, the impact of kidney protective bioactives in diminishing inflammation and oxidative stress in chronic renal failure signifies a paradigm shift towards integrative nephrology. The pathological basis of chronic renal failure is described by a self-perpetuating cycle of oxidative damage and inflammatory signaling that conventional therapies only partially address. Recently, nutraceuticals, ranging from polyphenols like curcumin and resveratrol to essential nutrients such as vitamin D and omega-3 fatty acids, present a multiple approach to interrupting this cycle. These compounds act as antioxidants that strengthen endogenous defense systems. Nonetheless, issues of bioavailability, product standardization, potential nephrotoxicity, and drug interactions require cautions and evidence-based approach. Importantly, individuals should not view nutraceuticals as a replacement for established medical treatment but rather as a complementary modality to be implemented under medical supervision. Therefore, information on the complex interactions between diet, bioactives, and kidney physiology is mandatory for safe, effective, and personalized nutraceutical treatments. Finally, our target is to extend the quality and quantity of life for CKD cases by keeping residual kidney function by a complete management approach that devotes the ameliorative impact of nature's bioactives alongside the precision of modern medicine.

Authors' contribution

Conceptualization: Hussein S Janabi, Abdul Amir H. Kadhum, Hussein Ali Al-Bahrani.
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Writing–review and editing: Hussein S Janabi, Abdul Amir H. Kadhum, Hussein Ali Al-Bahrani.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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