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Role of Dietary Antioxidant Agents in Chronic Kidney Disease

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Additional information is available at the end of the chapter

Abstract

Chronic kidney disease (CKD) is defined as the atrophy of the kidney or progressive decline of renal function mainly caused by chronic diseases such as diabetes mellitus and hypertension. CKD affects more than 10% of the world's population. Moreover, there is no single treatment to improve kidney function in CKD patients. Consequently, this condition is considered a worldwide public health problem. The development of novel CKD therapies is highly needed because current treatment methods are ineffective. Since oxidative stress plays a critical role in CKD, the study of the effect of antioxidants in this pathology is highly important. Dietary antioxidant agents have shown protective effects in CKD. Hence, they may be key for the development of feasible therapies. The aim of this chapter is to provide recent information about the therapeutic role of dietary antioxidants in experimental models of CKD and clinical trials, as well as to describe the mechanisms through which antioxidants exert nephroprotection. The dietary antioxidants revised in this chapter are curcumin, sulforaphane, resveratrol, quercetin, proanthocyanidins, flavan-3-ols, soy protein, red propolis, and Mediterranean diet.

Keywords: natural compounds, chronic kidney disease, diabetic nephropathy, oxidative stress, inflammation

1. Introduction

1.1. Function of the kidney

The aim of this overview on kidney function is to introduce readers unfamiliar with renal physiology to basic principles that are required for a better understanding of chronic kidney disease (CKD). A detailed and state-of-the-art description of the morphology and function of the kidneys and the structure of the nephrons can be found in standard handbooks of renal physiology [1, 2].

Human kidney contains around 1–3 millions of functioning units called nephrons. Each nephron consists of a glomerulus and a tubular system. The glomerulus filters the blood free of cells and large proteins (filtration), and produces an ultrafiltrate composed of small circulating elements. The ultrafiltrate enters the tubule, which is highly specialized at various segments, to produce the final urine by removing substances from the tubular fluid
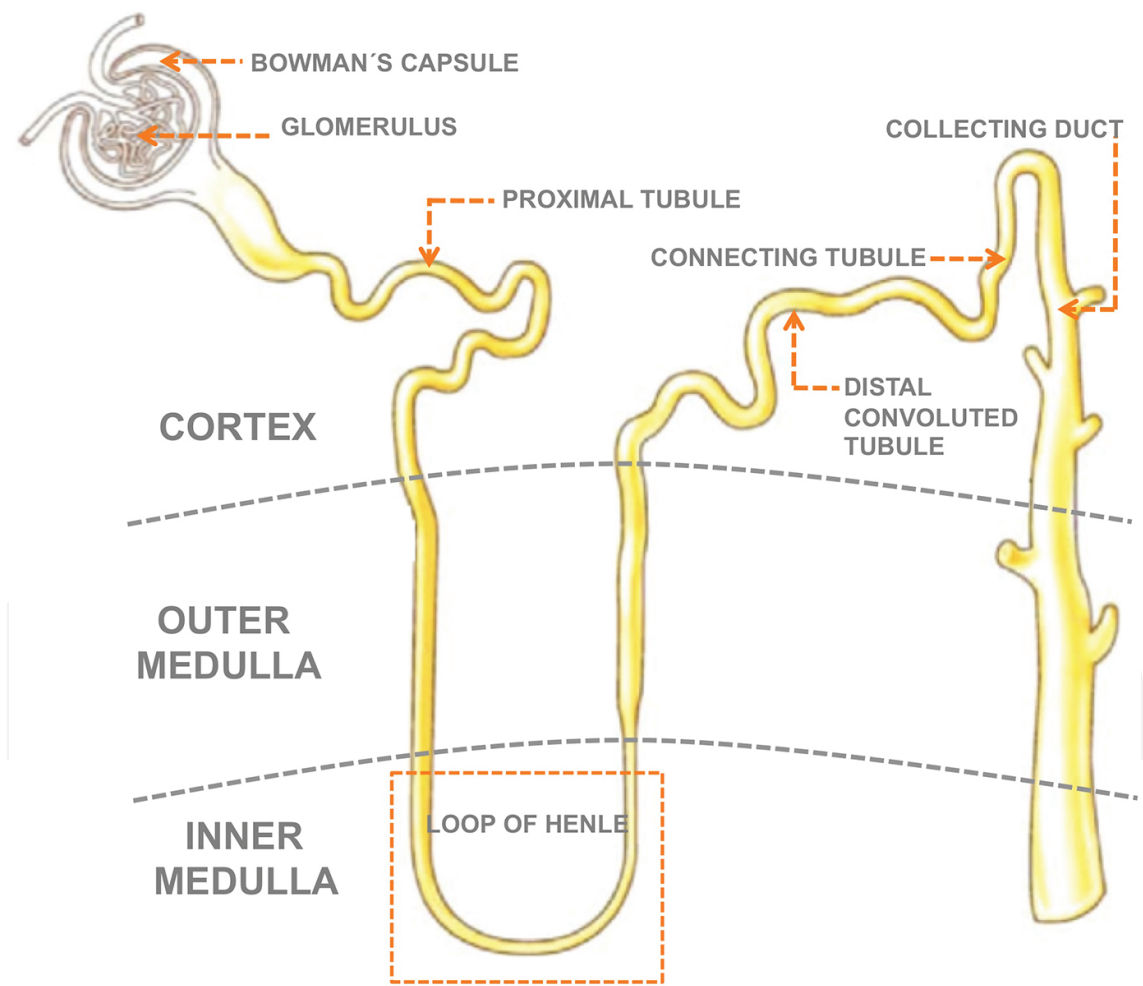
Figure 1. Structure of the nephron. Nephrons are constituted by glomeruli and the tubular system which encompasses the proximal tubule, the loop of Henle, the distal convoluted and connecting tubules and the collecting duct. Macroscopically nephrons can be divided into cortex, outer and inner medulla.

(reabsorption) or adding substances to the tubular fluid (secretion). Filtration, reabsorption, and secretion keep the organism in balance in terms of water, minerals, electrolytes, and hydrogen ion concentration and eliminate the toxic substances produced by the body.

Plasma is constantly equilibrated with the interstitial fluid of the extracellular space and with the intracellular space. Organs such as kidneys, lungs, and intestine maintain the physiological composition of the body fluids of mammals. The kidney carries out this process through the excretion of xenobiotics, solutes, water, and metabolic wastes by producing the urine. In the kidney, blood is filtered through the glomerulus, which is a capillary network composed of endothelial and mesangial cells and podocytes; this process is called ultrafiltration, whose driving force depends on blood pressure and filtration pressure in the glomerular capillaries. Filtered water and solutes still of use for the body are efficiently recycled to the circulation by obligatory and regulated reabsorptive processes in the tubular sections of the nephrons.

Primary ultrafiltrate contains essential nutrients and electrolytes that need to be actively reabsorbed to avoid critical losses and ensuing deficiencies. On the contrary, the kidney actively secretes some metabolic wastes since their rate of production exceeds their rate of glomerular filtration. All these selective processes are carried out by the nephrons, epithelial tubular structures that consist of several interconnected segments with specific morphological and functional characteristics, the proximal tubule (PT) with its convoluted segments S1 and S2 (proximal convoluted tubule, PCT) and straight segment S3, the loop of Henle (LOH), the distal tubule (DT) with its convoluted segment (distal convoluted tubule, DCT) and connecting tubule, and finally the collecting duct (CD) (**Figure 1**).

By these means, about 180 L of primary filtrate is generated every day to produce about 1–3 L of final urine. This indicates that about 99% of the primary urine is reabsorbed along the more than two million nephrons.

1.2. Chronic kidney disease

CKD is defined as the atrophy of the kidney or progressive decline of renal function [3]. CKD affects more than 10% of the world population [4]. Furthermore, treatment methods such as dialysis or transplantation are expensive or ineffective; therefore, this condition is considered a public health problem [5]. Renal dysfunction can be identified when the glomerular filtration rate (GFR) is below 60 mL/min/1.73 m^2 for more than 3 months and when albuminuria, defined as an albumin-to-creatinine ratio above 30 mg/g per day, is present [5].

Among different factors that induce CKD, diabetes mellitus and hypertension are the most important causes of this pathology [6]. Diabetic nephropathy (DN) is the main microvascular complication of diabetes often leading to CKD. As a matter of fact, DN is the main cause of dialysis admissions (34% of admissions) [7]. DN occurs when high blood glucose concentrations impair the function of renal blood vessels and glomerular and epithelial tubular cells [8]. Hypertension is the second leading cause of CKD [9]. Hypertensive nephropathy patients are advised to maintain their blood pressure to 130/80 mm Hg to prevent CKD development [10]. Several mechanisms are involved in CKD pathogenesis; some of them include inflammation, glomerulosclerosis, tubulointerstitial fibrosis, and mainly oxidative stress [11]. Oxidative

stress is a common phenomenon in CKD lesions, and it is considered to play a critical role in both the progression of CKD and related complications [12–15]. There is no single treatment to improve kidney function in CKD. Approaches to retard the progression of this disease are limited to normalization of blood pressure, blood glucose, and insulin. In this context, several antioxidants have been tested in CKD studies.

1.3. Oxidative stress

An imbalance between reactive oxygen (ROS) and nitrogen (RNS) species and cellular antioxidants, in favor of oxidant species, is termed oxidative stress [16, 17].

Oxidant formation is physiologically important in the process of tissue repair as a result of inflammation and in the self-defense mechanism against microorganisms and other foreign antigens. However, when this process occurs in chronic pathological conditions, such as CKD, it has a detrimental effect and contributes to cell and tissue damage.

ROS are produced when oxygen is partially reduced. Some ROS are free radicals as they have an unpaired electron in their outer orbit. Free radicals include superoxide ($O_2^{\bullet-}$) and hydroxyl ($^{\bullet}OH$) radicals while non-radicals include hydrogen peroxide (H_2O_2), and singlet oxygen ($^1\Delta_g O_2$). Sources of ROS include the mitochondrial electron transport chain, endothelial cells (xanthine oxidase reaction), inflammatory cells (myeloperoxidase and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase), catecholamine oxidation, and metabolism of arachidonic acid. The physiological formation of ROS is detoxified by endogenous antioxidants, which are classified into two types: enzymatic and non-enzymatic. Enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and glutathione S-transferase (GST). Glutathione (GSH) is the most abundant nonenzymatic antioxidant in the cell. Also, exogenous antioxidants obtained from daily food intake are classified as nonenzymatic antioxidants, which can be hydrophilic (ascorbic acid/vitamin C and flavonoids) or lipophilic (α-tocopherol/vitamin E and carotenoids).

Oxidative stress plays a critical role in CKD progression, directly by inducing glomerular and tubular damage or indirectly associated with inflammation, hypertension, and/or endothelial dysfunction [17]. Factors that cause oxidative stress are activation of NADPH oxidases, uncoupled endothelial nitric oxide synthase and mitochondrial dysfunction together with decreased antioxidant defenses such as decreased expression and activity of antioxidant enzymes and intracellular GSH content. In this context, ROS oxidize a wide variety of cellular components such as lipids, proteins, carbohydrates, and nucleic acids. Hence, the products of oxidant damage can be used as markers of oxidative stress. In fact, in patients with CKD, increased products of low-density lipoprotein (LDL) oxidation (ox-LDL) and levels of thiobarbituric acid-reactive substances (TBARS), which are markers of lipid peroxidation, have been found [18]. Antioxidants are widely used as a therapy to reduce oxidative stress. Therefore, the aim of this chapter is to provide recent information about the therapeutic role of dietary antioxidants in experimental models of CKD and clinical trials, as well as to describe the mechanisms through which antioxidants exert nephroprotection.

2. Dietary antioxidants

Dietary antioxidants encompass a wide range of molecules. The structures of some of the antioxidants reviewed in this chapter are shown in **Figure 2**. In addition, a scheme summarizing the mechanism of action of dietary compounds and their antioxidant properties in CKD is shown in **Figure 3**.
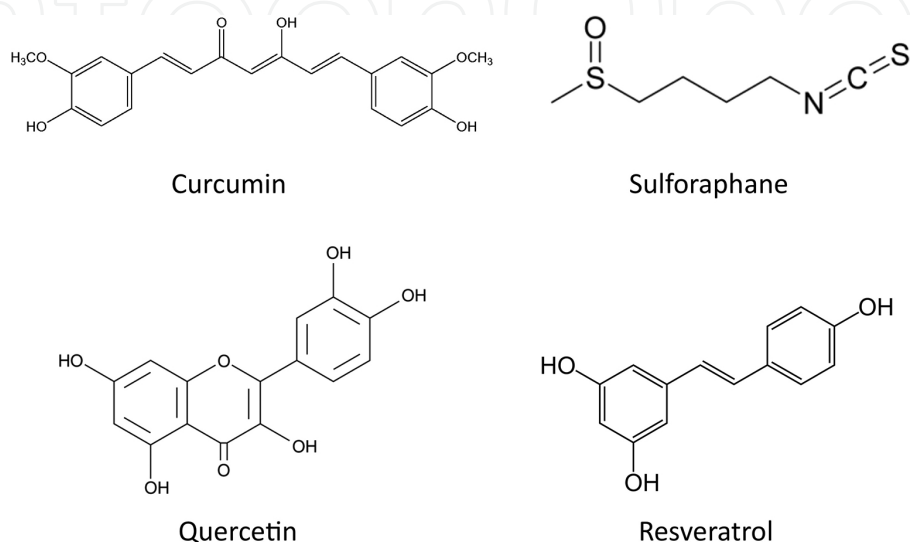

Figure 2. Molecular structure of the dietary antioxidants curcumin, sulforaphane, quercetin, and resveratrol.
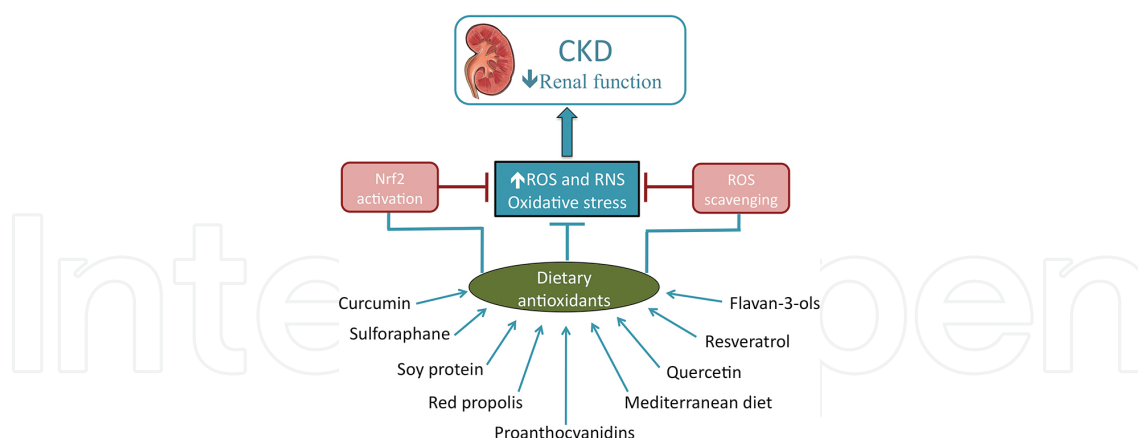

Figure 3. Beneficial properties of dietary antioxidants and its role in chronic kidney disease (CKD). Dietary compounds decrease renal dysfunction in CKD by inducing Nrf2 nuclear localization and scavenging reactive oxygen species (ROS) decreasing oxidative stress. Nrf2, nuclear factor E2-related factor 2; RNS, reactive nitrogen species.

2.1. Curcumin

Curcumin is the main curcuminoid found in turmeric (*Curcuma longa*), which is used as a spice or food colorant in curry, mustard, cheese, yogurt, soups, and cereals [19]. Curcumin is

classified as a bifunctional antioxidant agent due to its ability to scavenge ROS and to modulate cellular localization of nuclear factor E2-related factor 2 (Nrf2). Curcumin is able to scavenge superoxide anion ($O_2^-\cdot$) [20–22], hydroxyl radicals ($\cdot$OH) [22, 23], H_2O_2 [20, 22, 23], singlet oxygen [22, 24], nitric oxide [25, 26], peroxynitrite [22, 27], and peroxyl radicals (ROO$\cdot$) [22, 23].

Curcumin also exhibits anti-inflammatory properties [28, 29]. One of the main targets of curcumin are the pro-inflammatory transcriptional factors, such as nuclear factor (NF)-κB and activator protein (AP)-1, which have an important role in mediating inflammatory responses by modulating the production of pro-inflammatory cytokines [30].

Curcumin has been reported to reverse 5/6 nephrectomy (5/6 Nx)-induced damage in rats. Curcumin administration (120 mg/kg) 30 days after 5/6 Nx from day 31 to 60 was reported to reverse glomerular hypertension and hyperfiltration, induce cell proliferation and nuclear localization of Nrf2, and ameliorate 5/6 Nx-induced oxidative stress and decrease in antioxidant enzymes [31]. Moreover, curcumin administration (75 mg/kg) 7 days after 5/6 Nx for 9 weeks was reported to decrease blood urea nitrogen (BUN) and plasma creatinine levels, and attenuate proteinuria, segmental sclerosis, and tubular dilatation [32]. Furthermore, curcumin administration (60 mg/kg) for 7 days before and 30 days after 5/6 Nx was reported to attenuate proteinuria, systemic and glomerular hypertension, hyperfiltration, glomerular sclerosis, interstitial fibrosis, interstitial inflammation, and increased plasma creatinine and BUN. These effects were associated with Nrf2 nuclear translocation [33]. In addition, curcumin (75 mg/kg) administration 2 weeks after surgery for 11 weeks was also reported to decrease BUN and plasma creatinine levels, as well as ameliorate proteinuria [34].

Curcumin has also been reported to exert nephroprotection in DN models [29]. Sharma et al. [35] evaluated the effect of curcumin on renal function and oxidative stress in streptozotocin (STZ)-induced diabetic rats. Rats were given curcumin (15 or 30 mg/kg) 4 weeks after STZ administration for 2 weeks. STZ-induced diabetic rats showed polyuria, increased blood glucose, and decreased body weight compared with age-matched control rats. After 6 weeks, diabetic rats also exhibited renal dysfunction, as evidenced by reduced creatinine and urea clearance and increased proteinuria, along with a marked increase in oxidative stress, as determined by lipid peroxidation and activities of antioxidant enzymes. Curcumin was able to ameliorate both renal dysfunction and oxidative stress in diabetic rats [35].

Moreover, clinical trials have been conducted to evaluate the effect of turmeric on DN [36, 37]. In a randomized, double-blind and placebo-controlled study, patients with DN received turmeric (22.1 mg of curcumin, three times a day) for 2 months. Serum levels of transforming growth factor-β (TGF-β) and interleukin-8 (IL-8), and urinary levels of IL-8 were significantly decreased after turmeric supplementation. Moreover, proteinuria in DN patients was effectively improved by turmeric without adverse effects [36].

In another randomized, double-blind, and placebo-controlled study, patients under hemodialysis were randomly divided into control and trial groups [37]. Trial group received turmeric (22.1 mg of curcumin, three times a day) for 8 weeks, whereas control group received starch. Patients in both groups also received Nephrovit tablet as a previous regimen at least for 3 months. Plasma malondialdehyde (MDA) level decreased in both groups, the ratio of

decrease was significantly higher in the trial group. Activities of GPx, GR and CAT in red blood cells increased in both groups, the ratio of CAT increment was significantly higher in the trial group. Furthermore, a significant increment in albumin plasma level in the trial group was observed [37]. Therefore, turmeric attenuates oxidative stress and renal damage in hemodialysis patients.

2.2. Sulforaphane

Sulforaphane (SFN) is a naturally occurring isothiocyanate synthesized by the enzymatic action of myrosinase on glucoraphanin, a glucosinolate found in cruciferous vegetables of the genus Brassica as broccoli, brussel sprouts, mustard, cabbage, and cress [34]. SFN is classified as an indirect antioxidant agent due to its ability to increase Nrf2 nuclear localization. It has been proposed that Nrf2 activation may occur by disruption of interactions between Nrf2 and Kelch-like ECH-associated protein (Keap)-1 or by mitogen-activated protein kinases (MAPK) pathways activation [38–40].

The renoprotective effect of SFN has been evidenced in several *in vivo* studies [41–44]. In a STZ-induced diabetic mouse model, SFN treatment (started 2 weeks after STZ injection) was reported to improve metabolic dysfunction associated with diabetes, albuminuria, and glomerular sclerosis. This study further revealed that SFN attenuates high glucose-induced mesangial cell hypertrophy by Nrf2-mediated TGF-β signaling repression [41]. In addition, SFN administration (0.5 mg/kg) for 3 months was reported to prevent STZ-induced renal fibrosis and increment in albumin-to-creatinine ratio [42]. Moreover, SFN has shown beneficial effects in the unilateral ureteral obstruction (UUO) model. In rats, SFN was reported to preserve Nrf2 levels and attenuate mitochondrial-induced oxidative damage and renal fibrosis [43]. An additional study of UUO in rats showed that structural renal damage was improved by SFN treatment [44].

2.3. Quercetin

Quercetin is the main flavonol in human nutrition [45]. Quercetin is present in nuts, red onions, grapes, berries, citrus fruits, tea, pepper, coriander, fennel, radish, broccoli, tomatoes, apples, and red wine [46, 47]. Quercetin is a potent natural antioxidant and scavenger of ROS and RNS [48, 49].

The effect of quercetin in the STZ-induced diabetic rat model was evaluated. Four weeks after STZ injection, quercetin (10 mg/kg) was given orally for 4 weeks. At the end of the experiment, quercetin treatment reduced proteinuria, serum creatinine, and BUN [50]. Gomes et al. [51] evaluated whether quercetin could also have beneficial effects in concurrent STZ-induced DN and spontaneous atherosclerosis, using apolipoprotein E-deficient mice (apoE (−/−)). Six weeks after STZ or vehicle injection, mice were randomly divided into control mice, diabetic apoE (−/−) mice, and diabetic apoE (−/−) + quercetin (10 mg/kg) mice. Quercetin treatment diminished polyuria and glycemia, and normalized hypertriglyceridemia. Moreover, quercetin decreased serum creatinine and proteinuria. Furthermore, protective effects on renal structural changes, as normalization of the index of glomerulosclerosis

and kidney weight/body weight, were observed. Thus, quercetin could be a therapeutic option for DN, including diabetes-associated dyslipidemia [51].

2.4. Resveratrol

Resveratrol (RSV) is a polyphenolic compound found in berries, nuts, peanuts, grapes, red wine, coffee, legumes, and chocolate [52]. RSV is classified as a bifunctional antioxidant agent; it is able to scavenge $^{\bullet}OH$, $O_2^{\bullet-}$ and metal-induced radicals [53] as well as induce gene expression of antioxidant enzymes, such as SOD and GPx [54].

Sharma et al. [55] evaluated RSV effect on renal function and oxidative stress in STZ-induced diabetic rats. Rats were divided into four groups: control, diabetes, and diabetes + RSV (5 or 10 mg/kg) groups. Four weeks after STZ injection, RSV was administered from week 4 to 6. STZ-induced diabetic rats showed polyuria, an increase in blood glucose and a decrease in body weight. After 6 weeks, diabetic rats also exhibited renal dysfunction, as evidenced by reduced creatinine and urea clearance and increased proteinuria along with enhanced oxidative stress, as evidenced by increased MDA and decreased GSH level and SOD and CAT activities. RSV treatment significantly attenuated renal dysfunction and oxidative stress [55].

RSV effect on renal fibrosis induced by UUO was evaluated in mice by Liang et al. [56]. Mice were divided into three groups: control, UUO, and UUO + RSV (20 mg/kg) groups. RSV treatment attenuated renal injury including extracellular matrix deposition and tubulointerstitial damage. Renal cortical mRNA levels of intercellular adhesion molecule (ICAM)-1, tumor necrosis factor (TNF)-α, and TGF-β, protein expression of fibronectin, and mothers against decapentaplegic homolog 3 (Smad3) acetylation were significantly upregulated in the UUO group. RSV treatment decreased the expression of these proteins. Furthermore, RSV increased SOD activity and decreased MDA and 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels [56].

There is no clinical evidence showing RSV effects on CKD; however, several studies suggest it may exert beneficial effects on CKD patients. RSV supplementation in type 2 diabetic patients reduced insulin resistance and urinary excretion of ortho-tyrosine, a marker of oxidative stress [57]. Moreover, dietary supplementation with red grape juice exerted antioxidative and anti-inflammatory effects in hemodialysis patients [58, 59]. In 2006, red grape juice supplementation was reported to increase antioxidant capacity of plasma and decrease oxidized LDL and monocyte chemoattractant protein-1, an inflammatory biomarker, concentration in plasma [58]. Furthermore, in 2008, red grape juice supplementation was reported to decrease the neutrophil NADPH oxidase activity [58].

2.5. Proanthocyanidins

Proanthocyanidins are flavonoids found in cinnamon, sorghum, red wine, chocolate, berries, plums, apples, nuts, and grapes [52]. Anti-inflammatory and antioxidant properties have been attributed to proanthocyanidins [60].

The associations between habitual proanthocyanidin intake, renal function, and the risk of clinical renal outcomes in elderly women were studied by Ivey et al. [61]. Women aged over

75 years old, free of prevalent renal disease at baseline, were selected for this study. Proantho-cyanidin intake was determined using a food frequency questionnaire and the US Department of Agriculture proanthocyanidin food content database. Fasting serum cystatin C and creatinine were assessed at baseline. Renal failure hospitalizations and deaths were assessed over 5 years of follow-up. Participants in the highest tertile of proanthocyanidin intake had a 9% lower cystatin C concentration than participants with lower proanthocyanidin consumption. High proanthocyanidin consumers were at 50% lower risk of moderate chronic kidney insufficiency, and 65% lower risk of experiencing a 5-year renal disease event. Therefore, a high proanthocyanidin intake is associated with renal health preservation [61].

Recently, the effect of grape seed proanthocyanidin extract (GSPE) on renal injury in type 2 diabetic rats was evaluated [62]. Rats were divided into control and diabetic groups; this later was induced diabetes by a high-carbohydrate/high-fat diet and a low STZ dose. Diabetic rats were further divided into control and three experimental groups. Experimental groups received 125, 250, or 500 mg/kg bw of GSPE. After 16 weeks, GSPE administration increased body weight and decreased food and water consumption, and urine volume in rats. Diabetic rats treated with GSPE showed decreased fasting blood glucose, serum insulin, glycated hemoglobin (HbA1c), and systolic blood pressure. GSPE significantly improved renal function parameters, reduced the expression of tissue inhibitor of metalloproteinase 1 and also increased the activity of matrix metalloproteinase 9. Furthermore, GSPE increased the activity of antioxidant enzymes and reduced the levels of C reactive protein (CRP) in the serum and the expression of TNFα, monocyte chemoattractant protein 1, and ICAM1 in the kidney. Hence, the GSPE protective effect on renal injury in type 2 diabetic rats might be associated with decreased renal inflammation and oxidative stress [62].

2.6. Flavan-3-ols

Flavan-3-ols are naturally occurring flavonoids. Epigallocatechin-3-gallate (EGCG) and catechin are flavan-3-ols whose effect has been evaluated in CKD models. EGCG is found in green tea, berries, red grapes, plums, apples, and peaches, whereas catechins are found in tea, cacao, red wine, and fruit [52].

Nakagawa et al. [63] evaluated the effect of EGCG on methylguanidine (MG) production in adenine-induced CKD rats. MG is a strong uremic toxin produced from creatinine. Under CKD conditions, MG synthesis increases. Rats were divided into control and CKD groups; CKD group was fed a 0.75% adenine diet. After 25 days, BUN levels were measured, and rats with CKD were divided into five groups. Control group was divided into two groups. Four CKD groups were given water or EGCG (20, 100, and 500 mg/kg bw) orally 30 min before and after creatinine intraperitoneal injection (100 mg/100 g bw). One group of normal rats also received creatinine injections (100 mg/100 g bw) and water was given orally 30 min before and after creatinine injection. One CKD and one control group received water 30 min before and after physiological saline injection. MG production was significantly increased in rats with adenine-induced CKD. However, EGCG administration inhibited MG production [63].

Furthermore, Yamabe et al. [64] evaluated the effect of oral EGCG (25, 50, or 100 mg/kg) administration in rats with subtotal nephrectomy plus STZ-injection. After a 50-day adminis-

tration period, rats treated with EGCG showed suppressed hyperglycemia, proteinuria, and lipid peroxidation; however, there were only weak effects on the levels of serum creatinine and glycosylated protein. Further, EGCG reduced the renal accumulation of advanced glycation end-product and its related protein expression in the kidney cortex as well as associated pathological conditions [64].

Varatharajan et al. [65] evaluated the antioxidant and pro-oxidant effects of catechins-rich oil palm leaves extract (OPLE) on DN. Rats were divided into control, diabetes, and diabetes + OPLE groups. Diabetes and diabetes + OPLE groups were administered an intraperitoneal STZ injection. Seventy-two hours later, OPLE group received 1000 mg/kg of OPLE for 4 or 12 weeks. OPLE administration for 4 weeks attenuated renal dysfunction (hyperfiltration and proteinuria) and the development of glomerulosclerosis and tubulointerstitial fibrosis. Suppression of increased oxidative stress markers (8-OHdG and lipid peroxides) and the fibrotic cytokine, TGF-β1, was observed. OPLE also reduced renal expression of NADPH oxidase subunits p22^{phox} and p67^{phox}. Surprisingly, identical dose of OPLE when administered to diabetic animals for 12 weeks caused worsening of renal dysfunction and elevation of lipid peroxides and TGF-β1. These unfavorable effects were accompanied by increased expression of p22^{phox}. Therefore, OPLE exerts both antioxidant and pro-oxidant effects in DN depending on the duration of the treatment [65].

2.7. Soy protein

Soy has a high biologic value due to its essential amino acids, biologic active peptides, and nonprotein compounds, such as isoflavones, content.

Azadbakht and Esmaillzadeh [66] evaluated the effect of soy protein consumption on DN patients. A crossover clinical trial was conducted among 14 patients. One diet included 0.8 g/kg of protein of which 70% was animal protein and 30% vegetable protein. The other diet included the same protein amount of which 35% was animal protein, 35% soy protein, and 30% other vegetables protein. Both diets were prescribed in each phase of the trial for 7 weeks. There was a 4-week washout between the two phases of the study. As showed by the results, soy protein consumption was able to reduce proteinuria in DN patients [66].

Yeh et al. [67] investigated the effect of soybean β-conglycinin on DN. Forty rats were induced diabetes by STZ intravenous injection. Then, rats were divided into five groups: control group fed with standard diet and four groups fed with NaCl. DN rats were divided into control group, DN + soy protein 7% group, DN + soybean β-conglycinin 1.75 % group, and DN + soybean β-conglycinin 3.5% group. Results shown that soy protein and β-conglycinin were able to retard the progression of DN by increasing insulin sensitivity, regulating lipid metabolism, improving renal function, and inhibiting angiotensin-converting enzyme activity [67].

2.8. Red propolis

Propolis is a natural polyphenol-rich resinous substance collected by honeybees from a variety of plant sources [68]. Propolis is thought to improve human health and prevent disease [69].

Health-promoting properties are attributed to its polyphenolic composition. Red propolis (RP) has been classified as a separate type of propolis based on its unique chemical composition, particularly rich in isoflavonoids [70]. Anti-inflammatory and antioxidant properties have been attributed to RP [71, 72].

Teles et al. [73] evaluated the effect of RP in the 5/6 nephrectomy model. Rats underwent nephrectomy and, 30 days after surgery, they were divided into untreated nephrectomy and RP-treated nephrectomy groups. Animals were observed for 90 days after surgery; RP-treated group showed significant reduction of hypertension, proteinuria, serum creatinine, glomerulosclerosis, renal macrophage infiltration, and oxidative stress when compared to untreated rats.

RP treatment attenuated hypertension and structural renal damage in 5/6 nephrectomy model. Reduction of renal inflammation and oxidative stress could be involved in this protective effect.

2.9. Mediterranean diet

Nutritionists elaborated Mediterranean diet (MD) model from observations of the Northern Mediterranean countries food habits. These included consumption of whole grain cereals, vegetables and fruit, legumes, nuts, herbs, spices, fresh cheese from sheep and goat milk, fish, seafood, olive oil, and wine [74].

MD provides a high and varied intake of antioxidant compounds. For instance, virgin olive oil contains carotenes and phenolics [75]; white wine contains simple phenols; and whole grain cereals, nuts, fish, and seafood contain omega-3 fatty acids.

Migliori et al. [76] evaluated the effect of white wine and extra-virgin olive oil on inflammatory markers in 10 patients with CKD and 10 healthy volunteers. Two weeks before the study patients were not allowed to drink alcoholic beverages, then, they were randomized to a cross-over design A–B or B–A of a 2-week treatment with white wine (4 ml/kg) and extra-virgin olive oil (treatment A) or extra-virgin olive oil alone (treatment B). The two study periods were separated by 2 weeks in which patients were not allowed again to drink any alcoholic beverage. Plasma levels of inflammatory markers CRP, interleukin-6 (IL-6), TNF-α, and IL-8 were determined. During treatment A, plasma levels of CRP and IL-6 decreased in CKD patients and healthy volunteers. No significant variation versus baseline was observed during treatment B. Plasma markers of chronic inflammation were significantly reduced in CKD patients during the combined consumption of white wine and olive oil. Thus, this nutritional intervention could be effective as a therapy in CKD. The protective effect of omega-3 fatty acids in CKD has also been evaluated.

Gopinath et al. [77] evaluated the association between polyunsaturated fatty acids (PUFA; n-3, n-6, and α-linolenic acid) and fish consumption and the prevalence of CKD. Two-thousand six-hundred Blue Mountains Eye Study (1997–1999) participants aged ≥50 years were evaluated. Dietary data were collected using a semiquantitative food frequency questionnaire, and PUFA and fish intakes were calculated. Baseline biochemistry including serum creatinine was measured. Moderate CKD was defined as an estimated GFR of <60 ml/min per 1.73 m².

Participants in the highest quartile of long-chain n-3 PUFA consumption had a significantly reduced possibility of having CKD compared with those in the lowest quartile. α-linolenic acid intake was positively associated with CKD. Total n-3 PUFA or total n-6 PUFA were not significantly associated with CKD. The highest compared with the lowest quartile of fish intake was associated with a reduced possibility of having CKD. Hence, an increased dietary intake of long-chain n-3 PUFA and fish reduces the prevalence of CKD [77].

3. Conclusions and future directions

CKD is considered a public health problem because its incidence is about 10% of world population and treatment methods are ineffective or expensive. Consequently, the development of novel therapies is highly needed. This chapter summarizes information about dietary antioxidant agents, which have shown nephroprotection on CKD, showing what has been found and leading to future studies. Future studies might aim to study physical and chemical properties of these compounds as well as the mechanisms involved in nephroprotection. A better understanding of these aspects will be key in the improvement of therapies, which have been studied on clinical trials as well as in the design of clinical trials of those compounds, which have not been studied in humans.

In that way, therapies will be not only effective but also viable because of the easy access to these compounds.

Acknowledgements

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