Review

Protective Effect of Green Tea (*Camellia sinensis*) against Kidney Diseases

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Abstract: Kidney diseases are a global health problem, and their frequency is continuously increasing. Available treatments provide limited kidney protection. The protective effect of the green tea polyphenol epigallocatechin-3-gallate (EGCG) in several diseases have been extensively investigated. Experimental and clinical studies have shown that the antioxidant, anti-inflammatory, and anti-apoptotic properties of EGCG are promising for the treatment and/or prevention of kidney diseases. This review analyzes the available evidence on the effects, and the likely protective mechanisms of action, of EGCG in a broad spectrum of kidney diseases, including acute kidney injury, drug-induced nephrotoxicity, kidney stone disease, diabetic nephropathy, chronic kidney disease, and kidney fibrosis.

Keywords: green tea; EGCG; oxidative stress; acute kidney injury; chronic kidney disease; kidney stones; diabetic nephropathy

1. Introduction

There is an increased generation of reactive oxygen species (ROS) and reactive nitrogen species and/or a reduction in the local antioxidant defenses when a state of oxidative stress occurs [1]. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidases (GPxs), and thioredoxin (Trx) are some of the endogenous antioxidants that neutralize excess ROS and maintain cellular *redox* balance. One of the most important biological responses of the cell that is regulated by ROS and oxidative stress is autophagy, which is mainly the removal and recycling of damaged organelles and proteins to preserve cellular homeostasis [2]. However, oxidative stress may lead to inflammation, cell death, tissue damage, and lesion/disease progression [3]. The kidney is rich in mitochondria, with a high respiration rate, to meet its high metabolic demand and is therefore highly vulnerable to ROS generation and oxidative damage [4]. The pathogenesis of kidney diseases is associated with oxidative stress, the induction of autophagy, and mitochondrial dysfunction. A common link between all forms of acute and chronic kidney injury, regardless of etiology, is the generation of oxidative stress during the progression of the lesion/disease. Several studies have documented important roles of ROS in the pathogenesis of acute kidney injury (AKI) and chronic kidney disease (CKD), both in experimental animal models and in humans [2]. Traditional therapeutic options provide limited kidney protection, leading to the search for new therapeutic compounds. A systematic review of clinical trials focused on the efficacy and potential impact of natural plant bioactive compounds (LCPN) on kidney diseases showed a protective effect of several LCPNs, including green tea (*Camellia sinensis*), mainly through the activation of defensive antioxidant activity and downregulation of proinflammatory signaling pathways [5].

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*1.1. Green Tea (*Camellia sinensis*) and Mechanism of Action*

Green tea is the second most consumed beverage globally, after water. It is usually produced from the leaves of the *Camellia sinensis* plant. During the last four decades, adequate technologies have been used to define the active chemical ingredients of tea [6]. Among the 400 chemicals identified, most tea ingredients are polyphenolic constituents (flavonoids), which have anti-inflammatory, antioxidant, and anti-apoptotic properties and consequently are potentially beneficial against kidney diseases [5,6]. Based on the fermentation status, teas can be classified as green (unfermented), oolong (partially fermented), and black (fermented). Green tea is the richest in catechins (a subtype of flavonoids). Four main catechins are found in green tea: epicatechin, epigallocatechin, epicatechin-3-gallate, and epigallocatechin-3-gallate (EGCG), the latter being the most abundant, representing between 50 to 80% of all catechins. The benefits of green tea are generally referred to as the effects of EGCG, and it is the most widely investigated tea polyphenol [6]. Due to its antioxidant, anti-inflammatory, and anti-apoptotic properties, EGCG has been studied in the treatment and prevention of various kidney diseases associated with oxidative stress and inflammation. The body of evidence suggests that the properties of EGCG hold promise for the prevention or treatment of kidney diseases [5,6]. The antioxidant effects of catechins are exerted through the association of direct and indirect mechanisms. The direct mechanisms include removal and chelation of metal ions, such as iron, involved in the production of free radicals. Indirect mechanisms include the induction of antioxidant enzymes such as superoxide dismutase (SOD), CAT, and GPx, which play important roles in ROS elimination. Inhibition of pro-oxidant enzymes, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cyclooxygenase (COX), inducible nitric oxide synthase, xanthine oxidase, and lipoxygenase, and suppression of oxidative stress–related signaling pathways, such as those of tumor necrosis alpha (TNF-α), nuclear transcription factor κB (NF-κB), and activator protein 1 (AP-1), are important in the response to oxidative stress [7] (Figure 1).

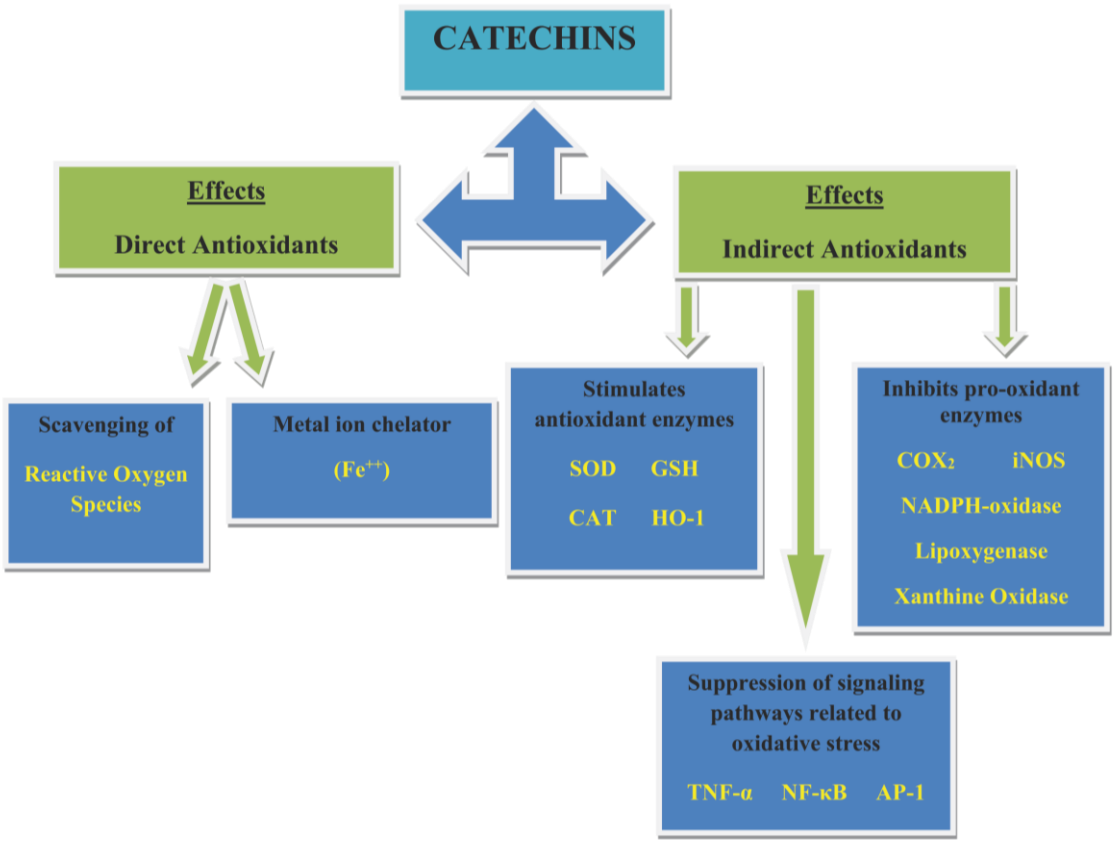

Figure 1. Antioxidant properties of catechins [7].

The beneficial effects of green tea catechins are mediated by different molecular mechanisms, mainly the direct inhibition of stimulus-induced oxidative stress. Catechins may also impact the Nrf2–Keap1–Cul-3 complex, resulting in the nuclear

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translocation of free Nrf2, which binds to the antioxidant response element within the promoter region of cytoprotective genes and those that encode antioxidant enzymes (HO-1, SOD, GPx, CAT), which are also modulated by NF-κB signaling pathways [6] (Figure 2).

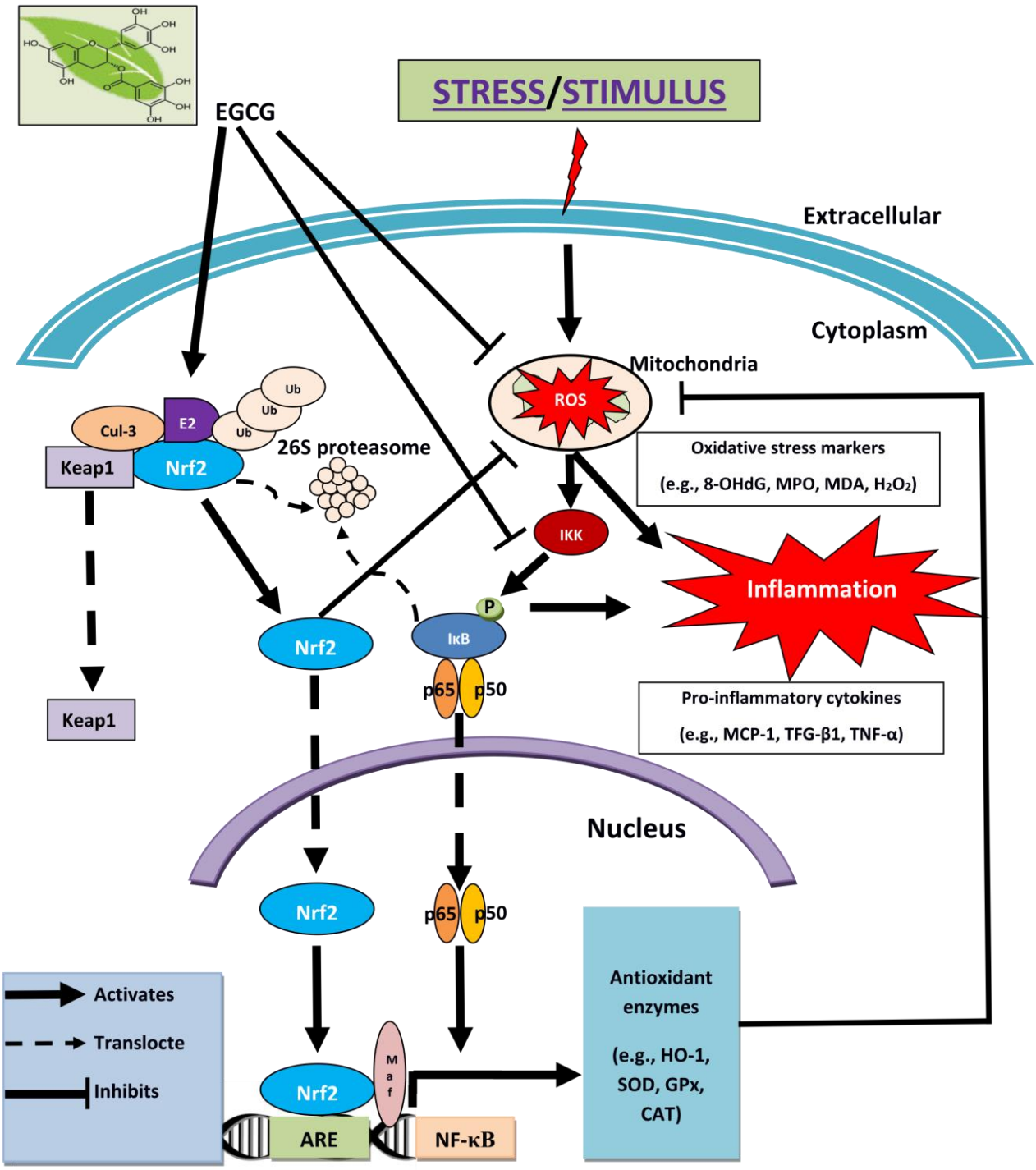

Figure 2. Molecular mechanisms of EGCG renoprotection. EGCG directly inhibits ROS overproduction induced by stress or stimuli. EGCG can also disrupt the Nrf2-Keap1-Cul-3 complex, leading to nuclear translocation of free Nrf2, which then heterodimerizes with the small Maf, which in turn facilitates the binding of Nrf2 to the antioxidant response elements within the promoter regions of cytoprotective genes and those that encode antioxidant enzymes. Stress/stimulus-induced ROS-mediated inflammation can be inhibited by EGCG by inhibiting the NF-κB signaling pathway, particularly the phosphorylation-induced IκB degradation step that can prevent NF-κB binding to DNA. EGCG, epigallocatechin-3-gallate; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; ARE, antioxidant

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responsive element; Cul-3, cullin-3; E2, E2 ubiquitin-conjugating enzyme; GPx, glutathione peroxidase; H_2O_2, hydrogen peroxide; IκB, κB inhibitor; *IKK*, IκB kinase; Keap1, protein 1 associated with Kelch-like ECH; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; MPO, myeloperoxidase; NF-κB, nuclear transcription factor κB; Nrf2, erythroid-related nuclear factor 2; Maf, musculoaponeurotic fibrosarcoma; ROS, reactive oxygen species; SOD, superoxide dismutase; TGF-β1, transforming growth factor β1; Ub, ubiquitin [6].

NF-κB is considered one of the most relevant proinflammatory regulators of gene expression, as it intervenes in the synthesis of several cytokines, such as TNF-α, interleukin (IL)-1β, IL-6, and IL-8, as well as COX-2 [8]. It is possible that different signaling pathways are involved in the anti-inflammatory action of green tea catechins. They can exert both anti-inflammatory and antioxidant actions, and it is believed that the central target of these agents is ROS. Tea catechins can eliminate ROS, which activate NF-κB to increase the expression of inflammatory cytokines and inflammation-related enzymes, including TNF-α, IL-1β, COX-2, and MMP-9 (Figure 3). Therefore, suppression of NF-κB activation by green tea as an antioxidant is likely linked to its anti-inflammatory effect [9].

Our objective was to review the literature on the protective effect of green tea (*Camellia sinensis*) in kidney diseases.

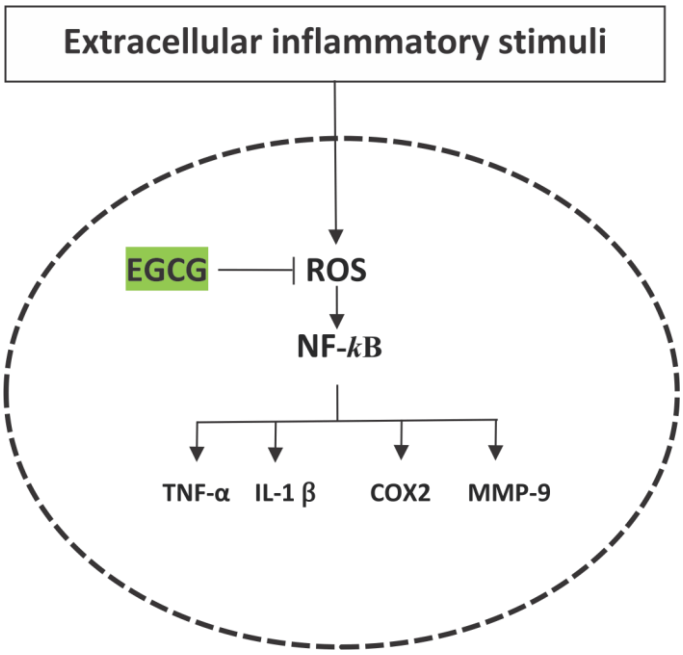

Figure 3. Anti-inflammatory action of EGCG. ROS generated by various extracellular inflammatory stimuli activate NF-κB, a transcription factor that upregulates the gene expression of proteins related to proinflammation, including TNF-α, IL-1β, COX-2, and MMP-9. EGCG acts as an antioxidant to eliminate ROS, leading to attenuation of its effects [9].

2. Methods

This review assessed experimental and clinical trials focused on the potential impact of green tea (*Camellia sinensis*) on its therapeutic efficacy in the treatment of kidney diseases in studies published between 2012 and 2021 in English and indexed in the PubMed and MEDLINE databases.

Relevant descriptors, specifically EGCG, oxidative stress, acute kidney injury, chronic kidney disease, kidney stones, and diabetic nephropathy, were searched for, initially yielding 2,158 publications.

The inclusion criteria adopted for the study were clinical or experimental manuscripts focusing on the protective effect of green tea in kidney diseases. Studies that did not address the proposed objectives were excluded. The full texts of the included studies were analyzed, and those that met the eligibility criteria were assessed in the review, resulting in a sample of 30 publications.

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3. Results

3.1. Protective Effect of Green Tea in Kidney Diseases

3.1.1. CKD

CKD has a high and increasing incidence in the world population and is associated mainly with diabetes and hypertension. Several molecular signaling pathways are implicated in the onset and progression of kidney damage, including the renin–angiotensin–aldosterone system and the activation of profibrotic growth factors, such as transforming growth factor (TGF)-β and connective tissue growth factor. TGF-β increases ROS production, downregulates the antioxidant system, and induces oxidative stress and/or cellular redox imbalance, accumulation of extracellular matrix (ECM), kidney fibrosis, epithelial dysfunction, and proinflammatory reactions. These pathways overlap and interact with each other, altering their biological activities, which promotes the evolution of kidney fibrosis and progression of CKD [5]. One recent literature review focused on the main sources of ROS, and antioxidant systems and redox signaling pathways related to inflammation and fibrosis in CKD. The authors stated that mitochondria and NADH oxidase are the main sources of ROS in the kidney and that the kidney antioxidant systems (SOD, CAT, GPx) counterbalance ROS-mediated kidney injury [10]. Therapeutic strategies to prevent these pathological progressions are limited. Drugs that block the renin–angiotensin–aldosterone system have partial efficacy in reducing proteinuria, improving kidney function, and delaying progression to end-stage kidney disease [11].

In vitro and *in vivo* studies have extensively investigated the renoprotective effect of EGCG in models of CKD and kidney fibrosis. EGCG acts as an antioxidant, mainly through the activation of the Nrf2–HO-1 pathway, resulting in the induction of antioxidant enzymes (SOD, CAT, GPx) and preservation of mitochondrial function. Antifibrotic action mediated by inhibition of TGF-β/Smad and epithelial–mesenchymal transition was also reported. Another beneficial action comes from its anti-apoptotic effects, which it executes by inhibiting the p38 mitogen-activated protein kinase (MAPK) signaling pathway. Finally, its anti-inflammatory activity comes from inhibiting the NF-κB signaling pathway, which regulates the expression of proinflammatory chemokines/cytokines such as TNF-α, IL-1β, and IL-6, as well as myeloperoxidase enzyme activity [10,12]. Several studies have reported that treatment with EGCG attenuated the increase of serum creatinine in animal models of obstructive nephropathy by [6].

3.1.2. Nephrolithiasis

Recently, it was confirmed that kidney epithelial cell injury associated to calcium oxalate stone genesis is mediated by oxidative stress, produced mainly by mitochondria or NADPH oxidase [13]. A review on the role of oxidative stress and endoplasmic stress in calcium nephrolithiasis concluded that the association between oxalate toxicity and endoplasmic reticulum stress may be associated with the pathogenesis of nephrolithiasis, although the interaction between ROS and endoplasmic reticulum stress is still controversial. Evidence indicates that calcium oxalate (CaOx) crystallization and oxidative stress are essential elements in the pathogenesis of nephrolithiasis [14].

The administration of green tea polyphenols inhibits the production of free radicals induced by CaOx monohydrate (COM) in kidney tubular epithelial cells, favoring the formation of calcium oxalate dihydrate (COD) and decreasing the expression of α-enolase (a receptor crystal COM) on the cell surface, as well as oxaluria. The crystal shape and kidney cell aggregation may compromise CaOx fixation to kidney tubular cells, which is crucial in stone formation. One of the positive signaling pathways of green tea polyphenols against oxidative stress in kidney lithiasis is through the increase in the expression of antioxidant enzymes (e.g., SOD, GTP, and CAT) [15,16].

There are few clinical studies on green tea in nephrolithiasis. A large cohort study in the United Kingdom included 439,072 participants, and the authors reported that only those who drank five cups of green tea per day had a significantly lower risk of kidney stones than nondaily tea drinkers [16]. Recently, a systematic review analyzed evidence for the effect of tea consumption and the risk of nephrolithiasis. The authors showed that the 13 studies included in the final review were not randomized, had significant heterogeneity in the study design, had publication bias, and had no standard type or method of preparation of the tea studied. A meta-analysis of these articles was not possible due to a lack of standardization of methods and data. The review suggested that tea exerts several protective effects against stone formation through water ingestion, the action of caffeine, and the effects of components with antioxidant properties [17].

A large prospective cohort study, with more than 500,000 adult Chinese adults was published recently. The authors reported that consumption of three cups of tea a day, consumption of 30 g of alcohol/day, and consumption of fruits at least four days/week were associated with a lower risk of kidney stones. Increased consumption of tea (whether green, oolong, or black), fruits, and alcohol (in moderation) was independently associated with a lower risk of nephrolithiasis [18].

Nutritional factors play an important role in the formation of kidney stones. A narrative review provided a comprehensive and up-to-date overview of the role of nutrition and diet in nephrolithiasis. The studies included were large

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cohort studies that generally supported a potentially preventive role for coffee and tea consumption against the formation of kidney lithiasis. The authors assumed that the beneficial effect of tea can be attributed mainly to the diuretic action of the consumption of large amounts of caffeine, which could offset, at least partially, the hypercalciuric effect. The antioxidant effect of polyphenols may be another explanation for the preventive effect of tea. A limitation of the cohort studies was that they did not distinguish between the different types of tea, such as black and green, which contain varying amounts of oxalate, depending on the origin, quality, harvest time, and preparation. Therefore, the exact mechanism of the protective effect of black and green tea against stone formation remains to be elucidated [19].

3.1.3. Diabetic Nephropathy

Diabetic nephropathy (DN) is one of the main microvascular complications of diabetes mellitus. It is defined as a decrease in glomerular filtration rate and proteinuria. Recent *in vitro*, *in vivo*, and clinical trials have supported the effects of tea in the prevention and treatment of diabetes mellitus and its complications. There is evidence that tea can modify the pathophysiological process of DN through antioxidant and anti-inflammatory properties [20], anti-apoptotic properties [6], decreasing proteinuria, and protecting kidney function [6,20]. A randomized, double-blinded, placebo-controlled study in 42 patients with DN demonstrated the efficacy and safety of adding dry green tea extract (polyphenols) to maximum doses of ACE inhibitors and/or angiotensin II receptor blockers through a significant decrease in proteinuria and reduction in podocyte apoptosis via the Wnt pathway [21]. Epidemiological cohort studies conducted in different countries (USA, China, Japan, South Korea) involving individuals of different races, sexes, and ages reported that tea intake may reduce the risk of diabetes mellitus and its complications, including ND. Among these studies, the majority drank green tea, black tea, or oolong tea. The molecular mechanism underlying the antioxidant and anti-inflammatory effects of EGCG is mediated mainly by the activation of the Nrf2 signaling pathway and inhibition of the NF-κB pathway. Due to the differences in tea doses and effects between experimental and clinical studies, there is still doubt about whether the effective doses used in animal studies can have beneficial effects in humans [20].

The causes of DN are the activation of the polyol pathways, advanced glycosylation end-products (AGEs), oxidative stress, and irregular activation of conventional protein kinase C (PKCc), secondary to hyperglycemia. In hyperglycemia, there is an increase in the synthesis of α-diacylglycerol (α-DAG), which irregularly activates PKCc, resulting in diabetic vascular complications, including DN. The activation of α-diacylglycerol kinase (α-DGK) can suppress the activation of PKCc, reducing the amount of α-DAG. An experimental study in a streptozotocin-induced type I diabetic mouse model revealed that EGCG effectively attenuated albuminuria in DN through the α-DGK signaling pathway. In addition, the authors reported that EGCG activated α-DGK through the 67 kDa laminin receptor (67LR), known as the EGCG receptor. The c-Src signaling pathway mediated the EGCG-induced α-DGK translocation and colocalization with 67LR. The results indicate that EGCG activated α-DGK via 67LR and c-Src and that activated α-DGK interacted with 67LR in the podocyte plasma membrane to inhibit PKCc. The authors suggested that α-DGK, c-Src, and 67LR formed complexes upon EGCG stimulation. In addition, EGCG attenuated podocyte loss in DN, preventing a decrease in focal adhesion under conditions of hyperglycemia. In view of their results, the authors concluded that α-DGK is an attractive therapeutic target and that the activation of this pathway may be a new strategy for the treatment of DN [22].

Interventions to slow the progression of DN include changes in lifestyle, nutritional counseling, regular exercise, and renoprotective drugs such as angiotensin II receptor blockers and angiotensin-converting enzyme (ACE) inhibitors. The most important biochemical mechanism proposed for this progression is mediated by advanced glycation end products (AGEs). Their interaction with their receptor (*RAGE*) participates in the metabolic and biochemical pathways of intracellular signaling, favoring or aggravating kidney damage. One isoform of this receptor is soluble RAGE (sRAGE), which binds to AGEs and can antagonize intracellular signaling. One of the mechanisms proposed for the development of DN is the increase in AGEs that bind to the RAGE receptor, favoring nephron cell damage. Green tea extract increases the expression of sRAGE, but it is not known if this can improve kidney function.

A randomized, double-blinded, placebo-controlled clinical trial conducted in Guadalajara, Mexico, evaluated the effect of green tea extract administration on sRAGE and kidney damage in patients with type 2 diabetes mellitus. The study included 39 individuals of both sexes, between 35 and 65 years of age, receiving oral hypoglycemic agents and/or insulin, with kidney impairment between grades 2 and 3a according to the Kidney Disease: Guidelines for the Improvement of Overall Outcomes (KDIGO) classification, and with HbA1c levels between 9 and 12%. Patients were treated with 400 mg green tea twice daily or placebo for three months. The authors reported that the administration of green tea extract significantly increased the serum concentration of sRAGE and the glomerular filtration rate and decreased the concentration of fasting serum glucose and triglycerides [23].

3.1.4. Acute Kidney Injury

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AKI is defined as an abrupt decrease in kidney function. Serum creatinine and urine output remain the fundamental measures for the diagnosis of AKI, although their limitations are well known [24]. AKI is a major global health challenge: approximately 13.3 million people worldwide are affected by AKI annually [25]. In the COVID-19 pandemic, AKI was common and was associated with higher morbidity and mortality. Several evidences have shown that EGCG may be promising as a protective or therapeutic agent in AKI. The possible mediators of the protective effects of EGCG include antioxidant, anti-inflammatory, and anti-apoptotic properties. The main signaling pathways involved are the activation of the Nrf2–HO-1 pathway and the inhibition of NF-κB by MAPK [6,26]. Studies in rats pretreated or treated with catechins showed significant protection or mitigation of the impairment of kidney function and glomerular and tubular lesions in models of AKI induced by glycerol, gentamicin, cisplatin, contrast, obstruction, ischemia/reperfusion, cardiopulmonary bypass, iron overload, cyclosporine, and tacrolimus [6,25,27,28]. Recent publications provided evidence that catechins can be used as antiviral and renoprotective agents in the prevention of COVID-19-induced AKI [27,29].

Catechins have antiviral activity against several RNA viruses, including coronaviruses. EGCG can inhibit the entry of these viruses into cells or their replication and transcription through different molecular mechanisms, which are not yet completely understood. What is known is that the effects of EGCG inhibition on SARS-CoV-2 replication occur through its actions on the host receptor ACE2, on the major protease (M^{pro}), and on RNA-dependent RNA polymerase (RdRp) [29]. The cell-surface receptor ACE2 is the binding site for the spike protein SARS-CoV-2 through the receptor binding domain of protein S (RBD) in the viral membrane, located in the S1 subunit of SARS-CoV-2, which recognizes ACE2 and forms the RBD–ACE2 complex, through which SARS-CoV-2 is activated for endocytosis, at which time its replication begins. *In vitro*, binding of EGCG to the spike protein of SARS-CoV-2 inhibits its interaction with ACE2 located on the host cell membrane and prevents endocytosis of SARS-CoV-2 [27]. Additionally, EGCG inhibits the initial replication of the virus by inhibiting M^{pro} and RdRp [30]. These results support the suggestion that tea catechins are promising as renoprotective therapy in AKI associated with COVID-19 due to their anti-SARS-CoV-2, antioxidant, and anti-inflammatory properties [27].

4. Conclusions

Kidney diseases are a global health problem, and their incidence is continuously increasing. The traditional available treatments provide limited kidney protection, pushing for the search for new therapeutic compounds. Several evidences have shown that the antioxidant, anti-inflammatory, and anti-apoptotic properties of EGCG are promising to treat or prevent kidney disease (Figure 4 summarizes the renoprotective effects of EGCG against several kidney diseases covered in our review). Experimental and clinical studies have documented the preventive effects of EGCG in acute kidney injury, drug-induced nephrotoxicity, kidney stone disease, diabetic nephropathy, chronic kidney disease, and kidney fibrosis. This review highlights the beneficial role of EGCG as a potent renoprotector through underlying molecular mechanisms, mainly by inhibiting oxidative stress (Nrf2–Keap1 pathway) and inflammation (NF-κB pathway).

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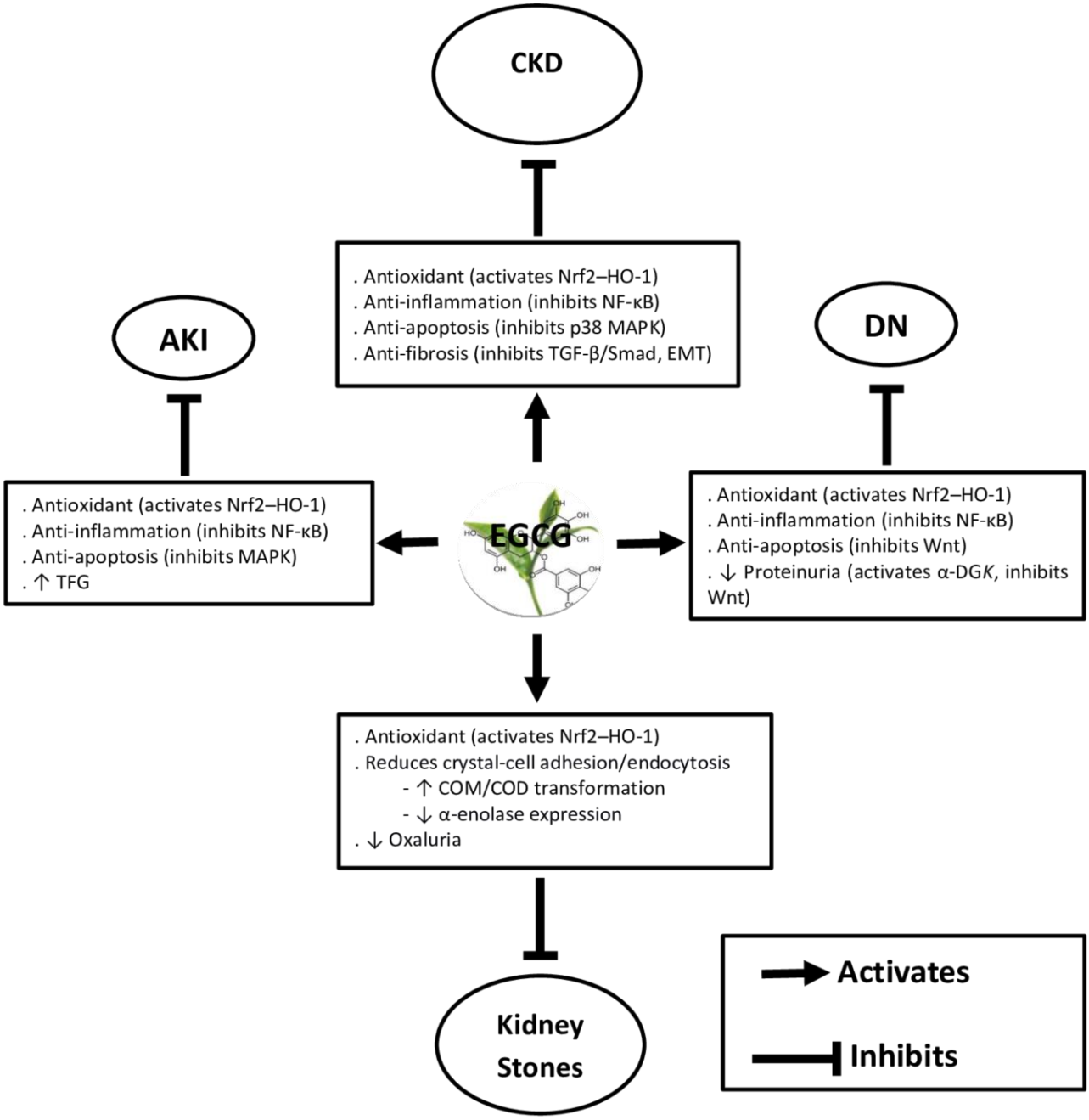

Figure 4. Renoprotective effects of EGCG against various kidney diseases. EGCG can prevent kidney diseases by several mechanisms, mainly through its antioxidant and anti-inflammatory properties. AKI, acute kidney injury; DN, diabetic nephropathy; CKD, chronic kidney disease; Nrf2, nuclear erythroid factor 2-related factor 2; HO-1, heme oxygenase-1; EGCG, epigallocatechin-3-gallate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinase; GFR, glomerular filtration rate; TGF-β, transforming growth factor-β; EMT, epithelial–mesenchymal transition; αDGK, α-diacylglycerol kinase; COM/COD, transformation of calcium oxalate monohydrate (COM) crystals to oxalate dihydrate (COD) crystals.

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