REVIEW

Protective Effects of Epigallocatechin-3-Gallate from Green Tea in Various Kidney Diseases

Rattiyaporn Kanlaya and Visith Thongboonkerd

Medical Proteomics Unit, Office for Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

ABSTRACT

Kidney diseases are common health problems worldwide. Various etiologies (e.g., diabetes, hypertension, drug-induced nephrotoxicity, infection, cancers) can affect renal function and ultimately lead to development of chronic kidney disease (CKD) and end-stage renal disease (ESRD). The global rise in number of CKD/ESRD patients during recent years has led to tremendous concern to look for effective strategies to prevent or slow progression of CKD and ESRD. Natural compounds derived from herbs or medicinal plants have gained wide attention for scientific scrutiny to achieve such goals. One of such natural compounds that has been extensively investigated is epigallocatechin-3-gallate (EGCG), a major polyphenol found in the tea plant (*Camellia sinensis*). A growing body of recent evidence has shown that EGCG may be a promising therapeutic or protective agent in various kidney diseases. This article thus highlights recent progress in medical research on beneficial effects of EGCG against a broad spectrum of kidney diseases, including acute kidney injury, cisplatin-induced nephrotoxicity, kidney stone disease, glomerulonephritis, lupus nephritis, renal cell carcinoma, diabetic nephropathy, CKD, and renal fibrosis. The renoprotective mechanisms are also detailed. Finally, future perspectives of medical research on EGCG and its potential use in clinical practice for treatment and prevention of kidney diseases are discussed. *Adv Nutr* 2019;10:112–121.

Keywords: cancer, diabetes, EGCG, glomerular disease, lupus, nephrolithiasis, prevention, renal disease, renoprotection, urolithiasis

Introduction

Kidney diseases are common and their incidence is rapidly growing worldwide (1, 2). Renal disorders are also common complications of other primary diseases, of which diabetes and hypertension are the 2 most common (3). Several kidney diseases ultimately lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD), both of which contribute to the global health crisis associated with catastrophic health expenditure, particularly in developing countries (4). Therefore, it is important to define effective strategies to mitigate development of CKD/ESRD.

Natural compounds from herbs or medicinal plants are widely used for therapy and prevention of various ailments. The common beverage tea is generally produced from *Camellia sinensis* leaves, thought to have health benefits in many age-related diseases (5, 6). Drinking tea was recommended as medication in ancient China (~4,000–5,000 y ago), as documented in several ancient Chinese books describing use of tea for treating some diseases and maintaining health (7). During the last 4 decades, modern and advanced sciences and technologies have been applied to define the chemical ingredients in tea. Among 400 chemicals identified, the majority of tea ingredients are polyphenolic constituents, particularly flavonoids (8).

Based on the fermentation status, teas can be categorized into green tea (unfermented), oolong (partially fermented), and black tea (fermented). Green tea is enriched by catechin (a subtype of flavonoids) (9). There are 4 main catechins found in green tea: epicatechin, epigallocatechin, epicatechin-3-gallate, and epigallocatechin-3-gallate (EGCG), the most abundant catechin accounting for 50–80% of all contents (10). Therefore, any health benefits of green tea are usually referred to as effects of EGCG (8, 11). As a result, EGCG is the most widely investigated tea polyphenol in medical research (8, 11). Because of its distinct antioxidative properties, protective effects of EGCG have been investigated in a wide range of diseases related to excessive oxidative

Supported by Mahidol University research grant and the Thailand Research Fund (IRN60W0004 and IRG5980006). Both authors are also supported by "Chalermphrakiat" and "Research Staff" grants from Faculty of Medicine Siriraj Hospital.
Author disclosures: RK and VT, no conflicts of interest.
Address correspondence to VT (e-mail: thongboonkerd@dr.com or vthongbo@yahoo.com).
Abbreviations used: AGEs, advanced glycation end products; AKI, acute kidney injury; CaOx, calcium oxalate; CKD, chronic kidney disease; COM, calcium oxalate monohydrate; DN, diabetic nephropathy; EGCG, epigallocatechin-3-gallate; EMT, epithelial mesenchymal transition; ESRD, end-stage renal disease; HO, heme oxygenase; LN, lupus nephritis; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor κB; Nrf2, nuclear factor erythroid 2-related factor 2; RCC, renal cell carcinoma; SOD, superoxide dismutase; TGF-β1, transforming growth factor-β1; UUO, unilateral ureteral obstruction

stress, including cancers, cardiovascular diseases, metabolic syndromes, diabetes, cerebral ischemic stroke, lung diseases, and neurodegenerative disorders (5, 11–14). Recently, EGCG has been studied for potential use in management and prevention of various kidney diseases, which are commonly associated with oxidative stress and inflammation (15). This review summarizes current knowledge on the beneficial effects of EGCG in various kidney diseases (**Figure 1**). The renoprotective mechanisms are also discussed (**Figure 2**).

Current Knowledge on EGCG in Kidney Diseases

Acute Kidney Injury (AKI)

Several etiologies can lead to AKI, which is generally defined as an abrupt and reversible decline of renal function as indicated by increased blood urea nitrogen and serum creatinine, with glomerular filtration rate decreased within hours to weeks (16). Treatment of AKI usually includes sufficient hydration, but medication depends largely on the etiologies of AKI (17). The medications may cause drug-induced nephrotoxicity or other (secondary) forms of AKI (17), therefore identifying novel and safer medications is crucial for AKI management.

Phytochemical EGCG has been demonstrated to have a protective role against AKI regardless of the etiology. Bao and colleagues (18) addressed the beneficial role of EGCG in renal damage induced by iron overload. They demonstrated that EGCG could act as an iron chelator (siderophore) by forming a stable complex with iron and neutrophil gelatinase associated lipocalin (Ngal), resulting in reduction of chemical reactivity of iron-reactive oxygen species (ROS) and, subsequently, protection against renal injury (18).

Two other studies have identified renoprotective effects of EGCG in AKI induced by cardiopulmonary bypass operation (19, 20). A decrease in pyknotic nuclei in renal cells of EGCG-treated animals was related to decline of poly-ADP-ribose and apoptosis-inducing factor, which are known effectors for induction of cellular apoptosis (19). EGCG was also shown to improve renal function and reduce hypoxic damage and nitrosative stress (19). The antioxidative and antiapoptotic properties of EGCG were suggested to be responsible for reversing such adverse effects of cardiopulmonary bypass (19). Similarly, another study demonstrated that pretreatment with EGCG could ameliorate cardiopulmonary bypass-induced AKI in diabetic rats (20). EGCG prevented renal tubular damage and reduced amounts of kidney injury molecule-1 (Kim-1) and Ngal, both of which are known biomarkers for AKI, associated with a lower amount of oxidative stress marker 8-hydroxy-2'-deoxyguanosine (20).

Kidney transplantation can result in AKI induced by ischemic-reperfusion (I/R) injury. In a rat model, Kakuta and colleagues (21) revealed that pre-injection of EGCG could protect the kidney from such I/R injury by reducing macrophage infiltration and renal fibrosis. Several molecules, which could link renal tubular injury to innate inflammatory response (i.e., Kim-1, major histocompatibility complex class II, Toll-like receptor 2, Toll-like receptor 4, monocyte chemoattractant protein-1, and IL-18) and activation of transforming growth factor-β1 (TGF-β1) signaling pathway, were significantly reduced by EGCG (21). These findings suggest that such protective effects of EGCG could be mediated via upregulation of the heme oxygenase (HO) system, which regulates antioxidant homeostasis during cellular injury (21).

Cisplatin-induced nephrotoxicity

Cisplatin is a common antineoplastic drug used for treatment of various cancers, including breast, ovarian, lung, head and neck, and urinary bladder cancers. Although it is included in most chemotherapy regimens, nephrotoxicity is very common and thus limits its efficacy (22). Therefore, it is vital to identify alternative anticancer drugs with lower adverse effects, and to develop strategies to counteract or recover cisplatin-induced kidney injury.

In mouse and rat models of breast cancer treated with cisplatin, EGCG has shown renoprotective effects by reducing leukocytosis, oxidative stress, and systemic inflammation (23). These EGCG-treated animals also had decreased amounts of malondialdehyde (a marker for lipid peroxidation) and inflammatory cytokine TNF-α, and their glomerular filtration rate could be recovered (24). Another study demonstrated that EGCG could trigger the nuclear factor erythroid 2-related factor 2 (Nrf2)/HO-1 signaling pathway in cisplatin-treated rats, resulting in a remarkable increase in activities of antioxidant enzymes and glutathione, while nuclear factor κB (NF-κB) and 4-hydroxynonenal were decreased (25). These findings suggest that the antioxidative and anti-inflammatory properties of EGCG accounted for its renoprotection (23–25). By modulating mitochondria, EGCG could preserve activities of electron transport chain and antioxidant enzymes [superoxide dismutase (SOD) and glutathione peroxidase] and lower mitochondrial ROS, leading to improved renal function in cisplatin-mediated kidney damage (26). In addition, EGCG also exhibited an antiapoptotic effect in cisplatin-treated mice, as demonstrated by decreased expression of Fas-L, p53, and proapoptotic Bax, whereas the antiapoptotic Bcl-2 was increased (27). Histological examination revealed that renal tubular damage was attenuated in mice co-treated with EGCG (28).

In addition to cisplatin-induced nephrotoxicity, EGCG has also shown renoprotection against nephrotoxicity induced by other chemicals, for example, cyclosporine (29) and FK506 (30), mainly via its antioxidative properties to reduce overproduction of intracellular ROS, and its antiapoptotic properties (29, 30).

Kidney stone disease

Kidney stone disease (nephrolithiasis or urolithiasis) is an ancient human disease (found in well-preserved Egyptian mummies) presenting with stone(s) inside the kidney or urinary tract (31, 32). Among various types of kidney stones, calcium oxalate (CaOx) stones are the most common, from calcium phosphate, uric acid, struvite, cysteine, etc. (33, 34).

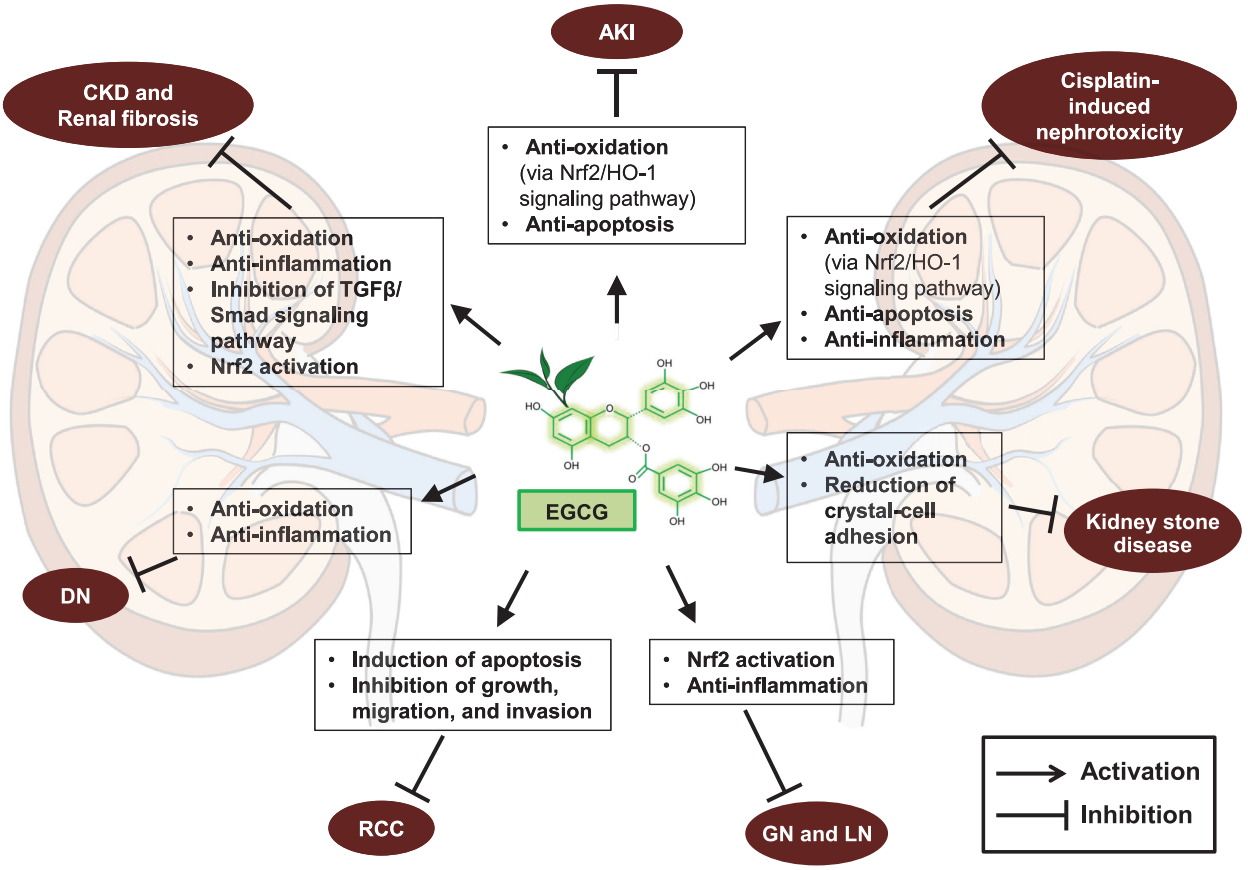

FIGURE 1 Renoprotective effects of EGCG against a broad spectrum of kidney diseases. EGCG could prevent kidney diseases by various mechanisms (mainly via its antioxidation and anti-inflammation properties). AKI, acute kidney injury; CKD, chronic kidney disease; DN, diabetic nephropathy; EGCG, epigallocatechin-3-gallate; GN, glomerulonephritis; LN, lupus nephritis; Nrf2/HO-1, nuclear factor erythroid 2-related factor 2/heme oxygenase-1; RCC, renal cell carcinoma.

Many studies have been conducted in recent decades, but the precise mechanisms of kidney stone formation remain unclear. More importantly, there is no effective preventive strategy for the disease occurrence and recurrence available and most of the stone formers (stone patients) ultimately develop ESRD (35–38). Therefore, there is an urgent need to better understand the disease pathogenesis and mechanisms, and to find an effective strategy to prevent kidney stone formation.

The protective role of EGCG from green tea in this context was initially unexpected because green tea also contains oxalate, a potential source of oxalate ions for generation of CaOx crystals (39). Therefore, it was previously recommended that green tea be avoided by patients with kidney stone disease. However, a study by Itoh et al. (40), in a rat model of ethylene glycol-induced kidney stones, yielded the surprising results that supplementation of green tea in drinking water or diet could lower the number of CaOx crystals deposited inside the kidney. Urinary oxalate excretion was decreased, whereas SOD activity was increased significantly in green tea–treated animals to protect from ethylene glycol–induced renal damage (40). Subsequent study by Jeong et al. (41) provided confirmatory results that both EGCG and green tea could prevent oxalate-induced injury in a renal tubular cell line and lower CaOx crystal deposition in oxalate-treated rats. The protective effect of green tea was also confirmed in glyoxylate-induced CaOx kidney stone formation in mice (42).

Based on these striking findings, our group therefore hypothesized that EGCG could alter proteins on apical membranes of renal tubular epithelial cells that have affinity to CaOx crystals (i.e., those serving as CaOx crystal receptors), thereby reducing the number of CaOx crystals retained inside renal tubules and lowering crystal deposition (31, 32). This hypothesis was addressed by pretreating renal tubular cells with EGCG, then performing CaOx monohydrate (COM) crystal-binding assay (43). COM is the most potent form of CaOx crystal involved in kidney stone formation (44–47). The results confirmed that EGCG markedly reduced the number of COM crystals adhered onto the renal tubular cell surface by decreasing surface expression of α-enolase (43), a potential COM crystal receptor identified by a large-scale affinity-based membrane proteomics study (48, 49). In another subsequent study, our

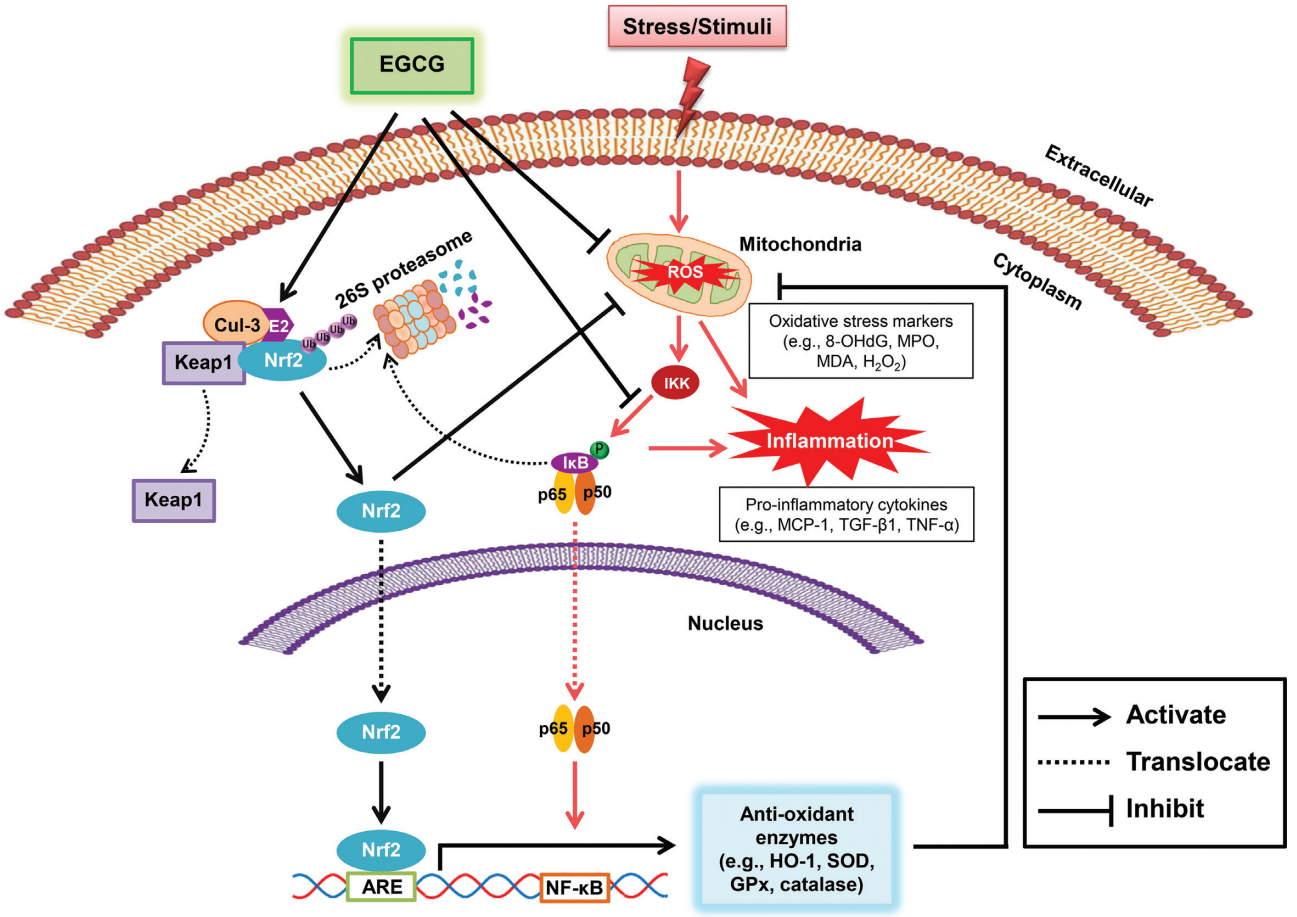

FIGURE 2 Molecular mechanisms for renoprotection of EGCG. EGCG could directly inhibit ROS overproduction induced by stress or stimuli. In addition, EGCG can disrupt the Nrf2-Keap1-Cul-3 complex, leading to nuclear translocation of free Nrf2, which then binds to ARE within the promoter region of the cytoprotective genes and those encoding antioxidant enzymes. Moreover, ROS-mediated inflammation induced by stress/stimuli could be inhibited by EGCG through inhibition of the NF-κB signaling pathway, particularly the phosphorylation-induced IκB degradation step which can prevent NF-κB from DNA binding. 8-OHdG, 8-hydroxy-2′-deoxyguanosine; ARE, antioxidant responsive element; Cul-3, cullin-3; E2, E2 ubiquitin-conjugating enzyme; EGCG, epigallocatechin-3-gallate; GPx, glutathione peroxidase; H_2O_2, hydrogen peroxide; IκB, inhibitor κB; IKK, IκB kinase; Keap1, Kelch-like ECH-associated protein 1; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; MPO, myeloperoxidase; NF-κB, nuclear transcription factor κB; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; SOD, superoxide dismutase; TGF-β1, transforming growth factor β1; Ub, ubiquitin.

group also reported the protective role of EGCG against microvillar injury in COM-treated renal tubular cells via an antioxidative stress mechanism as demonstrated by the decrease in oxidized proteins after EGCG pretreatment in association with microvillar structure preservation (50).

Glomerulonephritis and lupus nephritis (LN)

Glomerulonephritis is a common renal disorder associated with ESRD and high mortality rate. One of the most aggressive forms of glomerulonephritis is antiglomerular basement membrane nephritis, characterized by crescent formation of immune complex lining the glomerular basement membranes (51). Likewise, LN is a serious complication of systemic lupus erythematosus (38), an autoimmune disease characterized by immune complex deposition and chronic renal inflammation (52). Common treatment of glomerulonephritis and LN includes steroids and immunosuppressive agents, which, although effective, commonly have severe adverse events. Therefore, alternative regimens are required that minimize adverse events.

The first line of evidence showing therapeutic potential of EGCG in glomerulonephritis was reported in an animal model of antiglomerular basement membrane glomerulonephritis (53). EGCG significantly decreased glomerular and tubulointerstitial injury and could also reduce mortality rate when compared to vehicle-treated mice, indicating a potential therapeutic effect of EGCG in glomerulonephritis (53). In addition, oxidative stress markers (malondialdehyde, myeloperoxidase, and hydrogen peroxide), NAD(P), and antioxidant enzymes (glutathione peroxidase and catalase)

returned to baseline in the EGCG-treated group (54). Not only peroxisome proliferator-activated receptor γ but also Nrf2 signaling pathways contribute to the renoprotective effect of EGCG against experimental crescentic glomerulonephritis (55).

For LN, Tsai et al. (56) showed that renal function and histopathology were dramatically improved in EGCG-treated lupus-prone mice, although mild glomerular proliferation and interstitial inflammation were still observed (56). In addition, EGCG markedly reduced ROS in serum, urine, and renal tissue, and also activated the Nrf2-mediated antioxidant pathway, suggesting significance of the antioxidative property of EGCG against LN (56). EGCG could inhibit infiltrating immune cells and inflammasome activation as shown by lowered production of IL-1β, IL-18, and caspase-1 (56). Peairs and colleagues (57) demonstrated an anti-inflammatory effect of EGCG in mesangial cells isolated from MRL/lpr mice presenting lupus-like autoimmune syndrome. EGCG could attenuate inflammatory products, including IL-6, inducible nitric oxide synthase, and nitrite (stabilized product of nitric oxide) (57).

Renal Cell Carcinoma (RCC)

RCC is the most common type of kidney cancer, accounting for 95% of kidney cancers in adults (58, 59). RCC can be divided into several subtypes based on microscopic examination, including clear cell, papillary, chromophobe, and rare types of RCC (e.g., collecting duct carcinoma, medullary carcinoma, mucinous tubular and spindle cell carcinoma) (54, 60). Treatment modalities for RCC depend on its type and stage at diagnosis, with options including surgery, radiotherapy, immunotherapy, and targeted therapy. Chemotherapy is not recommended as standard treatment for RCC because chemoresistance is quite common (54, 60). Thus, there is a need for novel or alternative drugs for targeted therapy to increase efficacy and minimize side effects.

A chemopreventive effect of EGCG or green tea catechin in RCC was initially reported by Yoshioka et al. (61). Their results showed that green tea catechin could reduce tumor size in Wistar rats treated with 0.2% N-ethyl-N-hydroxyethylnitrosamine (61). Because disruption of gap junction intercellular communication in renal epithelial cells might contribute to renal carcinogenesis (62, 63), the same group of investigators later provided in vitro evidence demonstrating that pretreatment with EGCG could prevent disruption of the gap junction intercellular communication by dimethylnitrosamine, suggesting a chemoprotective role of EGCG in development of RCC (63).

Interestingly, EGCG could elevate expression of connexin 32 (Cx32) (64), which is usually suppressed in RCC because of hypermethylation of the *CpG* gene island (65, 66). It has also been demonstrated that restoration of Cx32 expression has a key role in enhancing vinblastine-induced cytotoxicity of RCC (67). In addition, EGCG could suppress multidrug resistance 1 protein via inactivation of Src and subsequent activation of c-Jun N-terminal kinase signaling (64). An in vitro study using a RCC cell line revealed that EGCG could inhibit cell growth and induce apoptosis via overexpression of the tumor suppressor gene *TFPI-2*, which is known to be downregulated through hypermethylation at the *CpG* island of the promoter gene in various cancers (68). Additional references have also demonstrated anticancer activity of EGCG in inhibition of cell migration and invasion in a dose-dependent manner (69, 70).

Diabetic Nephropathy (DN)

DN is a major microvascular complication of diabetes and is recognized as one of the leading causes of CKD and ESRD worldwide. Patients who develop DN also suffer from other microvascular complications caused by advanced glycation end products (AGEs), activation of mitogen activated protein kinases (MAPKs) and protein kinase C, in association with overproduction of various cytokines, chemokines, and growth factors (71, 72). Early diagnosis and medical management are essential and may mitigate or delay the progression of DN. To date, therapeutic strategies usually include blood pressure control by regulation of the renin-angiotensin system, and monitoring of sugar and lipid profiles. However, DN remains common and its prevalence and incidence are ever-increasing (73), but these may simply reflect the inefficacy of any previous DN prevention attempts.

Evaluation of beneficial effects of EGCG in DN was initially made in streptozotocin-induced diabetic rats with subtotal nephrectomy (74). The results showed that prolonged treatment with EGCG for 50 d in diabetic rats resulted in a significant decrease in renal lesions and suppression of hyperglycemia, proteinuria, and lipid peroxidation (74). In addition, EGCG could reduce accumulated AGEs and anti-inflammatory molecules (74). Another study in streptozotocin-induced diabetic mice showed consistent findings demonstrating that EGCG had renoprotective effects against DN (75). EGCG also improved renal function, as evidenced by reduction of serum creatinine and blood urea nitrogen, and decreased proteinuria and renal tissue damage (75). The renoprotective effect of EGCG was also demonstrated in a type 2 diabetes model using Goto-Kakizaki rats (76). Rats fed a diet containing catechins had lower blood glucose, systolic blood pressure, urinary albumin, and angiotensin-converting enzyme activity compared with those fed a normal diet (76).

A cellular study demonstrated that AGEs commonly induce upregulation of receptors for AGEs, activation of NF-κB, production of TNF-α, and cell apoptosis (77). However, such effects could be reversed by EGCG treatment, which has medical implications for patients with DN (77). In addition, a combination of EGCG and α lipoic acid could prevent high glucose-induced kidney cell damage (78). The underlying mechanisms were most likely based on antioxidative and anti-inflammatory properties as SOD increased whereas production of ROS and proinflammatory cytokines was suppressed (78).

A molecular signaling study confirmed that EGCG could ameliorate oxidative stress-induced renal damage in diabetic

animals (79). The striking results showed that EGCG treatment could decrease blood glucose, while increasing insulin in mice. In addition, urinary 8-iso-prostaglandin F2α and angiotensin II were also decreased in the EGCG-treated group (79). EGCG treatment could restore amounts of angiotensin II type 1 receptor, TGF-β1, p22-phox, p47-phox, phosphorylated extracellular signal-regulated kinase 1/2, phosphorylated p38 MAPK, and α-smooth muscle actin to baseline in renal tissues of the diabetic mice (79). Through the use of specific inhibitors to extracellular signal-regulated kinase 1/2 and p38 MAPK, which are the downstream molecules of angiotensin II signaling, functional data suggested that EGCG might act similarly to these inhibitors to mitigate oxidative stress and overproduction of TGF-β1 and α-smooth muscle actin, which are significant and potent inducers of renal fibrosis (79).

CKD and renal fibrosis

Renal fibrosis is a common pathological feature found in CKD and is characterized by renal tissue scars from overproduction and accumulation of extracellular matrix. Although many attempts have been made to identify the primary molecule causing renal fibrogenesis, currently, there is no specific and effective treatment for renal fibrosis and CKD. Thus, there is a need for new therapeutic targets and drugs to recover renal fibrosis.

Wang and colleagues (80–82) extensively investigated the renoprotective effects of EGCG in mice with unilateral ureteral obstruction (UUO), which is a common animal model of renal fibrosis. They initially demonstrated that a Smad-dependent TGF-β1 signaling pathway was activated in association with epithelial mesenchymal transition (EMT), which contributed to renal fibrosis (80). Histopathological study revealed glomerular and tubular injury with macrophage infiltration, indicating renal inflammation in the UUO group, together with increased chemokines (monocyte chemoattractant proteins 1 and 3) and proinflammatory cytokines (TNF-α and IL-1β) (80). However, these features could be reversed by EGCG administration (80). The results were also confirmed by in vitro experiments using a TGF-β1-treated cell line (80). In addition, inhibition of p38 MAPK using a specific inhibitor (SB203580) could attenuate TGF-β1-induced cell apoptosis, similar to the effect from EGCG treatment, implying that the preventive effect of EGCG against TGF-β1-induced tubular cell apoptosis in UUO mice might be mediated, at least in part, by inhibition of p38 MAPK signaling (80). Mice treated with EGCG had elevated antioxidant enzymes (SOD, catalase, and glutathione peroxidase), which initially had been decreased by UUO (81). In addition, EGCG could ameliorate UUO-induced inflammatory response by reducing activity of myeloperoxidase and release of proinflammatory cytokines (i.e., TNF- α, IL-6, and IL-1β). The underlying mechanism of such a protective effect of EGCG was mediated via inhibition of NF-κB activity and activation of Nrf2/HO-1 signaling (81), consistent with previous findings reported by Zhou et al. (83), demonstrating improved renal ultrastructure and increased Nrf2 and antioxidant enzyme γ-glutamylcysteine synthetase in EGCG-treated UUO rats.

Interestingly, TGF-β-induced EMT phenotypes in renal tubular cells could be prevented by pretreatment with EGCG in a dose-dependent manner (82). Chen et al. (84) demonstrated that EGCG could also prevent cadmium-induced chronic renal injury and renal fibrosis in rats. In addition, our group showed that EGCG could prevent oxalate-induced EMT in renal tubular cells (85). Oxalate (a known oxidative stress inducer) could induce EMT in renal tubular cells via ROS overproduction, which could be reversed by EGCG through activation of Nrf2 signaling (85).

Summary and Future Perspectives

Over the past decade, a large number of in vitro and in vivo studies have investigated the health benefits of green tea and its main chemical component, EGCG, in various human diseases including renal disorders. The antioxidative, anti-inflammatory, and antiapoptotic properties of EGCG hold great promise for its use as an alternative strategy to treat or prevent various kidney diseases (Figure 1). The molecular mechanism underlying such beneficial effects of EGCG is mediated mainly through Nrf2 and NF-κB signaling pathways (Figure 2).

Although several lines of evidence have demonstrated beneficial effects of EGCG against various kidney diseases, there are challenges that require further investigation before this compound can be used in clinical practice. First, the concentrations of EGCG used in most of the aforementioned studies were much higher than the physiologic range of EGCG concentration in human plasma, which is usually $<$1 μM after ingestion (86, 87). Such low bioavailability of EGCG may limit its beneficial effects in prevention or treatment of diseases in vivo. Vice versa, the previously positive data must be also confirmed using lower concentrations of EGCG.

Second, stability and bioavailability of EGCG are crucial for its efficacy. It is known that EGCG is unstable and can be auto-oxidized to form a radical dimer under cell culture conditions (88–90). However, it is rather stable in the blood circulation and the EGCG dimer has not been detected in the plasma (91, 92). Several factors, including the amount of EGCG in tea and foods, pH, temperature, oxygen partial pressure, and ionic strength, can affect stability and bioavailability of EGCG in human plasma (93, 94). Interestingly, EGCG is more stable in the acidic pH of the stomach, whereas the alkaline pH of the small intestine (in which EGCG absorption takes place) decreases its stability (95, 96). In addition, high temperature, oxygen partial pressure, and ionic strength tend to degrade EGCG. However, low oxygen partial pressure of the tissue ($<$20 mmHg) and the existence of plasma antioxidants may enhance stability of EGCG in blood (92). These findings suggest that the bioavailabilities of EGCG under in vitro cell culture and in vivo condition are inconsistent because of differences in stability, thereby influencing its biological activities. As a result, it is imperative

to understand the fate of EGCG in the human body after consumption.

Third, recent developments in pharmaceutical formulation have aimed to increase the stability and bioavailability of EGCG (94). Stabilizers, for example, antioxidants (SOD, ascorbic acid, and propyl gallate), protein carriers (serum albumin, β-casein, and gelatin), and amphiphilic compounds (glycerin, transcutol P, and polyethylene glycol 200) have been proven to increase the stability of EGCG (92, 96–98). Recent advances in drug delivery systems, such as encapsulation and nanotechnology, have been applied in attempts to increase stability and bioavailability of EGCG (99). Encapsulation by chitosan can increase intestinal retention time, stability, and absorption of EGCG, and thus increase its plasma concentration (100–102). Besides the encapsulated EGCG, various types of nanoparticles, for example colloidal mesoporous silica (103), nanoliposomes (104, 105), radioactive gold nanoparticles (106), and micellar nanocomplexes (107), have been developed to increase efficacy of EGCG in cancer research (94, 108). However, the challenge remains to apply the encapsulated nanotechnology for investigation of the therapeutic potential of EGCG in kidney diseases.

Fourth, examinations of the molecular targets of EGCG and the underlying mechanism of its action at the cellular level are necessary for specific treatment in each disease entity. A cellular trafficking study with fluorescein isothiocyanate (FITC)-conjugated EGCG demonstrated that EGCG binds to the cell membranes and then disseminates into the cytoplasm and accumulates at the perinuclear region (109). Apart from signal transduction via engagement to its surface receptor, direct cellular incorporation of EGCG can trigger signal transduction by direct interaction with its intracellular targets, including proteins and nucleic acids (110–113). Common consequences are alterations in activities of transcription factors, growth factors, protein kinases, and microRNA (114). These alterations, in turn, activate or suppress many signaling pathways depending on the cell types and stages (e.g., resting normal cells versus proliferating cancer cells). It would be of great value for specific therapies of kidney diseases to identify primary and secondary targets of EGCG.

Finally, almost all of the studies using EGCG or green tea in kidney diseases have been done in animal or cell culture models. Thus, clinical trials are needed to obtain conclusive evidence of the renoprotective effects of EGCG against kidney diseases. In addition, we anticipate more in-depth in vitro and in vivo studies to provide a holistic view of the renoprotective effects of EGCG and its mechanisms of action. Together with progress in development of drug design and delivery systems, all of these advancements could help to make EGCG a potent therapeutic agent for kidney diseases.

Acknowledgments

The authors' responsibilities were as follows—RK and VT, drafted the manuscript and are responsible for all aspects of the manuscript; and all authors: read and approved the final paper.

References

1. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney Int 2011;80:1258–70.
2. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. Nat Rev Nephrol 2017;13:104–14.
3. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet 2017;389:1238–52.
4. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW. Chronic kidney disease: global dimension and perspectives. Lancet 2013;382:260–72.
5. Chowdhury A, Sarkar J, Chakraborti T, Pramanik PK, Chakraborti S. Protective role of epigallocatechin-3-gallate in health and disease: a perspective. Biomed Pharmacother 2016;78:50–9.
6. Yang CS, Chen G, Wu Q. Recent scientific studies of a traditional Chinese medicine, tea, on prevention of chronic diseases. J Tradit Complement Med 2014;4:17–23.
7. Yong-xing Z, Li S. History and prospect of tea medicine in China. Int J Tea Sci 2006;5:19–27.
8. Kanwar J, Taskeen M, Mohammad I, Huo C, Chan TH, Dou QP. Recent advances on tea polyphenols. Front Biosci (Elite Ed) 2012;4:111–31.
9. Khokhar S, Magnusdottir SG. Total phenol, catechin, and caffeine contents of teas commonly consumed in the United Kingdom. J Agric Food Chem 2002;50:565–70.
10. Higdon JV, Frei B. Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions. Crit Rev Food Sci Nutr 2003;43:89–143.
11. Mak JC. Potential role of green tea catechins in various disease therapies: progress and promise. Clin Exp Pharmacol Physiol 2012;39:265–73.
12. Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. Curr Neuropharmacol 2009;7:65–74.
13. Khurana S, Venkataraman K, Hollingsworth A, Piche M, Tai TC. Polyphenols: benefits to the cardiovascular system in health and in aging. Nutrients 2013;5:3779–827.
14. Teshima Y, Takahashi N, Nishio S, Saito S, Kondo H, Fukui A, Aoki K, Yufu K, Nakagawa M, Saikawa T. Production of reactive oxygen species in the diabetic heart. Roles of mitochondria and NADPH oxidase. Circ J 2014;78:300–6.
15. Bao H, Peng A. The green tea polyphenol (-)-epigallocatechin-3-gallate and its beneficial roles in chronic kidney disease. J Transl Int Med 2016;4:99–103.
16. Makris K, Spanou L. Acute kidney injury: diagnostic approaches and controversies. Clin Biochem Rev 2016;37:153–75.
17. McCaffrey J, Dhakal AK, Milford DV, Webb NJ, Lennon R. Recent developments in the detection and management of acute kidney injury. Arch Dis Child 2017;102:91–6.
18. Bao GH, Xu J, Hu FL, Wan XC, Deng SX, Barasch J. EGCG inhibit chemical reactivity of iron through forming an Ngal-EGCG-iron complex. Biometals 2013;26:1041–50.
19. Twal M, Kiefer P, Salameh A, Schnabel J, Ossmann S, von Salisch S, Krämer K, Sobiraj A, Kostelka M, Mohr FW, et al. Renoprotective effects of epigallocatechin gallate in a small piglet model of extracorporeal circulation. Pharmacol Res 2013;67:68–78.
20. Funamoto M, Masumoto H, Takaori K, Taki T, Setozaki S, Yamazaki K, Minakata K, Ikeda T, Hyon SH, Sakata R. Green tea polyphenol prevents diabetic rats from acute kidney injury after cardiopulmonary bypass. Ann Thorac Surg 2016;101:1507–13.
21. Kakuta Y, Okumi M, Isaka Y, Tsutahara K, Abe T, Yazawa K, Ichimaru N, Matsumura K, Hyon SH, Takahara S, et al. Epigallocatechin-3-gallate protects kidneys from ischemia reperfusion injury by HO-1

upregulation and inhibition of macrophage infiltration. Transpl Int 2011;24:514–22.
22. Karasawa T, Steyger PS. An integrated view of cisplatin-induced nephrotoxicity and ototoxicity. Toxicol Lett 2015;237:219–27.
23. El Mowafy AM, Al Gayyar MM, Salem HA, El Mesery ME, Darweish MM. Novel chemotherapeutic and renal protective effects for the green tea (EGCG): role of oxidative stress and inflammatory-cytokine signaling. Phytomedicine 2010;17:1067–75.
24. El Mowafy AM, Salem HA, Al Gayyar MM, El Mesery ME, El Azab MF. Evaluation of renal protective effects of the green-tea (EGCG) and red grape resveratrol: role of oxidative stress and inflammatory cytokines. Nat Prod Res 2011;25:850–6.
25. Sahin K, Tuzcu M, Gencoglu H, Dogukan A, Timurkan M, Sahin N, Aslan A, Kucuk O. Epigallocatechin-3-gallate activates Nrf2/HO-1 signaling pathway in cisplatin-induced nephrotoxicity in rats. Life Sci 2010;87:240–5.
26. Pan H, Chen J, Shen K, Wang X, Wang P, Fu G, Meng H, Wang Y, Jin B. Mitochondrial modulation by epigallocatechin-3-gallate ameliorates cisplatin induced renal injury through decreasing oxidative/nitrative stress, inflammation and NF-kB in mice. PLoS One 2015;10: e0124775.
27. Zou P, Song J, Jiang B, Pei F, Chen B, Yang X, Liu G, Hu Z. Epigallocatechin-3-gallate protects against cisplatin nephrotoxicity by inhibiting the apoptosis in mouse. Int J Clin Exp Pathol 2014;7:4607–16.
28. Chen B, Liu G, Zou P, Li X, Hao Q, Jiang B, Yang X, Hu Z. Epigallocatechin-3-gallate protects against cisplatin-induced nephrotoxicity by inhibiting endoplasmic reticulum stress-induced apoptosis. Exp Biol Med (Maywood) 2015;240:1513–9.
29. Chang EJ, Mun KC. Effect of epigallocatechin gallate on renal function in cyclosporine-induced nephrotoxicity. Transplant Proc 2004;36:2133–4.
30. Hisamura F, Kojima-Yuasa A, Huang X, Kennedy DO, Matsui-Yuasa I. Synergistic effect of green tea polyphenols on their protection against FK506-induced cytotoxicity in renal cells. Am J Chin Med 2008;36:615–24.
31. Thongboonkerd V. Proteomics and kidney stone disease. Contrib Nephrol 2008;160:142–58.
32. Vinaiphat A, Thongboonkerd V. Prospects for proteomics in kidney stone disease. Expert Rev Proteomics 2017;14:185–7.
33. Hall PM. Nephrolithiasis: treatment, causes, and prevention. Cleve Clin J Med 2009;76:583–91.
34. Frochot V, Daudon M. Clinical value of crystalluria and quantitative morphoconstitutional analysis of urinary calculi. Int J Surg 2016;36:624–32.
35. Vupputuri S, Soucie JM, McClellan W, Sandler DP. History of kidney stones as a possible risk factor for chronic kidney disease. Ann Epidemiol 2004;14:222–8.
36. Gillen DL, Worcester EM, Coe FL. Decreased renal function among adults with a history of nephrolithiasis: a study of NHANES III. Kidney Int 2005;67:685–90.
37. Rule AD, Bergstralh EJ, Melton LJ, III, Li X, Weaver AL, Lieske JC. Kidney stones and the risk for chronic kidney disease. Clin J Am Soc Nephrol 2009;4:804–11.
38. Hippisley-Cox J, Coupland C. Predicting the risk of chronic kidney disease in men and women in England and Wales: prospective derivation and external validation of the QKidney Scores. BMC Fam Pract 2010;11:49.
39. Charrier MJ, Savage GP, Vanhanen L. Oxalate content and calcium binding capacity of tea and herbal teas. Asia Pac J Clin Nutr 2002;11:298–301.
40. Itoh Y, Yasui T, Okada A, Tozawa K, Hayashi Y, Kohri K. Preventive effects of green tea on renal stone formation and the role of oxidative stress in nephrolithiasis. J Urol 2005;173:271–5.
41. Jeong BC, Kim BS, Kim JI, Kim HH. Effects of green tea on urinary stone formation: an in vivo and in vitro study. J Endourol 2006;20:356–61.
42. Hirose M, Tozawa K, Okada A, Hamamoto S, Shimizu H, Kubota Y, Itoh Y, Yasui T, Kohri K. Glyoxylate induces renal tubular cell injury and microstructural changes in experimental mouse. Urol Res 2008;36:139–47.
43. Kanlaya R, Singhto N, Thongboonkerd V. EGCG decreases binding of calcium oxalate monohydrate crystals onto renal tubular cells via decreased surface expression of alpha-enolase. J Biol Inorg Chem 2016;21:339–46.
44. Thongboonkerd V, Semangoen T, Chutipongtanate S. Factors determining types and morphologies of calcium oxalate crystals: molar concentrations, buffering, pH, stirring and temperature. Clin Chim Acta 2006;367:120–31.
45. Thongboonkerd V, Semangoen T, Sinchaikul S, Chen ST. Proteomic analysis of calcium oxalate monohydrate crystal-induced cytotoxicity in distal renal tubular cells. J Proteome Res 2008;7:4689–700.
46. Vinaiphat A, Aluksanasuwan S, Manissorn J, Sutthimethakorn S, Thongboonkerd V. Response of renal tubular cells to differential types and doses of calcium oxalate crystals: integrative proteome network analysis and functional investigations. Proteomics 2017;17(15–16):1700192.
47. Peerapen P, Chaiyarit S, Thongboonkerd V. Protein network analysis and functional studies of calcium oxalate crystal-induced cytotoxicity in renal tubular epithelial cells. Proteomics 2018;18(8):e1800008.
48. Fong-ngern K, Peerapen P, Sinchaikul S, Chen ST, Thongboonkerd V. Large-scale identification of calcium oxalate monohydrate crystal-binding proteins on apical membrane of distal renal tubular epithelial cells. J Proteome Res 2011;10:4463–77.
49. Kanlaya R, Fong-ngern K, Thongboonkerd V. Cellular adaptive response of distal renal tubular cells to high-oxalate environment highlights surface alpha-enolase as the enhancer of calcium oxalate monohydrate crystal adhesion. J Proteomics 2013;80C: 55–65.
50. Fong-ngern K, Vinaiphat A, Thongboonkerd V. Microvillar injury in renal tubular epithelial cells induced by calcium oxalate crystal and the protective role of epigallocatechin-3-gallate. FASEB J 2017;31: 120–31.
51. Sanders JS, Rutgers A, Stegeman CA, Kallenberg CG. Pulmonary: renal syndrome with a focus on anti-GBM disease. Semin Respir Crit Care Med 2011;32:328–34.
52. Ortega LM, Schultz DR, Lenz O, Pardo V, Contreras GN. Review: lupus nephritis: pathologic features, epidemiology and a guide to therapeutic decisions. Lupus 2010;19:557–74.
53. Peng A, Ye T, Rakheja D, Tu Y, Wang T, Du Y, Zhou JK, Vaziri ND, Hu Z, Mohan C, et al. The green tea polyphenol (-)-epigallocatechin-3-gallate ameliorates experimental immune-mediated glomerulonephritis. Kidney Int 2011;80:601–11.
54. Low G, Huang G, Fu W, Moloo Z, Girgis S. Review of renal cell carcinoma and its common subtypes in radiology. World J Radiol 2016;8:484–500.
55. Ye T, Zhen J, Du Y, Zhou JK, Peng A, Vaziri ND, Mohan C, Xu Y, Zhou XJ. Green tea polyphenol (-)-epigallocatechin-3-gallate restores Nrf2 activity and ameliorates crescentic glomerulonephritis. PLoS One 2015;10:e0119543.
56. Tsai PY, Ka SM, Chang JM, Chen HC, Shui HA, Li CY, Hua KF, Chang WL, Huang JJ, Yang SS, et al. Epigallocatechin-3-gallate prevents lupus nephritis development in mice via enhancing the Nrf2 antioxidant pathway and inhibiting NLRP3 inflammasome activation. Free Radic Biol Med 2011;51:744–54.
57. Peairs A, Dai R, Gan L, Shimp S, Rylander MN, Li L, Reilly CM. Epigallocatechin-3-gallate (EGCG) attenuates inflammation in MRL/lpr mouse mesangial cells. Cell Mol Immunol 2010;7: 123–32.
58. Yu SS, Quinn DI, Dorff TB. Clinical use of cabozantinib in the treatment of advanced kidney cancer: efficacy, safety, and patient selection. Onco Targets Ther 2016;9:5825–37.
59. Kawashima A, Young SW, Takahashi N, King BF, Atwell TD. Inherited renal carcinomas. Abdom Radiol (NY) 2016;41:1066–78.

60. Young JR, Margolis D, Sauk S, Pantuck AJ, Sayre J, Raman SS. Clear cell renal cell carcinoma: discrimination from other renal cell carcinoma subtypes and oncocytoma at multiphasic multidetector CT. Radiology 2013;267:444–53.
61. Yoshioka N, Hiasa Y, Cho M, Kitahori Y, Hirao K, Konishi N, Kuwashima S. Effect of polyphenon-60 on the development of renal cell tumors in rats treated with N-ethyl-N hydroxyethylnitrosamine. Cancer Lett 1999;136:79–82.
62. Yamasaki H. Role of disrupted gap junctional intercellular communication in detection and characterization of carcinogens. Mutat Res 1996;365:91–105.
63. Takahashi H, Nomata K, Mori K, Matsuo M, Miyaguchi T, Noguchi M, Kanetake H. The preventive effect of green tea on the gap junction intercellular communication in renal epithelial cells treated with a renal carcinogen. Anticancer Res 2004;24:3757–62.
64. Sato A, Sekine M, Kobayashi M, Virgona N, Ota M, Yano T. Induction of the connexin 32 gene by epigallocatechin-3-gallate potentiates vinblastine-induced cytotoxicity in human renal carcinoma cells. Chemotherapy 2013;59:192–9.
65. Hirai A, Yano T, Nishikawa K, Suzuki K, Asano R, Satoh H, Hagiwara K, Yamasaki H. Down-regulation of connexin 32 gene expression through DNA methylation in a human renal cell carcinoma cell. Am J Nephrol 2003;23:172–7.
66. Yano T, Ito F, Kobayashi K, Yonezawa Y, Suzuki K, Asano R, Hagiwara K, Nakazawa H, Toma H, Yamasaki H. Hypermethylation of the CpG island of connexin 32, a candidate tumor suppressor gene in renal cell carcinomas from hemodialysis patients. Cancer Lett 2004;208: 137–42.
67. Takano Y, Iwata H, Yano Y, Miyazawa M, Virgona N, Sato H, Ueno K, Yano T. Up-regulation of connexin 32 gene by 5-aza-2'-deoxycytidine enhances vinblastine-induced cytotoxicity in human renal carcinoma cells via the activation of JNK signalling. Biochem Pharmacol 2010;80:463–70.
68. Gu B, Ding Q, Xia G, Fang Z. EGCG inhibits growth and induces apoptosis in renal cell carcinoma through TFPI-2 overexpression. Oncol Rep 2009;21:635–40.
69. Roomi MW, Ivanov V, Kalinovsky T, Niedzwiecki A, Rath M. Anticancer effect of lysine, proline, arginine, ascorbic acid and green tea extract on human renal adenocarcinoma line 786-0. Oncol Rep 2006;16:943–7.
70. Chen SJ, Yao XD, Peng BO, Xu YF, Wang GC, Huang J, Liu M, Zheng JH. Epigallocatechin-3-gallate inhibits migration and invasion of human renal carcinoma cells by downregulating matrix metalloproteinase-2 and matrix metalloproteinase-9. Exp Ther Med 2016;11:1243–8.
71. Ojima A, Ishibashi Y, Matsui T, Maeda S, Nishino Y, Takeuchi M, Fukami K, Yamagishi S. Glucagon-like peptide-1 receptor agonist inhibits asymmetric dimethylarginine generation in the kidney of streptozotocin-induced diabetic rats by blocking advanced glycation end product-induced protein arginine methyltranferase-1 expression. Am J Pathol 2013;182:132–41.
72. Juan YS, Chuang SM, Long CY, Lin RJ, Liu KM, Wu WJ, Huang CH. Protein kinase C inhibitor prevents renal apoptotic and fibrotic changes in response to partial ureteric obstruction. BJU Int 2012;110:283–92.
73. Gnudi L, Coward RJM, Long DA. Diabetic nephropathy: perspective on novel molecular mechanisms. Trends Endocrinol Metab 2016;27:820–30.
74. Yamabe N, Yokozawa T, Oya T, Kim M. Therapeutic potential of (-)-epigallocatechin 3-O-gallate on renal damage in diabetic nephropathy model rats. J Pharmacol Exp Ther 2006;319:228–36.
75. Yoon SP, Maeng YH, Hong R, Lee BR, Kim CG, Kim HL, Chung JH, Shin BC. Protective effects of epigallocatechin gallate (EGCG) on streptozotocin-induced diabetic nephropathy in mice. Acta Histochem 2014;116:1210–5.
76. Igarashi K, Honma K, Yoshinari O, Nanjo F, Hara Y. Effects of dietary catechins on glucose tolerance, blood pressure and oxidative status in Goto-Kakizaki rats. J Nutr Sci Vitaminol (Tokyo) 2007;53:496–500.
77. Liang YJ, Jian JH, Liu YC, Juang SJ, Shyu KG, Lai LP, Wang BW, Leu JG. Advanced glycation end products-induced apoptosis attenuated by PPARdelta activation and epigallocatechin gallate through NF-kappaB pathway in human embryonic kidney cells and human mesangial cells. Diabetes Metab Res Rev 2010;26:406–16.
78. Leu JG, Lin CY, Jian JH, Shih CY, Liang YJ. Epigallocatechin-3-gallate combined with alpha lipoic acid attenuates high glucose-induced receptor for advanced glycation end products (RAGE) expression in human embryonic kidney cells. An Acad Bras Cienc 2013;85: 745–52.
79. Yang XH, Pan Y, Zhan XL, Zhang BL, Guo LL, Jin HM. Epigallocatechin-3-gallate attenuates renal damage by suppressing oxidative stress in diabetic db/db mice. Oxid Med Cell Longev 2016;2016:2968462.
80. Wang Y, Wang B, Du F, Su X, Sun G, Zhou G, Bian X, Liu N. Epigallocatechin-3-gallate attenuates unilateral ureteral obstruction-induced renal interstitial fibrosis in mice. J Histochem Cytochem 2015;63:270–9.
81. Wang Y, Wang B, Du F, Su X, Sun G, Zhou G, Bian X, Liu N. Epigallocatechin-3-gallate attenuates oxidative stress and inflammation in obstructive nephropathy via NF-κB and Nrf2/HO-1 signalling pathway regulation. Basic Clin Pharmacol Toxicol 2015;117:164–72.
82. Wang Y, Liu N, Su X, Zhou G, Sun G, Du F, Bian X, Wang B. Epigallocatechin-3-gallate attenuates transforming growth factor-β1 induced epithelial-mesenchymal transition via Nrf2 regulation in renal tubular epithelial cells. Biomed Pharmacother 2015;70: 260–7.
83. Zhou P, Yu JF, Zhao CG, Sui FX, Teng X, Wu YB. Therapeutic potential of EGCG on acute renal damage in a rat model of obstructive nephropathy. Mol Med Rep 2013;7:1096–102.
84. Chen J, Du L, Li J, Song H. Epigallocatechin-3-gallate attenuates cadmium-induced chronic renal injury and fibrosis. Food Chem Toxicol 2016;96:70–8.
85. Kanlaya R, Khamchun S, Kapincharanon C, Thongboonkerd V. Protective effect of epigallocatechin-3-gallate (EGCG) via Nrf2 pathway against oxalate-induced epithelial mesenchymal transition (EMT) of renal tubular cells. Sci Rep 2016;6:30233.
86. Tachibana H. Green tea polyphenol sensing. Proc Jpn Acad Ser B Phys Biol Sci 2011;87:66–80.
87. Clifford MN, van der Hooft JJ, Crozier A. Human studies on the absorption, distribution, metabolism, and excretion of tea polyphenols. Am J Clin Nutr 2013;98:1619S–30S.
88. Mizooku Y, Yoshikawa M, Tsuneyoshi T, Arakawa R. Analysis of oxidized epigallocatechin gallate by liquid chromatography/mass spectrometry. Rapid Commun Mass Spectrom 2003;17: 1915–8.
89. Song S, Huang YW, Tian Y, Wang XJ, Sheng J. Mechanism of action of (-)-epigallocatechin-3-gallate: auto-oxidation-dependent activation of extracellular signal-regulated kinase 1/2 in Jurkat cells. Chin J Nat Med 2014;12:654–62.
90. Neilson AP, Song BJ, Sapper TN, Bomser JA, Ferruzzi MG. Tea catechin auto-oxidation dimers are accumulated and retained by Caco-2 human intestinal cells. Nutr Res 2010;30:327–40.
91. Ishii T, Ichikawa T, Minoda K, Kusaka K, Ito S, Suzuki Y, Akagawa M, Mochizuki K, Goda T, Nakayama T. Human serum albumin as an antioxidant in the oxidation of (-)-epigallocatechin gallate: participation of reversible covalent binding for interaction and stabilization. Biosci Biotechnol Biochem 2011;75:100–6.
92. Hou Z, Sang S, You H, Lee MJ, Hong J, Chin KV, Yang CS. Mechanism of action of (−)-epigallocatechin-3-gallate: auto-oxidation-dependent inactivation of epidermal growth factor receptor and direct effects on growth inhibition in human esophageal cancer KYSE 150 cells. Cancer Res 2005;65:8049–56.
93. Sang S, Lee MJ, Hou Z, Ho CT, Yang CS. Stability of tea polyphenol (-)-epigallocatechin-3-gallate and formation of dimers and epimers under common experimental conditions. J Agric Food Chem 2005;53:9478–84.

94. Krupkova O, Ferguson SJ, Wuertz-Kozak K. Stability of (-)-epigallocatechin gallate and its activity in liquid formulations and delivery systems. J Nutr Biochem 2016;37:1–12.
95. Krook MA, Hagerman AE. Stability of polyphenols epigallocatechin gallate and pentagalloyl glucose in a simulated digestive system. Food Res Int 2012;49:112–6.
96. Fangueiro JF, Parra A, Silva AM, Egea MA, Souto EB, Garcia ML, Calpena AC. Validation of a high performance liquid chromatography method for the stabilization of epigallocatechin gallate. Int J Pharm 2014;475:181–90.
97. Proniuk S, Liederer BM, Blanchard J. Preformulation study of epigallocatechin gallate, a promising antioxidant for topical skin cancer prevention. J Pharm Sci 2002;91:111–6.
98. Hatano T, Tsugawa M, Kusuda M, Taniguchi S, Yoshida T, Shiota S, Tsuchiya T. Enhancement of antibacterial effects of epigallocatechin gallate, using ascorbic acid. Phytochemistry 2008;69:3111–6.
99. Wang S, Su R, Nie S, Sun M, Zhang J, Wu D, Moustaid-Moussa N. Application of nanotechnology in improving bioavailability and bioactivity of diet-derived phytochemicals. J Nutr Biochem 2014;25:363–76.
100. Dube A, Nicolazzo JA, Larson I. Chitosan nanoparticles enhance the plasma exposure of (−)-epigallocatechin gallate in mice through an enhancement in intestinal stability. Eur J Pharm Sci 2011;44:422–6.
101. Hong Z, Xu Y, Yin JF, Jin J, Jiang Y, Du Q. Improving the effectiveness of (−)-epigallocatechin gallate (EGCG) against rabbit atherosclerosis by EGCG-loaded nanoparticles prepared from chitosan and polyaspartic acid. J Agric Food Chem 2014;62:12603–9.
102. Siddiqui IA, Bharali DJ, Nihal M, Adhami VM, Khan N, Chamcheu JC, Khan MI, Shabana S, Mousa SA, Mukhtar H. Excellent anti-proliferative and pro-apoptotic effects of (-)-epigallocatechin-3-gallate encapsulated in chitosan nanoparticles on human melanoma cell growth both in vitro and in vivo. Nanomedicine 2014;10:1619–26.
103. Ding J, Kong X, Yao J, Wang J, Cheng X, Tang B, He Z. Core-shell mesoporous silica nanoparticles improve HeLa cell growth and proliferation inhibition by (-)-epigallocatechin-3-gallate by prolonging the half-life. J Mater Chem 2012;22:19926–31.
104. Luo X, Guan R, Chen X, Tao M, Ma J, Zhao J. Optimization on condition of epigallocatechin-3-gallate (EGCG) nanoliposomes by response surface methodology and cellular uptake studies in Caco-2 cells. Nanoscale Res Lett 2014;9:291.
105. Radhakrishnan R, Kulhari H, Pooja D, Gudem S, Bhargava S, Shukla R, Sistla R. Encapsulation of biophenolic phytochemical EGCG within lipid nanoparticles enhances its stability and cytotoxicity against cancer. Chem Phys Lipids 2016;198:51–60.
106. Shukla R, Chanda N, Zambre A, Upendran A, Katti K, Kulkarni RR, Nune SK, Casteel SW, Smith CJ, Vimal J, et al. Laminin receptor specific therapeutic gold nanoparticles (198AuNP-EGCg) show efficacy in treating prostate cancer. Proc Natl Acad Sci U S A 2012;109:12426–31.
107. Chung JE, Tan S, Gao SJ, Yongvongsoontorn N, Kim SH, Lee JH, Choi HS, Yano H, Zhuo L, Kurisawa M, et al. Self-assembled micellar nanocomplexes comprising green tea catechin derivatives and protein drugs for cancer therapy. Nat Nanotechnol 2014;9:907–12.
108. Peter B, Bosze S, Horvath R. Biophysical characteristics of proteins and living cells exposed to the green tea polyphenol epigallocatechin-3-gallate (EGCg): review of recent advances from molecular mechanisms to nanomedicine and clinical trials. Eur Biophys J 2017;46:1–24.
109. Han DW, Matsumura K, Kim B, Hyon SH. Time-dependent intracellular trafficking of FITC-conjugated epigallocatechin-3-O-gallate in L-929 cells. Bioorg Med Chem 2008;16:9652–9.
110. Palermo CM, Westlake CA, Gasiewicz TA. Epigallocatechin gallate inhibits aryl hydrocarbon receptor gene transcription through an indirect mechanism involving binding to a 90 kDa heat shock protein. Biochemistry 2005;44:5041–52.
111. Kuzuhara T, Sei Y, Yamaguchi K, Suganuma M, Fujiki H. DNA and RNA as new binding targets of green tea catechins. J Biol Chem 2006;281:17446–56.
112. Huang Y, Sumida M, Kumazoe M, Sugihara K, Suemasu Y, Yamada S, Yamashita S, Miyakawa J, Takahashi T, Tanaka H, et al. Oligomer formation of a tea polyphenol, EGCG, on its sensing molecule 67 kDa laminin receptor. Chem Commun (Camb) 2017;53:1941–4.
113. Patra SK, Rizzi F, Silva A, Rugina DO, Bettuzzi S. Molecular targets of (-)-epigallocatechin-3-gallate (EGCG): specificity and interaction with membrane lipid rafts. J Physiol Pharmacol 2008;59(Suppl 9):217–35.
114. Lorenz M. Cellular targets for the beneficial actions of tea polyphenols. Am J Clin Nutr 2013;98:1642S–50S.