Polyphenols in Renal Pathophysiology

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Kidney diseases constitute a worldwide public health problem, contributing to morbidity and mortality. An overview of the published data regarding the potential beneficial effects of polyphenols on major kidney diseases, namely acute kidney injury, chronic kidney disease, diabetic nephropathy, renal cancer, and drug-induced nephrotoxicity.The biological effects of polyphenols can be highly attributed to the modulation of specific signaling cascades including those involved in oxidative stress responses, anti-inflammation processes, and apoptosis. There is increasing evidence that polyphenols afford great potential in renal disease protection. However, this evidence (especially when in vitro studies are involved) should be considered with caution before its clinical translation, particularly due to the unfavorable pharmacokinetics and extensive metabolization that polyphenols undergo in the human body. Future research should consider polyphenols and their metabolites that indeed reach kidney tissues.

polyphenols renal diseases acute kidney injury chronic kidney disease

1. Introduction

Kidney diseases constitute a worldwide public health problem, contributing to morbidity and mortality from non-communicable diseases, both as a direct cause and as a risk factor for cardiovascular disease [1]. The burden of renal pathologies is rising year after year in different regions of the world [2]. This increase is associated with higher mortality and treatment costs [2], demanding great attention in terms of global health policies. The variations in incidence, prevalence, and outcomes of renal diseases may depend on several biological, socioeconomic, and behavioral risk factors [3]. Several studies have explored the role of diet in the context of chronic kidney diseases or renal cancer [4][5]. However, the effects of dietary interventions on the outcome of kidney diseases remain to be clarified.

Despite the lack of conclusive epidemiological data, numerous in vitro and in vivo studies have dealt with the effects of polyphenols and kidney diseases. In addition to a dietary approach, polyphenols have been explored as potential therapeutic/nutraceutical agents against kidney diseases [6][7]. In this context, some studies use high doses, different administration routes and specific drug delivery systems to target kidney tissues [8][9]. The interest in these compounds is supported essentially by their ability to modulate redox and inflammatory pathways. Scientific evidence suggests that reactive oxygen species (ROS) and inflammation play a key role in the pathophysiologic processes of renal diseases. The kidney is an organ particularly vulnerable to ROS attack [10] and oxidative damage is associated with a wide range of renal impairments, including acute renal failure [11], obstructive nephropathy [12], glomerular damage [13] or chronic renal failure [14]. Therefore, dietary and pharmacological antioxidant/anti-inflammatory interventions could attenuate renal damage [15]. It should be noted that the use of the term antioxidant throughout the manuscript refers to its broader definition, instead of the classical view of antioxidants as merely scavenging/reducing agents. In biology and medicine, antioxidants can be defined as any substance that can prevent, reduce, or repair the ROS-induced damage of a target biomolecule, including via indirect mechanisms such as the upregulation of nuclear factor E2-related factor 2 (Nrf2) [16], which appears to be highly relevant in polyphenols mode of action.

2. Implication of Polyphenols in Renal Pathophysiology

2.1. Acute Kidney Injury

Acute kidney injury (AKI) is characterized by a loss of kidney function with an increase in serum creatinine, decrease in urinary output, or both for a period until 7 days [17][18]. AKI occurs in approximately 10–15% of patients admitted to the hospital, and its incidence in intensive care can even exceed 50% [17]. AKI is not a single disease entity, but a part of a heterogeneous functional group of disorders that can occur in the setting of acute or chronic illness [18][19]. Nevertheless, despite its complexity, AKI is usually seen as a single disease and classified according to anatomical categories [17]. In AKI, kidney homeostasis is disrupted and in severe cases, it can lead to multiorgan failure being potentially lethal [18]. AKI may be induced by cisplatin, an anticancer drug, and cisplatin treatment is a well-established model to study this kidney injury. The role of polyphenols in this particular cisplatin-induced AKI condition will be discussed in the section about drug-induced nephrotoxicity (2.5).

Many studies have shown that polyphenols can act against various factors that are linked to AKI. Resveratrol (3,5,4′-trihydroxystilbene) is a natural polyphenol that belongs to the stilbenes class. It is present in many plants, and it is the most studied polyphenol that has shown potential protection against AKI. Resveratrol ameliorated several kidney function markers and pathological damage of AKI. Resveratrol showed its effectiveness against AKI through the reduction of ROS in HK-2 human renal cells [20]. Additionally, resveratrol reduced inflammatory (e.g., TNF-α and IL-1β) and kidney injury (e.g., KIM-1) markers, and reversed the alterations of apoptosis-associated proteins (e.g., Bcl-2 and Bax) in different in vitro and in vivo models [21][22][23]. Sepsis is the most common cause of severe AKI in individuals that are extremely ill [17]. In this sense, some studies with septic AKI animal models have also been used to study the beneficial effects of polyphenols in this pathophysiological condition. Resveratrol decreased the mortality rate of septic rodents, alleviated AKI, improved renal microcirculation, protected the tubular epithelium, ameliorated oxidative stress and mitochondrial function, and reduced the inflammatory response [24][25][26]. Mitochondrial dysfunction is one of the characteristics of AKI. The resveratrol glycoside (resveratrol-3-*O*-β-mono-d-glucoside), also known as polydatin or piceid, protected renal tubular epithelial cell mitochondria from dysfunction, reduced inflammatory and oxidative stress parameters, and prolonged survival in a rat model of sepsis-induced AKI [27]. Gallic acid, a phenolic acid present in a large number of plants, also showed significant protection against renal ischemia/reperfusion (I/R)-induced AKI in a rat model [28]. Some studies revealed the antioxidant properties and the improvement in renal function by epigallocatechin-3-gallate (EGCG), the major flavanol present in the tea plant *Camellia sinensis*. EGCG reduced ROS and renal damage by iron overload, acting as an iron chelator, reducing hypoxic damage and oxidative and nitrosative stress [29][30]. EGCG also ameliorated cardiopulmonary bypass-induced AKI in diabetic rats, prevented renal tubular damage, and reduced the level of kidney injury and oxidative stress biomarkers [31]. Another study showed that EGCG could protect the kidney from I/R injury, reducing macrophage infiltration, renal fibrosis, and several molecules involved with an inflammatory response [32]. Curcumin, a biologically active polyphenolic compound obtained from the rhizomes of the plant *Curcuma longa* that is present in several spices, significantly decreased the rate of apoptosis and protected renal cells against I/R-induced AKI [33]. Ellagic acid, a natural polyphenol compound present in food (e.g., chestnut, pomegranate, and blackberry), attenuated the renal ischemia/reperfusion (I/R) injury, a primary reason for AKI, and preserved renal cell function in rats. Additionally, ellagic acid suppressed the levels of inflammatory, oxidative stress, and apoptosis markers in an I/R rat model [34]. Honokiol, a natural polyphenol from the traditional Chinese herb *Magnolia officinalis* attenuated sepsis-associated AKI and ameliorated oxidative stress and inflammatory signals in NRK-52E cells, as well as in a rat model with cecal ligation and puncture (CLP)-induced oxidative stress and inflammatory cytokine production [35].

2.2. Chronic Kidney Disease

Chronic kidney disease (CKD) is a condition defined as persistent alterations in kidney structure, function, or both of at least 3 months duration [36][37]. CKD is associated with urine and structural abnormalities and impaired excretory renal function, which are suggestive of irreversible loss of functional nephrons [37]. CKD arises from many heterogeneous disease pathways, with diabetes and hypertension being the main causes [36][37]. The prevalence of CKD varies between 7–12% worldwide [37]. The most relevant pathophysiologic changes include glomerular sclerosis, tubular atrophy, and interstitial fibrosis [36]. It is common to use animal models in which CKD is associated with diabetes. Nonetheless, the role of polyphenols in models of this particular kidney condition will be presented in the next Section 2.3.

The beneficial impact of polyphenols in CKD has been explored, mainly due to their antioxidant and anti-inflammatory properties. In a recent study, resveratrol alleviated the increase in markers of kidney function, the presence of glomerular sclerosis, and the tubulointerstitial fibrosis induced in nephrectomy rodent models [38]. In another study using a mice model, resveratrol treatment inhibited oxidative stress and renal interstitial fibrosis [39]. Mitochondrial dysfunction is one of the cellular alterations of CKD. In a study performed by Hui et al., (2017), resveratrol attenuated glomerular injury in the remnant kidney of nephrectomized rats and also improved mitochondrial function in vitro and in vivo [40]. Skeletal muscle atrophy is one of the clinical characteristics of CKD. Resveratrol prevented the increase in expression of important pathophysiologic proteins (e.g., MuRF1) in vitro and attenuated muscle atrophy induced by CKD in a rodent model [41]. EGCG exhibited renoprotective effects in mice with unilateral ureteral obstruction, by reducing the inflammatory response and oxidative stress [42]. Moreover, the preventive role of EGCG in CKD and renal fibrosis has also been discussed by its ability to preserve mitochondrial function, antiapoptotic effects, and anti-epithelial mesenchymal transition properties [43]. I/R-induced AKI can lead to renal fibrosis, which is a relevant risk factor for CKD. In a study performed by Hongtao et al. [44], curcumin alleviated I/R-induced late kidney fibrosis in a mouse model [44]. Salvianolic acid A demonstrated antioxidant effects in vitro and reduced kidney injury, inflammation, and oxidative stress markers in a nephrectomized rat model [45].

2.3. Diabetic Nephropathy

Diabetes is a highly prevalent chronic disease affecting more than four hundred million adults worldwide. The disease compromises several body functions, including diabetic nephropathy (DN), also referred as diabetic kidney disease (DKD). DN is among the most common causes of morbidity and mortality in individuals with diabetes as well as the main culprit for end-stage renal disease in the world. With multifactorial and complex pathophysiology, DN management has been considered a major challenge for physicians and the pharmaceutical industry. At the cellular level, DN is associated with several cellular pathways including autophagy dysregulation, oxidative stress, hypoxia, inflammation, and overactive renin-angiotensin-aldosterone system (RAAS) [46][47]. The multitarget effects and broad spectrum of health benefits of polyphenols have pointed these compounds as promising therapeutic intervenients to fight the multiple complications of such complex diseases. In fact, in vitro and preclinical studies have shown that stilbenes, flavonoids (in particular, anthocyanins), and lignans slow the progression of kidney damage and prevent ischemic events and DN [48].

The stilbene resveratrol has gained a great deal of attention thanks to its multiple, yet controversial, actions as an antioxidant, anti-inflammatory, anti-diabetic molecule particularly towards the dysfunction of the renal system in diabetes [49][50][51]. The nephroprotective action of resveratrol as determined in animal and in vitro studies includes the modulation of oxidative stress [50], advanced glycation end-product (AGE) cytotoxicity [52], autophagy, endoplasmic reticulum (ER) stress, apoptosis [53][54][55], lipotoxicity, mitochondrial dysfunction, angiogenesis [50], and inflammation [56]. Remarkably, resveratrol inhibited lipopolysaccharide (LPS)-induced rat glomerular mesangial cells proliferation and inflammation, suggesting that it may prevent and/or delay mesangial cell fibrosis independently of its hypoglycemic activity [57]. Additionally, interestingly, resveratrol and ramipril co-treatment showed reversibility of glomerulosclerosis in early stage DN, supporting the efficiency of a combined therapeutic strategy in the early DN intervention [58]. Polydatin has been also shown to protect against renal dysfunction in DN by mechanisms including the attenuation of mitochondrial, reversion of apoptosis, suppression of oxidative stress, and mitigation of renal inflammation and fibrosis [59][60][61][62][63][64]. Punicalagin, the major hydrolysable tannin from pomegranate, whose metabolism involves the formation of gallic acid, has been also associated with DN protection. The attenuation of inflammation and pyroptosis was pointed to as the molecular mechanisms underlying punicalagin-mediated effects [65]. Cyanidin 3-glucoside is the most widespread flavonoid from the anthocyanin sub-class. Its protective effects against DN have been associated with the alleviation of apoptosis, oxidative stress [66][67][68][69], improvement of autophagy, inhibition of epithelial-mesenchymal transition (EMT) [69], and attenuation of inflammation [66][70]. Protocatechuic acid, also referred as 3,4-dihydroxybenzoic acid, is a phenolic acid from the hydroxybenzoic acids sub-class and a major polyphenol metabolite derived from anthocyanins metabolism. Its reported beneficial effects against DN include the inhibition of high glucose (HG)-induced human mesangial cells proliferation and oxidative stress [71]. As stilbenes and anthocyanins, formononetin, a flavonoid from the isoflavonoids sub-class, was shown to alleviate oxidative stress burden in the kidney of diabetic animals, which may contribute to the control of hyperglycemia and insulin resistance and the reduction of triglyceride, cholesterol, creatinine, and urea in the blood [72]. The flavanol quercetin has also been associated with several protective activities against DN. It was shown to antagonize glucose fluctuation-induced renal injury by suppressing aerobic glycolysis [73], to inhibit proliferation in HG–treated glomerular mesangial cells and in early DN mouse [74], and to prevent the initiation and progression of DN in diabetic mice by improving the renal accumulation of lipid bodies [75]. Interestingly, quercetin liposomes improved DN biochemistry and pathological changes in a higher extent than non-encapsulated quercetin, which was attributed to the maintenance of quercetin in higher concentrations in the plasma [76]. Another study comparing the nephroprotective activities of quercetin and quercetin/nanoparticle complex revealed that both treatments prevented kidney pathological damage and improved renal function, alleviated renal oxidative stress, and attenuated inflammatory processes with a greater effect in animals treated with quercetin/nanoparticle complex [77], further supporting the efficacy of vehiculation strategies to improve the phenolics bioactivity towards DN. Quercetin 3-O-galactoside, also known as hyperoside or hyperin, exhibits bioactive properties related to the improvement of cell injury and relieve the signs of renal dysfunction via targeting the miR-499-5p/APC axis [78]. Additionally, dihydroquercetin was shown to mitigate the renal histopathological lesions associated with DN by mechanisms that may involve oxidative stress and inflammation suppression [79]. The nephroprotective action of the glycosyloxyflavone myricitrin, another compound belonging to flavonols, was found to be associated with the mitigation of oxidative stress as investigated both in vitro and in vivo, as well as to prevent renal inflammation [80][81]. Remarkably, vehiculation of myricitrin using solid lipid nanoparticles was shown to increment myricitrin effects in vivo [81]. EGCG has been associated with the modulation of several renoprotective signaling pathways [82]. It has shown beneficial effects towards DN via modulating oxidative stress responses [83][84][85]. An in vivo study investigating the role of EGCG and methylated EGCG, a metabolite with greater bioavailability than EGCG, on diacylglycerol kinase α (DGKα)-mediated alleviation of DN unveiled that both catechins ameliorated albuminuria and attenuated HG-induced podocytes loss by preventing a decrease in focal adhesion [86]. Moreover, it was observed that EGCG alleviates renal fibrosis, a histopathological feature of DN [87]. In addition, it was shown that ECGC promoted HG-podocyte cell proliferation, decreased apoptosis, and attenuated the expression of ER stress markers, suggesting that EGCG may protect podocytes against apoptosis via suppressing ER stress [88]. Testing of epicatechin and the metabolites derived from flavonoid intake, 2,3-dihydroxybenzoic acid, 3′,4′-dihydroxyphenylacetic acid and 3-(3′-hydroxyphenyl)propanoic acid, towards the prevention of inflammation and the accompanying redox imbalance in HG- and lipopolysaccharide-induced renal proximal tubular cells revealed that NOX-4/p38 plays a crucial role on the protective effect of epicatechin and 2,3-dihydroxybenzoic acid [89]. Procyanidin B2 is flavan-3-ol dimer composed of two molecules of (−)-epicatechin. Its reported protective effects on DN have been associated with the relief of HG-podocyte injury in vivo [90], apoptosis, mitochondrial dysfunction [91] and inflammation. It was also shown to reverse HG-induced EMT-associated morphological changes in renal tubular epithelial cells. At last, (+)-catechin was shown to ameliorate renal dysfunction in vivo through the inhibition of AGEs formation and inflammatory pathways via methylglyoxal trapping [92]. Oligonol, a phenolic product derived from lychee fruit, is produced by a manufacturing process that converts polyphenol polymers into oligomers being therefore rich in catechin-type monomers and oligomers of proanthocyanidins. It was shown to attenuate inflammation and glomerular hypertrophy in vivo and to suppress renal oxidative stress [93]. Its pleiotropic action was also associated with protection against AGE formation and apoptosis [94]. A plethora of oligonol renoprotective activities has been discussed elsewhere [95]. The effects of bergenin, a C-glycoside of 4-O-methylgallic acid also known as cuscutin, against DN include the downregulated oxidative stress thereby inhibiting extracellular matrix generation in glomerular mesangial cells and contributing to the alleviation of nephropathy both in vivo and in vitro [96]. Sinapic acid, a polyphenol metabolite also present in foodstuffs, was shown to be nephroprotective via regulation of oxidative stress and inflammation. The nuclear factor erythroid 2-related factor 2/heme oxygenase 1 (NRF2/HO-1) pathway appears as the main target underlying sinapic acid bioactivity [97]. Oleuropein, belonging to the polyphenols sub-class of tyrosols, is the most common phenolic compound in olives. Reduction of body weight, alleviation of kidney injury, and decrease of inflammatory response after oleuropein treatment was associated with the inhibition of cell apoptosis in renal sections and alleviation of kidney oxidative stress [98]. Regarding other polyphenols that do not belong to the classes referred before, salvianolic acid A renoprotective activities, namely the restoration of glomerular endothelial function and alleviation of renal structural deterioration, were shown to be associated with the suppression AGEs-induced rearrangement of actin cytoskeleton, attenuation of AGEs-induced oxidative stress with consequent alleviation of inflammation and restoration of autophagy, as determined in glomerular endothelial cells and diabetic rats [99]. In vivo, treatment with the natural biphenolic compound, honokiol, mitigates ROS production which translates into the attenuation of renal dysfunction markers such as albuminuria, glomerular damage, and podocyte injury [100].

2.4. Renal Cancer

Kidney cancers are the group of malignancies representing the 15th most common type of cancer worldwide, responsible for 2.2% of all new cases of cancer and nearly 180,000 deaths, in 2020 [101]. Renal cell carcinoma (RCC) is the most common type, comprising nearly 90% of all kidney cancers and representing a panel of heterogeneous tumor subtypes. The classification recognized by the World Health Organization (WHO) depicts histopathological dissimilarities between these tumors, establishing sixteen different subtypes of RCC. Clear cell renal cell carcinoma (ccRCC) is the most expressive of the RCC subtypes, generally initiating at the epithelial cells of the proximal tubule, as a result of the manifestation of different genetic events [102][103][104].

Evidence has supported the potential anticancer effects of polyphenols on different types of cancer, including RCC [70][105][106]. Resveratrol is among the most attractive polyphenols regarding cancer protection, and it has been suggested as a promising anti-cancer agent on RCC. Treatment of human renal cancer cells 786-O with resveratrol inhibited cell proliferation in a concentration-dependent manner and suppressed the expression of the vascular endothelial growth factor (VEGF) gene [107]. In 2015, Chen and colleagues reported that resveratrol was able to control tumor growth and modulate the tumor microenvironment in a mouse renal tumor model [108]. Resveratrol was further shown to inhibit cell proliferation, induce cell cycle arrest on S phase, suppress invasive phenotype and colony formation activity on RCC cell models, by preventing the activation of Janus activated kinases (JAKs) 1 and 2, and Src kinases, therefore blocking the JAK/STATs (Janus kinase/signal transducer and activator of transcription) signaling [109]. Other pathways involved in tumor progression have been identified as targets of resveratrol in RCC cell models. AT1R/VEGF pathway (Angiotensin II type 1 receptor/Vascular endothelial growth factor) was impaired in the presence of resveratrol, through downregulation of Angiotensin II, AT1R (Angiotensin II type 1 receptor), VEGF and ciclooxigenase-2 expression [110]. Moreover, this polyphenol was able to modulate the inflammatory response by inhibiting the activity of NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, which is highly expressed on RCC [106][111]. Akt (protein kinase B), ERK1/2 (Extracellular signal-regulated kinase 1/2) and p53/AMPK/mTOR (cellular tumor antigen p53/AMP-activated Protein Kinase/mammalian target of rapamycin)-induced autophagy signaling pathways were also reported as targets of resveratrol on RCC, leading to the suppression of cell proliferation, migration, invasion, and induction of apoptosis in a concentration and time-dependent manner [112][113]. This compound has also been shown to affect epigenetic mechanisms such as in impairment of histone acetylation leading to decreased activation of MMP-2/-9 (Matrix metalloproteinases 2 and 9) [114]. Resveratrol effects on RCC cell proliferation and apoptosis were shown to be enhanced in the presence of autophagy inhibitors [115]. In a different perspective, the combination of chemotherapeutic agents with resveratrol was also shown to have beneficial effects. Resveratrol enhances the apoptotic effect of sorafenib in 786-O cells, through blockage of the Jak2/STATs pathway [109]. In paclitaxel-resistant RCC cells, resveratrol increased sensitivity to this chemotherapeutic drug, through inhibition of the PI3K/AKT (Phosphatidylinositol 3-kinase/Protein kinase B) pathway [116]. Another approach has explored the potential anticancer effects of resveratrol combined with sitagliptin. A synergistic effect leading to the impairment of STAT3/NFKβ (signal transducer and activator of transcription/nuclear factor kappa-light-chain-enhancer of activated B cells) and NFR2/HO-1 pathways and promotion of apoptosis was found [117]. Zeng et al. have demonstrated that resveratrol plus a fiber-modified replication-deficient adenovirus Ad5/35-TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) significantly inhibited RCC xenograft growth in nude mice [118]. Interestingly, it has been suggested that resveratrol may regulate the expression of tumor suppressor genes by interaction with miRNAs, including mir-21, an important player in renal tumor development [119]. Another polyphenol, EGCG, has been reported to promote the expression of different tumor suppressor genes by interacting with miR-210, which is downregulated in several types of tumors, including RCC [120]. EGCG has been reported to inhibit cell proliferation and induce apoptosis in 786-O cells, by inducing the overexpression of TFPI-2 (tissue factor pathway inhibitor-2) [121]. Chen et al. observed an EGCG-derived decrease in migration and invasion abilities, associated with the downregulation of MMP-2/-9 [122]. EGCG was also found to increase the sensitivity of RCC cells to TRAIL-induced apoptosis, resulting from the downregulation of c-FLIP (cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein) via a ROS-dependent pathway [123]. Curcumin has also exhibited promising effects against RCC carcinogenesis by inhibition of cell viability and proliferation, together with the induction of cell cycle arrest and apoptosis through modulation of the PI3K/Akt signaling pathway [124]. Curcumin significantly enhanced the apoptotic effect of the mTOR inhibitor NVP-BEZ235 on RCC cells through p53-dependent Bcl-2 (B-cell lymphoma 2) mRNA down-regulation and impairment of Mcl-1 (myeloid cell leukemia-1) [125]. In a different approach, curcumin enhanced the radiosensitivity of RCC cells by suppressing NF-κB signaling pathway, revealing its potential to be used in combination with radiotherapy of RCC [126].

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