

Review

Nutrients, Nutraceuticals and Xenobiotics Affecting Renal Health

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Abstract:

Chronic kidney disease (CKD) affects worldwide 8-16% of the population. In developed countries, the most important risk factors for CKD are diabetes, hypertension and obesity, calling into question the importance of educating and acting on lifestyles and nutrition. A balanced nutrition and supplementation can indeed support the maintenance of a general health status, including preservation of renal function, and help to manage and curb the main risk factors for renal damage. While the concepts of protein and salt restriction in nephrology are historically acknowledged, the role of some nutrients on renal health and the importance of nutrition as a preventative measure for renal care are less known.

In this review, we provide an overview of the demonstrated and potential actions of some selected nutrients, nutraceuticals and xenobiotics on renal health and function. The effects on kidney of fibres, proteins, fatty acids, curcumin, steviol glycosides, green tea, coffee, nitrates, nitrites, and alcohol, both direct and indirect, in CKD and non-CKD condition, are reviewed here. In a view of a functional and personalized nutrition, understanding the renal and systemic effects of dietary components is essential since many chronic conditions and CKD are related to systemic dysfunctions such as chronic low-grade inflammation.

Keywords: CKD; renal function; nutrients; nutraceuticals; xenobiotics; inflammation; functional nutrition.

1. Introduction

Among the environmental factors that affect human health, nutrition is of utmost importance, since dietary habits heavily influence both incidence and progression of a variety of pathologies, particularly non-communicable diseases (NCDs). Chronic kidney disease (CKD) is an NCDs affecting worldwide from 8 to 16% of the population with diabetes, hypertension and obesity being the most important risk factors for its occurrence in developed countries [1].

The importance of nutrition in nephrology, with a special focus on protein and salt restriction, has long been recognized as crucial for the management of CKD patients along with pharmacological therapy, in order to slow down disease progression and correct uremia signs and symptoms [2]. Quite the contrary, notions about the role of nutrition as a measure to prevent renal disease are less prevailing.

A balanced nutrition and, if necessary, diet supplementation can indeed support the maintenance of a general health status, including preservation of renal function, and help manage and curb the main risk factors for renal damage: diabetes, hypertension and obesity. In this respect, protein [3] and fiber [4-6] intakes are fundamental tools in the dietary control of these risk factors. Some hints do exist pointing to the importance of gut microbiota balance in the prevention of renal function decline [7] with fibres playing a primary role in the modulation of microbial metabolism. In

a systemic and functional view of nutrition, controlling low-grade chronic inflammation is crucial, even for renal damage prevention. In this regard, functional molecules and nutrients such as fibers and fatty acids, and plant-derived nutraceuticals such as curcumin and steviol glycosides play a key role, either influencing the pro- and anti-inflammatory pathways or acting at the gut mucosal level [5,8,9]. Gut permeability is indeed pivotal in immune disorders aetiology and progression and in eliciting chronic inflammation, since exposure of gut-associated lymphoid tissue (GALT) to luminal antigens is one of the main triggers of these conditions [10]. Different dietary components can modulate gut barrier integrity both directly and indirectly, and there is evidence that curcumin and fibres, respectively, have positive effects on this regard. The beneficial effects of plant-based diets in hypertension are well known [11], along with those of sodium reduction [12]. We discuss here the less-known role of dietary fiber, nitrates, nitrites and stevia in endothelial function and blood pressure (BP) control [13,14]. Moreover, we report the effects of tea and coffee polyphenols, as well as those of bifaceted alcohol, on renal health.

In this review, we decided to focus on some pivotal nutrients, and on some less studied nutraceuticals and xenobiotics, reporting literature evidence of their beneficial or detrimental actions, in some cases offering potential treatment perspectives. We report here the current scientific evidence on fibre, proteins, fatty acids, curcumin, stevia, green tea, coffee, nitrates, nitrites and alcohol, and on their direct and indirect effects on renal health, both in CKD and in non-CKD individuals.

2. Fibres

From the human nutrition point of view, dietary fibres are not strictly classified as “nutrients” since they are technically indigestible by the human enzymatic panel, some of them being instead metabolized by intestinal microbial enzymes. For this reason, and given the increasingly growing importance attached to gut microbiota in terms of human health, fiber intake in human nutrition is in parallel attracting more and more attention [15]. Fibres are traditionally classified into insoluble and soluble, the first being responsible for stool weight and laxation, and the second having serum lipid-lowering effects. However, this rough categorization has recently been challenged [4]. Even so, when it comes to consider the health benefits of intestinal microbial fermentation, soluble fibres are of particular interest since they include the category of prebiotic fibres, characterized by their ability to reach undigested in the distal tract of the gastrointestinal tube, be selectively fermented by probiotic bacteria and induce the growth of these latter [4].

Given the crucial role of microbial dysbiosis in CKD progression and comorbidities, our group and other investigators have recently highlighted the importance of an adequate fiber intake in the dietary management of CKD [16-22]. Indeed, fiber intake reduces proteolytic putrefaction and increases saccharolytic fermentation [9,14,17], potentially counteracting the putrefactive dysbiosis featuring the decline of renal function [19,23,24].

On these grounds we have assumed a potential preventative actions of fiber on renal function decline, although this cause-effect relationship can just be inferred at the moment as, to the best of our knowledge, we still lack experimental confirmation by large-scale observational studies.

Importantly, a recent work has demonstrated the crucial role of intestinal wellness as a protective factor for renal health, underlining a close connection between these organs. The authors of this study found that constipation status and severity were correlated with an increased risk of incident CKD, ESRD and progressive decline of estimated glomerular filtration rate (eGFR) in a large cohort of 3,504,732 US veterans [21]. The reasons underlying this association are unknown, as they are likely to be potentially related to uremic toxins retention, intestinal barrier permeability, colonic and systemic inflammation. Indeed, fibres are fundamental in both intestinal and general wellness. On one hand they are beneficial in feeding the saccharolytic microbiota and decreasing local and systemic inflammation, both directly through short-chain fatty acids (SCFA) release and by ameliorating gut barrier integrity [5,9]. From the other hand, they guarantee an optimal bowel transit, favouring the enteric excretion of human and bacterial metabolites and preventing their systemic accumulation [20,21]. Moreover, there are some hints suggesting that a dysbiotic microbiota could account for a risk factor for CKD occurrence in genetically or epigenetically predisposed subjects

[7,25]. Again, an adequate fiber intake within a balanced diet is fundamental in maintaining a healthy gut metabolism and promoting intestinal wellness. The resulting reduction of uremic toxin production, induction of SCFA colonic release, decreased intestinal inflammation and restored intestinal barrier are all factors potentially contributing to renal health by reducing the risk of renal function decline.

Finally, fibres are an important allies in the control of metabolic and cardiovascular (CV) conditions known to be risk factors for CKD: obesity, diabetes and hypertension [4-6]. An adequate dietary fiber intake in diet can indeed modulate human metabolism thanks to its action on glycaemic index reduction [26], satiety induction, cholesterol absorption, and BP reduction [4]. Dietary fiber content in diet is also effective in supporting weight loss and glycaemic control, probably not only by the mechanisms of satiation, delayed gastric emptying and decreased absorption of nutrients [27,28], but also by modulating the gut endocrine and metabolic orchestra [5,27].

Among the CKD risk factors, the action of fiber on BP has not been yet extensively studied. While the indirect protective effect of fiber intake at CV level through the control of blood glucose and lipid levels has been well demonstrated [6,13], some recent studies also seem to highlight a direct action of fibres such as beta-glucans, psyllium, lupin kernel, soluble cocoa and grape fiber on endothelial function and hypertension [13,14].

3. Proteins

In the context of CKD, the positive clinical effects of a low protein diet (LPD) are not only related to the control of uremic symptoms, reduction in proteinuria and hyperfiltration, but also to the related reduction of sodium, inorganic acids and phosphorus content. Favourable renal outcomes have been reported with LPD. In the early stages of CKD, a normalization of the protein intake based on the current recommendations for the general population (0.8 g/Kg/day) is advised. With the worsening of renal function (CKD stages 3 and 4), more restrictive diets are necessary (0.6-0.7 g/Kg/day). Some experts advocate the use of a very low protein diet (VLPD) supplemented with ketoacids in CKD stage 5 to delay dialysis initiation, or as a way to keep the elderly free from dialysis. Starting dialysis in patients older than 75 years old is indeed related to an increased risk of mortality in the first year following initiation of haemodialysis (HD), and to the worsening of physical function and quality of life [29]. Available data show that in patients with moderate-to-advanced CKD, VLPD supplemented with ketoacids improves several metabolic abnormalities, including hyperphosphatemia, metabolic acidosis, hyper-parathyroidism, dyslipidaemia, protein carbamylation and urea levels [30-33], and contributes to the control of proteinuria, BP and haemoglobin [34-37], without compromising nutritional status [38,39]. Despite non conclusive data on the role of LPDs in preventing or slowing down additional loss of kidney function, the main role of this diet in more advanced stages of CKD relies in its ability to control CKD-related metabolic abnormalities. Even a slight reduction in protein intake of 0.2 g/kg/day may significantly improve the uremic state, metabolic acidosis and hyperphosphatemia [32,40].

As LPD renal protective role in CKD, the hypothesis is that unrestricted protein intake in the presence of a decrease in the number of functioning nephrons can lead to increased glomerular capillary pressure and result in single-nephron hyperfiltration [41]. These hemodynamic changes could contribute to glomerulosclerosis and further reduction in functioning nephrons. In fact, a 32% relative risk reduction in renal death in favour of a LPD over a higher protein intake was identified in a meta-analysis of 2,000 patients [2]. A 10g increase in protein intake in otherwise healthy females with mildly reduced renal function (eGFR > 55 but < 80 mL/min per 1.73 m²) was related to a significant reduction in eGFR over an 11-year period compared to women with normal renal function [42]. High protein intake was also associated with a worsened GFR compared with moderate and low protein intake in non-dialyzed stage 3 to 5 CKD patients [43]. When initiating a LPD, CKD patients should receive professional nutritional counselling, since unsupervised protein restriction may lead to protein energy wasting (PEW) if calorie requirements remain unmet thus leading to poor outcomes in terms of future morbid events, progression of renal disease and mortality [44]. Nevertheless, the problem of being on a LPD and at the same time meeting calorie requirements can be quite common

in patients with CKD even when professional nutritional counselling is available. Supplementation with essential amino acids allows for the intake of lower quality protein, better palatability, and a broader choice of foods [38]. LPDs can also be supplemented with special protein-free foods. Today these products are readily available as pasta, cookies, bread and flour but also as precooked soups and desserts, accounting for an invaluable resource for optimal low-protein dietary management of CKD with high energy intake, no phosphate, no protein and a lower sodium burden.

Unlike CKD patients, healthy people are advised to ingest a recommended daily allowance (RDA) of 0.8 g/kg body weight. This amount, which has been obtained by theoretical studies based on measurements of nitrogen urinary waste, assumed to be proportional to the body nitrogen turnover, indicates the minimum quantity necessary to cover the basal daily protein need of 97.5% of healthy people. Lately, an acceptable macronutrient distribution range (AMDR) has been established in order to cover a broader and differentiated range of protein needs, equal to 10-35% of daily calories, thus including values far beyond 0.8 g/kg body weight as safe for human health [45]. Actually, proteins exert different beneficial functions for human health. First, they guarantee an optimal structural turnover, both at an extra- and intracellular level. Second, they are crucial for a properly functioning immune system. Third, proteins are particularly required in some special life phases and situations: pregnancy and infancy, elderly, intensive physical activity. They also become critical in the context of low-calorie to achieve weight loss as they prevent lean mass waste [3].

The prevalent notion in the field of kidney disease that a strict control of protein intake is always required has led to the misleading idea that even in healthy people an excess of protein intake over the RDA would be harmful for kidney health and lead to an increased risk of CKD [46]. To date, no long-term study has confirmed the association between high protein intake and increased risk of CKD in the healthy population [46,47]. This has been confirmed by a research conducted on a population of 1,624 women belonging to the Nurses' Health Study that has demonstrated that high protein intake was not associated with renal function decline in women with normal renal function, being instead associated with a decline in renal function only in women with pre-existing mild renal insufficiency [42]. The hyperfiltration observed following high-protein diets seems to be linked more to an adaptive mechanism than to direct kidney damage [46,47], even if the long-term effects of a chronically elevated protein intake cannot be excluded [48]. On the contrary, an inadequate protein intake has been shown to lead to a reduction of kidney volume and filtration rate [49,50], in addition to accounting for a factor leading to PEW in the medium- long-term.

Interestingly enough recent studies support the idea that, beyond calorie restriction, protein restriction is likely to be a conserved mechanism linked to longevity [51]. Although the implications of this line of research could be interesting in the prevention of age-related diseases, attention should be focused on the fact that individuals over 65 do not seem to take advantage of protein restriction that, quite the contrary, seems to increase their mortality [51].

In summary, while CKD patients should be highly compliant with protein restriction, a right balance should be struck between risks and benefits when it comes to the general population. Obesity and its comorbidities such as hypertension, insulin resistance and diabetes, currently represent the main risk factors for CKD. In terms of prevention of renal diseases, diets with a protein intake that exceeds the RDA represent a valuable tool for weight control and should therefore be used in order to achieve or maintain the weight loss goal, or to prevent malnutrition in the elderly, thanks to their effects on basal metabolism and thermogenesis increase, satiety induction, and body recomposition boosting [3]. In our opinion, it is necessary to enhance the routine renal function testing in the general population, for both renal disease prevention and also to avoid wrong prescriptions of high-protein diets which can turn out to be harmful in case of kidney dysfunctions. In the presence of a normal renal function, to date there is no evidence against the adoption of high-protein diets for specific health purposes. These diets should be customized according to the clinical and nutritional pictures of the individual patients and supervised by a nutrition specialist.

4. Fatty Acids

Fatty acids (FA) are important lipid components, mainly represented by triglycerides and phospholipids, that can be derived from food or produced endogenously; they play a clear role in chronic degenerative diseases with an inflammatory component [52]. In fact, circulating FA levels are considered an index of endogenous production, dietary intake and pathophysiological conditions. Long-chain polyunsaturated FAs (LC-PUFA) cannot be produced endogenously in enough quantity, and thus are considered essential FAs. Essential FAs are known as omega-6 and omega-3 FAs and they are widely distributed in plant oils. Longer-chain fatty acids derived from the parental omega-3 FA alpha-linolenic acid (ALA) are partially produced endogenously, and are also considered essential: they are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), widely available in fatty fish. A great bulk of data on the association between PUFA metabolism and CV risk factors in the general population is available [53,54].

Significant modifications in the FA profile of circulating lipids have been observed in patients with CKD and nephrotic syndrome [55]. However, whether this condition is a consequence or a cause of the renal problem is still a matter of debate. Only few studies have investigated FA levels in CKD patients in comparison to healthy subjects. Taken together, the literature studies on nephrotic syndrome patients show a reduction in the stearic acid levels (a type of saturated fatty acid, SFA), as well as a reduction of omega-3 and a change in the enzymatic indicators of FA metabolism and synthesis [56-58]. As to CKD patients, the studies performed before any FA supplementation found lower levels of omega-3 FA, DHA, SFA and an increase in the oleic acid (a monounsaturated fatty acid, MUFA) levels, and omega-6 FAs [59-61]. The presence of proteinuria could explain more than 60% of the altered FA levels in nephropathic patients, since phospholipiduria correlates directly to proteinuria [58]. Also the presence of hypoalbuminemia is likely to contribute to the change in FA profiles [62]. Finally, the increased levels of MUFA and reduced levels of PUFA found in CKD patients could be a result of an increased oxidative stress, which affects the structure of PUFAs more easily than that of MUFA and SFA [63,64].

On the other hand, FAs imbalance may plausibly be not only a consequence of the kidney disease itself but also a factor influencing the function of kidney and other organs. For instance, a low level of omega-3 FA increases CV risk, compromises cognition, and increases the risk for neurodegenerative diseases [65,66]. The association between PUFA levels and the progression of kidney disease has also been documented, with increased levels of omega-6 PUFA arachidonic acid (AA) being responsible for the upregulation of mediators of the renal fibrotic process [67-69]. In addition, a change in PUFA levels can increase the expression of angiopoietin like-4 (Angpt-4), which encodes a glycosylated, secreted protein containing a C-terminal fibrinogen domain that can act as an apoptosis survival factor for vascular endothelial cells, and could have a key role in nephritic syndrome [70]. As to the development of comorbidities, an increase in the omega-3/omega-6 ratio, represented by DHA/AA and EPA/AA, has been shown to be protective against CV events in CKD patients [71], while an increase in the AA/n-6 dihomo- γ -linoleic acid (DGLA) ratio in HD patients has been found to be an independent predictor of poor clinical outcomes [72]. In general, higher levels of mead acid, an indicator of essential fatty acids deficiency, have been associated with increased levels of the inflammatory cytokine IL-6 and increased mortality [73].

In kidney disease, the positive or negative roles of FAs mainly depend on the effects of their metabolites [74,75], by modulating the inflammatory status and tissue fibrosis [76]. FA metabolism occurs in the cytochrome P450 (CYP), and the main enzymes involved are cyclooxygenase and lipoxygenase. Depending on the parental FA, the resulting metabolites can have different effects, acting in the vascular system as vasoconstrictors and dilators. The epoxyeicosatrienoic (EET) acids derived from the AA are a family of metabolites with important effects in the kidney [55]. They inhibit Na channels at the cortical collecting duct [77], maintain the glomerular permeability barrier to albumin [78], and also play a protective role against glomerular damage [79]. Like EETs, 20-hydroxyeicosatetraenoic (20-HETE) acid, another metabolite derived from AA, plays an important role in maintaining the integrity of the glomerular barrier to albumin [78], and has been demonstrated to have a protective role on the ischemia-reperfusion (IR) injury [80]. Omega-3 FA metabolites also have important roles in the kidney which are mainly related to counteracting inflammation.

Resolvins derive from DHA and facilitate the resolving phase of acute inflammation [81], and the metabolite 4-hydroxy hexenal increases the expression of genes with antioxidant and anti-inflammatory properties [82-85].

There are many studies investigating the role of omega-3 PUFA supplementation in CKD, and their results are controversial. One RCT evaluating the association between proteinuria and/or GFR and n-3 PUFA supplementation in non-dialyzed CKD patients demonstrated that in patients with IgA nephropathy proteinuria decreased by 72.9% with supplemental n-3 PUFA (3 grams/day) versus 11.3% with renin-angiotensin system (RAS) blockers alone [86]. Similarly, in a meta-analysis of 17 trials, reduction in proteinuria with n-3 PUFA supplementation (0.7 to 5.1 g/day) was greater than in controls, while GFR decline was not modified by n-3 PUFA supplementation [87]. Interestingly, in the Alpha Omega Trial, a low level of EPA and DHA were given together with the trial margarine for 40 months, amounting a total of 400 mg/day, which corresponds to two servings of fatty fish/week: the supplementation had pronounced effects in slowing GFR decline of CKD patients [88]. No differences in GFR were observed between patients receiving 2.1 g/day omega-3 fish oil and controls [89]. The effects of a high (EPA 1.88 g and DHA 1.47g) versus a very high (EPA 3.76 g and DHA 2.94 g) fish oil supplementation dose on IgA nephropathy were equally effective in slowing increases in serum creatinine levels, and in both groups the rates of renal decline were more pronounced in patients with moderate versus more advanced renal disease [90]. An increase in serum creatinine concentration $\geq 50\%$ was found in 7% of patients with IgA nephropathy randomized to supplemental fish-oil (EPA 0.85 g and DHA 0.58 g daily) versus 43% of patients receiving standard treatment [91]. The heterogeneity found in such trials can be explained by differences in basal EPA and DHA status, not always measured in every trial, type of omega 3 FA used (parental ALA, EPA or DHA), route of the supplementation (oral/parenteral), dose and non-linear dose response effects, and by differences in the levels of mediators [92].

5. Nutraceuticals and Xenobiotics

5.1. Curcumin

Curcumin is a biologically active polyphenolic compound found in turmeric, a spice derived from the rhizomes of the plant *Curcuma longa*, known for its pharmacologic, anti-inflammatory and anti-cancer properties [93,94].

Over the last years, different scientific studies have highlighted the nutraceutical properties of this molecule, at a systemic and also renal level. In the field of renal diseases, some *in vivo* and human studies suggest new therapeutic perspectives for curcumin use in CKD [95,96], acute kidney injury (AKI) [97], transplantation [98,99] and renal cell carcinoma [94]. The results of these research efforts need of course to be extensively validated by randomized clinical trials (RCTs).

In a recent *in vivo* study, oral administration of curcumin in mice models of CKD induced several beneficial effects: amelioration of cardiac function, decrease of BP and ROS production, improvement of mitochondrial integrity and functionality. While renal function seemed to be unaffected by curcumin administration, a reduction of the expression of MMP-2, a molecule involved in cardiac remodeling, was observed [95]. Collectively, curcumin appeared to reduce cardiac remodeling, mitochondrial dysfunction and cell death mediated by oxidative stress. The antioxidant effect of curcumin has recently been confirmed in a double-blind RCT carried on in diabetic and nondiabetic proteinuric CKD patients [96].

An important role of curcumin has also been shown in relation to the IR injury-induced AKI. Following IR induction in an animal model, reduction of serum creatinine and urea was observed in the group pre-treated with curcumin as compared to the control group. At molecular level, positive effects on tubular epithelial cells have been observed: curcumin prevented their apoptosis by increasing the expression of APPL1 and inhibiting AKT phosphorylation, pivotal pathway for the pathogenesis of IR-induced AKI [97].

Biological effects of curcumin have been reported also in the context of clear renal cell carcinoma (ccRCC), a tumour notoriously resistant to chemotherapeutic treatments. In an *in vitro* study

curcumin showed a double effect on RCC cells, promoting their viability at low doses, and inducing their autophagy at high doses [94], underlining the importance of carrying on accurate dose-effect *in vitro*, *in vivo* and ultimately human studies in order to define the exact pharmacological dose of this and other nutraceutical compounds.

Studies on curcumin activity have been performed in renal transplantation too. A RCT demonstrated that curcumin is effective in the functional recovery of the kidney transplanted from cadaver, a condition in which the delayed graft function is very common, implying the acute rejection of the organ. Forty-three HD-dependent cadaveric kidney recipients were administered for 1 month after surgery a curcumin-based supplement in a randomized scheme. Results showed an improved early graft function in the bioflavonoid-treated group, along with a reduced incidence of acute rejection and neurotoxicity [98].

Apart from potential therapeutic applications, thanks to its multifaceted actions curcumin could also be important in terms of prevention of renal function decline. As already reported for CKD animal model and human studies [95,96], curcumin exhibits antioxidant properties, potentially useful in a prevention setting. In this regard, in a very recent animal study curcumin has been shown to be able to prevent early damage induced by 5/6 nephrectomy, not only ameliorating total antioxidant capacity, but also improving renal blood flow and acting in terms of mitochondrial function and bioenergetics [100].

But probably the most interesting systemic action of curcumin occurs at the intestinal level. Indeed, there are some reports showing the capacity of curcumin to preserve the intestinal barrier integrity, thus reducing systemic inflammation. Among a variety of stimuli known to alter gut permeability and exposing gut-associated lymphoid tissue to mucosal antigens, intestinal lumen LPS is one of these. LPS, a component of Gram- bacterial wall, is able to promote the down-expression of tight junction proteins ZO-1 and claudin, that allow LPS to enter the bloodstream [101]. This results in a cascade of inflammatory events, including increased secretion of pro-inflammatory cytokines and chemokines, activation of macrophages and their infiltration within the renal tissues and the arterial walls, all predisposing to the development of CKD and atherosclerosis [102-104]. Intestinal Alkaline Phosphatase (IAP) has a very significant role in preserving mucosal barrier integrity. It is a membrane enzyme expressed by the intestinal epithelium, having the important role of detoxifying luminal LPS through the removal of one of the two phosphate groups from the lipid A [101,105,106]. The reduction of IAP (occurring in Western-style diets as well in CKD), results in increased active LPS in its turn causes the down-expression of ZO-1 and claudin. Oral intake of curcumin promotes increased IAP activity, reversing the downregulation of tight junction proteins [8].

5.2. Stevia

Stevia is a food additive extracted from the leaves of *Stevia rebaudiana*. The active elements are steviol glycosides, mainly rebaudioside A and stevioside [107]. With a sweetening index much higher than that of sucrose [108], stevia is not fermentable, stable at different pH and heat-resistant and, importantly, has no caloric value [109]. The beneficial properties of stevia have been evaluated in some animal studies over the past 20 years. The positive effects of stevia on the kidneys are known since the early 90s. In an *in vivo* study, Melis dispensed 2.67 g of dry stevia leaves/day for 30 days to normal and hypertensive rats, showing different beneficial effects such as reduced BP, increase in GFR, renal plasma and urinary flow, and sodium excretion [110, 111].

In a following study, the effects of polyphenols and fibers extracted from Stevia leaves on streptozotocin-induced diabetic rats were studied. The results showed a decrease in blood glucose levels, modulation of blood levels of AST and ALT indicating an improvement in liver function, an improvement in levels of antioxidant enzymes and a decrease in liver concentrations of malondialdehyde (MDA) (an indicator of hepatic damage and a marker of oxidative stress) in the group of rats administered with stevia powder and polyphenols extracts compared to control groups. Importantly, an improvement of the GFR after the renal damage was observed in the treated group [112].

An interesting aspect related to the effect of stevia has been found in a genetic hereditary renal disease, autosomal dominant polycystic kidney disease (ADPKD). Stevioside is metabolized by intestinal bacteria to steviol, which is readily absorbed at the intestinal level, reaching also the kidney. Stevia can become a new strategy for the treatment of ADPKD. In an animal model of ADPKD, some authors have described a key role for stevioside and steviol in delaying cystogenesis and in improving renal function, through the activation of AMP-activated protein kinase, in its turn inhibiting CFTR and mTOR/S6K protein expression, all involved in renal epithelial cell proliferation [113]. Moreover, steviol allowed a decrease in kidney weight and size, cysts index and area, compared with the control group. Furthermore, also stevioside treatment promoted similar effects such as a reduced kidney weight and decreased cysts index, but unlike steviol, an improvement in serum blood urea nitrogen and creatinine was not observed [114]. Furthermore, steviol enhances the expression of lysosomal enzyme marker (LAMP2), indicating the lysosomal degradation of CFTR (playing an important role in fluid accumulation in cysts) and of B-catenin (important in cell proliferation pathway). Collectively, the modulation of these pathways results into a slowdown of the cysts progression [115].

Aquaporin 2 (AQP2) is involved in fluid secretion, promoting cysts enlargement in polycystic kidney disease (PKD). Noitem *et al.* found that steviol remarkably inhibited cyst growth *in vitro* by decreasing AQP2 expression in mouse renal cystic epithelial cells [116].

Given steviol glycosides beneficial properties and potential therapeutic applications, it would be appropriate to test these functional molecules in pilot studies on CKD patients as well as in pharmacological studies meant to develop new innovative drugs by harnessing their chemical structure.

5.3. Green tea and coffee

Green tea contains, polyphenolic compounds (flavonoids) displaying antioxidants properties, known as catechins. These compounds have shown anti-oxidative, anti-inflammatory and anti-carcinogenic activities [117-119]. There is evidence that increased antioxidant status lowers oxidative damage to DNA, thus enhancing protection against cancer [117,120]. In addition, epidemiological data have indicated a lower incidence of cancer in subjects with higher intake of green tea [121-123]. Since oxidative stress and inflammation contribute to the development and progression of renal diseases one could speculate that frequent consume of green tea or green tea extracts could play a protective role on renal function. In a recent animal study [124], researchers investigated the renoprotective role of epigallocatechin-3-gallate (EGCG), the most abundant and active polyphenol present in green tea [120], in models of unilateral ureteral obstruction (UUO). The main findings of this study were that EGCG administration at a dose of 50 mg/Kg/day significantly improved renal function and increased the weight of the obstructed kidney in mice. In addition, increased antioxidant activity and reduction of pro-inflammatory cytokines induced by the obstruction were normalized [124]. In another very recent study, catechin administration at different dosages after cadmium exposure significantly attenuated the nephrotoxic effects of cadmium exposure by reducing oxidative stress, inflammation and by protecting the renal mitochondrial structure and function [125]. A protective role for EGCG in the development of diabetic nephropathy in mice has also been reported [126-130], by upregulating the nuclear factor erythroid 2-related factor 2 (NRF2), which plays a key role in cellular defence against diabetes-induced oxidative stress [130]. In a double-blind RCT, supplementation with green tea polyphenols containing 800 mg of EGCG was able to reduce albuminuria in patients with diabetic nephropathy receiving the maximum recommended dose of RAS inhibition through a reduction in the podocyte apoptosis by activation of the WNT pathway [131]. Additionally, recent findings show that antioxidants supplementation inhibits the progression of atherosclerosis and inflammation [132]. Catechins can inhibit pro-inflammatory and pro-apoptotic oxidative injury by reducing the production of reactive oxidative species (ROS), the translocation of NF- κ B and activated protein 1, and the expression of ICAM-1 [133]. In a study conducted in a population of forty-four HD patients, daily supplementation with 455 mg of catechins extracted from green tea (amount equivalent of 4

cups of green tea/day) reduced HD-enhanced ROS production, scavenging hydrogen peroxide, superoxide anion, and hypochlorous acid [134]. In HD patients hypochlorous acid production promotes the atherogenic oxidation of LDL [135], and amplifies the hydrogen peroxide-induced vascular injury [136]. Since HD is not able to mechanically remove oxidized pro-atherosclerotic products, including oxidized LDL and phosphatidylcholine hydroperoxide, the use of powerful antioxidants that reduce the production of intradialytic ROS and protect against oxidative damage, such as green tea catechins, could help to slow down the progression of atherosclerotic vascular disease.

Caffeine is another widely studied compound of hot beverages, such as tea and coffee, with bioactive properties. Although its role in the development of hypertension and cardiovascular diseases (CVD) is still debated [137,138], there is evidence regarding its inverse association with type 2 diabetes [139]. However, the effect of coffee and tea consumption on renal function, however, has been poorly investigated. In a cohort of Japanese adults, the consumption of coffee, but not tea, was associated to increased eGFR [140]. The same findings have been reported in another two studies performed in Japan [141,142]. One study in Korean women found a protective role of coffee only in women with diabetes [143], while another Japanese study found no association at all [144]. A more recent study on a Western cohort has investigated the association between coffee and tea consumption and changes in the eGFR [145]. In this study coffee, but not tea, was found to be associated with a slightly higher eGFR among subjects of ≥ 46 years of age, and higher doses of coffee intake were observed to be associated with higher eGFRs. However, no associations with subsequent changes in eGFR or risk of rapid decline in eGFR were identified. These findings suggest that the increase in eGFR may not be related to the development of hyperfiltration, which is considered a risk factor for worsening of renal function over time because of its reflection on glomerular hypertension. On the other hand, experimental data suggest that caffeine has a negative influence on renal function in the presence of hypertension and pre-existing renal dysfunction, with an increase in proteinuria [146-148]. The mechanism related to this nephrotoxic effect of caffeine could be ascribed to its capacity to block renal adenosine receptors, which may augment angiotensin II-induced glomerular hypertension [148].

Caffeine was also found to be associated with reduced incidence of kidney stones [149-151], even though it induces increased calcium excretion [151,152]. Probably the increased urine output and consequent urine dilution associated with caffeine consumption might contribute to a lower risk of developing kidney stones [151].

Hyperuricemia is a known risk factor for AKI and CKD progression [153]. An inverse association between coffee consumption and plasma uric acid was also described [154,155]. However, no association between total caffeine intake and hyperuricemia was found [155]. These findings suggest that components of coffee other than caffeine may have contributed to the associations observed, since both caffeinated and decaffeinated coffee were found to be inversely associated with hyperuricemia. Since there is a strong direct correlation between insulin resistance and hyperuricemia [156-159], decreased insulin resistance and insulin levels associated with coffee consumption may lead to lower uric acid levels. Coffee is also the major source of the phenolic compound chlorogenic acid, a strong antioxidant [160], that has been shown to reduce glycaemia [160,161]. It has also been speculated that non-caffeine xanthines in coffee may inhibit xanthine oxidase and reduce uric acid levels [154].

5.4. Nitrates and Nitrites

Hypertension is a known risk factor for the development of CKD [162].

The BP-lowering effects of either a low-salt or a plant-based dietary approaches, such as the DASH diet, have been well assessed [11,12]. The DASH study demonstrates the efficacy of the synergy among plant matrices in achieving an overall hypotensive effect, making it difficult to discriminate the effect of an isolated dietary component [11]. Anyway, beyond sodium, there are other dietary components accounting for exceptions to this general rule, since they have been demonstrated to affect vascular function and regulate BP, both when found in food matrices and as isolated dietary

supplements, namely nitrates and nitrites. While classified as carcinogenic to humans, because of their use as preservatives in processed meats that leads to conjugation with amino acids and release of toxic nitrosamines, the nitrates and nitrites we are exposed to on daily basis come from cured meat in a very small percentage (less than 5%) [163]. Interestingly, more than 85% of these molecules comes from vegetables, particularly from some of the world's healthiest roots and vegetables: beetroots and green leafy vegetables. On the contrary, many observational studies are revealing that nitrates and nitrites are protective against CV risk [163], especially when it comes to CKD [6]. This understanding has recently led some authors to propose to revise these compounds as actual dietary nutrients instead of mere additives, or even toxic substances [163].

The importance of dietary nitrates/nitrites for vascular health is traced to their action as precursors of nitric oxide (NO) via the enterosalivary pathway mediated by oral commensal bacteria [6]. In this context, oral microbiota dysbiosis could either represent a risk factor for endothelial dysfunction or a consequence of an imbalance in the microbiota-mediated nitrogen cycle [164].

NO is a fundamental modulator of endothelial function, vasodilatation and BP. NO circulating levels are increased after nitrate and nitrite ingestion, both as supplement and as diet-derived compounds [164,165]. In addition, many experimental studies demonstrated the effects of nitrate and nitrite in terms of decreased BP [166-170], better vascular compliance [169] and endothelial function [169] and reduced overall CV risk [171]. Moreover, a beneficial role for dietary nitrates/nitrites in improving physical performance has also been reported [163,166,168,170,171]. Nitrates and nitrites are fundamental in endogenous NO homeostasis and their insufficient dietary intake represents a risk factor both for development and progression of endothelial dysfunction and CVD [163,164]. In addition, there is evidence that nitrate supplementation has a beneficial effect on ameliorating renal injury in animal models of hypertension and renal IR [172, 173].

5.5. Alcohol

The adverse health effects caused by prolonged consumption of elevated amounts of alcohol and of acute alcohol intoxication are well-known [174]. As to renal function, alcoholism is associated with a higher risk of glomerulonephritis [175,176], AKI [177], loss of renal function [178] and kidney graft failure [179]. However, moderate alcohol consumption has been related with health benefits, and its protective effects against CV mortality [180-182] and heart failure are well documented [183]. The beneficial effects of alcohol are dose- and gender-dependent, since women have less alcohol dehydrogenase than men [184]. A number of prospective observational studies have reported that moderate alcohol consumption could have a beneficial effect on loss of renal function, also in patients with confirmed kidney disease [185-190]. In patients with IgA glomerulonephritis, proteinuria was found to be lower in light and moderate drinkers, while and their creatinine clearance was higher in compared with abstainers and heavy drinkers [190]. Detrimental effects of alcohol abuse may include glomerular damage [191], hypertension and hypertensive related nephrosclerosis [192,193]. On the contrary, the beneficial alcohol effects in the kidney may be associated to its effects on BP, lipid profile (increased HDL), and vasoactive peptides regulation [186], much as those seen in CVD. For instance, ethanol alters the activity of neurotransmitters and hormonal systems that affect the regulation of vasoactive substances, therefore affecting renal hemodynamics and function [186]. Additional mechanisms associating moderate alcohol intake with preserved renal function are: alcohol consumption association with less hyalinization of renal arterioles [194], the antioxidant activity of polyphenols content in some alcoholic beverages (such as red wine) and the increased activity of antioxidant enzymes [195], lower lipid peroxidation and reduced protein oxidation [196].

6. Conclusions

In light of the above pieces of evidence, some general concepts certainly need to be revised in patients with CKD and in healthy individuals, along with the presence of related/unrelated comorbidities. Importantly, CKD prevention is the result of a healthy lifestyle. Raising people's awareness of healthy lifestyles is a means to look after their own health by keeping modifiable risk

factors under control. Keeping and maintaining optimal weight control, getting the right protein intake, reducing calories and high-glycemic index food are all important steps toward weight loss and metabolic rebalance. An excess in refined carbohydrates and a poor intake of high-biological value proteins are predisposing factors for weight gain and insulin resistance development. Awareness-raising measures to correct behavioral risk factors in the general population should be put in place in order to CKD incidence.

Fibres are dietary components known for promoting a general intestinal wellbeing and healthy gut metabolism, as they act on the intestinal barrier modulating local and systemic inflammatory state. By acting on endothelial function, satiety, glycaemic index, cholesterol absorption, BP, fibres represent an invaluable help in dietary strategies against obesity, diabetes and hypertension, indirectly supporting renal function both in healthy individuals and in CKD patients.

Dietary protein intake has a bi-faceted action on human health and kidney function. While in CKD a progressive protein restriction is advisable in order to preserve renal function, maintaining an optimal protein intake is essential in non-CKD people for good health status and adequate body composition and functioning.

FA proportion, which is crucial in determining the right balance between the pro- and the anti-inflammatory state, turns out to be deranged in renal diseases. While this seems to be a result of the same pathology, it also accounts for a negative factor that contributes to the progression of renal function decline. Unfortunately literature studies exploring the role of supplementation of omega-3 FAs are still inconclusive, mainly because of the high heterogeneity of the studies in question. Bigger and better designed trials are needed to finally clarify the role of FA supplementation in CKD.

Nutraceuticals can represent a valid therapeutic help for both prevention and treatment of renal diseases, but many of the studies carried out so far have been made in animal models, therefore their therapeutic potential needs to be explored and validated in specifically designed RCTs. Curcumin exhibits a strong antioxidant activity, with a potential role in renal damage prevention and in CKD treatment, as it has been shown to reduce cardiac remodelling, mitochondrial dysfunction and apoptosis. In IR-induced AKI, curcumin reduces tubular injury and improves renal function. Similarly, in renal transplantation it improves early graft function, reducing acute rejection and neurotoxicity. Thanks to its IAP-mediated promotion of intestinal barrier integrity, curcumin potentially reduces systemic inflammation. Steviol glycosides are nutraceutical compounds characterized by beneficial properties on renal and hepatic functions, BP and blood glucose control, blood antioxidant balance. They also display anti-proliferative properties in ADPKD, worthy of further pharmacological investigation.

Green tea flavonoids possess antioxidative, anti-inflammatory and anti-carcinogenic activities, also at renal level, as demonstrated in mouse models of CKD, cadmium-induced nephropathy, and diabetic nephropathy. In humans, catechins have been shown to i) ameliorate renal damage in diabetic nephropathy, ii) inhibit the progression of atherosclerosis and inflammation and iii) reduce the pro-inflammatory and pro-apoptotic oxidative injury. Caffeine is associated to a non-hyperfiltration related increase in eGFR, and to a reduced incidence of kidney stones, probably because of increased urine dilution. On the other hand, experimental data suggest that caffeine negatively influence renal function in the presence of hypertension and pre-existing renal damage, with increased proteinuria. Coffee consumption correlates with decreased uric acid levels, probably because of components other than caffeine itself.

The control of hypertension is crucial in both prevention and management of CKD, and nitrates and nitrites have been shown to be protective against CV risk, as they probably contribute to the BP-lowering effects of plant-based dietary approaches, such as the DASH diet. NO deriving from the microbial nitrate/nitrite pathway is associated with decreased BP, amelioration of vascular compliance and endothelial function, improved physical performance, reduction of CV risk and amelioration of renal injury in animal models of hypertension and IR-injury. For these reasons, adequate dietary intakes of vegetables, particularly green leafy ones and beets, can be considered a healthy eating habit functional for vascular health that prevents the development of hypertension and its comorbidities, including CKD.

Alcohol is a xenobiotic whose abuse is associated with CV and renal damage. Lower gender-dependent doses of alcohol are instead related with health benefits, amelioration of BP, lipid profile, protection from CVD and renal function, also in CKD patients. The polyphenols found in some alcoholic beverages, such as red wine, have been shown to synergistically contribute to these healthy effects. Because of its sensible relationship with renal function, -with a moderate alcohol intake being beneficial and an excessive intake being deleterious-, a balanced approach in the management of patients with or without CKD should be considered.

In conclusion, nutrition is increasingly being recognized as something far more important than a mere supply of dietary substances that provide raw materials and energy to the human body. It rather represents the most habitual factor functionally acting on the human body, and influencing its metabolism and immunity as a whole.

According to the Paracelsus principle "*sola dosis facit venenum*", it is fundamental to establish the right dose of any substance for each individual and clinical condition. Nutrition does not make exception to this principle: even for recognized health-promoting components, extrapolating rules that fit all situations in the general population could be misleading. In the next future, the concept of personalized nutrition should be promoted even more. The nutrients, nutraceuticals and xenobiotics discussed in this review confirm this view, be they fibres, proteins, FAs, curcumin, alcohol beneficial or deleterious depending on the size of their intakes and to the clinical conditions of the individual, that should always be accurately evaluated before designing any customized nutritional therapy and supplementation.

Author Contributions: Conceptualization, CC and AS; Writing-Original Draft Preparation, CC, AS and IDB; Writing-Review & Editing, CC, AS, EF and LG.

Funding: This research received no external funding.

Acknowledgments: The authors thank Dr. Lucia Sollecito for English editing of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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