Food as medicine – could it be implemented in chronic kidney disease?

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Abstract:

The observation that unhealthy diets may be responsible for more deaths than other established risk factors has boosted interest in the concept of “Food as medicine”. This concept is especially relevant to metabolic diseases, such as chronic kidney disease (CKD) where dietary treatment, including protein restriction, is already a fundamental therapeutic component designed to ameliorate metabolic and nutritional complications. The increased awareness that toxic “uremic” metabolites originate not only from intermediary metabolism, but also from gut microbial metabolism - which is directly influenced by the diet - has fuelled interest in the potential of “Food as medicine” in CKD, beyond current strategies with restricted intake of protein, Na, K, and phosphate. The time seems ripe to investigate the potential of tailored, healthy diets - with bioactive nutrients included as part of the foodome – to prevent and treat CKD and its complications. Such a “Food as medicine” approach in CKD is warranted - and motivated by observations that bioactive nutrients 1) act as modulators of transcription factors involved in inflammation and oxidative stress; 2) mitigate mitochondrial dysfunction; 3) alter composition and metabolism of the microbiota; 4) act as senolytics and 5) alter one-carbon metabolism as part of the epigenetic regulation. This review highlights the potentials of “Food as medicine” using bioactive nutraceuticals that have the potential to beneficially affect the quality of life and survival of CKD patients.

Key Points:

- Epigenetic alterations, dysbiosis, mitochondrial dysfunction, inflammation, oxidative stress and premature ageing are common features of the uremic phenotype.

- The foodome - defined as the pool of all compounds present in a food sample and/or in a biological system interacting with the investigated food - can be implicated in the modulation of CKD complications.

- Imbalance in the relative diversity of the gut microbiota has been studied extensively in CKD due its links with inflammation and cardiovascular risk. In this direction, researchers are evaluating the effects of pre-, pro- and synbiotics and many others food components like polyphenol-rich foods, sugar, proteins, etc. on both the modulation of the diversity of the gut microbiota and reduction in the levels of uremic toxins .

- The use of bioactive compounds, found in curcumin, broccoli sprouts, berries, propolis, etc. may be valid nutritional therapeutic agents to modulate the expression of pro-inflammatory transcription factors, such as Nrf2, NF-kB and the inflammasome.

- Senotherapeutic dietary compounds may mitigate the effects of a dysregulated ageing process in CKD and associated complications. including disturbed mitochondrial metabolism.

Introduction

"Let food be thy medicine"

The ancient concept "*Let food be thy medicine*" (a misquote often attributed to Hippocrates of Kos) is supported by the Global Burden of Disease (GBD) Study 2017[1], which concluded that unhealthy diets – typically characterized by high intake of sodium and low intake of whole grains and fruits – may cause most of the non-communicable chronic burden of lifestyle diseases, such as hypertension, cardiovascular disease (CVD), cancer, type-2 diabetes and chronic kidney disease (CKD). According to the GBD study that involved 195 countries, dietary risk factors are a major contributor to as many as 11 million deaths and 255 million disability-adjusted life-years (DALYs), with non-optimal intake of sodium, whole grains, and fruits accounting for >50% of deaths attributable to a poor diet[1]. Ultraprocessed foods, which are widespread in the Western diet, were recently shown to be associated with a higher risk of type-2 diabetes[2]. These staggering data suggest that suboptimal diets may be responsible for more deaths than other established risk factors, including smoking. It highlights the urgent need for global efforts to improve the quality of human diet as a strategy to prevent and combat a cluster of burden of lifestyle diseases, including CKD[1].

Conceivably, improving poor dietary habits could have positive effects on CKD and its complications, as well as on the cluster of chronic burden of lifestyle diseases contribute to its complications. Underlying interlinked factors that accompany CKD, such as oxidative stress, mitochondrial dysfunction and gut dysbiosis, are all potentially influenced by foods[3]. Results from new studies not only support this assumption, but also illustrate that the effects of foods are complex. For example, ketogenic diets, with limitation of carbohydrates and liberal intake of fats, may reduce serum hemoglobin A1c in type-2 diabetes, but may also cause a substantial rise in low density lipoprotein cholesterol levels[4]. In adult polycystic kidney disease (ADPKD), ketogenic diets result in a chronic shift in energy production from mitochondrial oxidative phosphorylation to aerobic glycolysis (the Warburg effect), delaying cyst growth, thus rendering cyst cells exquisitely sensitive to glucose availability, and therefore delaying progression of the disease[5]. Intriguing new data suggest that even mild reduction in food intake promoting ketosis slows the progression of ADPKD in a mouse model[6]. Pertinent to CKD, which displays features of accelerated ageing, a broad-spectrum

beneficial effect of intermittent fasting on ageing and disease has also been described recently[7]. Beneficial effects of dietary component changes include an increased vegetarian diet or low protein diet, where red meat intake was reduced and which decreased generation of uremic toxins[8,9]. Additionally, high fruit and vegetable intake has also been associated with lower mortality, not only in the general population[1], but also hemodialysis (HD) patients[10].

To date, the main targets in pre-dialysis care have been to slow the progression of kidney failure and t control uraemic complications, such as inflammation, anemia, high blood pressure, insulin resistance, metabolic acidosis, bone mineral disease and protein energy wasting[11]. Epidemiological studies have consistently shown that plant-based diets rich in fruits, vegetables, seeds, nuts, tea, cocoa, coffee and whole grain cereals, slow the rate of decline in kidney function [12-14]. These examples suggest that there are unexplored opportunities to apply "*Food as medicine*" (FAM) as an effective preventive and therapeutic option in the context of renal disease.

Although many studies have focused on the effects of specific nutrients for specific complications, it has been suggested[15] that guidelines should move from being nutrient-based (using the recognized function of a bioactive compound) to a holistic food-based approach that considers all nutrients. Based on the view that all foods are functional, we suggest that the concept of the *foodome* should be introduced as part of a FAM approach to treating CKD. As an example, a single substance, such as selenium, derived from the Brazil nut, may present more benefits than selenium given alone as a supplement[16].

The *foodome*, or the food-intrinsic metabolome, is defined as the pool of all compounds present in a food sample and/or in a biological system, interacting with the investigated food. The *foodome* can be influenced by geographical origin, climate, cultural practices, processing and storage conditions and intrinsic factors in a biological system, which is immensely complex and dynamic[17]. Omics technologies, such as genomics, transcriptomics, proteomics, metabolomics, nutrigenetics, nutrigenomics and microbiomics are employed to investigate food and its nutritional and health-related effects[18]. The aim of a *"foodomic approach*" is to promote generalized applications of personalized nutrition based on solid scientific evidence. As recent studies have shown that dietary pattern has an impact on the progression of CKD[19] as well as on hard outcomes, including mortality[10,20],

CKD appears to be a suitable condition in which to test the validity of the FAM concept. Nutritional interventions may prove to be especially beneficial in CKD, as the customary diet of CKD patients is often of inferior quality due to restriction of vegetables and fruit intake[10, 21]. Due to a fear of hyperkalemia, dietary advice to patients with CKD has been different to that for the general population. However, as novel potassium binders may help to overcome dietary potassium restrictions in CKD, we argue that there are no reasons why dietary interventions should be different in CKD compared to other high-risk patient groups[22].

Before robust nutritional recommendations based on "*foodomics*" can be given, several crucial questions need to be addressed. Should the ideal diet differ at different stages of renal dysfunction? Can recommendations based on studies in the general population be extrapolated to CKD? In which aspects should food recommendations differ with regards to sex and age? As a recent approach to study ageing has identified marked non-linear alterations in the proteome with age[23], targets for nutritional therapies may differ dependent of age. Which food products should be avoided? Which components are worse for patient health? Can food modulate the transcription factors involved in inflammation? Can individual foodstuffs serve as a link between mitochondrial biogenesis and gut microbial dysbiosis? As we do not yet have answers to these questions, and suboptimal diets appear to play a major role in global health[1], the Renal Community needs to systematically address the specific effects of various nutrients on the uremic phenotype[24]. The large gap in knowledge on the bioavailability of bioactive nutrients also needs more attention. As dietary transitions toward greater consumption of healthier foods is also a way to improve environmental sustainability[25], this is yet another reason to aim for the use of healthier food in a renal context and apply the "Planetary health" concept[26].

This review addresses the concept of FAM and its potential impact on clinical outcomes in the context of renal disease. We focus on mechanisms by which food and specific nutrients may affect the uremic phenotype in the following six areas: 1) the epigenome, 2) gut microbiota composition and metabolism, 3) cellular stress and damage repair (i.e. anti-senescence) pathways, 4) mitochondrial function, 5) transcription factors involved in inflammation and oxidative stress, and 6) stimulation of nitric oxide. It should be emphasized that most nutrients, such as curcumin, anthocyanidins, resveratrol and quercetin, have pleiotropic effects. For example, nutrients that stimulate the cytoprotective

transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) may also improve mitochondrial function - by stimulating mitochondrial biogenesis[27] - and senescence by inducing anti-senescence pathways[28]. Moreover, nutrients affecting the microbiota may impact on the epigenetic landscape and mitochondrial biogenesis, since metabolites from gut microbiota metabolism, such as short chain fatty acids (SCFA), are taken up by the host and influence the epigenome[29].

Nutrients targeting epigenetic alterations in CKD

A link between nutrition and the epigenetic landscape is both intuitive and critical for normative physiological function. The epigenome comprises, in its canonical form, methylation of DNA and post-translational modification of chromatin associated proteins, typically histones, via acetylation, phosphorylation, ubiquitination, sumoylation and malonylation. In its non-canonical form, it extends the epigenetic landscape, through non-coding RNAs (e.g. miRNA, lncRNS) reciprocally regulating gene expression in response to environmental changes[30-33]. Nutrition can impact on these processes on two main fronts: 1) via regulation of the epigenetic landscape of ageing, a proven feature of CKD[34] which mediates nutrient sensing pathways at a cellular and molecular level and 2) via provision of nutritionally derived methyl donor groups to supplement maintenance of the methylome, critical for normal gene function[34].

Determination of associations between methylation changes and clinical features observed in CKD have yielded equivocal results. The reasons for this lack of consistency remain unclear. CKD, as part of the diseasome of ageing, is underpinned by dysregulation of normal ageing processes. A consistent feature of mammalian ageing is genomic hypomethylation[30,35]. However, most studies investigating global methylation changes in CKD have lacked significant power to provide an unambiguous assessment of methylation status[36], which may have contributed to the equivocal findings in the field. Additionally, these studies have lacked unified methodological and statistical methods[37]. A growing body of evidence has consistently indicated that the epigenome reciprocally mediates the progression and effects of CKD by modulating cell stress, cell defense and signaling systems aligned with ageing processes. For example, hyperhomocysteinemia, which is associated with a paradoxical survival advantage in CKD[38] impairs methyltransferase function resulting in DNA hypomethylation[39]. Moreover, DNA hypomethylation has been observed to correlate

with increased biological age and loss of physiological resilience in renal allografts undergoing delayed graft function[40]. Both these observations indicate that loss of methylation is associated with renal dysfunction. Conversely, inflammation and increased mortality in CKD have been associated with global DNA hypermethylation[41]; thus, the relationship between global DNA methylation and outcome may be context sensitive.

A link between the wider epigenetic landscape of ageing and renal dysfunction can also be discerned in the context of metabolism and regulation of nutrient intake and sensing (**FIG 1**). In keeping with DNA hypomethylation as a feature of the dysregulated ageing processes underpinning CKD, examination of the wider epigenetic landscape has indicated that the activity of chromatin modifiers (e.g. sirtuins) and non-coding RNAs link the "foodome" to the epigenetic landscape of ageing[42]. Modulation of age-related functions such as cellular stress and damage (i.e. anti-senescence pathways) by miRNAs regulating both the CDKN2 locus (which affects age related physiological capability)[43] and nutrient sensing pathways (e.g.via mTOR) indicate that nutritional interventions, targeting the methylome, or targeting chromatin, are eminently feasible, although caution is merited as any adverse cryptic intergenerational or transgenerational epigenetic effects remain undetermined at this stage. Potential candidate nutrients for such interventions include choline, betaine, folate, vitamin B12 and methionine, which have the potential to influence methyl group donation needed for the maintenance of the methylome[44-45].

What is not well understood about any such putative intervention, is the degree to which humans possess a natural synthetic ability for one significant component of this system, namely the osmo-protectant betaine. Betaine can be nutritionally derived through consumption of beets (hence its name, as it was isolated from sugar beets; *Beta vulgaris* subsp. *vulgaris*), spinach, wheat and crustaceans[46] or via oxidation of choline. In keeping with a thesis whereby maintenance of the methylome is affected by nutritional acquisition of methyl donor groups, evidence from pre-clinical models has indicated that betaine supplementation improves metabolism and insulin resistance in mice fed a high-fat diet[47] Pertinentl to CKD, low plasma betaine levels have been associated with metabolic syndrome and poor outcome[48]. While humans have some endogenous synthetic capacity for betaine, its availability and abundance is supplemented by the activities of gut microbiota. Consequently, nutritional modification of the microbiome can affect one-carbon metabolism and the capacity to methylate the genome in CKD[49]. In fact, imbalance in the gut

microbiota in CKD has been implicated both in epigenetic alterations and several CKD associated complications[30].

Nutrients targeting gut microbiota

In the adult human, the trillions of microorganisms making up the gut microbiota represent a metabolically active biomass of up to two kilograms. Disturbed composition, diversity and function of the gut microbiota, commonly referred to as gut dysbiosis, contributes to a range of diseases, such as obesity, type-2 diabetes, CVD and CKD, through complex and as yet only partly understood mechanisms, [50-52]. A bidirectional cause-effect relationship exists between CKD and gut dysbiosis[52, 53]. The research front has moved towards exploration of therapeutic strategies to revert gut microbiota composition and metabolism to a normative state, although a clear definition of the latter is still lacking. The gut microbiota has an innate ability to resist external influences. Nevertheless, studies have shown that long-term dietary interventions may overcome microbiotal resilience and drive changes in gut microbiota composition and metabolism[50,54,55]. The functional plasticity of the gut microbiota in repsonse to dietary variation is an open door for the application of FAM in CKD[50].

Studies exploring strategies to modulate gut microbiota in CKD have so far focused mainly on pre-, pro- or synbiotics. Studies with probiotic supplements (living organisms) have yielded inconsistent results[52,56,57]. For example, some authors have shown effectiveness for probiotics in lowering uremic toxins and urea plasma levels[58-60] while others have failed to confirm these benefits[57,61]. Although probiotics have the potential to improve health, they may not work in the same way for everyone, especially in patients whose gut environment is impaired by disease-related factors, such as those present in CKD[52,57]. It is also possible that the age of the patient has a role in these effects. Prebiotics (compounds that induce the growth of beneficial microorganisms) confer more consistent effects[62]. Through various mechanisms, prebiotics cause bacterial metabolism to shift towards a predominantly saccharolytic fermentation pattern. The “cross-feeding” concept has been adopted to explain the reciprocal cooperation phenomenon between different intestinal bacteria using efficiently fermentable substrates, optimizing the generation of beneficial metabolites and thus reciprocally benefiting each other and the host[63-66]. Several

clinical studies have reported positive effects for prebiotic supplementation on plasma urea levels, uremic toxins and inflammatory markers in CKD[67-70]. Fruits, vegetables and cereals are rich in dietary fibre,, which is prebiotic. This escapes digestion in the small intestine and is a major source of (fermentable) carbohydrate in the colon[71]. Resistant starch, non-starch polysaccharides, inulin and oligosaccharides also have prebiotic properties[72]. Naturally occurring prebiotics are found in foods such as soybeans, unrefined wheat, whole grain barley, raw oats, wheat bran, raw potato, green banana, onion, beans, asparagus, chicory and as a natural constituent of breast milk[62,73,74]. Synbiotics (i.e. the combination of pre- and probiotics) are considered of interest in CKD because of potential synergistic action of the individual components. Although synbiotics modulate the gut microbiota and mitigate the production of toxic substances[75-78] more evidence is needed to support synbiotics as a treatment option in CKD. Macronutrients not absorbed in the small intestine can be processed by gut microbiota in the colon. The stronger and more entangled the food matrix (i.e. interaction between physical domain with specific constituents of a food), the lower the conversion of food components into basic units to be absorbed, providing potentially more substrates for the gut microbiota. Micronutrients, including minerals and vitamins may also affect the gut microbiome[79].

High-**sugar** (glucose or fructose) promotes selective growth of particular bacteria, affecting the composition of the gut microbiota and consequently changes its metabolite profile. Consequently, high consumption of sugar decreases microbial diversity and increases the ratio of *Firmicutes* to *Bacteroidetes which is associated with poorer age related health*[80, 81]. A high sugar diet also might result in over-expressed of tight junction-disrupting cytokines, such as TNF, IL-1β and IFNγ, damaging the intestinal barrier[81]. This scenario contributes to endotoxemia, activation of the toll-like receptor-4 (TLR-4), inflammation and metabolic disorders[80, 81]. Gut dysbiosis may explain the association of high sugar consumption with increased incidence of albuminuria, CKD and CVD[82].

Dietary **protein** partly escapes digestion and absorption in the small intestine[9,83,84]. Protein fermentation results in the generation of both beneficial (e.g. polyphenols and SCFA) and toxic (e.g. ammonia, amines, sulphide, phenols, thiols, and indols) end products[85-87]. Not only the dietary protein content, but also the source, processing and cooking method have been identified as important determinants of microbial metabolism[88-90]. Red meat, for example, is rich in sulfur-containing amino acids, such as cysteine and methionine and

inorganic sulfur is often added as a preservative. As the degradation of sulfur compounds by sulphur-reducing bacteria like *E. coli* and *Clostridium spp*. increases the production of hydrogen suphde (H_2S), red meat, especially when processed, can modify the abundance of sulphur-reducing bacteria in the colon[89,91,92,93]. Soy protein is characterized by a relatively low digestibility and, thus, may be hypothesized to foster protein fermentation. As soy foods (such as soymilk, tofu, soy flour) are also rich in fiber and oligosaccharides with prebiotic properties, the overall impact on gut microbial metabolism may be neutral[94.]

High **fat** diets decrease total microbiota content in faeces, increase endotoxemia and intestinal permeability[95,96]. The effects of high fat diet on gut microbiota have been investigated in healthy young adults over a six months time peroid, with faecal metabolomic profiles and plasma inflammatory biomarkers measured. This diet had an unfavorable impact on gut microbial taxa and decreased concentration of faecal SCFA and elevated plasma proinflammatory markers, such as high sensitivity C-reactive protein and thromboxane B2[97].

Next to fat content, the free fatty acid (FFA) composition (saturated, trans-, mono- or polyunsaturated FFAs) of dietary fat influences composition and function of the gut microbiota [95,96]. Whereas saturated FFA enhances intestinal permeability and selects for H_2S-producing bacteria, supplementation with fish oil (source of omega-3) restores the barrier function[98]. Trans fatty acids, are also widely present in processed foods such as cakes, cookies, margarine, fried potatoes and snacks, and promote microbial dysbiosis and poor health[95].

Interestingly, omega-3 rich foods have shown a greater positive impact on the gut microbiota in comparison to supplements, reflecting food matrix effects[99]. Omega-3 FFAs also exert anti-inflammatory effects by enhancing secretion of intestinal alkaline phosphatase, an endogenous peptide known to inhibit the growth of lipopolysaccharide (LPS)-producing bacteria. The health promoting properties of virgin olive oil have been attributed not only to the monounsaturated FFA composition but also to its prebiotic activity due to its polyphenol content[100,101]. Importantly, refinement of the virgin oil depletes it of polyphenols. In fact, virgin olive oil has been observed to have distinct effects on the relative percentages of bacterial families (*Desulfovibrionaceae, Spiroplasmataceae, Helicobacteraceae, Erysipelotrichaceae and Sutterellaceae)* in mice in comparison to refined olive oil[102].

Although **sodium** occurs naturally in most foods, elevated levels in processed foods (like bacon, sausage, ham, pizza, pickles, ready-to-eat cereals) contributes to the high salt intake found among Western societies[103]. Mounting evidence indicates that gut dysbiosis may be in the causal pathway between high salt intake and renal damage or hypertension[103,104]. In mice, chronic high salt intake induces dysbiosis, gut barrier disruption and translocation of enteric bacteria into the kidney resulting in damage[104]. A possible mechanism by which salt affects the composition of the gut microbiota may be by changing osmotic pressure which suppress growth of certain bacteria[104]. **Iron** is an essential micronutrient (2.7 mg iron in 100 g red meat) for pathogenic and commensal bacteria, weith the exception of *Lactobacillus*[105]. Iron supplements increase intestinal permeability in children, thereby promoting translocation of pathogenic bacteria into the circulation and increasing the risk of diarrhea[106-108]. One study has reported that children on iron supplementation had signs of intestinal inflammation, with an increased number of *Enterobacteria* and a decrease in *Lactobacilli*[109]. Additionally, iron treatment reduced the levels of *Bifidobacteriaceae* and *Lactobacillaceae* and increased levels of *Roseburia* and *Prevotella*, while metagenomic analyses showed a change in the metabolome from the saccharolytic to a proteolytic profile[110]. Thus, as oral iron supplementation promotes gut dysbiosis and increases production of uremic toxins, which may induce erythrocyte senescence and anemia[111-113] this 'drug-bug' interaction has implications for anemia treatment in CKD.

Consumption of **polyphenol**-rich foods (i.e. grapes, red wine, pomegranates, garlic, coffee, green tea, chocolate, turmeric, blueberries and cranberries), especially plant-derived polyphenolic compounds associates with lower mortality in the general population[114]. Most dietary polyphenols enter the body via the colon, as bioavailability is low, and consequently may modulate gut microbial composition and function[115,116]. In keeping with such a thesis, observations a number of observationsn on dietary such supplememtation are pertinent. Firstly, healthy individuals having consumed flavanol-rich cocoa drinks for four weeks demonstrated increased prevalence of salutogenic *Bifidobacteria*l and *Lactobacilli* populations among the gut mirobiota, whereas the prevalence of the more typically pathogenic *Clostridia* were decreased significantly[117]. Secondly, in rats feed a high-fat diet[118,] blueberry supplementation promoted beneficial changes in the gut microbiota (increased prevalence of *Bifidobacterium* and *Lactobacillus sp*), which was

associated with improvements in systemic inflammation and insulin signaling. Thirdly, allicin, an organosulfur compound with antibacterial properties found in garlic, has been observed to prevent the generation of the uremic toxin trimethylamine N-oxide (TMAO) in mice supplemented with L-carnitine[119]. Fourthly, resveratrol (an agonist for NAD+ dependent regulation of the epigenome via sirtuin activity) present in grapes and red wine, has been demonstrated to inhibit microbial trimethylamine (TMA) production[120].

Furthermore, enzymatic microbial degradation of dietary polyphenols results in the generation of low molecular weight phenolic metabolites, which are readily absorbed and may exert beneficial effects in the host[115, 121]. Urolithin A, a microbial metabolite derived from polyphenols present in pomegranate fruits and berries, has been shown to upregulate epithelial tight junctions and attenuate colitis via stimulation of Nrf2-dependent pathways in mice[116].

Many processed foods, such as soda based drinks and yogurts, include **artificial sweeteners** as a supposedly healthier option to replace natural sugar. However, as sweeteners can exert bacteriostatic effects by inhibition of bacterial enzymes, or by altering the transport of essential nutrients for bacterial growth and survival, they may induce changes in the profile and function of the gut microbiota[122 -125]. Sweeteners interact directly with the community of micro-organisms in the colon causing changes in the relative diveristy and subsequent metabolic imbalances[124,126,127] as well as lymphocytosis in intestinal mucosa[128]. Acesulfame potassium, cyclamate and saccharin, for example, have all been shown to inhibit the anaerobic fermentation of glucose by the intestinal microbiota of rats[122]. Moreover, 12 weeks of exposure to a sucralose-based artificial sweetener (Splenda®), has been demonstrated to significantly alter the composition of the microbiota and was associated with weight gain in rats[125]. In healthy humans, sweeteners induced dysbiosis and glucose intolerance, suggesting that alterations in gut bacteria glycan degradation pathways may contribute to impaired glucose tolerance[124]. Thus, artificial sweeteners should be used with caution in CKD.

Because we eat various types of foods in different combinations and frequencies, the overall effects of diet on the gut microbiota is complex and results from parallel actions of several dietary components. A comparison between the celebrated Mediterranean diet with a more typical Western diet is informative in this respect. The Mediterranean diet, with its high content of vegetables, fruits, fish, extra virgin olive oil, nuts, whole grains, and

moderate intake of red wine, is a source of fermentable carbohydrates, vegetal protein, polyunsaturated fats and bioactive compounds. On the other hand, the Western diet is characterized by high content of red meat, ultra-processed foods and refined grains, providing high contents of sugar, salt, phosphate, additives, animal protein and saturated and hydrogenated fats. Thus, while the Mediterranean diet favors the growth of saccharolytic microbial species and a better metabolite profile , while the Western diet favors proteolytic bacteria and promotes dysbiosis[129]. In keeping with these observations, pre-clinical studies indicate that the gut microbiota do contribute to improved healthspan[130]. It is therefore an attractive prospect that normalization of the gut ecosystem in CKD by diet, or nutraceuticals, will reduce the colonic synthesis of uremic toxins and tighten the intestinal barrier with less risk of endotoxemia and inflammation. However, at present, studies showing effects of different dietary patterns on the uremic gut microbiota are scarce and current evidence supporting this approach is thus limited,. However, the prospect is that in the near future, we can move towards personalized dietary therapy directed to addressing the uremic gut microbiota. This remains a great challenge, but advances in metagenomics and biostatistics promise a bright future, ultimately positioning FAM as a fundament of standard renal care (**FIG. 2**).

Nutrients that target senescence

The desire for eternal youth is as old as mankind. Chronological age, the leading risk factor for chronic burden of life style diseases, such as CVD, rheumatoid arthritis, HIV, chronic obstructive pulmonary disease and CKD, is characterized by persistent low-grade inflammation, stem/progenitor cell exhaustion, dysfunction of macromolecules and cell organelles and cellular senescence[131,132]. Cellular senescence is an inherent feature of developmental processes[133,134] and wound healing in an acute setting[135,136]. It is typically triggered by a range of DNA damage responses, as a means of inducing growth arrest in potentially oncogenic cells[137]. Senescent cells comprise < 1% of the cells in a young tissue or an organ, but this number rises to >5% with increasing chronological and biological age and their number correlates directly with a loss of physiological function[138]. Senescent cells are metabolically active, but essentially, they are not physiologically contributory, and may persist in tissues and organs for many years[139]. The increase in senescent cells is reflective of

the burden of lifestyle and 'wear and tear' in individuals, subject to DNA damage and a range of physiological and environmental stressors[30,140]. Consequently, the uraemic milieu accelerates components of this underlying ageing process[141].

At a cellular level, senescence is characterized by a finite replicative capacity in primary cells[142] with consequential growth arrest and a characteristic senescence associated secretory phenotype (SASP)[137]. The SASP engenders a toxic pro-inflammatory environment, and mediates the generation of secondary senescence in adjacent cells[143], or promotes non-autonomous cellular senescence in distal tissues[144].

Among componentsof the SASP, interferon gamma (IFN-γ) has been identified as a mediator of age-related physiological function in the kidney[40,140.] As CKD[145], diabetes[146] and uremic vascular calcification[147] are conditions characterized by increased cellular senescence, targeting cellular senescence provides a means for novel treatment strategies, using senolytic drugs (i.e. therapeutic agents to target cellular senescence) such as dasatinab[148]. However, senolytic efficacy often requires synergistic use of another agent, such as quercetin, that both mitigates collateral damage to non-senescent cells and enhances senescent cell specificity of effect[139]. Compounds, such as quercetin, and related alkyl catechol based senolytic agents, such as fisetin, can also be acquired nutritionally, emphasizing the potential of FAM[149]. In the context of CKD, it is of interest that foods rich in polyphenols that exert anti-oxidant and anti-inflammatory actions have the potential to be used as senolytics, or senotherapeutics, in a nutraceutical approach to healthier ageing. A range of studies have indicated that diets lacking sufficient polyphenol intake accelerate ageing and age-related diseases and promote inflammation[150, 151].

A range of natural senolytic compounds can be acquired via nutritional intake, such as resveratrol, quercetin, fisetin, piperlongumine tocopherol, curcumin, berberine, rutin, catechin, proanthocyanidin and ginkgo biloba extract; compounds present in fruits and vegetables, wine, tea and chocolate[149, 152]. Notably, many of these are alkyl catechols that are derived from microbial processing of phenolic acids in these food stuffs. These agents are natural Nrf2 agonists and often missing in the Western diet, which has been associated with a poorer health span[153]. Nrf2 is a major mediator of cellular stress defenses and is a regulator of hundreds of stress-defense genes[3].

The health benefits of nutritionally derived polyphenols are manifold. Resveratrol, for example, is thought to mediate geroprotective (i.e. anti-ageing) effects through agonism of

NAD-dependent deacetylase sirtuin-1 (SIRT 1), enhancing chromatin stability and modulating cellular metabolism in response to stress, thereby reducing the oxidative and inflammatory burden[154]. Agonism of SIRT 1 promotes down-regulation of senescence-related proteins and decreases expression of pro-inflammatory cytokines[155]. As SIRT1 plays a vital role in regulating endothelial function, arterial remodeling, and vascular ageing[156], such an interventional strategy would be of high merit.

While the use of senolytics, or senotherapeutic agents, could potentially mitigate some of the effects of CKD, evidence from clinical studies is limited. Flavonoids appear to be important polyphenols in the context of senotherapy. Fisetin, found in large amounts in strawberries (160 μg/g) and apples (27 μg/g), has been identified as a potent senolytic agent in both mice and human tissue[157,158]. Moreover, fisetin has been demonstrated to attenuate metabolic dysfunction after a high-fructose diet in mice[159]. Quercetin is a related compound with demonstrated anti-inflammatory and antioxidant capacity. The clinical observation that increased intake of apples (rich in quercetin) protects against abdominal aortic calcification in older women[160] aligns with experimental data. Indeed, apple polyphenols, the major antioxidants in apples, have been shown to possess wide-ranging beneficial biological functions that could benefit patients with CKD[161]. In dipterans, acute treatment with quercetin has already been demonstrated to be geroprotective[162] and in a rat model of CKD quercetin protects kidney function[163]. Additionally, curcumin a natural senolytic agent, also acts as a Nrf2 agonist[3, 164]. Correpondingly, curcumin has been reported to reduce oxidative stress via activation of heme-oxygenase-1 (HO-1) and reduce the number senescent cells and inflammation in a murine model of vascular ageing[165].

Micronutrient supplementation may be yet another senolytic strategy. Indeed, vitamin E supplementation has been reported to reduce the numbers of senescent cells *in vitro*[166]. Zinc may also be involved in senescence; both high and low Zn levels in endothelial cells has been linked to apoptosis[167]. As the senolytic effect from these nutrients appears to be cell-type dependent, the link between micronutrient bioavailability[168] and the uremic phenotype and senescence deserves further studies. The adoption of a diet rich in potentially senolytic compounds could be a possibility to reduce premature ageing and the complications of senescence in CKD[149] (**FIG 3**).

Nutrients that target mitochondrial dysfunction

Mitochondria have many functions including production of ATP, via the oxidative phosphorylation system and regulation of the cellular redox state[169,170]. Due to their key role in cellular biochemistry, they have been implicated in the pathogenesis of chronic burden of life style diseases[170,171]. The main regulator of energy metabolism and mitochondrial biogenesis, proliferator-activated receptor coactivator-1α (PGC-1α), interacts with Nrf2 and mitochondrial transcription factor A (TFAM), which is involved in mitochondrial DNA (mtDNA) replication and transcription[169,172,173]. CKD is characterized by mitochondrial dysfunction[164,174] with downregulation of PGC-1α, dysregulation of mitochondrial biogenesis[169], reduced skeletal muscle expression of mitochondrial-derived peptides and decreased Nrf2 expression[175]. Mitochondria are extremely susceptible to oxidative stress, and mitochondrial dysfunction leads to the establishment of a vicious cycle of overproduction of ROS[169] and activation of the inflammasome and NF-κB, which triggers further mitochondrial dysfunction, [,173].

There is a bidirectional relationship between the gut microbiota and mitochondria[176,177]. While the gut microbiota influences mitochondrial function through bacterial metabolites, such as H_2S, secondary bile acids, uremic toxins, LPS and SCFA, mitochondria dysfunction could contribute to perturbation of the gut microbiota through impairment of redox balance[176,177]. In CKD, where there is both dysbiosis and mitochondrial dysfunction, these mechanisms work together as “partners in crime” to promote oxidative stress and inflammation[177]. New insights into the role of mitochondrial dysfunction in CKD suggest that mitochondria could be a therapeutic target for treatment with food compounds, such as fatty acids, amino acids, dietary fiber, selenium, resveratrol, curcumin, allicin, vitamin C and propolis (**FIG 4**).

Animal studies have demonstrated that increased fatty acid supply saturates mitochondrial oxidative capacity, resulting in the generation of lipid peroxides that contribute to lipotoxic damage to mtDNA and mitochondrial dysfunction[178]. Palmitic acid, the most common long-chain saturated fatty acid in the Western diet, has been reported to increase mitochondrial ROS production and decreases protein levels of PGC-1α and TFAM in rat skeletal muscle[179]. On the other hand, ω-3 fatty acids (e.g. present in fish oil) upregulate PGC-1α and Nrf1[180] and as such, induce, or increase, mitochondrial activity of carnitine palmitoyl transferase 1

and fatty acid β-oxidation[181]. These effects contribute to decreased mitochondrial lipid accumulation, while long-chain saturated fatty acids promote lipotoxicity[171].

Dairy products may influence energy metabolism in part owing to their high leucine content[182]. This amino acid stimulates the expression of mitochondrial biogenesis genes SIRT-1, PGC-1α and Nrf1, as well as oxygen consumption in myocytes and adipocytes[183]. Another amino acid, L-carnitine, has been suggested as a therapeutic agent for use in CVD to improve mitochondrial energy metabolism[184]. Carnitine inhibits mitochondrial dysfunction induced by FFA[184,185] by inhibiting FFA-induced mitochondrial membrane damage and subsequent down stream effects. Approximately 75% of the total body pool of carnitine originates from food sources (red meat, fish, egg and dairy products), or via nutritionally derived lysine and methionine, which are used for endogenous biosynthesis of carnitine[184,185]. L-carnitine treatment for uremic dyslipidemia has been reported[186], but as oral carnitine supplementation also contributes to TMAO production by gut microbiota fermentation, the overall effect on mitochondrial biogenesis is uncertain and may be context sensitive[187,188]. An elevated TMAO level is an independent predictor of poor outcome in CKD[48,189,190]. A randomized trial in healthy volunteers exposed to red meat, white meat and non-meat protein has shown that chronic intake of dietary red meat increases systemic TMAO levels via enhanced dietary precursors, increased microbial TMA/TMAO production from carnitine and reduced renal TMAO excretion[191]. As higher intake of processed and unprocessed red meat, but not fish or poultry, have been reported to correlate with increased mortality in 29,682 US adults, the source of the meat may thus be of importance[192]. Indeed, replacement of red meat with white meat (chicken) has been obsseved to reduce microalbuminuria in a randomized crossover-controlled trial of type-2 diabetic patients[193]. Thus, a diet with chicken as the only source of meat represents an attractive strategy for treatment of type-2 diabetes and microalbuminuria[193]. The amino acids tryptophan and tyrosine are also fermented by gut microbiota, leading to formation of uremic toxins, such as indoxyl sulfate (IS) and p-cresyl sulfate (p-CS). Indoxyl sulfate downregulates Nrf2[194], decreases mRNA expression of PGC-1α and decreases mitochondrial membrane potential in skeletal muscle cells[195]. As co-incubation with L-carnitine inhibits the development of IS-induced impaired mitochondrial functions[195], it is possible that carnitine

supplementation may have both positive and negative effects on uremic toxins in the clinical situation.

SCFAs (including acetic acid, butyric acid, and propionic acid), resulting from the fermentation of carbohydrates and protein in the large intestine, affects the metabolism of the host in several ways, including through modulation of mitochondrial biogenesis. Butyrate supplementation has been shown to result in increased expression of PGC-1α in rats[196] in keeping with butyrate metabolization providing acetyl-CoA and NADH, which increase ATP production in the electron transport chain[172,172,197].

Deficiency of selenium and reduced activity of the glutathione peroxidase (GSH-Px), a selenium dependent antioxidant enzyme, is common in CKD. Three months supplementation with one unit of Brazil nuts (*Bertholletia excelsa*), an important source of selenium, has been reported to improve inflammation and increase Nrf2 expression in HD patients[16], potentially via maintenance of mitochondrial function. In an animal model of colitis, a high selenium diet has been observed to result in a significant increase of selenium in colonic tissue, with preservation of tissue oxygen consumption and mtDNA, as well as upregulation of the expression of Nrf1 and TFAM, suggesting that selenium protects colonic mitochondria[198]. As selenium triggers Nrf2-mediated cell protection[199] and Nrf2 expression is low in the uremic milieu[172] this further supports a requirement for implementation of treatment for selenium deficiency in CKD.

Another approach to targeting mitochondrial dysfunction in CKD is via use of resveratrol. Beyond its effects on the epigeome and cellular metabolism, [200,201] resveratrol reduces mitochondrial ROS levels thus leading to decreased NLRP3 inflammasome activation[202]. This assertion has been evidenced In nephrectomized rats, where resveratrol has been demonstrated to improve mitochondrial function, mitochondrial membrane potential[203]. Several experimental studies have also shown that resveratrol can induce mitochondrial biogenesis in mammalian cells. As resveratrol has been shown to delay progression of ADPKD in rats, via inhibition of NF-kB induced inflammation[204], further studies on the nephroprotective effects of this bioactive compound are warranted[205].

Similarly, curcumin, a lipophilic polyphenol derived from turmeric used as aromatic herb conferring color and flavor to culinary preparations, is a polyphenol that has gained attention because of its antioxidant activity and ability to preserve mitochondrial

biogenesis[164,173,206]. Curcumin has been reported to decrease oxidative stress, inhibit mitochondrial permeability transition pore opening and enhances oxidative phosphorylation capacity in nephrectomized rats[207,208]. As curcumin has been observed to exert anti-fibrotic effects through reduction of inflammation in pre-clinical models [209], its' effects on CKD progression deserve attention. Moreover, as curcumin increases the expression of intestinal alkaline phosphatase and tight junction proteins and corrects gut permeability[210], this may also contribute to its documented anti-inflammatory potential. A significant problem with using curcumin therapeutically, is its' low bioavailability. It has been proposed that the combination of curcumin with piperine (a compound found in black pepper) and oil-in-water nanoemulsions[211] increase its bioavailability[212-213].

Allicin is an organosulfur compound found in garlic with bioactive redox-dependent properties[214]. Allicin is physiologically active in microbial, plant and mammalian cells and has antimicrobial, anti-cancer, immunomodulatory, metabolic and antioxidant effects and promotes mitochondrial biogenesis[215]. In obese insulin-resistant rats with metabolic changes induced by high-fat-diet, garlic extract decreased mitochondrial ROS production and increased mitochondrial membrane potential[216]. In another study, allicin decreased LPS-induced oxidative stress and inflammation induced by LPS by suppressing mitochondrial dysfunction and activating Nrf2[217]. Thus, allicin seems to be a promising compound that through interaction with mitochondria could potentially could confer benefits in CKD. Based on data in 5/6 nephrectomized rats it was suggested that the beneficial effect of allicin on blood pressure and renal function in CKD are comparable to that of losartan[218].

Dietary restrictions to prevent hyperkalemia in CKD contribute to low levels of vitamin C. Vitamin C has anti-oxidant and immunological effects and is commonly found in fruits and vegetables, such as guava, cashew, orange and sweet pepper[173,219]. High intracellular concentrations of vitamin C inhibit apoptosis in monocytes and are associated with inhibition of the activation of caspase-3, -8 and -10, diminished levels of ROS and improved mitochondrial membrane stabilization[220]. Vitamin C attenuated apoptosis in a myocardial ischemia/reperfusion injury model and maintained the functional integrity of mitochondria via alleviation of Ca^{2+} overload and ROS generation, inhibition of the opening of mitochondrial permeability transition pore, and prevention of mitochondrial membrane potential depolarization[221]. The risk of systemic oxalosis when CKD patients (especially on PD) ingest high doses of vitamin C needs the attention of nephrologists[222].

Propolis is not a food component but a natural multicomponent substance from bees that may be of value in CKD due the biological activity of its > 600 chemical compounds (pollen, vitamins, flavonoids, phenols and others) acting synergistically[223-225]. Propolis has been used for hundreds of years for medicinal purposes and several studies have confirmed therapeutic effects related to its antioxidant properties[224,225]. Propolis extract decreases intracellular and intramitochondrial ROS *in vitro* and restore the fall of mitochondrial membrane potential [224,226]. In a randomized, double-blind, placebo-controlled study, 12 months of Brazilian green propolis extract (500 mg/day) was shown to be safe, reduce proteinuria and urinary monocyte chemoattractant protein-1 levels in CKD patients[225]. Propolis has also been found to be effective in protecting against methotrexate-induced kidney injury in rats[227]. The effect of propolis on mitochondrial biogenesis in CKD remains to be determined.

Nutrients that target the Nrf2 pathway

In CKD, and in burden-of-lifestyle diseases that accumulate with age, the Nrf2 expression is reduced and associated with. "inflammaging"[3,35,228,229]. In inflammaging, NF-κB acts as a versatile conductor of an 'inflammation orchestra' that initiates immune responses through increasing production and release of cytokines such as IL-1, IL-6, IL-8, TNF, and INF-γ to protect the host[230]. Although *acute* inflammation is a healthy response and a key biological response to injury, potentially affecting all organs through inter-organ crosstalk[231], a *chronic* low-grade inflammatory response is not part of the natural healing process, but instead represents pathological alteration. This correlates with the accumulation of senescent cells, which generate of a pro-inflammatory secretome (i.e. SASP), that generate a bystander effect and spread the inflammatory phenotype locally. The SASP thus enables a vicious cycle of inflammation and cellular senescence, with concomitant telomere shortening and alterations in NF-kB, Wnt and Poly (ADP-Ribose) (PARP) signaling, thereby accelerating biological ageing and increasing the risk of age-related diseases[232].

Emerging evidence has shown that many nutrients, including dairy products[233], exert effects through modulation of factors regulating inflammation[234] and/or telomere attrition[235]. Below we discuss the effects of some nutrients with anti-inflammatory activities, for example polyphenols (involved in protection against ultraviolet radiation and pathogens in plants) present in spices, fruits, in red wine, tea, coffee and chocolate. There are >8000

naturally occurring polyphenols, most of which are flavonoids, such as isoflavones, flavones, flavanols, flavanones and anthocyanidins[236]. A systematic review and meta-analysis have concluded that despite a limited number of studies, available data suggest that polyphenol-rich interventions improve cardiovascular risk markers in dialysis patients[237].

Nrf2 plays a critical role in neutralizing the NF-κB-driven inflammatory response, inhibiting the expression of pro-inflammatory mediators including cytokines, chemokines, adhesion molecules, COX-2 and iNOS[238,239]. Nrf2 upregulates hundreds of anti-oxidative and anti-inflammatory genes responsible for detoxification of the organism through phase II antioxidant enzyme responses that protect the cells against oxidative stress[3]. Examples of such include heme oxygenase-1 NAD(P)H:quinone oxidoreductase 1, heme oxygenase, thioredoxin reductase 1, glutathione reductase, glutathione S-transferases, leukotriene B_4 dehydrogenase[240,241,242]. Compelling links exist between tissue hypoxia, senescence and a the Nrf2 system[3] which serves as a hub between inflammatory- and metabolism-related pathways in the kidney; consequently, this transcription factor may play a major role in renal disease[242].

Bioactive food stuffs, such as tomato skin, broccoli, turmeric spices, red-purple plant foods, coffee beans and rosemary are stimulators of Nrf2 expression[243]. They may therefore have a role in FAM-inspired nutritional strategies to arrest progression of CKD and to improve the inflammatory and pro-oxidative inflamed uremic phenotype [3,70]. Humans have been safely ingesting Nrf2 activators as part of their diet from ancient times and it might be speculated that Nrf2-activating nutrients have played a major role during evolution to protect species against oxidative stress. Whereas stimulation of the Nrf2-Keap-1 system may prevent smoldering inflammation and disease, overactivation of Nrf2-Keap1 may also promote disease[244]. As the diet in regions with documented longevity (i.e. Blue zones, such as Okinawa) is rich in nutrients that activate Nrf2[245], it has been speculated that healthy diets play a significant role in longevity. In the animal kingdom, Nrf2 activation seems to play a crucial protective role under extreme conditions, such as hibernation and hypoxia[246].

A recent bibliometric analysis has shown that among natural Nrf2 stimulants, sulforaphane, curcumin and resveratrol have attracted the most clinical interest[247]. It should be noted that not only bioactive compounds *per se*, but also the dietary pattern may modulate Nrf2 expression in CKD. Six months of low-protein diet with reduced red meat intake resulted in increased Nrf2 mRNA expression and decreased lipid peroxidation in CKD

patients[248]. It is possible that some nutrients, such as red meat and high fructose drinks, down-regulate the Nrf2-Keap1 system. As red meat promotes production of uremic toxins, such as IS, by the gut microbiota and IS downregulates Nrf2[195], this indirect link between Nrf2 and red meat could explain why red meat intake is correlated with an increased risk for CKD[249,250].

Researchers have shown a positive association between the rising consumption of sweetened high-fructose beverages and the risk of CKD[251]. Thus, it is of interest that plant-derived flavones prevent high fructose-induced metabolic syndrome by inhibiting the binding of Keap1 to Nrf2[252]. Moreover, nutrients rich in alkyl catechols, such as in fermented foods, are lacking in the present-day Western diet, and this may contribute to "inflammaging" and low Nrf2 expression that increase burden of lifestyle diseases[153]. Indeed, fermented cabbage (such as in kimchi) alleviates hepatic steatosis in mice via stimulation of Nrf2 and reduced lipid peroxidation[253]. Studies on the effects of fermented foods, such as kimchi and natto, on the uremic inflammatory phenotype are warranted.

Among numerous bioactive nutritional Nrf2-Keap1 agonists, sulforaphane, is the most potent[244]. Human tubular epithelial cells treated with sulforaphane (provided as concentrated broccoli sprout extract) have been demonstrated to activate Nrf2 a and reduce ROS production[254]. The mechanism by which sulforaphane attenuates inflammation is via chemical modification of the sensor cysteines and blocking Nrf2 degradation[241]. Moreover, as sulforaphane provided as broccoli sprout extract reduced fasting blood glucose and HbA1c in obese patients with dysregulated type-2 diabetes and reduced hepatic glucose production in a magnitude similar to that of metformin[255], it may be possible to improve metabolic control in type-2 diabetic CKD patients using FAM. Moreover, since supplementation with a broccoli powder rich in sulforaphane ameliorated kidney injury in the anti-oxidant glutathione S-transferase μ-1 *(Gstm1)* knockout, but not wild-type mice and high consumption of cruciferous vegetables was associated with fewer events of kidney failure in humans homozygous for the *GSTM1* deletion variant, cruciferous vegetables may retard progression in a genetically determined subset of the population[256] .The potential use of sulforaphane as an antioxidant that decreases expression of RUNX2 following calcification in rats[257] supports a role of FAM to also prevent early vascular ageing[258].

As epidemiological studies have indicated that the incidence of many types of cancer such as colon, prostate and skin cancer is much lower in countries where spices are

consumed daily, such as in India, than in countries in which spices are consumed less frequently, such as the United States, it has been speculated that the anti-inflammatory effects of spices protect against cancer[259] and atherosclerosis[260].

Although spices have a complex pharmacology including both beneficial and harmful actions, the current literature favors their positive attributes[261]. Turmeric (*Curcuma longa*), a herb that belongs to the ginger family and grows in Asia, has for centuries been used as a medical treatment for many different diseases, due to its purported anti-inflammatory, anti-oxidant and anti-cancer effects[262]. A systematic review has concluded that turmeric, or its derivative curcumin, had limited but positive effects on several inflammatory markers in chronic inflammatory diseases, including type-2 diabetes, fatty-liver disease, atherosclerosis, arthritis, cancer, depression and Alzheimer's disease[263]. In adenine-induced CKD in rats, curcumin treatment resulted in reduction of inflammation, fibrosis and markers of apoptosis, plus increased Nrf2 expression[264]. However, in the first clinical study of curcumin treatment in CKD, a reduction in lipid peroxidation and an increase in antioxidant enzyme activity, but no change in Nrf2 activation was reported[265]. As curcumin decreases the release of gut bacteria-derived LPS and stimulates intestinal alkaline phosphatase and tight junction proteins[210], beneficial effects on the intestinal barrier function[266] rather than direct Nrf2 stimulating effects, may explain the anti-inflammatory effects of this spice. Alternatively, the subjects in this study, may simply have had an insufficient gut microbiota to adequately enable a sufficient Nrf2 agonist response, or one that depressed it. Nutritionally derived Mycotoxin ochratoxin A [A. Limonciel and P. Jennings, "A review of the evidence that ochratoxin A is an Nrf2 inhibitor: implications for nephrotoxicity and renal carcinogenicity," *Toxins*, vol. 6, no. 1, pp. 371–379, 2014.] and the coffee alkaloid trigonelline [A. Arlt, S. Sebens, S. Krebs et al., "Inhibition of the Nrf2 transcription factor by the alkaloid trigonelline renders pancreatic cancer cells more susceptible to apoptosis through decreased proteasomal gene expression and proteasome activity," *Oncogene*, vol. 32, no. 40, pp. 4825–4835, 2013.] are known to prevent the nuclear translocation of NRF2.

Recently, no effect for prophylactic curcumin given before contrast infusion was reported in a randomized trial of 60 high risk patients aimed at reducing contrast-induced nephropathy[267]. The Renal Community now awaits the results from an ongoing multicenter, double-blind prospective randomized controlled trial that studies whether micro-particulate curcumin reduces albuminuria and slows the decline of renal function in CKD[268].

Epigallocatechin-3-gallate, the bioactive compound found in green tea, has also been reported to modulate NF-κB and Nrf2 nuclear translocation and increased HO-1 production in kidney in a unilateral ureteral obstruction murine model[271]. An epidemiological study has reported that daily coffee intake associated with decreased risk for CKD[272]. As constituent coffee components, such as chlorogenic acids, stimulate *Nrf2* gene expression through oxidation of Keap1 cysteine residues[273,274], this may contribute to its protective effects. In a randomized controlled trial intake of cocoa flavanols, chronic endothelial dysfunction was mitigated in patients undergoing HD[275]. Another bioactive compound that activates Nrf2 and which has beneficial effects in burden of lifestyle diseases is cinnamaldehyde[276]. Electrophilic forms of cinnamaldehyde found in polyphenols, interacts with cysteine residues in Keap1, leading to its disassociation from Nrf2, enabling its translocation to the nucleus[273]. Another such compound, the senolytic flavonoid quercetin, increases Nrf2 activation by inhibition of the proteasomal degradation pathway, with consequent release of Nrf2 from the Nrf2-Keap1 complex[277]. Thus, as natural Nrf2 activators have both significant positive laboratory and clinical effects, tailor-made nutritional interventions based on the FAM approach are merited for the treatment of CKD (**FIG 5**).

Diets rich in berries also provide health benefits, especially those containing blueberries/ bilberries which contain a large number of phytochemicals. The most prominent of these, termed anthocyanidins, have potent anti-inflammatory and antioxidant effects. In epidemiological studies, a regular, moderate intake of blueberries and/or other sources of anthocyanidins were associated with reduced risk of CVD, type-2 diabetes and obesity[278]. In younger women, a high intake of anthocyanidins correlated with a lower risk for myocardial infarction[279]. Data suggest that blueberries might also be useful for prevention of osteoporosis via prevention of osteoclastogenesis[280]. Additionally, blueberry-derived phenolic acids have been reprrted to enhance Nrf2-regulated antioxidant responses in human vascular endothelial cells[282]. In keeping with these data, pterostilbene, a bioactive component of blueberries, alleviated renal fibrosis in a mouse model of nephropathy[281], the effects of daily blueberry consumption on renal progression deserves attention.

Inflammasomes (NLRP3) are central regulators of inflammation and when activated they increase the synthesis of IL-1β and IL-18[283]. NLRP3 expression is activated in CKD[284] and although some nutrients may modulate NLRP3 and reduce the inflammatory process, to our knowledge, no study has reported the clinical effects of nutrients on the uremic

inflammasome. However, given recent evidence of crosstalk between the predominantly antagonistic relationship of the stress activated Nrf2 and inflammasome pathways at different levels, Nrf2 activating nutritional compounds may also affect the inflammasome[285].

In toto, although literature on nutritional components that activate Nrf2 are sparse in nephrology, emerging evidence in other persistently inflamed patient groups has shown that dietary interventions can increase Nrf2 expression and reduce NF-kB expression. Carefully executed studies on the effect of bioactive nutrients on Nrf2 and the uremic phenotype should therefore be of interest.

Nutrients that target nitrites

Nitrates (NO_3^-) are inorganic ions usually obtained through leafy green or root vegetables in the diet, such as lettuce, beetroot, cress, fennel, radish, celery, Chinese cabbage, parsley, spinach, rocket and radish.. Beetroot contains betaine and has been considered as a promising therapeutic treatment in a range of diseases associated with oxidative stress and inflammation[286]. In the mouth, nitrates are converted by bacterial nitrate reductases to nitrite (NO_2^-), which reaches the blood from the stomach and duodenum and increases nitric oxide (NO) production. As antibacterial mouth rinse alters concentrations of salivary and plasma nitrate resulting in a coexistent rise in blood pressure; antiseptic mouth rinses should not be used in patients with poor blood pressure control[287].

The second pathway that generates NO is oxidation of L-arginine by NO synthase in the wall of blood vessels and erythrocytes[287-291]. NO is a well-known promoter of vasodilation and plays an essential role in cardiovascular health, protecting against ischemia-reperfusion and inhibiting platelet aggregation. Anthocyanidin metabolites improve NO bioavailability and modulate vascular reactivity by inducing HO-1, modulating NOX activity and reducing superoxide production[292]. A recent 6-month double-blind randomized trial in patients with metabolic syndrome has shown sustained improvements in vascular function, lipid status and underlying NO bioactivity following intake of 1 cup blueberries/day[293]. With 12-15% reductions in CVD risk, this study has suggested that blueberries should be included in dietary strategies to reduce CVD risk. Although many studies and reviews have been published about the effects of nitrite on cardiovascular function in health and disease[294] the potential of nitrate-rich foods have not been studied much in CKD, but they can be a new strategy to modulate cardiovascular function in these patients (**FIG 6**). However, treatment

with an ethanolic extract of beetroot attenuated renal dysfunction and structural damage in gentamycin-induced nephrotoxicity, through reduction of inflammation oxidative stress and apoptosis[295]. In a clinical trial with 2799 adults followed for a median of 5.8 years, higher dietary NO_2^- intake was associated with lower risk of hypertension and CKD[296]. Moreover, four hours after nitrate intake, CKD patients presented reduction of blood pressure and renal resistance index[297].

Concluding remarks

A red thread - from antiquity in the Western Celtic (the cauldron of An Dagda) and Classical (Corpus Hippocraticum) traditions to the Eastern (e.g. China) hemispheres and over the subsequent centuries (e.g. Jean Anthelme Brillat-Savarin in 19th century: "*Tell me what you eat: I will tell you what you are*") through to the present day (GBD 2017 Diet Collaborators)[1] – is the insight that nutrition indeed matters and is crucial for improving the health- and lifespan: "*We are what we eat*". Although the FAM concept has been applied in Western medicine, alternative schools of medicine, e.g. in traditional Chinese medicine (TCM), have applied nutritional interventions targeting diseases like CKD, routinely. TCM researchers have explored areas such as the therapeutic potential of herbal remedies against influenza, cancer, type-2 diabetes and CVD. Gut microbiota targeted by dietary interventions against chronic inflammation, oxidative stress and the biological activities of complex polysaccharides present in medicinal plants have also been developed[298]. As most undiscovered plants are likely to be found in biodiverse hotspots[299], such as in Amazonia, rapid loss of animal and plant habitat due to environmental stress and poor political leadership is a major threat for human health[2].

It is obvious and perhaps even self-evident that macronutrients, micronutrients and specific bioactive nutrients, by affecting essentially all biochemical pathways - separately and especially when acting together as part of a dietary pattern in the "*foodome*" - will have the potential to influence most diseases, not least those linked to metabolic disorders, such as CKD, obesity and type-2 diabetes. Thus, there are many reasons why the FAM-foodome approach should get more attention in renal research and gain more ground in the clinical management of CKD. However, the reality is that research and developments aimed at improving clinical practice in these areas are lacking. One reason is lack of knowledge, as few well-designed basic, clinical and translational studies have been conducted in this area in

comparison to studies on pharmaceutical interventions. This in turn could be due to factors, such as lack of resources and perhaps a perception that only pharmaceutical interventions matter. Existing literature has mainly focused on the biological effects of different nutrients in animal models. However, as patients consume food and not nutrients, future research in CKD should focus on the total effects of food intake and weigh potential benefits versus harm caused by competing biological effects. The large gap in knowledge on the bioavailability of bioactive nutrients also needs more attention. As dietary transitions toward greater consumption of healthier foods is also a way to improve environmental sustainability[21], this is yet another reason to aim for the use of healthier food in a renal context.

The aim of this review on nutrition-based interventions using the FAM concept has been to highlight the potential of bioactive nutraceuticals to beneficially affect the health- and lifespan of CKD patients (**FIG 7**). There is already ample evidence that we, by using such an approach, can arrest progression of renal disease and affect the uremic phenotype by influencing the epigenetic landscape, mitigating cellular stress and improving stress defense mechanisms, modulating the gut microbiota, improving mitochondrial biogenesis and reducing pro-oxidative and inflammatory processes. The aim of applying the FAM concept in renal care is to provide precision medicine for prevention and treatment of CKD that takes into account available scientific evidence. We believe that many concerned CKD patients would be willing to improve their risk factor profile by adopting the FAM concept; which recognizes that the health of humans is intimately linked with the health of animals and the environment[25].

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Table 1: Factors to consider for optimal diets for CKD patients as part of the FAM-foodome approach.

Foods	Comments
Red meat[7, 88, 187, 244, 246]	Increases progression rate (epidemiological studies) Generates higher levels of TMAO Rich source of amino acids that preserve muscle mass Rich source of sulfur-containing amino acids that may impact on microbiota Rich source of iron - impact on microbiota Rich source of sodium – alters gut microbiota composition and is linked to hypertension Increases production of H_2S by *E. coli* and *Clostridium* spp. Rich in saturated fat – increases risk of cardiovascular disease and mitochondrial dysfunction
Fish and seafood[125, 176 ,80]	Rich source of w-3 fatty acids – gut microbiota balance, decrease mitochondrial dysfunction Deep-sea fish rich in TMAO Shallow fish low in TMAO Oysters rich in zinc - senolytic and antioxidant
Egg[180, 181]	Important source of minerals, protein and antioxidants Phosvitin (egg yolk) may have beneficial microbial effects Increase levels of TMAO
Dairy products[178, 180, 228]	Source of animal protein Source of lactose and oligosaccharides - growth of *Bifidobacterium* and *Bacteroides spp*
	Good matrix for probiotics
Olive Oil[95,96,97]	Rich source of monounsaturated fat fatty acid
	Provide phenolic compounds – may have prebiotic effects
Cereals and grains[10,12,67]	Soybeans, unrefined wheat, whole grain barley, raw oats, wheat bran rich in fibers – gut Microbiota modulation, production of SCFA – improve mitochondrial biogenesis Sunflower seed rich in vitamin E – senolytic
Beans[58,69,70]	Soy food – rich in protein, mono- and oligosaccharides and oil - beneficial to gut microbiota
Vegetables[10,68,145,148,169,214,250,281]	Green leafy or root vegetables: like lettuce, beetroot, cress, fennel, radish, celery, Chinese cabbage, parsley, spinach, rocket, radish – increase nitric oxide (NO) production Broccoli sprouts (sulforaphane) stimulate Nrf2 Epidemiological studies suggest that plant-based diet reduce the progression rate Beetroot, spinach and lettuce - rich in nitrates Raw potato, onion, beans, asparagus rich in resistant starch – gut microbiota modulation with prebiotics, downregulation of NF-kB and upregulation of Nrf2 Garlic - rich in allicin – improve mitochondrial biogenesis, downregulate NF-kB and upregulate Nrf2

	Onion and garlic – may decrease NLRP3 activation Spinach - rich in betaine Green leafy vegetables - rich in folate Cruciferous vegetables, - rich in sulforaphane – may decrease NLRP3 activation, Nrf2 activators Some vegetables, such as spinach, broccoli, potatoes, cucumbers, green leafy - rich in potassium.
Fruits[10,67,112,145,148,169,214,231]	Apples - rich in quercetin – may decrease NLRP3 activation, Nrf2 activator Cranberries – rich in *proanthocyanidins* Blueberries is a rich source of anthyanidins and urolithin Resistant starch such as green banana - gut microbiota modulation Grape, pomegranate, blueberry and cranberry - rich in polyphenols - gut microbiota composition Strawberry, tomatoes, onions, apples, peaches, grapes and kiwifruit - rich in fisetin Some fruits, such as avocados, guava, kiwi, bananas, apricots, cherry, oranges, grapefruit, mango, papaya, plums blackberries, strawberries - rich in potassium. Guava, cashew, orange, lemon - rich in vitamin C - antioxidant, good mitochondrial effects
Spices[160,161,201,202,204,205,243,254]	Curcumin, cinnamon – may decrease NLRP3 activation Curcumin, rosemary, cinnamon – Nrf2 activators Long pepper and curcumin - natural senolytics
Propolis[218-222]	Rich in pollen, vitamins, flavonoids, phenols – synergistic antioxidant effects
Fermented food[149,249]	Kimchi - stimulates Nrf2
Processed food (bacon, ham, pizza, cereals)[84,87,88,90,100,118]	Rich in sodium and phosphate additives – increase in cardiovascular risk Rich in saturated fat – cardiovascular risk and mitochondrial dysfunction Trans fatty acids – may contribute to dysbiosis
Drinks[110,116,195,196,231,268,269]	Red wine rich in *anthocyanidins* and polyphenols – cardioprotective, regulator of gut microbiota, activator of SIRT-1, natural senolytic, may decrease NLRP3 activation Wine, beer and soft drinks - significant sources of phosphate Coffee- source of polyphenols - Nrf2 activator Green tea - rich in polyphenols and senolytics; modulation of NF-κB and Nrf2 systems Pomegranate juice - rich in urolitin A
Nuts[14, 162]	Brazil nut – rich in selenium, fatty acids, phenolics, vitamin E – mitochondria protection, Nrf2 activation Vitamin E – antioxidant and senolytic
Chocolate[10,12,113,270]	Cocoa - increases bifidobacterial and lactobacilli populations

Low sugar foods/drinks[118-122]	Provide sweeteners – may change the gut microbiota causing metabolic imbalances
High sugar foods/drinks[76,77]	High glucose or fructose content – promote gut dysbiosis and metabolic syndrome

Legends to Figures

FIG 1: Foods with potential to influence DNA methylation. Methylation is an epigenetic mechanism that regulate the access for transcriptional machinery to adjust gene expression. Choline, betaine, folate, vitamin B12 and methionine have the potential to influence methylation providing methyl (CH_3) groups or acting as cofactors. Epigenetic alterations, such as those in DNA methylation, may provide molecular explanations for complications associated with altered gene expression in CKD.

FIG 2: The gut microbiota in CKD patients is affected by the decline in renal function and by ingested food. Food intake may influence production and release of bacterial lipopolysaccharide (LPS), hydrogen sulfide H_2S, short chain fatty acids (SCFA) and uremic toxins through modulation of transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB), toll-like receptor 4 (TLR4) and mitochondria function.

FIG 3: Hypothetical pathways by which food may alleviate premature ageing in CKD patients. The left panel shows that CKD is associated with increased production of reactive oxygen species (ROS) and other factors that result in apoptosis resistance and accumulation of senescent cells with senescence-associated secretory phenotypes (SASP) and this lead to activation of NF-κB and other inflammatory mediators such as transforming growth factor beta (TGFβ), plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein 1 (MCP-1) and WNT16B. Dietary modifications such as reduction of intake of calories and provision of nutraceutical senolytics in the food may delay the premature ageing phenotype by inhibiting the mTOR pathway and generation/release of ROS, NF-κB, senescence-associated beta-galactosidase (SA-βgal), Nrf2, heme oxygenase 1 (HO-1) and cytokines.

FIG 4: Possible mechanisms by which food and specific nutrients may affect mitochondria function in CKD. Fatty acids can saturate the oxidative capacity, contributing to mtDNA damage and increase mitochondrial ROS production. In contrast, ω-3 fatty acids upregulate PGC-1α and Nrf1. Dairy products may influence energy metabolism by leucine content, which

stimulates the expression of mitochondrial biogenesis genes. SCFAs can modulate mitochondrial biogenesis. Resveratrol is recognized as an activator of SIRT1 and reduces mitochondrial ROS production. Curcumin and vitamin C decrease oxidative stress, inhibits mitochondrial permeability transition pore opening and enhances oxidative phosphorylation capacities. Allicin and propolis reduce the mitochondrial ROS production.

FIG 5: Nrf2 food activators. Nuclear factor erythroid 2-related factor 2 (Nrf2) plays a critical role in the expression of anti-oxidative genes and in neutralizing the nuclear factor κB (NF-κB) driven inflammatory response. Bioactive nutrients may improve the inflammatory and pro-oxidative inflammaging phenotype of CKD patients.

FIG 6: Endogenous NO generation from diet. In the mouth, nitrates (NO_3^-) from foods are converted by bacterial nitrate reductases to nitrite (NO_2^-) which reach the blood and increase nitric oxide (NO) production. Thus, nitrate-rich foods may contribute to NO generation and cardiovascular benefits in CKD. On the other hands, antiseptic mouth rinses negatively alter concentrations of salivary and plasma nitrate.

FIG 7: Examples of pathways that are influenced by nutrition-based interventions based on the FAM-foodome approach, and that may reduce complications in CKD patients. There is a link among complications in CKD patients as DNA methylation, dysbiosis, endothelial function, oxidative stress, inflammation, mitochondrial dysfunction and senescence and, food can be an excellent strategy to reduce all these alterations.