Can nutritional interventions modulate the activation of the NLRP3 inflammasome in chronic kidney disease?

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Abstract

Inflammatory and innate immune responses triggered by pathogen-associated and other danger-associated signals emerging during infections, results in the activation of cytosolic inflammasomes . The nod-like receptor pyrin domain containing 3 (NLRP3) is one of the inflammasomes mediating such responses through the activation of caspase-1, which increases the production and release of pro-inflammatory cytokines, such as IL-1β and IL-18 and induces programmed cell death through pyroptosis., NLRP3 is thought to play a crucial role in the underlying inflammatory responses in many lifestyle related chronic diseases. Consequently, research on the NLRP3 inflammasome has expanded dramatically in recent years. Although several studies have investigated the role of NLRP3 activation in chronic kidney disease (CKD), few studies have evaluated strategies to modulate its activation by means of interventions using bioactive compound present in food. This review discusses bioactive compounds that have been shown to influence NLRP3 in experimental models of renal disease, and in CKD. It discusses how these compounds could potentially dampen NLRP3 associated inflammatory burden, as part of nutritional strategies to prevent and treat CKD and its complications.

Keywords: bioactive compound, chronic kidney disease, inflammation, inflammasome, oxidative stress.

1. Introduction

Inflammasomes are large cytoplasmic multiprotein complexes belonging to the innate immune system, that are formed in response to stimuli from pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), emerging during infections, tissue damage or cellular stress. These signals are sensed by pattern recognition receptors (PRRs) and lead to activation of inflammasome mediated caspase-dependent inflammatory responses, through the release of cytokines and induction of cell death by pyroptosis (a form of caspase induced inflammatory programmed cell death). To date, the following inflammasomes have been reported: leucine-rich repeat (LRR)-containing proteins, nucleotide-binding oligomerization domain (NOD) (also known as NOD-like receptors (NLRs), such as NLRP1, NLRP3, and NLRC4); absent-in-melanoma 2 (AIM2); and other similar complexes, such as NLRP2, NLRP6, NLRP7, NLRP12 and IFI16, are also considered inflammasomes (Guo et al., 2015; Kelley et al., 2019).- Might be useful to tabulate these?

Inflammasomes mediate activation of Caspase-1, which cleaves pro-interleukin-1β (pro-IL-1β) and pro-IL-18 into their mature IL-1β and IL-18 forms. This in turn, leads to a complex network of cellular reactions initiating local and systemic inflammatory reactions (Boaru et al., 2015; Afonina et al., 2017). Four inflammasomes (NLRP1, NLRP3, AIM2, and pyrin) contain an adaptor protein termed apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC), which leads to the recruitment of pro-caspase-1 (Kelley et al., 2019).

The best characterized inflammasome is the Nod-like receptor pyrin domain containing 3 (NLRP3), which responds to pathogen ingress, or damage signals arising from endogenous from tissue injury (Guo et al., 2015). NLRP3 activation induces cell death via caspase 1 dependent pyroptosis, 1. In this process, caspase 1 induces generation of plasma membrane pores that facilitate osmolytic cell death and the release of IL-1β (Swanson et al., 2019; Li et al., 2019; Broz & Dixit, 2016; Carty et al., 2019).

NLRP3 is primarily associated with host immune defenses against infections provoked by viruses, bacteria or fungi. However NLRP3 is also linked to the development of several chronic life style related diseases characterized by persistent inflammation, such as Alzheimer disease, gout, atherosclerosis, diabetes, autoinflammatory diseases, arthritis, obesity and CKD (Zamani et al., 2019; Masood et al., 2015; Guo et al., 2017; Kim et al., 2018; El-Horany et al., 2017).

Persistent low-grade inflammation is a prominent feature of the uremic phenotype and both a driver of cardiovascular diseases (CVD) (Mafra & Fouque, 2015; Farage et al., 2016; Jankowska et al., 2017; Koppe et al., 2019) and a common feature of the diseasome of ageing (Kooman et al., 2017). Thus, understanding the mechanisms and interplay between these complications in CKD patients, may help the development of therapeutic strategies to reduce mortality and improve the quality of life for these patients (Granata et al., 2015; Ding et al., 2015; Hautem et al., 2017). One non-pharmacological strategy proposed for clinical use to reduce inflammation in in CKD patients has been interventional nutrition, using bioactive nutraceuticals (Saldanha et al., 2016; Martins et al., 2018; Alvarenga et al., 2018; Mafra et al., 2019a; Alvarenga et al., 2019). The review will discuss the rationale and evidence underpinning such a nutraceutical based intervention in CKD, specifically with reference to the NLRP3 inflammasome.

2. Mechanisms of NLRP3 inflammasome activation

NLRP3 is a member of the Nod-Like Receptor (NLR) family, that is functionally active within the innate immune system (Chen et al., 2011; Kim et al., 2017). It possesses a C-terminal leucine-rich repeat protein-3; intermediate NOD domain (NACHT domain), which has ATPase activity; a variable N-terminal pyridine domain (PYD) and ASC adapter protein (protein associated with apoptosis of the adapter molecule containing a CARD - caspase activation and recruitment domain), which harbors the PYD and CARD domains (Yang et al., 2019; Kim et al., 2017; Gao et al., 2016). NLRP3 is expressed primarily in a range of tissues (principally the lungs, liver, kidney, colon, skin, eyes and ovaries), and in immune cells (such as neutrophils, macrophages, Th2 cells, monocytes, primary keratinocytes (PK), HaCaT cells derived from keratinocytes, primary mast cells (MS), granulocytes and B cells) (Chen et al., 2011).

NLRP3 can be activated by molecular patterns associated with pathogens (PAMPs) and molecular patterns associated with damage (DAMPs) (Swanson et al., 2019). Among factors involved in NLRP3 activation are toxins, or environmental irritants, which cause lysosomal disruption (Kelley et al., 2019). Microbes, extracellular ATP, RNA viruses, potassium efflux and calcium influx may also act as activators of NLRP3 (Gaidt & Hornung, 2018). In addition, a priming signal occurs through two pathways (i) on toll-like receptors (TLRs) activated by

104 microbes or (ii) on TNF and IL-1 receptors, which lead to the activation of the transcription
105 factor nuclear factor kappa B (NF-κB), which upregulates the expression of NLRP3 (Kelley et
106 al., 2019).
107 Activation of NLRP3 is through ubiquitination via DHX33 (cytosolic double-stranded RNA
108 sensor, a member of DExD/H-box helicase family), where NLRP3 is modified by specific
109 ubiquitin chains, mainly lysine 63(K63) (Kattah et al, 2017; Bednash et al, 2016). TRIM33 (a
110 member of the tripartite motif and E3 ubiquitin (Ub) ligases) binds DHX33 and induces the
111 K63-polyubiquitination, which is essential to form the DHX33-NLRP3 inflammasome
112 complex, resulting in to NLRP3 activation (Kattah et al, 2017).
113 When NLRP3 is activated, the PYD, present in the inflammasome structure, undergoes
114 oligomerization, which triggers the recruitment and nucleation of the apoptosis-associated
115 speck-like protein containing a CARD (ASC) adapter protein (Li et al. 2019). Thus, an
116 association between the NLRP3 inflammasome and the ASC protein adapter, generates the
117 formation of a complex structure (Tsuchiya, 2020). This structure initiates autocatalytic
118 activation of caspase-1, which cleaves cytokine precursors pro-IL1β and pro-IL18, generating
119 their active form, IL1β and IL18 (Li et al. 2019; Tsuchiya, 2020; Chan & Schroder, 2020).
120 Additionally, recent studies have demonstrated that the NLRP3 inflammasome can be
121 regulated by the transcriptional control of gene expression, via microRNAs (miRNAs) (Zamani
122 et al., 2019; Kim et al., 2017). It is also responsive to mitochondrial dysfunction, which leads
123 to ROS production that activates the phosphorylation of p65 NF-κB, thus inducing NLRP3
124 (Bauernfeind et al., 2016; Liang et al., 2017; Swanson et al., 2019). Some molecular signaling
125 mechanisms that have been shown to activate the NLRP3 inflammasome are illustrated in
126 **Figure 1**.
127
128 **3. Other substances: Negative regulation of NLRP3**
129 After the primary goal of the inflammatory response is achieved, the organism must
130 restore normal tissue homeostasis, hence resolution of the inflammatory response should
131 occur (Bauernfeind et al., 2012; Zamani et al., 2019). Additionally, it is important to
132 understand the negative regulatory pathways of the inflammasome, as they may provide
133 tools for more potent therapeutic strategies for the treatment of inflammatory diseases
134 related to the activation of the NLRP3 inflammasome (Yang et al., 2019).

The negative regulation of NLRP3 occurs through type I interferons (IFN-α and IFNβ), which are able to inhibit the activity of the NLRP3 inflammasome. To limit the initiation of NLRP3, type I IFNs influence the availability of the precursor forms of IL-1α and IL-1β by reducing their expression levels (Guarda et al., 2009; Guarda et al., 2011). Type I IFNs are involved in the activation of inducible nitric oxide synthase (iNOS), which in turn generates nitric oxide (NO). iNOS depletion leads to inhibition of NO production, which resulst in accumulation of dysfunctional mitochondria (a hallmark of age related loss of physiological function, in keeping with CKD being a disease of accelerated ageing) and increase in IL-1β production and caspase-1 activation (Mao et al., 2013). In this context, when iNOS is activated and there is production of NO, mitochondrial function is stabilised NLRP3 activivty is inhibited (Mao et al., 2013; Sutterwala et al., 2014).

Furthermore, the activation of antioxidant enzymes, especially heme oxygenase, can inactivate NLRP3 by inhibiting the expression of the ROS-sensitive thioredoxin-interacting protein (TXNIP). The most widely accepted pathway for this inhibition is via the activation of nuclear factor erythroid 2-related factor 2 (Nfr2) cytoprotective responses. This is an important transcription factor for the regulation of cellular antioxidant defences (Xiaoyu et al., 2017) that play a significant role in chronic lifestyle related diseases, where systemic expression of Nrf 2 is typically diminished (Stenvinkel et al., 2019; Arefin et al 2020 Nrf2 in early vascular ageing: calcification, senescence and therapy Clin Chim Acta. 2020 Feb 22. pii: S0009-8981(20)30089-9. doi: 10.1016/j.cca.2020.02.026). Consequently, when NLRP3 inflammasome function is dysregulated, it is observed in the context of a range of morbidities, including CKD, chronic inflammatory disorders , depression, colorectal cancer and metabolic disorders (Inserra et al., 2018; Chen et al., 2017).

4. Chronic kidney disease and NLRP3 inflammasome

The progression of CKD is closely related to levels of persistent inflammation and oxidative stress (Zoccali et al., 2017). CKD is characterized by increase in ROS production and impairment of the antioxidant responses, including a reduction in the expression of Nrf2 and increase in the expression of NF-κB expression, and consequential overexpression of pro-inflammatory cytokines (Mihai et al., 2018; Pedruzzi et al., 2012; Leal et al., 2015; Jankowska et al. 2017).

NLRP3 has been described as a promising candidate in mediating the inflammatory response in CKD, where cellular injury and inflammation coexist (Vilaysane et al., 2010; Ben et al., 2018; Mulay, 2019). Consequently, renal inflammation and fibrosis activate several NLRP3 agonists (Gong et al., 2016; Hutton et al., 2016). The renal NLRP3 exerts its' effects via activation of both the canonical regulation of caspase 1 pathway, with IL-1β and IL-18 secretion leading to GSDMD cleavage and consequent cellular pyroptosis and, by the non-canonical route of activation of alternative caspases, such as caspase -4, -5 and -11. Epithelial-mesenchymal transition, fibrosis and cell death are also intimately involved in this process (Masood et al., 2015; Darisipudi & Felix Knauf, 2016; Komada et al., 2019).

Animal and *in vitro* studies have shown a consistent link between NLRP3 function, mitochondrial damage and apoptosis in renal cells, leading to increased expression of IL-18 and IL-1β (Guo et al., 2017; Kim et al., 2018; Ding et al., 2016; Szeto et al., 2017). A study of renal tubule interstitial lesions, for example, has shown that the more severe the lesion, the greater the cellular expression of IL-1β, TLR-4 and NLRP3 mRNA expression, in keeping with the above hypothesis. Moreover, NRLP3 protein was expressed in greater amounts in cells with the highest degree of injury (Tashiro et al., 2016). Accordingly, Vilaysane et al. (2010) have reported that $NLRP3^{-/-}$ mice displayed less tubular injury, attenuation of the inflammatory process, decreased caspase-1 activation and inhibition of IL-1β and IL-18 maturation. Furthermore, in tissue from human renal biopsies from patients with diabetic nephropathy, increased expression of NLRP3 mRNA has been reported to correlat with renal function (Vilaysane et al., 2010).

Increased expression of NLRP3 mRNA and serum IL-1β level have been observed in CKD (Granata et al. 2015; El-Horany et al., 2017), which can be interpreted as being a consequence of hyperglycemia, oxidative stress and/or pathogenic mechanisms (Qiu & Tang, 2016). It is worth noting that uremic toxins, such as IS, indole 3-acetic acid (IAA), TMAO and p-cresyl sulphate (p-CS), are generated by the gut microbiota and contribute to the activation of inflammatory responses and mitochondrial dysfunction (Wong et al., 2014; Sogawa et al., 2018; Wakamatsu et al., 2018; Li et al., 2019; Mafra et al., 2019b). In support of this thesis, Chin et al. (2017) have observed a positive regulation of NLRP3, IL-1 and IL-18 in by indoxyl sulfate (IS), which contributed to myocardial apoptosis in nephrectomized rats. Recently El-Deeb et al., (2019) have observed that trimethylamine N-oxide (TMAO) can activate NLRP3 indirectly, because it induces oxidative stress and triggers

ROS/NLRP3 signaling, resulting in the release of inflammatory cytokines in CKD patients. However, the pathway of inflammasome activation through specific PAMPs and DAMPs in the gut remains largely unknown. It is possible that inflammatory porcesses are also trigerred by microbial ingress into the circulation via a leaky gut (O'Toole, P.W. and Shiels, P.G. The role of the microbiota in sedentary life style disorders and ageing: Lessons from the animal kingdom.J Intern Med. 2020 Jan 19. doi: 10.1111/joim.13021

Poore, G. D. *et al. Nature* https://doi.org/10.1038/s41586-020-2095-1 (2020)).

In toto, as NLRP3 appears to be involved in the pathogenesis of CKD, it may constitute a therapeutic target for prevention of CKD development and progression (Anders et al., 2016; Foresto-Neto et al., 2018).

5 Nutritional strategies to modulate the NLRP3 inflammasome

Bioactive compounds are substances present in food, such as vegetables and fruits that have beneficial effects on health (Liu, 2013). Diverse bioactive nutrients have been applied as part of preventive and/or therapeutic nutritional strategies to tackle non-communicable diseases (NCDs), such as diabetes mellitus, hypertension, CVD, CKD and cancer (Liu, 2013). In this context, several studies have found positive effects for bioactive compounds in modulating inflammation and oxidative stress (Saldanha et al., 2016; Martins et al., 2018; Alvarenga et al., 2018; Mafra et al., 2019; Alvarenga et al., 2019). It is thought that these effects – at least in part - could be attributed to these bioactive compounds mitigating harmful effects associated with inflammasome-related components in disease (Chuang et al., 2014). These observations are now discussed in detail with specific reference to individual bioactive compounds..

5.1 Catechins

Catechins are polyphenols present in food, such as apples, blueberries, gooseberries, grape seeds, kiwi, strawberries, green and black tea, grape and cocoa. The antioxidant properties of polyphenols are mainly due to their redox properties, as they act as reducing agents, hydrogen donors and free oxygen suppressors (Grzesik et al., 2018). Correspondingly, a number of groups have demonstrated salutogenic effects for catechins in pre=clinical models of disease. For example, Tsai et al. (2011) have shown in an animal model of lupus that epigallocatechin-3-gallate (EGCG) - a refined catechin from green tea - prevented

impaired renal function and proteinuria, increased Nrf2 activity, reduced NF-kB activation and NLRP3 mRNA protein expression. Furthermore, Jhang et al (2015) have demonstrated in rats with gout (induced by monosodium urate), that subcutaneous catechin injection reduced ROS production, secretion of IL-1β and the NLRP3 inflammasome activation.

5.2 Cinnamaldehyde

Cinnamaldehyde is one of the major bioactive compounds found in *Cinnamomum Osmophloeum* kaneh leaves. Cinnamaldehyde has been reported to reduce the expression of pro-inflammatory mediators in LPS-activated macrophages, inhibiting the generation of ROS and reducing NF-κB activation (Ka et al., 2016; Su-Chen et al., 2018). Cinnamaldehyde can prevent the activation of pro-caspase 1 and pro-IL-1β, thus avoiding the final activation of NLRP3 (Su-Chen et al., 2018). A number of groups have demonstrated that cinnamaldehyde can counter the effects of inflammasome activation in a range of disease and injury models (Qu et al.2019; Lee et al, 2018). In a renal setting in particular, it decreased albuminuria, glomerular sclerosis and peri-glomerular inflammation (Ka et al., 2016; Kang et al., 2016), via inhibition of NLRP3, diminution of ROS production and repressed activation of NF-κB and pro-inflammatory mediators (Ka et al., 2016). Additionally, in a murine model of fructose-induced metabolic syndrome, cinnamaldehyde reduced cardiac oxidative stress and attenuated the activation of NLPR3 and TGF-β, by inhibiting TLR-mediated signaling (Kang et al., 2016).

5.3 Curcumin

Curcumin is a curcuminoid found in Curcuma longa (Zingiberaceae), known for its anti-oxidant and anti-inflammatory potential. Guglielmo et al. (2017) have observed that LPS stimulated macrophages treated with curcumin decreased IL-1β secretion. In addition to this, curcumin may change S-glutathionylation critical to NLRP3 formation , thus limiting its capability to contribute to pathogenesis *per se* (Guglielmo et al, 2017). Other studies have shown that curcumin administration decreases the activation of the inflammasome via TXNIP associated NLRP3 inflammasome activation (TXNIP / NLRP3). Not only does curcumin participate in the cleavage of caspase-1 but it reduces expression of both inflammatory mediators IL-1β and TNF-α, (Ding et al., 2018; Li et al., 2015; He et al., 2018; Sun et al., 2017; Gong et al., 2018; Liu et al., 2018; Li et al., 2019; Zhang et al., 2019).).

Additionally, curcumin suppresses NLRP3 mediated inflammation through a number of distinct processes, including blocking potassium efflux from the cell and stimulation of ASC retention thus preventing the formation of NLRP3 in mitochondria (Yin et al., 2018; Gong et al., 2015). Additionally, curcumin reverses the activation of the purinergic 2X7 (P2X7R) siRNA receptor, thus reducing NLRP3 expression and caspase-1 /IL-1β secretion (Kong et al., 2016).

Pre-clinical models of systemic lupus erythematosus (SLE) and CKD have indicated reno-protective effects for curcumin. Female mice with SLE, supplemented with curcumin at 200 mg/kg/day for 8 weeks, presented with decreased glomerular cell inflammation and decreased renal expression of inflammasome NLRP3 and caspase-1, in addition to decreased serum levels of IL-1β (Zhao et al., 2019). Supplementation with theracurmin (a curcumin analog with high bioavailability) at 100 mg/kg/day for 5 weeks showed attenuated proteinuria and heart damage in a mouse model of CKD. These observatiosn were accompanied by an observed reduction in NLRP3 and mature IL-1β activation (Bugyei-Twum et al., 2016). Only one study has shown the effects of curcumin supplementation in hemodialysis patients, where 2.5 grams of turmeric (95%curcumin) given 3 times per week over three months, was not able to decrease the mRNA expression of the NLRP3 inflammasome, nor IL-1β. However, curcumin was able to reduce NF-kB trasncriptional expression and high sensitivity C-reactive protein (hsCRP) plasma levels (Alvarenga et al., 2020). These results suggest that curcumin may be a new therapeutic option to reduce inflammasome activation and protect against cardiovascular events in CKD (Bugyei-Twum et al., 2016; Zhao et al., 2019).

5.4 Emodin

Emodin is a bioactive compound present in rhubarb and oriental herbs, being the main active ingredient of the Chinese Qingyi decoction, and widely used to treat allergies and inflammation (Han et al., 2015). Some pre-clinical studies have shown that emodin can modulate the NLRP3 activation pathway, thus decreasing the inflammatory response by attenuation of IL-1β secretion, so inhibiting the activation of the NLRP3 inflammasome (Han et al., 2015). Ye et al., (2019) have observed that emodin is effective in protecting the myocardium against ischemic injury. via prevention of NLRP3-mediated pyroptotic cell death and and attenuation of NLRP3 activation. Additionally, in a rat model of pancreatitis,

emodin has been shown to inhibit NLRP3 signaling by blocking P2X7, thus inducing a reduction in IL-1β, IL-18 and myeloperoxidase plasma levels (Zhang et al., 2019).

5.5 Ginsenoside

Ginseng, a plant grown in East Asia and Northeast America, has long been used in traditional medicine. Ginseng is rich in ginsenoside, a steroidal saponin. belonging to a group of compounds, the ginsenosides, comprising Rb1, Rb2 and Rd, 20 (S) -Rg3 and 20 (R) -Rg3 (Yoon et al., 2015). Ginsenoside Rg3 exhibits cyto-protective and physiologically salutogenic properties, such anti-inflammatory, antioxidant, anti-obesity activities (Kim et al., 2014). Several experimental studies have shown that ginsenosides hold promise for suppressing activation of various types of inflammasomes, including NLRP3. Consistent with this, ginsenosides can also inhibit caspase-1 activation and reduce IL-1β and IL-18 expression (Yi, 2019). Furthermore, the salutogenic propertie attributed to ginsenoside Rg1 include increaseing expression of superoxide dismutase (SOD) and peroxisome proliferator-activated receptor-alpha (PPARα), thereby stimulating the oxidation of beta fatty acids, and regulation of inflammatory processes by inhibiting NLRP3, IL-1β and IL-18 (Xu et al., 2018), possibly via inhibition of P2X7 receptor activation and NF-κB (Han et al., 2018; Li et al., 2018). Another mechanism has also been proposed for Rb1 ginsenoside, via stimulation of Nfr2, thereby reducing the interaction of the NLRP3 inflammasome with TXNIP, thus imhibiting pro-IL-1B maturation (Chen et al., 2016; Zhai et al., 2018).

The non-saponin fraction of ginsenoside can also modulate the action of the NLRP3 inflammasome, by inhibiting NLRP3 signaling and preventing pro-IL1β maturation. by inhibition of TLR4-MyD88-NF-κB interaction (Byung-Cheol et al. 2017;Ahn et al., 2019).

5.6 Purple sweet potato

The anthocyanin giving purple sweet potato its colour, is a natural antioxidant and anti-inflammatory compound with geroprotective (anti-ageing) properties that may be beneficial in slowing and preventing the progression of CKD (Shan et al., 2014; Sun et al., 2015; Sun et al., 2019). Correspondingly, it It has been reported to retard glucose-induced endothelial senescence via inhibition of the NLRP3 inflammasome, activation of autophagy, and attenuation of ROS production (Sun et al., 2015; Sun et al., 2019).

Notably, Shan et al., (2014) have observed that rats with liver inflammation receiving purple sweet potato supplementation displayed reduced expression of the renal NLRP3 inflammasome,with concomitant inhibition of ASC, caspase-1 and IL-1β. Additionally, inhibition of IKKβ activation and NF-κB expression was reported. In the same animal model, purple sweet potato blocked hepatic oxidative stress by increasing the level of NAD+ in the endoplasmic reticulum. This lead to suppression of the nuclear translocation of NF-κB p65 (a structural protein of NF-κB), with consequent decreased activation of NLRP3 (Wang et al., 2017). This is also consistent with geroprotective activity ascribed to purple sweet potato, as NAD+ is a major substrate for the sirtuin family of proteins, which regulate the epigenetic landscape of ageing in response to metabolic stress (reviewed in Shiels et al Nat. Rev Neph 2017).

5.7 Quercetin

Quercetin is a polyphonic flavonoid found in onion, garlic, apple and red fruits. It possesses anti-oxidant and anti-inflammatory capabilities. Moreover, quercetin protects mitochondrial integrity and inhibits mitochondrial ROS release through its action on the NLRP3 inflammasome (Xue et al., 2017), NF-κB expression and the levels of IL-1β and IL-18 (Liu et al., 2018). Quercetin (and Ascorbic acid) may also diminsih inflammation by inhibiting TXNIP, which is one of the components that activates NLRP3 (Wu et al., 2014; Choe et al., 2017). In pre-clinical models of arthritis, quercetin has been reported to reduce post transcriptional expression of NLRP3, caspase-1 and IL-1β (Yang et al, 2018). Ding et al. (2018) have shown that dihydroquercetin supplementation modulates the overproduction of ROS and decreases NLRP3 activation in rats with diabetic nephropathy, resulting in nephroprotection and improvement in glucose and lipid control.

5.8 Resveratrol

Resveratrol, a powerful geroprotective compound, belonging to the polyphenol family, is found in wine, grapes and peanuts (Zhang et al., 2017). It is a Sirtuin 1 agonist with a proven capacity for mitigating the effects of cellular stress. Studies have shown that resveratrol plays an important role in controlling inflammatory and antioxidant responses. One of its modes of action is through modulation of the NLRP3 system (He et al., 2017; Ding et al., 2019). Resveratrol can block the transcriptional expression of NLRP3, caspase 1, IL-1β and IL-18, as well as that of their cognate proteins (Dong et al., 2015; Sui et al., 2016; Wu

& Huang, 2017). Resveratrol inhibits the expression of NLRP3 and cytokines by several mechanisms. Firstly, via blockade of the NLRP3 signaling pathway which leads to inhibition of inflammatory processes and production of mature cytokines (Misawa et al., 2015). Secondly, through the reduction of mitochondrial ROS production, by blocking TXNIP protein expression (Jiang et al., 2016; Li et al., 2016; Zou et al., 2018).

Misawa et al. (2015) have shown that resveratrol inhibits the accumulation of tubulin acetylates responsible for mitochondrial damage and consequent induction of NLRP3 Consequently, tubulin acetylate inhibition by resveratrol leads to inhibition of ASC on the mitochondria and NLRP3 inactivation. Notably, inhibition of mitochondrial damage impairs the assembly of inflammasome (Chalons et al., 2018).

Thirdly, via Syk dependent suppression of IL-1β secretion (Chung et al., 2019).

This mechanistic understanding is supported by a number of observations in pre-clinical models (including of CKD), demonstrating a capacity for resveratrol to mitigate NLRP3 mediated ischaemia- reperfusion damage in the rat intestine (Zhao et al., 2018), promotion of autophagy and in renal cells (Chang et al., 2015; Lin et al. 2017; Chen et al., 2019).

5.9 Silybin

Silybin is the major bioactive compounds found in silymarin, extracted from the medicinal plant Silybummarianum. IN a range of in vitro and in vivo experimental systems, silybin has been shown to attenuat the production of IL-1β and TNF, and decreases the recruitment of inflammatory cells, including macrophages, T cells, THP-1 cells and neutrophils (Tian et al., 2017; Zhang et al., 2018). The mechanistic basis for these observations has been attributed to an inhibitory effect for silybin on NF-κB and NLRP3 signaling (Tian et al., 2017; Zhang et al., 2017). Silybin modulates the NLRP3 inflammasome by blocking the TLR4 / NF-κB pathway and inhibits NLRP3 by reducing TXNIP expression, pro-caspase 1 activation, and IL-1β release (Zhang et al., 2018; Matias et al., 2019). In addition to these, silybin elevates the expression of Nrf2 and HO-1 thus enhancing physiological resilience.(Greaney et al., 2016; Yuan et al., 2017).

5.10 Sulforaphane

Sulforaphane, a bioactive compound found in cruciferous vegetables like broccoli, Brussel sprouts, cauliflower, cabbage, which has a range of geroprotective and salutogenic properties, including influencing the assembly and activation of NLRP3 (Yang et al., 2018). Sulforaphane can act as an antioxidant through the suppression of the production of mitochondrial ROS, thus depressing NLRP3 expression (Lee et al., 2016). Importantly, sulforaphane is an Nrf2 agonist, in addition to upregualting the expression fo a battery of other cytoprotective genes, including quinone oxidoreductase-1, HO-1, SOD1 and GPX1 (Dong et al., 2016; Li et al., 2019). The result of such activities is a consequential inhibition of p20 caspase-1, p17 IL-1β and ASC, which are primary components for the formation of the NLRP3 inflammasome (Li et al., 2019; Li et al, 2018).

Sulforaphane has also been reported to have anti-oncogenic properties (ref), though as Nrf 2 is specifically up-regulated in a range of tumours (and not systemically in cancer) . and sulforaphane is an Nrf 2 agonist, its clinicnal use must be treated with caution, until hermetic dosing levels are determined (ref)

5.11 Procyanidin

Procyanidins are flavonoids found in red fruits and red wine that inhibit the activation of NLRP3 by inactivating caspase-1 and secretion of IL-1β, decreasing ROS and the transcription of activator protein-1 (AP-1) (Yang et al., 2014).

Procyanidins can also inhibit the activation of NLRP3 by inactivating the NF-κB signaling pathway (Yang et al., 2014; Liu et al., 2017). The proposed mechanism is thought to be via inhibition of p65 nuclear expression and DNA binding, resulting in the transcriptional repression of target genes, such as COX2, iNOS and production of IL-6, IL-18, IL-1β and NO (Martinez-Micaelo et al., 2015).

Furthermore, procyanidins decrease the ASC and caspase-1 signalling, which consequently leads to less activation of NLRP3 (Jiang et al., 2018). Procyanidins have been shown to attenuate experimental colitis in vivo, by suppressing NF-κB and NLRP3 signaling expression in colon tissue in mice (Chen et al, 2018). A reduction in NLRP3 activation and serum IL-1β and IL-18 production was also found in rats with lupus nephritis receiving procyanidin supplementation for 8 weeks (100 mg/kg) (He et al., 2018).

5.12 Probiotics

Probiotics are natural or genetically modified microorganisms, capable of conferring a health benefit when established in the human gut (FAO/WHO, 2017). Among many suggested benefits, probiotics influence the expression of inflammasomes and modulate gut inflammation (Wang et al., 2016). Dolpady et al. (2016) have shown that rats receiving probiotic supplements (*Bifidobacteriaceae, Lactobacillaceae and Streptococcus thermophilus*), presented with reduced IL-1β expression and reduced differentiation of Th1 and Th17 cells in the intestinal mucosa. Supplementation of *Lactobacillus plantarum* for 8 weeks reduced LPS-induced intestinal inflammation in rats (Vilahur et al., 2015). Thus, stabilization and regulation of gut microbiota may lead to a reduction in inflammatory reactions related to the gut pathologies. In rats, probiotics (*Streptococcus thermophilus and thermophiles; Lactobacillus bulgaricus, lactis, acidophilus, reuteri and plantarum; Bifidobacterium lactis*) have also been reported to decrease hypothalamic expression levels of IL-1β, NLRP3, caspase-1 and NF-kB (Avolio et al, 2019) with salutogenic benefits..

5.13 Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) include agents such as omega-3; α-linolenic acid; Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA). The dietary sources of these nutrients are rapeseed oil, flaxseed oil, salmon, mackerel, sardines, sunflower oil, grape seed oil and corn oil. PUFAs have an important anti-inflammatory and antioxidant capabilities (Jarmakiewicz-Czaja et al, 2020).

Omega-3, as well as EPA and DHA, seems to inhibit expression of NLRP3, by activation of G protein-coupled receptor 120 (GPR120) and GPR40, via binding to NLRP3 (Yan et al, 2013; Williams-Bey et al, 2014). Apparently, a downstream scaffold protein of GPR40, β-Arrestin-2 (ARRB2), activates the interaction of GPR120 and GPR40 with NLRP3 and inhibits inflammation (Yan et al, 2013; Lin et al, 2017).

In addition to this, DHA inhibits the inflammasome-priming step, by suppressing the nuclear translocation of NF-κB and interfering with TLR4 signal transduction (Martínez-Micaelo et al, 2016). In fact, in hepatocytes, dietary PUFAs (DHA) regulate the expression and activity of NLRP3 inflammasome through direct inhibition of NF-κB (Sui et al, 2016). De Boer et al. (2016), in a study with macrophages in obese adipose tissue, have shown that omega-3 was able to decrease transcriptional expression of Caspase 1, IL-1β and IL-18. Additionally, omega-3 decreased the phosphorylation of p65 NF-kB and expression of NLRP3

453 inflammasome gene thus doing what?……. Furthermore, resolvins, which are DHA
454 metabolites- (e.g. resolvin D1 (RvD1), and 17S-hydroxy DHA (17SHDHA)), also have potent
455 anti-inflammatory effects. They have been demonstrated to prevent
456 hyperhomocysteinemia-induced formation of NLRP3 inflammasomes, ASC, caspase-1 and
457 interleukin-1 production. Moreover, *in vivo*, DHA metabolites have been observed to inhibit
458 podocyte NLRP3 inflammasome formation and activation (Li et al, 2017).
459 In a study with mice receiving diets containing palm oil, fish oil, echium oil (containing
460 18:4 n-3), or borage oil (containing 18:3 n-6), dietary PUFAs have been demonstrated to
461 inhibit inflammasome activation, decrease IL-1 β secretion and caspase-1 cleavage in
462 response to NLRP3 inflammasome activators (Shen et al, 2017).
463 Finally, a study with obese individuals has shown that 4g/day of fish oil supplements (EPA
464 and DHA) reduced expression of adipose inflammatory genes including inflammasome-
465 associated IL-18 and IL-1β and circulating IL-18 levels (Lee et al., 2018).
466
467 ***5.14 Other bioactive compounds***
468 Allicin, a bioactive compound of garlic, is able to inhibit the inflammatory activity of
469 NLRP3 by suppression of oxidative stress. Allicin decreases ROS production, lipid
470 peroxidation, and, consequently, activation of the NLRP3 inflammasome (Gao et al., 2019).
471 Endothelial cells treated with dihydromyricetin, a natural flavonoid found in
472 the Ampelopsis species *japonica (*known as peppervine), *megalophylla*, and *grossedentata*,
473 showed inhibition of caspase-1 activation, maturation and release of IL-1β and activation of
474 NLRP3. The proposed mechanism for these observations was suppression of ROS production
475 via increased Nrf2 signaling (Hu et al., 2018).
476 Olive leaf extracts suppress inflammation of placental tissues by inhibiting NF-κB p65
477 protein expression and, consequently decreasing NLRP3 protein expression and pro-IL-1β
478 (Kaneko et al., 2019). Piperine, the main bioactive component of pepper, was effective in
479 inhibiting NLRP3 inflammasome and reducing serum IL-1β in mice with lupus nephritis (Peng
480 et al., 2018).
481 Some vitamins can also modulate the activation and expression of the NLRP3
482 inflammasome. Rao et al. (2019) have observed that the vitamin D receptor may be a
483 negative regulator of NLRP3. Apparently, the vitamin D receptor can bind NLRP3 and block
484 the deubiquitination (cleave ubiquitin molecules from protein substrates) of NLRP3, leading

485 the NLRP3 inhibition. Paricalcitol, a vitamin D agonist, shown to be able to reduce the
486 expression of TGF-β and the NLRP3 inflammasome in epithelial cells, is associated with a
487 down-regulation of NOX activity (Ko et al, 2019). Vitamin D3 can downregulate intracellular
488 ROS and inhibit TXNIP and the NOD-like receptor family, involved in NLRP3 inflammasome
489 pathway activation (Lu et al, 2018). Furthermore, calcitriol protects cells against oxidative
490 stress and inflammation through inhibiting ROS-NLRP3-IL-1β signaling axis (Dai et al, 2019).
491
492 All these observations relative to vitamin D biology are pertinent to renal disease, as the
493 Vitamin D receptor controls expression of the anti-ageing gene klotho. Klotho is a co-
494 receptor with fibroblast growth factor receptor-1 and its FGF23 ligand that regulates renal
495 phosphate and calcium reabsorption (Kuro-o Nat Rev Neph 2019).
496
497
498 Vitamin E seems is also involved with NLRP3 inflammasome pathway. In murine
499 macrophages inflammasome activation, caspase-1 cleavage and IL 1β secretion have been
500 reported to be attenuated by gamma-tocotrienol treatment (Kim et al, 2016). Gamma-
501 tocotrienol may decrease the activation of NLRP3-inflammasome by change of the
502 macrophage lipidome, as reduction of lysophospholipids, diacylglycerol and free arachidonic
503 acid lead to the attenuation of TLR4-NFκB signaling axis activation, resulting in reduced
504 NLRP3 inflammasome activation (Kim et al, 2018). Vitamin B6 also inhibits NLRP3-dependent
505 caspase-1 missing word and secretion of mature IL-1β and IL-18 in LPS-primed macrophages
506 (Zhang et al., 2016).
507
508 ***5.15 Caloric restriction***
509 Caloric overload activates NLRP3 through mitochondrial damage, increased blood
510 pressure and insulin resistance (Traba & Michael, 2017). Although caloric restriction may
511 improve mitochondrial functioning and weaken the inflammasome (Traba & Michael, 2017;
512 Bang et al., 2019), few studies involving caloric restriction have evaluated its effects on the
513 formation and signaling of the inflammasome (Bang et al., 2019). Fann et al. (2014) have
514 observed that intermittent fasting in mice leads to inhibition of NF-κB and NLRP3 activation
515 and decreased plasma IL-1β and IL-18 concentrations. In healthy volunteers, Traba et al.,
516 (2015) have observed that after a 24-hour fast there was a reduced activation of NLRP3 as

compared to the fed state. Finally, a study in rats has shown that ketone bodies (β-hydroxybutyrate and acetoacetate) formed during a low caloric diet, decreased the activation of NLRP3. In addition, ketone bodies reduced NLRP3-mediated production of IL-1β and IL-18 interleukin (Youm et al., 2015).

6. Conclusion

The NLRP3 inflammasome has a key role in processes leading to chronic inflammation, which is an inherent feature of many clifestyle related and other NCDs including CKD. The internal uremic milieu activates NLRP3 and pro-inflammatory cytokines by several mechanisms. There are many naturally occcuring bioactive compounds, such as botanical polyphenols, that may influence the activation of the NLRP3 inflammasome. Accumulating data suggest that a diet rich in bioactive compounds, or the use of probiotics/ microbial biotherapeutics and caloric restriction could be promising strategies to decrease the activation of the NLRP3 inflammasome (**Figure 2**). However, to the best of our current knowledge, few experimental CKD studies have shown effectiveness for the clinical use of bioactive compounds as a means to control inflammation (**Table 1**). Further studies are warranted to explore the potentials of nutritional strategies using bioactive nutraceuticals and caloric restriction to control the activation of the NLRP3 inflammasome in CKD patients. This would fit a broader approach that is gaining increased attention of applying the concept of "Food as Medicine" using healthy diets - rather than relying only on pharmaceutical interventions - as an overall strategy to prevent and treat non-communicable chronic burden of lifestyle diseases including CKD.

Conflicts of interest

There are no conflicts of interest to declare.

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References	Samples	Intervention	Results

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Table 1. Summary of effects of bioactive compounds on chronic kidney disease and renal damage markers studies.

		In vitro studies	
Ka et al. (2016)	Murine macrophage cell lines RAW 264.7 and J774A.1	Cinnamaldehyde	↓ MAPK and PKC-α/δ phosphorylation ↓ ROS, ↓NF-κB activation ↓ NLRP3 and IL-1β secretion
Lin et al. (2017)	human kidney proximal tubular epithelial cell line HK-2 treated with LPS	4 mg/kg/day of resveratrol for 5 weeks	↓expression of NLRP3, ASC, caspase-1 and IL-1β
		In vivo studies (Animals)	
Shan et al. (2014)	24 male mice with kidney injury induced by high fat diet	700 mg/kg /day of Purple sweet potato color for 20 weeks	↓ urine albumin-to-creatinine ratio ↓ ROS and AGEs ↓ expression level of kidney NLRP3, ASC, Caspase-1 and IL1β ↓ activation of IKK β and NF-κB ↓ expression level of RAGE and TXNIP
Bugyei-Twum et al. (2016)	42 Sprague-Dawley rats with subtotal nephrectomy	100 mg/kg/day of theracurmin for 5 weeks	↓ kidney weight ↓ systolic hypertension ↓ RNAm expression of NLRP3, caspase-1 and IL1β
Lin et al. (2017)	Male C57BL/6 mice with CKD induced for adenine-containing diet	4 mg/kg/day of resveratrol for 5 weeks	↓ serum creatinine and blood urea nitrogen ↓the number of cells that expressed NLRP3 ↓expression of NLRP3, ASC, caspase-1 and IL-1β
Ding et al. (2018)	50 Sprague-Dawley rats with Diabetic nephropathy	100 mg/kg/day of Dihydroquercetin for 12 weeks	↓ urine microalbumin and serum creatinine ↓ LDL-c and total cholesterol ↓ renal fibrosis, ↓ ROS levels ↓ protein activations of NLRP3, caspase-1 and IL1β
He et al. (2018)	30 female mice with Lupus nephritis	100 mg/kg/day of procyanidin B2 for 8 weeks	↓ urine protein levels, serum creatinine and blood urea nitrogen ↓glomerular hypercellularity and glomerulonephritis ↓ NLRP3, ASC, and procaspase-1 ↓ renal and serum levels of IL-1β and IL-18
Chen et al. (2019)	32 male Sprague-Dawley rats with nephropathy	Injection of resveratrol (30 mg/kg) 60 min before induction of contrast-induced	↓ serum creatinine and blood urea nitrogen ↓ expression level of renal

		nephropathy	NLRP3, caspase-3 and IL1β
Zhao et al. (2019)	24 female mice with Lupus nephritis	200 mg/kg/day of curcumin for 8 weeks	↓ proteinuria and nephritis ↓ NLRP3 and caspase1 p20 expression ↓ IL-1β levels in the kidneys
Human studies			
Alvarenga et al. (2020)	28 hemodialysis patients	Control group (n-14): Juice with100 mL of orange juice with 12 g of carrot after each dialysis session/week for 3 months Curcumin group (n-14): Juice with 100 mL of orange juice with 12 g of carrot and 2.5 g of turmeric (95%curcumin) after each dialysis session/week for 3 months	Curcumin group: ↓NF-κB and hsCRP mRNA expression ↔ NLRP3 and IL-1β mRNA expression

Abbreviations: LPS: Lipopolysaccharides; I kappa B kinase beta (IKK β); nuclear translocation of nuclear factor kappa beta (NF-κB); Advanced Glycation End-products (AGEs); oxidative stress-associated AGE receptor (RAGE); thioredoxin interacting protein (TXNIP); Reactive oxygen species (ROS); Interleukin (IL); Adaptor Protein Apoptosis-Associated Speck-Like Protein Containing CARD (ASC); Nod-like receptor pyrin domain containing 3 (NLRP3); protein 20 (p20); Mitogen Activated Protein Kinases (MAPK); *protein kinase C alpha* and *delta* (PKC-α/δ); high sensitivity C-reactive protein (hsCRP)