# Cruciferous vegetables: Rationale for exploring potential salutary effects of sulforaphane-rich foods in patients with chronic kidney disease

Ludmila FMF Cardozo[1], Livia A Alvarenga[2], Marcia Ribeiro[3], Lu Dai[4], Paul G Shiels[5], Peter Stenvinkel[4], Bengt Lindholm[4], Denise Mafra[1,2,3]

[1] Graduate Program in Cardiovascular Sciences, Fluminense Federal University (UFF), Niterói, RJ, Brazil
[2] Graduate Program in Medical Sciences, Fluminense Federal University (UFF), Niterói, RJ, Brazil
[3]Graduate Program in Nutrition Sciences, Fluminense Federal University (UFF), Niterói, RJ, Brazil
[4]Division of Renal Medicine and Baxter Novum, Department of Clinical Science, Technology and Intervention, Karolinska Institutet, Stockholm, Sweden.
[5]Wolfson Wohl Translational Research Centre, Institute of Cancer Sciences, University of Glasgow

- Financial support: Conselho Nacional de Pesquisa (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) support Denise Mafra research.

- There are no conflicts of interest to declare.

- Running title: Sulforaphane and CKD

**Corresponding author:**
*Professor Denise Mafra*
*Unidade de Pesquisa Clínica-UPC. Rua Marquês de Paraná, 303/4 andar*
*Niterói-RJ, Brazil, Zip Code 24033-900*
*Federal Fluminense University Niterói-Rio de Janeiro (RJ), Brazil*
*Phone: +55 21 985683003*
*E-mail: dmafra30@gmail.com*

**Abstract**

Sulforaphane is a sulphur-containing isothiocyanate found in cruciferous vegetables (Family: Brassicaceae) and a well-known activator of the nuclear factor- erythroid 2-related factor 2 (Nrf2), considered a master regulator of cellular antioxidant responses. Patients with chronic diseases, such as diabetes, cardiovascular disease, cancer and chronic kidney disease (CKD) present with high levels of oxidative stress and a massive inflammatory burden, associated with diminished Nrf2 and elevated nuclear factor-kB (NF-kB) expression. Due to being a common constituent of dietary vegetables, the salutogenic properties of sulforaphane, especially it's anti-oxidative and anti-inflammatory properties, have been explored as a nutritional inervention in a range of diseases of ageing, though data on CKD remains scarce. In this brief review, we describe the effects of sulforaphane as a senotherapeutic agent,. With this as a background, we provide a rationale for studies aiming at exploring potential benefits of sulforaphane-rich foods in patients with CKD.

**Keywords:** chronic kidney disease, sulforaphane, oxidative stress, inflammation, gut microbiota, senescence, nrf2.

## Introduction

Cruciferous vegetables belonging to the Brassicaceae family, such as broccoli, broccoli sprouts, Brussels sprouts, cabbage, cauliflower, kale, and green cabbage, are highly nutritious foodstuffs in the diet, as highlighted by numerous clinical (Chan et al., 2015; Charron et al., 2018; Chartoumpekis et al., 2019) and epidemiological (Wang et al. 2014; Riboli & Norat, 2003) studies. These vegetables are rich in vitamins, minerals, (poly)phenolics, and contain sulphur-containing compounds, such as the sulphur-containing isothiocyanate, sulforaphane (SFN) (Vanduchova et al. 2019).

Recent studies have demonstrated that sulforaphane potentially has numerous essential roles as an antimicrobial, antioxidant, anti-inflammatory (Houghton, 2019; Vanduchova et al. 2019; Wang et al., 2020; Liu et al. 2020) and antioncogenic (Calcabrini et al., 2020) agent and as an epigenetic modulator (Hyun 2020; Mitsiogianni et al., 2020; Abbaoui et al., 2017).

Sulforaphane is a nuclear factor-erythroid 2-related factor 2 (Nrf2) agonist and as such, it indirectly can influence the transcription of a battery of antioxidant enzymes (Paunkov et al., 2019). SFN also exhibits cytoprotective properties, through increasing natural killer cell activity and p-53 expression, suppression of NF-κB, increase in inhibition of histone deacetylases, induction of apoptosis, as well as antimicrobial properties. SFN has been reported to act as a bactericidal agent against Helicobacter pylori by inhibiting bacterial urease synthesis (Houghton, 2019).

The beneficial properties of SFN have been extensively studied in the context of cancer, (Pham et al., 2004; Gamet-Payrastre et al., 2000; Fimognari et al., 2002; Choi et al., 2007). In addition, SFN may contribute to prevention and mitigation of complications in several other diseases such as diabetes, obesity, and cardiovascular and neurological diseases (Yagishita et al. 2019; Martins et al. 2018; Bai et al., 2015; Klomparens & Ding, 2019).

This review summarizes some of the potential beneficial effects of SFN in various diseases and with this as a background provides a rationale for studies exploring its potentials also in chronic kidney disease (CKD).

## Cruciferous vegetables as a source of sulforaphane

Sulforaphane (4-methyl-sulfinyl butyl isothiocyanate) is a naturally occurring oily isothiocyanate found in cruciferous vegetables. Glucoraphanin (4-methyl-sulfinyl butyl) is the inactive and chemically stable biological precursor of SFN, which belongs to a group of phytochemicals termed glucosinolates (GLS) that have a sugar component (i.e. D-glucose or dextrose), built into their structure (Nakagawa et al., 2006, Vanduchova et al. 2019).

When a cruciferous vegetable suffers tissue damage by a microbial attack, mechanical food processing, or chewing, the enzyme myrosinase, which usually is in the plant, is physically segregated from glucosinolates, released, and comes into contact with glucoraphanin. Myrosinase, catalyzes the hydrolysis of glucoraphanin, releasing glucose and sulphate components, the latter forming stable intermediate products, of which the most reactive is sulforaphane isothiocyanate (**Fig. 1**) (Shapiro et al.,1998; Zhen-xin et al., 2012).

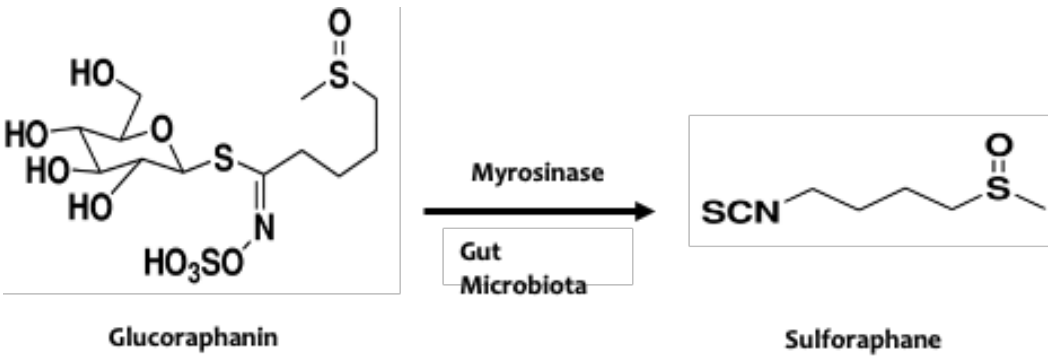


**Fig 1.** Conversion of glucoraphanin to sulforaphane.

Broccoli, cabbage, cauliflower, and kale are vegetables rich in SFN. Among these vegetables, broccoli contains the highest concentration of SFN (Nakagawa et al. 2006), and broccoli sprouts contain even higher SFN levels than mature broccoli , this being 1153 mg / 100 g dry weight, relative to the mature broccoli with 44-171 mg / 100 g dry weight (**Table 1**).(Nakagawa et al. 2006). SFN is prevalent in fresh vegetable material, but not in vegetable derivatives, such as powder and tablets, where it is not detectable (Nakagawa et al. 2006). Total concentrations of GLS in cruciferous vegetables can be influenced by processing methods and heat treatment (above 70°C), as in routine domestic cooking procedures, such as blanching, boiling and freezing (Cieslik et al. 2007, van Eylen et al. 2007), where the plant's myrosinase is inactivated, interrupting the

formation of sulforaphane (van Eylen et al. 2007). Blanching reduces total GLS concentrations by 13.0% in white cauliflower and 30.0% in Brussels sprouts and broccoli. In boiled vegetables, losses are more significant, reaching 35.3% in white cauliflower and 72.4% in curly kale. For broccoli, the loss of glucoraphanin has been reported as 39.1% by blanching and 60.6% by boiling (Cieslik et al. 2007). Apart from this, cold storage in a domestic refrigerator (temperature 4 to 8 °C) for seven days reduces the concentration of GLS in broccoli (-27%), Brussels sprouts (-20%), cauliflower (-11%) and green cabbage (-14%) (Song & Thornalley 2007). In contrast, microwaving and mild heating in the range of 40 to 60°C has been reported to increase the levels of glucoraphanin and sulforaphane in broccoli compared to raw broccoli (Lu et al. 2020).

Although mammals do not possess myrosinases, the conversion of glucoraphanin to sulforaphane still occurs and seems to be carried out by the intestinal microbiota, as will be discussed later.

The GLS fraction that is released from the plant matrix is bio-accessible as it is hydrolyzed by the myrosinase present in plants, or by the myrosinase-like activity of the human gut microbiota. The underlying biochemistry of these processes is exemplified by the mercapturic acid pathway, where isothiocyanates are conjugated to glutathione (GSH) by a reaction catalyzed by glutathione transferase (GST). Several cleavage reactions occur, giving rise to sulforaphane-N-acetylcysteine (Vanduchova et al., 2019; Shapiro et al.,1998). The isothiocyanate conjugates are then actively transported into the extracellular space by multidrug resistance-associated protein 1, 2, and P-glycoprotein (Kim et al., 2015).

Isothiocyanate-glutathione conjugates dissociate in the blood, partly due to the low plasma glutathione concentration and partly through further conjugation with serum albumin, which is a source of free thiol groups. Free isothiocyanate can be absorbed by peripheral organs, where it can accumulate in cells by reacting with thiol groups in glutathione and other proteins, with both forms excreted mainly in the urine (JI & Morris, 2003; Oliviero et al, 2018).

Several small clinical studies have evaluated SFN absorption and excretion in humans, and the evidence points to the fact that absorption is affected by the way SFN is consumed (Cramer et al 2011, Cramer et al 2012, Atwell et al, 2015, Vermeulen et al, 2008). SFN absorption was assessed in healthy individuals after a meal containing air-

dried broccoli sprouts rich in myrosinase, broccoli powder lacking myrosinase and a combination of both. The 24-hour urinary excretion of SFN was 74% for broccoli sprouts, 19% for broccoli powder, and 49% for the combination (Cramer et al, 2011), demonstrating that the presence of myrosinase appears to improve SFN absorption (Cramer et al, 2011; Atwell et al, 2015). Higher levels of sulforaphane were found in human blood and urine after consuming raw broccoli (bioavailability of 37%) compared to cooked broccoli (bioavailability of 3.4%). The time to reach the peak of plasma sulforaphane was also shorter in raw broccoli (1.6 h) compared to cooked broccoli (6 h) (Vermeulen et al, 2008).

In humans, a moderate dose of SFN appears safe, as the metabolites are rapidly eliminated (Hanlon et al 2009; Shapiro et al 2006) and daily administration of broccoli sprout extract for three months in type 2 diabetes patients resulted in no severe adverse effects (Axelsson et al 2017). Notably, in vitro studies have reported that while low doses of SFN (0.25μM) protected mesenchymal stem cells (MSCs) from cellular oxidative injuries and inhibited MSCs undergoing senescence (detected with b-galactosidase assay) and apoptosis, high doses of SFN (20μM) exerted a cytotoxic effect by boosting DNA damage and resulting in cell cycle arrest, senescence and apoptosis (Zanichelli et al, 2012). This finding suggests that a high dose of SNF potentially could be toxic and pro-oxidant by causing glutathione depletion and superoxide production. A study from Kubo et al (2017) has proposed that such toxic and pro-oxidant SNF activity was related with over-activation of NRF2-mediated Kruppel-like (Klf9) expression and downstream repression of peroxiredoxin 6 (Prdx6) (Nrf2/Klf9/Prdx6 axis), inducing unfavorable oxidative stress and cell death (Kubo et al 2017).

Sulforaphane has gained increased attention due to salutogenic effects mediated through the NRF2 pathway (Paunkov et al, 2019), especially in cancer, but also because of its potential preventive effects in, diabetes, cardiovascular and neurological disease (Yagishita et al. 2019; Bai et al, 2015; Klomparens & Ding, 2019). Here, we will discuss the potential effects of sulforaphane as an anti-inflammatory agent and anti-oxidant, an anti-oncogenic agent, and as a senotherapeutic, all in the context of CKD.

**Sulforaphane: Effects on Nrf2 and inflammation**

In a bibliometric review of the biological effects of sulforaphane, activation of Nrf2 was the most cited pathway (Paunkov et al, 2019). The Keap-Nrf2-ARE pathway is the primary regulator of cell cytoprotective responses to increased oxidative stress through an inducible expression of detoxification and antioxidant enzymes (Suzuki et al, 2013). Nrf2 is a protein that contains 605 amino acids and is expressed in several tissues and cell types. It belongs to a subgroup of fundamental leucine zipper genes (bZIP) that share a conserved structural domain called Cap-N-Collar (CNC) (Kaspar et al, 2009; Pedruzzi et al, 2012). In the absence of oxidative stress, the cytosolic repressor protein Kelch-like ECH-associated protein 1 (Keap1), an adapter component of the E3 ubiquitin ligase complex based on Cullin 3 (Cul3), inhibits the Nrf2, that then undergoes ubiquitination and promotes Nrf2 proteasomal degradation (Pedruzzi et al, 2012). Thus, Keap1 is a negative cysteine-rich Nrf2 regulator (McMahon et al, 2003), and these reactive cysteine residues act as sensors for oxidants and electrophiles (Dinkova-Kostova et al, 2017).

The main characteristic of sulforaphane is its electrophilicity, which occurs due to the high chemical reactivity of the central carbon of the isothiocyanate group, which reacts with nucleophiles containing a sulfur, nitrogen or oxygen center (Dinkova-Kostova et al, 2017). Thus, the isothiocyanates promote modification of the thiol groups of Keap1, inducing the dissociation of the two proteins and a consequent increase in Nrf2 intracellular levels (Kensler et al, 2013). Nrf2 moves to the nucleus and interacts with small musculoaponeurotic fibrosarcoma (sMAF) proteins and co-activating proteins, activating antioxidant response elements in their promoter regions, activating the transcription of the target gene (Pedruzzi et al, 2012, Takaya et al, 2012), leading to the expression of a high number of cytoprotective proteins with antioxidant and detoxifying functions such as NAD (P) H quinone oxidoreductase 1 (NQO1) and heme oxygenase 1 (HO-1) (Lee & Hu, 2020; Ma 2013). Also, Nrf2 binds to the regulatory regions of these inflammatory cytokine genes and their production (Kobayashi et al, 2016) and is also able to antagonize the nuclear transcription factor-kB (NF-kB), which coordinates the expression of inflammatory genes, by preventing the degradation of its cytosolic repressor (IkB) (Antunes & Han 2009; Kim et al 2010).

In vitro studies have shown a positive regulation of phase II antioxidant enzymes and a downregulation of NF-κB, decrease of ROS production, ICAM-1, VCAM-1, E-selectin and monocyte adhesion to endothelial expression in cells treated with sulforaphane (Angeloni et al, 2009; Leoncini et al, 2011; Rakariyatham et al 2018; Liu P et al, 2019; Huang et al, 2013).

SFN also shows anti-inflammatory activity in several contexts, such as human, cell, and animal studies (Table 2) (Rakariyatham et al 2018; Townsend & Johnson, 2016; Navarro et al, 2014; Giacoppo et al 2013). Evidence indicates that it not only activates Nrf2, but also targets other pathways associated with inflammation including direct inhibitory activity on NF-kB, and direct negative regulation of pro-inflammatory genes and inflammasomes (Henning et al, 2020; Clarke et al, 2008; Cheung & kong 2010; Liu et al, 2008; Greaney et al, 2016).

In cells, the direct activity of SFN in the NF-kB appears to be through the selective reduction in the DNA binding of NF-kB without interfering with NF-kB nuclear translocation as SFN can interact with thiol groups by the formation of dithiocarbamate, preventing redox-sensitive DNA binding and NF-kB transactivation. Besides, SFN appears to directly inactivate NF-kB subunits by binding to essential Cys residues or interacting with glutathione, or other redox regulators important to NF-kB function (Heiss et al, 2001). In another study, SFN also inhibited the nuclear translocation of NF-κB induced in lymphocytes cells (Checker et al 2015).

In animals, Wang et al. (2014) have demonstrated in mice with diabetes mellitus type 2 that 0.5 mg/kg of SFN subcutaneously for five days per week during four months increased the Nrf2 mRNA expression, with consequent increase of SOD-1 and HO-1, and prevention of changes in the wall thickness and structural derangement of aortic. Also, SFN decreased some inflammatory markers, such as TNF-$\alpha$ and VCAM-1. Giacoppo et al. (2013) have shown in mice model of multiple sclerosis that 10 mg/kg/day of (Rs)-glucoraphanin bioactivated with myrosinase decreased the NF-kB translocation to the nucleus with decreased of IL-1β and apoptosis (Bax protein and expression of caspase 3).

Inflammasomes are multiprotein cytoplasmic complexes from the innate immune system, formed in response to stimuli of pathogen-associated molecular patterns

(PAMPs) and danger-associated molecular patterns (DAMPs), in response to infections, tissue damage or cell stress. The inflammasomes promote the activation of Caspase-1, which through cleavages of IL -1β and IL-18, will give rise to its mature forms leading to local and systemic inflammatory reactions (Kelley et al 2019; Alvarenga et al 2020). Surprisingly, inflammasome inhibition by SFN seems to be independent of the transcription factor Nrf2 and the antioxidant response-element pathway. SFN inhibits the autoproteolytic activation of caspase-1 and IL-1β maturation and reduces the activation of NLRP1 and NLRP3 inflammasome (Greaney et al, 2016). These findings indicate that SFN can inhibit the inflammasomes and, consequently, the inflammatory process by another mechanism and contributes to understanding the anti-inflammatory effects of SNF. It is essential that the anti-inflammatory effects of SFN, independent of Nrf2, deserve more studies because SFN has a previously overlooked role in many inflammatory pathways (Greaney et al., 2016).

In this context, it is known that inflammation and oxidative stress are intrinsically involved in the pathogenesis of chronic non-communicable diseases such as cardiovascular disease, hypertension, obesity, CKD, diabetes, and cancer (Mazarakis et al., 2020). Accordingly, nutritional strategies have been studied tirelessly to decrease inflammation and oxidative stress, and to improve the quality of life of affected individuals (Tan et al., 2014; Mazarakis et al., 2020). According to previous studies summarized in this review, SFN seems to be an efficient anti-inflammatory and antioxidant strategy as shown the **Fig 2**. Clinical studies in humans should be encouraged since there a so far, a limited number of published reports dealing with this topic in the literature.

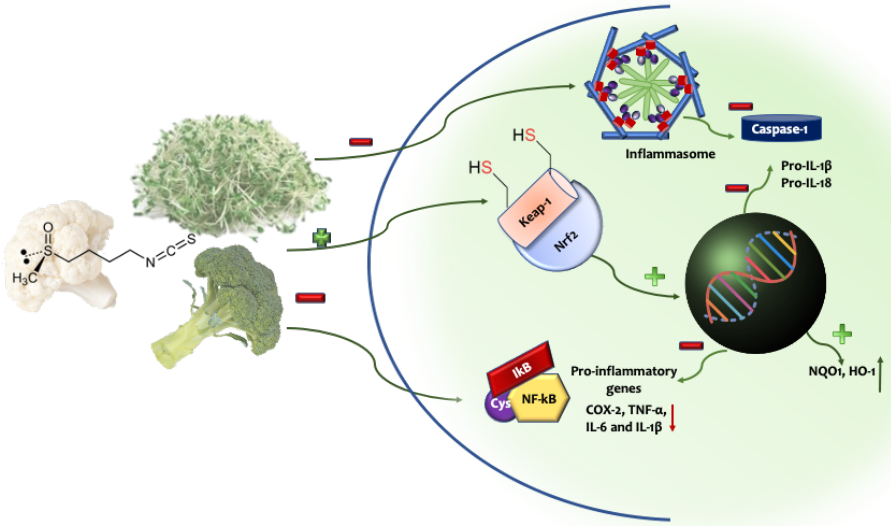


**Fig 2: Effects on Nrf2 and inflammatory factors in the cells.** Sulforaphane in cruciferous vegetables activates the nuclear factor- erythroid 2-related factor 2 (Nrf2) and through this and other pathways influence inflammatory factors in the cells. Sulforaphane modifies the thiol groups of Keap1, increases the availability of Nrf2 to the nucleus, binds to the essential Cys residues, inactivates NF-kB, and reduces the activation of NLRP3 inflammasome.

### Sulforaphane as a modulator of the epigenetic landscape

Ageing is a process characterized by diminished capacity to maintain homeostasis due to unfavorable structure and functional alterations, whereby the human body becomes susceptible to exogenous or endogenous stress stimuli and cellular insults, predisposing individuals at high risk of developing chronic degenerative diseases (e.g., cardiovascular disease, chronic kidney disease, diabetes, cancer, sarcopenia, and neurodegenerative diseases) [1]. One of the prominent features of premature ageing is the imbalanced increment of oxidative stress and the waning of the antioxidant defense system, which eventually lead to oxidative DNA damage and cellular senescence concomitant with chronic inflammation [2]. Accumulating evidence suggests that isothiocyanates, including sulforaphane (SFN), exert a multifaceted profile of counteracting the ageing process, with underlying mechanisms ranging from Nrf2-dependent/independent pathways to epigenetic modifications involved in cellular senescence and ageing [3].

Given the role of Nrf2 pathways in cellular senescence and premature ageing, recently reviewed in [6], it is tempting to speculate on the capacity of SFN in the prevention of ageing-related diseases. Indeed, the Nrf2-dependent anti-ageing potential

of SNF has been widely demonstrated in cardiovascular ageing both in preclinical and clinical studies, whereby SNF-mediated Nrf2 signaling could hurdle endothelial cell activation in the atherosclerotic plaque [7], regulate vascular smooth muscle proliferation [8], and mitigate the inflammatory and thrombosis burden [9]. Such a protective and anti-ageing role of SNF has also been observed in various neuropathological diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and multiple sclerosis [10–14]. Recently, Saleh et al [15] showed that SFN could improve liver ageing and inhibit hepatic fibrosis via Keap-1/Nrf2 pathways in D-galactose-induced liver ageing rats.

Aside from targeting Nrf2 signaling mediated oxidative DNA damage and inflammation, low dose treatment with SNF (1μM, once per week), was shown to delay and counter fibroblast senescence by repressing cellular glucose uptake and downregulating glycolysis, exerting a caloric restriction mimetic-like response [16]. Such anti-senescence activity of SNF has also been reported in mesenchymal stem cells (MSCs) culture under oxidative stress conditions (300 μM $H_2O_2$), whereby, intriguingly, a hormetic (biphasic dose response) behavior of SNF was observed [17].

Indeed, a dosage of SNF matters when it comes to prevent or to promote senescence; a different consideration should be made about SNF in the scenario of cancer. High concentrations of SNF can promote cancer cells undergoing senescence and apoptosis, thereby inhibiting the proliferation of cancer cells and favoring anti-cancer treatment. SNF acts as an epigenetic modulator in inducing cell cycle arrest and senescence in various cancer cell lines [19–21], which can be distinct from Nrf2-mediated redox signaling. Lewinska et al [19] showed that SNF (5-10 μM) promoted cell cycle arrest and senescence in breast cancer cells with elevated levels of p21 and p27 and further induced apoptosis concentration of SNF 20 μM.

Moreover, these cellular effects were accompanied by epigenetic modifications of DNA hypomethylation, decreased DNA methyltransferases and changes in microRNA profiles and SNF, and like other phytochemical-mediated therapeutic approaches, it can be considered as an epigenetic anti-cancer therapy. Another vivid example of SNF in epigenome-targeted cancer chemoprevention effect is attributed to its role as an inhibitor of histone deacetylase (HDAC), whereby it can re-activate the repressed genes of p21 and Bax in cancer cells and facilitate cells undergoing senescence and apoptosis

[22,23]. During in vitro treatment of SNF in human colon and prostate cancer cells, decreased HDAC activity was accompanied by increased histone H3 and H4 acetylation on the promoter of the p21 gene [20,21]. In vivo, a SFN rich diet retarded prostate cancer growth with significantly decreased HDAC activity both in localized prostate tissue and peripheral blood mononuclear cells, indicating an inhibited HDAC effect both locally and systemically [24].

The epigenetic landscape comprises canonical features such as DNA methylation and chromatin modification, as well as non-canonical features such as reciprocal regulatory networks of non-coding RNAs (Shiels et al., 2017). This landscape enables rapid genomic responses to environmental changes without the requirement to fix these in the DNA sequence, which would otherwise take many generations (Tortorella et al., 2015; Gianfredi et al, 2017). Dysregulation of the epigenome can lead to multistage carcinogenesis, accelerated ageing, and the development of chronic diseases (Shiels et al 2017; Kooman et al NRN 2014; Tortorella et al., 2015; Hyun 2020).

Cancer cells also display several DNA alterations, such as site-specific DNA hypermethylation, altered cellular histone deacetylase (HDAC) activity, and altered miRNA expression. DNA methyltransferases (DNMTs), enzymes that methylate DNA cytosine residues, and HDACs, function to enable stable gene repression (Watson et al., 2013). In this context, SFN has been characterized as a modulator of epigenetic enzymes, via inhibition of HDAC expression (Watson et al., 2013; Biersak, 2016).

Abbaoui et al. (2017) have shown in an in vitro study with bladder cancer that SFN inhibits HDAC, specifically HDACs 1, 2, 4, and 6 by decreased histone acetyltransferase activity. Additionally, SFN decreases the phosphorylation status of histone H1 and increases phosphatase PP1β and PP2A activity. These data support the assertion that SFN modulates histone status through HDAC inhibition and increase of phosphatase activity (Abbaoui et al., 2017). Additionally, a study with melanoma cell lines has shown that SFN reduced cell viability, total histone deacetylase activity, and modulated the expression levels of histone deacetylases, acetyl, and methyltransferases. These results indicate that SFN regulates the epigenetic response by modulation of acetylation and methylation in melanoma cells (Mitsiogianni et al., 2020).

A study on colorectal cancer in rats has shown that the single administration of 60 mg/kg of SFN by gavage decreased the HDAC3 expression, histone acetyltransferase

(HAT) activity, and increased pH2AX levels, a marker of DNA damage. These results have shown that SFN causes DNA damage in colon cancer cells and decreases their proliferation (Okonkwo et al., 2018). This hypothesis is an essential caveat for strategies using SFN to treat cancers, especially Nrf2 positive cancers, and that dosing requirement and demonstrate that signs of any hormetic effects need more investigation, robust data, and data analysis.

In another in vitro study, SFN has been described as affecting the hypomethylation of tensin homolog (PTEN) and retinoic acid receptor beta 2 (RARbeta2) promoters, which led to concomitant tumor suppressor gene upregulation. The PTEN and RARbeta2 promoters are involved in the tumor suppressor genes that are silenced in breast cancer cells. It is thus essential to recognize that PTEN and RARbeta2 promoters can decrease DNMT expression through negative regulation of the MAPKAP1 signaling pathway, an intracellular oncogenic (Lubecka-Pietruszewska et al., 2015). Another study in breast cancer cells has shown that the anti-cancer effects of SFN were mediated by global DNA hypomethylation, decreased levels of DNMT1, DNMT3B, and diminished N6-methyladenosine (m6A) RNA methylation. Additionally, SFN upregulated expression of sixty microRNAs and downregulated expression of thirty-two microRNAs (Lewinska et al., 2017).

Another study using human hepatocellular carcinoma cells has shown that SFN can downregulate DNA damage, and modulate expression of histone deacetylases, leading to downregulated genes involved in inflammatory signaling (HDAC5 and HDAC11) as well as upregulated and hypomethylated genes linked to the Nrf2 pathway, including NAD(P)H quinone oxidoreductase-1 (NQO1), heme oxygenase 1 (HO-1), glutamate-cysteine ligases, and thioredoxin reductase 1 (TXNRD1) (Dos Santos et al., 2020). Epigenetic regulation of Nrf2 through SFN promotes the transcription of Nrf2 and its nuclear translocation and activation (Su et al., 2018). Also, in primary effusion lymphoma cells, SFN was able to decrease cell viability and inhibit the phosphorylation of p38 mitogen-activated protein kinase (p38MAPK) and AKT, both of which are involved in the inflammatory response. Consequently, there was a reduction in cell growth and enhanced apoptosis (Ishiura et al., 2019).

In a study in dendritic cells, which have a pivotal role in host immune responses, SFN inhibited the lipopolysaccharide-induced HDAC6, HDAC10, and DNMT3a gene

expression. Moreover, SFN upregulated the expression of the DNMT1 gene and inhibited the global HDAC activity. SFN altered the induction of toll-like 4 receptor (TLR4) gene expression, consequently regulating the TLR4-induced activity of transcription factor NF-κB and leading to decrease of pro-inflammatory cytokine secretion (Qu et al., 2015).

Another epigenetic action of SFN is by inhibition of telomerase reverse transcriptase (hTERT) expression and activity. hTERT, a catalytic subunit of telomerase responsible for changes in chromatin structure and composition (Abbas et a, 2016) is elevated in 90% of cancers and essential for their proliferation (Martin et al., 2018). SFN mediates changes in histone post-translational modifications levels (Abbas et al., 2016), which is pertinent as HDAC1 regulates hTERT mRNA levels and expression (Martin et al 2018). Moreover, SFN has been reported to down-regulate telomerase protein expression levels and enzymatic activity. These effects lead to inhibition of cell viability and induced apoptosis of the colorectal cancer cells.

In in vitro studies, Chen et al. (2019) observed antitumor activities of SFN in nasopharyngeal carcinoma (NPC) and concluded that SFN could be useful in suppressing the development of NPC cells through the DNMT1/WIF1 axis pathways.

Nutraceutical combinations have been evaluated as a potent treatment for colon cancer, and among these substances, SFN has been evaluated. For its antioncogenic capabilities in HT-29 and Caco-2 colon cancer cells, wherein the combination with dihydrocaffeic acid was shown to be more effective. Subsequently, this combinatorial therapy has been proposed for use as a basis for the creation of effective food products in the prevention and even co-treatment of colon cancer (Santana-Gálvez et al., 2020).

Corroborating this, Lan et al. (2017) have evaluated the apoptotic potential of SFN in colon cancer cells. SW480 cells with P53 deficiency were treated with varying concentrations of SFN (5, 10, 15, and 20 μM). They observed that all studied concentrations of SFN were able to cause apoptosis and concluded that SFN might be a therapeutic strategy in the co-treatment of patients with p53-deficient colon cancer.

Lewinska et al. (2017) have observed the effects of SFN (concentrations of 5, 10, and 20 μM) on breast cancer cells. SFN at 5 and 10 μM was effective in stopping the cell cycle, increasing the levels of p21 and p27 and inducing cellular senescence, while at 20 μM it induced apoptosis. They also observed nitro-oxidative stress, genotoxicity,

reduced AKT signaling, negative regulation of microRNAs, and a significant reduction in the levels of miR-23b, miR-92b, miR-381 and miR-382 in three types of cancer cells, showing that SFN can exert its effect via the epigenetic landscape.

**Sulforaphane and Cancer: Studies in animals and humans**

According to the World Health Organization cancer is one of the top ten causes of morbidity and mortality in the world, accounting for 7.6 million deaths annually, and that statistical data foresees a significant increase in these numbers in the coming years (Gupta et al., 2014; Mcguire, 2016). Given these alarming projections, researchers have been looking at strategies for cancer prevention using bioactive compounds in the diet that could be promising chemopreventive agents, as they can act in the DNA repair mechanism, in cell growth, in response to apoptosis, and as cell signaling inducing transcription factors, in addition to effects on oxidative stress and inflammation (Remely et al., 2015; Braicu et al., 2017; Santos et al., 2019).

In this context, SFN has shown some benefits in preventing several types of cancer including pancreatic cancer, colon cancer, leukemia and prostate cancer (Gamet-Payrastre et al, 2000; Fimognari et al, 2002; Pham et al, 2004; Choi et al., 2007; Vanduchova et al., 2018).

Its chemopreventive potential can be explained by the fact that SFN can modulate several pathways that attenuate or modify compounds that damage DNA and favor the formation of cancer, including the phase I and phase II enzyme pathways (Gupta et al., 2014; Mokhtari et al., 2018). In general, SFN can inhibit phase 1 metabolizing enzymes, especially the cytochrome P450 enzyme complex, which causes the activation of detoxification enzymes in phase 2 and attenuates inflammation in the cell (Langouet et al., 2000). Furthermore, it acts secondarily by inducing epigenetic changes within the cell, enabling the transcription of apoptotic genes and cell cycle interruption, such as p21 and cyclin D1 (Kallifatidis et al., 2011).

Corroborating this, Pryia et al. (2011) have evaluated in an experimental study the anti-initiating potential of SFN concerning lung cancer induced by benzo (a) pyrene [B (a) P] in rats, and explored whether its ingestion was able to reach the lung tissue and increase the functional activity of detoxification enzymes. They concluded that the administration of SFN led to the reduction of phase I enzyme activity and the induction

of phase II enzymes and intensified the transcription of Nrf2, in addition to reducing the stress caused by carcinogens, thus elucidating the potential anti-initiator action of sulforaphane in the pre- and post-initiation stage of lung cancer.

Zhang et al (1994) have evaluated the chemopreventive effects of SFN in rats with mammary tumors, induced by dimethylbenzanthracene and after 150 days of SFN intervention, at 75, 100 and 150 μM per day, observed a decrease in the progression of tumor development, as well as weight reduction.

Xu et al. (2006) have elucidated the chemopreventive efficiency of SFN by stimulating antioxidant and detoxifying enzymes through transcription factor 2 related to nuclear factor E2 (Nrf2) in an experimental study. Skin carcinogenesis was induced using 7,12-dimethylbenz (a) anthracene in mice, and they were treated with topical use of 100 nmol SFN once daily for 14 days before induction to estimate the incidence. They reported a lower incidence and number of skin tumors per rat. Besides, they observed an increase in the expression of Nrf2 in the pretreatment with SFN and concluded that the chemopreventive potential also occurs through Nrf2.

Corroborating these findings, Dinkova-Kostova et al. (2006) induced skin cancer by UV irradiation (30 mJ / $cm^2$ per session twice a week for 20 weeks) in 30 mice and after irradiation treated for five days (for 11 weeks) topically with broccoli extract in concentrations of 0.3 μmol (low dose) or 1.0 μmol (high dose) SFN. At the end of the study, they observed that the topical SFN extract was able to induce the phase 2 reaction in the mouse skin, prevent cytokine-dependent iNOS induction in RAW 264.7 macrophages, inhibit carcinogenesis as well as tumor burden, incidence, and plurality, which showed a decrease of up to 50% in mice that were treated with a high dose of broccoli extract.

In human clinical studies, Lozanovski et al. (2014) have observed in a prospective, randomized, double-blind pilot study, the efficacy of lyophilized broccoli sprouts in the treatment of advanced pancreatic ductal adenocarcinoma. Forty patients were selected and received fifteen capsules a day (containing 90 mg of active sulforaphane) over a follow-up year. At the end of the study, they concluded that the intervention with 90 mg of sulforaphane per day, for one year, was effective in inhibiting the development and sensitivity of advanced pancreatic ductal adenocarcinoma.

Traka et al. (2019) evaluated in a randomized, double-blind, three-arm study, the effects of broccoli consumption on the progression of prostate cancer in 49 men under active surveillance diagnosed with low or medium risk prostate cancer for 12 months. One control group and two other groups were established with increased amounts of glucoraphanin, 3 and 7 times more than the control, and individuals were offered 300 mL of broccoli soup. They observed that there was a reduction in alterations in the expression of genes in non-neoplastic tissue and a reduction in expression in pathways with cancer potential, and thus, the consumption of broccoli was inversely associated with prostate development cancer.

In a recent systematic review, it was shown that the use of SFN in conjunction with anti-cancer therapy is useful in improving the pharmaco-toxicological scenario of chemotherapy (Calcabrini et al. 2020). Another review ratified the protective effects of broccoli concerning cancer, detaching its potential to protect cells and the arrangement of DNA through the activation of Nrf2, which occurs possibly through the binding of sulforaphane with one of the active sites of KEAP1 (suppressor protein of Nrf2) (Kaboli et al. 2020). This leads to the gathering of the ubiquitinated Nrf2 / Keap1 complex in cells, causing apoptosis by leading to intracellular toxic space, and thus can lead to intracellular toxic space. Furthermore, although further studies are needed to elucidate the anti-cancer efficacy of sulforaphane, it is plausible that sulforaphane may be a possible adjunct to anti-cancer therapy associated with other agents already known (DeJesus et al., 2019; Corssac et al., 2018; Ahmed et al., 2015; Bertrand et al., 2015; Hu et al., 2010).

**Sulforaphane and mitochondria**

Mitochondria are known as the most important providers of energy to the cell through cellular ATP and metabolic intermediaries. This organelle participates in several signaling processes leading to ROS production. As an adaptation against stress, mitochondria are dynamic, and they can build extensive interorganelle networks among themselves and isolated fragments (Bhargava et al., 2017). Maintenance of mitochondrial mass is an essential homeostatic function within the cell to optimize cellular metabolic capacity (Briones-Herrera et al., 2020).

Mitochondrial biogenesis is responsible for the increase in mitochondrial mass, which is mediated by the nuclear respiration factors (Nrfs). Nrfs are a group of transcription factors, whose targets are subunits of the electron transport system proteins and the mitochondrial transcription factor A. Nrfs are activated by the peroxisome proliferator-activated receptor-γ co-activator 1-α (PGC-1α) (Palikaras et al., 2014). The reorganization of the mitochondrial dynamics (i.e., fusion and fission) is carried out by mitofusins 1 and 2 (MFN1 and MFN2) and the optic atrophy protein-1 (OPA1). Any associated mitochondrial spoilage is attended to via mitophagy, mediated by the protein p62, and followed by recruitment to the autophagosome by the light-chain protein 3 (LC3). In the autophagosome, mitochondria are hydrolyzed and their components are recycled (Briones-Herrera et al., 2020).

In this context, some studies have reported that SFN acts as a protector for mitochondrial function and proteins and enzymes involved in mitochondrial biogenesis. This is supported by data from in vitro studies, where SFN induced mitochondrial biogenesis and stabilized the Nrf2 (Oliveira et al., 2018; Negrette-Guzman et al., 2017; Zhang and Jiang, 2020). Mitochondrial biogenesis has also been reported to play an essential role in cancer cell death (Negrette-Guzman et al., 2017). Furthermore, the induced knockdown of the nuclear respiratory factor-1 (NRF1) attenuated the sulforaphane activity on the cancer cells (Negrette-Guzman et al., 2017). These data indicate that SFN can induce the Nrf2 directly or by a transient increase of ROS. Nrf2 is an inducer of Nrf1 expression. Nrf1 activation leads to the production of proteins involved in mitochondrial biogenesis, such as mitochondrial transcription factor-A (TFAM) (Negrette-Guzman et al, 2017).

Oliveira et al. (2018) have shown that the pretreatment with SFN on mitochondria from human neuroblastoma cells exposed to hydrogen peroxide, prevented the loss of viability in these cells, decreased lipid peroxidation, protein carbonylation, and protein nitration in mitochondrial membranes. Also, SFN increased the levels of cellular and mitochondrial glutathione, maintained the mitochondrial bioenergetics state and increased the expression of Nrf2. The authors conclude that SFN abrogates mitochondrial impairment in a Nrf2-dependent manner.

Another study in human umbilical vein endothelial cells observed protective effects of SFN against angiotensin II. It was observed that angiotensin II decreased human

umbilical vein endothelial cells viability and mitochondria membrane potential by impaired cytochrome c release, activation of caspase 3/9, and induction of ROS production. Also, there was increased cell apoptosis. SFN was able to decrease the oxidative stress and mitochondrial apoptosis induced by angiotensin II through ROS scavenger, induction of Nrf2 activation, and expression (Zhang and Jiang, 2020).

Carrasco-Pozo et al. (2017) have shown that SFN prevented cholesterol-induced alterations in the efficiency of mitochondrial respiration, improved ATP turnover, and averted the impairment of the electron flow at complexes I, II, and IV. Also, SFN decreased the activation of the NF-κB pathway and normalized the expression of pro-inflammatory cytokines. Additionally, SFN inhibited the decrease of sirtuin-1 expression and increased PGC-1α expression in pancreatic β- cells. Moreover, SFN increased the expression of Nrf2 with a consequent increase of antioxidant enzyme expression, and prevented lipid peroxidation induced by cholesterol.

In a study of bladder dysfunction in diabetic rats, 12.5 mg/kg/day of SFN increased nuclear Nrf-2/HO-1 expression, decreased bladder ROS amount, mitochondrial Bax translocation, cytochrome c release, and caspase 3 activity/poly-(ADP-ribose)-polymerase (PARP)/apoptosis (Lin et al., 2019). The authors suggested that SFN can preserve mitochondrial function via modulation of the Nrf2/HO-1 pathway, with a consequent decrease of ROS production from damaged mitochondria (Lin et al., 2019). Usually, the increase of ROS produced by the mitochondrial damage leads to apoptosis by translocation of cytosolic Bax to mitochondria and release of mitochondrial cytochrome c into the cytosol while increase of caspase 3 activity leads to consequent PARP cleavage and, finally, apoptosis (Chung et al., 2012).

In a study with a lipid metabolism model in HHL-5 cells treated with SFN; and rats with the non-alcoholic fatty liver disease treated with 20 mg/kg of sulforaphane three times per day for ten weeks, have shown that SFN alleviates the swelling of mitochondria and stimulates mitochondrial biogenesis. SFN induced the expression of NRF1 and TFAM. Also, SFN increased the levels of antioxidant enzymes (SOD, HO-1, GST, NQO-1, and GSH), reduced the production of ROS, and kept the mitochondrial membrane potential ATP, and increased PGC-1α expression (Lei et al., 2019).

**Sulforaphane and microbiota**

Trillions of bacteria colonizing the intestinal microbiota can metabolize food components that have not been digested by enzymes, showing the potentials of microbiota modulation. Among the food components known as essential modulators of the gut microbiota, dietary fibers, and phytonutrients stand out (Holscher et al., 2018; Kaczmarek et al., 2018).

The consumption of cruciferous vegetables can alter the composition of the gut microbiota and lead to the growth of specific bacteria, thereby increasing the production of microbial SFN (Li et al., 2009; Liu et al., 2017) as gut microbiota can metabolize glycosinolates (GLS) into SFN (Angelino et al 2015; Kaczmarek et al., 2018). The evidence for this mechanism has been supported by data indicating that the suppression of intestinal microbiota with antibiotics and mechanical cleaning of the intestine, made the conversion of GLS into SFN insignificant (Shapiro et al.,1998).

Humblot et al. (2005), in a pioneering study on the effect of brussels sprouts, inulin, and fermented milk on the diversity of the fecal microbiota of rats associated with the human microbiota, observed that the brussels sprouts led to the homogeneity of lactobacillus levels and the increase of levels of butyrate and acetate, showing that cruciferous vegetables are capable of altering the variety and metabolic functions of the intestinal microbiota of rats.

Liu et al (2017) observed that the consumption of broccoli altered the composition of the cecal microbiota in rats, especially the genera of the phylum Clostridiales (Blautia, Clostridium, Dorea, Ruminococcaceae, Oscillospira), and led to an increase in the hydrolysis of glucoraphanin (the main glycosinolate of broccoli) to bioactive isothiocyanate.

According to these observations, Wu et al (2018) evaluated the effects of broccoli ingestion on the hydrolytic action of myrosinase, the NQO1 enzyme, and on the diversity and composition of the intestinal microbiota of rats fed diets containing cooked and hydrolyzed broccoli. At the end of the study, they observed that the ingestion of broccoli for six weeks increased the activity of the hydrolytic action of myrosinase present in the colon and cecum and intensified the NQO1 activity of the colon mucosa. Besides, it strongly interfered in the bacterial composition of the rat microbiota; both cooked broccoli and hydrolyzed broccoli led to a significant increase in the Bacteroidetes and firmicutes phyla and significantly decreased Proteobacteria.

He et al (2018) in a study in 90 rats with bladder cancer induced by N-butyl-N- (4-hydroxybutyl) -nitrosamine found that rats treated with SFN showed a reduction of IL-6, secretory immunoglobulin A, and less dysbiosis of the normalized intestinal microbiota. They also observed a significant increase in Bacteroides fragilis, one of the most abundant species in the mucosa that acts on the appearance and evolution of the immune system, and an increase in Clostridium cluster I, a fundamental phylum in the degradation of carbohydrates and production of butyric acid. Furthermore, rats treated with SFN showed increased levels of butyric acid and isobutyric acid in the colon and positive regulation of the expression of junction proteins and GLP2, which led to the restoration of the lesion of the mucosal epithelium of the colon and cecum (He et al., 2018). It should be noted that butyric and isobutyric acids are essential sources of energy used by intestinal cells, help in the formation of the intestinal barrier, and in the development of the intestinal epithelium (Eareal et al., 2006; Wang et al.,2008).

Corroborating these findings, Xu et al. (2020), in a recent study mentioned above, evaluated the impact of glucoraphanin from broccoli seeds on the intestinal microbiota and lipid parameters of 36 mice with a high-fat diet during 8-week. In conclusion, the glucoraphanin present in the broccoli was able to reduce the Firmicutes / Bacteroidetes fraction, and there was a reduction in total cholesterol, triglycerides, and LDL-cholesterol. They also observed a reduction in the weight of the liver and visceral fat, a reduction in the concentrations of inflammatory markers, and the actions of the genes of FAS, in addition to a significant increase in the liver in the expression of the PPARα, CPT1, ACOX genes. Finally, they emphasized that glucoraphanin can be a potent adjuvant in preventing obesity and can be used as a functional food in the form of flour, made from the seeds of cruciferous vegetables.

In human studies, Li et al (2009) conducted a randomized, crossover, controlled study with 17 participants who received for 14 days a regular diet with a low content of phytochemicals and fibers (refined grains without fruits or vegetables) versus a diet rich in cruciferous vegetables (14g / kg of weight). At the end of the study, they observed that the ingestion of cruciferous vegetables was able to modify the bacterial composition of the intestinal microbiota, especially the phyla of Eubacterium hallii; Phascolarctobacterium faecium; Alistipes putredinis and Eggerthella spp, such bacteria

use the glycosinolate present in cruciferous vegetables as a metabolic substrate (Clavel et al., 2005; Li et al., 2009).

Kellingray et al. (2017) in a randomized crossover study on the relationship between consumption of a diet rich in Brassica vegetables and a decrease in sulfate-reducing bacteria, showed that consumption for two weeks of a diet rich in Brassica (consisted of 6 portions of 84 g of broccoli, six 84g portions of cauliflower and six 300g portions of a broccoli and sweet potato soup) interfered with the bacterial composition of the microbiota of 10 healthy adults. Specifically, in the Brassica rich diet group, there was a significant reduction in the proportions of five bacterial taxa (four members of the phylum Clostridiales and one member of the phylum Bacteroidales).

Kaczmarek et al. (2018) evidenced in a controlled and randomized study, that broccoli can be a crucial piece in the modulation of the intestinal microbiota and, consequently, health promotion. These authors analyzed the effects of the intervention of 200g of cooked broccoli and 20g of raw radish a day on the intestinal microbiota of 18 healthy individuals in a study consisting of two 18-day sessions, interspersed with a 24-day washout period. At the end of the analyses, they found that the intervention with broccoli was able to modulate the intestinal microbiota of these individuals, leading to a significant reduction in the phylum Firmicutes and a significant increase in the phylum Bacteroidetes, concerning the control (Kaczmarek et al., 2018).

**Sulforaphane in chronic kidney disease**

The loss of renal function is accompanied by several physiological, biochemical, and anatomical changes in the body of the CKD patient (Stevens et al., 2013). Chronic inflammation and oxidative stress are common findings and associate with the uremic phenotype in patients with CKD. These patients have a decreased Nrf2 expression and translocation to the nucleus, with a consequent decrease in the production of antioxidant enzymes and greater ROS production. The increased ROS concentration is one of the triggers for the overexpression of NF-κB, which generates greater production of pro-inflammatory cytokines. This whole process generates an addictive cycle between oxidative stress and inflammation in CKD (Pedruzzi et al., 2012; Pedruzzi et al., 2015). The presence of inflammation and oxidative stress worsens the underlying unregulated ageing process, mitochondrial dysfunction, and gut dysbiosis in CKD and

increases the risk of cardiovascular events and mortality (Dai et al 2020, Kooman et al 2014; Mafra et al., 2019; Glorieux et al, 2020).

Moreover, patients with CKD have a gut microbiota imbalance, called uremic dysbiosis, that leads to overproduction of bacteria species responsible for the production of uremic toxins such as indoxyl sulfate (IS), p-cresyl sulfate (pCS), and indole-3 acetic acid (IAA) (Cigarran Guldris et al., 2017). The accumulation of these uremic toxins is linked with changes in the gut barrier, contributing to an increase of LPS production and of local and systemic inflammation and oxidative stress (Mafra & Fouque, 2015).

Some studies have shown that mitochondrial dysfunction is linked to CKD pathogenesis (Mafra et al., 2018; Fontecha-Barriuso et al., 2020; Bai et al., 2019). Therefore, in CKD, there is an overproduction of ROS, a decrease in ATP generation, loss of inner mitochondrial membrane potential, cytochrome C release, and PGC-1α (Enoki et al., 2017). All these factors together lead to cell apoptosis or cell injury and DNA mitochondrial damage, which stimulates the activation of Toll-like receptor (TLR) and inflammation in CKD (Galvan et al. 2017; Duann and Lin et al., 2017). Both acute kidney injury (AKI) and CKD associate with defects in mitochondrial biogenesis, demonstrated by the low PGC-1α levels, mitochondrial transcription factor A (TFAM), and Mfn2 (Fontecha-Barriuso et al., 2020; Su et al., 2017). Mitochondrial dysfunction is linked with CKD progression, muscle dysfunction, and sarcopenia in CKD (Gamboa et al., 2016; Enoki et al., 2017; Bai et al., 2019).

Additionally, in a recent review, Mafra et al. (2019) have described that in CKD, there are several epigenetic alterations linked with the uremic state. These include hypermethylation of the RAS protein activator like 1 (Rasal1) gene induced by the overproduction and retention of uremic toxins. This leads to kidney fibrosis and suppression of Klotho activity, which is a significant regulator of anti-ageing defenses (Kato et al., 2019; Mafra et al., 2019). Another factor in the epigenetic changes in CKD is the MTHFR gene, which leads to the production of methyl radical synthesis and provides methyl groups for global genomic methylation. This factor is associated with an increased cardiovascular disease risk and an increase in biological age (Mafra et al., 2019). In another literature review, Kato et al. (2019) have described the links between

CpG DNA methylation and CKD, where the DNA methylation in the glomerular and proximal tubular epithelial cell leads to dysregulation of functions.

Currently, studies using dietary components and their potent bioactive compounds to improve the alterations found in CKD patients are critical. Several studies have shown that bioactive compounds such as curcumin, prebiotics, and Brazilian nuts, among others, can be an adjuvant therapy to the CKD patient (Cardozo et al., 2016; Esgalhado et al., 2018; Mafra et al., 2019; Alvarenga et al., 2020a; Alvarenga et al., 2020b). As described above, SFN has been shown to be a promising nutritional therapy in several diseases. As far as we know, there are no studies about the SFN in CKD. However, some in vivo and in vitro studies have investigated the effects of this compound in the kidney and renal cells, as a renoprotective agent in CKD and AKI (Table 3).

Studies have shown that SNF can prevent cell death and renal and mitochondrial damage induced by cisplatin treatment (Guerrero-Beltrán et al, 2010a; Guerrero-Beltrán et al, 2010b). Also, SFN improves the nuclear translocation of Nrf2 in the cells, attenuating processes leading to renal dysfunction, structural damage, oxidative/nitrosative stress, and glutathione depletion, and decrease the activity of catalase, glutathione peroxidase, and glutathione-S-transferase (Guerrero-Beltrán et al, 2010a; Kim et al., 2015). Additionally, cisplatin-induced nephropathy leads to the activation of inflammation in the kidneys. The pretreatment with SFN can prevent renal injury and attenuate activation of inflammation pathway signaling (Guerrero-Beltrán et al, 2012).

Another study demonstrated in vitro and in vivo that Nrf2 plays a protective role against intravascular hemolysis-mediated AKI caused by hemoglobin (Hb)/heme-induced renal damage. SFN was able to activate Nrf2 expression, which led to protection against Hb toxicity in mice and cultured tubular epithelial cells, leading to amelioration of kidney injury, cell stress and death, and improvement in renal function (Rubio-Navarro et al., 2019). Some animal studies and in vitro studies in diabetic nephropathy with chronic renal dysfunction have shown that SFN can decrease the production of ROS and inflammation (IL-6 and caspase 3) in kidney tissues by activation of Nrf2-HO-1/NQO-1 and reduction in the activity of the glycogen synthase kinase 3beta (GSK3β) signaling pathway, with the improvement of renal function, prevention of

fibrosis and tubular atrophy (Shang et al., 2015; Daoyuan Lv et al., 2018; Shin et al., 2019; Khaleel et al., 2019; Kim et al., 2019).

In an animal model of renal injury, SFN increased Nrf2 pathway, reduced inflammation and apoptotic markers, and improved renal function. Animals receiving SFN also showed a significant increase in GSH and SOD activities, with a decrease in MDA levels in renal tissues (Shokeir et al, 2015; Zhao et al., 2018). Renal protection of SFN was deleted in diabetic Nrf2-null mice, confirming the central role of Nrf2 in the protection of SFN (Wu et al, 2015; Zheng et al 2011). Current evidence suggest that Nrf2 renal expression plays an essential role in SFN action to prevent renal damage and that the most critical effect of SFN on chemical or ischemia-induced renal damage is exerted by the induction of NRF2 (Dadras and Khoshjou, 2013; Cui et al., 2017; Choi et al., 2014).

SFN reduces ROS production and increases cytoprotective enzymes, quinone oxidoreductase 1 (NQO1), and γ-glutamyl cysteine ligase (γGCL). In maleic acid (MA)-induced nephropathy, SFN can avoid the decrease in fatty acid-related oxygen consumption rate, oxidative phosphorylation on proximal kidney tubule, and mitochondrial membrane potential, with consequent better control of respiratory index and decreased mitochondrial production of hydrogen peroxide (Briones-Herrera et al., 2018).

Cekauskas et al. (2013) have shown that SFN can decrease kidney injury in transplanted rats. SFN decreased reperfusion damage in the kidney and decreased blood urea nitrogen and creatinine serum levels. Moreover, mitochondrial microstructure was preserved and there was an increase in SOD 2 gene expression. Gigliotti et al. (2019) showed that supplementation with cruciferous broccoli powder improved kidney injury in a glutathione S-transferase m-1 (GSTM1) knockout mice line CKD model.

There are so far no clinical studies that explore the effects of SFN in patients with CKD (Table 2). The African American Study of Kidney Disease and Hypertension (AASK Trial) and the Atherosclerosis Risk in Communities (ARIC) studies suggest that deletion of GSTM1 (part of the superfamily of phase 2 antioxidant enzymes) is linked with CKD progression (Gigliotti et al., 2019). This could provide a mechanism whereby high vs. low consumption of cruciferous vegetables are associated with fewer kidney failure events and suggest an effect of protective metabolites from dietary intake when there is

GSTM1 deficiency (Tin et al., 2017). SFN can activate the Nrf2 signaling pathway and induce phase 2 detoxification enzymes indirectly (Gigliotti et al., 2019).

In toto, SFN could act in several pathways in renal injuries, especially in ameliorating inflammation and oxidative stress (**Fig 3**). SFN may represent an alternative strategy for improving the prognosis of patients with CKD by preventing progression of CKD and targeting common complications such as cardiovascular disease in these patient population. More studies on the effects of SFN in CKD are warranted.

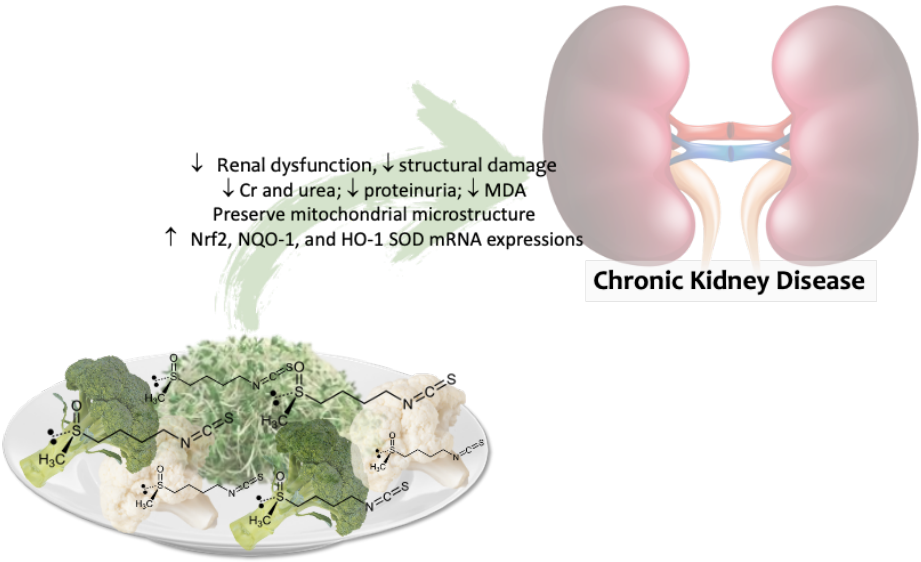


**Fig 3: Possible effects of sulforaphane in chronic kidney disease.** Sulforaphane seems to prevent structural damage in the kidney and reduce renal dysfunction including proteinuria by mitigating inflammation, increasing Nrf2, NQO-1, HO-1 SOD mRNA expressions and reducing oxidative stress.

## Summary and Conclusions

SFN is an important bioactive compound present in cruciferous vegetables. Throughout scientific studies in different diseases, several beneficial functions of the SFN have been observed regarding chronic non-communicable diseases. An extensive literature shows that the main route of action of SFN is by its antioxidant potential and activation of the transcription factor Nrf2 that has a key role in the antioxidant response. Also, actions of SFN modulate the epigenetic landscape, protect against mitochondrial damage, and improve the gut microbiota, and suggest a promising role of SFN for the control of several diseases.

In this context, CKD is characterized by several changes, from inflammation and oxidative stress to epigenetic changes due to disease. Although there are no clinical studies demonstrating an effect of SFN in these patients, the studies in other disease areas presented here suggest that SFN could be a promising adjunctive therapy for CKD. The SFN proved to be able to improve renal function, decrease inflammatory markers, and mitochondrial damage. In addition to beneficial epigenetic changes in various models of kidney injury. Clinical studies with CKD patients and SFN should be encouraged in order to promote improvement in patients' quality of life.

**References**


Alvarenga L, Cardozo LFMF, Borges NA, Lindholm B, Stenvinkel P, Shiels PG, Fouque D, Mafra D. Can nutritional interventions modulate the activation of the NLRP3 inflammasome in chronic kidney disease? Food Research International 136 (2020) 109306.

Angeloni C, Leoncini E, Malaguti M, Angelini S, Hrelia P, Hrelia S. Modulation of phase II enzymes by sulforaphane: Implications for its cardioprotective potential. *J. Agric. Food Chem.* 2009, 57, 5615–5622.

Antunes F, Han D. Redox regulation of NF-kappaB: from basic to clin- ical research. Antioxid Redox Signal. 2009;11:2055-2056.

Atwell LL, Hsu A, Won CP et al. Absorption and chemopreventive targets of sulforaphane in humans following consumption of broccoli sprouts or a myrosinase-treated broccoli sprout extract. *Mol. Nutr. Food Res.* 2015, 59, 424–433.

Axelsson AS, Tubbs E, Mecham B, S. Chacko, Nenonen HA, Tang Y, et al. Sulforaphane reduces hepatic glucose production and improves glucose control in patients with type 2 diabetes. Sci. Transl. Med., 9 (2017)

Bai Y, Wang X, Zhao S, Ma C, Cui J, Zheng Y. Sulforaphane Protects against Cardiovascular Disease via Nrf2 Activation. Oxid Med Cell Longev. 2015;2015:407580.

Bogaards, J.J.; Verhagen, H.; Willems, M.I.; van Poppel, G.; van Bladeren, P.J. Consumption of Brussels sprouts results in elevated alpha-class glutathione S-transferase levels in human blood plasma. *Carcinogenesis* **1994**, *15*, 1073–1075.

Cheung, K. L. & Kong, A. N. Molecular targets of dietary phenethyl isothiocyanate and sulforaphane for cancer chemoprevention. *AAPS J.* **12**, 87–97 (2010).

Cieslik E, Leszczynska T, Filipiak-Florkiewicz A, Sikora E, Pisulewski PM: Effects of some technological processes on glucosinolate contents in cruciferous vegetables. Food Chem 2007; 105:976–981.

Clarke, J. D., Dashwood, R. H. & Ho, E. Multi-targeted prevention of cancer by sulforaphane. *Cancer Lett.* **269**, 291–304 (2008).

Cramer JM & Jeffery EH (2011) Sulforaphane Absorption and Excretion Following Ingestion of a Semi-Purified Broccoli Powder Rich in Glucoraphanin and Broccoli Sprouts in Healthy Men, Nutrition and Cancer, 63:2, 196-201

Cramer JM, Teran-Garcia M, Jeffery EH. Enhancing sulforaphane absorption and excretion in healthy men through the combined consumption of fresh broccoli sprouts and a glucoraphanin-rich powder. British Journal of Nutrition (2012), 107, 1333–1338.

Rahul Checker, Lokesh Gambhir, Maikho Thoh, Deepak Sharma, Santosh K. Sandur . Sulforaphane, a naturally occurring isothiocyanate, exhibits anti-inflammatory effects by targeting GSK3β/Nrf-2 and NF-κB pathways in T cells. Journal of Functional Foods 19 (2015) 426–438

Cui W, Bai Y, Miao X, et al. Prevention of diabetic nephropathy by sulforaphane: possible role of NRF2 upregulation and activation. Oxid Med Cell Longev. 2012;2012:821936.

Dai L, Schurgers LJ, Shiels PG, Stenvinkel P. Early vascular ageing in chronic kidney disease: impact of inflammation, vitamin K, senescence and genomic damage. Nephrol Dial Transplant 2020;35:31–7.

Dinkova-Kostova, A.T.; Fahey, J.W.; Kostov, R.V.; Kensler, T.W. KEAP1 and Done? Targeting the NRF2 Pathway with Sulforaphane. *Trends. Food. Sci. Technol.* **2017**, *69*, 257–269.

Greaney AJ, Maier NK, Leppla SH, Moayeri M. Sulforaphane inhibits multiple inflammasomes through an Nrf2-independent mechanism. J Leukoc Biol. 2016 Jan; 99(1): 189–199.

Hanlon H, Coldham N, Gielbert A, Sauer MJ, Ioannides C. Repeated intake of broccoli does not lead to higher plasma levels of sulforaphane in human volunteers. Cancer Lett., 284 (2009), pp. 15-20.

Giacoppo S, Galuppo M, Iori R, De Nicola GR, Cassata G, Bramanti P, Mazzon E. Protective role of (RS)-glucoraphanin bioactivated with myrosinase in an experimental model of multiple sclerosis. CNS Neurosci Ther 2013;19:577–84

Hennig P, Fenini G, Di Filippo M, Beer HD. Electrophiles Against (Skin) Diseases: More Than Nrf2. *Biomolecules*. 2020;10(2):271.

Heiss, E., Herhaus, C., Klimo, K., Bartsch, H. & Gerhauser, C. Nuclear factor kappa B is a molecular target for sulforaphane- mediated anti-inflammatory mechanisms. *J. Biol. Chem.* **276**, 32008–32015 (2001).

Houghton CA. Sulforaphane: Its "Coming of Age" as a Clinically Relevant Nutraceutical in the Prevention and Treatment of Chronic Disease. Oxid Med Cell Longev. 2019, 2716870 2019.

Hyun TK. A Recent Overview on Sulforaphane as a Dietary Epigenetic Modulator. *Excli Journal 2020;19:131-134.*

Huang CS, Lin AH, Liu CT, et al. Isothiocyanates protect against oxidized LDL-induced endothelial dysfunction by upregulating Nrf2-dependent antioxidation and suppressing NFκB activation. *Mol Nutr Food Res*. 2013;57(11):1918-1930.

JI, Y.; MORRIS, M. E. Determination of phenethyl isothiocyanate in human plasma and urine by ammonia derivatization and liquid chromatography-tandem mass spectrometry. Anal Biochem, San Diego, v. 323, n. 1, p. 39-47, Dec, 2003.

Jin W, Wang H, Yan W, Xu L, Wang X, Zhao X, et al. Disruption of Nrf2 enhances upregulation of nuclear factor-kappaB activity, proinflammatory cytokines, and intercellular adhesion molecule-1 in the brain after traumatic brain injury, Mediators of Inflammation 2008 (2008) 1e7.

Kaspar JW, Niture SK, Jaiswal AK. Nrf2:INrf2 (Keap1) signaling in oxidative stress, Free Radic. Biol. Med. 47 (2009) 1304e1309.

Kensler, T.W.; Egner, P.A.; Agyeman, A.S.; Visvanathan, K.; Groopman, J.D.; Chen, J.G.; Chen, T.Y.; Fahey, J.W.; Talalay, P. Keap1-nrf2 signaling: A target for cancer prevention by sulforaphane. *Top. Curr. Chem.* **2013**, *329*, 163–177

KIM, Y. J. et al. Pharmacokinetics, Tissue Distribution, and Anti-Lipogenic/Adipogenic Effects of Allyl-Isothiocyanate Metabolites. PLoS One, San Francisco, v. 10, n. 8, p. e0132151, 2015.

Kim JH, Kim KM, Jeong JU, Shin JH, Shin JM, Bang KT. Nrf2-Heme oxygenase-1 modulates autophagy and inhibits apoptosis triggered by elevated glucose levels in renal tubule cells. *Kidney Res Clin Pract*. 2019;38(3):318-325. doi:10.23876/j.krcp.18.0152

J. Kim, Y.N. Cha, Y.J. Surh, A protective role of nuclear factor-erythroid 2- related factor-2 (Nrf2) in inflammatory disorders, Mutation Research 690 (2010) 12e23.

Kobayashi EH, Suzuki T, Funayama R. Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription. Nat Commun. 2016; 7: 11624.

Kooman JP, Kotanko P, Schols AMWJ, Shiels PG, Stenvinkel P. Chronic kidney disease and premature ageing. Nat Rev Nephrol 2014;10:732–42. https://doi.org/10.1038/nrneph.2014.185.

Klomparens EA, Ding Y. The neuroprotective mechanisms and effects of sulforaphane. Brain Circ. 2019 Apr-Jun; 5(2): 74–83.

Lee S, Hu L. Nrf2 activation through the inhibition of Keap1–Nrf2 protein–protein interaction. Medicinal Chemistry Research (2020) 29:846–867.

Leoncini E, Malaguti M, Angeloni C, et al. Cruciferous Vegetable Phytochemical Sulforaphane Affects Phase II Enzyme Expression and Activity in Rat Cardiomyocytes Through Modulation of Akt Signaling Pathway J Food Sci. 2011 Sep;76(7):H175-81.

Liu, H., Dinkova-Kostova, A. T. & Talalay, P. Coordinate regulation of enzyme markers for inflammation and for protection against oxidants and electrophiles. *Proc. Natl. Acad. Sci. U. S. A.* **105**, 15926–15931 (2008).

Liu H, Zimmerman AW, Singh K, et al. Biomarker Exploration in Human Peripheral Blood Mononuclear Cells for Monitoring Sulforaphane Treatment Responses in Autism Spectrum Disorder. Sci Rep 2020 Apr 2;10(1):5822.

Lu Y, Xinyi Pang X, Yang T. Microwave cooking increases sulforaphane level in broccoli. Food Sci Nutr. 2020 Apr; 8(4): 2052–2058.

Liu Y, Liu P, Wang Q, Sun F, Liu F. Sulforaphane Attenuates $H_2O_2$-induced Oxidant Stress in Human Trabecular Meshwork Cells (HTMCs) via the Phosphatidylinositol 3-Kinase (PI3K)/Serine/Threonine Kinase (Akt)-Mediated Factor-E2-Related Factor 2 (Nrf2) Signaling Activation. *Med Sci Monit*. 2019;25:811-818. Published 2019 Jan 28. doi:10.12659/MSM.913849

Ma, Q. Role of Nrf2 in oxidative stress and toxicity. *Annu. Rev. Pharmacol. Toxicol.* **2013**, *53*, 401–426.

Martins, T., Colaço, B., Venâncio, C., Pires, M. J., Oliveira, P. A., Rosa, E., & Antunes, L. M. (2018). *Potential effects of sulforaphane to fight obesity. Journal of the Science of Food and Agriculture.* J Sci Food Agric. 2018 Jun;98(8):2837-2844.

McMahon M, KItoh K, Yamamoto M, Hayes JD, "Keap1- dependent proteasomal degradation of transcription factor Nrf2 contributes to the negative regulation of antioxidant response element-driven gene expression," *The Journal of Bio- logical Chemistry*, vol. 278, no. 24, pp. 21592–21600, 2003.

Navarro SL, Shwarz Y, Song X et al. Cruciferous Vegetables Have Variable Effects on Biomarkers of Systemic Inflammation in a Randomized Controlled Trial in Healthy Young Adults J Nutr 2014 Nov;144(11):1850-7.

Nakagawa K, Umeda T, Higuchi O, Tsuzuki T, Suzuki T, Miyazawa T (2006) Evaporative light-scattering analysis of sulforaphane in broccoli samples: quality of broccoli products regarding sulforaphane contents. J Agric Food Chem 54(7):2479–2483

Nezu M, Suzuki NRoles of Nrf2 in Protecting the Kidney from Oxidative DamageInt J Mol Sci. 2020 Apr; 21(8): 2951.

OLIVIERO, T.; VERKERK, R.; DEKKER, M. Isothiocyanates from Brassica Vegetables-Effects of Processing, Cooking, Mastication, and Digestion. Mol Nutr Food Res, Weinheim, v. 62, n. 18, p. e1701069, Sep, 2018.

Paunkov, A.; Chartoumpekis, D.V.; Ziros, P.G.; Sykiotis, G.P. A bibliometric review of the Keap1/Nrf2 pathway and its related antioxidant compounds. *Antioxidants* 2019, *8, 353.*

Pedruzzi LM, Stockler-Pinto MB, Leite M Jr, Mafra D (2012) Nrf2-keap1 system versus NF-kappaB: the good and the evil in chronic kidney disease? Biochimie 94(12):2461–2466.

Riboli E., Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am. J. Clin. Nutr. 2003;78:559–569.

Shapiro, T.A.; Fahey, J.W.; Wade, K.L.; Stephenson, K.K.; Talalay, P. Human metabolism and excretion of cancer chemoprotective glucosinolates and isothiocyanates of cruciferous vegetables. *Cancer Epidemiol. Biomark. Prev.* 1998, *7*, 1091–1100.

Vanduchova A, Anzenbacher P, Anzenbacherova E. Isothiocyanate from broccoli, sulforaphane, and its properties. J Med Food 2019;22:121-6.

Vermeulen M, Klopping-ketelaars IWAA, Berg RVD, Vaes WHJ. Bioavailability and kinetics of sulforaphane in humans after consumption of cooked versus raw broccoli. J. Agric. Food chem. 2008, 56, 10505–10509.

Wang X., Ouyang Y., Liu J., Zhu M., Zhao G., Bao W., Hu F.B. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: Systematic review and dose-response meta-analysis of prospective cohort studies. BMJ. 2014;349:g4490.

Yagishita Y, Fahey JW, Dinkova-Kostova AT, Kensler TW. Broccoli or Sulforaphane: Is It the Source or Dose That Matters? Molecules, 24 (19) 2019 Oct 6

Wu H, Kong L, Cheng Y, et al. Metallothionein plays a prominent role in the prevention of diabetic nephropathy by sulforaphane via up-regulation of Nrf2. Free Radic Biol Med. 2015;89:431-442.

Zhen-xin GU, Qiang-hui GUO, Ying-juan GU. Factors Influencing Glucoraphanin and Sulforaphane Formation in Brassica Plants: A Review. Journal of Integrative Agriculture 11(11), 2012, 1804-1816.

Yang, G., Yeon, S.H., Lee, H.E., Kang, H.C., Cho, Y.Y., Lee, H.S., et al. (2018). Suppression of NLRP3 inflammasome by oral treatment with sulforaphane alleviates acute gouty inflammation. *Rheumatology (Oxford), 57*, 727-736.

Van Eylen D, Oey I, Hendrickx M, van Loey A. 2007. Kinetics of the stability of broccoli (*Brassica oleracea cv. Italica*) myrosinase and isothiocyanates in broccoli juice during pressure/temperature treatments. *Journal of Agricultural and Food Chemistry*, **55**, 2163-2170.

Shapiro TA, Fahey JW, Dinkova Kostova AT, Holtzclaw WD, Stephenson KK, Wade KL, et al. Safety, tolerance, and metabolism of broccoli sprout glucosinolates and isothiocyanates: a clinical phase I study. Nutr. Cancer, 55 (2006), pp. 53-62

Shokeir AA, Barakat N, Hussein AM, et al. Activation of Nrf2 by ischemic preconditioning and sulforaphane in renal ischemia/reperfusion injury: a comparative experimental study. Physiol Res. 2015;64:313-323.

Song L, Thornalley PJ. Effect of storage, processing and cooking on glucosinolate content of Brassica vegetables. Food and Chemical Toxicology 45 (2007) 216–224.

Sreerama, L.; Hedge, M.W.; Sladek, N.E. Identification of a class 3 aldehyde dehydrogenase in human saliva and increased levels of this enzyme, glutathione S-transferases, and DT-diaphorase in the saliva of subjects who continually ingest large quantities of coffee or broccoli. *Clin. Cancer Res.* **1995**, *1*, 1153–1163.

Suzuki T, Motohashi H, Yamamoto M (2013) Toward clinical application of the Keap1–Nrf2 pathway. Trends Pharm Sci 34:340–346.

Zheng H, Whitman SA, Wu W, et al. Therapeutic potential of Nrf2 activators in streptozotocin-induced diabetic nephropathy. Diabetes. 2011;60:3055-3066.

Takaya K, Suzuki T, Motohashi H, Onodera K, Satomi S, Kensler TW, Yamamoto M (2012) Validation of the multiple sensor mechanism of the Keap1-Nrf2 system. Free Radic Biol Med 53(4):817–827.

Townsend, B. E. & Johnson, R. W. Sulforaphane induces Nrf2 target genes and attenuates inflammatory gene expression in microglia from brain of young adult and aged mice. *Exp. Gerontol.* **73**, 42–48 (2016).

Ushida YSH, Yanaka A. Low dose of the sulforaphane precursor glucoraphanin as a dietary supplement induces chemoprotective enzymes in humans. *Food Nutr. Sci.* 2015, 6, 62147.

Bose C, Awasthi S, Sharma R, Beneš H, Hauer-Jensen M, Boerma M, Singh SP. Sulforaphane potentiates anticancer effects of doxorubicin and attenuates its cardiotoxicity in a breast cancer model. PLoS One. 2018;13(3).

Braicu C, et al. Nutrigenomics in cancer: Revisiting the effects of natural compounds. Semin Cancer Biol. 2017;46:84-106.

Calcabrini C, Maffei F, Turrini E, Fimognar C. Sulforaphane Potentiates Anticancer Effects of Doxorubicin and Cisplatin and Mitigates Their Toxic Effects. Front Pharmacol. 2020;11:567.

Chen L , Chana LS, Lunga HL, Yip TTC, Ngan RKC, Wonga JWC, Lod KW, Nge WT, Leef AWM, Tsaog GSW, Lungf ML, Mak NK. Crucifera sulforaphane (SFN) inhibits the growth of nasopharyngeal carcinoma through DNA methyltransferase 1 (DNMT1)/Wnt inhibitory factor 1 (WIF1) axis. Phytomedicine. 2019;63:153058.

Choi S, Lew KL, Xiao H, et al.: D,L-Sulforaphane-induced cell death in human prostate cancer cells is regulated by inhibitor of apoptosis family proteins and Apaf-1. Carcinogenesis 2007;28: 151–162.

Choi BH, Kang KS, Kwak MK. Effect of redox modulating NRF2 activators on chronic kidney disease. Molecules. 2014;19(8):12727-12759.

Dinkova-Kostova AT, Jenkins SN, Fahey JW, Ye L, Wehage SL, Liby KT, Stephenson KK, Wade KL, Talalay P. Protection Against UV-light-induced Skin Carcinogenesis in SKH-1 High-Risk Mice by Sulforaphane-Containing Broccoli Sprout Extracts. Cancer Let. 2006;240(2):243-52.

Fimognari C, Nusse M, Cesari R, et al.: Growth inhibition, cell cycle arrest and apoptosis in human T-cell leukemia by the isothiocyanate sulforaphane. Carcinogenesis 2002;23:581–586

Gamet-Payrastre L, Li P, Lumeau S, et al.: Sulforaphane, a naturally occurring isothiocyanate, induces cell cycle arrest and apoptosis in HT29 human colon cancer cells. Cancer Res 2000; 60:1426–1433.

Glorieux G, Gryp T, Perna A. Gut-Derived Metabolites and Their Role in Immune Dysfunction in Chronic Kidney Disease. Toxins (Basel), 2020 Apr 11;12(4):245.

Gupta P, Kim B, Kim SH, Srivastava SK: Molecular targets of isothiocyanates in cancer: Recent advances. Mol Nutr Food Res 2014;58:1685–1707.

Kallifatidis G, Labsch S, Rausch V, Mattern J, Gladkich J, Moldenhauer G, Büchler MW, Salnikov AV, Herr I. O sulforafano aumenta a citotoxicidade mediada por medicamentos para células-tronco cancerígenas do pâncreas e próstata. Mol Ther. 2011; 19 (1): 188-195.

Lan H, Yuan H, Lin C. Sulforaphane Induces p53-deficient SW480 Cell Apoptosis via the ROS-MAPK Signaling Pathway. Mol Med Rep. 2017;16(5):7796-7804.

Langouet S, Furge LL, Kerriguy N, Nakamura K, Guillouzo A, Guengerich FP. Inibição das enzimas do citocromo P450 humano por 1,2-ditiol-3-tiona, oltipraz e seus derivados e sulforafano. Chem Res Toxicol. 2000; 13 (4): 245–252.

Lewinska A, Adamczyk-Grochala J, Deregowska A, Wnuk M. Sulforaphane-Induced Cell Cycle Arrest and Senescence are accompanied by DNA Hypomethylation and Changes in microRNA Profile in Breast Cancer Cells. Theranostics. 2017;7(14):3461–3477.

Lozanovski VJ, Houben P, Hinz U, Hackert T, Herr I, Schemmer P. Pilot study evaluating broccoli sprouts in advanced pancreatic cancer (POUDER trial) - study protocol for a randomized controlled trial. Trials. 2014;15:204.

Mcguire S. World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. Adv Nutr, Rockville. 2016;7(2):418-9.

Mielczarek L, Krug P, Mazur M, Milczarek M, Chilmonczyk Z, Wiktorska K. In the triple-negative breast cancer MDA-MB-231 cell line, sulforaphane enhances the intracellular accumulation and anticancer action of doxorubicin encapsulated in liposomes. Int J Pharm. 2019;558:311-318.

Mokhtari BR, et al. The role of Sulforaphane in cancer chemoprevention and health benefits: a mini-review. J Cell Commun Signal, Dordrecht. 2018;(12)1:91-101.

Pham NA, Jacobberger JW, Schimmer AD, et al.: The dietary isothiocyanate sulforaphane targets pathways of apoptosis, cell cycle arrest, and oxidative stress in human pancreatic cancer cells and inhibits tumor growth in severe combined immunodeficient mice. Mol Cancer Ther 2004;3:1239–1248.

Priya DKD, Gayathri R, Sakthisekaran D. Role of sulforaphane in the anti-initiating mechanism of lung carcinogenesis in vivo by modulating the metabolic activation and detoxification of benzo(a)pyrene. Biomedicine & Pharmacotherapy. 2011;65:9–16.

Remely M, et al. Therapeutic perspectives of epigenetically active nutrients. Br J Pharmacol. 2015;172(11):2756-68.

Santana-Gálvez J, Villela-Castrejón J, Serna-Saldívar SO, Cisneros-Zevallos L, Jacobo-Velázquez DA. Synergistic Combinations of Curcumin, Sulforaphane, and Dihydrocaffeic Acid against Human Colon Cancer Cells. Int. J. Mol. Sci. 2020;21:3108.

Santos PWS. Influência do sulforafano, um inibidor de histonas desacetilases, sobre a instabilidade genômica e mecanismos epigenéticos em linhagens celulares humanas [Dissertação]. São Paulo, Faculdade de Ciências Farmacêuticas de Ribeirão Preto/USP. 2019.

Tomlinson L, Lu ZQ, Bentley RA, Colley HE, Murdoch C, Webb SD, Cross MJ, Copple IM, Sharma P. Attenuation of doxorubicin-induced cardiotoxicity in a human in vitro cardiac model by the induction of the NRF-2 pathway. Biomed Pharmacother. 2019;112():108637.

Vanduchova A, Anzenbacher P, Anzenbacherova E. Isothiocyanate from Broccoli, Sulforaphane, and Its Properties. J Med Food. 2018:1–6.

Volarevic V, Djokovic B, Jankovic MG, Harrell CR, Fellabaum C, Djonov V, Arsenijevic N. Molecular mechanisms of cisplatin-induced nephrotoxicity: a balance on the knife edge between renoprotection and tumor toxicity. J Biomed Sci. 2019;26(1):25.

Xu C, Huang M, Shen G, Yuan X, Lin W, Khor TO, Conney AH, Kong TA. Inhibition of 7,12-Dimethylbenz(a)anthracene-Induced Skin Tumorigenesis in C57BL/6 Mice by Sulforaphane Is Mediated by Nuclear Factor E2–Related Factor 2. Cancer Res. 2006;66(16):8293-6.

Zhang Y. et al. Anticarcinogenic activities of sulforaphane and structurally related synthetic norbornyl isothiocyanates. Proc Natl Acad Sci. 1994;91(8):3147-50.

Angelino D, Dosz EB, Sun J, Hoeflinger JL, Van Tassell ML, Chen P, et al. Myrosinasedependent and -independent formation and control of isothiocyanate products of glucosinolate hydrolysis. Front Plant Sci 2015;6:831.

Brabban AD, Edwards C. Isolamento de microrganismos degradantes de glucosinolato e seu potencial para reduzir o conteúdo de glucosinolato do rapemeal. FEMS Microbiol Lett. 1994; 119:83–8.

Cheng DL, Hashimoto K, Uda Y. In vitro digestion of sinigrin and glucotropaeolin by single strains of Bifidobacterium and identification of the digestive products. Food Chem Toxicol. 2004 Mar;42(3):351-7.

Elfoul L, Rabot S, Khelifa N, Quinsac A, Duguay A, Rimbault A. Formation of allyl isothiocyanate from sinigrin in the digestive tract of rats monoassociated with a human colonic strain of Bacteroides thetaiotaomicron. FEMS Microbiol Lett. 2001 Apr 1;197(1):99-103.

He C, Huang L, Lei P, Liu X, Li B, Shan Y. Sulforaphane Normalizes Intestinal Flora and Enhances Gut Barrier in Mice with BBN-Induced Bladder Cancer. Mol Nutr Food Res. 2018;62(24).

Holscher HD, Guetterman HM, Swanson KS, An R, Matthan NR, Lichtenstein AH, et al. Walnut consumption alters the gastrointestinal microbiota, microbial-derived secondary bile acids, and health markers in healthy adults: a randomized controlled trial. J Nutr 2018.

Holscher HD, Taylor AM, Swanson KS, Novotny JA, Baer DJ. Almond consumption and processing affects the composition of the gastrointestinal microbiota of healthy adult men and women: a randomized controlled trial. Nutrients 2018;10:126.

Humblot C, Bruneau A, Sutren M, Lhoste EF, Dore J, Andrieux C, Rabot S. Brussels sprouts, inulin and fermented milk alter the faecal microbiota of human microbiota-associated rats as shown by PCR-temporal temperature gradient gel electrophoresis using universal, Lactobacillus and Bifidobacterium 16S rRNA gene primers. British Journal of Nutrition. 2005;93:677–684.

Kaczmarek JL, Liu X, Charron CS, Novotny JA, Jeffery EH, Seifried HE, Ross SA, Miller MJ, Swanson KS, Holscher DH. Broccoli consumption affects the human gastrointestinal microbiota. JNB. 2018.

Kellingray L, Tapp HS, Saha S, Doleman JF, Narbad A, Mithen RF. Consumption of a diet rich in Brassica vegetables is associated with a reduced abundance of sulphate-reducing bacteria: A randomised crossover study. Mol. Nutr. Food Reyes. 61, 9, 2017.

Li F, Hullar MAJ, Schwarz Y, Lampe JW. Human Gut Bacterial Communities Are Altered by Addition of Cruciferous Vegetables to a Controlled Fruit- and Vegetable-Free Diet. J Nutr. 2009;139(9):1685–1691.

Liu X, Wang Y, Hoeflinger JL, Neme BP, Jeffery EH, Miller MJ. Dietary Broccoli Alters Rat Cecal Microbiota to Improve Glucoraphanin Hydrolysis to Bioactive Isothiocyanates. Nutrients. 2017 Mar; 9(3): 262.

Llanos Palop M, Smiths JP, Brink BT. Degradation of sinigrin by Lactobacillus agilis strain R16. Int J Food Microbiol. 1995 Jul; 26(2):219-29.

Mullaney JA, Kelly WJ, McGhie TK, Ansell J, Heyes JA. Lactic acid bacteria convert glucosinolates to nitriles efficiently yet differently from enterobacteriaceae. J Agric Food Chem. 2013 Mar 27; 61(12):3039-46.

Rabot S, Guerin C, Nugon-Boudon L, Szylit O. Degradação de glucosinolato por estirpes bacterianas isoladas de uma microflora intestinal humana. Anais do 9° Congresso Internacional de Colza, organizado pelo GCIRC (Grupo Internacional de Pesquisa em Pesquisa sobre Colza. Em inglês: Grupo Internacional de Pesquisa sobre Colza); 1995. 4 a 7 de julho; Cambridge, Reino Unido.

Wu Y, Shena Y, Zhua Y, Mupungaa J, Zouc L, Liuc C, Liua S, Maoa J. Broccoli ingestion increases the glucosinolate hydrolysis activity of microbiota in the mouse gut. Inter journ of food sciences and nutrition. 2018;1:10.

Abbas A, Hall JA, Patterson WL 3rd, et al. Sulforaphane modulates telomerase activity via epigenetic regulation in prostate cancer cell lines. Biochem Cell Biol. 2016;94(1):71-81

Dos Santos PWDS, Machado ART, De Grandis RA, et al. Transcriptome and DNA methylation changes modulated by sulforaphane induce cell cycle arrest, apoptosis, DNA damage, and suppression of proliferation in human liver cancer cells. Food Chem Toxicol. 2020;136:111047.

Houghton CA. Sulforaphane: Its "Coming of Age" as a Clinically Relevant Nutraceutical in the Prevention and Treatment of Chronic Disease. Oxid Med Cell Longev. 2019, 2716870 2019.

Hyun TK. A Recent Overview on Sulforaphane as a Dietary Epigenetic Modulator. *Excli Journal 2020;19:131-134*

Ishiura Y, Ishimaru H, Watanabe T, Fujimuro M. Sulforaphane Exhibits Cytotoxic Effects against Primary Effusion Lymphoma Cells by Suppressing p38MAPK and AKT Phosphorylation. Biol Pharm Bull. 2019;42(12):2109-2112

Mitsiogianni M, Trafalis DT, Franco R, Zoumpourlis V, Pappa A, Panayiotidis MI. Sulforaphane and iberin are potent epigenetic modulators of histone acetylation and methylation in malignant melanoma [published online ahead of print, 2020 Mar 25]. Eur J Nutr. 2020;10.1007/s00394-020-02227-y.

Riboli E., Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am. J. Clin. Nutr. 2003;78:559–569.

Tortorella SM, Royce SG, Licciardi PV, Karagiannis TC. Dietary Sulforaphane in Cancer Chemoprevention: The Role of Epigenetic Regulation and HDAC Inhibition. Antioxid Redox Signal. 2015;22(16):1382-1424

Vanduchova A, Anzenbacher P, Anzenbacherova E. Isothiocyanate from broccoli, sulforaphane, and its properties. J Med Food 2019;22:121-6.

Wang X., Ouyang Y., Liu J., Zhu M., Zhao G., Bao W., Hu F.B. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: Systematic review and dose-response meta-analysis of prospective cohort studies. BMJ. 2014;349:g4490.

Watson G, M Beaver L, E Williams D, H Dashwood R, Ho E. Phytochemicals from cruciferous vegetables, epigenetics, and prostate cancer prevention. AAPS J. 2013;15(4):951-961.

Yagishita Y, Fahey JW, Dinkova-Kostova AT, Kensler TW. Broccoli or Sulforaphane: Is It the Source or Dose That Matters? Molecules, 24 (19) 2019.

Daniel M, Tollefsbol TO. Epigenetic linkage of aging, cancer and nutrition. *J Exp Biol*. 2015;218(Pt 1):59-70.

Hyun TK. A recent overview on sulforaphane as a dietary epigenetic modulator. EXCLI J. 2020;19:131-134.

Gianfredi V, Vannini S, Moretti M, et al. Sulforaphane and Epigallocatechin Gallate Restore Estrogen Receptor Expression by Modulating Epigenetic Events in the Breast Cancer Cell Line MDA-MB-231: A Systematic Review and Meta-Analysis. J Nutrigenet Nutrigenomics. 2017;10(3-4):126-135

Lubecka-Pietruszewska K, Kaufman-Szymczyk A, Stefanska B, Cebula-Obrzut B, Smolewski P, Fabianowska-Majewska K. Sulforaphane Alone and in Combination with Clofarabine Epigenetically Regulates the Expression of DNA Methylation-Silenced Tumour Suppressor Genes in Human Breast Cancer Cells. J Nutrigenet Nutrigenomics. 2015;8(2):91-101

Biersack B. Non-coding RNA/microRNA-modulatory dietary factors and natural products for improved cancer therapy and prevention: Alkaloids, organosulfur compounds, aliphatic carboxylic acids and water-soluble vitamins. Noncoding RNA Res. 2016;1(1):51-63

Abbaoui B, Telu KH, Lucas CR, et al. The impact of cruciferous vegetable isothiocyanates on histone acetylation and histone phosphorylation in bladder cancer. J Proteomics. 2017;156:94-103

Martin SL, Kala R, Tollefsbol TO. Mechanisms for the Inhibition of Colon Cancer Cells by Sulforaphane through Epigenetic Modulation of MicroRNA-21 and Human Telomerase Reverse Transcriptase (hTERT) Down-regulation. Curr Cancer Drug Targets. 2018;18(1):97-106

Okonkwo A, Mitra J, Johnson GS, et al. Heterocyclic Analogs of Sulforaphane Trigger DNA Damage and Impede DNA Repair in Colon Cancer Cells: Interplay of HATs and HDACs. Mol Nutr Food Res. 2018;62(18):e1800228

Su X, Jiang X, Meng L, Dong X, Shen Y, Xin Y. Anticancer Activity of Sulforaphane: The Epigenetic Mechanisms and the Nrf2 Signaling Pathway. Oxid Med Cell Longev. 2018;2018:5438179

Mafra D, Esgalhado M, Borges NA, et al. Methyl Donor Nutrients in Chronic Kidney Disease: Impact on the Epigenetic Landscape. J Nutr. 2019;149(3):372-380

Qu X, Pröll M, Neuhoff C, Zhang R, Cinar MU, Hossain MM, et al. (2015) Sulforaphane Epigenetically Regulates Innate Immune Responses of Porcine Monocyte-Derived Dendritic Cells Induced with Lipopolysaccharide. PLoS ONE 10(3): e0121574. doi:10.1371/journal.pone.0121574

Lewinska A, Adamczyk-Grochala J, Deregowska A, Wnuk M. Sulforaphane-Induced Cell Cycle Arrest and Senescence are accompanied by DNA Hypomethylation and Changes in microRNA Profile in Breast Cancer Cells. Theranostics. 2017;7(14):3461-3477

Kato M, Natarajan R. Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. Nat Rev Nephrol. 2019;15(6):327-345

Cappuccilli M, Bergamini C, Giacomelli FA, et al. Vitamin B Supplementation and Nutritional Intake of Methyl Donors in Patients with Chronic Kidney Disease: A Critical Review of the Impact on Epigenetic Machinery. Nutrients. 2020;12(5):E1234

Haarhaus M, Gilham D, Kulikowski E, Magnusson P, Kalantar-Zadeh K. Pharmacologic epigenetic modulators of alkaline phosphatase in chronic kidney disease. Curr Opin Nephrol Hypertens. 2020;29(1):4-15.

Martinez-Moreno JM, Fontecha-Barriuso M, Martín-Sánchez D, et al. The Contribution of Histone Crotonylation to Tissue Health and Disease: Focus on Kidney Health. Front Pharmacol. 2020;11:393

Negrette-Guzmán M, Huerta-Yepez S, Vega MI, et al. Sulforaphane induces differential modulation of mitochondrial biogenesis and dynamics in normal cells and tumor cells. Food Chem Toxicol. 2017;100:90-102

Lin CF, Chueh TH, Chung CH, Chung SD, Chang TC, Chien CT. Sulforaphane improves voiding function via the preserving mitochondrial function in diabetic rats. J Formos Med Assoc. 2019;S0929-6646(19)30414-0

Palikaras K, N. Tavernarakis, Mitochondrial homeostasis: The interplay between mitophagy and mitochondrial biogenesis, Exp. Gerontol. 56 (2014) 182–188

Bhargava P, R.G. Schnellmann, Mitochondrial energetics in the kidney, Nat. Rev.

Nephrol. 13 (2017) 629–646. doi:10.1038/nrneph.2017.107.

Chung SD, Lai TY, Chien CT, Yu HJ. Activating Nrf-2 signaling depresses unilateral ureteral obstruction-evoked mitochondrial stress-related autophagy, apoptosis and pyroptosis in kidney. PLoS One 2012;7(10):e47299.

Hao-Yun Chang, Chao-Wen Lin, Chung-May Yang, Chang-Hao Yang,Nrf-2 activator sulforaphane protects retinal cells from oxidative stress-induced retinal injury,Journal of Functional Foods,Volume 71,2020,

Yan Liu, Zhiwei Zhang, Xiaofen Lu, Jian Meng, Xuying Qin, Jie Jiang,

Anti-nociceptive and anti-inflammatory effects of sulforaphane on sciatic endometriosis in a rat model,Neuroscience Letters,Volume 723,2020,

Liyang Wei, Jinjin Wang, Ling Yan, Shanshan Shui, Lei Wang, Wenxiu Zheng, Shuai Liu, Changhong Liu, Lei Zheng,Sulforaphane attenuates 5-fluorouracil induced intestinal injury in mice,Journal of Functional Foods,Volume 69,2020,

Sahar A. Khaleel, Nahed A. Raslan, Amany A. Alzokaky, Mohamed G. Ewees, Ahmed A. Ashour, Hala E. Abdel-Hamied, Adel R. Abd-Allah,Contrast media (meglumine diatrizoate) aggravates renal inflammation, oxidative DNA damage and apoptosis in diabetic rats which is restored by sulforaphane through Nrf2/HO-1 reactivation,Chemico-Biological Interactions,Volume 309,2019,

Luo Haodang, Qin Lianmei, Li Ranhui, Chen Liesong, He Jun, Zeng Yihua, Zhu Cuiming, Wu Yimou, You Xiaoxing,

HO-1 mediates the anti-inflammatory actions of Sulforaphane in monocytes stimulated with a mycoplasmal lipopeptide,Chemico-Biological Interactions,Volume 306,2019,

**Marcia -Ca**

Ahmed ZSO, Li X, Li F, Cheaito HA, Patel KESM, Mosallam GA, Elbargeesy EFH, Dou QP. Computational and biochemical studies of isothiocyanates as inhibitors of proteasomal cysteine deubiquitinases in human cancer cells, J. Cell. Biochem. 2018;119:9006–9016.

Bertrand HC, Schaap, Baird L, Georgakopoulos ND, Fowkes A, Thiollier C, Kachi H, Dinkova-Kostova AT, Wells G. Design, Synthesis, and Evaluation of Triazole Derivatives That Induce Nrf2 Dependent Gene Products and Inhibit the Keap1-Nrf2 Protein-Protein Interaction, J. Med. Chem. 2015;58:7186–7194.

Bose C, Awasthi S, Sharma R, Beneš H, Hauer-Jensen M, Boerma M, Singh SP. Sulforaphane potentiates anticancer effects of doxorubicin and attenuates its cardiotoxicity in a breast cancer model. PLoS One. 2018;13(3).

Braicu C, et al. Nutrigenomics in cancer: Revisiting the effects of natural compounds. Semin Cancer Biol. 2017;46:84-106.

Calcabrini C, Maffei F, Turrini E, Fimognar C. Sulforaphane Potentiates Anticancer Effects of Doxorubicin and Cisplatin and Mitigates Their Toxic Effects. Front Pharmacol. 2020;11:567.

Chen L , Chana LS, Lunga HL, Yip TTC, Ngan RKC, Wonga JWC, Lod KW, Nge WT, Leef AWM, Tsaog GSW, Lungf ML, Mak NK. Crucifera sulforaphane (SFN) inhibits the growth of nasopharyngeal carcinoma through DNA methyltransferase 1 (DNMT1)/Wnt inhibitory factor 1 (WIF1) axis. Phytomedicine. 2019;63:153058.

Choi S, Lew KL, Xiao H, et al.: D,L-Sulforaphane-induced cell death in human prostate cancer cells is regulated by inhibitor of apoptosis family proteins and Apaf-1. Carcinogenesis 2007;28: 151–162.

Corssac GB, Campos-Carraro C, Hickmann A, Araujo AAR, Fernandes RO, Bello-Klein A. Sulforaphane effects on oxidative stress parameters in culture of adult cardiomyocytes, Biomed. Pharmacother. 2018;104:165–171.

DeJesus GRE, Contreras L, Rodriguez-Palomares IA, Villanueva PJ, Balderrama KS, Monterroza L, Larragoity M, Varela-Ramirez A, Aguilera RJ. A new pyridazinone exhibits potent cytotoxicity on human cancer cells via apoptosis and poly-ubiquitinated protein accumulation, Cell Biol. Toxicol. 2019;1–17

Dinkova-Kostova AT, Jenkins SN, Fahey JW, Ye L, Wehage SL, Liby KT, Stephenson KK, Wade KL, Talalay P. Protection Against UV-light-induced Skin Carcinogenesis in SKH-1 High-Risk Mice by Sulforaphane-Containing Broccoli Sprout Extracts. Cancer Let. 2006;240(2):243-52.

Fimognari C, Nusse M, Cesari R, et al.: Growth inhibition, cellcycle arrest and apoptosis in human T-cell leukemia by the isothiocyanate sulforaphane. Carcinogenesis 2002;23:581–586

Gamet-Payrastre L, Li P, Lumeau S, et al.: Sulforaphane, a naturally occurring isothiocyanate, induces cell cycle arrest and apoptosis in HT29 human colon cancer cells. Cancer Res 2000; 60:1426–1433.

Gupta P, Kim B, Kim SH, Srivastava SK: Molecular targets of isothiocyanates in cancer: Recent advances. Mol Nutr Food Res 2014;58:1685–1707.

Hu L, Miao W, Loignon M, Kandouz M, Batist G. Putative chemopreventive molecules can increase Nrf2-regulated cell defense in some human cancer cell lines, resulting in resistance to common cytotoxic therapies, Cancer Chemother. Pharmacol. 2010;66:467–47.

Kaboli PJ, Khoshkbejari MA, Mohammadi M, Abiri A, Mokhtarian R, et al. Targets and mechanisms of sulforaphane derivatives obtained from cruciferous plants with special focus on breast cancer – contradictory effects and future perspectives. Biomedicine & Pharmacotherapy. 2020; 121:109635.

Kallifatidis G, Labsch S, Rausch V, Mattern J, Gladkich J, Moldenhauer G, Büchler MW, Salnikov AV, Herr I. O sulforafano aumenta a citotoxicidade mediada por medicamentos para células-tronco cancerígenas do pâncreas e próstata. Mol Ther. 2011; 19 (1): 188-195.

Lan H, Yuan H, Lin C. Sulforaphane Induces p53-deficient SW480 Cell Apoptosis via the ROS-MAPK Signaling Pathway. Mol Med Rep. 2017;16(5):7796-7804.

Langouet S, Furge LL, Kerriguy N, Nakamura K, Guillouzo A, Guengerich FP. Inibição das enzimas do citocromo P450 humano por 1,2-ditiol-3-tiona, oltipraz e seus derivados e sulforafano. Chem Res Toxicol. 2000; 13 (4): 245–252.

Lewinska A, Adamczyk-Grochala J, Deregowska A, Wnuk M. Sulforaphane-Induced Cell Cycle Arrest and Senescence are accompanied by DNA Hypomethylation and Changes in microRNA Profile in Breast Cancer Cells. Theranostics. 2017;7(14):3461–3477.

Lozanovski VJ, Houben P, Hinz U, Hackert T, Herr I, Schemmer P. Pilot study evaluating broccoli sprouts in advanced pancreatic cancer (POUDER trial) - study protocol for a randomized controlled trial. Trials. 2014;15:204.

Mcguire S. World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. Adv Nutr, Rockville. 2016;7(2):418-9.

Mielczarek L, Krug P, Mazur M, Milczarek M, Chilmonczyk Z, Wiktorska K. In the triple-negative breast cancer MDA-MB-231 cell line, sulforaphane enhances the intracellular accumulation and anticancer action of doxorubicin encapsulated in liposomes. Int J Pharm. 2019;558:311-318.

Mokhtari BR, et al. The role of Sulforaphane in cancer chemoprevention and health benefits: a mini-review. J Cell Commun Signal, Dordrecht. 2018;(12)1:91-101.

Pham NA, Jacobberger JW, Schimmer AD, et al.: The dietary isothiocyanate sulforaphane targets pathways of apoptosis, cell cycle arrest, and oxidative stress in human pancreatic cancer cells and inhibits tumor growth in severe combined immunodeficient mice. Mol Cancer Ther 2004;3:1239–1248.

Priya DKD, Gayathri R, Sakthisekaran D. Role of sulforaphane in the anti-initiating mechanism of lung carcinogenesis in vivo by modulating the metabolic activation and detoxification of benzo(a)pyrene. Biomedicine & Pharmacotherapy. 2011;65:9–16.

Remely M, et al. Therapeutic perspectives of epigenetically active nutrients. Br J Pharmacol. 2015;172(11):2756-68.

Santana-Gálvez J, Villela-Castrejón J, Serna-Saldívar SO, Cisneros-Zevallos L, Jacobo-Velázquez DA. Synergistic Combinations of Curcumin, Sulforaphane, and Dihydrocaffeic Acid against Human Colon Cancer Cells. Int. J. Mol. Sci. 2020;21:3108.

Santos PWS. Influência do sulforafano, um inibidor de histonas desacetilases, sobre a instabilidade genômica e mecanismos epigenéticos em linhagens celulares humanas [Dissertação]. São Paulo, Faculdade de Ciências Farmacêuticas de Ribeirão Preto/USP. 2019.

Traka MH, Melchini A, Coode-Bate J, Kadhi AO, Saha S, Defernez M, Troncoso-Rey P, et al. Transcriptional changes in prostate of men on active surveillance after a 12-mo glucoraphanin-rich broccoli intervention—results from the Effect of Sulforaphane on

prostate CAncer PrEvention (ESCAPE) randomized controlled trial. Am J Clin Nutr. 2019;109:1133–1144.
Tomlinson L, Lu ZQ, Bentley RA, Colley HE, Murdoch C, Webb SD, Cross MJ, Copple IM, Sharma P. Attenuation of doxorubicin-induced cardiotoxicity in a human in vitro cardiac model by the induction of the NRF-2 pathway. Biomed Pharmacother. 2019;112():108637.
Vanduchova A, Anzenbacher P, Anzenbacherova E. Isothiocyanate from Broccoli, Sulforaphane, and Its Properties. J Med Food. 2018:1–6.
Volarevic V, Djokovic B, Jankovic MG, Harrell CR, Fellabaum C, Djonov V, Arsenijevic N. Molecular mechanisms of cisplatin-induced nephrotoxicity: a balance on the knife edge between renoprotection and tumor toxicity. J Biomed Sci. 2019;26(1):25.
Xu C, Huang M, Shen G, Yuan X, Lin W, Khor TO, Conney AH, Kong TA. Inhibition of 7,12-Dimethylbenz(a)anthracene-Induced Skin Tumorigenesis in C57BL/6 Mice by Sulforaphane Is Mediated by Nuclear Factor E2–Related Factor 2. Cancer Res. 2006;66(16):8293-6.
Zhang Y. et al. Anticarcinogenic activities of sulforaphane and structurally related synthetic norbornyl isothiocyanates. Proc Natl Acad Sci. 1994;91(8):3147-50.

**References-Lu Dai**

1. López-Otín, C.; Blasco, M.A.; Partridge, L.; Serrano, M.; Kroemer, G. The Hallmarks of Aging. *Cell* **2013**, *153*, 1194–1217.
2. Franceschi, C.; Garagnani, P.; Parini, P.; Giuliani, C.; Santoro, A. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nature Reviews Endocrinology* **2018**, *14*, 576–590.
3. Santín-Márquez, R.; Alarcón-Aguilar, A.; López-Diazguerrero, N.E.; Chondrogianni, N.; Königsberg, M. Sulforaphane - role in aging and neurodegeneration. *GeroScience* **2019**, *41*, 655–670.
4. de Oliveira, M.R.; Brasil, F.B.; Fürstenau, C.R. Sulforaphane Attenuated the Pro-Inflammatory State Induced by Hydrogen Peroxide in SH-SY5Y Cells Through the Nrf2/HO-1 Signaling Pathway. *Neurotoxicity Research* **2018**, *34*, 241–249.
5. de Oliveira, M.R.; de Bittencourt Brasil, F.; Fürstenau, C.R. Sulforaphane Promotes Mitochondrial Protection in SH-SY5Y Cells Exposed to Hydrogen Peroxide by an Nrf2-Dependent Mechanism. *Molecular Neurobiology* **2018**, *55*, 4777–4787.
6. Dai, L.; Schurgers, L.J.; Shiels, P.G.; Stenvinkel, P. Early vascular ageing in chronic kidney disease: impact of inflammation, vitamin K, senescence and genomic damage. *Nephrology Dialysis Transplantation* **2020**, *35*, ii31-ii37.
7. Zakkar, M.; Van der Heiden, K.; Luong, L.A.; Chaudhury, H.; Cuhlmann, S.; Hamdulay, S.S.; Krams, R.; Edirisinghe, I.; Rahman, I.; Carlsen, H.; et al. Activation of Nrf2 in Endothelial Cells Protects Arteries From Exhibiting a Proinflammatory State. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2009**, *29*, 1851–1857.
8. Kwon, J.-S.; Joung, H.; Kim, Y.S.; Shim, Y.-S.; Ahn, Y.; Jeong, M.H.; Kee, H.J. Sulforaphane inhibits restenosis by suppressing inflammation and the proliferation of vascular smooth muscle cells. *Atherosclerosis* **2012**, *225*, 41–49.
9. Jayakumar, T.; Chen, W.-F.; Lu, W.-J.; Chou, D.-S.; Hsiao, G.; Hsu, C.-Y.; Sheu, J.-R.; Hsieh, C.-Y. A novel antithrombotic effect of sulforaphane via activation of platelet

adenylate cyclase: ex vivo and in vivo studies. *The Journal of Nutritional Biochemistry* **2013**, *24*, 1086–1095.
10. Liddell, J. Are Astrocytes the Predominant Cell Type for Activation of Nrf2 in Aging and Neurodegeneration? *Antioxidants* **2017**, *6*, 65.
11. Morroni, F.; Tarozzi, A.; Sita, G.; Bolondi, C.; Zolezzi Moraga, J.M.; Cantelli-Forti, G.; Hrelia, P. Neuroprotective effect of sulforaphane in 6-hydroxydopamine-lesioned mouse model of Parkinson's disease. *NeuroToxicology* **2013**, *36*, 63–71.
12. Jang, M.; Cho, I.-H. Sulforaphane Ameliorates 3-Nitropropionic Acid-Induced Striatal Toxicity by Activating the Keap1-Nrf2-ARE Pathway and Inhibiting the MAPKs and NF-κB Pathways. *Molecular Neurobiology* **2016**, *53*, 2619–2635.
13. Li, B.; Cui, W.; Liu, J.; Li, R.; Liu, Q.; Xie, X.-H.; Ge, X.-L.; Zhang, J.; Song, X.-J.; Wang, Y.; et al. Sulforaphane ameliorates the development of experimental autoimmune encephalomyelitis by antagonizing oxidative stress and Th17-related inflammation in mice. *Experimental Neurology* **2013**, *250*, 239–249.
14. Zhang, J.; Zhang, R.; Zhan, Z.; Li, X.; Zhou, F.; Xing, A.; Jiang, C.; Chen, Y.; An, L. Beneficial Effects of Sulforaphane Treatment in Alzheimer's Disease May Be Mediated through Reduced HDAC1/3 and Increased P75NTR Expression. *Frontiers in Aging Neuroscience* **2017**, *9*.
15. Saleh, D.O.; Mansour, D.F.; Hashad, I.M.; Bakeer, R.M. Effects of sulforaphane on D-galactose-induced liver aging in rats: Role of keap-1/nrf-2 pathway. *European Journal of Pharmacology* **2019**, *855*, 40–49.
16. Hariton, F.; Xue, M.; Rabbani, N.; Fowler, M.; Thornalley, P.J. Sulforaphane delays fibroblast senescence by curbing cellular glucose uptake, increased glycolysis, and oxidative damage. *Oxidative Medicine and Cellular Longevity* **2018**, *2018*.
17. Zanichelli, F.; Capasso, S.; Di Bernardo, G.; Cipollaro, M.; Pagnotta, E.; Cartenì, M.; Casale, F.; Iori, R.; Giordano, A.; Galderisi, U. Low concentrations of isothiocyanates protect mesenchymal stem cells from oxidative injuries, while high concentrations exacerbate DNA damage. *Apoptosis* **2012**, *17*, 964–974.
18. Kubo, E.; Chhunchha, B.; Singh, P.; Sasaki, H.; Singh, D.P. Sulforaphane reactivates cellular antioxidant defense by inducing Nrf2/ARE/Prdx6 activity during aging and oxidative stress. *Scientific Reports* **2017**, *7*, 1–17.
19. Lewinska, A.; Adamczyk-Grochala, J.; Deregowska, A.; Wnuk, M. Sulforaphane-induced cell cycle arrest and senescence are accompanied by DNA hypomethylation and changes in microRNA profile in breast cancer cells. *Theranostics* **2017**, *7*, 3461–3477.
20. Myzak, M.C.; Karplus, P.A.; Chung, F.-L.; Dashwood, R.H. A Novel Mechanism of Chemoprotection by Sulforaphane. *Cancer Research* **2004**, *64*, 5767–5774.
21. Myzak, M.C.; Hardin, K.; Wang, R.; Dashwood, R.H.; Ho, E. Sulforaphane inhibits histone deacetylase activity in BPH-1, LnCaP and PC-3 prostate epithelial cells. *Carcinogenesis* **2006**, *27*, 811–819.
22. Jones, P.A.; Baylin, S.B. The Epigenomics of Cancer. *Cell* **2007**, *128*, 683–692.
23. Fraga, M.F.; Ballestar, E.; Villar-Garea, A.; Boix-Chornet, M.; Espada, J.; Schotta, G.; Bonaldi, T.; Haydon, C.; Ropero, S.; Petrie, K.; et al. Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer. *Nature Genetics* **2005**, *37*, 391–400.
24. Myzak, M.C.; Tong, P.; Dashwood, W.-M. Sulforaphane Retards the Growth of Human PC-3 Xenografts and Inhibits HDAC Activity in Human Subjects. *Exp Biol Med*

*(Maywood)* **2007**, *232*, 227–234.

Livia:

Shang G, Tang X, Gao P, et al. Sulforaphane attenuation of experimental diabetic nephropathy involves GSK-3 beta/Fyn/Nrf2 signaling pathway. J Nutr Biochem. 2015;26(6):596-606

Zhao Z, Liao G, Zhou Q, Lv D, Holthfer H, Zou H. Sulforaphane Attenuates Contrast-Induced Nephropathy in Rats via Nrf2/HO-1 Pathway. Oxid Med Cell Longev. 2016;2016:9825623

Guerrero-Beltrán CE, Mukhopadhyay P, Horváth B, et al. Sulforaphane, a natural constituent of broccoli, prevents cell death and inflammation in nephropathy. J Nutr Biochem. 2012;23(5):494-500

Lv D, Zhou Q, Xia Y, et al. The Association Between Oxidative Stress Alleviation via Sulforaphane-Induced Nrf2-HO-1/NQO-1 Signaling Pathway Activation and Chronic Renal Allograft Dysfunction Improvement. Kidney Blood Press Res. 2018;43(1):191-205

Kim JH, Kim KM, Jeong JU, Shin JH, Shin JM, Bang KT. Nrf2-Heme oxygenase-1 modulates autophagy and inhibits apoptosis triggered by elevated glucose levels in renal tubule cells. Kidney Res Clin Pract. 2019;38(3):318-325.

Kim T, Kim YJ, Han IH, et al. The synthesis of sulforaphane analogues and their protection effect against cisplatin induced cytotoxicity in kidney cells. Bioorg Med Chem Lett. 2015;25(1):62-66

Khaleel SA, Raslan NA, Alzokaky AA, et al. Contrast media (meglumine diatrizoate) aggravates renal inflammation, oxidative DNA damage and apoptosis in diabetic rats which is restored by sulforaphane through Nrf2/HO-1 reactivation. Chem Biol Interact. 2019;309:108689

Shin JH, Kim KM, Jeong JU, et al. Nrf2-Heme Oxygenase-1 Attenuates High-Glucose-Induced Epithelial-to-Mesenchymal Transition of Renal Tubule Cells by Inhibiting ROS-Mediated PI3K/Akt/GSK-3β Signaling. J Diabetes Res. 2019;2019:2510105

Gigliotti JC, Tin A, Pourafshar S, et al. GSTM1 Deletion Exaggerates Kidney Injury in Experimental Mouse Models and Confers the Protective Effect of Cruciferous Vegetables in Mice and Humans. J Am Soc Nephrol. 2020;31(1):102-116

Tin A, Scharpf R, EstrellaMM, Yu B,GroveML, Chang PP, et al.: The loss of GSTM1 associates with kidney failure and heart failure. J Am Soc Nephrol 28: 3345–3352, 2017

Rubio-Navarro A, Vázquez-Carballo C, Guerrero-Hue M, et al. Nrf2 Plays a Protective Role Against Intravascular Hemolysis-Mediated Acute Kidney Injury. Front Pharmacol. 2019;10:740.

Cui W, Min X, Xu X, Du B, Luo P. Role of Nuclear Factor Erythroid 2-Related Factor 2 in Diabetic Nephropathy. J Diabetes Res. 2017;2017:3797802

Cekauskas A, Bruns H, Manikas M, et al. Sulforaphane decreases kidney injury after transplantation in rats: role of mitochondrial damage. Ann Transplant. 2013;18:488-496

Dadras F, Khoshjou F. NF-E2-related factor 2 and its role in diabetic nephropathy. Iran J Kidney Dis. 2013;7(5):346-351

Cigarran Guldris S, González Parra E, Cases Amenós A. Gut microbiota in chronic kidney disease. Microbiota intestinal en la enfermedad renal crónica. Nefrologia. 2017;37(1):9-19

Mafra D, Fouque D. Gut microbiota and inflammation in chronic kidney disease patients. Clin Kidney J. 2015;8(3):332-334

Mafra D, Borges NA, Lindholm B, Stenvinkel P. Mitochondrial dysfunction and gut microbiota imbalance: An intriguing relationship in chronic kidney disease. Mitochondrion. 2019;47:206-209. doi:10.1016/j.mito.2018.11.006

Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158(11):825-830

Tan SM, de Haan JB. Combating oxidative stress in diabetic complications with Nrf2 activators: how much is too much?. Redox Rep. 2014;19(3):107-117

Mazarakis N, Snibson K, Licciardi PV, Karagiannis TC. The potential use of l-sulforaphane for the treatment of chronic inflammatory diseases: A review of the clinical evidence. Clin Nutr. 2020;39(3):664-675

Chartoumpekis DV, Ziros PG, Chen JG, Groopman JD, Kensler TW, Sykiotis GP. Broccoli sprout beverage is safe for thyroid hormonal and autoimmune status: Results of a 12-week randomized trial. Food Chem Toxicol. 2019;126:1-6

Charron CS, Vinyard BT, Ross SA, Seifried HE, Jeffery EH, Novotny JA. Absorption and metabolism of isothiocyanates formed from broccoli glucosinolates: effects of BMI and daily consumption in a randomised clinical trial. Br J Nutr. 2018;120(12):1370-1379

Chang YW, Jang JY, Kim YH, Kim JW, Shim JJ. The Effects of Broccoli Sprout Extract Containing Sulforaphane on Lipid Peroxidation and Helicobacter pylori Infection in the Gastric Mucosa. Gut Liver. 2015;9(4):486-493

Abbas A, Hall JA, Patterson WL 3rd, et al. Sulforaphane modulates telomerase activity via epigenetic regulation in prostate cancer cell lines. Biochem Cell Biol. 2016;94(1):71-81

and mortality in the United States general population and CKD subpopulation. Clin J Am Soc Nephrol 2015;10:1145–1153

Bai M, Chen H, Ding D, et al. MicroRNA-214 promotes chronic kidney disease by disrupting mitochondrial oxidative phosphorylation. Kidney Int. 2019;95(6):1389-1404

Beddhu S, Wei G, Marcus RL, Chonchol M, Greene T. Light-intensity physical activities

Bhargava P, R.G. Schnellmann, Mitochondrial energetics in the kidney, Nat. Rev.

Biersack B. Non-coding RNA/microRNA-modulatory dietary factors and natural products for improved cancer therapy and prevention: Alkaloids, organosulfur compounds, aliphatic carboxylic acids and water-soluble vitamins. Noncoding RNA Res. 2016;1(1):51-63

Briones-Herrera A, Avila-Rojas SH, Aparicio-Trejo OE, et al. Sulforaphane prevents maleic acid-induced nephropathy by modulating renal hemodynamics, mitochondrial bioenergetics and oxidative stress. Food Chem Toxicol. 2018;115:185-197

Cappuccilli M, Bergamini C, Giacomelli FA, et al. Vitamin B Supplementation and Nutritional Intake of Methyl Donors in Patients with Chronic Kidney Disease: A Critical Review of the Impact on Epigenetic Machinery. Nutrients. 2020;12(5):E1234

Chung SD, Lai TY, Chien CT, Yu HJ. Activating Nrf-2 signaling depresses unilateral ureteral obstruction-evoked mitochondrial stress-related autophagy, apoptosis and pyroptosis in kidney. PLoS One 2012;7(10):e47299.

Daniel M, Tollefsbol TO. Epigenetic linkage of aging, cancer and nutrition. *J Exp Biol*. 2015;218(Pt 1):59-70.

Dos Santos PWDS, Machado ART, De Grandis RA, et al. Transcriptome and DNA methylation changes modulated by sulforaphane induce cell cycle arrest, apoptosis, DNA damage, and suppression of proliferation in human liver cancer cells. Food Chem Toxicol. 2020;136:111047.

Duann P, Lin PH. Mitochondria Damage and Kidney Disease. Adv Exp Med Biol. 2017;982:529-551

Enoki Y, Watanabe H, Arake R, et al. Potential therapeutic interventions for chronic kidney disease-associated sarcopenia via indoxyl sulfate-induced mitochondrial dysfunction. J Cachexia Sarcopenia Muscle. 2017;8(5):735-747

Fontecha-Barriuso M, Martin-Sanchez D, Martinez-Moreno JM, et al. The Role of PGC-1α and Mitochondrial Biogenesis in Kidney Diseases. Biomolecules. 2020;10(2):347

Galvan DL, Green NH, Danesh FR. The hallmarks of mitochondrial dysfunction in chronic kidney disease. Kidney Int. 2017;92(5):1051-1057

Gamboa JL, Billings FT 4th, Bojanowski MT, et al. Mitochondrial dysfunction and oxidative stress in patients with chronic kidney disease. Physiol Rep. 2016;4(9):e12780

Gianfredi V, Vannini S, Moretti M, et al. Sulforaphane and Epigallocatechin Gallate Restore Estrogen Receptor Expression by Modulating Epigenetic Events in the Breast Cancer Cell Line MDA-MB-231: A Systematic Review and Meta-Analysis. J Nutrigenet Nutrigenomics. 2017;10(3-4):126-135

Guerrero-Beltrán CE, Calderón-Oliver M, Tapia E, et al. Sulforaphane protects against cisplatin-induced nephrotoxicity. Toxicol Lett. 2010a;192(3):278-285

Guerrero-Beltrán CE, Calderón-Oliver M, Martínez-Abundis E, et al. Protective effect of sulforaphane against cisplatin-induced mitochondrial alterations and impairment in the activity of NAD(P)H: quinone oxidoreductase 1 and γ glutamyl cysteine ligase: studies in mitochondria isolated from rat kidney and in LLC-PK1 cells. Toxicol Lett. 2010b;199(1):80-92

Haarhaus M, Gilham D, Kulikowski E, Magnusson P, Kalantar-Zadeh K. Pharmacologic epigenetic modulators of alkaline phosphatase in chronic kidney disease. Curr Opin Nephrol Hypertens. 2020;29(1):4-15.

Houghton CA. Sulforaphane: Its "Coming of Age" as a Clinically Relevant Nutraceutical in the Prevention and Treatment of Chronic Disease. Oxid Med Cell Longev. 2019, 2716870 2019.

Hyun TK. A Recent Overview on Sulforaphane as a Dietary Epigenetic Modulator. *Excli Journal 2020;19:131-134*

Hyun TK. A recent overview on sulforaphane as a dietary epigenetic modulator. EXCLI J. 2020;19:131-134.

Ishiura Y, Ishimaru H, Watanabe T, Fujimuro M. Sulforaphane Exhibits Cytotoxic Effects against Primary Effusion Lymphoma Cells by Suppressing p38MAPK and AKT Phosphorylation. Biol Pharm Bull. 2019;42(12):2109-2112

Kato M, Natarajan R. Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. Nat Rev Nephrol. 2019;15(6):327-345

Lei P, Tian S, Teng C, et al. Sulforaphane Improves Lipid Metabolism by Enhancing Mitochondrial Function and Biogenesis In Vivo and In Vitro. Mol Nutr Food Res. 2019;63(4):e1800795

Lewinska A, Adamczyk-Grochala J, Deregowska A, Wnuk M. Sulforaphane-Induced Cell Cycle Arrest and Senescence are accompanied by DNA Hypomethylation and Changes in microRNA Profile in Breast Cancer Cells. Theranostics. 2017;7(14):3461-3477

Lin CF, Chueh TH, Chung CH, Chung SD, Chang TC, Chien CT. Sulforaphane improves voiding function via the preserving mitochondrial function in diabetic rats. J Formos Med Assoc. 2019;S0929-6646(19)30414-0

Lubecka-Pietruszewska K, Kaufman-Szymczyk A, Stefanska B, Cebula-Obrzut B, Smolewski P, Fabianowska-Majewska K. Sulforaphane Alone and in Combination with Clofarabine Epigenetically Regulates the Expression of DNA Methylation-Silenced Tumour Suppressor Genes in Human Breast Cancer Cells. J Nutrigenet Nutrigenomics. 2015;8(2):91-101

Mafra D, Esgalhado M, Borges NA, et al. Methyl Donor Nutrients in Chronic Kidney Disease: Impact on the Epigenetic Landscape. J Nutr. 2019;149(3):372-380

Mafra D, Gidlund EK, Borges NA, et al. Bioactive food and exercise in chronic kidney disease: Targeting the mitochondria. Eur J Clin Invest. 2018;48(11):e13020

Martin SL, Kala R, Tollefsbol TO. Mechanisms for the Inhibition of Colon Cancer Cells by Sulforaphane through Epigenetic Modulation of MicroRNA-21 and Human Telomerase Reverse Transcriptase (hTERT) Down-regulation. Curr Cancer Drug Targets. 2018;18(1):97-106

Martinez-Moreno JM, Fontecha-Barriuso M, Martín-Sánchez D, et al. The Contribution of Histone Crotonylation to Tissue Health and Disease: Focus on Kidney Health. Front Pharmacol. 2020;11:393

Mitsiogianni M, Trafalis DT, Franco R, Zoumpourlis V, Pappa A, Panayiotidis MI. Sulforaphane and iberin are potent epigenetic modulators of histone acetylation and methylation in malignant melanoma [published online ahead of print, 2020 Mar 25]. Eur J Nutr. 2020;10.1007/s00394-020-02227-y.

Negrette-Guzmán M, Huerta-Yepez S, Vega MI, et al. Sulforaphane induces differential modulation of mitochondrial biogenesis and dynamics in normal cells and tumor cells. Food Chem Toxicol. 2017;100:90-102

Nephrol. 13 (2017) 629–646. doi:10.1038/nrneph.2017.107.

Okonkwo A, Mitra J, Johnson GS, et al. Heterocyclic Analogs of Sulforaphane Trigger DNA Damage and Impede DNA Repair in Colon Cancer Cells: Interplay of HATs and HDACs. Mol Nutr Food Res. 2018;62(18):e1800228

Oliveira MR, de Bittencourt Brasil F, Fürstenau CR. Sulforaphane Promotes Mitochondrial Protection in SH-SY5Y Cells Exposed to Hydrogen Peroxide by an Nrf2-Dependent Mechanism. Mol Neurobiol. 2018;55(6):4777-4787

Palikaras K, N. Tavernarakis, Mitochondrial homeostasis: The interplay between mitophagy and mitochondrial biogenesis, Exp. Gerontol. 56 (2014) 182–188

Qu X, Pröll M, Neuhoff C, Zhang R, Cinar MU, Hossain MM, et al. (2015) Sulforaphane Epigenetically Regulates Innate Immune Responses of Porcine Monocyte-Derived Dendritic Cells Induced with Lipopolysaccharide. PLoS ONE 10(3): e0121574. doi:10.1371/journal.pone.0121574

Riboli E., Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am. J. Clin. Nutr. 2003;78:559–569.

Su X, Jiang X, Meng L, Dong X, Shen Y, Xin Y. Anticancer Activity of Sulforaphane: The Epigenetic Mechanisms and the Nrf2 Signaling Pathway. Oxid Med Cell Longev. 2018;2018:5438179

Su Z, Klein JD, Du J, et al. Chronic kidney disease induces autophagy leading to dysfunction of mitochondria in skeletal muscle. Am J Physiol Renal Physiol. 2017;312(6):F1128-F1140

Tortorella SM, Royce SG, Licciardi PV, Karagiannis TC. Dietary Sulforaphane in Cancer Chemoprevention: The Role of Epigenetic Regulation and HDAC Inhibition. Antioxid Redox Signal. 2015;22(16):1382-1424

Vanduchova A, Anzenbacher P, Anzenbacherova E. Isothiocyanate from broccoli, sulforaphane, and its properties. J Med Food 2019;22:121-6.

Wang X., Ouyang Y., Liu J., Zhu M., Zhao G., Bao W., Hu F.B. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: Systematic review and dose-response meta-analysis of prospective cohort studies. BMJ. 2014;349:g4490.

Watson G, M Beaver L, E Williams D, H Dashwood R, Ho E. Phytochemicals from cruciferous vegetables, epigenetics, and prostate cancer prevention. AAPS J. 2013;15(4):951-961.

Yagishita Y, Fahey JW, Dinkova-Kostova AT, Kensler TW. Broccoli or Sulforaphane: Is It the Source or Dose That Matters? Molecules, 24 (19) 2019.

Zhang M, Xu Y, Jiang L. Sulforaphane attenuates angiotensin II-induced human umbilical vein endothelial cell injury by modulating ROS-mediated mitochondrial signaling. Hum Exp Toxicol. 2020;39(5):734-747

De Oliveira, M. R., Brasil, F. B., & Fürstenau, C. R. (2018). *Sulforaphane Attenuated the Pro-Inflammatory State Induced by Hydrogen Peroxide in SH-SY5Y Cells Through the Nrf2/HO-1 Signaling Pathway. Neurotoxicity Research, 34(2), 241–249.*

De Oliveira, M. R., de Bittencourt Brasil, F., & Fürstenau, C. R. (2017). *Sulforaphane Promotes Mitochondrial Protection in SH-SY5Y Cells Exposed to Hydrogen Peroxide by an Nrf2-Dependent Mechanism. Molecular Neurobiology, 55(6), 4777–4787.*

Rakariyatham, K., Wu, X., Tang, Z., Han, Y., Wang, Q., & Xiao, H. (2018). Synergism between luteolin and sulforaphane in anti-inflammation. Food & Function. Food Funct., 2018, 9, 5115–5123

Wang Y, Zhang Z, Sun W, et al. Sulforaphane attenuation of type 2 diabetes-induced aortic damage was associated with the upregulation of Nrf2 expression and function. *Oxid Med Cell Longev*. 2014;2014:123963. doi:10.1155/2014/123963

Cox, A. G., Gurusinghe, S., Abd Rahman, R., Leaw, B., Chan, S. T., Mockler, J. C., … Wallace, E. M. (2019). *Sulforaphane improves endothelial function and reduces placental oxidative stress in vitro. Pregnancy Hypertension, 16, 1–10.*

Mirmiran P., Bahadoran Z., Hosseinpanah F., Keyzad A., Azizi F. Effects of broccoli sprout with high sulforaphane concentration on inflammatory markers in type 2 diabetic patients: A randomized double-blind placebo-controlled clinical trial. J. Funct. Foods. 2012;4:837–841.

López-Chillón MT, Carazo-Díaz C, Prieto-Merino D, Zafrilla P, Moreno DA, Villaño D. Effects of long-term consumption of broccoli sprouts on inflammatory markers in overweight subjects. *Clin Nutr*. 2019;38(2):745-752.

Townsend BE, Johnson RW. Sulforaphane induces Nrf2 target genes and attenuates inflammatory gene expression in microglia from brain of young adult and aged mice. *Exp Gerontol*. 2016;73:42-48. doi:10.1016/j.exger.2015.11.004

Table 2:

Chang Yu, Qi He, Jing Zheng, Ling Yu Li, Yang Hao Hou, Fang Zhou Song. Sulforaphane improves outcomes and slows cerebral ischemic/reperfusion injury via inhibition of

NLRP3 inflammasome activation in rats,International Immunopharmacology,Volume 45,2017,

Fangfang Zhao, Jianlei Zhang, Na Chang,Epigenetic modification of Nrf2 by sulforaphane increases the antioxidative and anti-inflammatory capacity in a cellular model of Alzheimer's disease,European Journal of Pharmacology,Volume 824,2018,

Meili Wang, Die Pu, Yuxing Zhao, Jinliang Chen, Shiyu Zhu, Ankang Lu, Zhilin Liao, Yue Sun, Qian Xiao,. Sulforaphane protects against skeletal muscle dysfunction in spontaneous type 2 diabetic db/db mice,Life Sciences,Volume 255,2020,

T. Matsui, N. Nakamura, A. Ojima, Y. Nishino, S.-i. Yamagishi,Sulforaphane reduces advanced glycation end products (AGEs)-induced inflammation in endothelial cells and rat aorta,Nutrition, Metabolism and Cardiovascular Diseases,Volume 26, Issue 9,2016,

Jiseon Lee, Huijeong Ahn, Eui-Ju Hong, Beum-Soo An, Eui-Bae Jeung, Geun-Shik Lee,Sulforaphane attenuates activation of NLRP3 and NLRC4 inflammasomes but not AIM2 inflammasome,Cellular Immunology,Volumes 306–307,2016,

Silva-Palacios, M. Ostolga-Chavarría, C. Sánchez-Garibay, P. Rojas-Morales, S. Galván-Arzate, M. Buelna-Chontal, N. Pavón, J. Pedraza-Chaverrí, M. Königsberg, C. Zazueta,Sulforaphane protects from myocardial ischemia-reperfusion damage through the balanced activation of Nrf2/AhR,Free Radical Biology and Medicine,Volume 143,2019,

Die Pu, Yuxing Zhao, Jinliang Chen, Yue sun, Ankang Lv, Shiyu Zhu, Cheng Luo, Kexiang Zhao, Qian Xiao,Protective Effects of Sulforaphane on Cognitive Impairments and AD-like Lesions in Diabetic Mice are Associated with the Upregulation of Nrf2 Transcription Activity,Neuroscience,Volume 381,2018,

Yike Sun, Shanshan Zhou, Hua Guo, Jian Zhang, Tianjiao Ma, Yang Zheng, Zhiguo Zhang, Lu Cai,

Protective effects of sulforaphane on type 2 diabetes-induced cardiomyopathy via AMPK-mediated activation of lipid metabolic pathways and NRF2 function,Metabolism,Volume 102,2020,

Sisi Qin, Canhong Yang, Weihua Huang, Shuhua Du, Hantao Mai, Jijie Xiao, Tianming Lü,

Sulforaphane attenuates microglia-mediated neuronal necroptosis through down-regulation of MAPK/NF-κB signaling pathways in LPS-activated BV-2 microglia, Pharmacological Research,Volume 133,2018,

Junjun Yang, Xiongbo Song, Yong Feng, Na Liu, Zhenlan Fu, Jiangyi Wu, Tao Li, Hao Chen, Jiajia Chen, Cheng Chen, Liu Yang,

Natural ingredients-derived antioxidants attenuate H2O2-induced oxidative stress and have chondroprotective effects on human osteoarthritic chondrocytes via Keap1/Nrf2 pathway,Free Radical Biology and Medicine,Volume 152,2020,

Javier Angulo, Mariam El Assar, Alejandro Sevilleja-Ortiz, Argentina Fernández, Alberto Sánchez-Ferrer, Javier Romero-Otero, Juan I. Martínez-Salamanca, José M. La Fuente, Leocadio Rodríguez-Mañas,Short-term pharmacological activation of Nrf2 ameliorates vascular dysfunction in aged rats and in pathological human vasculature. A potential target for therapeutic intervention,Redox Biology,Volume 26,2019,

Comparative effectiveness of 4 natural and chemical activators of Nrf2 on inflammation, oxidative stress, macrophage polarization, and bactericidal activity in an in vitro macrophage infection model.

Ali M, Bonay M, Vanhee V, Vinit S, Deramaudt TB.PLoS One. 2020 Jun 8;15(6):e0234484.

Sulforaphane reduces intracellular survival of Staphylococcus aureus in macrophages through inhibition of JNK and p38 MAPK induced inflammation.
Deramaudt TB, Ali M, Vinit S, Bonay M.Int J Mol Med. 2020 Jun;45(6):1927-1941.
Ruhee RT, Ma S, Suzuki K.Antioxidants (Basel). 2020 Feb 4;9(2):136. Protective Effects of Sulforaphane on Exercise-Induced Organ Damage via Inducing Antioxidant Defense Responses.
Sulforaphane alleviates retinal ganglion cell death and inflammation by suppressing NLRP3 inflammasome activation in a rat model of retinal ischemia/reperfusion injury.
Gong Y, Cao X, Gong L, Li W.Int J Immunopathol Pharmacol. 2019 Jan-Dec;33:2058738419861777.
Ahmed Nadeem 1, Sheikh F Ahmad 2, Naif O Al-Harbi 2, Sabry M Attia 2, Saleh A Bakheet 2, Khalid E Ibrahim 3, Faleh Alqahtani 2, Mohammed Alqinyah
Nrf2 Activator, Sulforaphane Ameliorates Autism-Like Symptoms Through Suppression of Th17 Related Signaling and Rectification of Oxidant-Antioxidant Imbalance in Periphery and Brain of BTBR T+tf/J Mice Behav Brain Res. 2019 May 17;364:213-224.
Nadeem, A., Ahmad, S. F., AL-Ayadhi, L. Y., Attia, S. M., Al-Harbi, N. O., Alzahrani, K. S., & Bakheet, S. A. (2020). Differential regulation of Nrf2 is linked to elevated inflammation and nitrative stress in monocytes of children with autism. Psychoneuroendocrinology, 113, 104554. doi:10.1016/j.psyneuen.2019.104554
Sulforaphane has a therapeutic effect in an atopic dermatitis murine model and activates the Nrf2/HO 1 axis.
Wu W, Peng G, Yang F, Zhang Y, Mu Z, Han X.Mol Med Rep. 2019 Aug;20(2):1761-1771.
J Asian Nat Prod Res 2020 Apr;22(4):386-396.
Hepatic Protective Effects of Sulforaphane Through the Modulation of Inflammatory Pathways
Changhun Lee 1, Sumin Yang 1, Bong-Seon Lee 1, So Yeon Jeong 1, Kyung-Min Kim 2, Sae-Kwang Ku 3, Jong-Sup Bae 1
Lalita Subedi 1, Jae Hyuk Lee 1 , Silvia Yumnam 1, Eunhee Ji 2 and Sun Yeou Kim. Anti-Inflammatory Effect of Sulforaphane on LPS-Activated Microglia Potentially through JNK/AP-1/ NF-κB Inhibition and Nrf2/HO-1 Activation. Cells 2019, 8, 194
Passant E. Moustafa,1,3 Noha F. Abdelkader,2 Sally A. El Awdan,1 Osama A. El-Shabrawy,1 and Hala F. Zaki2 Extracellular Matrix Remodeling and Modulation
of Inflammation and Oxidative Stress by Sulforaphane in Experimental Diabetic Peripheral Neuropathy Inflammation 2018 Aug;41(4):1460-1476.
Tongliang Ma 1, Decai Zhu 1, Duoxue Chen 2, Qiaoyun Zhang 1, Huifang Dong 1, Wenwu Wu 1, Huihe Lu 3, Guangfu Wu 1Sulforaphane, a Natural Isothiocyanate Compound, Improves Cardiac Function and Remodeling by Inhibiting Oxidative Stress and Inflammation in a Rabbit Model of Chronic Heart Failure Med Sci Monit 2018 Mar 12;24:1473-1483.
de Oliveira MR, Brasil FB, Fürstenau CR. Sulforaphane Attenuated the Pro-Inflammatory State Induced by Hydrogen Peroxide in SH-SY5Y Cells Through the Nrf2/HO-1 Signaling Pathway. Neurotox Res. 2018;34(2):241-249. doi:10.1007/s12640-018-9881-7
Eren, E., Tufekci, K. U., Isci, K. B., Tastan, B., Genc, K., & Genc, S. (2018). Sulforaphane Inhibits Lipopolysaccharide-Induced Inflammation, Cytotoxicity, Oxidative Stress, and miR-155 Expression and Switches to Mox Phenotype through Activating Extracellular Signal-Regulated Kinase 1/2–Nuclear Factor Erythroid 2-Related Factor 2/Antioxidant Response Element Pathway in Murine Microglial Cells. Frontiers in Immunology, 9.

Erden Eren 1 2, Kemal Ugur Tufekci 1 2, Kamer Burak Isci 1 2, Bora Tastan 1 2, Kursad Genc 2, Sermin Genc 1 2Sulforaphane Inhibits Lipopolysaccharide-Induced Inflammation, Cytotoxicity, Oxidative Stress, and miR-155 Expression and Switches to Mox Phenotype Through Activating Extracellular Signal-Regulated Kinase 1/2-Nuclear Factor Erythroid 2-Related Factor 2/Antioxidant Response Element Pathway in Murine Microglial CellsFront Immunol 2018 Jan 23;9:36.

Yang, G., Yeon, S. H., Lee, H. E., Kang, H. C., Cho, Y. Y., Lee, H. S., & Lee, J. Y. (2018). Suppression of NLRP3 inflammasome by oral treatment with sulforaphane alleviates acute gouty inflammation. Rheumatology, 57(4), 727–736.

Xin, Y., Bai, Y., Jiang, X., Zhou, S., Wang, Y., Wintergerst, K. A., … Cai, L. (2018). Sulforaphane prevents angiotensin II-induced cardiomyopathy by activation of Nrf2 via stimulating the Akt/GSK-3ß/Fyn pathway. Redox Biology, 15, 405–417.

Carrasco-Pozo, C., Tan, K. N., Gotteland, M., & Borges, K. (2017). Sulforaphane Protects against High Cholesterol-Induced Mitochondrial Bioenergetics Impairments, Inflammation, and Oxidative Stress and Preserves Pancreaticβ-Cells Function. Oxidative Medicine and Cellular Longevity, 2017, 1–14.

Wang Y, Wu H, Xin Y, et al. Sulforaphane Prevents Angiotensin II-Induced Testicular Cell Death via Activation of NRF2. Oxid Med Cell Longev. 2017;2017:5374897. doi:10.1155/2017/5374897

Bai Y, Chen Q, Sun YP, et al. Sulforaphane protection against the development of doxorubicin-induced chronic heart failure is associated with Nrf2 Upregulation. Cardiovasc Ther. 2017;35(5):10.1111/1755-5922.12277. doi:10.1111/1755-5922.12277

Dong Z, Shang H, Chen YQ, Pan LL, Bhatia M, Sun J. Sulforaphane Protects Pancreatic Acinar Cell Injury by Modulating Nrf2-Mediated Oxidative Stress and NLRP3 Inflammatory Pathway. Oxid Med Cell Longev. 2016;2016:7864150. doi:10.1155/2016/7864150

Qin WS, Deng YH, Cui FC. Sulforaphane protects against acrolein-induced oxidative stress and inflammatory responses: modulation of Nrf-2 and COX-2 expression. Arch Med Sci. 2016;12(4):871-880. doi:10.5114/aoms.2016.59919

Zhao X, Wen L, Dong M, Lu X. Sulforaphane activates the cerebral vascular Nrf2-ARE pathway and suppresses inflammation to attenuate cerebral vasospasm in rat with subarachnoid hemorrhage. Brain Res. 2016;1653:1-7. doi:10.1016/j.brainres.2016.09.035

Xu Z, Wang S, Ji H, et al. Broccoli sprout extract prevents diabetic cardiomyopathy via Nrf2 activation in db/db T2DM mice. Sci Rep. 2016;6:30252. Published 2016 Jul 26. doi:10.1038/srep30252

Townsend BE, Johnson RW. Sulforaphane reduces lipopolysaccharide-induced proinflammatory markers in hippocampus and liver but does not improve sickness behavior. Nutr Neurosci. 2017;20(3):195-202. doi:10.1080/1028415X.2015.1103463

Holloway PM, Gillespie S, Becker F, et al. Sulforaphane induces neurovascular protection against a systemic inflammatory challenge via both Nrf2-dependent and independent pathways. Vascul Pharmacol. 2016;85:29-38. doi:10.1016/j.vph.2016.07.004

**Table 3**

Albertas Cekauskas et al.Sulforaphane decreases kidney injury after transplantation in rats: role of mitochondrial damage. Ann Transplant, 2013; 18: 488-496

Guerrero-Beltrán et al. Sulforaphane protects against cisplatin-induced nephrotoxicity 2010

Rubio- Navarro.Nrf2 Plays a Protective Role Against Intravascular Hemolysis-Mediated Acute Kidney Injury

Saito et al, 2014. Hepatic Sulfotransferase as a Nephropreventing Target by Suppression of the Uremic Toxin Indoxyl Sulfate Accumulation in Ischemic Acute Kidney Injury

Shin et al, 2019 Nrf2-Heme Oxygenase-1 Attenuates High-Glucose-Induced Epithelial-to-Mesenchymal Transition of Renal Tubule Cells by Inhibiting ROS-Mediated PI3K/Akt/GSK-3β Signaling

Khaleel et al, 2019. Contrast media (meglumine diatrizoate) aggravates renal inflammation, oxidative DNA damage and apoptosis in diabetic rats which is restored by sulforaphane through Nrf2/HO-1 reactivation

Kim et al, 2019. Nrf2-Heme oxygenase-1 modulates autophagy and inhibits apoptosis triggered by elevated glucose levels in renal tubule cells

Gamarallage V.K. Senanayake et al 2012 The Dietary Phase 2 Protein Inducer Sulforaphane Can Normalize the Kidney Epigenome and Improve Blood Pressure in Hypertensive Rats

Lv et al, 2018The Association Between Oxidative Stress Alleviation via Sulforaphane-Induced Nrf2- HO-1/NQO-1 Signaling Pathway Activation and Chronic Renal Allograft Dysfunction Improvement

Guerrero-Beltrán et al. 2012.Sulforaphane, a natural constituent of broccoli, prevents cell death and inflammation in nephropathy

Shang et al, 2015. Sulforaphane attenuation of experimental diabetic nephropathy involves GSK-3 beta/Fyn/Nrf2 signaling pathway

Zhao et al 2016.Sulforaphane Attenuates Contrast-Induced Nephropathy in Rats via Nrf2/HO-1 Pathway

Cristian González-Guerrero2013.Calcineurin inhibitors recruit protein kinases JAK2 and JNK, TLR signaling and the UPR to activate NF-κB-mediated inflammatory responses in kidney tubular cells

Thangapandiyan S, Ramesh M, Miltonprabu S, Hema T, Jothi GB, Nandhini V. Sulforaphane potentially attenuates arsenic-induced nephrotoxicity via the PI3K/Akt/Nrf2 pathway in albino Wistar rats. Environ Sci Pollut Res Int. 2019;26(12):12247-12263.

Atilano-Roque A, Wen X, Aleksunes LM, Joy MS. Nrf2 activators as potential modulators of injury in human kidney cells. Toxicol Rep. 2016;3:153-159. Published 2016

Zhang W, Li Y, Ding H, Du Y, Wang L. Hydrogen peroxide prevents vascular calcification induced ROS production by regulating Nrf-2 pathway. Ren Fail. 2016;38(7):1099-1106.

Ryoo IG, Ha H, Kwak MK. Inhibitory role of the KEAP1-NRF2 pathway in TGFβ1-stimulated renal epithelial transition to fibroblastic cells: a modulatory effect on SMAD signaling. PLoS One. 2014;9(4):e93265.

Ebihara S, Tajima H, Ono M. Nuclear factor erythroid 2-related factor 2 is a critical target for the treatment of glucocorticoid-resistant lupus nephritis. Arthritis Res Ther. 2016;18(1):139.

**Reference Microbiota**

1. Angelino D, Dosz EB, Sun J, Hoeflinger JL, Van Tassell ML, Chen P, et al. Myrosinasedependent and -independent formation and control of isothiocyanate products of glucosinolate hydrolysis. Front Plant Sci 2015;6:831.
2. Brabban AD, Edwards C. Isolamento de microrganismos degradantes de glucosinolato e seu potencial para reduzir o conteúdo de glucosinolato do rapemeal. FEMS Microbiol Lett. 1994; 119:83–8.
3. Cheng DL, Hashimoto K, Uda Y. In vitro digestion of sinigrin and glucotropaeolin by single strains of Bifidobacterium and identification of the digestive products. Food Chem Toxicol. 2004 Mar;42(3):351-7.
4. Clavel T, Henderson G, Alpert CA, Philippe C, Rigottier-Gois L, Doré J, Blaut M. Intestinal bacterial communities that produce active estrogen-like compounds enterodiol and enterolactone in humans. Appl Environ Microbiol. 2005; 71(10):6077-85.
5. Earel JK, VanOosten RL, Griffith TS. Histone deacetylase inhibitors modulate the sensitivity of tumor necrosis factor-related apoptosis-inducing ligand-resistant bladder tumor cells. Cancer research 2006, 66, 499-507.
6. Elfoul L, Rabot S, Khelifa N, Quinsac A, Duguay A, Rimbault A. Formation of allyl isothiocyanate from sinigrin in the digestive tract of rats monoassociated with a human colonic strain of Bacteroides thetaiotaomicron. FEMS Microbiol Lett. 2001 Apr 1;197(1):99-103.
7. He C, Huang L, Lei P, Liu X, Li B, Shan Y. Sulforaphane Normalizes Intestinal Flora and Enhances Gut Barrier in Mice with BBN-Induced Bladder Cancer. Mol Nutr Food Res. 2018;62(24).
8. Holscher HD, Guetterman HM, Swanson KS, An R, Matthan NR, Lichtenstein AH, et al. Walnut consumption alters the gastrointestinal microbiota, microbial-derived secondary bile acids, and health markers in healthy adults: a randomized controlled trial. J Nutr 2018.
9. Holscher HD, Taylor AM, Swanson KS, Novotny JA, Baer DJ. Almond consumption and processing affects the composition of the gastrointestinal microbiota of healthy adult men and women: a randomized controlled trial. Nutrients 2018;10:126.
10. Humblot C, Bruneau A, Sutren M, Lhoste EF, Dore J, Andrieux C, Rabot S. Brussels sprouts, inulin and fermented milk alter the faecal microbiota of human microbiota-associated rats as shown by PCR-temporal temperature gradient gel electrophoresis using universal, Lactobacillus and Bifidobacterium 16S rRNA gene primers. British Journal of Nutrition. 2005;93:677–684.
11. Kaczmarek JL, Liu X, Charron CS, Novotny JA, Jeffery EH, Seifried HE, Ross SA, Miller MJ, Swanson KS, Holscher DH. Broccoli consumption affects the human gastrointestinal microbiota. JNB. 2019.
12. Kellingray L, Tapp HS, Saha S, Doleman JF, Narbad A, Mithen RF. Consumption of a diet rich in Brassica vegetables is associated with a reduced abundance of sulphate-reducing bacteria: A randomised crossover study. Mol. Nutr. Food Reyes. 61, 9, 2017.

13. Li F, Hullar MAJ, Schwarz Y, Lampe JW. Human Gut Bacterial Communities Are Altered by Addition of Cruciferous Vegetables to a Controlled Fruit- and Vegetable-Free Diet. J Nutr. 2009;139(9):1685–1691.
14. Liu X, Wang Y, Hoeflinger JL, Neme BP, Jeffery EH, Miller MJ. Dietary Broccoli Alters Rat Cecal Microbiota to Improve Glucoraphanin Hydrolysis to Bioactive Isothiocyanates. Nutrients. 2017; 9(3): 262.
15. Llanos Palop M, Smiths JP, Brink BT. Degradation of sinigrin by Lactobacillus agilis strain R16. Int J Food Microbiol. 1995 Jul; 26(2):219-29.
16. Mullaney JA, Kelly WJ, McGhie TK, Ansell J, Heyes JA. Lactic acid bacteria convert glucosinolates to nitriles efficiently yet differently from enterobacteriaceae. J Agric Food Chem. 2013 Mar 27; 61(12):3039-46.
17. Rabot S, Guerin C, Nugon-Boudon L, Szylit O. Degradação de glucosinolato por estirpes bacterianas isoladas de uma microflora intestinal humana. Anais do 9° Congresso Internacional de Colza, organizado pelo GCIRC (Grupo Internacional de Pesquisa em Pesquisa sobre Colza. Em inglês: Grupo Internacional de Pesquisa sobre Colza); 1995.
18. Wang D, Wang Z, Tian B, Li X, Li S, Tian Y. Two-hour exposure to sodium butyrate sensitizes bladder cancer to anticancer drugs. International journal of urology: official journal of the Japanese Urological Association. 2008;15:435-441.
19. Wu Y, Shena Y, Zhua Y, Mupungaa J, Zouc L, Liuc C, Liua S, Maoa J. Broccoli ingestion increases the glucosinolate hydrolysis activity of microbiota in the mouse gut. Inter journ of food sciences and nutrition. 2018;1:10.
20. Xu X, Dai M, Lao F, Chen F, HU X, Liu Y, Wu J. Effect of glucoraphanin from broccoli seeds on lipid levels and gut microbiota in high-fat diet-fed mice. Journal of Functional Foods. 2020:103858.