Review

Triggers for the Nrf2/ARE Signaling Pathway and Its Nutritional Regulation: Potential Therapeutic Applications of Ulcerative Colitis

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Abstract: Ulcerative colitis (UC), which affects millions of people worldwide, is characterized by extensive colonic injury involving mucosal and submucosal layers of the colon. Nuclear factor E2-related factor 2 (Nrf2) plays a critical role in cellular protection against oxidant-induced stress. Antioxidant response element (ARE) is the binding site recognized by Nrf2 and leads to the expression of phase II detoxifying enzymes and antioxidant proteins. The Nrf2/ARE system is a key factor for preventing and resolving tissue injury and inflammation in disease conditions such as UC. Researchers have proposed that both Keap1-dependent and Keap1-independent cascades contribute positive effects on activation of the Nrf2/ARE pathway. In this review, we summarize the present knowledge on mechanisms controlling the activation process. We will further review nutritional compounds that can modulate activation of the Nrf2/ARE pathway and may be used as potential therapeutic application of UC. These comprehensive data will help us to better understand the Nrf2/ARE signaling pathway and promote its effective application in response to common diseases induced by oxidative stress and inflammation.

Keywords: antioxidant response element; Kelch-like ECH-associated protein 1; nuclear factor E2-related factor 2; nutritional regulation; ulcerative colitis

1. Introduction

Ulcerative colitis (UC) is an idiopathic, chronic, and relapsing inflammatory bowel disease characterized by cycles of acute inflammation, ulceration, and bleeding of the colonic mucosa [1,2]. It usually has a lifelong impact with long-term disabling symptoms that increase the risk of colorectal cancer, which is the third most common malignancy in humans. Etiopathogenesis of UC remains uncertain, but many studies reported that oxidative stress is associated with the pathogenesis of chronic inflammatory bowel disease [3]. Oxidative stress develops particularly in inflammatory reactions because inflammatory cells, neutrophils, and macrophages produce large amounts of ROS (Figure 1). Accumulated ROS can cause oxidative damage to cell structures (proteins, DNA, lipids, and membranes), and they also act as chemical messengers to activate signaling pathways, such as NF-κB and p38 MAPK, that affect cell proliferation, differentiation, and apoptosis [4,5]. Most current therapies for UC are effective; however, they can cause severe side effects, including diarrhea, abdominal cramps, and high blood pressure, with extended treatment periods [6]. Hence, the underlying mechanisms of UC and therapeutic strategies still require investigation for the prevention and treatment of UC (Figure 1).

Nuclear factor E2-related factor2 (Nrf2) is an important sensor protein expressed in many tissues that plays a crucial role in cellular detoxification in response to oxidative stress [6]. Upon oxidative and electrophilic insults, Nrf2 dissociates from its cytoplasmic

repressor, Kelch-like ECH-associated protein 1 (Keap1), and then translocates to the nucleus [7]. As a result, expression of cytoprotective enzymes, such as NADPH: quinone oxidoreductase 1 (NQO1) and heme oxygenase 1 (HO-1), increases to enhance cellular defense against ROS, which confers protection against various deleterious oxidative stresses, inflammation, and apoptosis [8]. A growing body of evidence indicates that Nrf2 could play a potentially important role in protecting against UC through regulation of proinflammatory cytokines and induction of phase II detoxifying enzymes [9]. For this reason, Nrf2/ARE plays important roles in mitigating oxidative stress. The underlying mechanisms of controlling Nrf2/ARE activation need to be summarized and thoroughly investigated.
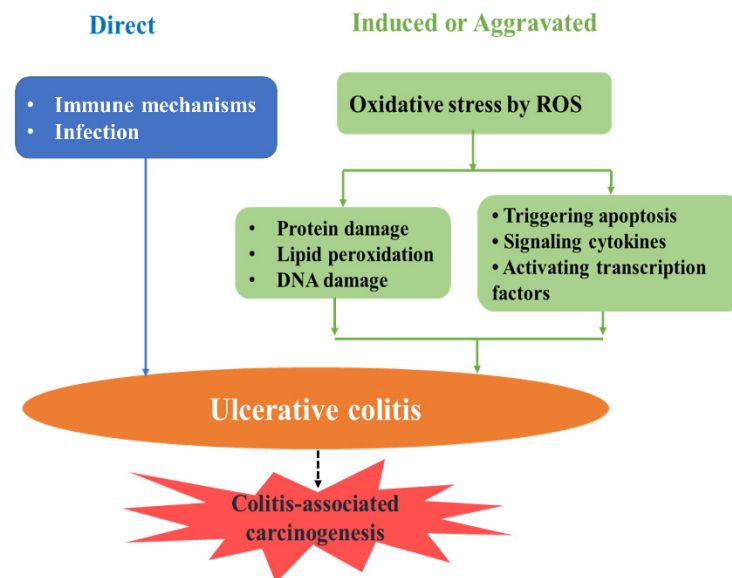

Figure 1. Hypothetic mechanisms involved in oxidative stress-induced ulcerative colitis, which may lead to colitis-associated carcinogenesis. Oxidative stress develops as the inflammatory cells, neutrophils, and macrophages produce large amounts of ROS, which are associated with the pathogenesis of chronic inflammatory bowel disease.

2. Triggers for Activation of the Nrf2/ARE Signaling Pathway

Nrf2 contains six highly conserved domains, known as Neh1–Neh6. The N-terminal domain of Neh2 is the major regulatory domain [10]. Neh2 attaches to Keap1 at the ETGE and DLG binding sites, which help regulate the stability of Nrf2. The Neh2 domain also contains seven lysine residues which are responsible for conjugation with ubiquitin [11]. Neh1 contains a CNC-type bZIP DNA-binding motif that allows Nrf2 to bind DNA and dimerize with other transcription factors [12]. The Neh3, Neh4, and Neh5 domains mediate transactivation of Nrf2 by interacting with coactivators, including histone acetyltransferases [13]. Recently, a seventh Neh domain (Neh7) was identified and shown to interact with the retinoic X receptor α, an Nrf2 repressor, to repress Nrf2 target gene transcription [14].

The antioxidant response element (ARE) is the consensus sequence defined as 5′-TGACnnnGC-3′, where essential nucleotides are in capitals and the "n" represents any nucleotide [15]. In the nucleus, the binding of Nrf2 to the ARE is facilitated via hetero dimerization with the musculoaponeurotic fibrosarcoma (Maf) protein family [16]. This binding stimulates a wide variety of downstream transcriptions that play important roles in cytoprotection and metabolism.

2.1. Keap1-Dependent Activation of Nrf2/ARE Pathway

Keap1 contains four characteristic domains, including a broad complex/tramtrack/bric-a-brac (BTB) domain, an intervening region (IVR), a double glycine repeat (Kelch/DGR) domain, and the C-terminal region (CTR). The BTB domain binds Cul3 and serves in the dimerization of Keap1 in cytoplasm [17]. The Kelch/DGR-CTR domain is critical

for maintaining physical interaction between Keap1 and the Neh2 domain of Nrf2 [18]. The IVR contains several redox-sensitive cysteine residues which mainly modify Keap1 activity [19]. Thus, each of the four domains is thought to play a unique role in mediating Nrf2 ubiquitination and repression.

Under basal conditions, Nrf2 synthesized in the cell primarily binds to a complex with Keap1 so that concentration of free Nrf2 is low in homeostasis (Figure 2) [20]. This phenomenon could be explained by the "Hinge and latch" model, which indicates that two Keap1 bind, respectively, to the ETGE motif (hinge) and the DLG motif (latch) of Nrf2 in a favorable position which promotes Nrf2 to be ubiquitinated and degraded by 26S proteasomes [17]. After oxidative or electric stimulus, Keap1 conformation is modified to release Nrf2 from the low-affinity DLG motif [21]. However, Nrf2 remains attached to Keap1 with the high-affinity ETGE motif (hinge). Consequently, polyubiquitination and subsequent proteasomal degradation are broken [22]. The end result is that Keap1 molecules become saturated with Nrf2, and concentration of newly synthesized, free Nrf2 increases [6]. These changes activate Nrf2 and promote its translocation to the nucleus (Figure 2).
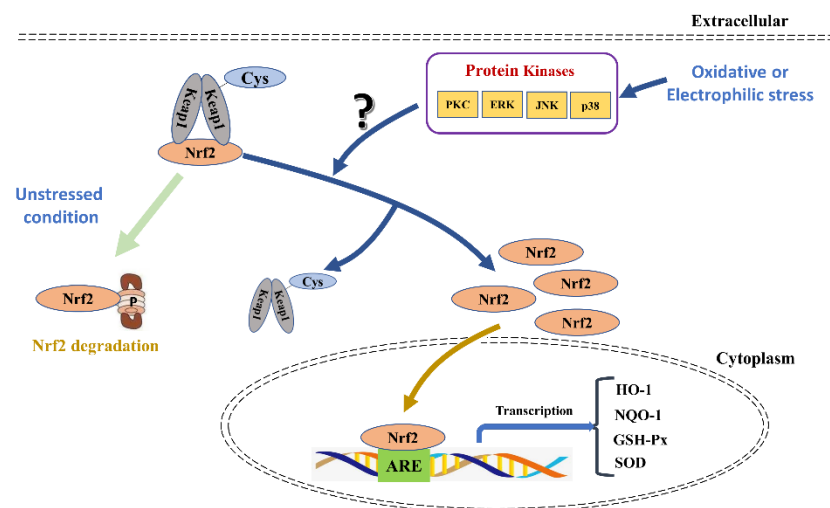

Figure 2. The role of Nrf2/ARE pathway in antioxidant response and its regulatory mechanism. In unstressed condition, Nrf2 synthesized in the cell is primarily bound to a complex with Keap1 and degraded by the 26S proteasomes. After oxidative or electrophilic stress, Keap1 molecules become saturated with Nrf2, and the number of newly synthesized, free Nrf2 is increased and promotes its translocation to the nucleus. In the nucleus, binding of Nrf2 to the ARE is facilitated and transcription of a wide variety of downstream are stimulated, which play an important role in cytoprotection and metabolism.

2.2. Keap1-Independent Activation of Nrf2/ARE Pathway

2.2.1. Protein Kinase C

Protein Kinase C (PKC) is a family of phospholipid-dependent serine/threonine kinases. PKC activation increases concentration of the antioxidant proteins GST, SOD, and γ-GCS and depresses ROS content in rats, leading to an anti-oxidative effect [23]. Previous studies have also demonstrated that PKC plays important roles in the activation and expression of Nrf2. Lin et al. reported that Nrf2 and phase II detoxification gene expression could be induced via activation of the PKC signaling pathways [24]. In an in vitro model, Guo et al. asserted that protocatechualdehyde provided neuroprotection via the PKC pathway to promote Nrf2 dissociation from Keap1 and translocation into the nucleus, which up-regulated HO-1 expression [25]. Further investigation demonstrated that PKC catalyzed Nrf2 activation by phosphorylation of Nrf2 at Ser40, which is necessary for Nrf2 dissociation from Keap1 and nuclear translocation [26]. Since PKC has various isoforms including α, β, γ, δ, and ε, Chen et al. identified PKC-δ as the major PKC isoform

that phosphorylated Nrf2 Ser40 [27]. In addition, PKC α and β work to activate Nrf2 at different (early or late) time points. These authors believe that each PKC isoform might trigger phosphorylation of Nrf2 by differentially inducing activation of Nrf2 [28]. The exact mechanism by which PKC isoforms regulate and activate Nrf2 is not fully understood and needs further investigation.

2.2.2. AMP-Activated Protein Kinase

AMP-activated protein kinase (AMPK) is a metabolically sensitive serine/threonine protein kinase ubiquitously expressed in many different tissues [29]. It is a heterotrimeric complex consisting of a catalytic α-subunit and two regulatory subunits, β and γ [30]. AMPK was identified initially as a "fuel gauge" whose activation allows cells to enhance fuel oxidation in response to an increase in the AMP-to-ATP ratio [31]. The signaling pathway for AMPK to maintain cellular energy homeostasis is activated by phosphorylation at Thr172 in the activation loop of the catalytic α-subunits [32]. Interestingly, AMPK was characterized recently as a novel regulator and upstream signal for modulating the redox state of cells under oxidative stress. AMPK induces SOD and HO-1 expression via the Nrf2/ARE signaling pathway, which enables the cell to increase its antioxidant capacity and survival [33]. Using a chemical–biological approach, Zimmermann et al. revealed the positive influence of AMPK on Nrf2 activation and subsequent antioxidant enzyme production in response to oxidative stress [34]. Furthermore, several researchers indicated that activated AMPK/Nrf2 pathways exhibit anti-inflammatory effects on LPS-stimulated macrophages and microglia [30,35]. After a series of studies investigating the potential mechanism of AMPK/Nrf2dependent pathway, Joo et al. reported that phosphorylation of Nrf2 at the Ser550 residue by AMPK promotes Nrf2 dissociation from Keap1 and nuclear accumulation of Nrf2 for ARE-driven gene transactivation [36]. Notably, Sid et al. discovered that 5-aminoimidazole-4-carboxamide riboside could induce Nrf2 activation to modulate the redox state of human hepatocarcinoma cells via an AMPK-independent mechanism [31]. In summary, studies are in progress that aim for a complete understanding of the crosstalk between AMPK and the transcription of Nrf2.

2.2.3. Mitogen-Activated Protein Kinases

Mitogen-activated protein kinases (MAPKs) belong to a family of serine/threonine kinases and play a central role in coupling various extracellular signals to a variety of biological processes, such as gene expression, cell proliferation, cell differentiation, and cell death [37]. To date, three MAPKs have been extensively studied: extracellular signal-regulated kinases (ERK), c-Jun NH2-terminal kinases (JNKs, also called stress-activated protein kinases), and p38 [38]. Activity of these MAPKs is induced through phosphorylation of their threonyl and tyrosyl residues by a dual specificity kinase termed MAP kinase kinase (MAPKK), which is phosphorylated and activated by an upstream kinase generally called MAPK kinase kinase (MAPKKK) [39]. These kinases are able to activate JNK through MKK4 and p38 through MKK3 or MKK6, but they do not affect the ERK pathway [40]. Although JNK, p38, and ERK may be regulated by different upstream kinases, they are preferentially activated by various stress stimuli and are involved in the regulation of stress signals.

Extracellular-Signal-Regulated Kinase 1/2

Extracellular-signal-regulated kinases 1 and 2 (ERK1/2) are isoforms of the "classical" MAPK and rely on the Thr–Glu–Tyr (TEY) activation motif. Both ERK1 and ERK2 are activated by growth factors and play an important role in regulation of cell proliferation and cell differentiation [41]. ERK1/2 is activated by MAP/ERK kinase 1 (MEK1) and MAP/ERK kinase 2 (MEK2), which are referred to as MEK1/2 [42]. Activated ERK1/2 phosphorylates many substrates, including protein kinases such as ribosomal S6 kinase (RSK), and the transcription factors Elk1 and Nrf2 [43]. ERK1/2 is an important contributor to cell proliferation and defense. Wang et al. suggested that the antioxidant pathway

activated by gastrodin involves ERK1/2 phosphorylation, which increases Nrf2 nuclear translocation and leads to an elevation of phase II detoxifying enzyme and antioxidant enzyme levels [44]. Hu et al. demonstrated that up-regulating the phosphorylation of ERK 1/2 in rats could significantly activate Nrf2/ARE pathways and induce Nrf2 nuclear translocation with enhances HO-1 and NQO1 expression [43].

C-Jun N-Terminal Kinases and p38

C-Jun N-terminal kinases (JNKs) are also called stress-activated protein kinases (SAPKs). Recent studies have suggested that JNK and p38 play critical roles in mitigating oxidative stress. Vari et al. reported that JNK-mediated phosphorylation of Nrf2 plays an essential role in the expression of antioxidant proteins and phase II detoxifying enzymes induced by protocatechuic acid [45]. Ma et al. provided evidence that expression of Nrf2 could be induced by activation of p38 MAPK signaling in glioma cells [46]. Additionally, p38 or JNK may play a role without activation of the Nrf2/ARE pathway. Jiang et al. suggested that activation of p38/JNK but attenuation of the Nrf2/Akt pathway plays an important role in the suppression of gastric cancer by diallyl trisulfide [47]. Evidently, Nrf2 plays dual roles in cancer prevention and progression depending on the cellular context and environment. These authors suggest that a better understanding of Nrf2 is necessary to understand this balance between antioxidant pathways and the inhibition of tumor progression.

Phosphatidylinositol-3-Kinase/Protein Kinase B

Phosphatidylinositol-3-kinase (PI3K) is a lipid kinase that generates phosphatidylinositol-3,4,5-trisphosphate (PI (3,4,5) P3), which is a second messenger essential for translocation of Akt to the plasma membrane where it is phosphorylated [48]. Activation of Akt plays a pivotal role in fundamental cellular functions, such as cell proliferation and survival, by phosphorylating a variety of substrates [49]. Qi et al. demonstrated that activation and crosstalk between PI3K/Akt and Nrf2/HO-1 signaling pathways plays a potential role in regulating the hormesis of Z-ligustilide in PC12 cells under oxygen and glucose deprivation [50]. Likewise, Lee et al. indicated that ROS generation and/or activation of PI3K/Akt signaling regulates cell survival and Nrf2-driven HO-1 expression in sulforaphane-treated cells [51].

2.2.4. Histone Modifications
Histone Deacetylases

Acetylation of lysine residues in histones or other transcription factors plays an important role in the regulation of transcription and gene expression [52]. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) include a series of enzymes that regulate acetylation/deacetylation, which alter many physiological and pathological processes [53]. HDAC inhibition can induce hyperacetylation of target proteins, leading to an alteration of target gene transcription and expression [54]. Recent studies indicated that Nrf2 is a protein acetylation target. Nrf2 acetylation promotes its translocation capacity and downstream gene expression, thus increasing oxidative and inflammatory protection in animal and cell models [54,55]. Known as HDAC inhibitor, sodium butyrate can similarly induce Keap1/Nrf2 dissociation, Nrf2 nuclear translocation, and expression of downstream antioxidant responses [56]. Interestingly, Mercado et al. reported that reduced HDAC2 activity in COPD may account for increased Nrf2 acetylation, reduced Nrf2 stability, and impaired anti-oxidant defenses [57]. Mercado explained that Class I and II HDACs are inhibited in a COPD model, which leads to increased acetylation of Nrf2, decreasing stability and anti-oxidant potential. Similarly, inhibition of HDAC activity by TSA can cause acetylation of other residues in Nrf2 that might play a critical role in Nrf2 protein stability [57]. Currently, studies are focused on understanding the crosstalk between the HDAC and transcription of Nrf2.

Silent Information Regulator 2-Related Protein 1

Silent information regulator 2-related protein 1 (Sirt1) is a NAD+-dependent class III histone deacetylase that plays important roles in proliferation, cell oxidative stress, and inflammation [58]. Previous studies have demonstrated that crosstalk between Sirt1 and the Keap1/Nrf2/ARE pathway are important in the response of cells to oxidative stress [59,60]. In brief, Sirt1 can activate Nrf2 by modifying the structure of Keap1, thereby inducing nuclear translocation of Nrf2 [61]. In the nucleus, Nrf2 combines with ARE and up-regulates the expression of antioxidant proteins and phase II detoxifying enzymes to protect against oxidative stress [58]. Zhang found that Resveratrol promotes Nrf2/ARE anti-oxidative pathway through activation of Sirt1 to resist oxidative stress [62]. In addition, the deacetylation ability of Sirt1 can inhibit the transcription activity of NF-κB p65 subunits, thereby reducing the extent of inflammation [63]. Therefore, regulating Sirt1 is a potential research direction for tissue protection. Taken together, considering multiple beneficial advantages in relieving metabolic disorders, anti-oxidative responses, and inflammation, further studies are needed to investigate the regulatory mechanisms of Sirt1 in response to multiple forms of stress.

3. Nutritional Regulation of Nrf2/ARE Pathway

Most recently, our understanding of how nutrition plays a potential role in the prevention and/or treatment of various chronic diseases has grown tremendously [64,65]. A balanced diet based on the food components can bring health benefits. Siracusa et al. reported that cashew nuts could have beneficial action for the treatment of colitis with antioxidant and anti-inflammatory properties [66]. Antioxidant compounds may act indirectly by enhancing the endogenous cellular antioxidant defenses, such as through activation of Nrf2 (Table 1). Nutritional components may modulate the Nrf2/ARE system and may be of fundamental importance to demonstrate beneficial effects of this system in various chronic diseases such as UC [67,68]. Therefore, additional investigations are warranted into nutritional modulation of Nrf2, which may be contributory to the development of new nutritional therapies.

Table 1. Modulation of Nrf2/ARE signaling pathways by nutritional components.

Nutritional Compounds	Components	Conclusions	Reference
Probiotics	*Lactobacillus rhamnosus*	Multifactorial anti-oxidative and anti-inflammatory defenses in a Nrf2-dependent system	[69]
	Lactobacillus gasseri	Modulation of Nrf2-mediated cytoprotection and cell surface antigens	[70]
	Bacillus amyloliquefaciens	Increase in gene expression of antioxidant enzymes and elevated Nrf2 concentration in jejunum	[71]
Prebiotic	*Lycium barbarum polysaccharide*	Regulation of the Nrf2/ARE pathway via activation of PI3K/Akt signaling	[72]
	Alfalfa polysaccharide	Prevention of H2O2-induced oxidative damage by activating MAPK/Nrf2 signaling pathways	[73]
	Bacterial polysaccharide	Regulation of MAPK-mediated Nrf2/Keap1 homeostatic signaling	[74]
	Chitosan oligosaccharide	Protective effects on oxidative damage of IPEC-1 cells	[75]
Short chain fatty acids	Butyrate	Regulation of Th17/Treg cell balance to ameliorate uveitis via the Nrf2/HO-1 pathway	[76]

Table 1. *Cont.*

Nutritional Compounds	Components	Conclusions	Reference
Amino acids	Methionine	Inducing an endogenous antioxidant response via activation of the Nrf2-ARE pathway	[77]
	Tryptophan	Improvement of antioxidant status and enhancement of immunity in blunt snout bream	[78]
	Glutamine	Increase in glucose-6-phosphate dehydrogenase via Nrf2 pathway	[79]
	Leucine	Modulation of Nrf2 antioxidant signaling pathway and immune response	[80]
Polyphenolic	Curcumin	Activation of heterodimers of the Nrf2/ARE pathway and increase in expression of HO-1	[81]
	Resveratrol	Modulation of antioxidant enzyme activity protecting human keratinocytes from oxidative stress	[82]
	Proanthocyanidin	Effective in improving antioxidant status and reducing inflammation in weaned pigs	[83]

3.1. Probiotics

Probiotics are defined as "live microorganisms that, when administrated in adequate amounts, confer a health benefit on the host" [84]. One of the dietary-based strategies currently in vogue explores probiotics for the amelioration of oxidative stress-related diseases by augmentation of antioxidant defense systems operating in the human body [85]. A large body of evidence demonstrates that probiotics could have anti-oxidative effects via the Nrf2/ARE pathway. Saeedi reported that the probiotic *Lactobacillus rhamnosus* is adequately equipped with multifactorial anti-oxidative and anti-inflammatory defenses in a Nrf2-dependent system [69]. Likewise, *Lactobacillus gasseri* possesses distinctive abilities to modulate Nrf2-mediated cytoprotection and cell surface antigens to influence crosstalk between DCs and enterocytes [70]. Besides *Lactobacillus*, probiotic *Bacillus* has also shown strong anti-oxidative potential. *Bacillus amyloliquefaciens* increased gene expression of antioxidant enzymes and elevated Nrf2 concentration in jejunum. These characteristics may serve as a potential substitute for antibiotics [71].

3.2. Prebiotics

Prebiotics are food ingredients selectively metabolized by beneficial intestinal bacteria [86]. Dietary modulation of gut microflora by prebiotics is designed to improve health by stimulating the numbers and/or activities of *Bifidobacteria* and *Lactobacilli* [87]. Having an 'optimal' gut microflora can increase resistance to pathogenic bacteria, increase stimulation of the immune response, and reduce the risk of cancer [88]. *Polysaccharides* are one of the major constituents of prebiotics. Both plant *polysaccharides* and bacterial *polysaccharides* are being applied to the improvement of human health. Zhao et al. reported that dietary *Lycium barbarum polysaccharide* modified the Nrf2/ARE pathway and ameliorated insulin resistance induced by a high-fat diet via activation of PI3K/Akt signaling [72]. *Alfalfa polysaccharide* and aloe *polysaccharide* can also prevent H_2O_2-induced oxidative damage in MEFs by activating MAPK/Nrf2 signaling pathways and suppressing NF-κB signaling pathways [73]. In addition, Choedhury et al. indicated that low fucose-containing *bacterial polysaccharide* facilitated mitochondria-dependent, ROS-induced apoptosis of human lung epithelial carcinoma via controlled regulation of MAPK-mediated Nrf2/Keap1 homeostatic signaling [74]. Chitosan oligosaccharide (COS) also showed protective effects on oxidative damage of IPEC-1 cells [75]. However, the mechanisms of action of COS involved in the modulation of several important pathways, including the suppression of NF-κB and activation of AMP-activated protein kinase, are not known clearly.

3.3. Short Chain Fatty Acids

Short chain fatty acids (SCFAs), mostly generated in the colon, are produced during the fermentation of dietary fibers by gut microbiota [89]. The main SCFAs include acetate, propionate, and butyrate. These SCFAs lower lumen pH in the gut and exhibit protective effects, including maintenance of IEC integrity and immune homeostasis, and suppression of inflammation [90]. Wu et al. reported that sodium butyrate enhanced physical barrier function in the intestine of young grass carp [91]. Sodium butyrate also regulates Th17/Treg cell balance to ameliorate uveitis via the Nrf2/HO-1 pathway [76]. Additionally, sodium butyrate attenuates diabetes-induced aortic endothelial dysfunction via p300-mediated transcriptional activation of Nrf2 [92]. However, currently, the Nrf2 activation effect of other SCFAs except butyrate is not understood clearly.

3.4. Amino Acids

In addition to serving as the substrates for protein synthesis, amino acids in diets can act as precursors for numerous metabolic pathways involved in anti-inflammatory and antioxidant activities [93]. Specifically, Li et al. elucidated that methionine plays a critical role in inducing an endogenous antioxidant response via activation of the Nrf2/ARE pathway [77]. The optimal dietary tryptophan level could improve antioxidant status and enhance immunity in blunt snout bream [78]. Besides essential amino acids, Polat et al. unveiled that glutamine induced an increase of glucose-6-phosphate dehydrogenase via the Nrf2 pathway [79]. Dietary leucine modulated the Nrf2 antioxidant signaling pathway and immune response in juvenile blunt snout bream [80]. Indeed, more studies are needed to explore the impact of amino acids in diets on antioxidant response through Nrf2/ARE pathway.

3.5. Polyphenolic Compounds

Polyphenols are a group of chemical substances found in plants which are characterized by the presence of aromatic ring(s) bearing one or more hydroxyl moieties [94]. Polyphenols include resveratrol and curcumin. In addition to their antibiotic and anti-inflammatory potential, polyphenols also activate Nrf2 [95–97].

Curcumin, a polyphenol found in the spice turmeric, strongly induces the expression of HO-1 and its activity in different brain cells by activating heterodimers of the Nrf2/ARE pathway [81]. For this reason, curcumin protective action extends to various endocrine and metabolic diseases. Resveratrol (3,40,5-trihydroxy-trans-stilbene) is a secondary plant metabolite found in grapes, red wine, and vaccinium berries [98]. Recent research has demonstrated that resveratrol can regulate Nrf2 expression. Liu et al. observed that resveratrol protected human keratinocytes from ultraviolet A-induced oxidative stress and increased antioxidant enzyme activity [82]. They hypothesized that these actions were the result of increased Nrf2 expression and its accumulation in the nucleus. Besides resveratrol, proanthocyanidin is an important antioxidant polyphenol from grape seeds. Animal studies have manifested that proanthocyanidin was effective in improving antioxidant status and reducing inflammation in weaned pigs [83]. Similarly, polyphenols in green tea and apples showed myriad benefits owing to its potent antioxidant properties [99]. As mentioned, some polyphenols such as quercetin, kaempferol, and ellagic acid also possess protective effects on ulcerative colitis attributed to Nrf2-associated antioxidant capacity [100–102].

4. Conclusions and Perspective

Accumulating evidence supported that the Nrf2/ARE pathway plays a key role in the protective mechanism of cells through the induction of phase II detoxifying and antioxidant enzymes against exogenous and endogenous damage species. Several upstream signaling pathways, including mitogen-activated protein kinases, protein kinase C, phosphatidylinositol 3-kinase, and HDAC, are implicated in the regulation of Nrf2/ARE activity. Some signals may also work together to regulate activation of Nrf2 and translation of ARE

through cooperation with other signals. Nutritional compounds as described in this review have been studied and indicated as effective modulation of the Nrf2/ARE pathway. Several classes among them have manifested their benefits for the management of colitis. However, more mechanistic studies are needed to elucidate which upstream pathways are involved in the activation processes.

Taken together, our current understanding of the molecular mechanism in activation of the Nrf2/ARE defense pathway is in its early phase. Much more researches are needed to investigate the mechanism and crosstalk of various upstream signaling pathways. Furthermore, special attention to nutritional supplements that may promote Nrf2/ARE signaling pathway is necessary. Nutritional regulation of UC with food components may reveal "nutritional therapies" in the defense against oxidative stress and inflammation via activation of the Nrf2/ARE pathway.

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