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Astaxanthin and Nrf2 signaling pathway: a novel target for new therapeutic approaches

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Abstract:

Astaxanthin (AST) is a naturally occurring compound isolated from various sources such as fungi, plants, salmon and crab. However, *Haematococcus Pluvialis*, a green alga, is the primary source of this beta carotenoid compound. AST has several favourable biological and pharmacological activities such as antioxidant, anti-inflammatory, anti-tumor, anti-diabetes, hepatoprotective and neuroprotective. Nevertheless, the exact molecular mechanisms of these protective effects of AST is unclear yet. The Nrf2 signaling pathway is one of the critical candidate signaling pathways which may be involved in these beneficial effects of AST. This signaling pathway is responsible for maintaining the redox balance in the physiologic state. Upon nuclear translocation, Nrf2 signaling activates antioxidant enzymes to reduce oxidative stress and protect cells against damage. In the current study, we have reviewed the effects of AST on Nrf2 signaling pathway which could potentially be developed as a novel therapeutic approache for the management of various diseases.

Keywords: Astaxanthin, Oxidative Stress, Cardioprotective, Neuroprotective, Nrf2 Signaling Pathway, Renoprotective, Diabetes Mellitus.

Introduction

The herbal-based pharmacological agents for treatment of various medical conditions have been used worldwide for thousands of years [1, 2]. Ancient physicians such as Avicenna and Hippocrates used plant-derived agents for managing various diseases [2, 3]. In recent decades, due to some undesirable side effects of synthetic medications and lack of available treatment for some disorders, once again, more attention has been paid to these plant-derived pharmacological agents [4-8]. There is growing evidence about the molecular mechanisms by which these natural pharmaceuticals exert their therapeutic effects on various tissues [9-11].

Astaxanthin (AST) is a naturally occurring beta-carotenoid found mainly in some plants. Similar to other beta carotenes, it has potent antioxidative properties as well as other beneficial effects [12-14]. This terpene-based chemical compound is widely used in experimental studies to suppress the pathophysiologic processes involved in various disease states [13, 15]. However, the exact molecular mechanisms by which AST exerts its beneficial effects are not well established. Recent evidence suggests that AST acts mainly via Nrf2-dependent molecular mechanism, a molecular pathway which has prominent roles in cellular antioxidative defense system [16, 17], which could potentially be translated into developing novel therapeutic targets [18]. In this current study, the effects of AST on Nrf2 molecular pathway in different tissues are discussed.

Astaxanthin

Carotenoids are a large family with more than 700 naturally occurring active compounds which give colors such as orange, yellow and red to various plants [19-21]. In addition to its coloring properties, it has been demonstrated that carotenoids play significant physiological roles [22]. They are considered as vital components of photosynthesis and photoprotection as well as

provide substances for the synthesis of strigolactones. All plants can biosynthesize carotenoids. Even some microorganisms, including fungi and bacteria, have demonstrated the potential for the synthesis of carotenoids [23]. AST (3, 3′-dihydroxy-β, β′-carotene-4, 4′-dione) is a naturally occurring carotenoid which belongs to the Xanthophylls [24]. AST is found in fungi, plants, salmon and crab but it is found extensively in *Haematococcus Pluvialis*, a green microalgae [25, 26].

There are limited data and experiments on the bioavailability of AST, however, long term consumption of AST is associated with its increased concentration in the body which is independent of the source of AST [27]. There have been attempts to enhance the bioavailability as well as target delivery of AST and nano-soldiers have been shown to have promising effect [28]. Polymeric nanoparticles, liposomes and cyclodextrins have been used to encapsulate AST, however, more efforts are needed to enhance the bioavailability of AST. This naturally occurring compound has a number of therapeutic and biological activities (**figure 1**) such as anti-oxidant [29, 30], anti-inflammatory [31], anti-tumor [31], anti-diabetic [32] and hepatoprotective [33].

AST has also been demonstrated to have a lung-protective activity. In a study, Cai and colleagues in 2019 examined the ameliorative effect of AST against lipopolysaccharide (LPS)-mediated lung injury and sepsis [34]. The results of this study demonstrated that AST administration is associated with decreased levels of inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Also, in vivo experiment showed that AST promotes the survival time of animals and protects against lung injury. In another study by Choi et al. in 2019, the neuroprotective effect of AST in newborn rats exposed to prenatal maternal seizures was evaluated [35]. It was found that prenatal AST administration is associated with alleviation of neuronal lesions, decreased level of oxidative stress and attenuation of placental ischemic

damage in epileptic mothers. It seems that antioxidant and anti-inflammatory activities are responsible for most of the protective effects of AST. AST has shown great potential in the modulation of other signaling pathways such as peroxisome proliferator-activated receptor (PPAR) [36]. However, there are no reviews to assess the impacts of AST on the Nrf2 signaling pathway.

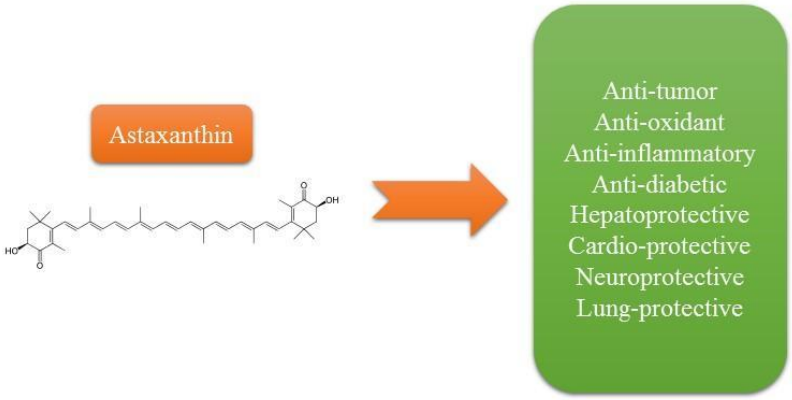

Figure 1: The main known biological and therapeutic activities of Astaxanthin as anti-tumor, mainly by modulating apoptotic processes and growth factors; antioxidant by potentiating antioxidative systems; reduction in inflammatory responses, hypoglycemic effects via several pathways as insulin sensitization and protective effects in tissues as liver, cardiovascular system, neuronal system and lungs [37]

Nrf2 signaling pathway

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a highly conserved signaling pathway belonging to the Cap "n" Collar family [38]. Nrf2 has several domains including, Neh1-Neh7 with their activities such as binding to DNA [39]. The Nrf2 signaling pathway has been developed with the aim to provide redox balance (**figure 2**); so that at ordinary conditions, this pathway is inhibited and has a basal level of activity to prevent severe oxidative stress condition. However, on conditions of stress such as increased level of oxidative stress, Nrf2 signaling

pathway is activated. Kelch-like ECH-associated protein 1 (Keap1) is considered as the most important modulator of the Nrf2 signaling pathway [40, 41].

During physiological conditions when the antioxidant defence system has adequate capacity to encounter excessive oxidative molecules, Nrf2 signaling is inhibited. Exposure to high levels of oxidative molecules results in damages in lipids, proteins and DNA and predisposes them to various pathological conditions. By the action of Keap1, a complex of Nrf2/Keap1/cullin 3 (cul3) is formed. This complex functions as an indicator of degradation, leading to the ubiquitination and consequent proteasomal degradation [42]. When the generation of reactive oxygen species (ROS) increases, a modification takes place in the structure of Keap1, resulting in disruption of Keap1-Nrf2-cul3 complex. So, the level of Nrf2 degradation decreases and simultaneously, high concentrations of Nrf2 accumulate in the cytoplasm. This signal urges Nrf2 to translocate into the nucleus where it stimulates the transcription of its target genes; notably, Nrf2 aims genes which have antioxidant response element (ARE) or electrophile-response element (EpRE) in their promoter region. Heme-oxygenase 1 (HO-1), NADPH quinone oxidoreductase 1 (NQO1), catalase (CAT) and superoxide dismutase (SOD) are components which undergo induction under the activation of the Nrf2 signaling pathway. Due to the potential role of Nrf2 signaling pathway in biological processes and pathological conditions, particularly cancer, it would be advantageous to modulate this signaling pathway [43-45].

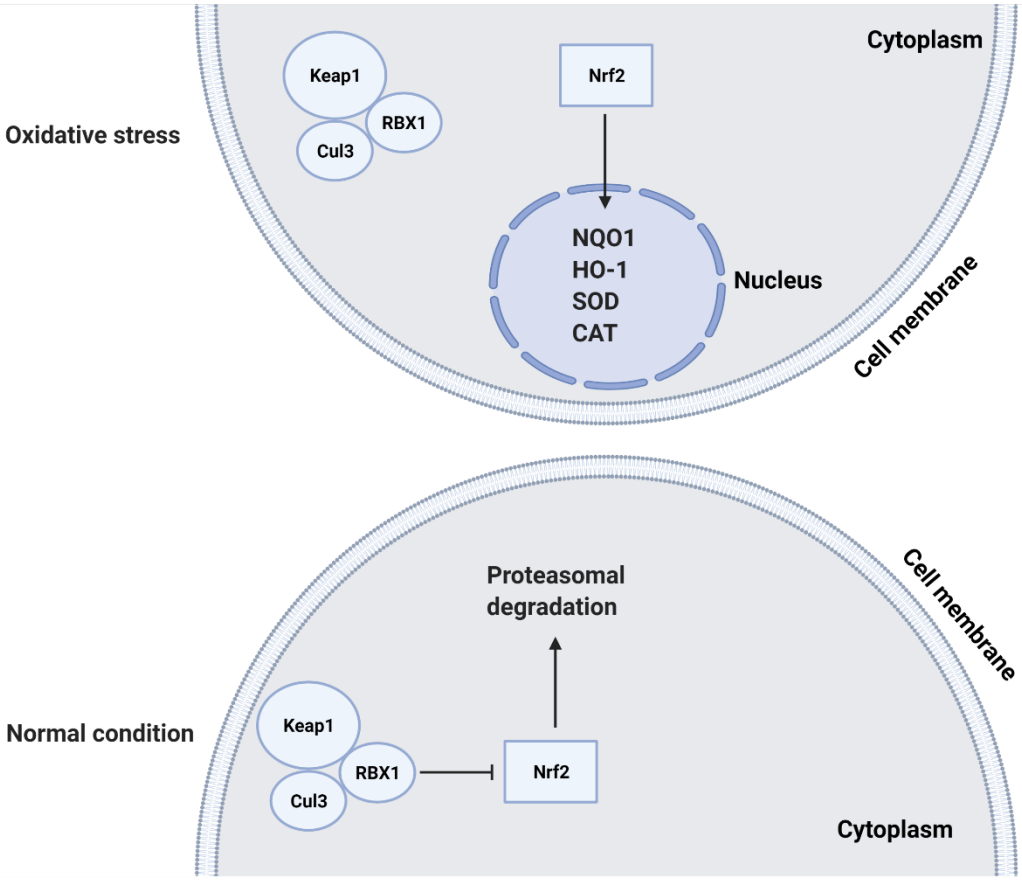

Figure 2: Modulation of the Nrf2 signaling pathway. The left figure demonstrates the Nrf2 signaling pathway during the physiological condition that the complex of cul3-Nrf2-Keap1 is degraded and suppresses the entering of Nrf2 into the nucleus. Figure in the right shows that during stress the complex of cul3-Nrf2-Keap1 is disrupted due to the modification in the structure of Keap1. Then, the Nrf2 translocates to the nucleus, and up-regulate the cellular antioxidant elements such as glutathione and Thioredoxin reductase 1.

Protective Effects of AST Mediated by Nrf2 Signaling Pathway

As mentioned earlier, there is growing evidence that the therapeutic potentials of AST are mainly mediated by Nrf2 signaling pathways [18, 46]. It must be noted that AST has different sources including, plants [46] and marine sources [47]. In the following paragraphs, the various protective effects of AST through modulation of Nrf2 molecular pathways are discussed.

Cardioprotective effects

In a recent study, Xue and colleagues in 2019 evaluated the impact of AST on the cardiomyocyte apoptosis after coronary microembolization (CME) [46]. The results of this study demonstrated that AST administration is associated with improvement in cardiac function and reduced levels of apoptosis and myocardial infarction. In order to examine the underlying pathway in the AST action, HO-1 inhibitor was used. It was found that inhibition of HO-1, as a downstream mediator of Nrf2, decreases the therapeutic effects of AST [46]. Also, Ooi et al. in 2018 suggested that cardioprotective effects of AST are mediated via Nrf2 up-regulation in which it has potent stimulatory impacts on Nrf2 expression [48]. This relationship was suggested by Visioli et al. in 2017 that the cardioprotective effects of AST are at least mainly via Nrf2 molecular mechanism and potentiation of antioxidant defence systems [49]. By activating Nrf2 signaling, AST can be advantageous in protecting cells against toxic agents such as ochratoxin A (OTA). Mice exposed to OTA demonstrate a decrease in activity and expression of antioxidant enzymes including SOD, CAT and GSH. AST administration reduces Keap1 expression to induce Nrf2 signaling, leading to improvement in antioxidant defense system and protecting against OTA-induced apoptosis and oxidative stress in heart [50].

Immunomodulatory Effects

In a study, the anti-inflammatory effect of AST in macrophages was evaluated [18]. An inflammatory response was induced in macrophages by LPS, resulting in an elevation in IL-6 and IL-1beta, an increase in ROS generation and nuclear factor-κB (NF-κB). It was revealed that AST administration remarkably decreases the concentrations of ROS and inflammatory cytokines through stimulation of the Nrf2 signaling pathway [18].

Hepatoprotective Effects

In a study, the ameliorative effect of AST-rich *Haematococcus Pluvialis* microalgae on the hepatic alterations related to D-galactose (D-Gal)-mediated ageing in rats was investigated [51]. After the injection of D-Gal (200mg/kg/day), the levels of hepatic oxidative stress biomarkers such as CAT, glutathione transferase (GST) and myeloperoxidase (MPO) were increased. Also, D-Gal administration increased the levels of inflammatory cytokines such as IL-6 by induction of NF-κB. It was found that AST treatment restores the levels of CAT, GST and MPO and reduces the levels of IL-6 and NF-κB by stimulation of the Nrf2 signaling pathway [51]. In another study, Islam and colleagues evaluated the hepatoprotective activity of AST in carbon tetrachloride (CCL_4)-administered rats [33]. It was shown that CCl_4 injection negatively affects all aspects of the liver so that CCl_4 enhanced the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP). Also, CCL_4 increased MDA, nitric oxide (NO) and advanced protein oxidation product (APOP) in plasma and tissues. Besides, CCL_4 injection diminished the activities of SOD and CAT. It was found that AST administration reverses these harmful effects by induction of Nrf2 signaling pathway [33] .

Li and colleagues examined the potential of AST for the treatment of ischemia/reperfusion (I/R) injury of the steatotic liver in mice. Notably, AST treatment significantly diminished the serum concentrations of ALT and AST, Bax and caspase and enhanced the levels of Bcl-2. AST administration was associated with decreased levels of inflammatory cytokines. Mechanistically, it was demonstrated that these protective effects are partially mediated by activation of the Nrf2/HO-1 signaling pathway [52]. Doxorubicin (DOX) is applied for eliminating cancer cells. However, it has been reported that this chemotherapeutic agent possesses adverse effects and

liver is one of its main target organs. AST administration down-regulates expression of Keap1 to induce Nrf2/HO-1 axis. This signaling network leads to an increase in activities of antioxidant enzymes such as SOD, CAT and GPx to ameliorate DOX-mediated liver injury [53].

Anti-diabetic effects

In a study, Chen and colleagues assessed the protective impact of AST against diabetes-mediated renal oxidative stress and fibronectin (FN) accumulation [54]. AST administration remarkably decreased oxidative stress and FN accumulation. Mechanistically, it was found that these ameliorative impacts are mediated by induction of Nrf2/ARE signaling pathway via connexin 43 (Cx43) [55]. Feng and coworkers examined the impact of AST on diabetes-induced cognitive dysfunction [54]. The protective effects of AST in this study was a combination of antioxidant and anti-inflammatory effects so that AST administration remarkably reduced the levels of IL-6, IL-1β and malondialdehyde (MDA) as well as increased the activity of SOD. Besides, AST diminished escape latency and expression of NF-κB p65. It was found that these protective effects are mediated through activation of the Nrf2/HO-1 signaling pathway [54]. In another study, Zhu and colleagues examined the ameliorative impact of AST on the renal FN and collagen IV accumulation in diabetic rats [56]. It was demonstrated that AST administration decreases MDA, renal morphological injury and FN and collagen IV accumulation, while it improves the activity of SOD. Mechanistically, it was found that these protective effects are mediated through stimulation of the Nrf2/HO-1 signaling pathway [57].

Renoprotective effects

Xie and coworkers investigated the efficacy of AST in the prevention of high glucose (HG)-mediated renal fibrosis in glomerular mesangial cells (GMCs) [17]. HG stimulated metabolic disorders, renal injury, extracellular matrix (ECM) accumulation and enhanced the levels of transforming growth factor-β1 (TGF--β1), ROS and intracellular adhesion molecule-1 (ICAM-1). It was found that AST effectively reverses all these adverse effects through the induction of Nrf2 signaling pathway and its downstream mediators such as SOD, NQO1 and HO-1 [17]. Another study conducted by Liu and coworkers emphasized the ameliorative impact of AST on the adriamycin-mediated focal segmental glomerulosclerosis [58]. AST administration resulted in a reduction in glomerular and interstitial fibrosis, improvement in renal function and inhibition of nucleotide-binding oligomerization domain-like receptor protein 3 inflammasome (NLRP3). Mechanistically, it was shown that nephroprotective effects of AST are mediated through the induction of Nrf2 signaling pathway [58].

Antioxidant effects

Niu and colleagues in 2018 investigated the antioxidant activity of AST in human umbilical vein endothelial cells (HUVEC) [59]. AST stimulates the activation of Nrf2 signaling pathway to exert its antioxidant effect. In this study, it was found that AST enhances the generation of ROS (by 9.35%, 14.8% and 18.06% compared to the control group) which subsequently leads to activation of Nrf2/HO-1 signaling pathway thereby remarkably reducing ROS production [59]. In another study, the modulatory effect of AST on the oxidative stress in HUVECs was evaluated [60]. In this study, AST was encapsulated by hydroxypropyl-beta-cyclodextrin (CD-A). It was

shown that CD-A significantly suppresses cellular and mitochondrial ROS, modifies impairments in the redox state of the cell and prevents the infiltration of lipid peroxidation radicals. Mechanistically, it was found that these protective effects are partially mediated through stimulation of the Nrf2/HO-1 signaling pathway [60]. Inoue and coworkers investigated the impact of AST and its analogs, adonixanthin and lycopene, on the light-mediated photoreceptor degeneration [16]. It was found that administration of AST and its analogs remarkably inhibits ROS generation and protects against cell damage via induction of Nrf2 signaling pathway and its downstream mediators, HO-1 and NQO1 [16]. The protective impact of AST on the irradiation-mediated hematopoietic progenitor cells (HPCs) injury was examined and was found that AST administration remarkably improves hematopoietic self-renewal and regeneration by decreasing ROS generation and apoptosis through stimulation of Nrf2 signaling pathway [61].

Neuroprotective effects

In a study, Wen and colleagues in 2015 examined the ameliorative impact of AST against the glutamate-mediated cytotoxicity in HT22 cells [62]. It was shown that treating cells with AST effectively decreases glutamate-mediated apoptosis and lactate dehydrogenase (LDH) release, diminishes the levels of caspase-3, -8 and -9 and cleaved PARP and inhibits ROS generation. Mechanistically, it was found that these protective effects are mediated through stimulation of the Nrf2/HO-1 signaling pathway [62]. Besides, AST is beneficial in decreasing the adverse impacts of early brain injury [47], so that AST is able to alleviate oxidative stress, diminish brain edema, blood-brain barrier (BBB) disruption, cellular apoptosis and neurological dysfunction in experimental model of subarachnoid hemorrhage (SAH) by stimulation of Nrf2 signaling pathway and its downstream mediators, HO-1 and NQO-1 [47].

Enhanced levels of oxidative stress sensitize neuronal cells to apoptosis. Therefore, Nrf2 induction by astaxanthin can be beneficial in preventing neurological disorders. AST administration after 1, 3 and 7 days of traumatic brain injury (TBI) increased Nrf2 expression that is vital for reducing ROS levels, leading to apoptosis inhibition in neuronal cells [63]. Neuronal cells are sensitive to insults and various strategies should be considered in preventing neuronal damage. Oxygen and glucose deprivation one of the insults and due to potent neuroprotective impact of AST, this plant derived-natural compound can inhbit ROS overgeneration, loss of mitochondrial membrane potential and caspase-3-mediated apoptosis. Mechanistically, AST induces PI3K/Akt signaling to provide nuclear translocation of Nrf2, leading to upregulation of HO-1 as downstream target of Nrf2 and improving neuronal damage [63]. Ischemia is one of the pathological events, occurring due to decrease in blood supply to a certain organ. Increased levels of ROS play a major role in ischemia-mediated apoptosis and damage [64]. As AST is a regulator of Nrf2 signaling, it can be beneficial in ischemia treatment. It has been reported that AST treatment promotes expression level of Nrf2 to exert antioxidant and anti-apoptotic roles that are of importance in preventing ischemia damage in optic nerve cells [65]. It is worth mentioning that in vivo experiments have also highlited role of AST in neuroprotection via Nrf2 activation. It has been reported that exposing mice to La_2O_3 nanoparticles is associated with apoptosis, oxidative stress and neuroinflammation. AST administration accelerates nuclear translocation of Nrf2 via inducing PI3K/Akt signaling, leading to a decrease in ROS levels, and inhibiting apoptosis in neuronal cells [66]. Overall, studies are in agreement with the fact that AST is a potential agent in protecting cells against oxidative stress and inhibiting disease progression via inducing Nrf2 signaling (**figure 3**) [67-69].

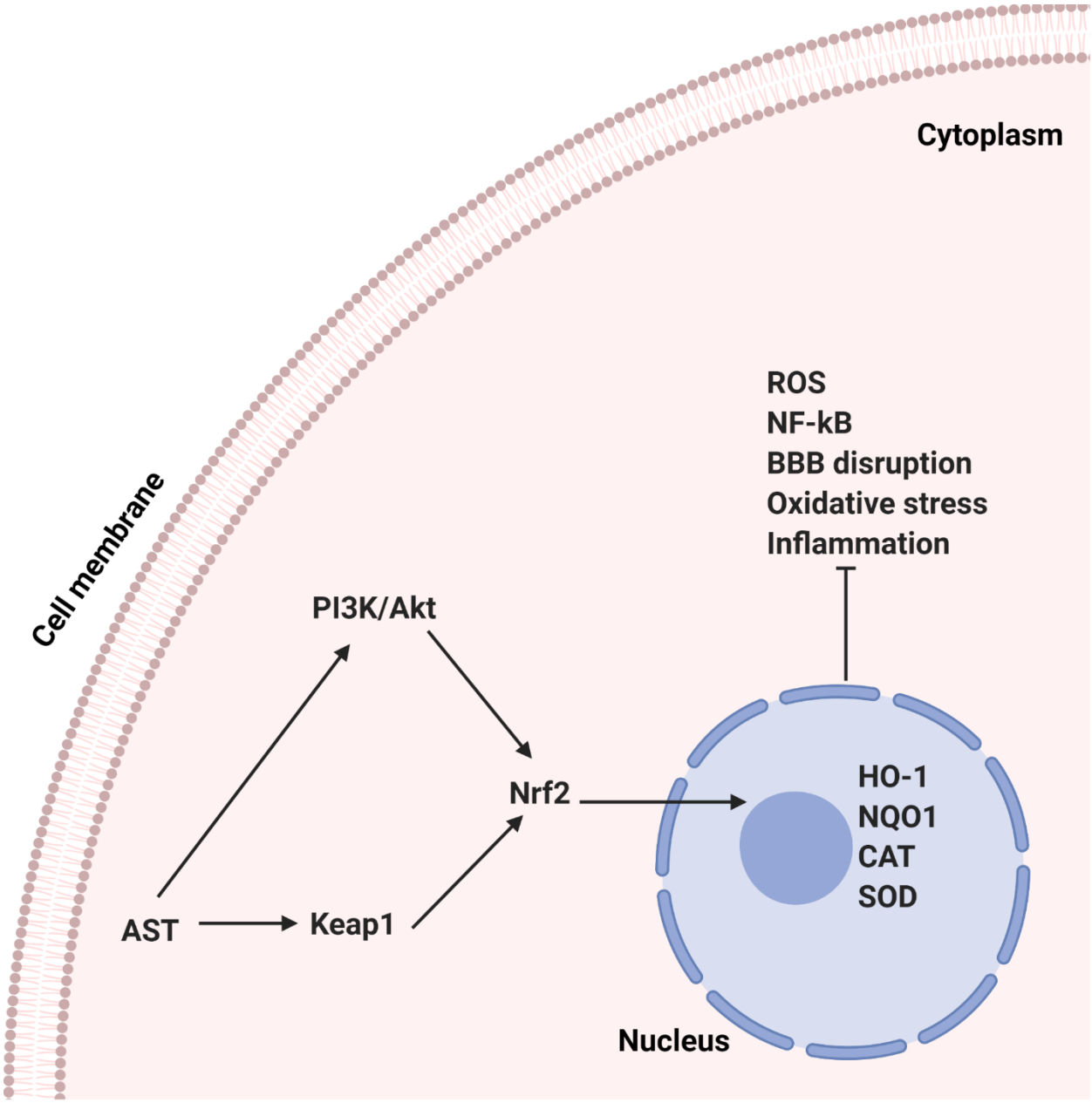

Figure 3: Upstream mediators of Nrf2 and also, Keap1 are affected by astaxanthin in regulating Nrf2 expression and its nuclear translocation that are of importance for disease therapy.

Table 1: Experimental evidence demonstrating the modulatory effects of AST on the Nrf2 signaling pathway

In vitro	In vivo	Effect	Dosage	Major Outcomes	Ref.
-	Rat	Cardioprotective	40mg/kg/day	Decreasing oxidative stress and apoptosis and improving cardiac function through Nrf2/HO-1 signaling pathway	[46]
RAW 264.7 macrophages	-	Immunomodulatory	25μM	Reducing inflammatory cytokines through activation of Nrf2 signaling pathway	[18]
-	Db/db mice	Anti-diabetic	35mg/kg	Decreasing renal oxidative stress and FN accumulation through Nrf2/ARE pathway activation	[54]
-	Rat model of type II diabetes	Anti-diabetic	25mg/kg	Decreasing oxidative stress and inflammatory cytokines through induction of Nrf2/HO-1 signaling pathway	[54]
-	Rat	Anti-diabetic	25mg/kg	Enhancing SOD activity and decreasing FN and collagen IV accumulation through induction of Nrf2/HO-1 signaling pathway	[56]
-	Rat	Hepatoprotective	10mg/kg	Decreasing the levels of MDA, NO and APOP and improving CAT and SOD activities through induction of Nrf2 signaling pathway	[33]
-	Rat	Hepatoprotective	30mg/kg	Restoring the levels of CAT, GST and MPO and decreasing the levels of IL-6 and NF-kB through induction of Nrf2 signaling pathway	[51]
-	Mice	Hepatoprotective	25mg/kg	Decreasing AST and ALT levels, reducing inflammatory cytokines and caspase activation via induction of Nrf2/HO-1 signaling pathway	[52]
HT22 cells	-	Neuroprotective	1.25-5μM	Reducing ROS production and improving cell viability through induction of Nrf2/HO-1 signaling pathway	[62]
-	Rat	Renoprotective	25mg/kg	Decreasing ROS, TGF-β1, ICAM-1 and improving renal function via stimulation of Nrf2 signaling pathway	[17]
-	Balb/c mice	Renoprotective	50 mg/kg	Alleviation of renal fibrosis and improving renal function via induction of Nrf2 signaling pathway	[58]
-	Mice	Renoprotective	100 mg/kg	Decreasing oxidative stress Enhancing activity of antioxidant enzymes such as HO-1, GSH and NQO1 Inducing Nrf2/HO-1 signaling	[70]

-	Experimental model of subarachnoid hemorrhage	Neuroprotective	0.1mM	Attenuation of oxidative stress and improving brain function through induction of Nrf2 signaling pathway	[47]
U937 cells	-	Antioxidant	10μM	Improving the activities of CAT and SOD through activation of Nrf2 signaling pathway	[71]
661W cell model	-	Antioxidant	5-100 μM	Functioning as a ROS scavenging Decreasing retinal cell damage Triggering PI3K/Akt/Nrf2 signaling	[72]
Retinal photoreceptor cells	-	Antioxidant	0-50 μM	Prventing high glucose-mediated oxidative stress Enhancing activity of antioxidant enzymes Stimulating PI3K/Akt/Nrf2 signaling	[73]
Human umbilical vein endothelial cells	-	Antioxidant	0.1, 1 and 10μM	Exerting antioxidant activity via stimulation of Nrf2/HO-1 signaling pathway	[59]
HUVECs	-	Antioxidant	5μM	Decreasing lipid peroxidation and inhibiting cellular and mitochondrial ROS through activation of Nrf2/HO-1 signaling pathway	[60]
Murine photoreceptor cell line (661 W)	-	Antioxidant	3-20μM	Decreasing ROS generation and inhibition of cell damage via stimulation of Nrf2 signaling pathway	[16]
Hematopoietic progenitor cells	-	Antioxidant	25, 50 and 100mg/kg	Decreasing ROS generation and apoptosis via induction of Nrf2 signaling pathway	[61]

Conclusion

The Nrf2 signaling pathway is one of the most important molecular mechanisms that are responsible for preserving the redox balance nearer to the physiologic milieu and it is impaired in various pathological conditions, particularly in cancer. Hence, targeting this signaling pathway may be potentially advantageous in the treatment of various disorders as well as cancer. AST is a naturally occurring β-carotenoid mainly found in algae, fungi, plants and salmon. This natural-based active compound has different pharmacological effects including antioxidant, anti-inflammatory, anti-tumor and anti-diabetes effects. In the present study, we demonstrated how AST affects the Nrf2 signaling pathway to exert its therapeutic and biological activities (Table 1). Cardioprotection is one of the activities of AST which is mediated through the Nrf2 signaling pathway and it seems that AST improves the overall function of the heart by induction of this pathway. In terms of immunomodulatory activities, AST stimulates Nrf2 signaling pathway to reduce the levels of inflammatory cytokines and to inhibit the NF-κB activity and expression. The hepatoprotective potential of AST is a combination of improvement in antioxidative elements such as CAT, SOD and GST while suppressing the apoptotic events. In order to achieve its neuroprotective, anti-diabetes and renoprotective effects, AST exerts antioxidant and anti-inflammatory effects through Nrf2 signaling pathway.

Abbreviations:

AST, astaxanthin; LPS, lipopolysaccharide; IL-6,interleukin-6; TNF-α, tumor necrosis factor-α; PPAR, peroxisome proliferator-activated receptor; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; ROS, reactive oxygen species; Cul3, cullin 3; ARE, antioxidant response element; EpRE, electrophile-response element; HO-1, heme

oxygenase-1; NQO1, NADPH quinone oxidoreducatase 1; CAT, catalase; SOD, superoxide dismutase; CME, coronary microembolization; OTA, ochratoxin A; NF-κB, nuclear factor-kappaB; D-gal, D-galactose; GST, glutathione transferase; MPO, myeloperoxidase; CCL4, carbon tetrachloride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; NO, nitric oxide; APOP, advanced protein oxidation product; I/R, ischemica/reperfusion; DOX, doxorubicin; FN, fibronectin; Cx-43, connexin 43; MDA, malondialdehyde; HG, high glucose; GMC, glomerular mesangial cells; ECM, extracellular matrix; TGF-β1, transforming growth factor-beta1; ICAM-1, intracellular adhesion molecule-1; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3 inflammasome; HUVEC, human umbilical vein endothelial cell; HPCs, hematopoietic progenitor cells; LDH, lactate dehydrogenase; BBB, blood-brain barrier; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

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Conflict of interest:

The authors declare that they have no conflict of interest.

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