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LETTER TO THE EDITOR

WILEY

Astaxanthin, COVID-19 and immune response: Focus on oxidative stress, apoptosis and autophagy

Dear Editor,

Researchers are aware of a global pandemic on novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). It has been a serious leading cause of morbidity and mortality worldwide (Wang et al., 2020; Wu et al., 2020).

Despite advancements in providing antiviral drugs, no effective treatment has now been approved for the prevention/management/treatment of COVID-19. Therefore, there exists a dire need to discover new, safe, and more efficacious treatment options to achieve ideal results. Besides, considering the contagiousness and unabated spread of COVID-19 infection, there is considerable interest in providing novel treatments. Accordingly, natural products possess promising antiviral effects through interfering with several aspects of viral infection like viral entry, genome release processes, gene expression, and replication (Pour, Fakhri, Asgary, Farzaei, & Echeverria, 2019). Besides, several reports have indicated the crucial role of oxidative stress, inflammation, apoptosis, autophagy, in triggering the pathogenesis and complications of COVID-19. So, providing novel treatments with potential anti-inflammatory, antioxidative, antiapoptotic effects, as well as ameliorative candidates on autophagy, would be grateful in preventing the progression of COVID-19. Additionally, during the past viral infections such as SARS-CoV and influenza, natural origin based medicinal plants have been widely used for counteracting viral infections (Ang, Lee, Choi, Zhang, & Lee, 2020). Astaxanthin (3,3′-dihydroxy-β,β-carotene-4,4′-dione) is a keto-carotenoid with a wide variety of health-promoting properties through its effects on a plethora of molecular targets (Fakhri, Yosifova Aneva, Farzaei, & Sobarzo-Sánchez, 2019). From the mechanistic point of view, considering the antioxidant, anti-inflammatory, antiapoptosis, and autophagy-modulatory activities (Fakhri, Dargahi, Abbaszadeh, & Jorjani, 2019; Heidari Khoei et al., 2019), astaxanthin underscores a great potential in alleviating the complications of COVID-19.

Astaxanthin is a lipid-soluble carotenoid with a polar–nonpolar–polar structure that could easily pass through and fix into the double layers of cell membrane. While the polar zones of astaxanthin's structure scavenge free radicals inside and outside the cell membrane, its polyene chain captures radicals in the cell membrane (Augusti et al., 2012). This effect has been found to be several folds more than other antioxidants, like vitamin E (Heidari Khoei et al., 2019; Østerlie, Bjerkeng, & Liaaen-Jensen, 2000; Shimidzu, Goto, & Miki, 1996). In terms of pharmacological mechanisms, astaxanthin decreased the membrane fluidity and increased the activation of nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway (Wu et al., 2014). The pathway, in turn, elevates the antioxidant enzymes, including catalase (CAT), superoxide dismutase (SOD), peroxidase, thiobarbituric acid reactive substances (TBARS), NAD(P)H quinine oxidoreductase-1 (NQO-1) glutathione-S-transferase-α1 (GST-α1) (Fakhri, Abbaszadeh, Dargahi, & Jorjani, 2018). Astaxanthin also showed potential inhibitory effects on superoxide radicals, nitrogen dioxide radicals, cytosolic calcium (Otton et al., 2010), reactive oxygen species (ROS), myeloperoxidase (MPO), and other oxidative mediators, as well as lipid peroxidation (Campoio, Oliveira, & Otton, 2011; Kamath, Srikanta, Dharmesh, Sarada, & Ravishankar, 2008). All the reports, are in the way to introduce astaxanthin as a super antioxidant, which could be a promising candidate in combating COVID-19.

Astaxanthin is a multi-target agent which employs several mechanisms to apply potential anti-inflammatory effects. For instance, astaxanthin reduced the expression of N-methyl-D-aspartate receptor subtype 2B (NR2B), tumor necrosis factor-α (TNF-α), p-p38 mitogen-activated protein kinase (MAPK) (Fakhri, Dargahi, Abbaszadeh, & Jorjani, 2018), p-extracellular signal-regulated kinases (p-ERK)/ERK, and increased p-Akt/Akt to modulate inflammation (Fakhri, Dargahi, et al., 2019). Astaxanthin also suppressed nuclear factor-κB (NF-κB) and down-stream mediators, including interleukin (IL)-6, IL-1β, matrix metalloproteinase (MMP-9) (Bhuvaneswari, Yogalakshmi, Sreeja, & Anuradha, 2014; Speranza et al., 2012), nitric oxide (NO), and cyclooxygenase-2 (COX-2) (Choi, Park, Choi, & Chang, 2008). The modulatory effects of astaxanthin on the phosphoinositide 3-kinases (PI3K)/Akt, ERK/MAPK, and the up-stream macrophage migration inhibitory factor (MIF) has also been shown regarding its anti-inflammatory effects (Fakhri, Abbaszadeh, et al., 2018).

Considering the role of Janus kinase/signal transducer and activator of transcription (JAK/STAT) in the initiation of interferon-stimulated response elements (ISRE), attenuating the pathway would play a pivotal role in preventing the inflammation occurs in COVID-19. In this regard, the inhibitory effects of astaxanthin on JAK2/STAT3 has been revealed (Kowshik et al., 2014). All the pharmacological and mechanistic evidence are confirming a bright future for astaxanthin to be used against the destructive inflammatory pathways then related complications in COVID-19.

Growing evidence is also making a precise association between the therapeutic effects of astaxanthin and its antiapoptotic properties (Fakhri, Yosifova Aneva, et al., 2019). Astaxanthin exerted antiapoptotic effects by inhibiting Bax/Bcl-2, and caspases-3/9 (Masoudi et al., 2017). Astaxanthin also reduced apoptosis through PI3K/Akt pathway to

overcome associated side effects (Wang, Cai, & Wen, 2016). Liu et al. also showed the ameliorative effects of astaxanthin on reducing ROS, cytochrome C release, mitochondrial membrane potential, and apoptosis (Liu, Shibata, Hisaka, & Osawa, 2009). Accordingly, ROS-mediated apoptosis could be a promising target for astaxanthin to prevent the progression of several organ damages. Moreover, astaxanthin inhibited mitochondrial dysfunction and 6-hydroxydopamine (6-OHDA)-induced apoptosis via suppressing p-p38MAPK, caspases, and poly(ADP-ribose) polymerase (Ikeda et al., 2008). Altogether astaxanthin could be introduced as an auspicious antiapoptotic agent in combating apoptotic events during COVID-19.

As the type II programmed death of cells, autophagy degrades unused cell components, including microautophagy, macroautophagy, and chaperone-mediated autophagy. It is worth noting that autophagy acts as a double sword knife, so its modulating is very important. Various autophagy mediators, including LC3, Beclin, and autophagy-related protein (Atg) are affected by PI3K/Akt/mammalian target of rapamycin (mTOR), c-Jun N-terminal kinase (JNK), AMPK, and p38MAPK (Kim & Kim, 2019). COVID-19 dysregulates the autophagy, thereby make organ damages. Since, it is regulated by several signaling pathways, targeting autophagy is of great importance. Astaxanthin has shown modulatory effects on the aforementioned pathways to reduce the autophagy-related complications of COVID-19. Astaxanthin phosphorylates/activates AMPK to activate autophagy through mTOR inhibition (Yang et al., 2018). Of the mediatory role of PI3K/Akt on the astaxanthin's effects on autophagy, it modulated Akt, to induce autophagy through the Akt/mTOR pathway. Besides, astaxanthin activated peroxisome proliferator-activated receptors (PPAR)-α while inhibited PPAR-γ, to regulate autophagy (Jia, Wu, Kim, Kim, & Lee, 2016). In the other study by Li et al., astaxanthin blocked JNK, thereby modulated autophagy in an in vivo model of autoimmune hepatitis (Li, Xia, et al., 2015). On the other hand, treatment with astaxanthin reduced LC3 and Beclin1, and inhibited autophagy by modifying MAPK, to confirm its modulatory effect on autophagy, depend on the situation (Kim & Kim, 2019; Li, Wang, et al., 2015).

It is worth noting that astaxanthin has been already used in related clinical trials for the treatment of metabolic syndrome, atherosclerosis, cognitive impairment, muscle damage, visual fatigue, and dermatological diseases with hopeful results. The administrated doses were shown to be ranged between 2 and 24 mg/day with no safety concerns (Brendler & Williamson, 2019; Williamson, Liu, & Izzo, 2020). Therefore, clinical trials are also needed to evaluate the possible potential of astaxanthin in combating COVID-19.

CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

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