Astaxanthin is a Promising Therapy for Wound Healing in Diabetic Conditions: A Review

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Abstract

Hyperglycemia conditions in diabetes mellitus can lead to delayed wound healing. One of the wounds in the oral cavity that occurs in diabetes patients is traumatic ulcers.

The persistence of long-term inflammation in this condition can be attributed to a significant polarization towards the M1 phenotype. Additionally, the transition from the pro-inflammatory M1 state to the pro-regenerative, anti-inflammatory M2 state is severely hindered.

The delayed wound healing observed in individuals with diabetes mellitus may be linked to the activation of the Pyrin domain-containing protein 3 (NLRP3) Inflammasome pathway. Nuclear factor-erythroid-2 related factor 2 (Nrf2), a vital regulator of the body's antioxidant defenses that can limit the inflammatory response induced by NF-κB.

Antioxidant and anti-inflammatory derived from astaxanthin. Astaxanthin can activate the transcription factor Nrf2 and affect NLRP3. This review reviews the effects of astaxanthin so that it can be a therapeutic candidate for wound healing in diabetes mellitus

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Introduction

Inadequately managed diabetes is linked to conditions such as gingivitis, periodontal diseases, and loss of bone in the jaw. Another complication of diabetes is delayed wound healing in oral traumatic ulcers.[1,2] This condition is associated with hyperglycemia in patients. Hyperglycemia conditions in diabetes mellitus result in increased production of free radicals (ROS). Increased ROS through the polyol pathway resulted in a decrease in the adaptive immune system, and increased degradation of mast cells and pro-inflammatory macrophages (M1).[3] In diabetic wounds, there is solid polarization towards the M1 phenotype, and the transition from the pro-inflammatory M1 to the pro-regenerative anti-inflammatory M2 phenotype is markedly impaired.[4] This mechanism involves the activation of the NLRP3 Inflammasome pathway.[5]

Another mechanism possibility is the binding of Advanced Glycation Endproduct (AGE) and AGE receptor (RAGE) on monocytes increases cellular oxidative stress and activates the transcription factor nuclear factor-κB (NFκB), resulting in increased production of proinflammatory cytokines.[6] AGEs not only harm endothelial cells but also bring about alterations in the structure and function of both extracellular structural (ECM) and intracellular (ICM) proteins. These changes impede the activation of fibroblasts responsible for secreting ECM proteins, resulting in delayed wound healing, thereby prolonging the inflammatory phase and the overall wound healing process.[3]

Topical corticosteroids, topical anesthetics, and analgesics are recommended as ulcer treatments aimed at reducing the pain and duration of the ulcer by suppressing the local immune response and preventing secondary infections. However, long-term exposure to such drugs can lead to oral flora imparity, secondary fungal infections, and drug resistance.[7] Based on this, the use of ingredients from natural products can be recommended for oral cavity ulcers.

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One candidate from natural products is Astaxanthin (ASX). The anti-inflammatory mechanism of ASX is through targeting multiple signaling pathways and inflammatory biomarkers, including inhibiting NF-κB to relieve inflammation.[8,9] The anti-inflammatory and antioxidant effects of ASX may be through the mechanism of decreasing M1 polarization and increasing M2 polarization and activating the Nrf-2/HO-1 antioxidant pathway by producing small amounts of ROS.[10,11] Astaxanthin significantly inhibits M1 polarization as evidenced by suppressing Il-1β mRNA levels during M1 polarization, and increasing Arg-I mRNA levels during M2 polarization.[10]

In this comprehensive review, we conducted a search on PubMed for articles published within the last five years using the keywords "Astaxanthin" in conjunction with "NLRP3" and "Astaxanthin" in conjunction with "NRF2." After applying specific inclusion criteria, we carefully selected and incorporated the chosen articles into this review. we obtained eight articles that we combined in this review. This article will explore the potential of astaxanthin in oral wound healing through Nrf2 activation and NLRP3 Inflammasome pathway inhibition.

Mechanism of delayed healing in diabetes mellitus

Hyperglycemia condition in diabetes mellitus (DM) provides the progress of atherosclerosis, thus precluding nutrient circulation from reaching the wound, and impairing healing.[12] Elevated blood sugar levels hinder crucial processes in re-establishing epithelial tissue, including the synthesis of proteins, the movement, and growth of keratinocytes and fibroblasts.[13,14] Free radical damage triggered by diminished functioning of the antioxidant enzymes superoxide dismutase and glutathione peroxidase is another manner in which hyperglycemia interferes with wound healing.[15] Hyperglycemia can potentially initiate the generation of reactive oxygen species (ROS) through several pathways, including polyol, hexosamine, protein kinase C, and AGE pathways. [16] Excessive production of ROS has been shown to have detrimental effects on the later stages of the wound-healing process. Increased levels of reactive oxygen species (ROS) can negatively impact blood circulation, metabolic functions, and the integrity of peripheral nerves. This can potentially lead to sensory, motor, and autonomic issues in these nerves. These alterations caused by poorly managed high blood sugar levels make the skin more vulnerable to harm and infections, ultimately hindering the body's ability to heal wounds.[12]

Hyperglycemia inflicts substantial harm on the defensive capabilities of both humoral and immune cells, leading to the sustained presence of bacteria in wounds of diabetic patients in the form of biofilms over an extended period.[17] Patients with diabetes mellitus (DM) exhibit various immunological and neuroendocrine irregularities, such as reduced T-cell activation, impaired neutrophil function, and decreased levels of thromboxane B2, prostaglandin E, and leukotrienes.[18] These dysfunctions can result in delayed wound healing. In diabetes, the normal aerobic processes responsible for microbial inactivation by neutrophil granulocytes, including the generation of reactive oxygen species (ROS) and the respiratory burst, are disrupted. This is due in part to the overactivation of the polyol pathway in diabetes, resulting in a deficit of NADPH, which limits the release of oxygen free radicals. precisely, as a result, non-specific pathogen eradication is compromised.[3] Increased flux through the polyol and hexosamine pathways, increased formation of advanced glycation end products (AGEs), and activation of protein kinase C isoforms result in increased superoxide generation, activation of inflammatory pathways, and aberrant host responses.[19] In a hyperglycemic environment, it has been observed that elevated mast cell degradation and enhanced recruitment of proinflammatory M1 macrophages contribute to the disruption.[3] Neutrophil dysfunction reduces the efficiency of wound healing, the ability to regenerate tissue successfully, and the immune system's capacity to monitor and combat harmful pathogens.[19] Extended cellular and inflammatory responses can likewise lead to delayed wound healing.[3]

The delayed wound healing process in individuals with diabetes mellitus can also be attributed to the activation of the NLRP3 Inflammasome pathway, triggered by an increase in reactive oxygen species (ROS) due to high blood sugar levels in diabetes.[15] Inflammasome regulation of NLRP3 in macrophages has been widely studied. Pyrin domain-containing protein 3

(NLRP3) inflammasome formation occurs in these cells via a two-step process known as priming and activation.[20] During the initial three days, the wound-healing process is controlled by the M1 phenotypes. Following that, a change to the M2 phenotype was noted, peaking on the seventh day.[21] The persistence of chronic, low-level inflammation is the primary factor behind non-healing wounds in diabetic individuals, where the M1 phenotype remains dominant and fails to convert into the M2 phenotype.[5] Ganesh and Ramkumar (2020)[22] discovered that diabetic wounds exhibit elevated levels of proinflammatory cytokines like interleukin-1 beta (IL-1), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). The imbalance of macrophage phenotypes is intimately tied to NLRP3 Inflammasome activity, which is regulated by a variety of proinflammatory stimuli.[23] The transition from the proinflammatory M1 phenotype to the anti-inflammatory M2 phenotype can be delayed or entirely absent, impeding the shift from the inflammatory phase to the proliferative phase in tissue repair and consequently delaying the overall wound healing process.[5]

Nuclear factor-erythroid-2 related factor 2 (Nrf2) in Healing Process

In situations involving endogenous and exogenous stress conditions, nuclear factor-erythroid-2 related factor 2 (Nrf2) plays a crucial role in maintaining cellular redox balance. It achieves this by binding to antioxidant response elements (AREs) found in genes responsible for encoding antioxidant enzymes. This binding process occurs after Nrf2 forms a complex with the Musculoaponeurotic Fibrosarcoma Oncogene Homolog (Maf) protein.[24] Typically, under normal conditions, Nrf2 is bound to Keap1, which inhibits Nrf2 by directing it towards proteasomal degradation. However, when the cell experiences stress, Nrf2 dissociates from the Nrf2-Keap1 complex and translocates into the cell nucleus.[25] Most of the enzymatic antioxidants are controlled by genes driven by Antioxidant Response Elements (ARE), and their transcriptional regulation is orchestrated by Nrf2. Nrf2 is primarily recognized for its role in safeguarding cells against oxidative and xenobiotic stress. The Nrf2-ARE pathway plays a protective role in guarding against the occurrence of DNA damage.[26] The activation of the Nrf2-ARE pathway leads to the upregulation of antioxidant genes like heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase-1 (NQO1). This activation serves to protect against oxidative stress and inflammation and mitigate the harm caused by these processes.[25] HO-1 can suppress the translocation and secretion of HMGB1 which plays a role in activating inflammation.[27]

Nrf2 has the capacity to mitigate inflammation by limiting the inflammatory reaction induced by NF-kB.[5] Because Nrf2 plays an important role in normal endothelial angiogenesis, the decreased signaling of Nrf2 might account for the observed decrease in angiogenesis during the healing of diabetic wounds.[28] Enhancing Nrf2 activity and inhibiting NF-κB holds promise as a potential therapeutic strategy for improving the healing of diabetic wounds.

Astaxanthin Effect on the Healing Process

Astaxanthin (ASX) is most commonly found in the green algae Haematococcus pluvialis marine biota.[29] Astaxanthin is a xanthophyll carotenoid possessing potent antioxidant properties capable of diminishing inflammation, oxidative stress, and apoptosis.[8]

The following are the anti-inflammatory and antioxidant effects of astaxanthin:

Effects	Results	Marker	References
Antiinflammatory	Reduce pro-inflammatory cytokines	Interleukin (IL)-1β	33, 34, 35
		Interleukin (IL)-6	34
		tumor necrosis factor α (TNF-α)	33, 35
	Reduce complex protein	Pyrin domain-containing protein 3 (NLRP3) inflammasome	33
	Reduce cell inflammation	Neutrophil	36
		macrophage	36
	Transcription Factor	Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)	37, 38
Antioxidant	Reduce enzyme	p38 mitogen-activated protein kinases (P38 MAPK)	39
	Upregulated Protein	Caspase 3	34, 35, 38, 40
	Enhance/ Activating Transcription Factor	Nrf2	36, 37, 38, 39, 40, 41
	Reduce ROS	Malondialdehyde (MDA)	38, 40, 41
		Catalase	
		Superoxide dismutase (SOD)	

The molecular structure of ASX with a hydroxyl and ketone group at the terminal group has a major influence on its chemical and biological properties as a strong antioxidant.[30] Astaxanthin shows better biological activity compared to other antioxidants because it can bind to cell membranes from the inside out.[31] Astaxanthin is situated within bilayer membranes

and offers defense against oxidative stress in both the inner and outer layers of cell membranes, distinguishing it from many other antioxidants that typically act either internally (e.g., vitamin E and β-carotene) or externally on the membrane surface (e.g., vitamin C).[32]

Mechanism of antioxidant activity of Astaxanthin

Astaxanthin regulates the suppression and activation of enzymes responsive to oxidative stress, including heme oxygenase-1 (HO-1). HO-1 serves as both an indicator of oxidative stress and a control mechanism in how cells respond to oxidative harm. This control is carried out by stress-responsive transcription factors, with erythroid-associated nuclear factor 2 (Nrf2) being a prime example. Nrf2 binds to antioxidant response elements located in the promoter region of enzymes responsible for detoxifying metabolic processes, thus influencing HO-1 and the cell's oxidative stress response.[42] Several authors have found that astaxanthin activates the Nrf2 or HO-1 antioxidant pathway by generating small amounts of ROS. Xue et al. (2020)[43] showed that Nrf2 expression in irradiated cells could increase due to astaxanthin. In addition, astaxanthin significantly regulated irradiated cells with proteins targeted at Nrf2 HO-1 and the antioxidant enzymes catalase (CAT), superoxide dismutase 2 (SOD2), and glutathione peroxidase 1 (GPX1).[38,40,41,43]

The significant antioxidant activity of astaxanthin from astaxanthin can not only remove radicals directly but also through the cellular antioxidant defense system by modulating the Nrf2 pathway.[44] There are different mechanisms of astaxanthin as protection against oxidative damage, namely neutralizing single oxygen, taking radicals to prevent chain reactions, maintenance of membrane structures through inhibition of lipid peroxidation (LPO), where lipid peroxidation produces aldehydes (malondialdehyde-MDA).[45] Malondialdehyde as an end product is used to determine the degree of oxidative damage caused by lipid peroxidation.[46]

Anti-inflammatory Response to Astaxanthin to Accelerate the Healing Process

Astaxanthin has the ability to reduce inflammation in tissues and organs.[45] Astaxanthin can reduce iNOS, COX-2, prostaglandin E2, and neutrophil counts.[47] Astaxanthin can also inhibit several gene expressions of pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and NF-κB in primary macrophage cells and lipopolysaccharide, thus showing a new strategy for treating inflammation.[33-38] Astaxanthin also exhibits anti-inflammatory effects by inhibiting the enzyme cyclooxygenase-1 (COX-1) and nitrogen monoxide (NO)-induced NO-synthase activity. Astaxanthin blocks the NF-κB signaling pathway which results in decreased production of inflammatory cytokines and decreased transcription of pro-inflammatory genes.[45]

Astaxanthin can potentially reduce wound size by boosting basic fibroblast growth factor (bFGF) levels during the remodeling and proliferation phase of wound healing. In this phase, bFGF plays a crucial role in the formation of granulation tissue, reepithelialization, matrix formation, and overall tissue remodeling.[48] According to one study, astaxanthin was found to suppress the expression of MMP-1, MMP-3, and MMP-13 in chondrocytes stimulated by IL-1. This inhibition occurred by blocking the activation of p38 and ERK1/2, along with the degradation of IB.[49] Lee et al. (2022)[50] discovered that astaxanthin successfully reduced MMP-7 and MMP-10 production as well as invasive cells in H. pylori-infected cells by downregulating PI3K/AKT/mTOR signaling and reducing NF-kB activation. Matrix metalloproteinases are a complex collection of endopeptidases that degrade extracellular matrix (ECM) components.[51] Degradation of ECM components will result in tissue injury. This reduction in MMP causes faster tissue healing.

Conclusions

Wound healing is hampered by the condition of hyperglycemia in diabetes mellitus is a condition that often occurs. This hyperglycemia can cause oxidative stress that can activate inflammation from various pathways. One of them is through the inflammasome Pyrin domain-containing protein 3 (NLRP3) pathway. activation of this pathway activates the inflammatory pathway. The long period of inflammation in diabetes mellitus is due to the disruption of the macrophage switching process from proinflammatory (M1) to anti-inflammatory (M2) macrophages. To inhibit inflammation, astaxanthin therapy can be a good alternative because it has anti-inflammatory and antioxidant

effects. anti-inflammatory effects are proven by studies showing a decrease in several anti-inflammatory markers. while the antioxidant effect has been proven in several studies by activating Nrf2 as a key regulator of antioxidants, decreasing ros, and increasing antioxidant enzymes.

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Declaration of Interest

The authors report no conflict of interest.

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