International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 02 Issue 12 December 2022

Page No: 1591-1595

DOI: https://doi.org/10.47191/ijmscrs/v2-i12-37, Impact Factor: 5.365

The Protective Role of Strong Antioxidant Astaxanthin on Burn Wound and Burn-Induced Early Acute Kidney Injury through Abilities to Relieve Oxidative Stress and Inhibit Apoptosis by Modulating Mitochondrial-Apoptotic Pathways

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ABSTRACT

Summary: Burns are skin damage caused by heat trauma or cold trauma (frost bite). Causes include fire, hot water, electricity, chemicals, radiation, and cold (frostbite). This damage may involve subcutaneous tissue. Burn injuries are associated with high incidence and prevalence, high risk of morbidity and mortality, resource-intensive, and costly. One of the most common complications in burn patients is acute kidney injury (AKI). The mechanism of early AKI after burn injury is multifactorial, and previous studies have mainly focused on oxidative stress injury, tubular apoptosis, and systemic or local inflammation. Previous results (from our group and others) suggested that ROS-induced oxidative stress damage and apoptosis play an important role in the development of early AKI due to burn injury, and that 24 h after burn injury are useful for observing changes in burn injury. It shows that it provides an important timeframe. Kidney function and levels of oxidative stress and apoptosis. Astaxanthin (ATX) is a naturally occurring carotenoid that is readily obtained from marine organisms and stronger antioxidant effects than other carotenoids. Given the critical role of oxidative stress and secondary renal inflammation in severe burn-induced early AKI, a protective role of ATX through its anti-inflammatory effects and potential mechanisms of action in early post-burn AKI is reasonable.

KEYWORDS: Astaxanthin, Burn Injury, Acute Kidney Injury

ARTICLE DETAILS

Published On:
27 December 2022

Available on:
https://ijmscr.org/

INTRODUCTION

A burn is damage to the skin caused by heat or cold trauma (frostbite). Causes include fire, hot water, electricity, chemicals, radiation, and cold (frostbite).[1] This damage may involve subcutaneous tissue. Burn injuries are associated with high incidence and prevalence, high risk of morbidity and mortality, resource-intensive and costly.[1] One of the most common complications in burn patients is acute kidney injury (AKI), with an incidence of 1-30% for each burn event. Risk factors known to increase the incidence of burn AKI include older age, extensive burns, sepsis, and multiple organ failure.[2] AKI can occur within 24 hours after a patient's burn injury or at any time during resuscitation. AKI can be defined as a sudden loss of function that persists for a period of time.[3]

Astaxanthin (3,3′-dihydroxy-b,b'-carotene-4,4′-dione, ATX) is a natural carotenoid easily obtained from marine organisms and exhibits more robust and powerful antioxidative effects than other carotenoids.[5] Previously, researchers demonstrated that pretreatment or immediate administration of ATX reduced oxidative stress, inflammation, and tubular apoptosis, thereby reducing oxidative stress-induced toxicity and I/R-induced or diabetes-related effects in tubular epithelial cells in mice. Given the critical role of oxidative stress and secondary renal inflammation in severe burn-induced early AKI, a protective role of ATX through its anti-inflammatory effects and potential mechanisms of action in early post-burn AKI is reasonable.[6]

Acute Kidney Injury Pathway in Burn Patients

Thermal injury to the skin is an oxidative process associated with biological and metabolic changes. It produces free radicals from various cell populations through multiple pathways and modulation of production. Antioxidant free radical activity appears to play an important role in the pharmacological treatment of burn injuries.[2,4]

Acute Kidney Injury in burn patients is caused by decreased renal perfusion followed by decreased glomerular filtration rate (GFR) and renal plasma flow. This process causes a decrease in creatinine clearance and the appearance of oliguria in patients. If renal hypo-perfusion damage progresses progressively in a burn patient, renal failure may occur. Early renal failure in burns can occur when renal failure develops quickly when a patient receives a burn, ultimately resulting in hypovolemic ischemic injury and reduced blood circulation. Early renal failure in burn patients is one of the complications of burn injury that causes mortality rates of up to 70-100%. In the past, intermittent hemodialysis therapy was one of the methods used to treat a burn patient's AKI. However, because of the hemodynamic instability and circulatory shock associated with burns, burn patients usually do not tolerate hemodialysis therapy.[4]

In the early stages after burn injury, the risk of shock, with generalized reduction in renal blood flow (RBF), causes a range of endothelial and tubular changes, including impairment of the coagulation system and vascular reactivity, leading to post-burn injury. Injury that leads to premature tubular damage contributes. A subsequent investigation revealed that burn injury induced a remarkable increase in ROS generation and a decrease in antioxidant enzymes, representing increased oxidative stress 6 hours post burn injury, which persisted during the early stage after burn injury.[2,3]

After burn injury, leukocytes, endothelial cells, tubular epithelium contributes to the formation of several pro-inflammatory cytokines such as MPO, IL-6 and IL-1β. Increased release of proinflammatory mediators results in increased vasoconstriction, vascular occlusion, and decreased microvessel numbers, leading to lateral medullary edema, increased tubular injury, and and possible tubulointerstitial fibrosis.[2]

Role of Astaxanthin as Strong Antioxidant for Burn Cases

Astaxanthin (3,3'-dihydroxy-b,b'-carotene-4,4'-dione, ATX) has stronger antioxidant activity than other free radical-scavenging carotenoids commonly found in marine organisms such as algae, crustaceans, salmon, shrimp, and crab. According to many previous in vitro and in vivo studies, ATX protects against cell or tissue damage caused by oxidative stress. In addition, regulation of mitochondrial signaling is thought to be involved in the protective effects of ATX against burn-induced acute kidney injury, subarachnoid hemorrhage, colon carcinogenesis, obesity, and ischemia/reperfusion injury of the brain or myocardium.[5,6]

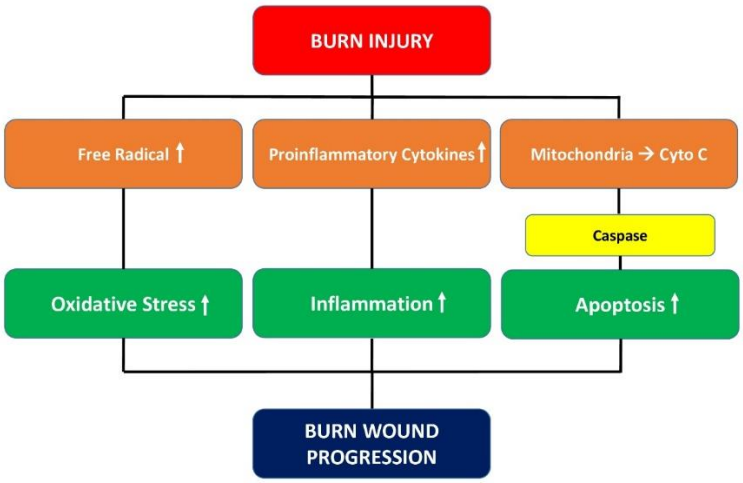

Figure 1. The Schematic of Burn Wound Progression

Considering its reported effects on oxidative stress, apoptosis, and inflammation, ATX may be of value during stasis zone transformation. In previous study, the potential impact of ATX on burn injury progression was described. 1) ATX attenuates histological changes due to burn injury. 2) ATX inhibits lipid peroxidation, activates the NADPH-dependent oxidase system, and increases the activity of endogenous antioxidant enzymes, thereby reducing oxidative stress in the early stages after burn injury in response to free radical generation. Attenuates in a dose-dependent manner. 3) ATX may reduce inflammation in the early stages of burns. 4) Increasing ATX dose further reduces cell apoptosis in the stasis zone by affecting mitochondria-associated apoptotic pathways.[7,8,12]

Oxidative stress has been shown to contribute to local inflammation and apoptosis of tissue cells in burns and other organs. Mitochondria are ROS-sensitive organelles, and mitochondrial membrane function can be compromised by

ROS-induced lipid peroxidation, resulting in Cyto C release.[7] Previous studies on burn injury have shown that ROS are involved in progressive tissue damage in the stasis zone. Therefore, ROS-induced oxidative stress is a potential therapeutic target to prevent burn injury progression. Figure 2 explain that a powerful natural antioxidant, ATX reduces oxidative stress and protects against tissue and organ damage by influencing the activity of antioxidant enzymes or oxidases (XO or Nox) that contribute to the production of free radicals. Provides a protective effect. Local and systemic inflammation, the physiological response to external stress, are usually stimulated after burn injuries and contribute to skin or organ damage caused by heat stress.[7]

In burn injury, long-term inflammatory responses mediated by complement system activation, release of inflammatory mediators, delayed inflammatory cell apoptosis, inflammatory signaling, and ROS are involved in burn injury development. ATX exhibits anti-inflammatory effects mediated by reduced PMNL infiltration and cytokine release. These effects may be mechanisms underlying the protective effects of ATX on thermal injury transformation. Cell death also plays an important role in the early development of burn injury, and there are three types of cell death: necrosis, apoptosis, and autophagy.[1,4]

Previous studies have shown that sustained apoptosis in the zone of stasis contributes to tissue loss and structural damage, and treatment of this zone is beneficial for burn wound healing. Caspase is the one of the most sensitive markers of apoptosis (Figure 1). Caspases can be classified as either initiator (usually caspase 9) or effector (usually caspase 3), and activation of the initiator caspase leads to subsequent cleavage and final activation of the internal aspartate residue of the effector caspase. be connected. Activated caspase cascades induce morphological and biochemical changes characteristic of apoptosis in biological tissues through proteolytic cleavage of target proteins. Last study showed a significant increase in the number of apoptotic cells in burn wounds over time, and this effect paralleled his upregulation of CC9 or CC3 expression. Furthermore, the reduction in the number of apoptotic cells and the expression of CC9 or CC3 indicated that ATX treatment had a dose-dependent effect of eliminating apoptosis in the stasis zone. Furthermore, ATX significantly downregulated the upregulation of cyto C expression in burn injury, suggesting that mitochondria may be involved in regulating the role of ATX in apoptosis (Figure 2).

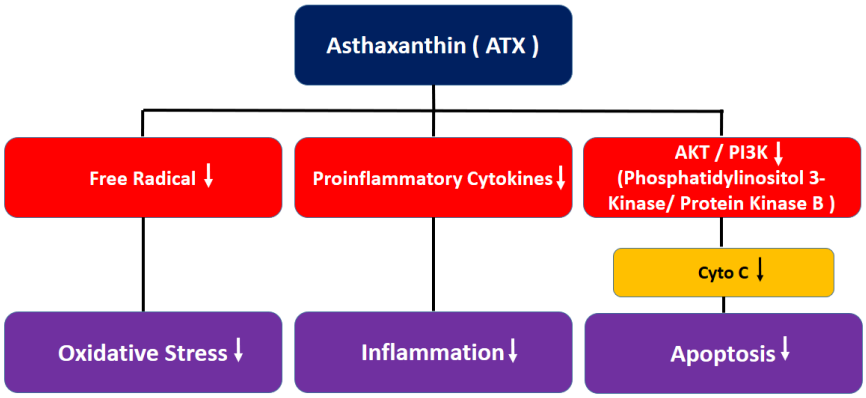

Figure 2. The Protective Role of Astaxanthin (ATX) in Burn Injury

In Figure 1, Cyto C is commonly released by mitochondria under cellular stress caused by insults and can combine with Apaf-1 and caspase 9 to form an activated complex, which eventually cleaves caspase 3 into CC3 (activated state) and induces apoptosis. As a member of the antiapoptotic Bcl-2 subfamily, Bcl-xL usually combines with Bad to build a proapoptotic complex, which increases mitochondrial membrane permeability by acting on voltage-dependent anion channels, resulting in the release of Cyto C from mitochondria. In the previous study, there is no obvious change in Bcl-xL expression after ATX treatment, which may suggest that the effect of ATX is mediated by the proapoptotic Bcl-2 subfamily rather than the antiapoptotic subfamily. In addition, according to several studies based on rodent models, ATX administration effectively attenuates cell apoptosis secondary to brain jury or burn-induced kidney injury by regulating the Akt/Bad/Cyto C signaling cascade. Moreover, ATX can further induce phosphorylation of Akt and Bad. Phosphorylated Akt is generally in an active status, which may promote Bad to dissociate from Bcl-xL. All the above results suggest that the mitochondrial apoptotic signaling pathway mediates the beneficial effects of ATX on cellular apoptosis during burn injury progression.[7,17]

Protective Effect of Astaxanthin to Early Acute Kidney Injury in Burn Patient

Similar to other severe traumatic injuries, burn insults with large body surface areas (usually TBSA ≥20%) causes a

series of secondary remote organ damage effects in addition to the direct thermal injury to local skin. Common devastating complications in critical care patients after severe burns include acute lung injury, myocardial injury, AKI, and sepsis, and these complications are associated with higher morbidity and mortality.[9] There has been a global initiative to reduce the enormous and increasing burden and consequences of AKI, which is a syndrome of abrupt loss of kidney function. Clinical doctors are eager to develop effective ways of preventing and intervening in early AKI in severely burned patients given its poor outcome.[10] The mechanism of early AKI post burn is multifactorial, and previous studies mostly focused on oxidative stress injury, renal tubular apoptosis and systemic or local inflammation. Previous results (from our group and others) have shown that ROS-induced oxidative stress injury and apoptosis play important roles in the development of burn-induced early AKI and that 24 h post burn is a significant time-window for observing the changes in renal function and the levels of oxidative stress and apoptosis.[10,11] Astaxanthin (ATX) is a powerful natural antioxidant and previous studies have shown the protective value of ATX, primarily in burn-induced early AKI, and found that its mechanism of action is related to its ability to attenuate oxidative stress and secondary renal cell apoptosis. [13]

In terms of burn injury ATX's beneficial effect is to prevent burn injuries from worsening by reducing inflammation in wound tissue. Previous studies have shown that the anti-inflammatory properties of ATX are due to the regulation of specific inflammation-associated signaling molecules, example NF-Kb (Nuclear Factor Kappa B Cells), PI3K/Akt, all of which might lead to secondary release of inflammatory cytokines.[9] Nuclear factor (NF)-κB is regarded as a potential and crucial intermediate regulator of local inflammatory conditions in early AKI after burn injury. ATX may inhibit burn-induced release of inflammatory cytokines in kidneys through an NF-κB-mediated signaling pathway and ultimately attenuate early AKI and reduce apoptosis.[14,15]

Dose of Astaxanthin protect against Burn-Induced Early Acute Kidney Injury

ATX showed a dose-dependent effect, peaking at a dose of 20 mg/kg. This dose showed ATX to protect against early AKI after burn by attenuating ROS-induced oxidative stress and restoring the activity of suppressed endogenous antioxidant enzymes.[9,10,16]

CONCLUSION

Astaxanthin which is a strong antioxidant has the ability as an anti-inflammatory which can relieve oxidative stress and inhibit apoptosis by modulating the mitochondrial-apoptotic pathway which can help in burn wound healing and prevent Burn-Induced Early Acute Kidney Injury.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil

CONFLICTS OF INTEREST

There are no conflicts of interest.

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