



PROTECTIVE EFFECTS OF ANTIOXIDANTS AGAINST BURN-RELATED INJURIES

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ABSTRACT:

Thermal burn injuries are still a serious public health concern. Severe burns cause both local skin and distant-organ injuries. Many pathological mechanisms are involved in burn-induced injuries. Overproduction of reactive oxygen species (ROS) and oxidative stress play key roles in the pathogenesis of the systemic response and serious complications after burns. Antioxidants are intensively studied, and their beneficial effects are documented. Regardless of that, they still attract the researchers' interest in uncovering new evidence about their favorable impact on burn injuries. This review aims to describe recent evidence related to the mechanisms of tissue protection after administering some antioxidants with biogenic origins in burns.

Keywords: burn injury, reactive oxygen species (ROS), oxidative stress, antioxidants,

INTRODUCTION

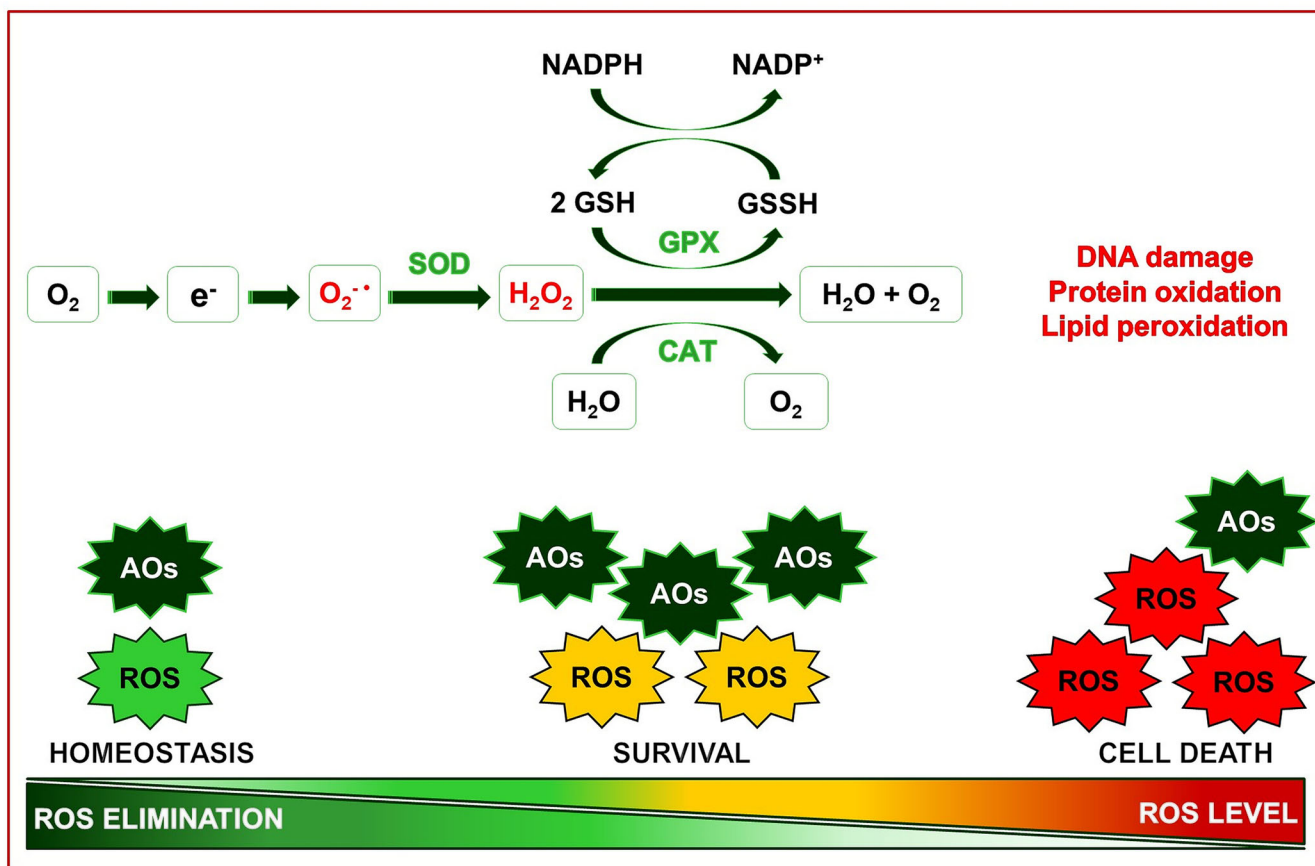
Thermal burn injuries are still a serious public health concern. According to the World Health Organization burn injury induces numerous organ dysfunctions, resulting in high levels of morbidity and mortality [1].

Burn injuries are highly variable in terms of the tissues affected, the severity and resultant complications [2]. Initial epidermal injury compromises its function as an effective epithelial barrier between organism and the environment. [3] They become increasingly traumatic with the introduction of comorbidities such as shock, respiratory and renal failure, intestinal alterations and immunosuppression [2]. On the other hand, even relatively small burns (<20% of the TBSA) can be incapacitating, disfiguring and painful [4].

Pathophysiology of burn-related injury includes many mechanisms, occurring both locally in the insulted area and in systemic response to the thermal trauma. Various cellular and molecular interactions between neutrophils and macrophages, cytokine overproduction, depletion of glutathione and mitochondrial dysfunction are involved in these processes [5]. Mediators, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), are increased in the affected tissues [6].

ROS and RNS play a dual role since they can be both harmful and beneficial to living systems (Figure 1) [7]. Experimental and clinical studies show that oxidative stress is involved in the "systemic response" in burns. Oxidative stress, depending on the level and mode, is one of the triggers to activate various defense mechanisms, assuring cellular survival [8]. On the other hand, ROS/RNS overproduction and weak endogenous defense lead to oxidative stress that harms lipids, proteins, DNA and the cellular redox state [8] and may result in cellular damage and dysfunction [7].

Fig. 1. Relationship between the ROS production and removal and cell fate during burn.



A correlation has been demonstrated between the quantity of lipid peroxidation and the degree of burn [5]. These facts defined oxidative stress as a key mechanism for burn-related injuries.

Previous reports demonstrated that antioxidants and trace elements supplementation may reduce oxidative stress alleviate inflammation and hypermetabolism, thus improving clinical outcomes [9]. Beneficial effects of antioxidants application include reduction of wound infection, shortening of healing time and improvement in the mortality rate in burn patients [10].

Natural extracts are a source of active molecules and antioxidant substances, and they have the potential to be useful as complementary therapy for diseases associated with oxidative stress [11, 12]. This review focuses on issues related to ROS sources and oxidative stress, as well as antioxidant therapy in thermal trauma. Recent evidence is presented for cellular and molecular mechanisms of tissue protection and beneficial effects of administration of some antioxidants with biogenic origin in burns.

MATERIALS AND METHODS:

The present review includes recent studies on the protective effects of natural antioxidants in burns. The

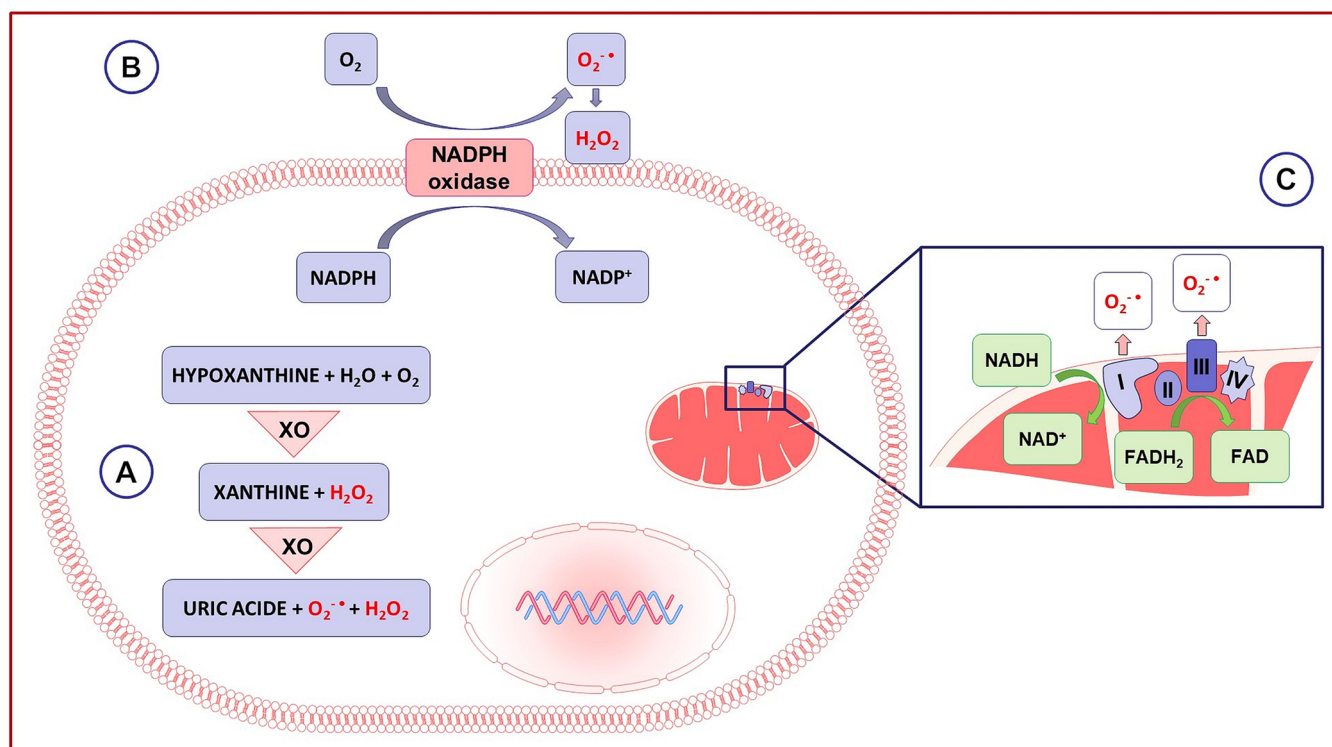
electronic databases used for the collection of relevant information include PubMed and Google Scholar. The search considered original articles published in the last 5 years. The search keywords and phrases used were various keyword combinations: “burn injury”, “reactive oxygen species (ROS)”, “oxidative stress”, “antioxidants”, and “lung”, “myocardial”, “kidney”, “gastric”, “intestinal”. After reviewing titles and abstracts, studies deemed potentially eligible were further evaluated by full-text reading. The inclusion criteria consisted of original articles or animal studies, herbal and natural remedies for burn-induced injury, and studies investigating the effects of antioxidants on burn wounds or burn-induced systemic response. The exclusion criteria were lack of relation between applied antioxidants and oxidative stress-related markers and pharmaceuticals derived from semi-synthetic and synthetic chemicals.

RESULTS AND DISCUSSION:

ROS sources and oxidative stress in thermal trauma

Ischemia and reperfusion (I/R), neutrophil infiltration and activation, and mitochondrial dysfunction are major sources of ROS/RNS in thermal trauma (Figure 2).

Fig. 2. Cellular sources of ROS production during burn. (A): Generation of ROS by XO; (B): Generation of ROS by NADPH oxidases; (C): Generation of ROS in mitochondria.



Xanthine oxidase and thermal burn

I/R, ischemia, hypoxia, increase xanthine oxidase activity [13].

Xanthine oxidase (XO) is one of the main sources of ROS. Widely distributed in various organs and tissues, the enzyme catalyzes the oxidation of hypoxanthine to xanthine and can further catalyze the oxidation of xanthine to uric acid. Superoxide (O₂^{•-}) and hydrogen peroxide (H₂O₂) are produced during the catalytic reaction. Elevated levels of uric acid and O₂^{•-} radicals damage tissues by increasing vascular permeability, neutrophil infiltration and development of inflammation [13].

There is evidence for the involvement of XO in burn-induced oxidative stress [14, 15]. Injured skin is a source of increased plasma XO activity after thermal injury, too [15]. Excision of the burn-injured skin immediately after thermal injury significantly diminished the increased activity of XO in plasma. Additionally, the xanthine oxidase inhibitors (allopurinol and Iodoxamide tromethamine) were found to have protective effects on burn-induced skin edema [16].

NADPH oxidases and thermal burn

Another endogenous source of ROS is nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) enzymes. The NOX family consists of NOX1, NOX2, NOX3, NOX4, NOX5, DUOX1 and DUOX2 enzymes [17].

(NADPH) oxidases (NOX) enzymes are membrane-bound proteins, and their main function is to transfer electrons across the plasma membrane to molecular oxygen, which results in the generation of superoxide anions and other ROS, products of O₂^{•-}, including H₂O₂, hydroxyl radi-

cal (OH[•]), and hypochlorous acid (HClO). NOX enzymes are ubiquitously expressed, they have unique distribution patterns and expression levels in different tissues throughout the body [17].

Activation of phagocytic NADPH oxidase is crucial for killing pathogens during phagocytosis [18]. Therefore, effective polymorphonuclear neutrophil (PMN) activation is important for successful host defense [19]. PMN activation and NADPH oxidase upregulation are important in I/R injury. Reperfusion of the ischemic tissues is accompanied by a more profound injury response that has been linked to the generation of ROS [20].

NOXs mediate oxidative stress in the burn, too. It was found that Nox4 expression was significantly increased in the zone of stasis of rat burn wounds [15]. Downregulation of the NOX4 expression successfully reduced ROS production and cell apoptosis in burn-induced acute lung injury [21].

Mitochondrial dysfunction and thermal burn

In aerobic cells, mitochondria are necessary for numerous fundamental functions, including respiration and oxidative energy production, regulation of the intracellular calcium concentration and control of the fatty acid β -oxidation [7]. Also, mitochondria are heavily involved in ROS/RNS overproduction. Mitochondrial ROS are mainly produced through the electron transport chain during the oxidative phosphorylation process when molecular oxygen (O₂) is reduced to H₂O [22].

Usually, the rate of mitochondrial ROS generation is relatively low, resulting in minimal damage because mitochondria have a highly efficient antioxidant defense sys-

tem that can scavenge many of the produced ROS [7]. Various antioxidant enzyme systems are involved in their elimination as soon as they are generated. The generated superoxide is dismutated to H₂O₂ by Mn-SOD in the matrix or Cu/Zn SOD in the intermembrane space. The hydrogen peroxide formed during normal mitochondrial activity can be degraded by catalase, thioredoxin, and glutathione peroxidases, which form water [22]. However, under some conditions, overgenerated ROS can evade the antioxidant defense system, compromising important mitochondrial functions [7].

Severe burn injury causes mitochondrial dysfunction in multiple organs [23, 24].

Antioxidant therapy and thermal burn

Cells own an abundance of protective factors, providing three lines of defense. Enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX); metal-binding proteins; and minerals such as Se, Cu and Zn are the first line of defense. Their functional activity is associated with preventing the formation of new free radicals. The second line includes glutathione, vitamins C and E, carotenoids and flavonoids. These antioxidants remove free radicals and prevent oxidative chain reactions. DNA repair enzymes, lipases, proteases, transferases and methionine-sulfoxide reductases form the third line. They repair oxidatively damaged biomolecules [8].

Although cells possess a large repertoire of enzymes and antioxidants, sometimes these endogenous agents are insufficient to normalize the redox state produced by intense oxidative stress. Exposure to oxidant can deplete the antioxidants at the target sites and induce lipid peroxidation and protein oxidation [6]. Serious damage to the cell may even lead to its death [12]. In these cases, exogenous antioxidant supplements may be required to restore the cell redox homeostasis [8].

An antioxidant has been defined by Halliwell and Gutteridge as “any substance that delays, prevents or removes oxidative damage to a target molecule [25]. The good antioxidant is a molecule that reacts with the ROS at low concentrations, and the product of its oxidation is either a stable chemical or can be easily recycled back to an active antioxidant. *In vivo* is its ability to achieve sufficient concentrations at the sites where it is supposed to act [26].

The composition of antioxidant supplements is variable. They can contain vitamins, minerals or a combination of them. Antioxidant supplementation can also include mixtures of oils and vitamins or minerals, or plant extracts [8].

Natural sources of antioxidants rather than synthetically produced ones are considered to be more beneficial for the maintenance of good health. That is why, as a powerful tool of contemporary medicine, plant-derived phytochemicals are used to balance the antioxidant/prooxidant status for the prevention and treatment of diseases [11].

Flavonoids are a large group of naturally occurring phenolic compounds which are present at high levels in the human diet. They are commonly found in several medicinal plants. Certain therapeutic properties, mainly anti-inflammatory, wound healing, antioxidant, are mostly at-

tributed to these plants [27].

Carotenoids have strong antioxidant, repairing, antiproliferative and anti-inflammatory effects. Their application can prevent oxidative stress-related diseases and chronic inflammation [28].

Astaxanthin is one of the most powerful carotenoids [28] and belongs to the xanthophyll class of carotenoids [29]. Astaxanthin is extensively produced by algal species and by yeast [28]. Similar to other carotenoids, it cannot be synthesized by animals and must be included in the diet [29]. Astaxanthin has a unique molecular structure that allows it to cross the bilayer cell membrane and scavenges ROS and free radicals in both the inner and outer layers of the membrane [28]. Intensively studied, the beneficial potential of Astaxanthin was documented against neurological disorders [30], insulin resistance, diabetes mellitus complications, muscle performance, recovery and atrophy [28], including skin health [29].

This report presents recent evidence of the beneficial effects of Curcumin, Astaxanthin and some herbal products applied to burn-induced tissue injury.

Action of natural antioxidants on burn wound

Burn wounds present an evolutionary progression in which the initial wound tissue deepens and expands following thermal injury. Burn wound progression contributes to the development of wound contraction, hypertrophic scarring, wound infection and sepsis. According to Jackson's model of thermal wound injury, the burn wound is divided into three concentric zones: a central zone of coagulation, an intermediate zone of stasis and an outer zone of hyperemia. The recovery of the zone of stasis is vital in preventing tissue injury [15].

It is known that inflammatory cells infiltration is an important phase of wound repair. The prolonged presence of inflammatory cells in the wound bed produces various reactive radicals, which contribute to oxidative imbalance and further negatively regulate the healing process [31].

Together with the persistent inflammatory phase, the oxidative microenvironment was also observed in non-healing wounds. In this light, the effective modulation of inflammation and oxidative stress are important for promoting burn wound repair.

A recent study showed that preconditioning of adipose-derived mesenchymal stem cells (ASCs) with Curcumin contributes to the efficacy of transplanted ASCs in the wound and their tolerance to the hostile niche of acid inflicted burns. Curcumin increased antioxidant defense via upregulation of SOD1 expression in wound healing. Curcumin-ASCs exhibited greater proliferation, migration and paracrine potential *in vitro*. Additionally, treatment with Curcumin-ASCs resulted in a faster wound recovery rate and re-epithelization of acid inflicted burns compared to the treatment with naïve ASCs. The elevated switch from pro-inflammatory status to pro-healing status was evidenced via the reduction of the mRNA and protein expressions of pro-inflammatory mediators (IL-1 β , IL-6 and TNF- α) and upregulation of pro-angiogenic factors, as well as collagen content markers [31].

Zhou H et al. demonstrated the protective effects of Abnormal Savda Munziq (ASMq), a traditional herbal for-

mula, against early burn wound progression in rats. ASMq administration contributed to the attenuation of burn wound progression following thermal injury in a dose-dependent manner. These results are associated with the downregulation of malondialdehyde (MDA) levels, a marker of lipid peroxidation, and significant downregulation of XO and Nox4 expression, participating in the regulation of oxygen free radicals. ASMq suspension significantly enhanced the activity of endogenous antioxidant enzymes GPx and SOD in the zone of stasis of rat burn wounds. Furthermore, ASMq treatment decreased cell apoptosis [15].

The present work investigated the combination of two polyphenols, Curcumin and resveratrol, in a nanoemulsion-based gel system (nanoemulgel) in a rat burn model. Topical treatment resulted in increased antioxidant activity, reflected by the significantly lower MDA and nitric oxide levels. Results were significant for curcumin nanoemulgel compared to those for resveratrol nanoemulgel. The combined nanoemulgel was superior to the individual nanoemulgels [32].

Vitamin E is an important naturally occurring antioxidant in skin tissue. Thermal injury depletes the skin's antioxidants, particularly vitamin E. Treatment with Curcumin or resveratrol alone resulted in a significant increase in vitamin E content. In combination, the effects were synergistic. Another favorable finding was the correlation between histopathological and biochemical parameters in the healing wounds [32].

Action of natural antioxidants on burn-induced systemic response

Thermal trauma can damage organs away from the skin burn site and lead to multiple organ dysfunction. Severe burns cause a systemic response of inflammatory reactions that produce toxins and reactive oxygen radicals that lead to peroxidation [7, 33]. Antioxidant therapy can improve distant oxidative organ damage, limit systemic inflammatory response and decrease recovery time after thermal injury [33, 34, 35].

Although the number of presented studies investigating the effects of natural antioxidants on burn-induced systemic response is limited, they provide strong evidence for their benefit in burns.

The administration of *Myrtus communis* leaves ethanol extract orally significantly decreased the elevated MDA levels in the lungs and small intestine after thermal injury, and it also increased SOD, CAT, GST activities, as well as GSH levels. Authors think that the negative effects of burn-induced oxidative damage and antioxidant response reversed remarkably due to the phenolic compounds found in *M. communis* [33].

It was documented that Astaxanthin protects against early acute kidney injury in severely burned rats [34]. The increased renal oxidative stress after burn injury was presented with a significant increase of MDA levels and a marked decrease of endogenous antioxidant enzyme SOD, accompanied on significantly higher levels of MPO, IL-1 α and IL-6. Another investigated marker is heat shock protein HO-1, which can be induced rapidly to address both oxidative and cellular stress, presenting powerful antioxidant or anti-inflamma-

tory characteristics. Burn induced a significant upregulation of HO-1 expression in the kidneys, while medium- and high-dose Astaxanthin administration further increased renal HO-1 expression after burn injury. Additionally, Astaxanthin ameliorated the burn-induced renal inflammation. Thus, Astaxanthin manifests beneficial effects through its ability to attenuate the oxidative and inflammatory response in burn-induced acute kidney injury [34].

Astaxanthin use has a beneficial role in smoke inhalation injury accompanying 30% of TBSA burn in rats [35]. Smoke inhalation injury leads to the inflammatory process, acute respiratory distress syndrome and systemic inflammatory response syndrome. Again, markers of oxidative stress and inflammation were investigated. Astaxanthin leads to lowered tissue levels of 4-hydroxynonenal and MDA, as well as decreased glutathione reductase levels. Levels of pro-inflammatory cytokines TNF- α , IL-1 β and IL-6 decreased, too. Thus, Astaxanthin prevents systemic response due to oxidative stress and inflammatory processes after combined injury of smoke inhalation injury and >30% burns [35].

CONCLUSION:

Studies clearly revealed the useful effect of biogenic origin antioxidants in burn-related injury treatment. Regardless of the route of administration (local, oral or intravenous), they have a beneficial effect on both local and remote organ injury. Natural antioxidants limit burn-induced oxidative stress as stimulated cellular protective mechanisms and reduce lipid peroxidation products. In addition, their use is related to a lower level of pro-inflammatory markers in the investigated tissue samples. Reduced system response and ameliorated organ dysfunction are factors associated with lower morbidity and mortality rate in major burn patients. Based on the experimental results pointing to their beneficial effects, antioxidants show potential to be included as adjuvant therapy for burn-related injuries.

Abbreviations:

O₂ - molecular oxygen;
O₂^{•-} - superoxide;
H₂O - water;
H₂O₂ - hydrogen peroxide;
e⁻ - electrons;
NADH - reduced nicotinamide adenine dinucleotide;
NAD⁺ - oxidized nicotinamide adenine dinucleotide;
SOD - superoxide dismutase;
GPX - glutathione peroxidase;
CAT - Catalase;
GSH - glutathione;
GSSG - oxidized form of GSH;
AOs - Antioxidants;
XO - xanthine oxidase;
NADPH - oxidase, nicotinamide adenine dinucleotide phosphate oxidase;
FADH₂ - reduced flavin adenine dinucleotide;
FAD - oxidized flavin adenine dinucleotide.

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