

Role of oxidative stress in post-burn wound healing

Ruiqi Chen^{1,2,3,4,†}, Hongbiao Xu^{5,†}, Xueshi Li^{6,†}, Jie Dong⁷, Shengli Wang^{1,2,*}, Jianlei Hao^{1,2,*}, Guangping Liang^{8,9,*}

¹The Affiliated Guangdong Second Provincial General Hospital of Jinan University, No. 466, Middle Xingang Road, Haizhu District, Guangzhou, Guangdong 510317, China

²State Key Laboratory of Bioactive Molecules and Druggability Assessment, The Biomedical Translational Research Institute, Health Science Center (School of Medicine), Jinan University, No. 601 Huangpu Avenue West, Tianhe District, Guangzhou, Guangdong 510632, China

³School of Traditional Chinese Medicine, Guangdong Pharmaceutical University, No. 280, Outer Ring East Road, Guangzhou University City, Guangzhou, Guangdong 510006, China

⁴Guangdong Provincial Key Laboratory of Spine and Spinal Cord Reconstruction, The Fifth Affiliated Hospital of Jinan University Heyuan 517000, China

⁵Department of Thyroid and Breast Surgery, The First Affiliated Hospital, Sun Yat-sen University, No. 58 Zhongshan 2nd Road, Guangzhou, Guangdong 510275, China

⁶Department of Orthopedic Surgery, The First Affiliated Hospital, Jinan University, 613 Huangpu Avenue West, Tianhe District, Guangzhou, Guangdong 510632, China

⁷Department of Clinical Laboratory, Guangzhou Twelfth People's Hospital, No. 1 Tianqiang Road, Huangpu Avenue West, Guangzhou, Guangdong 510620, China

⁸State Key Laboratory of Trauma, Burn and Combined Injury, Institute of Burn Research, Southwest Hospital, Third Military Medical University (Army Medical University), No. 30, Yanzheng Street, Gaotian, Shapingba, Chongqing 400038, China

⁹Chongqing Key Laboratory for Disease Proteomics, No. 30 Gaotianyan, Shapingba District, Chongqing 400038, China

*Corresponding authors. Shengli Wang, E-mail: wangshengli630@stu2018.jnu.edu.cn; Jianlei Hao, E-mail: haojianlei@jnu.edu.cn; Guangping Liang, E-mail: maggie_liang@tmmu.com.cn

†Ruiqi Chen, Hongbiao Xu, and Xueshi Li contributed equally.

Abstract

Oxidative stress is an inherent pathophysiological feature in burn wound healing. Severe burns trigger rapid changes in patients' conditions, leading to ischemia–reperfusion injury from early fluid resuscitation, neuroendocrine stress, and fluid imbalances, which exacerbate oxidative damage and organ dysfunction. This review highlights the critical role of oxidative stress in post-burn wound healing, its potential to cause cellular and tissue damage, and oxidative stress mechanisms. Antioxidant therapy is recommended as a cost-effective method of modulating inflammation and burn outcome. Preparative measures of successful antioxidant therapy should be developed in improving burn patients' wound healing.

Keywords: Burn; Wound healing; Oxidative stress; Antioxidant therapy; Reactive oxygen species; Antioxidant

Highlights:

- Oxidative stress plays a very important role in post-burn wound healing, devastating redox homeostasis and enhancing tissue damage through overpowering reactive oxygen species (ROS) production.
- Severe burns cause systemic oxidative stress, with inflammation, organ dysfunction, and impairment of wound repair, and the levels of ROS are closely related to the severity of burns.
- Antioxidant therapy offers itself as a promising treatment, targeting ROS-mediated injury to limit inflammation and improve burn patient clinical outcomes.
- The primary mechanisms of oxidative stress include neutrophil activation, mitochondrial dysfunction, and impaired antioxidant defenses, all of which collectively inhibit the healing process.
- Novel therapies like Nrf2 activators and mitochondrially targeted antioxidants have the potential to restore redox homeostasis and enhance recovery in burns.

Background

Burn injuries are one of the most common forms of trauma with the potential to induce significant complications, elevated mortality rates, and serious long-term effects on the quality of life for patients. For severe burns, oxidative stress arises through various mechanisms: local production of reactive oxygen species (ROS) at site of burning, systemic generation of ROS due to inflammation, and interference with antioxidant defense mechanisms. This cascade leads to increased production of inflammatory factors, activation of

inflammatory signaling pathways, increased inflammatory cell infiltration and inflammatory cell activation, and resulting organ dysfunction [1, 2]. All of these are unfavorable factors for burn wound healing. Therefore, mitigation of oxidative stress damage after severe burn is an important clinical problem.

Systemic inflammatory reactions to burn damage have their pathophysiology intrinsically linked to mechanisms of oxidative stress. The oxidative stress response following injury not only deteriorates wound healing and decreases skin graft

Received: December 20, 2024. Revised: February 20, 2025. Accepted: June 6, 2025

© The Author(s) 2025. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

survival rates of skin grafts but also maximizes tissue damage, thereby worsening patient prognosis [3]. As such, the management of oxidative stress remains a critical therapeutic strategy to improving wound healing in burn patients.

ROS production is caused by both endogenous cellular metabolic processes and external sources after gross tissue damage. Under normal physiological conditions, redox homeostasis within the human organism is regulated by a multi-dimensional antioxidant defense mechanism that involves key enzymes such as copper-zinc superoxide dismutase (Cu, Zn-SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). These enzymes regulate ROS levels to prevent toxicity [4]. However, the deep metabolic changes due to burn trauma may disturb this balance and lead either to the depletion of antioxidants or to the excess generation of ROS, thereby adding to oxidative stress. A characteristic manifestation of post-burn oxidative stress is the disturbance of redox homeostasis, as illustrated by a disequilibrium between ROS generation and antioxidant defense. The degree of oxidative stress in vital organs following severe injury due to burns can be quantitatively determined using the combined reduced antioxidant markers and elevated level of markers of oxidative stress indicators, i.e. myeloperoxidase (MPO) and xanthine oxidase (XOD) activity, which are reliable biomarkers of thermal injury-induced oxidative damage [5].

The present research supports the application of antioxidant therapy in burn wound healing, and the evidence supports the use of systemic delivery of exogenous antioxidants in aiding recovery after burns. This approach offers novel perspectives for the design of antioxidant treatment regimens in patients with burns [6]. Designing secure, efficient, quick-acting, and easy-to-use therapeutic drugs to manage blood glucose levels and enhance critical organ antioxidant ability during the initial phase of critical burns is a significant research focus toward the establishment of burn wound healing therapies.

This review incorporates latest research findings related to ROS-induced oxidative damage in burn wound healing and contrasts existing antioxidant treatment strategies for burn patients.

Review

Definition and biological basis of oxidative stress

Oxidative stress is a condition in which there is an imbalance between oxidants, such as ROS and reactive nitrogen species (RNS), and antioxidants, leading to a predominance of oxidative reactions. The imbalance leads to neutrophil inflammatory infiltration, increased secretion of proteases, and the generation of numerous oxidative intermediates [7]. Excessive ROS under oxidative stress conditions can damage cellular proteins, lipids, and DNA, causing lethal cellular damage and contributing to various pathologies, including aging, cancer, neurodegenerative diseases, cardiovascular diseases, and diabetes [8].

The biological source of oxidative stress includes ROS like the superoxide anion ($\cdot\text{O}_2^-$), hydroxyl radical ($\cdot\text{OH}$), and hydrogen peroxide (H_2O_2) and RNS like nitric oxide ($\cdot\text{NO}$), nitrogen dioxide ($\cdot\text{NO}_2$), and peroxynitrite ($\cdot\text{ONOO-}$) [9].

Generation and elimination of reactive oxygen species

Reactive oxygen species are chemically reactive molecules that are generated through the incomplete reduction of oxygen

and play a vital role as inflammatory mediators of inflammation [10]. ROS primarily include hydroxyl radicals ($\cdot\text{OH}$), superoxide anion (O_2^-), single linear state oxygen ($^1\text{O}_2$), and hydrogen peroxide (H_2O_2) [11].

ROS are generated through three primary mechanisms (Figure 1):

- (1) Mitochondrial electron transport chain (METC): The majority of ROS are of METC origin. During cellular oxidation, electrons that are transferred through the METC are coupled with proton production across the mitochondrial inner membrane. While most of the electrons are safely transferred from the donor to the acceptor molecule via redox pathways, some may leak too early, reducing oxygen to O_2^- , which then mutate to H_2O_2 [12]. Increased mitochondrial membrane permeability allows ROS produced by the METC to be made available for release into the cytoplasm and induce inflammation by signal transduction or biomolecular toxicity [10].
- (2) Cellular enzymes: ROS are also produced as byproducts of various cellular enzymes, such as nicotinamide adenine dinucleotide phosphate oxidases (NOX), xanthine oxidoreductase (XOR), and lipoxygenases (LOX) [13]. NOX produces ROS by its catalytic subunit that delivers electrons from nicotinamide adenine dinucleotide phosphate (NADPH) to molecular oxygen. The NOX family comprises seven members, including NOX-1 through NOX-5 and dual oxidases (DUOX)-1 and DUOX-2; both DUOX and NOX-4 produce predominantly H_2O_2 [14]. XOR, the molybdenum metalloenzyme, catalyzes the hydroxylation of xanthine to uric acid and exists in two functionally equivalent forms: xanthine dehydrogenase (XDH) and xanthine oxidase (XO). XO utilizes O_2 and serves as the terminal electron acceptor utilized by XO to produce ROS [15]. LOX also catalyzes the oxidation of arachidonic acid (AA) and polyunsaturated fatty acid (PUFA) to form hydroperoxylated derivatives and transitory ROS byproducts [16].
- (3) Ionizing radiation (IR): IR is a significant source of ROS, primarily through the radiolysis of water. Low linear energy transfer (LET) IR, such as gamma rays and X-rays, results in the ionization and excitation of water molecules, producing ROS, primarily in the form of free radicals [17]. These reactive radicals may react with water and oxygen molecules further, producing more reactive radicals through indirect effects [18].

ROS-scavenging mechanisms

In order to preserve homeostasis within the body, organisms strive to control highly reactive ROS with an antioxidant network [4]. Two primary pathways of ROS scavenging are as follows (As shown in Figure 1):

- (1) Endogenous antioxidant enzymes: They include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). SOD, the first line of defense, rapidly converts superoxide into molecular oxygen and H_2O_2 , thereby lessening the reactivity of ROS [19]. CAT inactivates H_2O_2 by decomposing it into molecular oxygen and water [4]. GPx utilizes glutathione (GSH) to catalyze the reduction of H_2O_2 to water [20].
- (2) Low molecular weight scavengers: These include vitamins, β -carotene, coenzyme Q, selenium, and zinc.

Generation and elimination of reactive oxygen species (ROS)

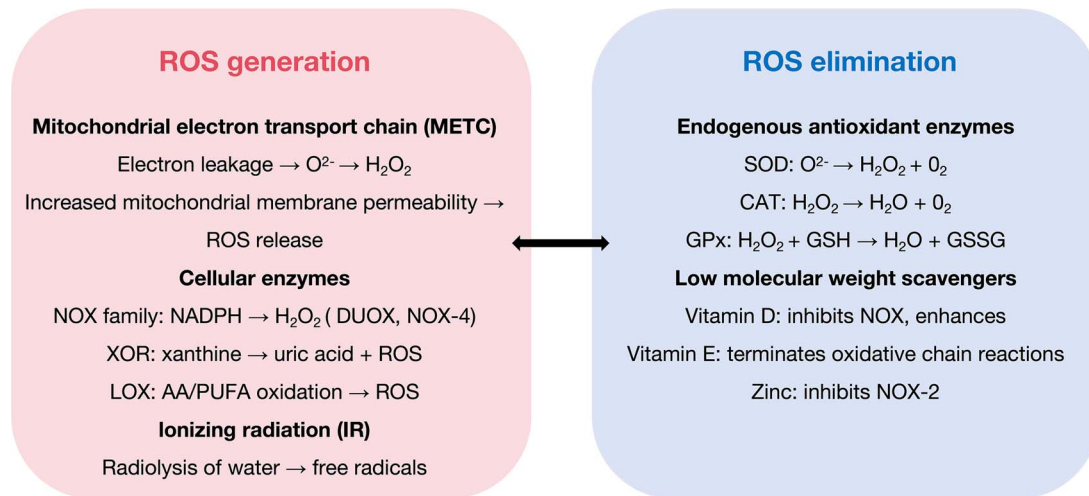


Figure 1. Generation and elimination of reactive oxygen species (ROS). *METC* mitochondrial electron transport chain, *NOX* nicotinamide adenine dinucleotide phosphate oxidase, *DUOX* dual oxidase, *XOR* xanthine oxidoreductase, *LOX* lipoxygenases, *AA* arachidonic acid, *PUFAs* polyunsaturated fatty acids, *IR* ionizing radiation, *SOD* superoxide dismutase, *CAT* catalase, *GPx* glutathione peroxidase, *GSH* reduced glutathione, *GSSG* oxidized glutathione, *Zn* zinc

These scavengers either trigger antioxidant enzymes or halt oxidative chain reactions. For instance, vitamin D inhibits NOX activity and enhances antioxidant enzyme activity, facilitating the scavenging of ROS [21]. Vitamin E functions as a peroxyl radical scavenger, preventing chain reactions through the donation of phenolic hydrogens to peroxyl radicals, which results in the formation of inactive tocopherol radicals [22]. Zinc inhibits NOX-2, exhibiting antioxidant activity, but its accumulation in mitochondria can cause mitochondrial ROS (mtROS) levels to increase, thereby activating the downstream signaling molecule nuclear transcription factor (NTF) [23].

Biomarkers of oxidative stress

ROS are inherently unstable molecules in themselves with extremely short half-lives, such that the valid clinical measurement of individual ROS such as $O_2^{\cdot-}$ and H_2O_2 is particularly challenging [24]. To bypass this limitation, methods have been developed to quantify stable byproducts of ROS activity as surrogates of oxidative status. Current biomarkers used to analyze redox status in human samples primarily include oxidation products of lipids, DNA, and proteins [25].

1) Lipid peroxidation

Polyunsaturated fatty acids (PUFAs) like phospholipids, glycolipids, and cholesterol are particularly susceptible to oxidative damage. Raised levels of ROS initiate lipid peroxidation, and the best-studied biomarkers for this reaction are malondialdehyde (MDA) and isoprostanes [26]. MDA, a secondary product of peroxidation of PUFAs, can also bind to proteins to give rise to adducts and are commonly estimated using the thiobarbituric acid (TBA) test. This colorimetric assay is the one which measures TBA-reactive substances (TBARS), which react with MDA to yield a characteristic pink chromophore upon reaction with MDA [27]. F2-isoprostanes, lipid peroxidation end products that are stable, are measurable tissues and in some of the human biological fluids, such

as urine, plasma, and cerebrospinal fluid [28]. There have been some experimental and clinical studies that have demonstrated significant correlations between plasma and urine F2-isoprostane concentrations and systemic ROS production and oxidative stress [29].

2) Non-enzymatic total antioxidant capacity

Total antioxidant capacity refers to the overall activity of non-enzymatic antioxidants in biological systems, excluding enzymic defenses such as superoxide dismutase, catalase, and peroxidase. This assay quantifies both water-soluble and lipid-soluble low molecular weight antioxidants like urates, bilirubin, vitamin C, thiols, flavonoids, carotenoids, and vitamin E [30, 31].

3) Oxidative modification of DNA and proteins

DNA and proteins are particularly susceptible to redox disturbance-induced oxidative changes. The most common oxidative changes include nitrosylation, S-glutathionylation, peroxidation, and carbonylation [32, 33].

The most commonly employed methods for the quantification of oxidative stress are as follows: (1) assessment of blood biomarkers, which includes ROS metabolite measurement, in the form of hydrogen peroxide (H_2O_2) and superoxide anion ($O_2^{\cdot-}$), and measurement of antioxidant enzyme activities, including SOD and glutathione peroxidase (GSH-Px), and lipid peroxidation products, such as MDA; (2) tissue sample analysis, which includes assessment of protein oxidative modification markers, such as high-profile protein carbonyl content, and oxidative damage markers to DNA, in particular 8-hydroxydeoxyguanosine (8-OHdG); (3) monitoring urine biomarkers, such as the isoprostanoide 8-isoprostane $F_2\alpha$ [34].

Relationship between oxidative stress and burn wound healing

Burn wound healing is a complex and dynamic process comprising four overlapping phases: hemostasis, inflammation,

proliferation, and remodeling [1]. During the inflammatory phase, neutrophils and macrophages are recruited to the wound bed to eliminate pathogens and debris and secrete ROS and pro-inflammatory cytokines [35]. During proliferative phase, fibroblasts and endothelial cells migrate into the wound, depositing extracellular matrix (ECM) and forming granulation tissue, which is supported by angiogenesis [36]. Keratinocytes subsequently proliferate and differentiate to re-epithelialize the wound. Finally, the remodeling phase entails the reorganization of the ECM reorganization and scar formation, which is mediated by matrix metalloproteinases and tissue inhibitors of metalloproteinases [37].

Under physiologic conditions, the production and removal of intracellular ROS are tightly regulated by a number of mechanisms to maintain ROS at optimal levels for cell signaling without causing damage. Burn injury, on the other hand, disrupts this equilibrium by inducing either ROS overproduction or impaired clearance. This imbalance leads to excessive inflammation and significantly greatly hinders the wound healing processes [38].

Severe burn injury has been widely investigated to demonstrate significant increases in ROS levels both locally in wounds and systemically. Histological analysis of burn tissue samples from animal models reveals very high concentrations of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a specific marker of DNA oxidative damage [39]. Clinical studies have revealed that serum concentrations of MDA are markedly elevated in burn patients, indicating enhanced lipid peroxidation [40]. Also, wound tissues have significantly reduced activity of key antioxidant enzymes like SOD and GSH-Px, indicating compromised antioxidant defenses [41]. Electron spin resonance spectroscopy analysis also verified substantial increases in free radical signals in burn wound tissues [42].

Time course of ROS generation following burn injury exhibits typical phases. During the acute stage (0–72 h), levels of ROS increase significantly, primarily due to neutrophil respiratory burst [42]. During the subacute stage (3–14 days), ROS remains elevated, directly proportional to persistent inflammatory responses and mitochondrial dysfunction [43]. During the chronic stage (>14 days), ROS levels drop slowly but continue to be above physiological levels, continuing to interfere with wound healing mechanisms [44].

Clinical research has established significant correlations between the extent of ROS levels and burn injury severity. Specifically, ROS content is well positively correlated with the total body surface area (TBSA) burned [45]. Histological findings indicate that third-degree burn injury has significantly higher levels of ROS levels compared to second-degree burns [46].

Certain levels of concentration for ROS-induced tissue damage have been established by research. Local tissue ROS concentrations of more than two to three times the normal level are capable of causing widespread cellular apoptosis and tissue damage [47]. Systemic damage occurs at greater thresholds, with serum ROS concentrations greater than four times the normal level having the potential to cause multiple organ dysfunction syndrome [48].

As immune activation and the effector phase, the removal of foreign or altered self-antigens is succeeded by inflammatory responses. Oxidation and inflammation are connected during the immune homeostasis, with a moderate level of ROS keeping normal immune defense mechanisms [49, 50]. ROS

play dual roles as cytotoxic agents against malignant cells and microbes and as regulators of antibody and cytokine production. The membrane composition of immune cells makes them particularly susceptible to oxidative injury compared with other cells [49]. Oxygen free radicals are mediators of the inflammatory responses, and their unchecked production triggers inflammation by pattern recognition receptor (PRR) and non-PRR pathways [50].

The cross-talk between inflammation and free radical-catalyzed oxidative stress drives a self-promoting cycle through transcriptional activation, becoming a vicious cycle of ROS, oxidative stress, and inflammation. Oxidative stress is an obligatory component of inflammation, augmenting inflammation through oxidative injury, while inflammatory mediators simultaneously cause subsequent oxidation. Such pathologic circle ultimately results in the impairment of wound healing in burn injury [51].

Mechanisms of oxidative stress in burn wound healing

Enhanced local ROS generation during burn wound healing

Burn trauma and resulting fluid resuscitation cascade trigger traumatic and wound healing cascades involving macrophage activation and chemotaxis through cytokine, leading to generation of excessive ROS at injury sites, causing systemic imbalance of oxidative stress. The primary mechanisms responsible for ROS overproduction are as follows:

- (1) Neutrophil activation and production of radicals: Neutrophils are rapidly mobilized to traumatized wounds and damaged organs following extensive burns [52]. Neutrophils demonstrate a significant stimulation of oxygen consumption during phagocytosis of bacteria. This activity involves the reduction of coenzyme II oxidase and coenzyme I oxidase, enzymes catalyzing electron transfer reactions, yielding the formation of considerable amounts of ROS [35]. Respiratory burst is characterized by increased oxygen consumption, ROS generation, and increased activity of the pentose phosphate pathway.
- (2) Xanthine oxidase activity: Following a burn, xanthine dehydrogenase is converted to xanthine oxidase. In reperfusion, deranged cellular energy metabolism decreases adenosine triphosphate (ATP) production, leading to adenine ribonucleotides being degraded to hypoxanthine. Hypoxanthine and xanthine generate substantial quantities of ROS in the presence of xanthine oxidase [53].
- (3) Complement activation: Complement activation following a burn trauma augments oxygen free radical respiratory burst. Neutrophil phagocytosis of *Candida albicans* through complement has been reported to be greatly increased after severe burn trauma, confirming complement participation in neutrophil activation and ROS generation [54].

Local tissues release a broad spectrum of cytokines and chemokines, including IL-8, CCL2, and CCL1, following a burn injury. These mediators solicit and activate the immune cells like neutrophils and macrophages, which migrate to the wound. The neutrophils, the very first immune cells to

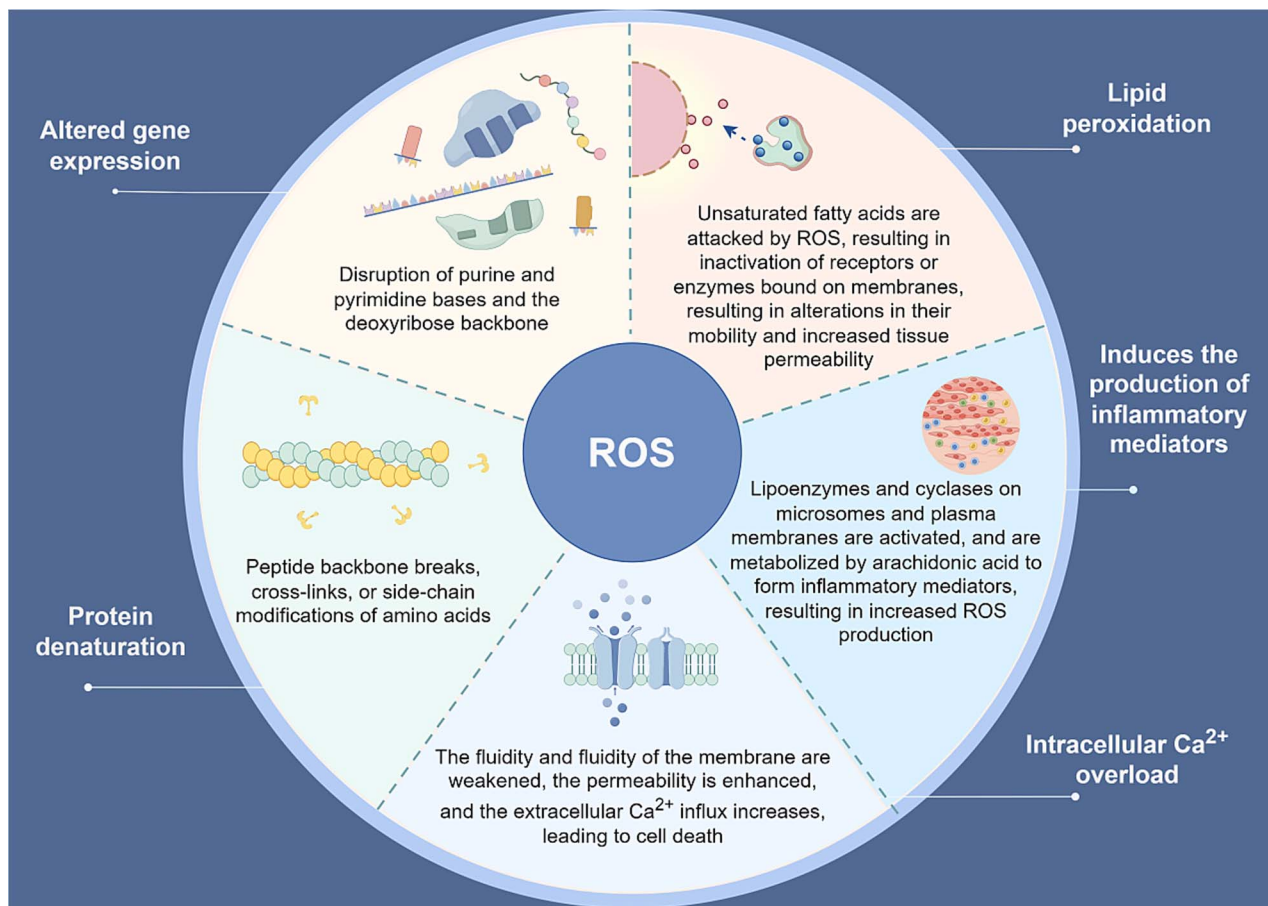


Figure 3. Mechanism underlying the systemic inflammatory response and generation of reactive oxygen species (ROS) production in burn wound healing process. Extensive fluid loss occurs in severe burns with compromised cardiac output and reduction in effective circulating volume of blood, ultimately culminating in inadequate tissue perfusion. While the initial fluid resuscitation can re-establish blood volume and increase tissue perfusion, it at the same time accelerates oxygen delivery and, therefore, leads to ischemic tissue damage. Conversely, delayed resuscitation partially corrects tissue oxygenation and instead induces an abnormal ischemia–reperfusion model that enables the excessive formation of ROS

lipid peroxidation possess endotoxin-like activity and result in multi-organ damage. Burn patients have a persistent oxidative-antioxidant imbalance, with systemic levels of oxidative stress corresponding to burn severity [67]. MDA, a terminal product of lipid peroxidation, is a widely used biomarker of oxidative stress due to its detectability and sensitivity.

- (2) Intracellular Ca^{2+} overload: Free radical-induced lipid peroxidation reduces membrane fluidity and increases permeability, leading to the influx of extracellular Ca^{2+} and ultimately leading to cell death [68, 69].
- (3) DNA strand breaks and chromosomal aberrations: ROS directly damage DNA, leading to strand breaks and chromosomal abnormalities. Inflammatory responses are induced after burns, during which a great amount of ROS, including superoxide anions and hydroxyl radicals, are produced in the body. These free radicals possess strong oxidizing capability and can attack DNA molecules. They specifically cause the breakage of phosphodiester bonds in DNA strands, resulting in ultimate single-stranded DNA breakage [70].
- (4) Denaturation of protein and enzymatic activity reduction: ROS result in protein denaturation and loss of enzyme activity. After burn injury, the body's oxidative stress response is initiated, and a great quantity of

free radicals like ROS and RNS is generated. The free radicals possess the capability of inducing carbonylation modification of protein molecules. More specifically, carbonyl groups are introduced to the protein structure, altering charge distribution and space conformation, thereby favoring protein denaturation. In the case of enzymes, these oxidative modifications may occur directly at the enzyme's active site or at nearby regions that are functionally related. This disturbance interferes with the enzyme's binding to the substrate, blocking the process of catalytic reaction process and leading to a decrease in enzyme activity [70].

- (5) Induction of inflammatory mediators: ROS enhance intracellular free calcium levels, which activate lipoxygenase and cyclooxygenase in plasma membranes and microsomes. These enzymes break down arachidonic acid into biologically active products, including prostaglandins, thromboxanes, and leukotrienes [65].

Faulty antioxidant defense system

Burn injury triggers the activation of excess oxygen free radicals, which induce lipid peroxidation of cellular and organelle membranes. Lipid peroxidation degrades unsaturated fatty acids, destroying the membrane's structural integrity and

Role of oxidative stress in post-burn wound healing

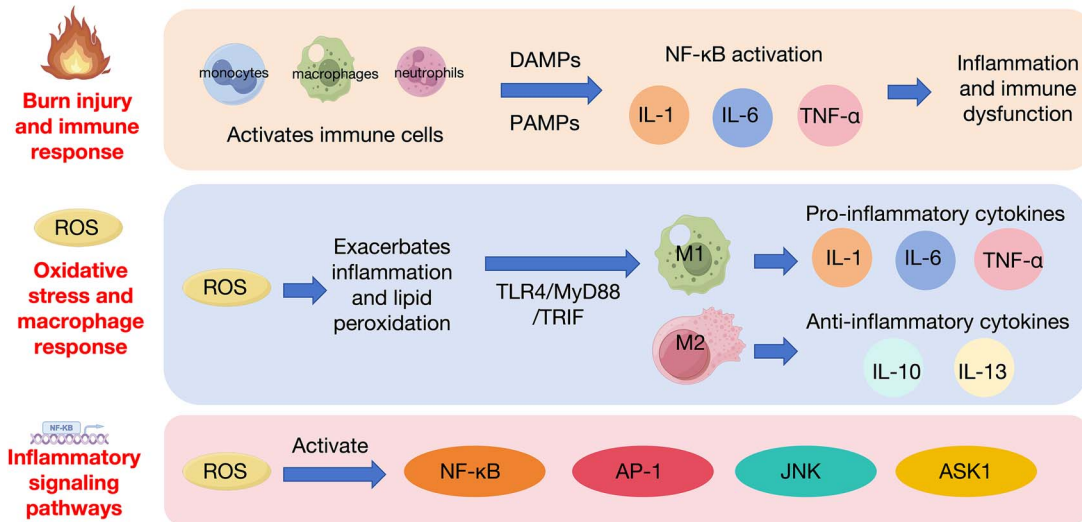


Figure 4. Oxidative stress role in wound healing after burns. Burn triggers monocytes, macrophages, and neutrophils. They recognize DAMPs and PAMPs by TLRs, NLRs (PRRs), stimulating NF- κ B, secretion of IL-1, IL-6, and TNF- α , initiating systemic inflammation and immune impairment. ROS generated enhances inflammation and lipid peroxidation. Macrophages get polarized to M1 (producing IL-1, etc.) or M2 (secreting IL-10, etc.). LPS stimulates M1 through TLR4/MyD88/TRIF. TNF- α binds to TNF-R1, activates NF- κ B and AP-1; excessive ROS inactivates MKPs and activates JNK for apoptosis. ROS inhibits the IKK phosphatases, continues NF- κ B, and activates ASK1 and JNK, leading to cell death. Oxidative stress impairs immune function and slows wound healing. DAMPs damage-associated molecular patterns, PAMPs pathogen-associated molecular patterns, PRRs pattern recognition receptors, TLRs toll-like receptors, NLRs nucleotide-binding oligomerization domain-like receptors, NF- κ B nuclear factor kappa B, IL-1 interleukin-1, IL-6 interleukin-6, TNF- α tumor necrosis factor-alpha, LPS lipopolysaccharide, MyD88 myeloid differentiation primary response 88, TRIF TIR-domain-containing adaptor inducing interferon- β , IL-10 interleukin-10, IL-13 interleukin-13, TNF-R1 tumor necrosis factor receptor 1, AP-1 activator protein-1, MKPs mitogen-activated protein kinase phosphatases, JNK c-Jun N-terminal kinase, IKK inhibitor of kappa B kinase, ASK1 apoptosis signal-regulating kinase 1

fluidity, permeability, ion transport, and barrier functions. Lipid peroxidation is the primary mechanism of oxidative membrane damage and cell necrosis and is the most significant oxidative stress-induced injury following a burn [71–73].

Excess production of ROS following burns increases Ca^{2+} influx, resulting in intracellular Ca^{2+} overload. Intracellular Ca^{2+} overload results in DNA breakage, protein denaturation, and reduced enzyme activity. Additionally, ROS also directly damage DNA by activating poly ADP-ribose polymerase (PARP). Hyperactivation of PARP drains adenosine triphosphate (ATP), which induces apoptosis and impairs the antioxidant defense system [74, 75].

In summary, the mechanisms involved in healing of burn injuries significantly increase the levels of ROS, leading to oxidative stress that adversely impacts tissue repair and recovery.

Role of oxidative stress effect on post-burn wound healing

Burn injuries have a significant impact on the immune system (Figure 4) [76]. Immune cells like monocytes, macrophages, and neutrophils become activated in hours following the injury to recognize endogenous damage-associated molecular patterns (DAMPs) or alarm proteins that are secreted from damaged tissues [77]. DAMPs and pathogen-associated molecular patterns (PAMPs) are recognized by PRRs, like Toll-like receptors (TLRs) and NOD-like receptors (NLRs). Ligand binding of these receptors activates downstream inflammatory processes, which initiate NF- κ B, a master transcription factor responsible for the release of inflammatory mediators such as IL-1, IL-6, IL-8, IL-18, and TNF. The release of

the cytokines and chemokines perpetuates the inflammatory cycle, leading to a wound healing syndrome presenting as uncontrolled cytokine release of cytokines, hyperleukocytosis, fever or hypothermia, tachycardia, and tachypnea [2, 78]. Notably, other immune functions like macrophage antigen presentation and neutrophil pathogen-killing activity are significantly compromised [79]. Furthermore, T-cell proliferation and IL-2 generation are blocked, resulting in impaired adaptive immune responses and increased susceptibility to infection [80, 81].

Macrophage response in burn wound healing

Research has established that ROS generated during the healing of burns enhance inflammation and lipid peroxidation, a significant marker of oxidative damage in burns [82–84]. Myeloperoxidase activity and MDA, the end product of lipid peroxidation, cause acute tissue injury and pose challenging obstacles to the healing of wounds. During the pathogenesis of burns, macrophages are activated through the classical NF- κ B pathway. Classically activated macrophages (M1) secrete pro-inflammatory cytokines such as IL-1, IL-6, IL-12, TNF- α , and chemokines promoting pathogenic events and contributing to inflammatory T-cell differentiation [85]. In contrast, alternatively activated macrophages (M2) secrete anti-inflammatory cytokines like IL-10 and IL-13 that decrease inflammation and contribute to wound healing [86]. Lipopolysaccharide (LPS), a TLR4 ligand, enhances M1 differentiation by employing MyD88-dependent and TRIF pathways [87]. Genetic studies have revealed that activation of M1 leads to the expression of pro-inflammatory cytokines [88].

Activation of inflammation signaling pathways in burn wound healing

TNF- α , a strong pleiotropic cytokine, plays a critical role in cell growth, differentiation, and septic shock pathogenesis and apoptosis [89]. TNF- α interacts with tumor necrosis factor receptor 1 (TNF-R1), which triggers NF- κ B and AP-1 transcription factor pathways, which regulate cell survival following TNF-R family stimulation. In physiological conditions, NF- κ B controls the ROS level and, together with mitogen-activated protein (MAP) kinase phosphatases (MKPs), inhibits the c-Jun N-terminal kinases (JNKs) pathway, which controls programmed cell death by necrosis or apoptosis [90]. Increased ROS generation during burn wound healing lead to oxidative stress, which causes damage to DNA, lipids, and proteins. While NF- κ B activation by TNF-R1 downstream initially inhibits inflammation by regulating antioxidants such as thioredoxin-1 and thioredoxin-2, the elevated ROS [91, 92] and cytokine levels activate MAP kinase kinases (MAP3Ks), e.g. apoptosis signal-regulated kinase 1 (ASK1), and inactivate MKPs. The outcome is the activation of the JNK pathway, which triggers necrosis or apoptosis [90]. ROS also regulate NF- κ B activity by inhibiting IKK phosphatases [93], thereby ensuring cell survival. ROS mediation of JNK activation causes production of mitochondrial ROS by SAB (SH3 domain-binding protein 5), which involves SH3 structural domain-binding protein 5. CYTOP overload through inhibition of thioredoxin activates ASK1 and JNK, but ROS-mediated phosphatase 5 negatively regulates ASK1, further activating the JNK pathway [94, 95].

Inflammatory cell responses to burns

Activated phagocytes, including neutrophils, eosinophils, and macrophages, are major producers of ROS. Phagocytes, as the first line of defense against invading organisms, utilize ROS to kill invaders by going through the process of the “respiratory burst,” characterized by an immediate surge in oxygen consumption [96]. This leads to the generation of ROS, including superoxide anion, hydrogen peroxide, nitric oxide, and hypochlorous acid. While these molecules are effective against pathogens, they can also cause harm to surrounding tissues and be involved in pathological processes such as carcinogenesis and atherosclerosis [97].

The increased level of ROS produced in the healing of burns severely damages immunity by leading to the infiltration and activation of inflammatory cells. This leads to systemic infection and increased morbidity and mortality [98]. Oxidative stress also raises intracellular Ca^{2+} , which induces the activity of lipoxygenase and cyclooxygenase found in microsomes and plasma membranes. The mechanism drives the arachidonic acid cycle, resulting in the creation of prostaglandins [99]. Prostaglandins, an essential immunomodulating factor, inhibit the synthesis of IL-1 and IL-2 expression in helper T lymphocytes. Schwacha speculated that the post-burns hyperproduction of prostaglandins is a significant etiology of immunosuppression [100]. Valenti *et al.* demonstrated that ROS generated during healing of burn wounds suppress the splenic T-lymphocyte function directly, which implies the direct immunosuppressive effect of oxidative stress [101].

Relationship between oxidative stress during wound healing and post-burn organ dysfunction

Severely burned patients are at great risk for infectious complications during the wound healing process, of which

ventilator-associated pneumonia is most notable [102]. Infection may also result from the patient’s own flora from the skin, lung, and gastrointestinal tract. Violation of the skin barrier and impaired host defenses predispose to bacterial, yeast, fungal, and viral infections; enhance the virulence of pathogens; and result in secondary organ failure [103, 104]. Autopsy findings show that infectious complications account for >60% of all burn deaths, and nearly all are marked by the presence of at least one organ failure, with common progression to multiple organ failure [105, 106]. It is reported that each septic episode will lead to organ dysfunction and ultimately cause failure of vital organs such as the kidneys, lungs, liver, gastrointestinal tract, heart, and bone marrow.

Excessive production of ROS in wound healing results in systemic oxidative injury that is not restricted to the wound location but also includes uninjured organs through systemic inflammation (Figure 5) [107]. Sequestration of neutrophils in gastric mucosa, liver, and lungs takes place early in wound healing. Neutrophil sequestration, facilitated by ROS, exacerbates local wound healing and induces distal organ injury [108]. ROS are major contributors to burn shock and distal organ injury—including the lungs, heart, liver, kidneys, and gastrointestinal mucosa—in animal models and are significant contributors to mortality in full-thickness third-degree burns [39, 109].

Lung injury

Glutathione (GSH), a crucial non-enzymatic antioxidant, is mostly produced in the liver and utilized in the lungs and thus the lungs are very vulnerable to oxidative damage. Oxidative stress due to burns leads to lung injury through two major mechanisms:

- (1) Direct cellular damage: Free radicals produced by the xanthine-xanthine oxidase system in pulmonary vascular endothelial cells play a significant role in lung injury. Elevated levels of hypoxanthine in the blood of patients with acute respiratory distress syndrome (ARDS) correlate with the severity of lung damage [110, 111].
- (2) Inhalation injury: Chemical irritants in smoke trigger uncontrolled pulmonary inflammation, resulting in leukocyte infiltration, activation, and oxidative damage. This process leads to airway mucosal ulceration, sub-mucosal edema, and systemic inflammatory responses due to increased oxygen demand and microvascular permeability [112, 113].

Liver injury

Severe burns may lead to impaired wound healing that causes the release of excessive amounts of pro-inflammatory cytokines, such as IL-1 β , IL-6, or TNF- α [114–116]. Elevated cytokine levels disrupt the anti-inflammatory control regulated by IL-10 and lead to hepatocyte dysfunction [117]. ROS and RNS released during wound healing activate NF- κ B, which further induces pro-inflammatory cytokines production and causes liver injury through via TNF- α -mediated cytotoxicity [118].

The liver, as a major site for ROS scavenging, produces huge amounts of GSH for detoxifying oxidative stress. During burn wound healing, neutrophils infiltrate the liver in large numbers, having been stimulated by hepatic macrophages, which generate overwhelming ROS, inducing intracellular and extracellular oxidative stress in hepatocytes [119]. The

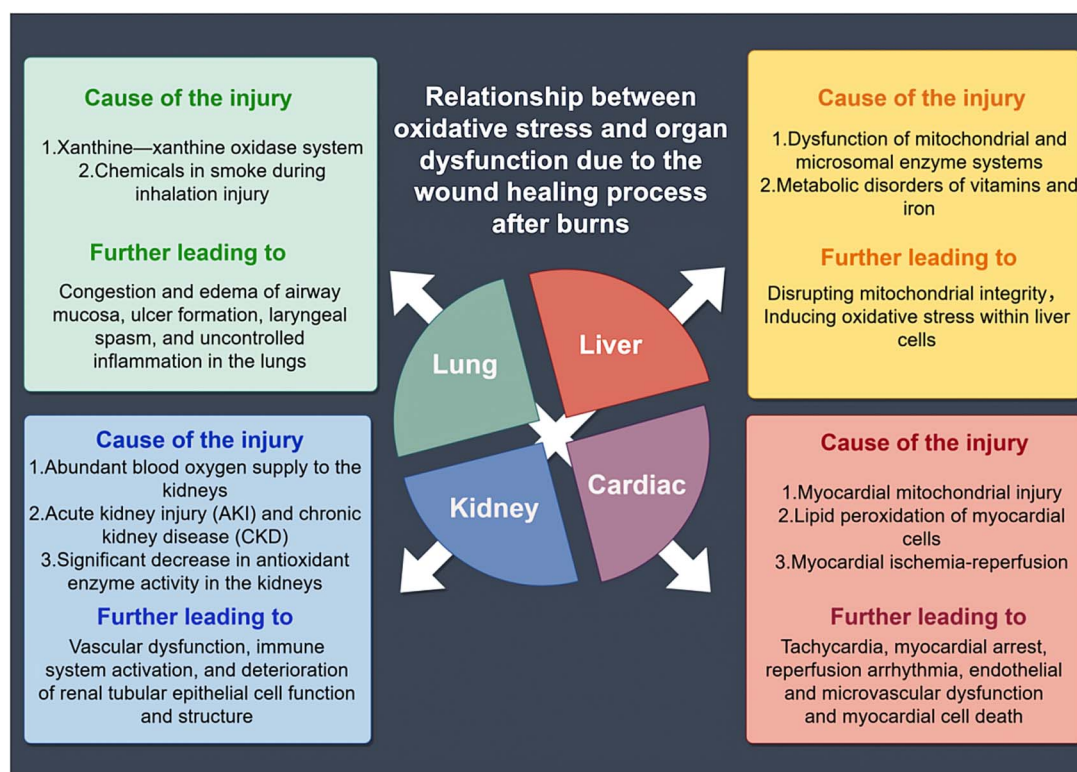


Figure 5. Relationship between oxidative stress and organ dysfunction due to the wound healing process after burns. AKI acute kidney injury, CKD chronic kidney disease.

intracellular stress results from mitochondrial and microsomal injury [120], while extracellular stress is mediated by neutrophils and hepatic stellate cells (HSCs). Activated HSCs release superoxide anions, hydrogen peroxide (H_2O_2), and nitric oxide (NO), all of which contribute to oxidative injury. Meanwhile, endothelial cells increase the synthesis of antioxidants to neutralize oxidative stress and protect hepatocytes [121, 122]. Experiments have indicated that there is a drastic reduction of in hepatic GSH content in burn wound healing, pointing to the central role of oxidative stress in liver failure [123, 124].

Renal injury

Acute kidney injury (AKI) is a common and severe complication in burn patients with burns affecting $\geq 20\%$ of the total body surface area (TBSA), occurring in 15%–40% of critically ill patients [125]. Early-stage AKI, which develops within 5 days of the burn, has a poor prognosis and a high mortality rate of $\sim 80\%$ [126]. The mechanism of pathogenesis of AKI is due to intravascular hypovolemia, systemic vasoconstriction, early organ dysfunction, and myoglobinuria due to oxidative stress or apoptosis [127]. ROS-mediated oxidative stress is the central feature of renal insufficiency and AKI through the induction of cellular process disruption and mitochondrial-associated apoptosis [128, 129].

The high content of polyunsaturated fatty acids in the kidney makes it particularly susceptible to ROS-dependent injury [130]. Apoptosis, a conserved renal reaction to injury, is exacerbated by circulating pro-apoptotic mediators and ROS-induced mitochondrial injury in tubular epithelial cells [131, 132]. Inflammatory processes also perpetuate AKI progression, with cellular necrosis of cells initiating the uncontrolled

release of inflammatory mediators, increased vascular permeability, and causing tubular injury [133, 134].

Cardiac injury

Oxidative stress is a major contributor to acute myocardial injury during burn wound healing [135]. Severe burns cause excessive production of ROS overproduction and oxidative overload in the cardiomyocytes, which are extremely vulnerable to oxidative damage [136]. ROS can cause damage to lipids, protein, and DNA, resulting in irreversible cellular damage and targeted cardiac injury [137].

Mitochondrial failure is an important determinant of myocardial injury. Since cardiomyocytes are mitochondrially dense ($\sim 35\%$ of cell volume) and depend on mitochondrial energy production to maintain cardiac function [138], the hypermetabolic response following burn, by increasing mitochondrial uncoupling and oxidative stress, impairs cardiac function [139]. Experiments have demonstrated that burn injury cripples mitochondrial ROS defense mechanisms, resulting in reduced antioxidant enzyme activity (e.g. MnSOD, GPx) and enhanced lipid peroxidation, which ultimately results in myocardial dysfunction [140]. Antioxidant therapies, such as vitamin supplementation, have been shown to enhance myocardial function through the restoration of mitochondrial antioxidant defenses [137, 141].

Mitochondrial reactive oxygen species (mtROS) and fragments of mitochondrial DNA (mtDNA) from the damaged mitochondria induce apoptotic signals, which further exacerbate cardiac injury [142, 143]. Healing of burn wounds increases the release of mitochondrial cytochrome c, mtROS, and mtDNA into the cytoplasm, leading to apoptosis of cardiomyocytes [144, 145].

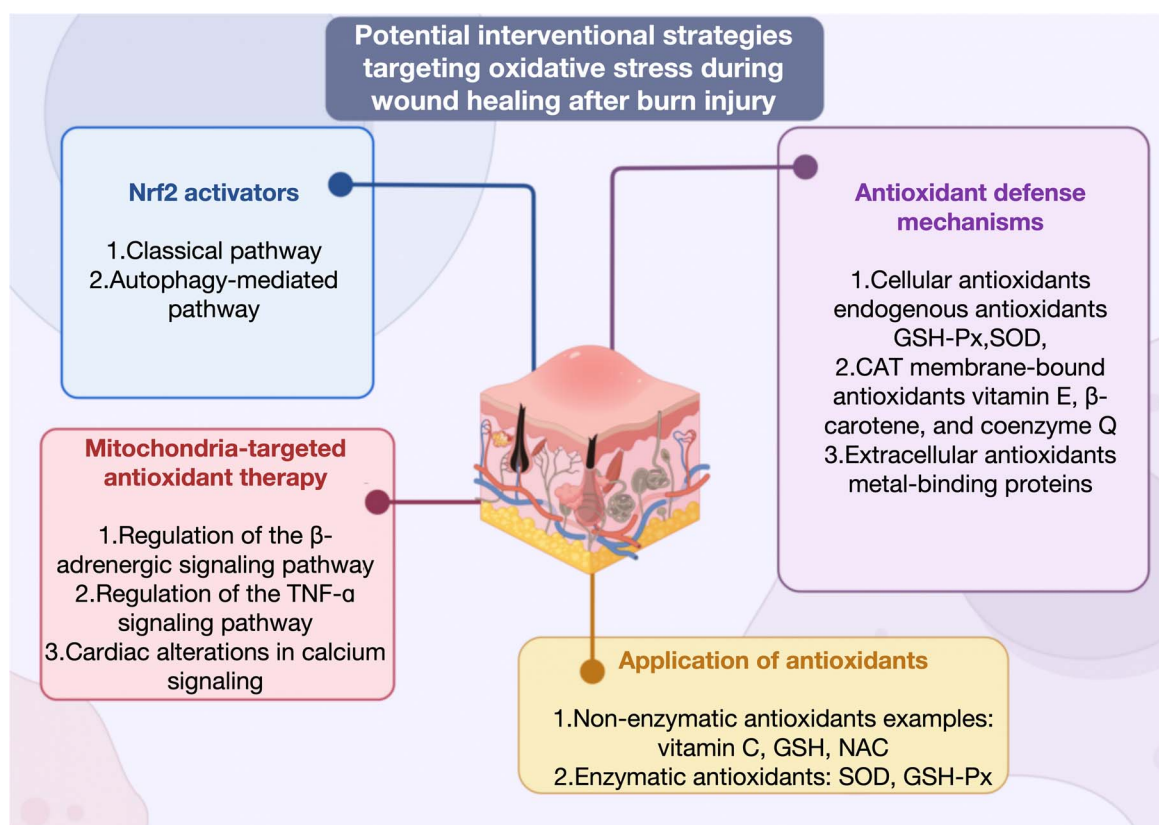


Figure 6. Interventional strategies targeting oxidative stress during wound healing after burn injury. *Nrf2* nuclear factor erythroid 2-related factor 2, *GSH-Px* glutathione peroxidase, *SOD* superoxide dismutase, *CAT* catalase, *TNF- α* tumor necrosis factor- α , *GSH* glutathione, *NAC* N-acetylcysteine.

Potential interventional strategies targeting oxidative stress during burn wound healing

Cells possess a battery of antioxidant defense mechanisms to counteract excess oxidants. Antioxidants are compounds that prevent or inhibit the oxidation of susceptible substrates. They occur as cellular, membrane, and extracellular mechanisms. The cellular antioxidant mechanism utilizes endogenous antioxidants such as GSH-Px, SOD, and CAT. SOD, found in mitochondria and cytoplasmic lysates, catalyzes the dismutation of superoxide anions to oxygen and hydrogen peroxide. GSH-Px, also found in these compartments, detoxifies hydrogen peroxide, while CAT, found in peroxisomes, detoxifies large amounts of hydrogen peroxide [6] [36].

Membrane-associated antioxidants include vitamin E, β -carotene, and coenzyme Q. Vitamin E (α -tocopherol) scavenges peroxy radicals and inhibits lipid peroxidation chain reactions. In addition, membrane structures with optimal cholesterol-to-phospholipid ratios are resistant to oxidative damage [146]. Extracellular antioxidant defenses include metal-binding proteins such as transferrin, lactoferrin, albumin, haptoglobin, urate, vitamin C, and bilirubin. They chelate reactive metal ions (i.e. copper and iron) so that they cannot participate in lipid peroxidation and ROS formation [147, 148]. All these mechanisms in combination provide an optimum balance for oxidants and antioxidants to favor optimum biological function. The potential intervention strategies targeting oxidative stress during wound healing after burn injury are shown in Figure 6, and the specific methods and drugs are shown in Table 1.

Utilization of antioxidants (e.g. vitamin C, glutathione)

Antioxidants are classified into two categories: non-enzymatic and enzymatic.

- (1) **Non-enzymatic antioxidants:** Non-enzymatic antioxidants, such as ascorbic acid, vitamin C, GSH, mannitol, N-acetylcysteine (NAC), vitamin A, and vitamin E, play a crucial role in reducing mortality, reducing cellular dynamics, protecting the microcirculation, reducing lipid peroxidation, improving cardiac output, and diminishing the need for resuscitation fluids in burn wound healing. NAC, a precursor of GSH, increases intracellular GSH levels, deactivates ROS, and reduces oxidative stress. Experiments have shown that NAC significantly decreases oxidative stress markers, i.e. MDA, and improves burn patient clinical outcomes [149]. Treatment with antioxidant vitamins combined with fluid resuscitation inhibits NF- κ B nuclear translocation; suppresses release of $TNF-\alpha$, IL-1 β , and IL-6 from cardiomyocytes; and enhances cardiac contractility [150]. Mannitol, a diuretic agent with ROS-scavenging properties, should be used cautiously in severe burns in order to avoid exacerbating hypovolemia and worsening of renal damage [151, 152].
- (2) **Enzymatic antioxidants:** Enzymes such as SOD, GSH-Px, glutathione reductase (GSH-Rd), and CAT enzymes reduce edema, tissue damage, and inflammation in burn wound healing. The enzymes decrease peroxide generation of lipid, increase serum copper and selenium levels,

Table 1. Interventional therapeutic strategies to overcome oxidative stress in burn patients and wound patients

Classify	Intervention strategy	Specific methods	Mechanism of action
Application of antioxidants	Non enzymatic antioxidants	Vitamin C, glutathione (GSH), mannitol, N-acetylcysteine (NAC), vitamin A, vitamin E, etc	Reduce mortality, protect microcirculation, decrease lipid peroxidation, improve cardiac output, and reduce the demand for resuscitation fluid
	Enzyme antioxidants	Superoxide dismutase (SOD), glutathione peroxidase (GSH Px), catalase (CAT), etc	Reduce edema, tissue damage, and inflammation, decrease the formation of lipid peroxides, and enhance the ROS scavenging ability of non enzyme antioxidants
Application of Nrf2 activators	Classical pathway	Keap1 conformational changes release Nrf2, which forms heterodimers with sMaf protein and binds to ARE, inducing expression of cell protective genes	Protect cells from oxidative damage, apoptosis, inflammation, and tumorigenesis
	Autophagy mediated pathway	SQSTM1/p62 competes with Keap1 for binding, promoting Nrf2 stability and activation	Enhancing Nrf2 activity through autophagy pathway, improving oxidative stress and inflammation
Mitochondrial-targeted antioxidant therapy	Regulation of β -adrenergic signaling pathway	Mitochondrial targeted antioxidants, such as vitamin C, vitamin E, etc	By regulating β -adrenergic receptors, reducing mitochondrial ROS generation, and improving cardiac function
	Regulation of TNF- α signaling pathway	Inhibit TNF- α -induced mitochondrial dysfunction and reduce ROS generation	By inhibiting the TNF- α signaling pathway, improving mitochondrial respiration and ATP synthesis, and reducing cardiac dysfunction
	Calcium signal regulation	Taurine and mitochondrial calcium inhibitors	By regulating calcium signaling, reducing mitochondrial calcium overload and arrhythmia, and improving cardiac function
Other antioxidant strategies	Vitamin C supplementation	Intravenous injection of vitamin C	By neutralizing the toxicity of oxygen free radicals, reducing inflammation and oxidative stress, and promoting wound healing
	Subcutaneous injection of insulin	Subcutaneous injection of insulin	Promote wound healing after burns by controlling blood sugar, reducing fluid intake, and controlling infections
	Combination therapy with antioxidants	Combination use of anti-inflammatory and potent antioxidants	Promote wound healing by reducing inflammation while neutralizing toxic substances in affected organs

and enhance the activity of non-enzymatic antioxidants in scavenging ROS [153, 154].

Application of Nrf2 activators

Nuclear factor-E2-related factor 2 (Nrf2) is a significant transcription factor of OS regulation in burn wound healing, playing key roles in redox homeostasis, drug metabolism and excretion, iron and amino acid metabolism, cell survival, and proteasomal degradation. It is also involved in the regulation of cell cycle homeostasis, cytoprotection, and innate immunity in response to cellular stress [155]. Nrf2 activation protects cells from oxidative damage, apoptosis, inflammation, and tumorigenesis and therefore is a major target for OS-related diseases [156–158]. Activation of Nrf2 occurs primarily through two pathways:

- (1) Classical pathway: Under OS [159], Keap1 (Kelch-like ECH-associated protein 1) undergoes conformational changes, releasing Nrf2 from ubiquitin-proteasome degradation. Nrf2 translocates to the nucleus, heterodimerizes with small Maf proteins (sMafs), and binds to the antioxidant response elements, thereby initiating the transcription of cytoprotective genes [160, 161].

- (2) Autophagy-mediated pathway: Sequestosome-1 (SQSTM1/p62) competes with Nrf2 for Keap1 binding, thereby inducing Nrf2 stabilization and activation [162, 163]. Synthetic Nrf2 activators, such as bardoxolone methyl, inhibit Keap1, thereby enhancing Nrf2 activity and alleviating oxidative stress and inflammation in burn patients [37].

Additionally, MAPK signaling molecules (e.g. p38, JNK) and protein kinase C (PKC) can activate Nrf2 via phosphorylation of its Neh2 domain, causing its dissociation from Keap1 [164, 165]. P21, a cell cycle regulator, stabilizes Nrf2 as well by inhibiting Keap1-dependent ubiquitination, with further facilitation of its cytoprotective activity [166–168]. Nrf2 activators thus have tremendous potential as a promising therapeutic strategy in minimizing oxidative stress in burn wound healing.

Mitochondria-targeted antioxidant therapy

1. Regulation of the β -adrenergic signaling pathway:

Burn wound healing induces sustained catecholamine elevation of catecholamines, which stimulates β -adrenergic receptors (β -ARs) and promotes mitochondrial ROS generation. Sustained β -AR stimulation exacerbates cardiovascular

dysfunction and arrhythmias by augmenting sarcoplasmic reticulum Ca^{2+} leakage [169–171]. Mitochondria-targeted antioxidants restore Ca^{2+} management and inhibit arrhythmias [172]. The NO-cGMP-PKG pathway, activated by β -AR stimulation, also safeguards mitochondria and triggers ischemic preconditioning [173, 174].

2. Regulation of the TNF- α signaling pathway:

TNF- α levels rise significantly in serum and cardiac tissue following burn injury, repressing mitochondrial respiration, reducing complex I activity, and increasing ROS production. TNF- α -induced mitochondrial dysfunction impacts ATP generation and Ca^{2+} regulation, causing cardiac dysfunction [175–177].

3. Cardiac alterations in calcium signaling:

Regular cardiac contraction requires stringent Ca^{2+} regulation. Burn wound recovery disrupts Ca^{2+} recovery, leading to mitochondrial Ca^{2+} overload and arrhythmias. Taurine and mitochondrial Ca^{2+} blockers antagonize these processes by reducing ROS formation and increasing cardiac function [178, 179].

Conclusions

Briefly, post-burn wound healing is regulated by oxidative stress with its characteristic feature of hyperproduction of ROS, impaired antioxidant defenses, and systemic inflammation that collectively exacerbate organ dysfunction and tissue injury. The disturbance in redox homeostasis following the burn activates inflammatory cascades such as NF- κ B and JNK, leading to chronic inflammation and extended recovery. Antioxidant treatments, enzymatic and non-enzymatic interventions, and Nrf2 activators are promising for minimizing oxidative damage and outcome benefits. Optimal treatment regimens remain to be further clinically validated to normalize variability of burn severity and responses. The future direction of studies should be to optimize antioxidant protocols to further define their effectiveness and integration into protocols of standard care for burns.

Abbreviations

Cu, *Zn-SOD* copper-zinc superoxide dismutase, *CAT* catalase, *GSH-Px* glutathione peroxidase, *MPO* myeloperoxidase, *XOD* xanthine oxidase, *ROS* reactive oxygen species, *RNS* reactive nitrogen species, $\cdot\text{O}_2^-$ superoxide anion, $\cdot\text{OH}$ hydroxyl radical, H_2O_2 hydrogen peroxide, $\cdot\text{NO}$ nitric oxide, $\cdot\text{NO}_2$ nitrogen dioxide, $\cdot\text{ONOO}^-$ peroxynitrite, $^1\text{O}_2$ single linear state oxygen, *METC* mitochondrial electron transport chain, *NOX* nicotinamide adenine dinucleotide phosphate oxidases, *XOR* xanthine oxidoreductase, *LOX* lipoxygenases, *NADPH* nicotinamide adenine dinucleotide phosphate, *DUOX* dioxygenases, *XDH* xanthine dehydrogenase, *XO* xanthine oxidase, *AA* arachidonic acid, *PUFAs* polyunsaturated fatty acids, *IR* ionizing radiation, *LET* low linear energy transfer, *SOD* superoxide dismutase, *GPx* glutathione peroxidase, *SOD1* cytoplasmic CuZn-SOD, *SOD2* mitochondrial MnSOD, *SOD3* extracellular SOD, *GSH* glutathione, *mtROS* mitochondrial reactive oxygen species, *NTF* nuclear transcription factor, *MDA* malondialdehyde, *TBA* thiobarbituric acid, *TBARS* TBA-reactive species, *PRRs* pattern recognition receptors, *CCL2* C-C motif chemokine ligand 2, *CCL1* C-C motif chemokine ligand 1, *NF- κ B* nuclear factor kappa B, *IFN- γ* interferon-gamma, *TCR*

T-cell receptor, *PARP* poly ADP-ribose polymerase, *DAMPs* damage-associated molecular patterns, *PAMPs* pathogen-associated molecular patterns, *TLRs* toll-like receptors, *NLRs* NOD-like receptors, *MyD88* myeloid differentiation primary response protein 88, *TNF-R1* tumor necrosis factor receptor 1, *AP-1* activator protein-1, *MAP* mitogen-activated protein, *MKPs* kinase phosphatases, *JNKs* c-Jun N-terminal kinases, *MAP3Ks* MAP kinase kinases, *ASK1* apoptosis signal-regulated kinase 1, *IKK* inhibitor of kappa B kinase, *ARDS* acute respiratory distress syndrome, *AKI* acute kidney injury, *TBSA* total body surface area, *mtDNA* mitochondrial DNA, *Nrf2* nuclear factor-E2-related factor 2, *PKC* protein kinase C, *CKI* cyclin-dependent kinase inhibitor, β -AR β -adrenergic receptor, *cAMP* cyclic adenosine monophosphate, *PDE5* phosphodiesterase 5, *ATP* adenosine triphosphate, *RyR2* ryanodine receptor 2

Acknowledgements

We would like to thank DeepL (<https://www.deepl.com/>) for English language editing. Figures were created by Figdraw (<https://www.figdraw.com/>), and the export IDs of the images are TTSUIccc7a, PURYA56398, IITWR42819, RPASA41076, WSIIA5d65, and USI-TYf8fa4.

Author contributions

Ruiqi Chen and Hongbiao Xu contributed equally to this work and were mainly responsible for literature review and drafting the manuscript. Xueshi Li and Jie Dong performed linguistic editing and grammar proofreading of papers. Shengli Wang refined the manuscript. Jianlei Hao and Guangping Liang guided the research strategy, critically reviewed the intellectual content of the manuscript, and were responsible for the final approval of the submitted version. All authors have read and approved the final manuscript. Ruiqi Chen (Writing—original draft [equal]), Hongbiao Xu (Writing—original draft [equal]), Shengli Wang (Visualization [equal], Writing—review & editing [equal]), Jianlei Hao (Conceptualization [equal], Funding acquisition [equal], Resources [equal], Writing—review & editing [equal]), and Guangping Liang (Conceptualization [equal], Methodology [equal], Project administration [equal], Supervision [equal])

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors agree to publish this review.

Conflict of interest

None declared.

Funding

This work was supported by the grants from National Natural Science Foundation of China (32370921 to J.H.). This work was also supported by the Science and Technology Program of Guangzhou (2025A03J3586 to J.D. and 2025A03J4241 to X.L.).

Data availability

Not applicable.

References

- Yang T, Zhang J, Sun L, Zhu X, Li J, Wang J. *et al.* Combined effects of a neutrophil elastase inhibitor (sivelestat sodium) and a free radical scavenger (edaravone) on lipopolysaccharide-induced acute lung injury in rats. *Inflamm Res* 2012;61:563–9. <https://doi.org/10.1007/s00011-012-0445-7>.
- Balamuth F, Scott HF, Weiss SL, Webb M, Chamberlain JM, Bajaj L. *et al.* Validation of the pediatric sequential organ failure assessment score and evaluation of third international consensus definitions for sepsis and septic shock definitions in the pediatric emergency department. *JAMA Pediatr* 2022;176:672–8. <https://doi.org/10.1001/jamapediatrics.2022.1301>.
- Filippou D, Papadopoulos VP, Triga A, Filippou G, Rizos S, Skandalakis P. *et al.* Nitric oxide, antioxidant capacity, nitric oxide synthase and xanthine oxidase plasma levels in a cohort of burn patients. *Burns J Int Soc Burn Inj* 2007;33:1001–7. <https://doi.org/10.1016/j.burns.2006.11.019>.
- He L, He T, Farrar S, Ji L, Liu T, Ma X. Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. *Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol* 2017;44:532–53. <https://doi.org/10.1159/000485089>.
- Rani M, Zhang Q, Schwacha MG. Gamma delta T cells regulate wound myeloid cell activity after burn. *Shock Augusta Ga.* 2014;42:133–41. <https://doi.org/10.1097/SHK.0000000000000176>.
- Abuja PM, Albertini R. Methods for monitoring oxidative stress, lipid peroxidation and oxidation resistance of lipoproteins. *Clin Chim Acta Int J Clin Chem* 2001;306:1–17. [https://doi.org/10.1016/S0009-8981\(01\)00393-X](https://doi.org/10.1016/S0009-8981(01)00393-X).
- Zhang Y, Xu Y, Lu W, Ghergurovich JM, Guo L, Blair IA. *et al.* Upregulation of antioxidant capacity and nucleotide precursor availability suffices for oncogenic transformation. *Cell Metab* 2021;33:94–109.e8. <https://doi.org/10.1016/j.cmet.2020.10.002>.
- Diwanji N, Bergmann A. An unexpected friend - ROS in apoptosis-induced compensatory proliferation: implications for regeneration and cancer. *Semin Cell Dev Biol* 2018;80:74–82. <https://doi.org/10.1016/j.semcdb.2017.07.004>.
- Sánchez-de-Diego C, Valer JA, Pimenta-Lopes C, Rosa JL, Ventura F. Interplay between BMPs and reactive oxygen species in cell signaling and pathology. *Biomolecules*. 2019;9:534. <https://doi.org/10.3390/biom9100534>.
- D'Autréaux B, Toledano MB. ROS as signalling molecules: mechanisms that generate specificity in ROS homeostasis. *Nat Rev Mol Cell Biol* 2007;8:813–24. <https://doi.org/10.1038/nrm2256>.
- Xue C, Tian J, Cui Z, Liu Y, Sun D, Xiong M. *et al.* Reactive oxygen species (ROS)-mediated M1 macrophage-dependent nanomedicine remodels inflammatory microenvironment for osteoarthritis recession. *Bioact Mater* 2024;33:545–61. <https://doi.org/10.1016/j.bioactmat.2023.10.032>.
- Zhao RZ, Jiang S, Zhang L, Yu ZB. Mitochondrial electron transport chain, ROS generation and uncoupling (review). *Int J Mol Med* 2019;44:3–15. <https://doi.org/10.3892/ijmm.2019.4188>.
- Sedeek M, Nasrallah R, Touyz RM, Hébert RL. NADPH oxidases, reactive oxygen species, and the kidney: friend and foe. *J Am Soc Nephrol JASN* 2013;24:1512–8. <https://doi.org/10.1681/ASN.2012111112>.
- Minakami R, Sumimoto H. Phagocytosis-coupled activation of the superoxide-producing phagocyte oxidase, a member of the NADPH oxidase (nox) family. *Int J Hematol* 2006;84:193–8. <https://doi.org/10.1532/IJH97.06133>.
- Takac I, Schröder K, Brandes RP. The Nox family of NADPH oxidases: friend or foe of the vascular system? *Curr Hypertens Rep* 2012;14:70–8. <https://doi.org/10.1007/s11906-011-0238-3>.
- Cho KJ, Seo JM, Kim JH. Bioactive lipoxygenase metabolites stimulation of NADPH oxidases and reactive oxygen species. *Mol Cells* 2011;32:1–6. <https://doi.org/10.1007/s10059-011-1021-7>.
- Luchtefeld M, Drexler H, Schieffer B. 5-Lipoxygenase is involved in the angiotensin II-induced NAD(P)H-oxidase activation. *Biochem Biophys Res Commun* 2003;308:668–72. [https://doi.org/10.1016/S0006-291X\(03\)01456-6](https://doi.org/10.1016/S0006-291X(03)01456-6).
- Kawamura K, Qi F, Kobayashi J. Potential relationship between the biological effects of low-dose irradiation and mitochondrial ROS production. *J Radiat Res (Tokyo)* 2018;59:ii91–7. <https://doi.org/10.1093/jrr/rrx091>.
- Wang Y, Branicky R, Noë A, Hekimi S. Superoxide dismutases: dual roles in controlling ROS damage and regulating ROS signaling. *J Cell Biol* 2018;217:1915–28. <https://doi.org/10.1083/jcb.201708007>.
- Melo D, Ferreira F, Teles MJ, Porto G, Coimbra S, Rocha S. *et al.* Catalase, glutathione peroxidase, and peroxiredoxin 2 in erythrocyte cytosol and membrane in hereditary spherocytosis, sickle cell disease, and β -thalassemia. *Antioxid Basel Switz* 2024;13:629. <https://doi.org/10.3390/antiox13060629>.
- Haq A, Hasnain SE, Razzaque MS. Diverse functions of vitamin D in health and disease. *J Steroid Biochem Mol Biol* 2020;200:105668, 0960-0760. <https://doi.org/10.1016/j.jsbmb.2020.105668>.
- (PDF) Article no.JOCAMR.107300 Original Research Article Usman *et al* [Internet]. [cited 2025 Apr 5]. Available from: https://www.researchgate.net/publication/374472012_Article_noJOCAMR107300_Original_Research_Article_Usman_et_al
- Li MS, Adesina SE, Ellis CL, Gooch JL, Hoover RS, Williams CR. NADPH oxidase-2 mediates zinc deficiency-induced oxidative stress and kidney damage. *Am J Physiol Cell Physiol* 2017;312:C47–55. <https://doi.org/10.1152/ajpcell.00208.2016>.
- Zhou G, Lu J, Xu T, Lu Y, Chen W, Wang J. *et al.* Clinical lipidomics analysis reveals biomarkers of lipid peroxidation in serum from patients with rheumatoid arthritis. *Microchem J* 2021;169:106607. <https://doi.org/10.1016/j.microc.2021.106607>.
- Lee R, Margaritis M, Channon KM, Antoniadou C. Evaluating oxidative stress in human cardiovascular disease: methodological aspects and considerations. *Curr Med Chem* 2012;19:2504–20. <https://doi.org/10.2174/092986712800493057>.
- Bairova TA, Kolesnikov SI, Kolesnikova LI, Pervushina OA, Darenskaya MA, Grebenkina LA. Lipid peroxidation and mitochondrial superoxide dismutase-2 gene in adolescents with essential hypertension. *Bull Exp Biol Med* 2014;158:181–4. <https://doi.org/10.1007/s10517-014-2717-4>.
- Ferlazzo N, Currò M, Isola G, Maggio S, Bertuccio MP, Trovato-Salinaro A. *et al.* Changes in the biomarkers of oxidative/nitrosative stress and endothelial dysfunction are associated with cardiovascular risk in periodontitis patients. *Curr Issues Mol Biol* 2021;43:704–15. <https://doi.org/10.3390/cimb43020051>.
- Wang L, Zhang W, Li C, Chen X, Huang J. Identification of biomarkers related to copper metabolism in patients with pulmonary arterial hypertension. *BMC Pulm Med* 2023;23:31. <https://doi.org/10.1186/s12890-023-02326-6>.
- Basu S. Bioactive eicosanoids: role of prostaglandin F(2 α) and F₂-isoprostanes in inflammation and oxidative stress related pathology. *Mol Cells* 2010;30:383–92. <https://doi.org/10.1007/s10059-010-0157-1>.
- Vichaibun V, Khananurak K, Sophonnithiprasert T. Comparative analysis of plasma total antioxidant capacity in patients with hyperglycemia and hyperglycemia plus dyslipidemia. *Diabetes Metab Syndr* 2019;13:90–4. <https://doi.org/10.1016/j.dsx.2018.08.029>.
- Fraga CG, Oteiza PI, Galleano M. In vitro measurements and interpretation of total antioxidant capacity. *Biochim Biophys Acta* 2014;1840:931–4. <https://doi.org/10.1016/j.bbagen.2013.06.030>.
- Shacter E. Quantification and significance of protein oxidation in biological samples. *Drug Metab Rev* 2000;32:307–26. <https://doi.org/10.1081/DMR-100102336>.

33. Jones DA, Prior SL, Barry JD, Caplin S, Baxter JN, Stephens JW. Changes in markers of oxidative stress and DNA damage in human visceral adipose tissue from subjects with obesity and type 2 diabetes. *Diabetes Res Clin Pract* 2014;106:627–33. <https://doi.org/10.1016/j.diabres.2014.09.054>.
34. Marín R, Abad C, Rojas D, Chiarello DI, Alejandro TG. Biomarkers of oxidative stress and reproductive complications. *Adv Clin Chem* 2023;113:157–233. <https://doi.org/10.1016/bs.aacc.2022.11.004>.
35. Willis ML, Mahung C, Wallet SM, Barnett A, Cairns BA, Coleman LG. *et al.* Plasma extracellular vesicles released after severe burn injury modulate macrophage phenotype and function. *J Leukoc Biol* 2022;111:33–49. <https://doi.org/10.1002/JLB.3MIA0321-150RR>.
36. Liao Q, Wang Z, Cadena SMSC. Editorial: Targeting oxidative stress in cancer: what is new in the prevention, diagnostic, treatment and prognostic strategies? *Front Pharmacol* 2023;14:1229785. <https://doi.org/10.3389/fphar.2023.1229785>.
37. Pang Z, Jiang Z, Zhu R, Song C, Tang H, Cao L. *et al.* Bardoxolone-methyl prevents oxidative stress-mediated apoptosis and extracellular matrix degradation in vitro and alleviates osteoarthritis in vivo. *Drug Des Devel Ther* 2021;15:3735–47. <https://doi.org/10.2147/DDDT.S314767>.
38. Yang SR, Park JR, Kang KS. Reactive oxygen species in mesenchymal stem cell aging: implication to lung diseases. *Oxidative Med Cell Longev* 2015;2015:486263. <https://doi.org/10.1155/2015/486263>.
39. AbuBakr HO, Aljuaydi SH, Abou-Zeid SM, El-Bahrawy A. Burn-induced multiple organ injury and protective effect of lutein in rats. *Inflammation*. 2018;41:760–72. <https://doi.org/10.1007/s10753-018-0730-x>.
40. Wen JJ, Cummins C, Radhakrishnan RS. Sildenafil recovers burn-induced cardiomyopathy. *Cells*. 2020;9:1393. <https://doi.org/10.3390/cells9061393>.
41. Wen H, Xing L, Sun K, Xiao C, Meng X, Yang J. Loganin attenuates intestinal injury in severely burned rats by regulating the toll-like receptor 4/NF- κ B signaling pathway. *Exp Ther Med* 2020;20:591–8. <https://doi.org/10.3892/etm.2020.8725>.
42. Sikora JP, Sobczak J, Zawadzki D, Przewratil P, Wysocka A, Burzyńska M. Respiratory burst and TNF- α receptor expression of neutrophils after sepsis and severe injury-induced inflammation in children. *Int J Environ Res Public Health* 2021;18:2187. <https://doi.org/10.3390/ijerph18042187>.
43. Li Q, Hua X, Li L, Zhou X, Tian Y, Deng Y. *et al.* AIP1 suppresses neovascularization by inhibiting the NOX4-induced NLRP3/NLRP6 imbalance in a murine corneal alkali burn model. *Cell Commun Signal CCS* 2022;20:59. <https://doi.org/10.1186/s12964-022-00877-5>.
44. Ji Q, Chen K, Yi H, He B, Jiang T. A paintable small-molecule hydrogel with antimicrobial and ROS scavenging activities for burn wound healing. *Gels* 2024;10:621. <https://pubmed.ncbi.nlm.nih.gov/39451274/>.
45. Cai W, Ji P, Fan L, Han J, Hu X, Wang S. *et al.* Effects of reactive by burn rat serum oxygen species on apoptosis of pulmonary microvascular endothelial cells induced. *Zhonghua Shao Shang Za Zhi Zhonghua Shaoshang Zazhi Chin J Burns* 2014;30:320–4.
46. Qi X, Yang Y, Huang J, Sun R, Liu L, Sun B. Mechanism of delayed apoptosis of peripheral blood neutrophils in severely burned patients. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2019;31:1208–11. <https://doi.org/10.3760/cma.j.issn.2095-4352.2019.10.006>.
47. Sun Z, Liu H, Hu Y, Luo G, Yuan Z, Liu W. *et al.* KLF2/PPAR γ axis contributes to trauma-induced heterotopic ossification by regulating mitochondrial dysfunction. *Cell Prolif* 2024;57:e13521. <https://doi.org/10.1111/cpr.13521>.
48. Parihar A, Parihar MS, Milner S, Bhat S. Oxidative stress and anti-oxidative mobilization in burn injury. *Burns J Int Soc Burn Inj* 2008;34:6–17. <https://doi.org/10.1016/j.burns.2007.04.009>.
49. Yang SR, Park JR, Kang KS. Reactive oxygen species in mesenchymal stem cell aging: implication to lung diseases. *Oxid Med Cell Longev*. 2015;2015:486263. <https://pubmed.ncbi.nlm.nih.gov/26273422/>.
50. Caliceti C, Rizzo P, Giuliano M. Role of natural compounds in oxidative stress and inflammation linked to cardiometabolic disorders: from biochemical aspects to clinical evidences. *Oxidative Med Cell Longev* 2018;2018:1479309. <https://doi.org/10.1155/2018/1479309>.
51. Yang Y, Pan Y, Liu B, Zhang Y, Yin C, Wang J. *et al.* Neutrophil-derived oxidative stress contributes to skin inflammation and scratching in a mouse model of allergic contact dermatitis via triggering pro-inflammatory cytokine and pruritogen production in skin. *Biochem Pharmacol* 2024;223:116163. <https://doi.org/10.1016/j.bcp.2024.116163>.
52. Wang Z, Dayang EZ, Zwiers PJ, Hernandez Garcia ML, Luxen M, van Meurs M. *et al.* Recruitment of neutrophils in glomeruli in early mouse sepsis is associated with E-selectin expression and activation of endothelial nuclear factor kappa-light-chain-enhancer of activated B cells and mitogen-activated protein kinase pathways. *J Leukoc Biol* 2024;116:1479–97. <https://doi.org/10.1093/jleuko/qiae146>.
53. Nishino T. The conversion of xanthine dehydrogenase to xanthine oxidase and the role of the enzyme in reperfusion injury. *J Biochem (Tokyo)* 1994;116:1–6. <https://doi.org/10.1093/oxfordjournals.jbchem.a124480>.
54. Santa-Cecília FV, Santos GB, Fuzissaki CN, Derogis PBMC, Freitas LAS, Gontijo VS. *et al.* 7-Epiclusianone, the natural prenylated benzophenone, inhibits superoxide anions in the neutrophil respiratory burst. *J Med Food* 2012;15:200–5. <https://doi.org/10.1089/jmf.2011.0043>.
55. Koo MA, Hee Hong S, Hee Lee M, Kwon BJ, Mi Seon G, Sung Kim M. *et al.* Effective stacking and transplantation of stem cell sheets using exogenous ROS-producing film for accelerated wound healing. *Acta Biomater* 2019;95:418–26. <https://doi.org/10.1016/j.actbio.2019.01.019>.
56. Koo MA, Lee MH, Kwon BJ, Seon GM, Kim MS, Kim D. *et al.* Exogenous ROS-induced cell sheet transfer based on hematoporphyrin-polyketone film via a one-step process. *Biomaterials*. 2018;161:47–56. <https://doi.org/10.1016/j.biomaterials.2018.01.030>.
57. Koo MA, Kim BJ, Lee MH, Kwon BJ, Kim MS, Seon GM. *et al.* Controlled delivery of extracellular ROS based on hematoporphyrin-incorporated polyurethane film for enhanced proliferation of endothelial cells. *ACS Appl Mater Interfaces* 2016;8:28448–57. <https://doi.org/10.1021/acsami.6b07628>.
58. Wu X, Woodside KJ, Song J, Wolf SE. Burn-induced gut mucosal homeostasis in TCR delta receptor-deficient mice. *Shock Augusta Ga*. 2004;21:52–7. <https://doi.org/10.1097/01.shk.0000104268.15342.8f>.
59. Toth B, Alexander M, Daniel T, Chaudry IH, Hubbard WJ, Schwacha MG. The role of gammadelta T cells in the regulation of neutrophil-mediated tissue damage after thermal injury. *J Leukoc Biol* 2004;76:545–52. <https://doi.org/10.1189/jlb.0404219>.
60. Song Y, Li Y, Hu W, Li F, Sheng H, Huang C. *et al.* Luminol-conjugated cyclodextrin biological nanoparticles for the treatment of severe burn-induced intestinal barrier disruption. *Burns Trauma*. 2024;12:tkad054. <https://doi.org/10.1093/burnst/tkad054>.
61. Bernal-Alferez B, Gómez-Mosqueira R, Ortega-Tapia GT, Burgos-Vargas R, García-Latorre E, Domínguez-López ML. *et al.* The role of $\gamma\delta$ T cells in the immunopathogenesis of inflammatory diseases: from basic biology to therapeutic targeting. *J Leukoc Biol* 2023;114:557–70. <https://doi.org/10.1093/jleuko/qiad046>.
62. Freen-van Heeren JJ. Broad-spectrum defenders: $\gamma\delta$ T cells take on a multitude of immune challenges. *J Leukoc Biol* 2024;115:794–6. <https://doi.org/10.1093/jleuko/qiae044>.

63. Munoz LD, Sweeney MJ, Jameson JM. Skin resident $\gamma\delta$ T cell function and regulation in wound repair. *Int J Mol Sci* 2020;21:9286. <https://doi.org/10.3390/ijms21239286>.
64. Rani M, Zhang Q, Scherer MR, Cap AP, Schwacha MG. Activated skin $\gamma\delta$ T-cells regulate T-cell infiltration of the wound site after burn. *Innate Immun* 2015;21:140–50. <https://doi.org/10.1177/1753425913519350>.
65. Horton JW, White DJ, Maass DL, Hybki DP, Haudek S, Giroir B. Antioxidant vitamin therapy alters burn trauma-mediated cardiac NF-kappaB activation and cardiomyocyte cytokine secretion. *J Trauma* 2001;50:397–406discussion 407–408. <https://doi.org/10.1097/00005373-200103000-00002>.
66. Mange H, Becker K, Fuchs D, Gostner JM. Antioxidants, inflammation and cardiovascular disease. *World J Cardiol* 2014;6:462–77. <https://doi.org/10.4330/wjc.v6.i6.462>.
67. Pintaudi AM, Tesoriere L, D'Arpa N, D'Amelio L, D'Arpa D, Bongiorno A. *et al.* Oxidative stress after moderate to extensive burning in humans. *Free Radic Res* 2000;33:139–46. <https://doi.org/10.1080/10715760000300691>.
68. Watson F, Edwards SW. Stimulation of primed neutrophils by soluble immune complexes. *Biol J Int Assoc Biol Stand* 1996;24:307–11. <https://doi.org/10.1006/biol.1996.0042>.
69. Kim-Park WK, Moore MA, Hakki ZW, Kowolik MJ. Activation of the neutrophil respiratory burst requires both intracellular and extracellular calcium. *Ann N Y Acad Sci* 1997;832:394–404. <https://doi.org/10.1111/j.1749-6632.1997.tb46267.x>.
70. Despa F, Orgill DP, Neuwalder J, Lee RC. The relative thermal stability of tissue macromolecules and cellular structure in burn injury. *Burns J Int Soc Burn Inj* 2005;31:568–77. <https://doi.org/10.1016/j.burns.2005.01.015>.
71. Cevik O, Oba R, Macit C, Cetinel S, Kaya OTC, Sener E. *et al.* Lycopene inhibits caspase-3 activity and reduces oxidative organ damage in a rat model of thermal injury. *Burns J Int Soc Burn Inj* 2012;38:861–71. <https://doi.org/10.1016/j.burns.2012.01.006>.
72. Sener G, Sehrlir AO, Gedik N, Dülger GA. Rosiglitazone, a PPAR-gamma ligand, protects against burn-induced oxidative injury of remote organs. *Burns J Int Soc Burn Inj* 2007;33:587–93. <https://doi.org/10.1016/j.burns.2006.10.381>.
73. Kabasakal L, Sener G, Cetinel S, Contuk G, Gedik N, Yeğen BC. Burn-induced oxidative injury of the gut is ameliorated by the leukotriene receptor blocker montelukast. *Prostaglandins Leukot Essent Fatty Acids* 2005;72:431–40. <https://doi.org/10.1016/j.plefa.2005.02.008>.
74. Sener G, Kabasakal L, Cetinel S, Contuk G, Gedik N, Yeğen BC. Leukotriene receptor blocker montelukast protects against burn-induced oxidative injury of the skin and remote organs. *Burns J Int Soc Burn Inj* 2005;31:587–96. <https://doi.org/10.1016/j.burns.2005.01.012>.
75. Sayeed MM. Neutrophil signaling alteration: an adverse inflammatory response after burn shock. *Medicina (Mex)* 1998;58:386–92.
76. Sood RF, Gibran NS, Arnoldo BD, Gamelli RL, Herndon DN, Tompkins RG. *et al.* Early leukocyte gene expression associated with age, burn size, and inhalation injury in severely burned adults. *J Trauma Acute Care Surg* 2016;80:250–7. <https://doi.org/10.1097/TA.0000000000000905>.
77. Ito S, Goto H, Tanoue K, Koiwai K, Ishikiriyama T, Kearney BM. *et al.* Early treatment with C-reactive protein-derived peptide reduces septic acute kidney injury in mice via controlled activation of kidney macrophages. *J Leukoc Biol* 2023;113:400–13. <https://doi.org/10.1093/jleuko/jiad015>.
78. Dunn JLM, Kartchner LB, Gast K, Sessions M, Hunter RA, Thurlow L. *et al.* Mammalian target of rapamycin regulates a hyperresponsive state in pulmonary neutrophils late after burn injury. *J Leukoc Biol* 2018;103:909–18. <https://doi.org/10.1002/JLB.3AB0616-251RRR>.
79. Miyazaki H, Kinoshita M, Ono S, Seki S, Saitoh D. Burn-evoked reactive oxygen species immediately after injury are crucial to restore the neutrophil function against postburn infection in mice. *Shock Augusta Ga*. 2015;44:252–7. <https://doi.org/10.1097/SHK.0000000000000404>.
80. Schlüter B, König W, Köller M, Erbs G, Müller FE. Differential regulation of T- and B-lymphocyte activation in severely burned patients. *J Trauma* 1991;31:239–46. <https://doi.org/10.1097/00005373-199102000-00015>.
81. Kanagalingam T, Solomon L, Vijeyakumaran M, Palikhe NS, Vliagoftis H, Cameron L. IL-2 modulates Th2 cell responses to glucocorticosteroid: a cause of persistent type 2 inflammation? *Immun Inflamm Dis* 2019;7:112–24. <https://doi.org/10.1002/iid.3249>.
82. Till GO, Hatherill JR, Tourtellotte WW, Lutz MJ, Ward PA. Lipid peroxidation and acute lung injury after thermal trauma to skin. Evidence of a role for hydroxyl radical. *Am J Pathol* 1985;119:376–84.
83. Mulder PPG, Koenen HJPM, Vlieg M, Joosten I, de Vries RBM, Boekema BKHL. Burn-induced local and systemic immune response: systematic review and meta-analysis of animal studies. *J Invest Dermatol* 2022;142:3093–3109.e15. <https://doi.org/10.1016/j.jid.2022.05.004>.
84. Hoşnüter M, Gürel A, Babuçcu O, Armutcu F, Kargi E, Işıkdemir A. The effect of CAPE on lipid peroxidation and nitric oxide levels in the plasma of rats following thermal injury. *Burns J Int Soc Burn Inj* 2004;30:121–5. <https://doi.org/10.1016/j.burns.2003.09.022>.
85. Wang N, Liang H, Zen K. Molecular mechanisms that influence the macrophage m1-m2 polarization balance. *Front Immunol* 2014;5:614. <https://doi.org/10.3389/fimmu.2014.00614>.
86. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest* 2012;122:787–95. <https://doi.org/10.1172/JCI59643>.
87. Gao Y, Jin H, Tan H, Cai X, Sun Y. Erythrocyte-derived extracellular vesicles aggravate inflammation by promoting the proinflammatory macrophage phenotype through TLR4-MyD88-NF- κ B-MAPK pathway. *J Leukoc Biol* 2022;112:693–706. <https://doi.org/10.1002/JLB.3A0821-451RR>.
88. Yu M, Zhou H, Zhao J, Xiao N, Roychowdhury S, Schmitt D. *et al.* MyD88-dependent interplay between myeloid and endothelial cells in the initiation and progression of obesity-associated inflammatory diseases. *J Exp Med* 2014;211:887–907. <https://doi.org/10.1084/jem.20131314>.
89. Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. *Nat Rev Immunol* 2003;3:745–56. <https://doi.org/10.1038/nri1184>.
90. Papa S, Bubici C, Zazzeroni F, Pham CG, Kuntzen C, Knabb JR. *et al.* The NF-kappaB-mediated control of the JNK cascade in the antagonism of programmed cell death in health and disease. *Cell Death Differ* 2006;13:712–29. <https://doi.org/10.1038/sj.cdd.4401865>.
91. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V. *et al.* Oxidative stress: harms and benefits for human health. *Oxidative Med Cell Longev* 2017;2017:8416763. <https://doi.org/10.1155/2017/8416763>.
92. Fan H, Li D, Guan X, Yang Y, Yan J, Shi J. *et al.* MsrA suppresses inflammatory activation of microglia and oxidative stress to prevent demyelination via inhibition of the NOX2-MAPKs/NF- κ B signaling pathway. *Drug Des Devel Ther* 2020;14:1377–89. <https://doi.org/10.2147/DDDT.S223218>.
93. Blaser H, Dostert C, Mak TW, Brenner D. TNF and ROS crosstalk in inflammation. *Trends Cell Biol* 2016;26:249–61. <https://doi.org/10.1016/j.tcb.2015.12.002>.
94. Morgan MJ, Liu Z, gang. Crosstalk of reactive oxygen species and NF- κ B signaling. *Cell Res* 2011;21:103–15. <https://doi.org/10.1038/cr.2010.178>.
95. Qi C, Shao Y, Liu X, Wang D, Li X. The cardioprotective effects of icariin on the isoprenaline-induced takotsubo-like rat model: involvement of reactive oxygen species and the TLR4/NF- κ B signaling pathway. *Int Immunopharmacol* 2019;74:105733. <https://doi.org/10.1016/j.intimp.2019.105733>.

96. Sierawska O, Małkowska P, Taskin C, Hryniewicz R, Mer-towska P, Grywalska E. *et al.* Innate immune system response to burn damage-focus on cytokine alteration. *Int J Mol Sci* 2022;23:716. <https://doi.org/10.3390/ijms23020716>.
97. Lim EY, Lee SY, Shin HS, Kim GD. Reactive oxygen species and strategies for antioxidant intervention in acute respiratory distress syndrome. *Antioxid Basel Switz* 2023;12:2016. <https://doi.org/10.3390/antiox12112016>.
98. Schwacha MG. Macrophages and post-burn immune dysfunction. *Burns J Int Soc Burn Inj* 2003;29:1–14. [https://doi.org/10.1016/S0305-4179\(02\)00187-0](https://doi.org/10.1016/S0305-4179(02)00187-0).
99. Luo G, Peng D, Zheng J, Chen X, Wu J, Elster E. *et al.* The role of NO in macrophage dysfunction at early stage after burn injury. *Burns J Int Soc Burn Inj* 2005;31:138–44. <https://doi.org/10.1016/j.burns.2004.09.009>.
100. Valenti L, Mathieu J, Chancerelle Y, Levacher M, Chanaud B, De Sousa M. *et al.* Nitric oxide inhibits spleen cell proliferative response after burn injury by inducing cytostasis, apoptosis, and necrosis of activated T lymphocytes: role of the guanylate cyclase. *Cell Immunol* 2003;221:50–63. [https://doi.org/10.1016/S0008-8749\(03\)00064-9](https://doi.org/10.1016/S0008-8749(03)00064-9).
101. Galili U. Accelerated burn healing in a mouse experimental model using α -gal nanoparticles. *Bioeng Basel Switz* 2023;10:1165. <https://doi.org/10.3390/bioengineering10101165>.
102. Lachiewicz AM, Hauck CG, Weber DJ, Cairns BA, van Duin D. Bacterial infections after burn injuries: impact of multidrug resistance. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2017;65: 2130–6. <https://doi.org/10.1093/cid/cix682>.
103. Siddique R, Mehmood MH, Hussain L, Malik A, Sethi A, Farrukh M. *et al.* Role of medicinal herbs and phytochemicals in post burn management. *Inflammopharmacology*. 2023;31:1695–714. <https://doi.org/10.1007/s10787-023-01246-5>.
104. Rech MA, Mosier MJ, McConkey K, Zelisko S, Netzer G, Kovacs EJ. *et al.* Outcomes in burn-injured patients who develop sepsis. *J Burn Care Res Off Publ Am Burn Assoc* 2019;40:269–73. <https://doi.org/10.1093/jbcr/irz017>.
105. Gur I, Zilbert A, Toledano K, Roimi M, Stern A. Clinical impact of fungal colonization of burn wounds in patients hospitalized in the intensive care unit: a retrospective cohort study. *Trauma Surg Acute Care Open* 2024;9:e001325. <https://doi.org/10.1136/tsaco-2023-001325>.
106. Ballard J, Edelman L, Saffle J, Sheridan R, Kagan R, Bracco D. *et al.* Positive fungal cultures in burn patients: a multicenter review. *J Burn Care Res Off Publ Am Burn Assoc*. 2008;29: 213–21. <https://doi.org/10.1097/BCR.0b013e31815f6ecb>.
107. Bertin-Maghit M, Goudable J, Dalmás E, Steghens JP, Bouchard C, Gueugniaud PY. *et al.* Time course of oxidative stress after major burns. *Intensive Care Med* 2000;26:800–3. <https://doi.org/10.1007/s001340051250>.
108. Gökakın AK, Atabey M, Deveci K, Sancakdar E, Tuzcu M, Duger C. *et al.* The effects of sildenafil in liver and kidney injury in a rat model of severe scald burn: a biochemical and histopathological study. *Ulus Trauma Ve Acil Cerrahi Derg Turk J Trauma Emerg Surg TJTES* 2014;20:319–27.
109. Hristova M, Tasinov O, Tzanava M, Chivchibashi D, Kiselova-Kaneva Y, Bekyarova G. Effect of melatonin on the gastric antioxidant defence in experimental burn trauma. *Vet Med (Praha)* 2022;67:379–86. <https://doi.org/10.17221/109/2021-VETMED>.
110. Quinlan GJ, Lamb NJ, Tilley R, Evans TW, Gutteridge JM. Plasma hypoxanthine levels in ARDS: implications for oxidative stress, morbidity, and mortality. *Am J Respir Crit Care Med* 1997;155:479–84. <https://doi.org/10.1164/ajrccm.155.2.9032182>.
111. Gao L, Rafaels N, Dudenkov TM, Damarla M, Damico R, Maloney JP. *et al.* Xanthine oxidoreductase gene polymorphisms are associated with high risk of sepsis and organ failure. *Respir Res* 2023;24:177. <https://doi.org/10.1186/s12931-023-02481-8>.
112. Demling R, Lalonde C, Picard L, Blanchard J. Changes in lung and systemic oxidant and antioxidant activity after smoke inhalation. *Shock Augusta Ga*. 1994;1:101–7. <https://doi.org/10.1097/00024382-199402000-00004>.
113. Carvalho FO, Silva ÉR, Nunes PS, Felipe FA, Ramos KPP, Ferreira LAS. *et al.* Effects of the solid lipid nanoparticle of carvacrol on rodents with lung injury from smoke inhalation. *Naunyn Schmiedeberg's Arch Pharmacol* 2020;393:445–55. <https://doi.org/10.1007/s00210-019-01731-1>.
114. Agay D, Andriollo-Sanchez M, Claeysen R, Touvard L, Denis J, Roussel AM. *et al.* Interleukin-6, TNF-alpha and interleukin-1 beta levels in blood and tissue in severely burned rats. *Eur Cytokine Netw* 2008;19:1–7. <https://doi.org/10.1684/ecn.2008.0113>.
115. Xie C, Hu J, Cheng Y, Yao Z. Researches on cognitive sequelae of burn injury: current status and advances. *Front Neurosci* 2022;16:1026152. <https://doi.org/10.3389/fnins.2022.1026152>.
116. Abraham P, Monard C, Schneider A, Rimmelé T. Extracorporeal blood purification in burns: for whom, why, and how? *Blood Purif* 2023;52:17–24. <https://doi.org/10.1159/000525085>.
117. Schneider CP, Schwacha MG, Chaudry IH. The role of interleukin-10 in the regulation of the systemic inflammatory response following trauma-hemorrhage. *Biochim Biophys Acta* 2004;1689:22–32. <https://doi.org/10.1016/j.bbadi.2004.01.003>.
118. Schindler CR, Woschek M, Franz JN, Störmann P, Henrich D, Marzi I. Influence of antibiotic management on microbial selection and infectious complications after trauma. *Front Med* 2021;8:678382. <https://doi.org/10.3389/fmed.2021.678382>.
119. Bohannon JK, Luan L, Hernandez A, Afzal A, Guo Y, Patil NK. *et al.* Role of G-CSF in monophosphoryl lipid A-mediated augmentation of neutrophil functions after burn injury. *J Leukoc Biol* 2016;99:629–40. <https://doi.org/10.1189/jlb.4A0815-362R>.
120. Horton JW. Free radicals and lipid peroxidation mediated injury in burn trauma: the role of antioxidant therapy. *Toxicology*. 2003;189:75–88. [https://doi.org/10.1016/S0300-483X\(03\)00154-9](https://doi.org/10.1016/S0300-483X(03)00154-9).
121. Valko M, Morris H, Cronin MTD. Metals, toxicity and oxidative stress. *Curr Med Chem* 2005;12:1161–208. <https://doi.org/10.2174/0929867053764635>.
122. Sikora JP, Karawani J, Sobczak J. Neutrophils and the systemic inflammatory response syndrome (SIRS). *Int J Mol Sci* 2023;24:13469. <https://doi.org/10.3390/ijms241713469>.
123. Osborne T, Wall B, Edgar DW, Fairchild T, Wood F. Current understanding of the chronic stress response to burn injury from human studies. *Burns Trauma* 2023;11:tkad007. <https://doi.org/10.1093/burnst/tkad007>.
124. Palackic A, Suman OE, Porter C, Murton AJ, Crandall CG, Rivas E. Rehabilitative exercise training for burn injury. *Sports Med Auckl NZ* 2021;51:2469–82. <https://doi.org/10.1007/s40279-021-01528-4>.
125. Mosier MJ, Pham TN, Klein MB, Gibran NS, Arnoldo BD, Gamelli RL. *et al.* Early acute kidney injury predicts progressive renal dysfunction and higher mortality in severely burned adults. *J Burn Care Res Off Publ Am Burn Assoc* 2010;31:83–92. <https://doi.org/10.1097/BCR.0b013e3181c8c87>.
126. Curiel Balsera E, Palomino MAP, Ordoñez JM. Acute kidney injury in critically ill burn patients. *Burns J Int Soc Burn Inj* 2010;36:1139–40author reply 1140–1141. <https://doi.org/10.1016/j.burns.2010.02.010>.
127. Jeong R, Wald R, Bagshaw SM. Timing of renal-replacement therapy in intensive care unit-related acute kidney injury. *Curr Opin Crit Care* 2021;27:573–81. <https://doi.org/10.1097/MCC.0000000000000891>.
128. Quoilin C, Mouithys-Mickalad A, Lécart S, Fontaine-Aupart MP, Hoebeke M. Evidence of oxidative stress and mitochondrial respiratory chain dysfunction in an in vitro model of sepsis-induced kidney injury. *Biochim Biophys Acta* 2014;1837: 1790–800. <https://doi.org/10.1016/j.bbabi.2014.07.005>.
129. Palipoch S. A review of oxidative stress in acute kidney injury: protective role of medicinal plants-derived antioxidants.

- Afr J Tradit Complement Altern Med AJTCAM* 2013;10:88–93. <https://doi.org/10.4314/ajtcam.v10i4.15>.
130. Elks CM, Reed SD, Mariappan N, Shukitt-Hale B, Joseph JA, Ingram DK. *et al.* A blueberry-enriched diet attenuates nephropathy in a rat model of hypertension via reduction in oxidative stress. *PLoS One* 2011;6:e24028. <https://doi.org/10.1371/journal.pone.0024028>.
 131. Rana A, Sathyanarayana P, Lieberthal W. Role of apoptosis of renal tubular cells in acute renal failure: therapeutic implications. *Apoptosis Int J Program Cell Death* 2001;6:83–102. <https://doi.org/10.1023/A:1009680229931>.
 132. Deng F, Zheng X, Sharma I, Dai Y, Wang Y, Kanwar YS. Regulated cell death in cisplatin-induced AKI: relevance of myo-inositol metabolism. *Am J Physiol Renal Physiol*. 2021;320:F578–95. <https://pubmed.ncbi.nlm.nih.gov/33615890/>.
 133. Colpaert K, Hoste EA. Acute kidney injury in burns: a story of volume and inflammation. *Crit Care Lond Engl* 2008;12:192. <https://doi.org/10.1186/cc7106>.
 134. Nguyen TT, Deng Z, Guo RY, Chai JW, Li R, Zeng QY. *et al.* Periplaneta americana extract ameliorates LPS-induced acute lung injury via reducing inflammation and oxidative stress. *Curr Med Sci* 2023;43:445–55. <https://doi.org/10.1007/s11596-023-2723-8>.
 135. Deng J, Wang G, Huang Q, Yan Y, Li K, Tan W. *et al.* Oxidative stress-induced leaky sarcoplasmic reticulum underlying acute heart failure in severe burn trauma. *Free Radic Biol Med* 2008;44:375–85. <https://doi.org/10.1016/j.freeradbiomed.2007.09.023>.
 136. Clerk A, Cullingford TE, Kemp TJ, Kennedy RA, Sugden PH. Regulation of gene and protein expression in cardiac myocyte hypertrophy and apoptosis. *Adv Enzym Regul* 2005;45:94–111. <https://doi.org/10.1016/j.advenzreg.2005.02.007>.
 137. Zang Q, Maass DL, White J, Horton JW. Cardiac mitochondrial damage and loss of ROS defense after burn injury: the beneficial effects of antioxidant therapy. *J Appl Physiol Bethesda Md* 1985 2007;102:103–12. <https://doi.org/10.1152/japplphysiol.00359.2006>.
 138. Marín-García J, Goldenthal MJ. Understanding the impact of mitochondrial defects in cardiovascular disease: a review. *J Card Fail* 2002;8:347–61. <https://doi.org/10.1054/jcaf.2002.127774>.
 139. Porter C, Herndon DN, Børsheim E, Chao T, Reidy PT, Borack MS. *et al.* Uncoupled skeletal muscle mitochondria contribute to hypermetabolism in severely burned adults. *Am J Physiol Endocrinol Metab* 2014;307:E462–7. <https://doi.org/10.1152/ajpendo.00206.2014>.
 140. Wen JJ, Cummins CB, Szczesny B, Radhakrishnan RS. Cardiac dysfunction after burn injury: role of the AMPK-SIRT1-PGC1α-NFE2L2-ARE pathway. *J Am Coll Surg* 2020;230:562–71. <https://doi.org/10.1016/j.jamcollsurg.2019.12.029>.
 141. Szczesny B, Brunyánszki A, Ahmad A, Oláh G, Porter C, Toliver-Kinsky T. *et al.* Time-dependent and organ-specific changes in mitochondrial function, mitochondrial DNA integrity, oxidative stress and mononuclear cell infiltration in a mouse model of burn injury. *PLoS One* 2015;10:e0143730. <https://doi.org/10.1371/journal.pone.0143730>.
 142. Lu X, Costantini T, Lopez NE, Wolf PL, Hageny AM, Putnam J. *et al.* Vagal nerve stimulation protects cardiac injury by attenuating mitochondrial dysfunction in a murine burn injury model. *J Cell Mol Med* 2013;17:664–71. <https://doi.org/10.1111/jcmm.12049>.
 143. Povea-Cabello S, Brischigliaro M, Fernández-Vizarra E. Emerging mechanisms in the redox regulation of mitochondrial cytochrome c oxidase assembly and function. *Biochem Soc Trans* 2024;52:873–85. <https://doi.org/10.1042/BST20231183>.
 144. Yao X, Wigginton JG, Maass DL, Ma L, Carlson D, Wolf SE. *et al.* Estrogen-provided cardiac protection following burn trauma is mediated through a reduction in mitochondria-derived DAMPs. *Am J Physiol Heart Circ Physiol* 2014;306:H882–94. <https://doi.org/10.1152/ajpheart.00475.2013>.
 145. Zhang D-X, Sheng HY, Tao ZS, Dong LX. An experimental study on large fragment deletion of rat myocardial mitochondrial DNA during early postburn stage. *Zhonghua Shao Shang Za Zhi Zhonghua Shaoshang Zazhi Chin J Burns* 2004;20:271–4.
 146. Saito-Takatsuji H, Yoshitomi Y, Ishigaki Y, Yamamoto S, Numata N, Sakai Y. *et al.* Protective effects of collagen tripeptides in human aortic endothelial cells by restoring ROS-induced transcriptional repression. *Nutrients*. 2021;13:2226. <https://doi.org/10.3390/nu13072226>.
 147. Allen RG. Oxidative stress and superoxide dismutase in development, aging and gene regulation. *Age*. 1998;21:47–76. <https://doi.org/10.1007/s11357-998-0007-7>.
 148. Kröller-Schön S, Daiber A, Steven S, Oelze M, Frenis K, Kalinovic S. *et al.* Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. *Eur Heart J* 2018;39:3528–39. <https://doi.org/10.1093/eurheartj/ehy333>.
 149. Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Arch Surg Chic Ill 1960* 2000;135:326–31. <https://doi.org/10.1001/archsurg.135.3.326>.
 150. Li X, Cannon AR, Hammer AM, Morris NL, Choudhry MA. IL-23 restoration of Th17 effector function is independent of IL-6 and TGF-β in a mouse model of alcohol and burn injury. *J Leukoc Biol* 2017;102:915–23. <https://doi.org/10.1189/jlb.3A1216-527R>.
 151. Miličević D, Hlaváč J. Novel peptide-based fluorescent probe for simultaneous sensing of chymotrypsin and hydrogen peroxide. *ACS Omega* 2024;9:17481–90. <https://doi.org/10.1021/acsomega.4c00303>.
 152. Nizami ZN, Aburawi HE, Semlali A, Muhammad K, Iratni R. Oxidative stress inducers in cancer therapy: preclinical and clinical evidence. *Antioxid Basel Switz*. 2023;12:1159. <https://doi.org/10.3390/antiox12061159>.
 153. Mueller-Buehl AM, Buehner T, Pfarrer C, Deppe L, Peters L, Dick BH. *et al.* Hypoxic processes induce complement activation via classical pathway in porcine neuroretinas. *Cells*. 2021;10:3575. <https://doi.org/10.3390/cells10123575>.
 154. Latha B, Ramakrishnan M, Jayaraman V, Babu M. Serum enzymatic changes modulated using trypsin: chymotrypsin preparation during burn wounds in humans. *Burns J Int Soc Burn Inj* 1997;23:560–4. [https://doi.org/10.1016/S0305-4179\(97\)00080-6](https://doi.org/10.1016/S0305-4179(97)00080-6).
 155. Motohashi H, Yamamoto M. Nrf2-Keap1 defines a physiologically important stress response mechanism. *Trends Mol Med* 2004;10:549–57. <https://doi.org/10.1016/j.molmed.2004.09.003>.
 156. Bekyarova GY, Vankova DG, Madjova VH, Bekyarov NA, Salim AS, Ivanova DG. *et al.* Association between Nrf2, HO-1, NF-κB expression, plasma ADMA, and oxidative stress in metabolic syndrome. *Int J Mol Sci* 2023;24:17067. <https://doi.org/10.3390/ijms242317067>.
 157. Mohmad Saberi SE, Chua LS. Potential of rosmarinic acid from Orthosiphon aristatus extract for inflammatory induced diseases and its mechanisms of action. *Life Sci* 2023;333:122170. <https://doi.org/10.1016/j.lfs.2023.122170>.
 158. Lu CW, Lee CJ, Hsieh YJ, Hsu BG. Empagliflozin attenuates vascular calcification in mice with chronic kidney disease by regulating the NFR2/HO-1 anti-inflammatory pathway through AMPK activation. *Int J Mol Sci* 2023;24:10016. <https://doi.org/10.3390/ijms241210016>.
 159. Keleku-Lukwete N, Suzuki M, Yamamoto M. An overview of the advantages of KEAP1-NRF2 system activation during inflammatory disease treatment. *Antioxid Redox Signal* 2018;29:1746–55. <https://doi.org/10.1089/ars.2017.7358>.
 160. Takaya K, Suzuki T, Motohashi H, Onodera K, Satomi S, Kensler TW. *et al.* Validation of the multiple sensor mechanism of

- the Keap1-Nrf2 system. *Free Radic Biol Med* 2012;53:817–27. <https://doi.org/10.1016/j.freeradbiomed.2012.06.023>.
161. El-Azab MF, Baldowski BRB, Mysona BA, Shanab AY, Mohamed IN, Abdelsaid MA. *et al.* Deletion of thioredoxin-interacting protein preserves retinal neuronal function by preventing inflammation and vascular injury. *Br J Pharmacol* 2014;171:1299–313. <https://doi.org/10.1111/bph.12535>.
 162. Freigang S, Ampenberger F, Spohn G, Heer S, Shamshiev AT, Kisielow J. *et al.* Nrf2 is essential for cholesterol crystal-induced inflammasome activation and exacerbation of atherosclerosis. *Eur J Immunol* 2011;41:2040–51. <https://doi.org/10.1002/eji.201041316>.
 163. He Q, You H, Li XM, Liu TH, Wang P, Wang BE. HMGB1 promotes the synthesis of pro-IL-1 β and pro-IL-18 by activation of p38 MAPK and NF- κ B through receptors for advanced glycation end-products in macrophages. *Asian Pac J Cancer Prev APJCP* 2012;13:1365–70. <https://doi.org/10.7314/APJCP.2012.13.4.1365>.
 164. Kong X, Thimmulappa R, Kombairaju P, Biswal S. NADPH oxidase-dependent reactive oxygen species mediate amplified TLR4 signaling and sepsis-induced mortality in Nrf2-deficient mice. *J Immunol Baltim Md* 1950 2010;185:569–77. <https://doi.org/10.4049/jimmunol.0902315>.
 165. Gao B, Doan A, Hybertson BM. The clinical potential of influencing Nrf2 signaling in degenerative and immunological disorders. *Clin Pharmacol Adv Appl* 2014;6:19–34.
 166. Wang J, Cao Y, Lu Y, Zhu H, Zhang J, Che J. *et al.* Recent progress and applications of small molecule inhibitors of Keap1-Nrf2 axis for neurodegenerative diseases. *Eur J Med Chem* 2024;264:115998. <https://doi.org/10.1016/j.ejmech.2023.115998>.
 167. Liu J, Han X, Zhang T, Tian K, Li Z, Luo F. Reactive oxygen species (ROS) scavenging biomaterials for anti-inflammatory diseases: from mechanism to therapy. *J Hematol Oncol J Hematol Oncol* 2023;16:116. <https://doi.org/10.1186/s13045-023-01512-7>.
 168. Gao S, Wang K, Xiong K, Xiao S, Wu C, Zhou M. *et al.* Unraveling the Nrf2-ARE signaling pathway in the DF-1 chicken fibroblast cell line: insights into T-2 toxin-induced oxidative stress regulation. *Toxins*. 2023;15:627. <https://doi.org/10.3390/toxins15110627>.
 169. Guillory AN, Clayton RP, Herndon DN, Finnerty CC. Cardiovascular dysfunction following burn injury: what we have learned from rat and mouse models. *Int J Mol Sci* 2016;17:53. <https://doi.org/10.3390/ijms17010053>.
 170. Kulp GA, Herndon DN, Lee JO, Suman OE, Jeschke MG. Extent and magnitude of catecholamine surge in pediatric burned patients. *Shock Augusta Ga*. 2010;33:369–74. <https://doi.org/10.1097/SHK.0b013e3181b92340>.
 171. Żwierello W, Piorun K, Skórka-Majewicz M, Maruszczyńska A, Antoniewski J, Gutowska I. Burns: classification, pathophysiology, and treatment: a review. *Int J Mol Sci* 2023;24:3749. <https://doi.org/10.3390/ijms24043749>.
 172. Tapking C, Popp D, Herndon DN, Branski LK, Hundeshagen G, Armenta AM. *et al.* Cardiac dysfunction in severely burned patients: current understanding of etiology, pathophysiology, and treatment. *Shock Augusta Ga*. 2020;53:669–78. <https://doi.org/10.1097/SHK.0000000000001465>.
 173. Bovo E, Lipsius SL, Zima AV. Reactive oxygen species contribute to the development of arrhythmogenic Ca²⁺ waves during β -adrenergic receptor stimulation in rabbit cardiomyocytes. *J Physiol* 2012;590:3291–304. <https://doi.org/10.1113/jphysiol.2012.230748>.
 174. Seya K, Ono K, Fujisawa S, Okumura K, Motomura S, Furukawa K. *et al.* Cytosolic Ca²⁺-induced apoptosis in rat cardiomyocytes via mitochondrial NO-cGMP-protein kinase G pathway. *J Pharmacol Exp Ther* 2013;344:77–84. <https://doi.org/10.1124/jpet.112.198176>.
 175. Herndon D, Zhang F, Lineaweaver W. Metabolic responses to severe burn injury. *Ann Plast Surg* 2022;88:S128–31. <https://doi.org/10.1097/SAP.0000000000003142>.
 176. Yang Y, Hu Q, Kang H, Li J, Zhao X, Zhu L. *et al.* Urolithin A protects severe acute pancreatitis-associated acute cardiac injury by regulating mitochondrial fatty acid oxidative metabolism in cardiomyocytes. *MedComm*. 2023;4:e459. <https://doi.org/10.1002/mco2.459>.
 177. Mariappan N, Elks CM, Haque M, Francis J. Interaction of TNF with angiotensin II contributes to mitochondrial oxidative stress and cardiac damage in rats. *PLoS One* 2012;7:e46568. <https://doi.org/10.1371/journal.pone.0046568>.
 178. Hulsurkar MM, Lahiri SK, Karch J, Wang MC, Wehrens XHT. Targeting calcium-mediated inter-organellar crosstalk in cardiac diseases. *Expert Opin Ther Targets* 2022;26:303–17. <https://doi.org/10.1080/14728222.2022.2067479>.
 179. White DJ, Maass DL, Sanders B, Horton JW. Cardiomyocyte intracellular calcium and cardiac dysfunction after burn trauma. *Crit Care Med* 2002;30:14–22. <https://doi.org/10.1097/00003246-200201000-00003>.