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# OXIDATIVE STRESS IN SKIN AGING (Part-1)

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*Abstract: This article presents a literature review and data showing that during aging, the intensity of reactive oxygen species (ROS) formation exceeds the antioxidant defense capacity of structural skin components—the stratum corneum, epidermis, and dermis. ROS are shown to be involved in the pathogenesis of inflammatory processes and allergic reactions in the skin. The role of ROS and antioxidant systems in cellular responses associated with MAP kinase activity in the skin is discussed. Particular attention is paid to the effects of UV radiation on the skin, including its genotoxic, immunosuppressive, and carcinogenic effects.*

*Keywords: oxidative stress, ROS, MAP kinases, skin antioxidant system, fibroblasts, keratinocytes, carcinogenesis*

Skin aging is influenced by various factors, including genetic predispositions, environmental exposure, hormonal changes, and alterations in metabolic activity. With age, the skin becomes thinner, looser, drier, develops pigmentation spots, and loses elasticity. Extracellular matrix atrophy, accompanied by increased protein degradation during aging, is reflected in a decrease in the number of fibroblasts due to suppressed protein synthesis, including type I and III collagen, as well as elastin [12]. Type I collagen is abundant in the skin's connective tissue. Other components, such as type III and V collagen, elastin, fibronectin, proteoglycans, and other extracellular matrix proteins, also undergo age-related structural changes leading to loss of skin firmness and elasticity. Oxidative stress plays a key role in these changes.

Although the skin has an effective antioxidant defense system, ROS production during skin aging surpasses the antioxidant potential. Excessive and uncontrolled ROS production is a significant pathogenic factor in the development of various skin diseases, including those with neoplastic origins [8, 11].

Sources of oxidative stress in the skin include environmental pollutants, UV radiation, food preservatives, cosmetic products, and medications. ROS include superoxide and hydroxyl radicals, hydrogen peroxide, and singlet oxygen. Superoxide anion reacts with nitric oxide to form the highly toxic and reactive peroxynitrite ($ONOO^-$). Mitochondria are the main ROS producers, along with other sources like cytochrome P-450 enzyme systems, xanthine oxidase, non-enzymatic reactions initiated by oxygen and ionizing radiation, and prostaglandin synthesis [43]. Intermediate products of heme metabolism also exhibit pro-oxidant activity [46]. Additionally, leukocytes activated during inflammation and migrating into the skin produce ROS. These cells, which show high myeloperoxidase and NO synthase activities, release superoxide, nitric oxide, and hypochlorite anion—agents that destroy pathogens and damaged cell structures [13, 14].

Antioxidant defense in the skin, as in other tissues, is provided by enzymatic systems including superoxide dismutase (SOD), catalase, glutathione peroxidase, glutathione-S-transferase, peroxidases, and thiol-specific antioxidant enzymes. Low-molecular-weight compounds such as ascorbic acid, glutathione, α-carotene, β-tocopherol, uric acid, and bilirubin also contribute [9, 43]. The skin contains both forms of SOD (Cu,Zn-SOD and Mn-SOD) and catalase, which maintain redox balance and can be modulated during photoaging caused by UV exposure [33, 44]. This exposure significantly reduces the expression of antioxidant enzymes in the stratum corneum and epidermis [47, 48].

Photoaging leads to the accumulation of glycation and lipid peroxidation products [24, 53, 61]. Skin aging is associated with changes in the molecular structures of DNA, proteins, lipids, and prostaglandins—oxidative stress markers in all organs. However, these changes may also result from spontaneous errors and non-oxidative modifications [45, 51]. Recently, protein oxidation by free radicals has gained attention because this process may precede lipid peroxidation

[1]. Oxidation targets include lysine, arginine, proline, and threonine residues in proteins, forming carbonyl derivatives [6, 34].

Protein carbonyl group detection in keratinocytes and fibroblasts is a marker of oxidative damage in skin tissue [20, 54, 55]. Evidence shows that in keratinocytes and fibroblasts exposed to UV-A, UV-B, or hydrogen peroxide—as well as in skin biopsies from chronically sun-damaged skin with elastosis—catalase activity sharply decreases, while protein oxidation increases [48]. This suggests that photoaging is accompanied by intensified protein oxidative modification due to weakened antioxidant defense.

ROS participate in numerous physiological processes, not only as damaging agents but also as signaling molecules regulating normal cell functions [1, 10, 32]. ROS induce transcription factors like activator protein-1 (AP-1) and NF-κB [18]. MAP kinases play a vital role in ROS-initiated cell responses, including proliferation, repair, UV resistance, and response to oxidative stress [30]. MAPKs enter the nucleus and phosphorylate transcription factors. These signaling pathways regulate many cellular functions, such as growth and differentiation [62], matrix metalloproteinase (MMP) expression [21], and type I procollagen synthesis [15].

Studies show increased levels of three MMPs in aged skin: collagenase (MMP-1), 72 kDa gelatinase (MMP-2), and 92 kDa gelatinase (MMP-9). Simultaneously, type I procollagen synthesis—comprising nearly 90% of dermal connective tissue proteins—is significantly reduced [57]. Vitamin A (retinol) can counteract this deficiency by stimulating type I procollagen synthesis, enhancing cell growth, and reducing MMP-1 and MMP-9 levels.

MAP kinases include three families with distinct roles: extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), and p38 MAP kinases. These pathways often overlap, but ERKs mainly respond to growth factors [62], while JNK and p38 respond to cytokines and physical stress [59, 62]. The balance between ERK and JNK/p38 pathways is crucial for cell survival. During skin aging, ERK function declines, while JNK and p38 activity increases [16]. Induction of ERK and p38, as well as JNK activation, is inhibited by ROS scavengers and antioxidants such as reduced glutathione [35]. This supports the theory that ROS-induced MAPK regulation plays a central role in skin aging pathophysiology.

ROS may also contribute to inflammatory and allergic skin conditions. Th1 and Th2 lymphocytes show different cytokine expression profiles [7]. Th1 cells, which mediate cellular immunity, secrete IL-2 and γ-interferon, while Th2 cells, responsible for humoral immunity, produce IL-4, IL-5, IL-6, IL-10, and IL-13.

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