Zhu et al. *Zool. Res.* 2025, 46(5): 1219−1243
https://doi.org/10.24272/j.issn.2095-8137.2025.127
https://cstr.cn/32248.14.zr.2025.127

ZR | Zoological Research

Review Open Access

Amphibians as a source of bioactive antioxidant peptides: Emerging insights and therapeutic potential

Yi-Yun Zhu[1,2,3,5,#], Li-Mei Zhao[4,#], Xin-Yi Jia[6], Guo-Jian Liao[2,*], Yi-Peng Wang[1,3,5,*]

[1] *Yantai Institute of Coastal Zone Research*, *Chinese Academy of Sciences*, *Yantai*, *Shandong* 264003, *China*
[2] *Medical Research Institute*, *College of Pharmaceutical Sciences*, *Southwest University*, *Chongqing* 400715, *China*
[3] *Department of Biopharmaceutical Sciences*, *College of Pharmaceutical Sciences*, *Soochow University*, *Suzhou*, *Jiangsu* 215123, *China*
[4] *Department of Pathology and Pathophysiology*, *School of Basic Medical Sciences*, *Suzhou Medical College of Soochow University*, *Suzhou*, *Jiangsu* 215123, *China*
[5] *University of Chinese Academy of Sciences*, *Beijing* 100049, *China*
[6] *Department of Food Science and Technology*, *Food Science and Technology Center*, *National University of Singapore*, *Singapore* 119077, *Singapore*

ABSTRACT

Oxidative stress arises from disruption of the balance between reactive oxygen species (ROS) production and detoxification and constitutes a fundamental driver of diverse pathological diseases. Skin photoaging is a well-recognized example, primarily driven by chronic ultraviolet (UV) exposure and marked by progressive structural and functional deterioration. UV-induced ROS accelerate macromolecular degradation and impair epidermal and dermal barrier integrity, highlighting the urgent need for effective antioxidant interventions. Antioxidant peptides (AOPs), whether naturally occurring or synthetically engineered, have shown considerable potential in mitigating ROS-induced cellular damage. Amphibians, which possess highly permeable skin and are continuously challenged by fluctuating environmental conditions, represent a rich source of bioactive peptides with potent antioxidant properties. In particular, AOPs isolated from amphibian skin secretions demonstrate notable efficacy in ROS scavenging and mitigation of oxidative damage, offering promising candidates for anti-photoaging therapies. This review provides an integrated overview of ROS generation and signaling, the molecular mechanisms linking oxidative stress to skin photoaging, and the emerging biomedical potential of amphibian-derived AOPs. Deeper mechanistic insight into their structure and function is expected to accelerate the development of novel peptide-based interventions for photoaging and other oxidative stress-associated dermatological disorders.

Keywords: Antioxidant peptides (AOPs); Reactive oxygen species (ROS); Amphibians; Skin photoaging; Peptide drugs

INTRODUCTION

Oxygen sustains aerobic life, yet its continuous use in mitochondrial respiration inevitably generates reactive oxygen species (ROS) as byproducts of electron transfer reactions (Forrester et al., 2018). These reactive, oxygen-containing molecules, often with unpaired electrons, arise as intermediate metabolites within biological systems (Lushchak, 2014). Under controlled levels, ROS participate in signaling processes; however, excessive accumulation disrupts cellular homeostasis and induces oxidative stress (Zuo et al., 2015). Elevated ROS levels damage lipids, proteins, and nucleic acids, and are closely associated with diverse pathophysiological conditions, including inflammation, aging, and cancer (Forrester et al., 2018). Among the visible manifestations of oxidative stress, skin photoaging represents a clinically significant outcome of chronic ultraviolet (UV) irradiation (Kammeyer & Luiten, 2015). UV radiation not only directly damages dermal and epidermal structures but also drives ROS overproduction, thereby exacerbating oxidative damage and accelerating aging-related phenotypes (Dunaway et al., 2018). Consequently, there is a growing demand for safe and effective antioxidant strategies to mitigate UV-induced skin deterioration, with particular relevance to dermatology and cosmetic science.

Antioxidant peptides (AOPs) have emerged as a versatile class of bioactive molecules capable of scavenging ROS and attenuating oxidative stress. These peptides, derived from

Received: 10 August 2025; Accepted: 02 September 2025; Online: 03 September 2025

Foundation items: This work was supported by the National Natural Science Foundation of China (32070439), Key Research & Development Plan in Social Development of Jiangsu Province (BE2022723), and Suzhou Agricultural Science and Technology Innovation Project (SNG2022054)

[#]Authors contributed equally to this work

*Corresponding authors, E-mail: gjliao@swu.edu.cn; ypwang@yic.ac.cn

natural sources or synthetically engineered, can bind and quench ROS, thereby reducing intracellular oxidative burden and preventing downstream cellular damage (Zhu et al., 2024). By stabilizing macromolecular integrity and maintaining redox equilibrium, AOPs can delay or even prevent the onset of oxidative stress-induced pathologies. Due to their high specificity, biocompatibility, and functional versatility, the therapeutic application of AOPs has expanded across various sectors including food technology, nutraceuticals, pharmaceuticals, and dermatological formulations (Sila & Bougatef, 2016). Notably, AOPs derived from amphibians, particularly those secreted from the skin of anurans, have garnered increasing attention owing to their robust antioxidant capacities, high biosafety profiles, and structural diversity (Yang et al., 2012). These attributes highlight amphibian-derived AOPs as promising candidates for interventions against photoaging, while also reflecting evolutionary adaptations that provide valuable templates for pharmacological innovation.

Amphibians occupy critical ecological niches and are distinguished by highly permeable skin that supports respiration, osmoregulation, and environmental sensing (Feng et al., 2018). However, this physiological specialization also increases their susceptibility to environmental stressors, particularly elevated UV radiation (Bovo et al., 2018). Long-term monitoring indicates that global surface UV intensity rose by approximately 15% between 1978 and 1998, thereby exposing amphibians to increased UV levels during sensitive reproductive and developmental periods (Burrow & Maerz, 2022). During aquatic developmental stages, amphibians are further exposed to UV-driven oxidative stress through both direct irradiation and photochemical processes in surrounding waters (Wang et al., 2017). To counteract these pressures, amphibians have evolved a variety of biochemical and morphological adaptations to mitigate oxidative damage induced by UV radiation, dehydration, and pathogen exposure (Barbosa et al., 2021).

Biochemically, amphibian skin secretions contain a broad spectrum of AOPs, enzymatic antioxidants such as superoxide dismutase (SOD) and catalase (CAT), and non-enzymatic antioxidants including glutathione (GSH) and vitamins C and E. These components function synergistically to neutralize ROS, scavenge free radicals, and maintain redox homeostasis (Yang et al., 2016). Additional protective factors include melanin, which absorbs UV radiation, and metallothioneins, which chelate metal ions (Feng et al., 2018). Morphologically, amphibians also possess mucous and granular glands that secrete antioxidant-rich mucus and bioactive compounds (Mailho-Fontana et al., 2014). Pigmented cells within the skin absorb UV radiation to reduce oxidative damage, while keratinized epidermal layers provide a physical barrier (Feng et al., 2018, 2021). Periodic shedding of the epidermis further facilitates the removal of oxidized material. In species adapted to extreme environments, such as high-altitude frogs, these antioxidant defenses are often enhanced, reflecting evolutionary selection for resilience under persistent oxidative stress (Jared et al., 2018; Tang et al., 2025). Collectively, these mechanisms underscore the ecological and evolutionary significance of AOPs in amphibian lineages and provide a foundation for exploring their structural and functional diversity.

Amphibians have evolved complex protective strategies, including the secretion of AOPs from skin glands, to neutralize ROS and preserve tissue integrity (Demori et al., 2019; Xu & Lai, 2015). Amphibians granular glands are widely recognized as sources of bioactive defensive compounds, including antimicrobial and antioxidant peptides, although much of this evidence is derived from studies on anuran species (frogs and toads) (Benítez-Prián et al., 2024). In contrast, the order Gymnophiona (caecilians) has received comparatively little attention. Caecilians are limbless, tropical amphibians with elongated, annulated bodies, vestigial eyes, and paired sensory tentacles that facilitate their fossorial lifestyle (Taylor, 1968; Prakash et al., 2024). Many species also possess dermal scales embedded within annular folds, a unique trait among extant tetrapods, although the function of these scales remains poorly understood (Taylor, 1968). Compared with Caudata and Anura, caecilians exhibit lower diversity and abundance of bioactive peptides, which may reflect adaptations to their subterranean habitat. While generally stable in moisture and temperature, soil environments harbor diverse microbial communities, including potentially pathogenic bacteria, protozoa, and fungi (Benítez-Prián et al., 2024), exposing caecilians to different selective pressures (Benítez-Prián et al., 2024). Notably, genomic and transcriptomic analyses have revealed a high degree of sequence conservation among caecilian species, with no defensin-related sequences detected, suggesting loss of defensin genes during evolution. Instead, several peptides with putative antimicrobial activity identified in caecilians belong to hormone- or neuropeptide-related families, such as adrenomedullin and neuropeptide W. These peptides are hypothesized to function primarily as antipredator toxins that act through hormone receptor interactions in predators, rather than serving as classical antimicrobial peptides (AMPs) (Benítez-Prián et al., 2024). These findings suggest that different amphibian lineages have evolved distinct biochemical repertoires to cope with a wide range of survival pressures, including oxidative stress, shaped by their unique ecological niches and evolutionary trajectories (Zhu et al., 2022).

Given the established association between ROS accumulation and skin photoaging, amphibian-derived AOPs represent a promising biological approach for alleviating UV-induced skin damage (Yin et al., 2019). Produced as part of the innate immune defense of amphibian skin, these peptides exhibit potent ROS-scavenging activity and have demonstrated efficacy in reducing oxidative damage in both *in vitro* and *in vivo* models (Zhu et al., 2024). In contrast to conventional antioxidants, AOPs frequently display greater specificity, stability, and compatibility under physiological conditions, attributes that underscore their value for dermatological applications (Yang et al., 2012). Their capacity to neutralize photoinduced ROS highlights their considerable therapeutic potential in delaying or preventing photoaging, a process with cosmetic and clinical implications, including compromised barrier integrity and heightened vulnerability to dermatological disorders (Scharffetter-Kochanek et al., 2000). Importantly, the identification of amphibian-derived AOPs indicates that these peptides are not merely passive metabolic byproducts, but rather adaptive responses shaped by ecological pressures and evolutionary selection (Barbosa et al., 2018). They exemplify an effective biological strategy for managing environmental oxidative stress and offer novel avenues for therapeutic intervention in human skin aging. Despite this potential, research on AOPs remains underexplored within the broader context of conservation biology. Integrating biochemical investigations of AOPs with amphibian conservation efforts presents an interdisciplinary opportunity for simultaneously promoting biomedical innovation while reinforcing biodiversity

preservation.

This review highlights amphibian-derived AOPs as a unique class of naturally evolved biomolecules with dual relevance, functioning as adaptive defenses against oxidative stress in amphibians and as promising pharmacological agents for mitigating photoaging in humans. Elucidation of their molecular mechanisms and systematic discovery of novel AOPs across diverse amphibian lineages hold the potential to bridge key gaps between comparative skin biology and translational medicine. Ultimately, AOP-based interventions may provide effective approaches for preventing skin aging while simultaneously advancing amphibian conservation and reinforcing the ecological significance of their bioactive chemical defenses.

SKIN AGING AND OXIDATIVE STRESS

What is ROS?

Oxygen is essential for sustaining life, yet it also poses certain challenges. Aerobic oxidation, a continuous process in cellular respiration and energy metabolism, inevitably generates significant ROS as byproducts of electron transfer. The concept of the "free radical", first introduced by Guyton de Morveau in 1786, describes molecules containing one or more unpaired electrons that can exist independently, with each unpaired electron residing in its own orbital (Di Meo & Venditti, 2020). These species are highly reactive and unstable, and readily attack biological macromolecules such as lipids, proteins, and nucleic acids. Despite their deleterious effects at high levels, free radical formation is an unavoidable outcome of aerobic metabolism (Lushchak, 2014). By the mid-1970s, it became evident that non-radical compounds, such as hydrogen peroxide (H_2O_2), also function as potent oxidants and participate in free radical reactions (Di Meo & Venditti, 2020). This finding led to the introduction of the broader term "reactive oxygen species", encompassing both radical and non-radical oxygen-containing intermediates. These include H_2O_2, superoxide anion ($O_2^{\bullet-}$), hydroxyl radical (•OH), alkoxy radical (RO•), peroxy radical (ROO•), peroxynitrite (ONOO•), and nitric oxide (NO•) (Table 1). Consequently, the terms "free radicals" and "ROS" are often used interchangeably (Zhu et al., 2024).

Among the diverse ROS generated in biological systems, $O_2^{\bullet-}$ plays a central role as a precursor in formation of other ROS. $O_2^{\bullet-}$, a one-electron reduction product of molecular oxygen, is produced primarily in mitochondrial respiratory chain complexes I and III (Bouayed & Bohn, 2010; Rammal et al., 2010; Valko et al., 2007). SOD, a homodimeric enzyme localized in the cytoplasm, mitochondria, and nucleus, catalyzes the dismutation of $O_2^{\bullet-}$ into molecular oxygen (O_2) and H_2O_2 via the reaction $2O_2^{\bullet-}+2H^+\rightarrow O_2+H_2O_2$ (Fridovich, 1986; Halliwell, 1996; Kinuta et al., 1989). This enzymatic process plays a vital role in protecting cells from ROS-induced cellular injury (Fransen et al., 2012).

H_2O_2, formed through the two-electron reduction of molecular oxygen, functions as a relatively stable oxidant with a half-life of approximately 1^{-5} seconds. It is continuously generated as a byproduct of oxidative metabolism (Miller & Sadeh, 2014). Although less reactive than many radicals, H_2O_2 can participate in the Fenton reaction by reacting with ferrous iron (Fe^{2+}) to generate highly reactive •OH ($Fe^{2+}+H_2O_2\rightarrow Fe^{3+}+\bullet OH+OH^-$) (Schreck & Baeuerle, 1994; Sen & Packer, 1996). Much of the H_2O_2 generated in peroxisomes diffuses into the cytosol, where it is efficiently decomposed by CAT into water and oxygen ($2H_2O_2\rightarrow 2H_2O+O_2$). CAT, a homotetrameric heme-containing enzyme highly abundant in mammalian peroxisomes, particularly in the liver, prevents toxic H_2O_2 accumulation and inhibits •OH formation via the Fenton pathway (Schreck & Baeuerle, 1994; Sen & Packer, 1996).

The •OH radical, generated by electron loss from hydroxide (OH^-), is the most reactive ROS, with a half-life of approximately 1^{-9} seconds. As a result, •OH reacts almost immediately at the site of its formation (Diplock et al., 1998). Urocanic acid (UCA), a histidine metabolite enriched in mammalian skin and secretions, is a notable •OH scavenger (Safer et al., 2007). Upon UV irradiation, *trans*-UCA undergoes photoisomerization to *cis*-UCA both *in vivo* and *in vitro*, with the latter form exhibiting immunosuppressive activity. Through these properties, UCA contributes to photoprotection and oxidative stress defense in skin (Kammeyer & Luiten, 2015).

NO• is an important signaling molecule involved in diverse

Table 1 Chemical properties of common ROS produced in biological systems[a]

ROS	Chemical formula	Chemical reactivity
Hydrogen peroxide	H_2O_2	H_2O_2 is relatively unreactive with most biomolecules, exhibits moderate stability with a half-life of approximately 1^{-5} seconds, and persists longer in the cellular environment. However, it has very low membrane permeability.
Superoxide anion	$O_2^{\bullet-}$	$O_2^{\bullet-}$ exhibits selective reactivity and does not readily attack biological macromolecules. It has a very short half-life of approximately 10^{-6} seconds and demonstrates low membrane permeability.
Hydroxyl radical	•OH	•OH is extremely short-lived, with a half-life of approximately 10^{-9} seconds. It exhibits reactivity almost immediately at the site of its generation. It also has very low membrane permeability.
Peroxynitrite	ONOO•	ONOO• directly reacts with thiol groups and transition metal centers. It has a biological half-life of approximately 1 second and exhibits very low membrane permeability.
Nitric oxide	NO•	NO• is an important cellular signaling molecule, with both physiological and pathological functions, and is involved in various metabolic regulatory processes. It rapidly reacts with $O_2^{\bullet-}$ to form ONOO• and has a half-life of less than 1 second, with very high membrane permeability.
Carbonate radical anion	$CO_3^{\bullet-}$	$CO_3^{\bullet-}$ is fairly reactive and can oxidize guanine in DNA, as well as amino acids such as cysteine, tyrosine, and tryptophan.
Hypochlorous acid	HOCl	HOCl is a powerful oxidant that primarily reacts with methionine and thiol groups.
Hypobromous acid	HOBr	HOBr reacts with amines to form secondary chloramines and bromamines, which possess significant oxidative capacity.
Singlet oxygen	$^1O_2$	$^1O_2$ is unstable and exhibits high selectivity and reactivity when interacting with organic molecules, leading to harmful effects on cells.
Nitrogen dioxide radical	NO_2 •	NO_2 • is a major air pollutant that undergoes addition reactions, resulting in the formation of nitrated compounds with radicals derived from lipids, tryptophan, tyrosine, and DNA bases.

[a]: This table was modified from Zuo et al. (2015).

physiological and pathological processes, including metabolic regulation (Katsumi et al., 2007). While essential at controlled levels, excessive NO• can become cytotoxic. NO• readily reacts with $O_2^{\bullet -}$ to form ONOO • through the reaction NO • +$O_2^{\bullet -}$→ ONOO •. As a highly reactive oxidant, NO • can damage biological macromolecules, disrupt protein synthesis, and induce lipid peroxidation. Peroxiredoxins, a family of thiol-dependent peroxidases, can detoxify ONOO• by reducing it to nitrite, thereby limiting oxidative injury (Beckman, 1996; Lowenstein et al., 1994).

Lipids represent key targets of oxidative attack, particularly by •OH and ONOO•. Lipid peroxidation initiates chain reactions leading to formation of ROO •, which subsequently generates RO • and lipid hydroperoxides (ROOH). These processes compromise membrane architecture, alter membrane fluidity and permeability, and disrupt normal cellular functions of DNA and proteins (Esterbauer et al., 1992; Reaven & Witztum, 1996). To counteract these effects, most biological tissues express glutathione peroxidase (GSH-Px), an enzyme that catalyzes the reduction of both H_2O_2 and lipid hydroperoxides using GSH as a substrate, through the reactions H_2O_2+2GSH →2H_2O+GSSG and ROOH+2GSH→ROH+H_2O+GSSG (Elias et al., 2008).

What is oxidative stress?

Research on ROS in biological systems remains both dynamic and challenging due to their intrinsic chemical properties and context-dependent functions. First, ROS are short-lived and highly reactive, which complicates accurate detection and quantification in living systems. Second, their biological impact is determined not only by concentration but also by subcellular localization, cell type, developmental stage, and environmental context. Third, the same ROS can function as a signaling molecule at low concentrations while inducing oxidative damage to nucleic acids, proteins, and lipids at higher levels. Furthermore, the balance between ROS production, antioxidant defenses, and downstream signaling cascades introduces additional layers of regulation that remain incompletely understood (Bodega et al., 2019). Under physiological conditions, ROS function as important modulators of redox signaling by interacting with defined molecular targets, thereby regulating diverse processes, including calcium homeostasis, embryonic development, autophagy, apoptosis, and cell proliferation. However, when ROS accumulate excessively, redox homeostasis collapses, leading to oxidative stress and widespread cellular dysfunction (Zuo et al., 2015).

The concept of oxidative stress was first defined in 1990 (Sohal & Allen, 1990). In living organisms, ROS are considered potent molecular disruptors. Under normal conditions, tightly regulated cellular systems maintain ROS at steady-state concentrations, supported by endogenous antioxidants that detoxify excess ROS by converting them into less reactive products (Apel & Hirt, 2004; D'Autréaux & Toledano, 2007; Sohal & Allen, 1990). However, disruption of this balance results in oxidative stress, which damages cellular macromolecules and perturbs normal physiology. Oxidative stress contributes to a wide spectrum of disorders, including skin photoaging, diabetes, neurodegeneration, cardiovascular disease, and cancer. In the skin, oxidative stress is particularly significant, driving DNA, protein, and lipid damage that underlies photoaging and other pathologies (Chiorcea-Paquim, 2022; Zhou et al., 2021). DNA is a major target of ROS. Interactions with purines and pyrimidines generate diverse oxidative lesions. The highly reactive •OH radical reacts with pyrimidines to form cytosine glycol and thymine glycol. Cytosine glycol can undergo deamination to yield uracil glycol, 5-hydroxyuracil, and 5-hydroxycytosine (Cooke et al., 2003). Among the four DNA bases, guanine is the most susceptible to ROS-induced oxidation. Oxidation of guanine leads to the guanine radical cation (G^+), which reacts with •OH to form 8-oxo-7,8-dihydroguanine (8-oxoG) (Urbaniak et al., 2020). Guanine also reacts with $O_2^{\bullet -}$ and NO• to generate 8-nitroguanine (Zuo et al., 2015). Oxidative guanine derivatives such as 8-hydroxy-2'-deoxyguanosine (8-OHdG) and its tautomerized form 8-oxodG are widely used as biomarkers of oxidative stress (Urbaniak et al., 2020). Proteins are equally susceptible. Oxidative stress induces structural and functional modifications, including denaturation, fragmentation, cross-linking, and post-translational alterations. Aromatic and sulfur-containing amino acids are preferential targets (Zuo et al., 2015). Their modification leads to the generation of protein carbonyls, 3-nitrotyrosine (3-NO-Tyr), and advanced oxidation protein products (Marrocco et al., 2017). Protein carbonyl groups form when ROS attack amino acid side chains. Elevated blood carbonyl levels and urinary excretion of 8-OHdG have been documented following aerobic exercise (Urso & Clarkson, 2003). Such oxidative changes impair protein function, destabilize enzymes, and increase susceptibility to proteolysis, thereby disrupting cellular metabolism and promoting disease (Zuo et al., 2015). ROS interact with macromolecular components of biological membranes, such as phospholipids and polyunsaturated fatty acids, leading to the formation of lipid peroxidation products (Elias et al., 2008). The degradation of fatty acids during this process produces hydrocarbon gases and aldehydes. Lipid peroxidation induces alterations in the fluidity and permeability of cell membranes, ultimately leading to changes in cellular structure and function (Radak et al., 2011). Common biomarkers used to assess lipid peroxidation include malondialdehyde (MDA), isoprostanes (F2-IsoPs), lipid hydroperoxides, conjugated dienes, expired pentane, and 4-hydroxynonenal (Urso & Clarkson, 2003).

Oxidative stress and skin aging

The rapid expansion of aging populations in the 21st century has made the biological and clinical consequences of aging increasingly significant. Among visible indicators of aging, the skin is particularly prominent, exhibiting changes such as hyperpigmentation, laxity, and wrinkling (Jenkins, 2002). Skin condition strongly influences perceived age and overall appearance, and in many societies youthfulness is closely linked to attractiveness and vitality. This has driven substantial investment of time, effort, and resources into strategies aimed at preserving skin health and delaying visible deterioration (Kammeyer & Luiten, 2015). As the largest organ and outermost barrier of the body, the skin is continuously exposed to endogenous and environmental challenges that contribute to aging. Skin aging is broadly categorized into intrinsic, or chronological, aging and extrinsic, or environmentally driven, aging (Gu et al., 2020). Beyond cosmetic changes, skin aging impairs physiological functions, compromises barrier integrity, and increases susceptibility to dermatological disorders and malignancies (Hashizume, 2004).

Among extrinsic drivers, UV radiation plays a critical role in accelerating cutaneous aging through photoaging. This process, observed in humans and other animals subjected to chronic UV exposure, involves complex molecular and

structural alterations, including oxidative stress, inflammation, and extracellular matrix (ECM) degradation, that undermine skin resilience (Gu et al., 2020; Kammeyer & Luiten, 2015). Comprehensive investigation of photoaging mechanisms is required in both humans and non-human animals, as each system provides complementary insights. Research on human skin provides clinically relevant knowledge that clarifies the cellular and molecular basis of photoaging, while studies in diverse animal species, particularly under natural environmental conditions, can reveal conserved pathways of UV-induced damage as well as lineage-specific protective adaptations.

Prolonged UV exposure significantly increases the risk of skin photoaging. This section outlines the central role of UV radiation and ROS in skin aging and highlights the mechanistic connection between them (Farage et al., 2008; Landau, 2007). It is widely accepted that both direct photochemical injury and indirect ROS-mediated damage contribute to the cumulative deterioration of skin structure and function (Bernhard et al., 2007; Farage et al., 2008). ROS generated by UV irradiation accelerate oxidative modification of DNA, proteins, and lipids, amplifying the deleterious effects of sunlight on the skin (Dunaway et al., 2018). Regulation of ROS levels is therefore fundamental to the maintenance of skin homeostasis and protection from oxidative injury. A detailed understanding of the molecular pathways that govern both intrinsic aging and photoaging will be critical for the development of targeted interventions to delay skin deterioration, reduce disease susceptibility, and clarify evolutionary adaptations to environmental stressors such as UV radiation.

Skin structure and function

The skin is a highly specialized, multifunctional tissue that envelops the vertebrate body, establishing a vital interface with the external environment (Gu et al., 2020). As the largest organ in most vertebrate species, it fulfills essential physiological roles, including protection, thermoregulation, metabolism, sensory perception, and systemic homeostasis (Lephart, 2016). Acting as the primary barrier, the skin protects the organism from physical, chemical, and microbial insults while simultaneously supporting broader regulatory processes across taxa (Dunaway et al., 2018).

In mammals, the skin is organized into three principal layers: the epidermis, dermis, and subcutaneous tissue (Baek & Lee, 2016; Eckhart & Zeeuwen, 2018). It also contains various appendages, including hair, nails, sweat glands, and sebaceous glands, which collectively enhance protective, regulatory, and sensory functions (Rabe et al., 2006; Wang et al., 2019). The epidermis, the outermost barrier, consists of stratified layers—the stratum corneum, granular, spinous, and basal layers—reflecting progressive stages of keratinocyte differentiation from superficial to deep (Scharffetter-Kochanek et al., 2000). Beneath the epidermis, the dermis provides mechanical strength and elasticity, serving as the structural scaffold of the skin. It is primarily composed of fibroblasts embedded in an ECM enriched with collagen and elastin fibers, glycosaminoglycans (GAGs), proteoglycans (PGs), and specialized macromolecules such as fibronectin, fibrillin, laminin, and hyaluronic acid (Gu et al., 2020; Kammeyer & Luiten, 2015).

Although architectural and molecular features vary among vertebrate clades, the fundamental functions of the skin as a dynamic barrier for defense, environmental sensing, and physiological regulation are highly conserved (Rabe et al., 2006). Comparative and integrative perspectives on skin biology not only illuminate the evolutionary trajectory of vertebrate integumentary systems but also reveal diverse adaptive strategies that organisms employ to maintain homeostasis under changing environmental conditions.

Intrinsic aging

Intrinsic aging manifests as progressive thinning of subcutaneous fat, increased dryness and fragility of the skin, and the gradual formation of wrinkles. This process is primarily regulated by genetic determinants and affects the entire integument, although its clinical presentation varies across anatomical regions (Scharffetter-Kochanek et al., 2000). At the cellular level, intrinsic aging reflects the cumulative decline in the proliferative capacity of keratinocytes, reduced renewal of epidermal stem cell populations, and progressive degeneration of connective tissue architecture (Gu et al., 2020).

ROS are widely recognized as primary drivers of intrinsic skin aging. An estimated 1.5%–5.0% of oxygen consumed in cutaneous metabolism is converted into ROS via various metabolic pathways (Poljšak et al., 2012). Keratinocytes and fibroblasts serve as the main sources of these reactive species in the skin (Dimri et al., 1995). With advancing age, skin exhibits a reduced capacity for cellular replication and an increased proportion of senescent, non-dividing cells (Applegate et al., 1985; Giangreco et al., 2008; Lowry, 2020; Rittié & Fisher, 2015). Concurrently, dermal ECM degradation accelerates and fibroblast density declines (Man et al., 2009). ROS-driven DNA damage in genes encoding elastin and collagen contributes to diminished synthesis of these structural proteins, weakening the dermal matrix (Gu et al., 2020). Beyond direct genetic injury, ROS also modulate gene expression by up-regulating enzymes and activating signaling cascades implicated in the molecular progression of skin aging (Millis et al., 1992).

Extrinsic aging

Extrinsic aging is driven by environmental oxidative stressors, including UV radiation and cigarette smoke exposure. Among these, UV-induced photoaging accounts for approximately 80% of facial aging (Friedman, 2005). Once initiated, photoaging triggers progressive degradation of collagen fibers and leads to clinical features distinct from intrinsic aging. Extrinsically aged skin exhibits profound loss of elasticity, coarse or leathery texture, hyperpigmentation, impaired wound healing, and deep wrinkling, whereas intrinsically aged skin typically appears thinner and smoother, lacking the pronounced textural changes associated with chronic sun exposure (Scharffetter-Kochanek et al., 2000). Photoaging is a complex biological process characterized by cumulative structural damage to dermal connective tissue (Krieg et al., 1988). The severity of UV-induced injury is influenced by multiple factors, including the extent of sun-exposed skin, altitude, and the solar zenith angle, with highly exposed areas such as the face, hands, and legs particularly vulnerable (Freedberg, 1995). Both direct and indirect mechanisms contribute to photodamage.

Ultraviolet A (UVA) constitutes more than 80% of daily solar UV radiation, as it penetrates the atmosphere largely unabsorbed (Dunaway et al., 2018). Due to its limited absorption by epidermal components, UVA penetrates deeply, reaching the dermis and in some cases extending to the subcutaneous layer. This high penetrative capacity makes the ECM highly susceptible to UVA-induced injury (Kammeyer & Luiten, 2015). Cellular chromophores absorb UVA and undergo photochemical reactions that generate ROS, initiate covalent

bond cleavage, and engage in electron transfer and hydrogen abstraction reactions, collectively accelerating biomolecular damage and skin aging (Svobodová et al., 2012; Pattison & Davies, 2006). Ultraviolet B (UVB), although less abundant, is more biologically potent. It is primarily absorbed within the stratum corneum, but attenuated levels can penetrate the viable epidermis, where they induce significant biological damage. Epidermal components such as NADH, NADPH, aromatic amino acids, and lipids are the primary absorbers of UVB (Svobodová et al., 2012; Young, 1997). Despite the significant role of UVA, UVB is considered the primary contributor to sunburn and a major driver of photoaging. Notably, experimental evidence indicates that UVB is approximately 1 000 times more effective than UVA in inducing erythema (Diffey, 2002).

UV radiation targets DNA, RNA, lipids, and proteins, initiating molecular alterations that culminate in photodamage. Among UV wavelengths, UVB exerts the strongest impact on DNA, inducing base-specific lesions that drive mutagenesis, impair keratinocyte proliferation and differentiation, and disrupt apoptosis (Hussein, 2005). Genomic instability and DNA damage are widely recognized as key contributors to the aging process (Wallace et al., 1998). Mitochondrial DNA (mtDNA), with a mutation rate of approximately 20 times higher than nuclear DNA, is particularly vulnerable. Mutations in mtDNA promote mitochondrial dysfunction, elevate oxidative stress, and generate additional mtDNA lesions, thereby creating a vicious cycle that accelerates cellular aging (Scharffetter-Kochanek et al., 2000; Wallace, 1992). Singlet oxygen ($^1O_2$) generated by UVA has been shown to induce mtDNA deletions, which accumulate more frequently in photoaged skin (Scharffetter-Kochanek et al., 2000). Without effective repair, DNA lesions can progress to chronic tissue injury and malignant transformation. UVB also damages RNA, leading to impaired protein synthesis in normal cells (Brash et al., 1991). In addition, absorption of UVB by proteins promotes cellular component degradation and triggers oxidative stress. ROS generated directly or through UV-activated photosensitizers further exacerbate protein damage and modification, and the progressive accumulation of oxidatively altered proteins plays a major role in the advancement of skin aging (Pattison & Davies, 2006; Watson et al., 2014).

Beyond direct biomolecular injury, UV radiation accelerates photoaging through indirect pathways mediated by ROS. Elevated ROS levels are widely regarded as principal effectors of the deleterious outcomes of UVA and UVB exposure (Lephart, 2016; Rabe et al., 2006). While low concentrations of ROS contribute to redox signaling and cellular homeostasis, excess levels overwhelm endogenous antioxidant defenses and induce oxidative damage (Wang et al., 2019). The cumulative impact is evident in the pronounced alterations observed in photoaged skin, affecting both cellular components and the ECM of connective tissue (Kammeyer & Luiten, 2015; Scharffetter-Kochanek et al., 2000). Collagen, elastin, and GAGs are fundamental constituents of the dermal ECM that collectively maintain tissue skin structure, elasticity, and tensile strength (Oxlund & Andreassen, 1980). Collagen and elastin levels typically peak around the age of 30 but decline thereafter (Lephart, 2016), with photoaging accelerating both their quantitative loss and qualitative modification. These alterations arise from enzymatic degradation, dysregulation of signaling pathways, and transcriptional changes (Kohl et al., 2011; Lowry, 2020; Seite et al., 2006). Collagen, the predominant structural protein of the dermis, is profoundly reduced in photoaged skin. Type I and type III collagens secreted by fibroblasts form the essential scaffold that preserves dermal stability and skin appearance (Oxlund & Andreassen, 1980). While UV radiation can directly degrade and modify collagen, indirect mechanisms mediated by ROS are regarded as the dominant contributors to connective tissue deterioration (Hideg et al., 2013).

ROS stimulate the expression of matrix metalloproteinases (MMPs), including MMP-1 (collagenase), MMP-2 (92 kDa gelatinase), MMP-3 (stromelysin), and MMP-9 (72 kDa gelatinase), which are central mediators of collagen degradation. These enzymes contribute to both physiological remodeling and pathological degeneration of the skin by targeting basement membrane proteins and connective tissue components (Birkedal-Hansen, 1987). The induction of MMP-1, MMP-2, and MMP-3 by UVA irradiation is largely mediated by H_2O_2 and $^1O_2$, whereas •OH and lipid peroxidation intermediates drive the induction of MMP-1 and MMP-3 under UVB exposure (Birkedal-Hansen, 1987; Krieg et al., 1988). *In vivo* studies have shown that topical application of retinoic acid, a derivative of vitamin A, prior to UVB exposure can effectively inhibit MMP production (Scharffetter-Kochanek et al., 2000). In addition to stimulating MMPs, ROS-derived oxidative products activate multiple intracellular signaling pathways. Oxidative inactivation of receptor-type protein tyrosine phosphatase κ (RPTP-κ) abolishes its inhibitory effect on tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and epidermal growth factor (EGF) receptors, which are expressed on fibroblasts and keratinocytes and belong to the G protein-coupled receptor family (Xu et al., 2006). This loss of regulation leads to the activation of mitogen-activated protein kinases (MAPKs), including p38 MAPK, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK), some of which can also be directly activated by ROS (Ashworth et al., 1999; Fisher et al., 1998). These kinases promote the assembly of transcription factor complexes such as activator protein-1 (AP-1) and nuclear factor κB (NF-κB). In addition to inducing MMP expression, AP-1 and NF-κB modulate the transcription of tissue inhibitors of metalloproteinases (TIMPs) (Hall et al., 2003). UV-irradiated fibroblasts produce significantly more MMPs than TIMPs, resulting in collagen degradation (Lahmann et al., 2001; Oh et al., 2004). Activated NF-κB also enhances the transcription of pro-inflammatory cytokines, including TNF-α, IL-1, and vascular endothelial growth factor (VEGF), which recruit inflammatory cells like neutrophils. These cells release MMP8 (neutrophil collagenase), amplifying collagen breakdown (Sárdy, 2009). Stimulation of inflammatory cells by cytokines activates NADPH oxidase (NOX), generating additional ROS and exacerbating collagen degradation (Kammeyer & Luiten, 2015). Moreover, NF-κB activates cyclooxygenase-2 (COX-2), which catalyzes the conversion of arachidonic acid to prostaglandin E2 (PGE2). Elevated PGE2 is associated with localized vasodilation, pain, and swelling, and is frequently observed in squamous and basal cell carcinomas (Dunaway et al., 2018). Concurrently, AP-1 suppresses transcription of type I and type III procollagen genes, further diminishing collagen synthesis (Quan et al., 2004; Talwar et al., 1995). Collectively, these pathways establish a multifaceted role for ROS in driving connective tissue deterioration and accelerating skin aging (Figure 1).

Elastin is the primary component of elastic fibers and is a key constituent of connective tissue architecture (Naylor et al., 2011). A defining feature of photoaged skin is the accumulation

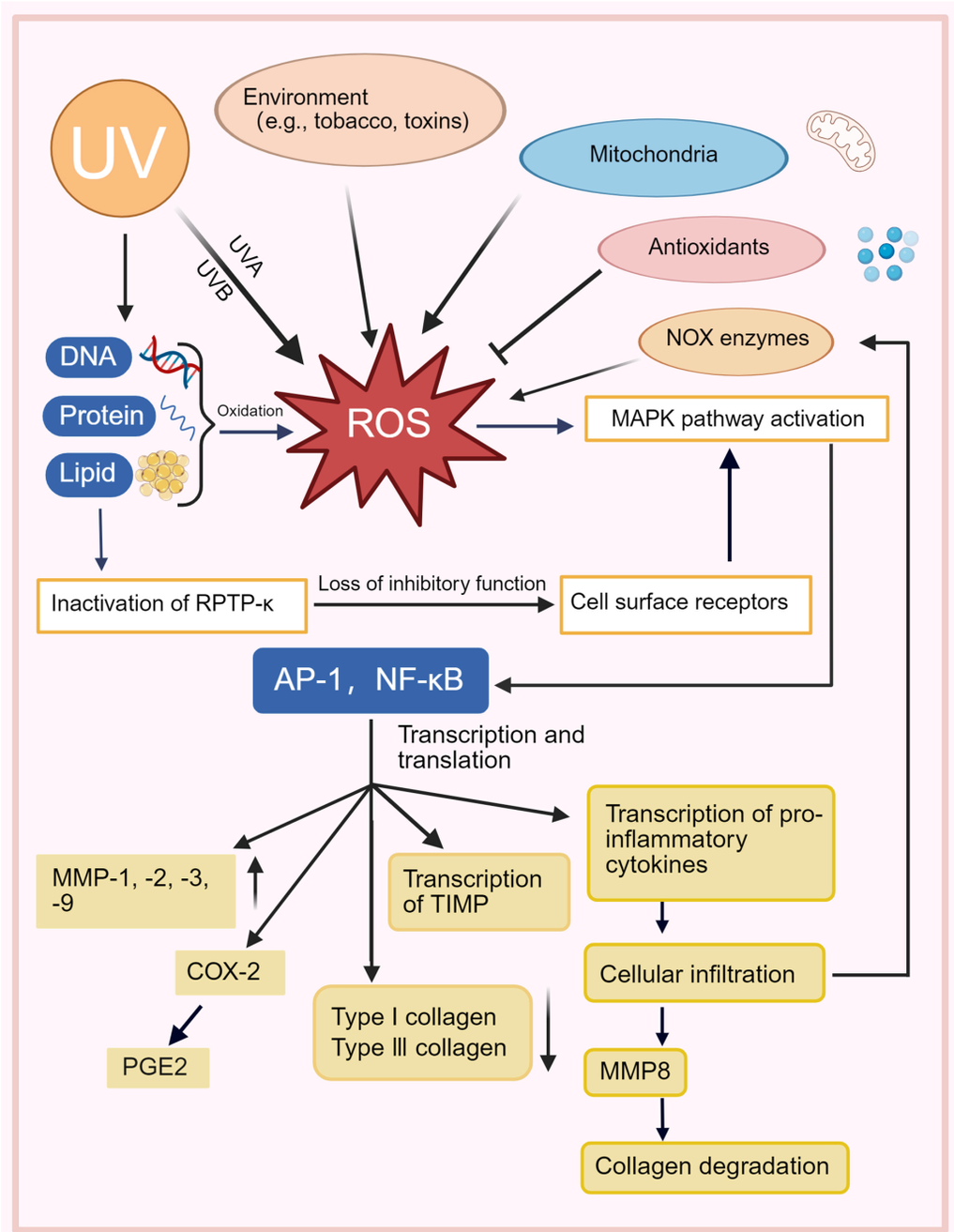

Figure 1 Mechanistic overview of ROS-mediated skin photoaging triggered by ultraviolet (UV) exposure and environmental factors

UV radiation and environmental stressors (e.g., tobacco, toxins) promote the generation of reactive oxygen species (ROS) both directly and via mitochondrial and NADPH oxidase (NOX) pathways. Excessive ROS accumulation oxidizes DNA, proteins, and lipids, inactivates receptor protein–tyrosine phosphatase κ (RPTP-κ), and activates mitogen-activated protein kinase (MAPK) pathways through cell surface receptors. These events lead to the activation of transcription factors AP-1 and NF-κB, which induce the transcription of matrix metalloproteinases (MMPs), pro-inflammatory cytokines, and cyclooxygenase-2 (COX-2), contributing to extracellular matrix (ECM) degradation. Inflammatory cytokines promote immune cell infiltration and further MMP release. Prostaglandin E2 (PGE2) generated by COX-2 causes inflammation. Although antioxidants counteract ROS, their imbalance results in structural ECM alterations characteristic of photoaged skin. The figure was created in BioRender.com.

of dysfunctional and disorganized elastin, fibrillin, and elastin-degrading products within the deep dermis (Kawaguchi et al., 1997). Both UV radiation and ROS contribute to the aberrant formation and degradation of elastin. ROS and infiltrating inflammatory cells can activate the intracellular MAPK pathway, leading to the release of elastin-degrading enzymes, including MMP3 (stromelysin-1) and MMP9 (gelatinase B) (Starcher & Conrad, 1995). Additionally, ROS interfere with elastin synthesis and secretion while also modulating transcriptional programs in dermal fibroblasts, further reducing the production of structurally intact elastin (Kawaguchi et al., 1997; Lavker et al., 1995). GAGs, a structurally heterogeneous group of unbranched polysaccharides located within the ECM and cell surfaces, are integral components of connective tissue, contributing to mechanical stability and the maintenance of dermal hydration due to their hygroscopic properties (Kjellén & Lindahl, 1991). Long-term UVB exposure in mouse models has been shown to deplete dermal GAGs and induce profound

structural changes in the ECM, effects that are compounded by ROS-mediated oxidative injury to molecular scaffolds (Tammi et al., 2005).

Under physiological conditions, ROS production and elimination are maintained in equilibrium. However, oxidative stress arises when ROS generation exceeds antioxidant capacity in response to internal or external environmental factors, such as UV radiation or hyperglycemia. AOPs, naturally occurring or synthetically engineered, act as effective modulators of redox balance by neutralizing ROS and other pro-oxidants. Both natural and synthetic AOPs have demonstrated robust ROS-scavenging activity (Zou et al., 2016). Several AOPs, such as carnosine and GSH, are currently under clinical evaluation for the treatment of oxidative stress-related disorders. Their superior antioxidant capacity, often enhanced when combined with complementary antioxidant or tissue-repairing components, has led to incorporation into pharmaceutical formulations designed for the treatment of photodamaged skin. In addition, AOPs are used as dietary supplements and nutraceuticals because of their bioavailability and participation in various metabolic pathways (Elias et al., 2008). Amphibians represent an especially rich source of AOPs due to their permeable skin and constant exposure to environmental stressors. Their skin secretions contain diverse bioactive peptides that contribute to barrier integrity and defense against oxidative and environmental stress. A growing body of evidence highlights the therapeutic potential of amphibian-derived AOPs as drug candidates for the prevention or attenuation of UV-induced photoaging and oxidative stress (Barbosa et al., 2018). Consequently, the isolation and purification of amphibian-derived AOPs has become a rapidly expanding research frontier in the development of novel interventions against skin photoaging.

AMPHIBIANS AND AOPS

ROS are generated primarily through oxygen metabolism and UV radiation. Amphibians, due to their ecological and physical traits, are particularly vulnerable to oxidative stress. Despite this susceptibility, amphibian skin exhibits remarkable capacities for self-repair and regulation under oxidative stress (Feng et al., 2021). Excessive ROS generally promote biomolecular injury and drive a wide spectrum of disorders, yet amphibian-derived AOPs demonstrate potent protective effects by neutralizing or attenuating oxidative damage. These bioactive molecules have therefore emerged as a prominent subject of biomedical research. This section will explore the relationship between amphibians, oxidative stress, and AOPs.

Amphibian class

Amphibians represent one of the most ancient groups of vertebrates and mark a critical evolutionary transition from aquatic to terrestrial life. As the earliest vertebrates to colonize land, they have attracted sustained scientific attention. Frogs, in particular, have long served as both biologically compelling organisms and as versatile experimental models. During the 18th and 19th centuries, amphibian-based research flourished in the fields of taxonomy, anatomy, and physiology, while the 20th century witnessed a proliferation of studies in developmental biology, embryology, immunology, and toxicology, accompanied by growing interest in their natural history and ecology (Forzán et al., 2017). Amphibians were the first vertebrates to evolve a keratinized epidermis, enabling survival in both aquatic and terrestrial environments. However, their skin remains highly permeable and is continuously exposed to environmental stressors such as UV radiation, microbial colonization, and physical injury. Beyond their physiological distinctiveness, amphibians play a critical role in maintaining ecosystem biodiversity and function. Given their sensitivity to environmental fluctuations, they are widely regarded as indicator species for ecosystem health. Consequently, amphibian conservation is essential for safeguarding the long-term stability and resilience of global ecosystems (Iyer & Briggman, 2021; Wake & Koo, 2018).

Amphibians are a taxonomically diverse vertebrate lineage comprising three orders, 77 families, and approximately 8 885 recognized extant species (as of May 2025, AmphibiaWeb: https://amphibiaweb.org/). Amphibians are distributed on every continent except Antarctica and are classified into Gymnophiona (caecilians), Caudata (salamanders and newts), and Anura (frogs and toads) (Duellman & Trueb, 1994) (see Supplementary Table S1 for taxonomic details). The three groups are morphologically distinct and easily distinguishable, yet all share a common feature: moist skin that functions as a respiratory organ and secretes an array of bioactive compounds, many of which are toxic to potential predators (Wake & Koo, 2018). Vividly colored poisonous frogs exemplify this adaptation, displaying aposematic coloration and releasing toxic alkaloids or other metabolites through specialized cutaneous glands, with many of these substances acquired from diet or influenced by environmental conditions (Forzán et al., 2017).

In addition to their ecological diversity, amphibians have long served as valuable experimental models in biology. The tetraploid African clawed frog (*Xenopus laevis*) and its diploid relative *X. tropicalis* remain indispensable in developmental and cell biology studies, while the axolotl (*Ambystoma mexicanum*) provides an unparalleled system for investigating limb and tail regeneration (Wake & Koo, 2018). Amphibians are especially abundant in tropical montane habitats, where they contribute to ecological stability, insect population control, and food webs, while also providing cultural and aesthetic value (Burrow & Maerz, 2022; Yan et al., 2016). The distinctive physiology, ecological niches, and environmental sensitivity of amphibians have driven the evolution of complex chemical defenses, many of which hold potential for the treatment of diverse human diseases. Amphibian skin, which serves as a multifunctional organ essential for survival, exhibits extraordinary chemical diversity, with more than 100 000 bioactive molecules identified to date (Demori et al., 2019). Among these, bioactive peptides have attracted the most extensive research attention and can be broadly categorized into diverse functional groups, including myotropical peptides, opioid peptides, corticotropin-releasing peptides, angiotensins, protease inhibitor peptides, neuropeptides, AOPs, lectins, insulin-releasing peptides, mast cell degradation/histamine-releasing peptides, wound-healing peptides, immunomodulatory peptides, neuronal nitric oxide synthase inhibitors, AMPs, antiviral peptides, antitumor peptides, antiparasitic peptides, pheromone peptides, and granains (Xu & Lai, 2015). The distinctive biosynthetic pathways and functional breadth of these secretions provide an exceptional resource for biomedical innovation, with promising clinical applications against major global health challenges such as cancer, HIV, and drug-resistant *Staphylococcus aureus* (Xu & Lai, 2015; You et al., 2009).

Amphibians constitute a taxonomically diverse and globally

distributed vertebrate group that fulfills multiple ecological, economic, and cultural roles. As integral components of ecological communities, they contribute to biodiversity maintenance, function as food sources for higher trophic levels, provide raw materials for trade and traditional medicine, and hold symbolic significance in cultural belief systems. They also serve practical roles in biological control strategies, regulating agricultural pests and disease vectors (Valencia-Aguilar et al., 2013). Positioned at critical trophic levels, amphibians link energy pathways within food webs. By preying on invertebrates and small vertebrates, they can indirectly influence processes such as pollination and seed dispersal, while simultaneously providing a high-quality food source for numerous taxa (Hocking & Babbitt, 2014). Their ecological roles further extend to nutrient cycling and energy transfer across terrestrial and aquatic systems. For instance, the coquí frog (*Eleutherodactylus coqui*) enhances soil nutrient availability through waste deposition and dispersal during terrestrial migrations, thereby accelerating nutrient turnover in forest ecosystems (Beard et al., 2002). In aquatic environments, tadpoles of *Espadarana prosoblepon* stimulate fungal activity in decomposing leaf litter, promoting nutrient release and recycling (Whiles et al., 2013). The loss of amphibians from freshwater systems has been shown to disrupt primary productivity, alter algal community composition, restructure aquatic food webs, and reduce energy transfer between aquatic and terrestrial habitats through impaired nutrient cycling (Campos et al., 2017).

Compared to other vertebrate groups, amphibians face an exceptionally high risk of extinction, with multiple stressors frequently acting in combination (Brooks & Kindsvater, 2022). These include extreme climatic events, habitat degradation, infectious disease outbreaks, and invasive species (Grant et al., 2016). Approximately 44% of frog species exhibit biphasic life cycles, exposing them to distinct ecological challenges at successive developmental stages (Nolan et al., 2023; Steigerwald et al., 2024). Embryonic and larval stages, typically confined to aquatic or water-saturated environments, experience high mortality rates—often exceeding 90%—due to predation, competition, and environmental variability (Miller et al., 2018). Species that encounter starkly contrasting habitats across life stages frequently rely on environmentally induced phenotypic plasticity, which may generate carryover effects where early-life responses shape subsequent development. Such effects can influence survival, reproduction, and long-term population dynamics, underscoring their importance for understanding amphibian persistence under accelerating global change (Ohmer et al., 2023).

Amphibians are widely regarded as sensitive indicators of ecosystem health due to their reliance on cutaneous respiration and osmoregulation, as well as their high sensitivity to environmental changes in both aquatic and terrestrial habitats (Cordeiro et al., 2024; Hopkins, 2007). The timing and duration of their aquatic and terrestrial life stages determine the nature and severity of stressors encountered, with terrestrial challenges such as UV radiation and extreme temperatures posing substantial risks (González-del-Pliego et al., 2019). Like other organisms, amphibians rely on a suite of biochemical and physiological mechanisms to sustain fitness under biotic and abiotic stress. At elevations of 3 120–4 100 m a.s.l., they endure harsh environmental conditions characterized by low temperatures, prolonged photoperiods, and intense UV radiation. Their permeable skin heightens vulnerability to UVB, which exerts a paradoxical influence: at moderate levels it modulates the neuroendocrine system and supports homeostatic regulation, but in excess it drives overproduction of ROS, leading to photodamage, dermatological disorders, and potentially carcinogenesis (Feng et al., 2022a). These challenges are intensified by climate change and ozone depletion, which further increase UVB levels at high altitudes (Luedtke et al., 2023). The plateau frog (*Rana kukunoris*), an endemic highland species with broad geographic distribution, illustrates population-level divergence in adaptive strategies against UVB stress. High-altitude populations exhibit constitutively dark pigmentation, minimizing reliance on inducible melanogenesis, coupled with enhanced immune capacity, elevated antioxidant enzyme activity, and stable DNA repair processes, conferring resilience to chronic UVB exposure. In contrast, low-altitude populations display more acute responses, including rapid skin darkening, elevated leukocyte counts indicative of immune activation, and biochemical evidence of oxidative damage such as increased MDA accumulation and reduced SOD and CAT activity (Tang et al., 2025). Although environmental UVB regulates important physiological processes, it simultaneously imposes lethal and sublethal constraints across multiple species. Under accelerating global change, elucidating amphibian responses to UVB at molecular, cellular, and systemic levels is essential for predicting vulnerability and informing conservation strategies (Hird et al., 2024). Cold tolerance represents another critical adaptation among amphibians inhabiting high-latitude or high-altitude environments. Species such as the wood frog (*Rana sylvatica*; *Lithobates sylvaticus*) and several Siberian salamanders can survive prolonged freezing, entering states where cryoprotection preserves tissue integrity (Storey & Storey, 2017). However, thawing reintroduces oxygen and triggers reperfusion, elevating ROS levels and creating a risk of oxidative injury. Consequently, antioxidant defense systems have been identified as central to freeze tolerance, particularly in wood frogs (Sinclair et al., 2013). Amphibians are also highly sensitive to aquatic pollutants, including pharmaceutical contaminants. Exposure to these compounds disrupts development and induces cellular and molecular toxicity, with oxidative stress emerging as a central pathogenic mechanism. Several environmentally relevant pharmaceuticals have been shown to induce oxidative stress in species such as *Rhinella arenarum*, *Xenopus laevis*, and *Lithobates catesbeianus*, as demonstrated by *in vivo* studies that report significant perturbations in oxidative biomarkers and elevated tissue damage following exposure (Cardoso-Vera et al., 2024).

The global decline of amphibians continues unabated, with climate change now recognized as a dominant force driving species deterioration (Luedtke et al., 2023). Confronted with simultaneous and interacting threats, the persistence of amphibian populations will likely depend on the integration of diverse conservation measures. While some species can tolerate moderately adverse conditions within artificial wetlands, extreme climatic events can precipitate rapid collapses in adult populations (Ohmer et al., 2023). Habitat restoration and the construction of new breeding sites remain central interventions, as exemplified by efforts to recover populations of the endangered green bell frog (*Litoria aurea*) (Beranek et al., 2022). Conservation effectiveness can be enhanced by maintaining high levels of wetland vegetation cover and preserving habitat connectivity, both of which buffer the impacts of climate change-induced disturbances (Campbell Grant et al.,

2023; Moor et al., 2022). Urban environments present unique challenges, and the development of dedicated amphibian-focused frameworks is essential to counteract habitat degradation and fragmentation in these settings (Lee et al., 2022). Complementary approaches, including captive breeding programs, assisted reproductive technologies, and the establishment of genetic resource biobanks, further contribute to safeguarding amphibian diversity and long-term population viability (Byrne & Silla, 2010).

Amphibian skin

Amphibians represent some of the earliest vertebrates to colonize terrestrial habitats and display remarkable diversity in life history strategies. Many species undergo biphasic development, with an aquatic larval stage followed by a terrestrial or semi-aquatic adult phase. However, this pattern is far from universal. Certain viviparous lineages, such as some caecilians, bypass an aquatic stage entirely (Gower et al., 2008; Kupfer et al., 2004), while others, including most pipid frogs, typhlonectid caecilians, and cryptobranchid salamanders, remain fully aquatic throughout their life cycle (Jones et al., 2022; Laudet, 2011; Sillar et al., 2023). A defining characteristic of amphibians is their highly specialized skin, which distinguishes them from all other vertebrates. Amphibian skin is richly vascularized and functions as a major respiratory surface (Schumacher et al., 1994). It is equipped with an extensive network of specialized glands that secrete compounds essential for hydration and barrier integrity, as well as a wide variety of toxins and bioactive peptides with defensive and regulatory functions (Wake & Koo, 2018). The outer epidermal layer is only slightly keratinized, representing an evolutionary compromise that permits cutaneous respiration while still providing mechanical protection. The evolution of keratinized skin in early amphibians represented a pivotal innovation during the transition from aquatic to terrestrial life (Demori et al., 2019), facilitating resistance to desiccation, mechanical injury, and environmental stress, thereby enabling the successful radiation of tetrapods into diverse terrestrial niches (Xie et al., 2021). As the primary interface with the environment, amphibian skin serves as both barrier and sentinel, providing protection against persistent biological, physical, and chemical threats, including pathogens, extreme temperatures, and UV radiation (Qin et al., 2018). However, its role extends well beyond surface protection, encompassing essential physiological functions such as gas exchange, respiration, osmotic regulation, excretion, reproduction, and, to a lesser extent, thermoregulation. This multifunctionality, coupled with its permeability and repair capacity, underpins the ecological versatility of amphibians and their ability to survive across a broad spectrum of terrestrial and aquatic environments (Yang et al., 2009).

Amphibians alternate between aquatic and terrestrial habitats, exposing their skin to pronounced fluctuations in oxygen availability and UV radiation on a daily basis. Direct sunlight presents a particular challenge, as amphibian skin lacks a protective outer layer and is covered only by a thin cuticle, leaving it highly vulnerable to UV penetration (Demori et al., 2019). These environmental shifts profoundly influence ROS production. Moreover, the constant hydration of amphibian skin in moist or aquatic environments creates favorable conditions for bacterial and fungal colonization. To survive in such unpredictable environments, amphibians rely on a complex interplay of ecophysiological, behavioral, and immunological strategies (Yu et al., 2015). During their evolutionary transition from aquatic to terrestrial life, amphibians developed a range of specialized defense mechanisms to protect their skin from internal and external threats. It is therefore plausible that amphibian skin secretions contain molecular components specifically adapted to mitigate damage caused by ROS and pathogenic organisms.

Central to these defenses is the synthesis, storage, and secretion of peptide-based compounds from granular glands distributed across the skin (Liu et al., 2010). This system not only protects against viral and microbial infections but also yields diverse biomolecules with distinct structures and functions. Extensive research has demonstrated that amphibian skin secretions contain peptides essential for preserving skin integrity and defending against pathogenic and environmental challenges. These peptides display potent antioxidant properties that mitigate UV-induced damage, alongside antimicrobial, wound-healing, and immunomodulatory functions (Xu & Lai, 2015). In addition to deterring microbial pathogens, peptide secretions support survival under harsh environmental conditions and reduce predation risk through toxic or deterrent effects. Among these molecules, AMPs represent one of the most extensively studied groups (Benítez-Prián et al., 2024; Zhu et al., 2022). Research on amphibian skin peptides continues to offer valuable insights into the resilience of these species to extreme environments, particularly in the context of oxidative stress-related diseases. Furthermore, accumulating evidence of their pharmacological efficacy highlights significant potential for human health applications, emphasizing the need for sustained and systematic exploration.

The epidermis of amphibians consists of the stratum corneum, a keratinized layer of flattened cells, and the underlying stratum germinativum, a basal regenerative layer, separated by irregular intercellular spaces (Figure 2). Beneath the epidermis lies the dermis, which is demarcated by collagen fibers extending to the basal membrane. The dermis is organized into two strata: the spongious dermis and the compact dermis (Felsemburgh et al., 2009). Embedded within the dermis are two principal types of specialized secretory glands that underpin cutaneous defense: mucous glands and granular glands, also referred to as poison or serous glands (Demori et al., 2019). Mucous glands secrete highly glycosylated mucins and mucopolysaccharides that constitute the mucosal layer of the skin (Smith et al., 2018). These secretions maintain hydration, reduce evaporative water loss, and act as a physical barrier against pathogenic invasion (Schumacher et al., 1994). In contrast, granular glands generate potent defensive secretions enriched with diverse bioactive compounds, including alkaloids, AMPs, tetrodotoxins, immunoglobulins, steroids, lysozymes, and neuropeptides. The composition of these secretions varies among species, although they consistently play critical roles in host immune defense and protection against both predators and microbial pathogens (Ramsey et al., 2010; Rollins-Smith et al., 2011; Rollins-Smith & Conlon, 2005). Both gland types share a basic architecture consisting of an epithelial cell layer encasing a central secretory zone (Rollins-Smith, 2009). In granular glands, the core is densely packed with peptide granules, surrounded by a myoepithelial cell layer equipped with adrenoreceptors. Stress stimuli such as mechanical injury or irritation trigger the release of epinephrine and norepinephrine, which activate myoepithelial contraction and result in the rapid expulsion of glandular contents (Apponyi et al., 2004). Following secretion, the glands regenerate and replenish their peptide reserves, ensuring

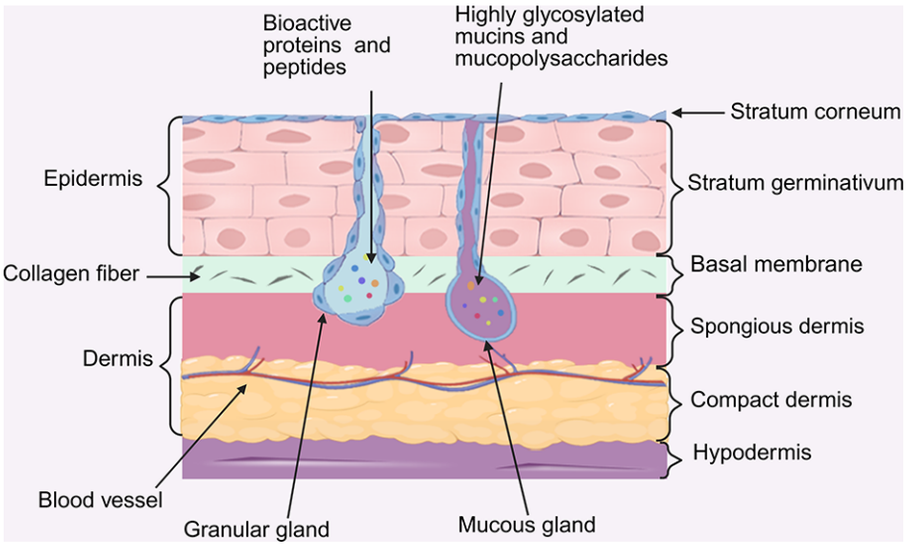

Figure 2 Anatomical structure and functional components of amphibian skin

Amphibian skin consists of two primary layers: the epidermis and dermis. The epidermis includes a superficial stratum corneum, composed of keratinized cells, and an underlying stratum germinativum, a regenerative basal layer, both separated by irregular intercellular spaces. The dermis lies beneath the epidermis and is further subdivided into the spongious dermis and compact dermis. The dermis contains abundant mucous and granular glands, also referred to as serous or poison glands. Mucous glands secrete glycosylated mucins and mucopolysaccharides that help retain skin moisture and form a protective barrier against dehydration and pathogen invasion. Granular glands produce and store various bioactive substances involved in defense. Collagen fibers extend to the basal membrane and delineate the boundary between the epidermis and dermis. This figure was adapted from Demori et al. (2019) and created using BioRender.com.

sustained defensive capacity (Nicolas & Mor, 1995). In addition to glandular secretions, amphibian skin is covered by the mucosome, a dynamic extracellular layer formed by a combination of glandular secretions and a diverse microbiota and their metabolites (Woodhams et al., 2014). Each amphibian species produces a unique repertoire of peptides with well-defined sequences (Rollins-Smith et al., 2011). Since 2015, more than 2 000 peptides have been isolated and characterized from amphibian skin (Lauer et al., 2007; Pask et al., 2012; Xu & Lai, 2015), underscoring the extraordinary biochemical diversity and therapeutic potential of these secretions.

Caecilians, limbless amphibians belonging to the order Gymnophiona, display highly specialized skin architectures that reflect their fossorial adaptations. Distributed across Southeast Asia, Central and South America, and Africa (Jared et al., 2018), they possess a compact skull, a rudimentary visual system, and a pair of sensory tentacles that facilitate navigation in subterranean habitats. Due to their cryptic lifestyle and predominance in tropical regions, caecilians remain one of the least studied vertebrate groups (Antoniazzi et al., 2022). Compared with anurans and salamanders, their skin exhibits various distinctive features. Unlike many amphibians that develop conspicuous macroglands such as the parotid structures used in antipredator defense, Gymnophiona generally lack such externalized glandular accumulations (Mailho-Fontana et al., 2014; Regis-Alves et al., 2017). Instead, granular glands in caecilians are regionally specialized, with marked enlargement and abundance in the posterior body. In *Siphonops annulatus*, for example, glandular clusters occur in the dermis of both head and tail regions (Jared et al., 2018), forming honeycomb-like aggregations encased by collagenous walls, although the external skin surface remains smooth and lacks visible protuberances (Mauricio et al., 2021). Regional differentiation is evident in both morphology and biochemical output. Head-region accumulations are dominated by mucus glands, whereas those in the posterior region are largely composed of poison glands. Comparative analyses have revealed profound compositional differences, with head-derived mucus secretions enriched in lubricating proteins and lipids, while posterior secretions display greater chemical complexity and diversity, consistent with defensive specialization (Jared et al., 2018; Schwartz et al., 2003). These spatially distinct glandular systems align with functional demands imposed by fossoriality (Jared et al., 2018; Mauricio et al., 2021). Anterior mucus macroglands, together with the tapered cranial morphology, secrete viscous compounds that reduce friction and facilitate burrowing through compact soil, enhancing subterranean locomotion. In contrast, the caudal region houses internalized poison glands that release deterrent compounds likely contributing to antipredator defense and preventing intrusion by other organisms into occupied burrows (Mauricio et al., 2021; Sachslehner & Eckhart, 2022).

The complex organization of amphibian skin, encompassing diverse gland types, stratified architecture, and multifunctional secretions, represents a finely tuned system evolved to counteract various environmental challenges. These include microbial invasion, desiccation, predation, and oxidative stress. This multifunctionality highlights the adaptive significance of skin-derived peptides and underscores the value of underexplored lineages such as caecilians for bioprospecting efforts aimed at therapeutic discovery.

Amphibians, oxidative stress, and AOPs

Long-term environmental monitoring has revealed a steady rise in surface-level UV radiation, driven by climate change, anthropogenic activity, and other contributing factors. Elevated UV exposure exerts profound stress on amphibians throughout their life cycle (Dunaway et al., 2018). The larval stages are particularly vulnerable, as UV radiation penetrates aquatic environments and the photochemical degradation of dissolved organic matter, amplifying oxidative stress in freshwater

habitats (Rollins-Smith et al., 2011). Amphibian skin, a multifunctional organ essential for gas exchange, osmoregulation, and defense, is directly exposed to these environmental stressors. In response, it demonstrates remarkable regenerative and regulatory capacity, with antioxidant activity playing a critical role in survival under oxidative challenge (Tran et al., 2021). ROS generation is closely associated with UV exposure and oxygen availability. When ROS levels exceed endogenous antioxidant defense capacity or when free radical scavenging systems fail, the resulting imbalance disrupts redox homeostasis and drives irreversible oxidative damage to lipids, proteins, and nucleic acids (Magalhães et al., 2008). Within this framework, amphibian-derived AOPs have gained prominence as molecular mediators of oxidative stress, offering valuable insight into the maintenance of cellular equilibrium and adaptive strategies against environmental stress.

Antioxidants are indispensable in mitigating ROS burden and preventing oxidative injury. Although they can alleviate UV-induced oxidative stress in the skin, chronic or high-dose administration, such as excessive vitamin C intake, is associated with adverse gastrointestinal effects. Furthermore, synthetic antioxidants may bioaccumulate and exert toxic or carcinogenic effects in organs including the liver, spleen, and lungs. Widely used chemical antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), tert-butylhydroquinone (TBHQ), and propyl gallate (PG) are subject to strict regulation due to potential health hazards. Even naturally occurring antioxidants like vitamins C and E present limitations in dosage and application contexts (Chalamaiah et al., 2012; Tanzadehpanah et al., 2012). These constraints underscore the urgent need for safe, effective, and biocompatible alternatives,

Recent research has revealed that amphibian-derived peptides possess distinctive molecular architectures and chemical properties that make them highly promising candidates as biological antioxidants. These AOPs, whether naturally occurring or synthetically designed, demonstrate strong capacity to scavenge and neutralize ROS. By reducing intracellular concentrations of ROS and other pro-oxidants, AOPs protect cellular structures and tissues from oxidative stress-related disorders (Pisoschi et al., 2016). In addition to their biomedical relevance, AOPs also show potential in the food and cosmetic industries by delaying oxidative degradation. Their relatively simple structures, high stability, and low toxicity further enhance their value as natural antioxidants. Moreover, many AOPs exhibit additional biological functions, including antibacterial, anti-inflammatory, and wound-healing activities, further enhancing their therapeutic potential (Luppi & Drain, 2017; Prokopieva et al., 2016).

Amphibian skin possesses three major antioxidant defense systems that have evolved to counter oxidative stress-induced damage. The first consists of gene-encoded enzymatic antioxidants, such as CAT, GSH reductase, peroxidase, and SOD (Wang et al., 2020). The second comprises non-enzymatic low molecular weight antioxidants (LMWAs), including NADH, lipoic acid, and GSH, which neutralize ROS through electron donation. The third includes genetically encoded small peptides with antioxidant activity. Extensive investigations have demonstrated that amphibian-derived AOPs represent a critical component of this defense network, with considerable potential and application value (Liu et al., 2010; Yang et al., 2009). Of particular importance is their role in the prevention of photoaging, a process closely linked to ROS accumulation. Although AOPs lack enzymatic activity, they share genetic origins with classical antioxidant enzymes and function similarly to LMWAs as direct radical scavengers. Therefore, AOPs are increasingly recognized as a distinct third antioxidant system with potentially unique modes of action (Xie et al., 2021). Exploration of natural AOPs in amphibian skin not only advances understanding of innate defense mechanisms but also provides a foundation for developing clinically relevant

Table 2 AOPs derived from amphibians[a]

Peptide	Sequence	Number of amino acids	Molecular weight	PI[b]	Origin	References
Andersonin-AOP1	FLPGLECVW	9	1 063.28	4.00	*Odorrana andersonii*	Yang et al., 2016
Andersonin-AOP2	SLSCFLSFTR	10	1 160.35	7.96		
Andersonin-AOP10a	SYLNSLSCFLSFT	13	1 481.68	5.24		
Andersonin-AOP11a	GMGYMMLCGLSGM	13	1 350.71	5.52		
Andersonin-AOP14d	TGKHMAGCFKFGES	14	1 499.72	7.90		
Andersonin-AOP15	AYMKQHMYCAASFF	14	1 698.00	8.23		
Andersonin-AOP16	VVKCSYRQGSPDSR	14	1 581.77	9.31		
Andersonin-AOP23	GLFSMILGVGKKTLCGLSGLW	21	2 180.69	9.31		
Wuchuanin-AOP5	TVWGFRPSKPPSGYR	15	1 734.98	11.00	*Odorrana wuchuanensis*	
Antioxidin-RL	AMRLTYNRPCIYAT	14	1 672.98	9.31	*Odorrana livida*	Qin et al., 2018
Antioxidin-2	YMRLTYNRPCIYAT	14	1 765.08	9.19	*Odorrana livida*	Zhang et al., 2017
Antioxidin-PN	FLPSSPWNEGTYVLKKLKS	19	2 194.56	9.53	*Pelophylax nigromaculatus*	Song et al., 2013
Ansin2	TRCFRVCS	8	971.16	9.00	AOP derived from amphibians for de novo molecular design	Feng et al., 2018
Antioxidin-I	TWYFITPYIPDK	12	1 543.78	5.50	*Physalaemus nattereri*	Barbosa et al., 2018
APBMH	LEQQVDDLEGSLEQEKK	17	1 988.14	4.08	*Aquarana catesbeiana*	Je et al., 2007
APBSP	LEELEEELEGCE	12	1 421.49	3.41	*Aquarana catesbeiana*	Qian et al., 2008
Cathelicidin-NV	ARGKKECKDDRCRLLMKRGSFSYV	24	2 847.37	9.90	*Nanorana ventripunctata*	Feng et al., 2022b
Cathelicidin-OA1	IGRDPTWSHLAASCLKCIFDDLPKTHN	27	3 039.48	6.90	*Odorrana andersonii*	Cao et al., 2018
FW-1	FWPLI-NH2	5	674.84	5.52	*Hyla annectans*	Liu et al., 2021
FW-2	FWPMI-NH2	5	692.87	5.52		

Continued

Peptide	Sequence	Number of amino acids	Molecular weight	PI[b]	Origin	References
Frog Protein Hydrolysates (FPHs)	L/IK	2	259.16	10.05	*Hylarana guentheri*	Gu et al., 2014
	FK	2	293.15	10.05		
Fragilin-A1	VKRRGQDCIHGFCSD	15	1 720.94	8.04	*Limnonectes fragilis*	Yu et al., 2015
Fragilin-B1	GQFNDKRWIPFG	12	1 464.65	8.75		
Odorranain-Q-Lf	APIRMWYMYRKLTDMEPKPVA	21	2 597.15	9.53		
Jindongenin-1a	DSMGAVKLAKLLIDKMKCEVTKAC	24	2 596.22	8.79	*Amolops jingdongensis*	Chen et al., 2012
Palustrin-2AJ1	GFMDTAKNVAKNVAVTLIDKLRCKVTGGC	29	3 053.65	9.31		
Hainanenin-1	FALGAVTKLLPSLLCMITRKC	21	2 278.90	9.50	*Amolops hainanensis*	Zhang et al., 2012
Hainanenin-5	FALGAVTKRLPSLFCLITRKC	21	2 337.91	10.11		
OA-GL21	GLLSGHYGRVVSTQSGHYGRG	21	2 188.39	9.99	*Odorrana andersonii*	Bian et al., 2018
OA-VI12	VIPFLACRPLGL	12	1 298.65	8.22	*Odorrana andersonii*	Yin et al., 2019
OM-GL15	GLLSGHYGRASPVAC	15	1 487.70	8.23	*Odorrana margaretae*	Zhang et al., 2021
OM-GF17	GFFKWHPRCGEEHSMWT	17	2 135.40	6.92	*Odorrana margaretae*	Wang et al., 2020
OM-LV20	LVGKLLKGAVGDVCGLLPIC	20	1 968.49	8.05	*Odorrana margaretae*	Li et al., 2018
OS-LL11	LLPPWLCPRNK	11	1 336.66	9.51	*Odorrana schmackeri*	Xie et al., 2021
Odorranain-M-OM	ATALVLPPRGLLPIGFKFKDIILCRKD	27	2 995.71	9.78	*Odorrana margaretae*	Ling et al., 2013
Odorranain-G-OT	FVPAILCSILKTC	13	1 407.79	8.06	*Odorrana tiannanensis*	He et al., 2012
Odorranain-A-OT	VVKCSFRPGSPAPRCK	16	1 732.10	10.11		
Pleurain-E-OT	ATAWRMPPNGIPPIVAVRIRPLCGTV	26	2 786.40	11.70		
Parkerin	GWANTLKNVAGGLCKITGAA	20	1 945.27	9.31	*Nanorana parkeri*	Lu et al., 2010
PaT-2	FPPWL-NH2	5	658.80	5.52	*Pithecopus azureus*	Barbosa et al., 2021
Salamandrin-I	FAVWGCADYRGY-NH2	12	1 407.57	5.83	*Salamandra salamandra*	Plácido et al., 2020
Spinosan A	DLGKASYPIAYS	12	1 284.43	5.83	*Paa spinosa*	Dong et al., 2015
Spinosan B	DYCKPEECDYYFSFPI	16	2 019.23	3.92		
Spinosan C	DLSMMRKAGSNIVCGLNGLC	20	2 082.50	8.06		
Spinosan D	MEELYKEIDDCVNYGNCKTLKLM	23	2 753.21	4.51		
Taipehensin-1TP1	TLIWEFYHQILDEYNKENKG	20	2 540.81	4.83	*Hylarana taipehensis*	Guo et al., 2014
Taipehensin-2TP1	CLMARPNYRCKIFKQC	16	1 974.45	9.50		
Temporin-TP1	FLPVLGKVIKLVGGLL-NH_2	16	1 666.17	10.00		
Brevinin-1TP1	FLPGLIKAAVGVGSTILCKITKKC	24	2 461.11	9.70		
Brevinin-1TP2	FLPGLIKAAVGIGSTIFCKISKKC	24	2 495.12	9.70		
Brevinin-1TP3	FLPGLIKVAVGVGSTILCKITKKC	24	2 489.16	9.70		
Brevinin-1LF1	FLPMLAGLAANFLPKIICKITKKC	24	2 634.38	9.70	*Amolops lifanensis*	
Palustrin-2GN1	GLWNTIKEAGKKFALNLLDKIRCGIAGGCKG	31	3 275.92	9.59	*Amolops granulosus*	
Daiyunin-1	CGYKYGCMVKVDR	13	1 521.83	8.82	*Amolops daiyunensis*	
Ranacyclin-HB1	GAPKGCWTKSYPPQPCFGKK	20	2 180.57	9.60	*Pelophylax hubeiensis*	
Temporin-MS1	FLTGLIGGLMKALGK	15	1 518.92	10.00	*Hylarana maosuoensis*	Wang et al., 2017
Maosonensis-1MS1	QYRPGSFGPLNQK	13	1 491.67	9.99		
Odorranaopin-MS2	DNVYSRPPQRFGQNVIS	17	1 977.17	8.75		
Nigroain-B-MS1	CVVSSGWKWNYKIRCKLTGNC	21	2 445.90	9.42		
Nigroain-C-MS1	FKTWKNRPILSSCSGIIKG	19	2 135.56	10.32		
Nigroain-D-SN1	CQWQFISPSRAGCIGP	16	1 750.02	8.07		
Nigroain-K-SN1	SLWETIKNAGKGFILNILDKIRCKVAGGCKT	31	3 378.05	9.59		
Pleskein-2	FFLLPIPNDVKCKVLGICKS	20	2 234.79	8.86	*Nanorana pleskei*	
Pleurain-A1	SIITMTKEAKLPQLWKQIACRLYNTC	26	3 053.69	9.30	*Rana pleuraden*	Yang et al., 2009
Pleurain-D1	FLSGILKLAFKIPSVLCAVLKNC	23	2 478.14	9.39		
Pleurain-E1	AKAWGIPPHVIPQIVPVRIRPLCGNV	26	2 831.46	10.86		
Pleurain-G1	GFWDSVKEGLKNAAVTILNKIKCKISECPPA	31	3 360.98	8.79		
Pleurain-J1	FIPGLRRLFATVVPTVVCAINKLPPG	26	2 779.43	10.86		
Pleurain-K1	DDPDKGMLKWKNDFFQEF	18	2 260.51	4.36		
Pleurain-M1	GLLDSVKEGLKKVAGQLLDTLKCKISGCTPA	31	3 186.82	8.79		
Pleurain-N1	GFFDRIKALTKNVTLELLNTITCKLPVTPP	30	3 344.02	9.20		
Pleurain-P1	SFGAKNAVKNGLQKLRNQCQANNYQGPFC DIFKKNP	36	4 042.61	9.79		
Pleurain-R1	CVHWMTNTARTACIAP	16	1 775.09	8.08		
Antioxidin-RP1	AMRLTYNKPCLYGT	14	1 630.94	9.20		
Antioxidin-RP2	SMRLTYNKPCLYGT	14	1 646.94	9.19		

Continued

Peptide	Sequence	Number of amino acids	Molecular weight	PI[b]	Origin	References
Odorranain-A-OA11	VVKCSYRQGSPDSR	14	1 581.77	9.31	*Odorrana andersonii*	
Hejiangin-A1	RFIYMKGFGKPRFGKR	16	1 988.43	11.74	*Odorrana hejiangensis*	
Macrotympanain-A1	FLPGLECVW	9	1 063.28	4.00	*Odorrana macrotympana*	Yang et al., 2012
Margaratain-A1	VTPPWARIYYGCAKA	15	1 696.01	9.19	*Odorrana margaretae*	
Wuchuanin-A1	APDRPRKFCGILG	13	1 429.70	9.51	*Odorrana wuchuanensis*	
W3	LGWVSKGKLL-NH2	10	1 351.61	10.00	*Boana pulchella*	Sanchis et al., 2022

[a]: This table was modified from Zhu et al. (2024). [b]: PI: Isoelectric point.

antioxidant formulations. Currently identified amphibian-derived AOPs are listed in Table 2.

FUNCTIONS OF AMPHIBIAN-DERIVED AOPS

Mechanisms of AOPs

The antioxidant capacity of AOPs arises from a combination of structural and chemical determinants. While α-helical and β-sheet motifs have been observed in certain AOPs, secondary structure generally exerts minimal influence on activity due to the low molecular weight of many AOPs (Zou et al., 2016). Instead, amino acid composition and sequence play decisive roles (Qian et al., 2008). The 20 naturally occurring amino acids serve as fundamental building blocks of peptides and proteins and are essential for regulating diverse physiological processes. The physicochemical traits of individual residues, including reducibility, hydrophobicity, and electron transfer potential, govern interactions with free radicals and mediate redox reactions that underpin antioxidant defense (Yu et al., 2015).

Aromatic residues such as phenylalanine, tryptophan, and tyrosine are particularly effective at scavenging free radicals. Their ability to donate electrons to electron-deficient ROS, while stabilizing resulting radicals through resonance delocalization, enables efficient neutralization of oxidative intermediates (Barbosa et al., 2018). Previous studies have demonstrated that the phenolic group of tyrosine and the indole ring of tryptophan donate hydrogen atoms to neutralize ROS, generating resonance-stabilized phenoxy and indole radicals that suppress oxidative chain reactions (Barbosa et al., 2018; Rajapakse et al., 2005). Through this mechanism, these residues confer notable antioxidant activity, protect against oxidative stress-induced cellular damage, and contribute to the maintenance of redox homeostasis (Wen et al., 2020). For instance, antioxidantin-I (TWYFITPYIPDK), a peptide isolated from the skin of *Physalaemus nattereri*, effectively reduces ROS and exhibits potential neuroprotective activity. Notably, its sequence is enriched in aromatic residues, with phenylalanine, tyrosine, and tryptophan accounting for approximately 33% of its total composition (Barbosa et al., 2018). Similarly, the heptapeptide HFGDPFH, derived from the blue mussel (*Mytilus edulis*) exhibits potent free radical scavenging activity. This peptide incorporates two phenylalanine and two histidine residues, the latter contributing imidazole side chains that act as electron donors and chelate Fe^{2+} ions, thereby inhibiting hydroxyl radical formation through the Fenton reaction (Rajapakse et al., 2005). Furthermore, the spatial arrangement of amino acids can strongly influence peptide antioxidant capacity. Histidine and phenylalanine are positioned near the N- and C-termini of the peptide, respectively. Previous studies have reported that histidine located at the C-terminus is particularly effective in scavenging free radicals, while phenylalanine positioned near the N-terminus contributes additional stabilizing effects (Chen et al., 1998). Sulfur-containing residues such as cysteine and methionine also play critical roles. The thiol group of reduced cysteine confers potent reducing activity, and peptides with free cysteine residues consistently display strong antioxidant properties (Wang et al., 2017). Methionine, through reversible oxidation, further enhances redox buffering. Acidic residues such as aspartic and glutamic acid, together with hydrogen-donating residues like glycine and tyrosine, can neutralize radicals by proton transfer (Barbosa et al., 2018). Sequences enriched in acidic or basic residues also exhibit metal-chelating activity. Among basic residues, histidine, lysine, and arginine provide both metal-binding capacity and direct radical scavenging through their functional side chains (Wen et al., 2020). Carnosine (β-alanyl-L-histidine), a naturally occurring dipeptide in humans, exemplifies this dual action by combining metal ion chelation and ROS neutralization via the imidazole group of histidine (Kohen et al., 1988). Hydrophobic amino acids, including glycine, proline, valine, alanine, leucine, isoleucine, methionine, tryptophan, and phenylalanine, further enhance antioxidant efficiency by increasing lipid solubility, thereby facilitating interactions with membranes and inhibiting lipid peroxidation (Wu et al., 2015).

Amphibian-derived AOPs combat skin photoaging

AOPs represent a potent line of defense against skin photoaging by counteracting the excessive accumulation of ROS. Beyond directly scavenging ROS, AOPs enhance endogenous antioxidant defenses, regulate intracellular signaling cascades, and mitigate downstream oxidative effects such as inflammation, lipid peroxidation, and protein modification. One well-characterized example is the bullfrog-derived peptide APBSP (LEELEEELEGCE), isolated from the skin of *Aquarana catesbeiana* (Qian et al., 2008). APBSP efficiently neutralized a broad spectrum of free radicals, including DPPH, hydroxyl, superoxide anion, and peroxyl radicals, while also exhibiting strong inhibitory activity against lipid peroxidation in linoleic acid emulsions, maintaining protection for up to 7 days. This stability underscores its potential as both a therapeutic candidate for oxidative stress-related diseases and as a functional additive in food preservation (Nanjo et al., 1995). In standard polyunsaturated fatty acid (PUFA) oxidation assays, linoleic acid incubated in water/ethanol emulsions in a dark room at 40 ± 1 °C undergoes auto-oxidation (Guo et al., 1999; Rosen & Rauckman, 1984), generating ROO • and RO • radicals from pre-existing lipid peroxides that drive peroxidation processes (Hill et al., 2012; Hiramoto et al., 1993). Cytotoxicity testing using MTT assay on human embryonic lung fibroblasts (MRC-5) confirmed that APBSP exhibited no detectable cytotoxic effects (Qian et al., 2008). Furthermore, three AOPs purified from *Limnonectes*

fragilis—fragilin-A1 (VKRRGQDCIHGFCSD), fragilin-B1 (GQFNDKRWIPFG) and odorranain-Q-Lf (APIRMWYMYR KLTDMEPKPVA)—displayed potent $ABTS^+$ and DPPH radical scavenging activity, significant reducing power, and negligible cytotoxic and hemolytic effects. When added to linoleic acid emulsions, all three peptides significantly inhibited lipid peroxidation compared with controls over a 7-day test period (Yu et al., 2015).

Natural animal-derived antioxidants have become promising candidates for biomedical application, with accumulating evidence highlighting the therapeutic potential of AOPs in disorders driven by oxidative stress. UV radiation and the resulting production of excessive ROS contributes to photoaging, sunburn, hyperpigmentation, and irreversible skin damage (Feng et al., 2018). While synthetic antioxidants such as resveratrol offer partial protection against UV-induced oxidative damage, their long-term or high-dose use is limited by safety concerns, including gastrointestinal toxicity, systemic accumulation, and carcinogenic risk. These constraints have hindered the clinical translation of synthetic antioxidants (Xie et al., 2021). Given the increasing burden of UV-mediated skin injury and the scarcity of safe and effective interventions, amphibian-derived AOPs have attracted attention as a novel class of bioactive molecules with strong photoprotective capacity.

Cathelicidin-NV (ARGKKECKDDRCRLLMKRGSFSYV), purified from the skin of the spot-bellied plateau frog (*Nanorana ventripunctata*), has demonstrated significant protective efficacy against UVB-induced skin photoaging in murine models (Feng et al., 2022b). Based on DCFH-DA fluorescence analysis, this peptide rapidly neutralized $ABTS^+$ radicals within a minute and effectively suppressed intracellular ROS accumulation in UVB-irradiated HaCaT keratinocytes. *In vivo*, cathelicidin-NV preserved dermal collagen integrity, down-regulated MMP-1 levels in a concentration-dependent manner, and suppressed phosphorylation of JNK and c-Jun. Measurements of MDA levels revealed that UVB exposure elevated lipid peroxidation, whereas treatment with cathelicidin-NV reversed this effect. The peptide also protected nuclear integrity by preventing UVB- and ROS-induced DNA fragmentation in HaCaT cells and reducing γH2AX expression, a marker of DNA double-strand breaks generated through PI3K-like kinase-mediated phosphorylation of histone H2AX at Ser139. Moreover, cathelicidin-NV enhanced endogenous antioxidant defenses *in vivo*, elevating CAT and SOD activities (Feng et al., 2022b; Luo et al., 2021).

Two additional peptides, FW-1 (FWPLI-NH2) and FW-2 (FWPMI-NH2), isolated from the skin of the tree frog *Hyla annectans*, also exhibited robust protection against UVB-induced skin photodamage (Liu et al., 2021). Notably, both peptides significantly reduced intracellular ROS levels in keratinocytes, performing comparably to the positive control N-acetyl cysteine (NAC). UVB typically induces epidermal growth factor receptor (EGFR) phosphorylation, activating downstream ERK1/2 and JNK MAPK pathways, with ROS acting as secondary mediators. Treatment with FW-1 and FW-2 markedly suppressed UVB-induced phosphorylation of ERK1/2 and JNK, thereby modulating MAPK signaling. Additionally, based on western blot analysis, FW-1 and FW-2 markedly reduced activation of the NF-κB signaling pathway, which reduced irradiation-induced pro-inflammatory cytokine release (Liu et al., 2021).

Antioxidin-RL (AMRLTYNRPCIYAT), a peptide isolated from the skin secretions of *Odorrana livida*, provides compelling evidence for a widespread AOP defense system in amphibian skin. At a concentration of 3 μmol/L, antioxidin-RL reduced $ABTS^+$ radicals by 75% within 5 seconds and demonstrated strong concentration-dependent reducing power (Liu et al., 2010). Nuclear magnetic resonance (NMR) titration identified Tyr6, Cys10, and Tyr12 as the main residues mediating this activity, with radical scavenging primarily facilitated by Cys10 and supported by hydrogen-donating capacity of Tyr. *In vivo*, antioxidin-RL significantly attenuated UVB-induced photoaging, which *in vitro* assays showed marked reductions in oxidative damage and inflammation in both HaCaT keratinocytes and human skin fibroblasts (HSF). Treatment with antioxidin-RL immediately after UVB exposure reduced protein nitration and oxidative DNA damage, as evidenced by decreased nitrotyrosine and 8-OHdG levels. In addition, antioxidin-RL restored intracellular GSH balance by lowering the menadione-induced disulfide (GSSG) to total GSH (GSH-eq) ratio and up-regulating depleted GSH levels, effects comparable to those of vitamin C (Barbosa et al., 2018).

Another bioactive peptide, OS-LL11 (LLPPWLCPRNK), was isolated from *Odorrana schmackeri* (Xie et al., 2021). OS-LL11 prevented UVB-induced photodamage through a combination of radical scavenging, anti-inflammatory, and anti-apoptotic mechanisms. At equivalent concentrations, its $ABTS^+$ scavenging capacity slightly exceeded that of vitamin C. In PAM 212 keratinocytes, OS-LL11 maintained cell viability under UVB and H_2O_2 stress, suppressing increases in ROS, MDA, lactic dehydrogenase (LDH), and lipid peroxidation, while restoring CAT activity. Pretreatment with OS-LL11 also up-regulated antioxidant response proteins, including Keap1, HO-1, GLCM, and NQO1. *In vivo*, OS-LL11 effectively alleviated erythema, edema, crusting, and ulceration in UVB-injured mouse skin. Biochemical analyses revealed H_2O_2 and enhanced levels of SOD, GSH, and NO, accompanied by down-regulation of pro-apoptotic and inflammatory mediators such as TNF-α, IL-6, IL-1α, IL-1β, Bax, and 8-OHdG, and increased expression of the anti-apoptotic protein Bcl-2. Representative structures of these amphibian-derived AOPs are depicted in Figure 3.

Clinical applications of AOPs

Amphibian-derived AOPs and related small molecules have attracted significant clinical interest due to their ability to neutralize ROS and modulate specific signaling pathways involved in disease progression. Several representative AOPs are currently under clinical evaluation, as summarized in Table 3. Among these, GSH is a ubiquitous tripeptide composed of glutamate, cysteine, and glycine, and constitutes the principal intracellular antioxidant in both prokaryotic and eukaryotic systems. It is predominantly maintained in the reduced form (GSH), maintaining redox homeostasis through diverse mechanisms, including direct scavenging of ROS, acting as a cofactor for GSH-Px, and regenerating other antioxidants such as vitamins C and E. The cysteine thiol (-SH) group confers strong nucleophilic and redox-active properties, enabling detoxification of free radicals, peroxides, and electrophilic xenobiotics. In addition, GSH participates in protein S-glutathionylation, cellular detoxification, and regulation of immune responses (Sies, 1999). Clinical investigations of GSH have yielded encouraging outcomes across a broad spectrum of disorders (Forman et al., 2009). Trials have reported efficacy in treating conditions such as diabetes, Parkinson's disease,

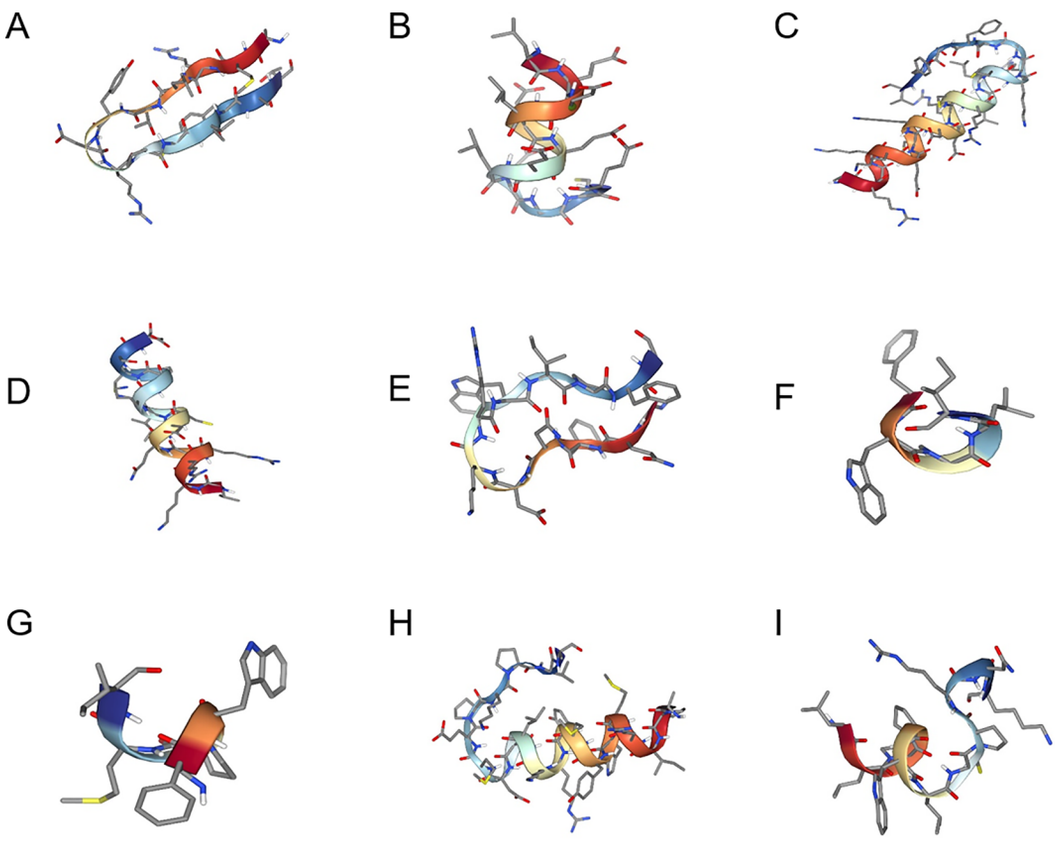

Figure 3 Structures of representative AOPs

A: Antioxidin-RL; B: APBSP; C: Cathelicidin-NV; D: Fragilin-A1; E: Fragilin-B1; F: FW-1; G: FW-2; H: Odorranain-Q-Lf; I: OS-LL11. Secondary structures of AOPs were computationally predicted using *de novo* modeling with PEP-FOLD v.4.0 (https://mobyle2.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py#forms::PEP-FOLD4). The predicted models are theoretical representations and may not fully reflect the dynamic conformations of peptides under physiological conditions. The predicted structures exhibit diverse secondary features: α-helices are predominant in peptides such as APBSP (B), Cathelicidin-NV (C), and Fragilin-A1 (D), whereas β-turns and disordered regions are more pronounced in Antioxidin-RL (A), Fragilin-B1 (E), FW-1 (F), FW-2 (G), and OS-LL11 (I), highlighting the structural diversity among amphibian-derived AOPs.

cystic fibrosis, hyperpigmentation, and other conditions associated with oxidative stress. GSH has been widely applied as a skin-whitening agent through both oral and intravenous administration (Forman et al., 2009) and randomized, double-blind, placebo-controlled trials continue to evaluate its efficacy as an oral formulation (NCT01016080). In Parkinson's disease, where excessive oxidative stress and reduced GSH are both implicated in pathogenesis, intravenous GSH administered three times per week over one month was tested in a Phase II clinical trial (NCT01177319). Exogenous antioxidant supplementation has also shown promise in mitigating diabetic complications and nephropathies linked to oxidative damage. Contrast-induced nephropathy (CIN), a leading cause of hospital-acquired acute renal failure associated with widespread use of radiographic contrast agents, results in prolonged hospitalization, increased medical expenses, and substantial mortality. The pathogenesis of CIN involves toxic injury to renal tubular epithelial cells, medullary hypoxia, and oxidative stress-driven inflammatory responses that impair renal function. Consequently, oxidative stress has become a major focus in research investigating the pathophysiology of CIN. GSH has also been intensively researched in this context, including ongoing clinical studies investigating its efficacy as a preventive and therapeutic agent (NCT01142024).

Carnosine is a low-molecular weight dipeptide naturally present in human muscle and nerve tissue, where it exerts broad-spectrum antioxidant activity. Its high bioavailability, stability within cellular membranes, rapid gastrointestinal absorption, and ability to cross the blood-brain barrier highlight its potential as a clinically relevant antioxidant (Prokopieva et al., 2016). Beyond its direct radical scavenging activity, carnosine exhibits considerable promise as a therapeutic agent for metabolic and neurodegenerative disorders. Obesity, characterized by excessive adiposity and chronic, low-grade inflammation, is strongly associated with metabolic abnormalities such as dyslipidemia and hyperglycemia (Song et al., 2014). According to a recent ongoing clinical study, carnosine supplementation reduced lipid peroxidation products in skeletal muscle, leading to improved glycemic management and cardiometabolic health (NCT05329610). Diabetic peripheral neuropathy (DPN), a common and debilitating complication of diabetes with an estimated prevalence of nearly 50%, severely impacts quality of life. Oxidative stress is a major driver of DPN pathogenesis, as ROS accelerate axonal degeneration, disrupt the microvascular network of peripheral nerves, and damage the lipid-rich myelin sheath (Giacco & Brownlee, 2010). Exogenous antioxidants are therefore considered crucial for limiting ROS-mediated neuronal injury (Fedorova et al., 2009). Carnosine, through the imidazole moiety of its histidine residue, can chelate divalent metal ions and scavenge hydroxy radicals with its imidazole moiety, thereby protecting cellular macromolecules from oxidative damage (Boldyrev et al., 2013). Carnosine may also function as a superior antioxidant in diabetes mellitus, based on a

Table 3 Selected AOPs in clinical trials[a]

Peptide name	Medical target	Phase	Status	Sponsor/collaborators	Clinical trial identifier
Glutathione	Skin Whitening	Phase 1	Completed	Chulalongkorn University	NCT01016080
		Phase 1	Completed	Dr Irma Bernadette S Sitohang/Rumah Sakit Pusat Angkatan Darat Gatot Soebroto	NCT04105504
	Skin Conditions	Not Applicable	Recruiting	Hangzhou Agile Groups Network Technology Co., Ltd.	NCT06066151
	Post-polio Syndrome/Physical Activity/Depression	Not Applicable	Completed	University of Michigan/Penn State University	NCT01402570
	Autism Spectrum Disorder	Phase 4	Terminated	University of Chicago	NCT05954052
	Autism/Severe Behavior Disorder	Not Applicable	Completed	University of Louisville/Cumberland Pharmaceuticals/Norton Healthcare	NCT00889538
	Parkinson’s Disease	Phase 2	Completed	University of South Florida/Wellness Health & Pharmaceuticals, Inc.	NCT01177319
		Phase 1	Completed	University of Washington/Michael J. Fox Foundation for Parkinson's Research	NCT02324426
		Phase 2	Completed	Bastyr University/Michael J. Fox Foundation for Parkinson's Research	NCT02424708
		Phase 1	Completed	Bastyr University/National Center for Complementary and Integrative Health	NCT01398748
		Phase 1	Recruiting	Baylor College of Medicine/The Methodist Hospital Research Institute	NCT04740580
	Type 2 Diabetes/Oxidative Stress/Mitochondrial Reactive Oxygen Species Production	Not Applicable	Completed	University of Copenhagen	NCT02948673
	Type 2 Diabetes	Not Applicable	Completed	University of California, San Diego	NCT04386187
	Type 2 Diabetes Mellitus/Chronic Periodontitis	Not Applicable	Completed	Suleyman Demirel University	NCT01467674
	Nephropathy/Oxidative Stress	Not Applicable	Completed	Huashan Hospital	NCT01142024
	Oxidative Stress	Phase 1	Completed	Charles Drew University of Medicine and Science	NCT01251315
		Not Applicable	Completed	Société des Produits Nestlé	NCT05041179
		Not Applicable	Recruiting	Calla IVF Center	NCT05575739
		Phase 2	Completed	VA Office of Research and Development/National Center for Complementary and Integrative Health	NCT01265563
	Diabetic Neuropathies	Not Applicable	Completed	Beni-Suef University	NCT05422352
	Type 1 Diabetes/Oxidative Stress/Diabetic Nephropathy	Not Applicable	Completed	Ain Shams University	NCT02928250
	Prediabetes/Hyperglycemia	Not Applicable	Completed	Nottingham Trent University/Aston University	NCT05329610
	Poor Glycemic Control/Cardiovascular Risk Factors	Phase 2	Recruiting	Monash University	NCT02917928
Carnosine	Parkinson Disease /Subjective Cognitive Impairment/Mild Cognitive Impairment	Not Applicable	Unknown	Slovak Academy of Sciences/Comenius University/University Hospital Bratislava/National Cheng Kung University	NCT03330470
SS-31 (Elamipretide / MTP-131 /Bendavia)	Oxidative Stress	Not Applicable	Completed	Tufts University	NCT00721708
	Peripheral Arterial Disease	Phase 1/2	Recruiting	University of Louisville	NCT05371145
		Phase 2	Completed	University of Louisville	NCT04870229
	Inflammation/Sarcopenia/Gut Permeability	Not Applicable	Recruiting	Azienda di Servizi alla Persona di Pavia	NCT05730985
	Friedreich Ataxia	Phase 1/2	Active, not recruiting	Children's Hospital of Philadelphia/Friedreich's Ataxia Research Alliance/Stealth BioTherapeutics Inc.	NCT05168774
	Mitochondrial Myopathies/Mitochondrial Pathology/Mitochondrial DNA Mutation	Phase 3	Active, not recruiting	Stealth BioTherapeutics Inc.	NCT05162768
	Mitochondrial Diseases/Barth Syndrome	Not Applicable	Available	Stealth BioTherapeutics Inc.	NCT04689360
	Skeletal Muscle Mitochondrial Dysfunction in the Elderly	Phase 2	Completed	Stealth BioTherapeutics Inc.	NCT02245620
	Primary Mitochondrial Disease	Phase 2	Completed	Stealth BioTherapeutics Inc.	NCT02805790
	Age-related Macular Degeneration	Phase 2	Completed	Stealth BioTherapeutics Inc.	NCT03891875
	Diabetic Macular Edema/Age-related Macular Degeneration	Phase 1/2	Completed	Stealth BioTherapeutics Inc.	NCT02314299
	Age-Related Macular Degeneration	Phase 1	Completed	Stealth BioTherapeutics Inc.	NCT02848313

Continued

Peptide name	Medical target	Phase	Status	Sponsor/collaborators	Clinical trial identifier
C-peptide	Type 1 Diabetes Mellitus	Not Applicable	Completed	Royal Devon and Exeter NHS Foundation Trust/Leiden University Medical Center/King's College London	NCT03490773
		Not Applicable	Recruiting	National Institute of Allergy and Infectious Diseases/Immune Tolerance Network	NCT02734277
		Not Applicable	Completed	University Hospitals Bristol and Weston NHS Foundation Trust	NCT01227538
		Not Applicable	Recruiting	University of Exeter/Royal Devon and Exeter NHS Foundation Trust/King's College London	NCT03369821
	Diabetes Mellitus	Not Applicable	Active, not recruiting	Royal Devon and Exeter NHS Foundation Trust/National Institute for Health Research, United Kingdom/Diabetes UK/University of Exeter	NCT03737799
	Diabetes Mellitus, Type 1/Diabetic Polyneuropathy	Phase 2	Completed	Creative Peptides Sweden Inc.	NCT00278980
	Type 2 Diabetes Treated With Insulin	Not Applicable	Completed	Goztepe Training and Research Hospital	NCT04005261
	Insulin Sensitivity	Not Applicable	Completed	Pennington Biomedical Research Center	NCT04774081
		Not Applicable	Completed	Albert Einstein College of Medicine	NCT03005951
	Chronic Pancreatitis/Diabetes Mellitus	Not Applicable	Active, not recruiting	Changhai Hospital	NCT05764629
	Fetal Macrosomia/Obesity Complicating Childbirth/Gestational Diabetes	Not Applicable	Recruiting	University of Kansas Medical Center	NCT06067685

[a]: Part of this table was adapted from https://clinicaltrials.gov/.

current clinical study examining the impact of carnosine supplementation on patients with type 2 diabetes mellitus for the prevention of diabetic neuropathy (NCT05422352). Carnosine has also been investigated as a dietary supplement with systemic antioxidant benefits. Pharmacokinetic studies in healthy adults confirmed efficient absorption and favorable bioavailability following oral administration (NCT00721708). Together, these findings underscore the translational promise of carnosine as a versatile antioxidant applicable to both metabolic and neurological disease contexts.

Clinical evaluation of the synthetic AOP SS-31 (Elamipretide/MTP-131/Bendavia) has demonstrated its ability to target the inner mitochondrial membrane and protect cells from oxidative damage. In a Phase II trial, the long-term safety and tolerability of daily SS-31 injections were established in 28 patients with genetically confirmed primary mitochondrial myopathy (PMM) (NCT02976038). Another randomized, double-blind, placebo-controlled Phase II study enrolled 41 elderly individuals with documented evidence of mitochondrial dysfunction to determine the effects of intravenous SS-31 on skeletal muscle energetics and performance (NCT02245620) (Karaa et al., 2018; Xu et al., 2019).

Amphibian-derived AOPs represent a promising class of natural antioxidants with applications extending beyond photoprotection to diabetes, neurodegeneration, and wound repair. OA-VI12 (VIPFLACRPLGL), isolated from the skin secretions of *Odorrana andersonii*, demonstrated strong radical scavenging activity against $ABTS^+$, DPPH, and NO and inhibited Fe^{3+} formation (Yin et al., 2019). Both animal and cellular studies confirmed that OA-VI12 protected cells against UV irradiation and H_2O_2 stimulation. Pretreatment of HaCaT cells with OA-VI12 conferred protection against UVB- and H_2O_2-induced reductions in cell viability. *In vivo* markers of oxidative damage, including CAT, LDH, and ROS, further support these findings (Marrocco et al., 2017). HaCaT cells treated with OA-VI12 displayed lower ROS release and LDH activity, but higher CAT activity compared with UVB- and H_2O_2-challenged controls. In a mouse model of UV-induced photodamage, OA-VI12 exhibited protective efficacy comparable to vitamin C without observable adverse effects on behavior, body weight, or general health. Earlier studies demonstrated that endogenous antioxidant enzymes and peptides are depleted in a dose-dependent manner under conditions of photodamage (Dunaway et al., 2018; Kammeyer & Luiten, 2015; Scharffetter-Kochanek et al., 2000). Consistent with this, OA-VI12 treatment was shown to significantly inhibit oxidative stress in UVB-irradiated mouse skin and markedly elevate GSH levels and SOD activity. Western blot analyses further revealed that oxidative stress in HaCaT cells triggered the MAPK signaling pathway, leading to notable phosphorylation of the ERK1/2 and P38 proteins, an effect suppressed by OA-VI12.

Another AOP, cathelicidin-OA1 (IGRDPTWSHLAASCLK CIFDDLPKTHN) identified from the skin of *Odorrana andersonii*, demonstrated dose-dependent scavenging of DPPH and $ABTS^+$ free radicals without hemolytic activity or acute toxicity (Cao et al., 2018). Keratin-producing epidermal cells known as keratinocytes quickly migrate to the site of the lesion and multiply to facilitate re-epithelialization as the wound heals (Liu et al., 2014; Mu et al., 2014). Fibroblasts, in addition to keratinocytes, are essential for the production of granulation tissue, the healing of skin wounds, and the formation of extracellular matrix (Barrientos et al., 2008; Koh & DiPietro, 2011). In wound healing models, cathelicidin-OA1 promoted re-epithelialization by stimulating TNF-α secretion, which enhanced macrophage recruitment, regulated repair cell migration, and accelerated proliferation. It also promoted scratch closure in HaCaT keratinocytes and HSFs, and

stimulated TGF-β1 release, further supporting granulation tissue formation and matrix deposition (Breitkreutz et al., 2009; Tang et al., 2014).

Additional evidence for the therapeutic promise of amphibian-derived AOPs is provided by antioxidin-I (TWYFITPYIPDK), isolated from the skin secretions of Physalaemus nattereri. This peptide exhibited robust radical-scavenging activity in ABTS, DPPH, ORAC, and NO assays, with ORAC results indicating superior antioxidant capacity compared with positive controls (Barbosa et al., 2018). Antioxidin-I alleviated menadione-induced redox imbalance in NIH3T3 fibroblasts by normalizing the GSSG/GSH-eq ratio, which had increased eight-fold under oxidative stress. It also reduced ROS levels in hypoxic microglia, cells that contribute significantly to neurotoxicity during stroke through excessive ROS release (Bordt & Polster, 2014; Rojo et al., 2014). Stroke, a leading cause of global mortality, is associated with impaired oxygen delivery and oxidative injury that exacerbate neuronal death (Chouchani et al., 2014; Hankey, 2014). The observed ability of antioxidin-I to scavenge microglial ROS implies a potential neuroprotective role. Such findings are consistent with broader evidence linking oxidative imbalance and macromolecular damage to the pathogenesis of neurodegenerative disorders.

Food system applications of AOPs

AOPs have gained considerable interest in food science due to their multifunctional properties and potential to replace synthetic additives. Their utilization in food systems is largely as natural preservatives that suppress lipid peroxidation and extend shelf life and as bioactive additives that enhance flavor and nutritional quality.

Lipid oxidation remains a major obstacle in the preservation of meat and meat-derived products. Despite their high nutritional value as sources of proteins, lipids, vitamins, and trace minerals, these products are vulnerable to chemical degradation during processing and storage. In particular, unsaturated fatty acids are prone to oxidative deterioration under improper storage conditions, giving rise to secondary oxidation products that not only compromise product quality and sensory attributes (Elias et al., 2008) but may also pose considerable health risks. Preventing lipid oxidation is therefore essential for ensuring product quality and consumer safety. Although synthetic antioxidants have long been incorporated into processed foods to control oxidation, growing concerns regarding their safety has prompted a shift toward natural alternatives. In this context, naturally derived AOPs show substantial promise (Chalamaiah et al., 2012; Sila & Bougatef, 2016), with evidence indicating that these peptides can effectively delay the initiation and propagation of lipid oxidation in model meat systems, thereby preserving flavor and texture (Tkaczewska et al., 2021). As a result, the incorporation of AOPs into food matrices is increasingly being explored to maximize their stability and functional efficacy. For example, recent studies have shown that rice germ enzymatic hydrolysates, used as natural antioxidant supplements, reduce fat oxidation and extend shelf life. Compared to synthetic additives, such as sodium nitrite, these hydrolysates are more acceptable to consumers and pose lower carcinogenic risk, making them ideal for application in meat products. In addition to its high nutritional value, rice germ is a rich source of protein, and its fractions exhibit diverse antioxidant activity (Hartmann & Meisel, 2007; Zaky et al., 2022), with strong potential for food industry application.

CONCLUSIONS AND OUTLOOK

The generation and elimination of ROS remain central themes in biomedical research due to their dual roles in essential cellular signaling and oxidative stress-related damage. Among ROS-related pathologies, skin photoaging is particularly relevant, arising from both direct structural injuries caused by UV radiation and the substantial generation of intracellular ROS upon UV exposure (Gu et al., 2020; Kammeyer & Luiten, 2015). In addition to weakening barrier integrity and increasing the risk of skin cancer, photoaging disrupts fundamental physiological processes. Amphibian-derived AOPs, shaped by unique ecological pressures and physiological adaptations, exhibit exceptional radical-scavenging activity, and have emerged as promising candidates for mitigating oxidative stress and preventing UV-induced photodamage. Growing interest in these peptides reflects their potential utility in dermatological therapeutics and functional skincare applications. This review has outlined the biological generation of ROS, the mechanistic connections between oxidative stress and photoaging, and the distinctive antioxidant properties of amphibian-derived peptides, highlighting their pharmaceutical relevance.

Amphibian-derived AOPs have shown robust capacity to attenuate ROS-mediated injury and photoaging via mechanisms refined by evolutionary adaptation to extreme habitats. These findings not only establish a foundation for the development of peptide-based pharmacological and cosmetic formulations but also highlight a novel convergence between amphibian conservation and dermatological drug discovery. Recognizing amphibians as both a vulnerable taxonomic group and a source of untapped therapeutic biomolecules reinforces the dual importance of biodiversity preservation and biomedical innovation, a relationship with profound but largely underexplored strategic value.

Despite notable progress, significant gaps remain. First, although numerous AOPs have been identified—particularly from anurans—their *in vivo* functions, regulatory mechanisms, and contributions to endogenous oxidative stress responses remain poorly defined. Future studies should prioritize functional characterization in native physiological contexts, which may uncover both conserved and lineage-specific strategies evolved under diverse ecological conditions. Second, research remains heavily biased toward frogs and toads, with salamanders and caecilians largely overlooked. This taxonomic imbalance limits understanding of AOP structural diversity, evolutionary origins, and ecological functions. Expanding discovery efforts across all amphibian orders through integrative genomics, transcriptomics, and proteomics will broaden the molecular landscape and enrich the repertoire of antioxidant candidates. Third, most mechanistic studies have focused on individual peptides, leaving the potential synergistic or antagonistic interactions, both among AOPs and with other skin-derived bioactive peptides such as AMPs, essentially unexplored. Investigating these interactions may reveal cooperative effects that enhance antioxidant efficacy, broaden biological functionality, or modulate immune responses. Such studies would not only improve therapeutic design but also reflect the natural complexity of amphibian skin secretions as integrated defense systems. From a translational perspective, challenges such as the high cost and complexity of peptide synthesis and purification remain significant barriers to industrial application. Novel strategies, including recombinant expression in microbial or plant hosts, biosynthetic pathway engineering, and affinity-based purification platforms represent promising avenues to

improve yield and reduce costs without compromising bioactivity. At the same time, large-scale exploitation of amphibian-derived resources must be pursued within a conservation-sensitive framework. Integrating peptide research with amphibian biobanking, captive breeding, and habitat restoration will be critical for ensuring sustainability. Ethical sourcing, rigorous environmental assessment, and community-based conservation programs should be embedded within all stages of development to align therapeutic innovation with biodiversity stewardship.

In conclusion, amphibian-derived AOPs occupy a unique position at the nexus of ecological adaptation and therapeutic innovation. They represent an emerging frontier in oxidative stress research with direct implications for the treatment and prevention of skin photoaging. Bridging current knowledge gaps through interdisciplinary, conservation-aware, and omics-driven research strategies will be essential for unlocking the full biomedical potential of these peptides while supporting global efforts to preserve amphibian biodiversity.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Y.Y.Z., L.M.Z., and X.Y.J. wrote the manuscript. Y.P.W. and G.J.L. supervised the project and revised the manuscript. All authors read and approved the final version of the manuscript.

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