Low-Dose Singlet Oxygen as a Hormetic Agent: Mechanisms, Physiological Effects, and Physiological Potential

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Singlet Oxygen Low-Dose Technology (patented in the U.S., South Korea, China, India, Mexico, Europe, and other countries worldwide) **ORCID:** 0009-0001-8793-0096

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Abstract

This review characterizes the role of singlet oxygen ($^1O_2$) as a non-pharmacological, hormetic agent, capable of activating adaptive stress responses to support cellular resilience without inducing oxidative damage. Low-dose gas-phase singlet oxygen acts as a biophysical trigger at the plasma membrane, initiating a systemic adaptive relay. We detail the biochemical mechanisms of this response, focusing on the Nrf2-Keap1-SIRT6 axis, MAPK-mediated kinase rheostats, and the induction of autophagic flux (mitophagy, lipophagy). The review contrasts traditional irradiative singlet oxygen generation with a novel, non-irradiative catalytic technology (U.S. Patent No. 11,007,129 B2), highlighting its advantages in maintaining a stable, sub-toxic output suitable for continuous therapeutic application. Integrated clinical observations across respiratory, sleep, and metabolic contexts provide preliminary evidence for the "systemic recalibration" induced by this technology.

Keywords

Singlet Oxygen, Hormesis, Nrf2, Autophagy, Redox Signaling, SIRT6, Mitophagy, U.S. Patent 11,007,129 B2, Adaptive Stress Response, Non-irradiative Catalysis.

Disclosure

The author serves as an independent consultant for the patent registration and scientific aspects of the technology described herein. This work was conducted to provide a theoretical framework for observed physiological outcomes and received no direct commercial funding.

1. Introduction

Redox biology has revolutionized our understanding of how organisms manage internal and environmental challenges. Reactive oxygen species (ROS), once viewed exclusively as harmful metabolic byproducts, are now recognized as essential signaling molecules that modulate adaptive stress responses, immune regulation, and cellular repair. Among these ROS, singlet oxygen ($^1O_2$), an electronically excited form of molecular oxygen, plays a unique dual role as both a cytotoxic agent at high concentrations and a physiological regulator at controlled low levels.[1]

Singlet oxygen is naturally generated through enzymatic reactions, mitochondrial activity, and photoactivation processes in plants[2] and animals[3], influencing diverse physiological and pathological pathways. Its effects depend strongly on concentration and exposure duration: while excessive levels cause oxidative damage, sub-toxic doses can activate hormetic mechanisms that enhance resilience, reduce inflammation, and support regeneration.[4]

Recent advances in delivery technologies, particularly non-irradiative gas-phase catalytic generation, offer new opportunities to administer low-dose singlet oxygen in a controlled, non-invasive manner, potentially extending its application from laboratory and photodynamic contexts to broader preventive and wellness domains. This approach circumvents the limitations of photosensitizer-based systems, such as photobleaching, optical alignment constraints, and environmental sensitivity, while enabling stable output for long-term use.

While the hormetic properties of other ROS are well established, the specific signaling and systemic effects of continuous low-dose singlet oxygen exposure in humans remain insufficiently studied. There is a lack of controlled clinical data defining optimal dosing, safety margins, and mechanistic biomarkers for long-term application. The present review integrates current mechanistic knowledge with observational clinical reports to outline plausible biological pathways, highlight Physiological potential, and identify priorities for future research.

Through this comprehensive lens, singlet oxygen is positioned as a distinctive agent in redox biology, bridging environmental sensing and systemic resilience, and warranting further exploration as a novel hormetic stimulus in human health.

This review explores the potential of low-dose singlet oxygen as a hormetic agent that activates adaptive stress responses without inducing oxidative damage. We examine the molecular pathways it influences, its role in organ and systemic regulation, and the supportive role in biological maintenance of these effects. Importantly, we highlight a novel, non-irradiative method for delivering singlet oxygen and review both mechanistic evidence and case observations supporting its use.

2. Singlet Oxygen: Properties and Generation

2.1. Chemistry and Electronic States of Oxygen

Oxygen constitutes approximately 20% of atmospheric air and is vital for aerobic life. In its most stable form, dioxygen (O_2) exists as a diradical in the ground triplet state ($^3\Sigma g^-$), characterized by two unpaired electrons in separate degenerate orbitals (Figure 1a). This electronic configuration imposes spin restrictions on reactions with singlet-state molecules (which most biological molecules are) but allows reactivity with radicals.

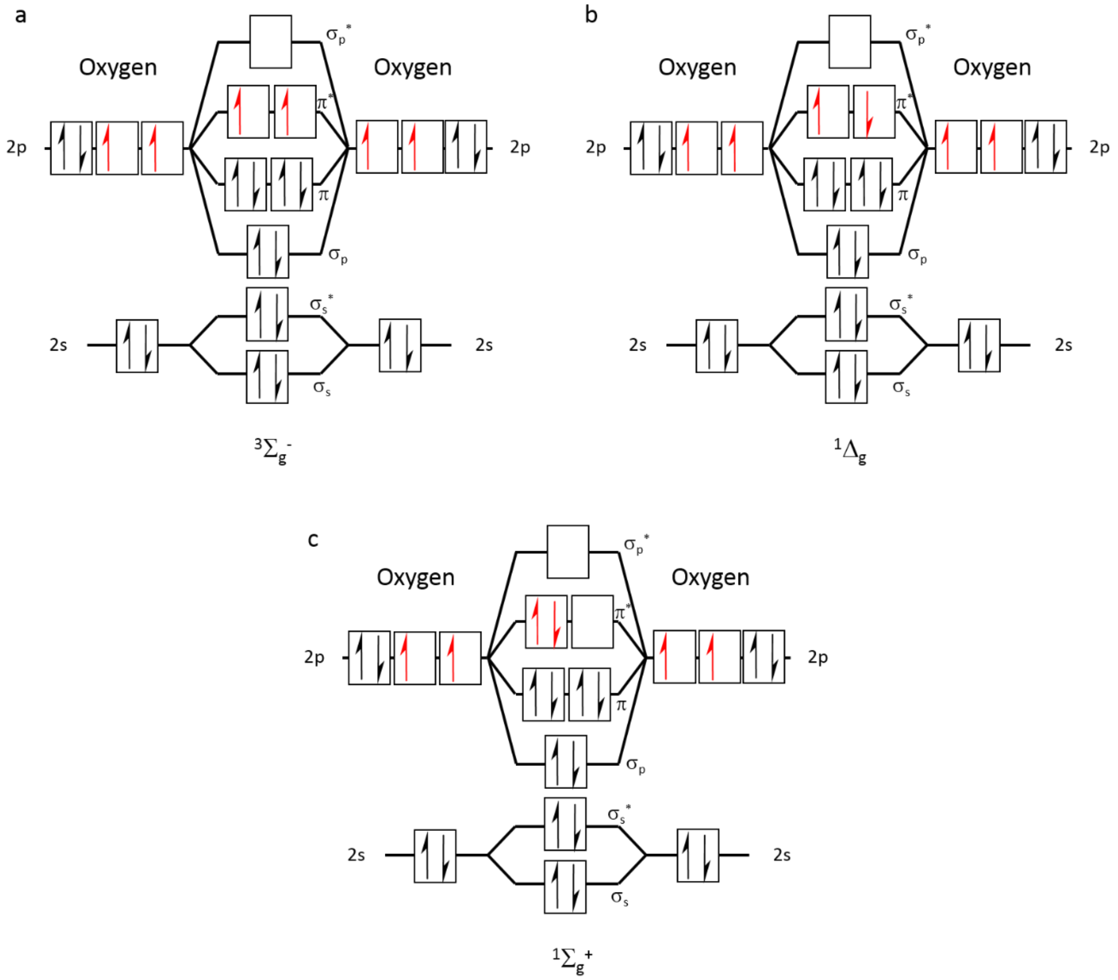

Figure 1 Occupation of molecular orbitals in oxygen at different energetic states: (a) triplet ground state, $^3\Sigma_g^-$, (b) Most stable singlet state, $^1\Delta_g$, (c) Highest energy, short- lived singlet state, $^1\Sigma_g^+$.

Excitation of molecular oxygen leads to two singlet states: $^1\Delta g$ and $^1\Sigma g^+$ (Figure 1b and Figure 1c, respectively). The higher-energy $^1\Sigma g^+$ state is extremely reactive but short-lived, rapidly relaxing to the lower-energy $^1\Delta g$ state, commonly referred to as singlet oxygen

($^1O_2$). In the gas phase, isolated singlet oxygen ($^1\Delta g$) has a relatively long lifetime (~72 minutes),[5] but this decreases significantly with increased probability of collisions in liquids or under higher pressure/temperature. Under these conditions, the lifetime can reduce to mere seconds in the gas phase.[6] In solutions, the lifetime of singlet oxygen is even shorter, ranging from microseconds to nanoseconds, depending on the solvent properties.[7]

2.2.Common Methods for Singlet Oxygen Generation

Singlet oxygen can be artificially produced through a range of methods, with most traditional techniques relying on liquid-phase systems. One of the most established is chemical generation,[8] which involves reactions such as the decomposition of trioxidane in water or reaction of hydrogen peroxide with sodium hypochlorite (Figure 2). This method is effective in liquids but produces reactive byproducts and has short diffusion range. Another common method is photosensitization,[9] in which light-excitable compounds (photosensitizers) such as porphyrins transfer energy to ground-state triplet oxygen, producing singlet oxygen via a type II energy transfer mechanism (Figure 3). This light-driven process is the foundation of photodynamic therapy (PDT), a clinically validated modality used in the treatment of certain cancers,[10] microbial infections,[11] and dermatological disorders.[12] Despite its efficacy, photosensitized singlet oxygen production requires localized light exposure, often limiting treatment to surface tissues or necessitating invasive delivery systems. Moreover, outcomes are influenced by complex pharmacokinetics, oxygen availability, and potential phototoxicity.[13] Other methods include Plasma-induced excitation which generates mixed ROS, including singlet oxygen, without photosensitizers and laser/microwave excitation which is used primarily in specialized high-energy applications.

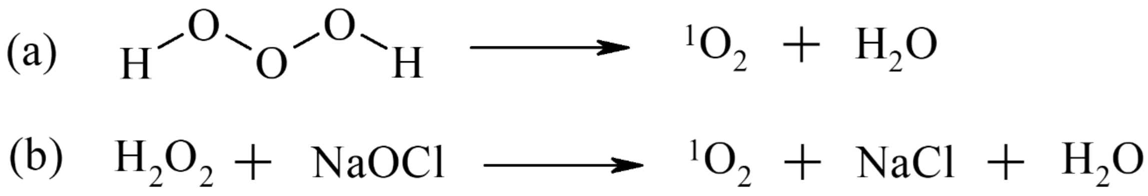

Figure 2 Examples for chemical reactions to produce singlet oxygen, $^1O_2$: (a) decomposition of trioxidane in water; (b) reaction of hydrogen peroxide with sodium hypochlorite.

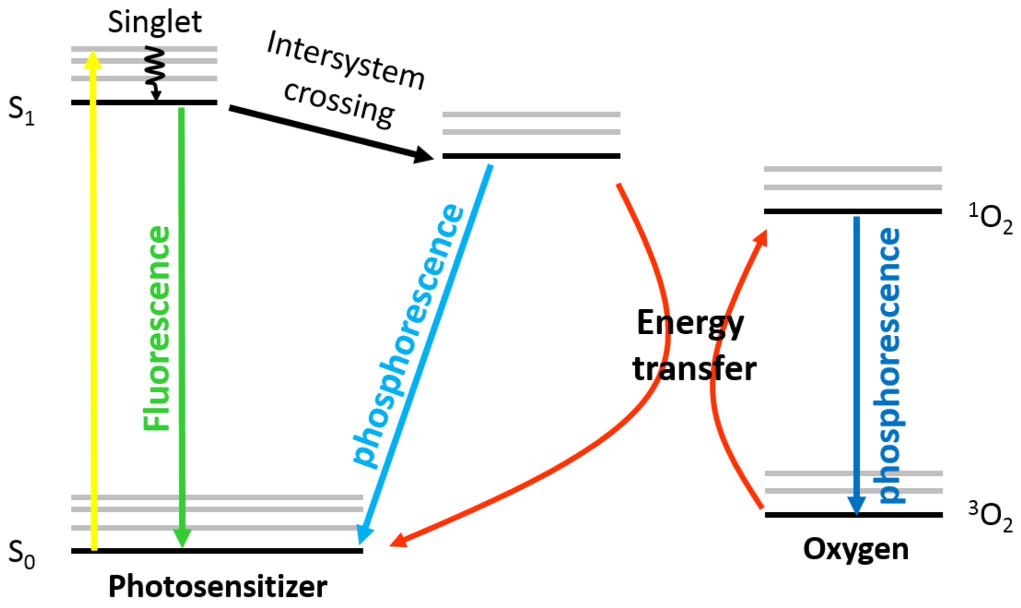

Figure 3 Energy diagram illustrating singlet oxygen ($^1O_2$) that is generated from ground state triplet oxygen ($^3O_2$) via energy transfer from the excited state of a photosensitizer to the oxygen molecule upon irradiation.

To expand singlet oxygen applications beyond solution-phase systems, alternative gas-phase generation strategies have been developed.

2.2.1. Singlet Oxygen Generation in Gas Phase

Gas-phase singlet oxygen has a longer intrinsic lifetime and greater diffusion capacity compared with singlet oxygen generated in liquid or solution-constrained environments.[6] These properties enable non-invasive delivery across larger biological or environmental surfaces and remove the need for liquid media, photonic targeting, or pharmacokinetic considerations.

Historically, the most common method is photosensitization, in which immobilized dyes (e.g., porphyrins, Rose Bengal) absorb light and transfer energy to ground-state oxygen.[14] While effective in laboratory settings, these irradiative systems face significant challenges for continuous or low-dose clinical use. Organic sensitizers are prone to photobleaching, which is a gradual loss of catalytic efficiency due to light-induced degradation, which can lead to inconsistent dosing over time. Furthermore, irradiative systems are sensitive to humidity and temperature fluctuations and require precise optical alignment, limiting their scalability for unattended domestic or long-term therapeutic operation. [15]

Other methods include plasma-based generation, which employs non-thermal plasma to excite molecular oxygen, without the need for light or sensitizers. However, plasma methods often generate a broad, high-energy mixture of reactive oxygen species (ROS), including ozone (O_3) and nitrogen oxides (NO_x), which can introduce collateral toxicity that overrides the desired hormetic effect.[16] Similarly, heterogeneous photocatalysis using doped metal oxides (e.g., doped TiO_2, ZnO) generate singlet oxygen from atmospheric oxygen under visible light or UV, which may carry secondary irradiative risks. [17]

A novel, non-irradiative catalytic approach (as detailed in U.S. Patent No. 11,007,129 B2)[18] produces gas-phase singlet oxygen by passing ambient air through engineered metal-based substrates. This method utilizes specific metal alloys with controlled oxygen affinity to facilitate a "soft" electronic excitation.[19] In this process, oxygen molecules are transiently adsorbed and excited to the singlet state before release, without fully oxidizing the metal surface or requiring an external light source.

The primary advantage of this patented catalytic principle is its energy purity and stability. By bypassing high-energy plasma and degradable photosensitizers, the system avoids the production of high-toxicity oxidants and maintains a constant, reproducible output. This technical precision allows for the delivery of a "sub-threshold" or low-dose signal that is inherently self-limiting. By controlling airflow parameters and catalytic residence time, the technology ensures the output remains within the hormetic zone- providing enough oxidative stimulus to trigger cellular recalibration (e.g., Nrf2 and autophagy pathways) without reaching the levels of oxidative stress that induce apoptosis or tissue damage.

Consequently, while traditional gas-phase systems are well established for industrial disinfection, these non-irradiative catalytic platforms offer a light-independent, low-maintenance alternative uniquely suited for therapeutic contexts. The physiological implications of this controlled, "pure" singlet oxygen signal are explored in the subsequent sections of this review.

3. Endogenous Sources and Biological Role of Singlet oxygen

3.1. Natural Generation in Plants and Animals

Singlet oxygen, as mentioned before, is considered to be an ROS and is a natural product of various biological processes in both animals and plants. For instance, photosensitization can also occur in plants,[20] as chlorophyll, that is the green pigment essential for photosynthesis in leaves, can function as a natural photosensitizer, especially under high light intensity. At these conditions, the chlorophyll molecules facilitate the formation of singlet oxygen, which acts as a signaling molecule, as it triggers photoinhibition, a protective mechanism that prevents damage to the photosynthetic apparatus from excessive light exposure. [21]

More commonly, singlet oxygen is mainly generated endogenously through light-independent pathways. In non-photosensitized tissues, enzymatic systems such as myeloperoxidase (MPO) in neutrophils and eosinophils can catalyze reactions involving hydrogen peroxide and chloride ions, leading to the formation of hypochlorous acid and subsequently singlet oxygen.[22] In addition, singlet oxygen is generated within different cellular compartments, such as peroxisomes, the endoplasmic reticulum, the cytosol, and, most notably, mitochondria. [23] Mitochondria, the organelles responsible for energy (ATP) production through aerobic respiration, use oxygen as an electron source. This process results in the formation of ROS, including hydrogen peroxide (H_2O_2), hydroxyl radicals ($OH\bullet$), superoxide anion radicals ($O_2\bullet^-$), and singlet oxygen ($^1O_2$). Interestingly, it has been shown that singlet oxygen at controlled levels may enhance mitochondrial activity and energy metabolism. [24] These internal sources suggest that singlet oxygen is not confined to exogenous or photodynamic contexts but may act as an intrinsic modulator of redox signaling under physiological or inflammatory conditions.

3.2. Dose-Dependent Effects and Thresholds of Toxicity

The biological activity of singlet oxygen is defined by a delicate balance between concentration and exposure duration. The constant production of singlet oxygen in the body leads to a baseline concentration estimated to be around 10^{-13} M under neutral conditions, which is far below the threshold for cellular damage. In contrast, concentrations reaching approximately 10^{-8} M can damage cell membranes, while local concentrations of 10^{-5}–10^{-4}M are associated with irreversible oxidative damage and cell death.[25]

Cellular and tissue damage occurs when ROS, including singlet oxygen, oxidize electron-rich sites, such as double bonds and thiol groups, in key biomolecules (**Error! Reference source not found.**). Critical cellular targets include pigments and antioxidants (e.g., chlorophyll, hemoglobin), proteins (e.g., enzymes, structural and transport proteins, receptors),[26] lipids (e.g., membrane phospholipids), and nucleic acids.[27] Damage to these macromolecules disrupts cellular integrity and function, contributing to pathological conditions.

The concept of oxidative stress arises when reactive species like singlet oxygen accumulate beyond the buffering capacity of cellular antioxidant systems. This threshold-based response underscores the necessity of maintaining a redox equilibrium and opens the door for hormetic interventions, where sub-threshold exposures may prime cellular defenses rather than cause harm.

Understanding these concentration-response relationships is essential for the safe therapeutic application of singlet oxygen and provides a framework for distinguishing between beneficial and deleterious exposure. Having outlined the toxicity thresholds of singlet oxygen, we now turn to the beneficial cellular processes activated within the safe, sub-toxic range, processes that exemplify the concept of redox hormesis.

Table 1 Chemical Activity of Singlet Oxygen With Various Biomolecules.[21,25-27]

Biomolecule Type	**Key Reactive Groups**	**Reaction Type**	**Example Products**	**Biological Outcomes**
Lipids (PUFAs)	Allylic C=C double bonds	Ene reaction	Lipid hydroperoxides (e.g., 13-HPODE)	Membrane damage, lipid peroxidation chain reactions, formation of signaling aldehydes (e.g., 4-HNE), inflammation
Proteins	Trp, His, Met, Cys	Oxidation of side chains	Methionine sulfoxide, N-formylkynurenine, 2-oxo-histidine	Loss of enzyme activity, altered protein folding, proteasomal degradation, redox signaling
Nucleic Acids	Guanine (mainly)	Base oxidation	8-oxo-7,8-dihydroguanine (8-oxoG)	Mutagenesis, transcriptional errors, impaired DNA replication, contributes to age-related diseases and cancer
Cholesterol	Allylic hydrogens, Δ5 double bond	Addition/Oxidation	7-hydroperoxycholesterol, 25-hydroxycholesterol	Altered membrane structure, LXR pathway modulation, potential atherogenesis, implicated in inflammatory diseases
Pigments and antioxidants (e.g., carotenoids, tocopherols)	Conjugated π-systems	Physical/chemical quenching	Inert or less-reactive byproducts	Impair function and protection from oxidative stress

4. Oxidative Stress, Homeostasis, and Hormesis

4.1. The Importance of Maintaining Homeostasis and the Onset of Stress

Every biological system, from single cells to complex multicellular organisms, relies on maintaining specific internal conditions to function optimally. These conditions include stable temperature, pH, and precise concentrations of minerals and biomolecules, collectively referred to as "homeostasis." However, as both external and internal environments are constantly changing, organisms have evolved specialized mechanisms to sustain homeostasis.

When an organism's intrinsic mechanisms are unable to maintain stable internal conditions, the system enters a state of "stress." This failure disrupts the optimal functioning of biological systems and, over time, leads to structural and functional damage. Various biomolecules and biostructures suffer chemical and physical damage, which might lead to various diseases and pathological syndromes.

Given that most organisms inhabit dynamic and often volatile environments, the induction of stress is inevitable. To survive and thrive, organisms must develop adaptive mechanisms to mitigate stress and restore homeostasis.

4.2. Oxidative Stress as a Biological Challenge

Oxidative stress is one of the most prevalent forms of stress experienced by organisms, particularly those relying on aerobic respiration. It arises when the ROS levels exceed the capacity of baseline antioxidant defenses to neutralize them. Elevated ROS levels pose a significant risk, as they can oxidize critical biomolecules altering their chemical and structural properties. Such changes often render these molecules ineffective, and in some cases, even harmful. As a result, at high levels, oxidative species are harmful to the body and may result in diseases.[28]

The potential for cellular and tissue damage underscores the importance of preventing ROS from reaching harmful levels. It has been found that at low concentrations, ROS essentially act as signalling molecules, as they activate cellular stress-response pathways[1] that include the upregulation of antioxidant defences and mechanisms to repair existing damage. In this way, ROS play a crucial role in supporting cellular health and adaptability. By acting as signalling molecules, they not only alert the system to potential threats but also help initiate processes that restore balance and promote resilience in the face of environmental and physiological challenges.

4.3. The Plasma Membrane: A Redox-Sensing Platform for Singlet Oxygen Signaling

Singlet oxygen is increasingly recognized not merely as a byproduct of oxidative stress but as a key signaling molecule in cellular regulation. Its role has been demonstrated across diverse biological systems, including plants[29,30], bacteria[31] and mammals[20]. One of its primary sites of action is the plasma membrane, where it chemically modifies specific lipids and proteins that function as primary oxidative targets, effectively acting as that trigger or inhibit downstream processes).[24,32]

Among the most reactive are polyunsaturated fatty acids (PUFAs), whose oxidation produces stable secondary messengers like 4-hydroxynonenal (4-HNE). These messengers activate redox-sensitive transcription factors such as Nrf2 and NF-κB,[33] initiating an antioxidant response that extends beyond the individual cell via paracrine signaling.

Furthermore, cholesterol, a major component of lipid rafts, is readily oxidized by singlet oxygen to form cholesterol hydroperoxides and oxysterols, such as 7-ketocholesterol and 25-hydroxycholesterol. These modulate lipid raft dynamics and membrane signaling.[34] The oxidized derivatives influence membrane fluidity and can engage Liver X Receptors (LXRs) and Toll-like receptors (TLRs), amplifying metabolic and immunological responses.

Crucially, singlet oxygen oxidizes cysteine and methionine residues on membrane proteins, modulating ion channels and receptor conformations[35] Together, these modifications convert the plasma membrane into a dynamic redox-sensitive signaling platform.

These modifications (summarized in *Table 2*) convert the plasma membrane into a dynamic, redox-sensitive signaling platform. The transformation of these localized membrane-centered redox events into a coordinated organism-level response necessitates a multi-tiered signal propagation system. This transition from a surface biophysical trigger to systemic adaptation is governed by three interconnected layers of communication. First, the intensity of the initial oxidative cue is decoded by a cytoplasmic kinase rheostat, primarily the **ASK1-MAPK axis**, which dictates the threshold between survival-oriented autophagy and apoptosis (see **Section 5.3.1**). Second, this signal is amplified and transported to distant tissues via **extracellular vesicles** and **paracrine signaling**, enabling a localized respiratory stimulus to influence systemic energy and sleep patterns. Finally, rapid physiological shifts are facilitated by **neuroimmune relay systems** that bypass slower transcriptional pathways to provide immediate homeostatic recalibration. The specific mechanics of these long-range propagation vehicles, and their role in bridging local sensing with systemic physiology, are detailed in **Section 8.**

Table 2 Molecular Targets in The Plasma Membrane That Act as 'Biophysical Sensors' For Singlet Oxygen

Molecular Target	**Primary Modification**	**Systemic Significance**
PUFAs / Lipids	4-HNE Production	Initiation of Paracrine/Vesicular Signaling
Cholesterol	Oxysterol Formation	Modulation of Lipid Rafts and TLR activity
Membrane Proteins	Thiol/Methionine Oxidation	Activation of Ion Channels and Neural Reflexes

5. Hormetic Mechanisms Induced by Singlet Oxygen

Singlet oxygen exerts concentration-dependent effects on biological systems. At elevated levels, it contributes to oxidative damage and cell death. However, at sub-toxic concentrations, singlet oxygen triggers a hormetic response, activating intrinsic cellular defense mechanisms by upregulation of antioxidant enzymes, redox-sensitive signaling, immune modulation, and autophagic processes. This hormetic response promotes resilience, repair, and redox homeostasis. [36]

This chapter outlines the molecular pathways and systems influenced by low-dose singlet oxygen, providing a mechanistic foundation for its Physiological potential.

5.1. Nrf2-Keap1 Pathway, Sirt6 and ARE Gene Activation

One of the primary oxidative stress sensors activated by singlet oxygen is Nrf2 (Nuclear factor erythroid 2–related factor 2),[37] which is a transcription factor that regulates the antioxidant defense system through the Nrf2-Keap1 pathway. A homodimer of Keap1 (Kelch-like ECH-associated protein 1) inhibits Nrf2 transcriptional activity by binding to its evolutionarily conserved N-terminal regulatory domain, thereby targeting Nrf2 for ubiquitin-proteasome-dependent degradation.[38] Exposure to ROS or lipid-derived secondary messengers (such as 4-HNE), generated via the oxidation of primary membrane targets (as described in section 4.3), oxidize specific cysteine residues on Keap1. This triggers a conformational change in the Keap1 homodimer, disrupting its inhibitory 'clamp' on Nrf2 and preventing further ubiquitination and degradation. Freed Nrf2 translocates to the nucleus, where it binds to antioxidant response elements (AREs) in the promoter regions of detoxification and cytoprotective genes, promoting their transcription.

SIRT6, a NAD$^+$-dependent histone deacetylase, supports the antioxidant response by enhancing Nrf2 stability and facilitating access to the regulatory regions of antioxidant genes. Upon oxidative stress, SIRT6 expression increases and contributes to Nrf2 activation by reducing its degradation, promoting its accumulation in the nucleus,[39] and enabling robust transcription of antioxidant targets. SIRT6 also modulates chromatin structure, promoting an open configuration at specific Nrf2-responsive loci, which enhances recruitment of transcriptional machinery and efficient expression of antioxidant genes to counteract oxidative damage.[40]

Major downstream targets include:

5.1.1. Glutathione synthesis

Nrf2 upregulates the catalytic (GCLC) and modifier (GCLM) subunits of glutamate-cysteine ligase, the rate-limiting enzyme in glutathione (GSH) biosynthesis.[41,42] GSH is a central redox buffer that neutralizes hydrogen peroxide, lipid peroxides,[43] and electrophilic agents via enzymatic and non-enzymatic reactions.[44] Critically, it maintains cellular proteins in their reduced thiol form, preventing aberrant disulfide cross-linking that can impair enzymatic activity and cellular signaling.[45] By preserving this thiol-disulfide balance, GSH supports proper protein folding, redox-sensitive signal regulation, and cytoskeletal organization.[46]

Importantly, Nrf2-dependent enhancement of GSH synthesis also contributes to tissue repair mechanisms. Elevated GSH levels facilitate fibroblast migration, reduce oxidative delay in re-epithelialization, and accelerate wound closure under inflammatory conditions.[47] Thus, GSH not only buffers oxidative insults but orchestrates a redox environment conducive to regeneration.

5.1.2. Detoxification

Nrf2 activation leads to the upregulation of multiple Phase II detoxifying enzymes, including NAD(P)H quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), and peroxiredoxins (PRDXs). These enzymes mitigate oxidative and electrophilic stress not by directly scavenging ROS, but by converting reactive intermediates into less harmful, excretable forms.

- NQO1 catalyzes the two-electron reduction of quinones to hydroquinones, thereby preventing redox cycling and ROS amplification. [48]
- HO-1 degrades pro-oxidant heme into biliverdin, free iron, and carbon monoxide; biliverdin and its product bilirubin act as potent endogenous antioxidants, while carbon monoxide exhibits anti-inflammatory effects. [49]
- Peroxiredoxins (PRDX1–6) catalyze the reduction of peroxides and modulate redox signaling by buffering fluctuations in H_2O_2 levels. [50]

Together, these enzymes form a highly inducible frontline defense that complements glutathione systems and enhances the cell's capacity to detoxify harmful byproducts of oxidative stress and inflammation.

5.1.3. Redox regulation and lipid-derived mediators

Nrf2 supports redox homeostasis not only through antioxidant enzymes but also regulating enzymes that maintain thiol integrity and modulate lipid signaling. A core component of this system includes thioredoxin reductase 1 (TXNRD1) and superoxide dismutases (SOD1–3). SODs catalyse the dismutation of superoxide anions into hydrogen peroxide,[51] a less reactive species that is further detoxified by catalase[52] or glutathione peroxidase. TXNRD1 maintains thioredoxin in its reduced form, enabling it to reduce disulfide bonds in proteins, thus repairing them, and ensuring redox signal fidelity.[53]

Additionally, Nrf2 influences the metabolism of oxidized lipids through enzymes like ALOX15 (Arachidonate 15-lipoxygenase)**,** which converts polyunsaturated fatty acids into mediators such as 15-HETE and lipoxins. These bioactive lipids help resolve inflammation, promote macrophage polarization toward anti-inflammatory phenotypes, and regulate redox-sensitive immune responses. [54]

To complement its antioxidant functions, Nrf2 also supports proteasome activity under stress conditions by promoting the transcription of specific proteasome subunits. This enhances both 20S and 26S proteasomal capacity, which is especially important when misfolded or oxidized proteins accumulate.[55] In addition, Nrf2-driven adaptation enhances the efficiency of ATP-independent degradation by the 20S core proteasome — a critical pathway in cells where autophagic function or ATP supply is limited.[56]

Such Nrf2–proteasome interplay is particularly relevant in non-dividing or long-lived cells, including muscle fibers and neurons, where sustained proteotoxic stress can disrupt cellular function.

In parallel, oxidative stress and thiol imbalance can trigger protein unfolding and aggregation. Nrf2 indirectly supports proteostasis by sustaining redox conditions that favor proper protein folding and by coordinating with heat shock proteins (**HSPs**), which refold or triage misfolded proteins. Heat shock protein 70 (HSP70)[57] assists in protein folding and prevents aggregation under stress, activating transcription factor 4 (ATF4)[58] that coordinates the integrated stress response, regulating redox balance and cell survival. This redox–chaperone axis is particularly important in long-lived cells, such as neurons, where oxidative injury can destabilize protein structure and impair cellular function.[59]

Through these pathways, Nrf2-linked redox systems contribute broadly to cellular stability in the face of oxidative stress. In redox-sensitive tissues like the nervous[60] and cardiovascular[61] systems, these mechanisms support resilience by modulating stress signaling, protecting structural proteins, and promoting inflammatory resolution,[62] without relying on direct ROS scavenging alone.

5.1.4. Mitochondrial regulation

Nrf2 contributes to mitochondrial health and metabolic adaptation under oxidative stress by regulating transcriptional programs that coordinate mitochondrial biogenesis, quality control, and antioxidant defense. Key among these is PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha), a central coactivator that stimulates the expression of nuclear respiratory factors (NRF1, NRF2/GABPA)[63] and mitochondrial transcription factor A (TFAM), together promoting mitochondrial DNA replication and respiratory enzyme synthesis.[64]

Mitochondrial adaptation to low-dose singlet oxygen is not a result of direct molecular interaction, but rather a coordinated response to the membrane-initiated redox relay described in section 4.3. The secondary messengers generated at the plasma interface (e.g., 4-HNE) diffuse through the cytosol to interact with mitochondrial-resident proteins, such as DJ-1 (PARK7).

Acting as a redox sentinel, DJ-1 stabilizes the Nrf2 protein by further inhibiting its Keap1-mediated degradation, specifically shielding the mitochondria from potential oxidative injury.[65] This 'mitohormetic' signaling triggers a transcriptional program led by PGC-1α, which coordinates with SIRT6 and Nrf2 to promote mitochondrial biogenesis and enhance the expression of mitochondrial-specific antioxidants like SOD2 and GPX4, which are critical in detoxifying mitochondrial ROS and preventing lipid peroxidation.[66]

In addition to the Nrf2–DJ-1 axis, the sirtuin family member SIRT6 serves as a critical co-regulator of mitochondrial homeostasis and metabolic resilience under oxidative stress.[67] As mentioned above, SIRT6 functions as a "redox-sensor" that can directly interact with and stabilize Nrf2, thereby amplifying the expression of the aforementioned ARE-dependent genes, such as HO-1 and NQO1.[40] Beyond its nuclear roles, SIRT6 is essential for maintaining mitochondrial quality control by preventing mitochondrial fragmentation and supporting efficient ATP production, which is a process that aligns with the activity of PGC-1α and AMPK in responding to transient hormetic signals.[67,68] By coordinating nuclear antioxidant defenses with mitochondrial bioenergetics, SIRT6 ensures that low-dose singlet oxygen exposure results in metabolic adaptation rather than energetic failure, reinforcing the systemic resilience characteristic of redox hormesis.[69]

By aligning nuclear antioxidant defenses with mitochondrial bioenergetics, this relay ensures that the cell increases its ATP production efficiency and respiratory capacity. Consequently, the transient biophysical trigger at the membrane is translated into long-term metabolic resilience, preventing mitochondrial fragmentation and ensuring energetic homeostasis during periods of physiological stress.

5.1.5. Anti-Inflammatory and Cytoprotective Roles of Nrf2 [70]

In addition to regulating antioxidant gene expression, Nrf2 plays a pivotal role in modulating inflammation. Upon activation, Nrf2 suppresses the expression of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β by interfering with NF-κB signaling and by inducing anti-inflammatory mediators like HO-1 and ferritin.

The anti-inflammatory efficacy of Nrf2 is significantly augmented by its crosstalk with SIRT6, that serves as a potent repressor of pro-inflammatory gene expression.[71] While Nrf2 suppresses the transcription of cytokines, SIRT6 acts directly at the chromatin level by deacetylating Histone H3 at the promoters of NF-κB target genes. This 'epigenetic silencing' effectively dampens the inflammatory response even in the presence of persistent stress signals. Under hormetic conditions, low-dose singlet oxygen may enhance the stability of both Nrf2 and SIRT6, creating a synergistic anti-inflammatory axis that prevents the transition from acute, protective signaling to chronic, systemic inflammation.[72] This coordinated regulation is particularly relevant in age-related 'inflammaging', where the concurrent decline of Nrf2 and SIRT6 otherwise leaves tissues vulnerable to cytokine-mediated damage.

This modulation reduces systemic inflammation, limits immune overactivation, and contributes to tissue protection in conditions such as:

- Autoimmune diseases:[73] Nrf2 activation mitigates cytokine storms (e.g., in lupus or multiple sclerosis).
- Metabolic syndromes:[74] Suppresses inflammation in diabetes and obesity.
- Pulmonary disorders: [75] Reduces airway inflammation in asthma and COPD.
- Neurodegeneration:[76] Damps neuroinflammation via microglial modulation.

Thus, as summarized in Table 3, Nrf2 serves as a dual-function regulator, both antioxidant and anti-inflammatory, essential to the hormetic adaptation elicited by singlet oxygen.

Table 3 Integrated Defense Systems Regulated by the Nrf2-ARE Axis

Functional Category	Primary Enzymes/Factors	Physiological Outcome
Glutathione System	GCLC, GCLM, GSH	Thiol-disulfide balance; accelerated wound closure and re-epithelialization.
Phase II Detox	NQO1, HO-1, PRDXs	Neutralization of quinones; degradation of pro-oxidant heme; H_2O_2 buffering.
Proteostasis	20S/26S Proteasomes, HSP70	Clearing of oxidized/misfolded proteins; prevention of protein aggregation.
Mitochondria	PGC-1α, TFAM, DJ-1	Mitochondrial biogenesis; protection of mtDNA; metabolic adaptation.
Anti-Inflammatory	IL-6/TNF-α inhibition	Suppression of cytokine storms; resolution of "inflammaging."

5.2. MAPK Signaling and Oxidative Stress Sensors

Beyond the Nrf2-Keap1 pathway, the membrane-initiated relay activates several additional signaling pathways involved in stress response, inflammation regulation, cell death and repair mechanisms. These pathways ensure that cells maintain homeostasis, limit damage, and initiate adaptive processes during oxidative stress.

For example, the p53 tumor suppressor protein,[77] a key regulator of DNA repair and apoptosis, is activated in response to oxidative stress, helping cells manage or eliminate damage. Similarly, the MAPK family consists of several key protein kinases, including ERK1/2 (extracellular signal-regulated kinase), JNK (c-Jun N-terminal kinase), and p38 MAPK, which are activated through upstream stress sensors, including oxidative modifications of receptor proteins, mitochondrial ROS signaling, and changes in redox balance (Table 4).[78]

- The ERK1/2 pathway is central to the regenerative effects of low-dose therapy. By promoting fibroblast proliferation and keratinocyte migration,[79] this pathway orchestrates the structural remodeling of the extracellular matrix, facilitating the 'smoothing' of tissue and accelerated closure of wounds.
- While JNK and p38 are often associated with apoptosis at high ROS concentrations, under hormetic (low-dose) conditions, they act as metabolic rheostats. They modulate the activity of transcription factors involved in the integrated stress response, ensuring that the cell prioritizes repair over programmed cell death.[78,80]

Through this multi-layered signaling network, the cell converts the initial biophysical trigger at the membrane into a sophisticated 'decision-making' process that favors repair, survival, and structural rejuvenation.

Table 4 MAPK Functional Specialization

Kinase Pathway	Primary Trigger	Major Biological Outcome
ERK 1/2	Membrane Receptor Oxidation	**Tissue Repair & Proliferation** (Wound healing/Skin smoothing)
JNK / p38	Redox Imbalance / Lipid Mediators	**Stress Adaptation** & Homeostatic Calibration
p53 Axis	Redox-Sensitive Kinases	**Genomic Stability** & DNA Repair coordination

5.3. Autophagy and Cell Fate Regulation

The "Relay" logic holds that the cell does not wait for internal damage to reach a critical mass; instead, the biophysical trigger at the membrane initiates a preemptive "quality control" protocol, with the capacity to promote either cell survival or cell death. This duality is mediated through its ability to induce autophagy or apoptosis, two distinct yet interconnected processes that are often activated sequentially in response to stress. Autophagy, a highly conserved mechanism present in all eukaryotes, from unicellular organisms to mammals,[81] is responsible for selectively degrading oxidized and damaged intracellular components, such as proteins and organelles (particularly mitochondria), via the lysosomal pathway. This process is essential for preserving cellular integrity and function during mild stress.[82]

5.3.1. Oxidative Stress Intensity as a Determinant of Cell Fate

The outcome of oxidative stress is not binary but graded, depending on its intensity, duration, and localization.[33,83,84] At low to moderate levels, oxidative stress initiates adaptive responses, including Nrf2 activation and the induction of autophagy, enabling cells to restore homeostasis. In contrast, sustained or intense oxidative insults can overwhelm these defenses, tipping the balance toward apoptosis or necrosis (Figure 4).

As established in earlier sections, singlet oxygen acts as a metabolic rheostat. At low hormetic doses, secondary messengers (like 4-HNE) and redox-sensitive kinases (ASK1) favor the induction of Autophagy, a survival-oriented process that clears the "biological clutter" before it can trigger Apoptosis (cell death).[85] In addition, A key non-transcriptional effect of singlet oxygen is the oxidative modification of the Bcl-2 protein. This disruption releases Beclin-1, the "master switch" for autophagy initiation, allowing for rapid cellular response that bypasses the need for slower nuclear transcription. [82,83,86]

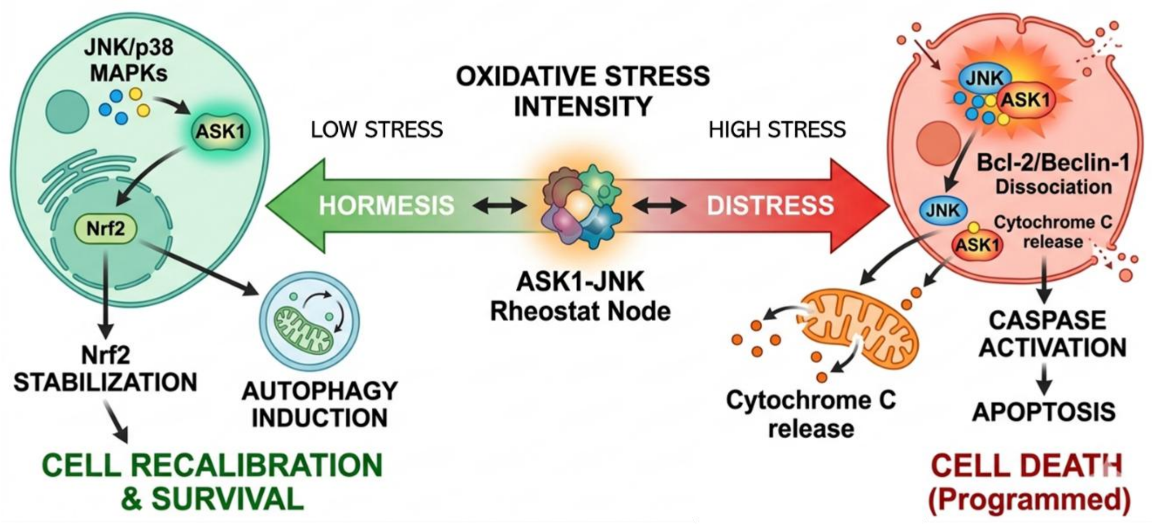

Figure 4 Schematic representation of the cellular decision-making process in response to varying intensities of singlet oxygen-induced stress. (Left) The Hormetic Zone: Under low-intensity oxidative conditions, the membrane-initiated relay activates a transient and moderate signaling surge through ASK1 and JNK/p38 MAPKs. This level of activation favors the stabilization of Nrf2 and the induction of Autophagy, specifically Mitophagy and CMA, to selectively sequester and degrade oxidatively damaged organelles and proteins. This 'quality control' phase promotes cellular recalibration and homeostatic recovery. (Center) The Rheostat Switch: The ASK1-JNK axis functions as a molecular rheostat, where the duration and amplitude of the oxidative signal determine the functional outcome. (Right) The Distress Zone: Under conditions of high-intensity or chronic oxidative stress, the sustained over-activation of these kinases leads to the phosphorylation-dependent dissociation of the Bcl-2–Beclin-1 complex and the subsequent release of pro-apoptotic factors, such as Cytochrome c. This shifts the cellular fate from survival-oriented cleanup to Caspase-dependent Apoptosis, ensuring the programmed elimination of irreversibly damaged cells. Together, these pathways illustrate the graded, non-binary nature of the stress response, where controlled oxidation acts as a primary messenger for survival.

Furthermore, singlet oxygen can influence the hypoxia-inducible factor 1 (HIF-1) pathway, which plays a pivotal role in cellular responses to low oxygen levels.[87] While the HIF-1 pathway is primarily known for regulating genes that adapt to hypoxic conditions, it also intersects with autophagy mechanisms.

These immediate oxidative modifications allow singlet oxygen to act as a first messenger in stress adaptation, influencing the balance between repair and cell death independently of transcription. This reinforces the concept of oxidative stress as a rheostat, where controlled oxidation promotes survival pathways, while excess shifts the balance toward irreversible damage.

5.3.2. Subtypes of Autophagy

The primary forms of autophagy implicated are macroautophagy, mitophagy, and chaperone-mediated autophagy (CMA), each targeting distinct cellular liabilities within the cell.

Macroautophagy (often just referred to as autophagy) is responsible for bulk degradation of damaged or oxidized cytoplasmic material. Upon low-level oxidative stress, singlet oxygen can trigger macroautophagy by oxidizing redox-sensitive regulators, enabling the sequestration of dysfunctional proteins and organelles into autophagosomes. Although traditionally viewed as non-selective, macroautophagy often targets specific substrates based on oxidative modification patterns.[82,88]

Mitophagy, a specialized subset of macroautophagy, mitophagy, specifically eliminates damaged or dysfunctional mitochondria. Mitochondria are central to cellular energy production. However, as organisms age, mitochondrial DNA (mtDNA) accumulates mutations, leading to decreased efficiency in the electron transport chain and increased production of ROS. The increased oxidative stress may further damage cellular components, thus accelerating aging and age-related diseases,[89] including neurodegenerative disorders, [90] cardiovascular diseases, [91] and metabolic syndromes[92]. This underscores the importance of inducing mitophagy to remove these compromised organelles and prevent further ROS production. Two mitophagy pathways have been identified. In one pathway, JNK influences mitophagy through the modulation of PINK1/Parkin Pathway, as JNK activation can promote the stabilization of PINK1 on the outer membrane of depolarized mitochondria, facilitating the recruitment of Parkin, an E3 ubiquitin ligase. Parkin ubiquitinates mitochondrial proteins, marking the mitochondria for autophagic degradation.[93]

Independently of the PINK/Parkin pathway, mitophagy can also occur through the phosphorylation of FUNDC1.[94] JNK phosphorylates FUNDC1, a mitochondrial receptor, which enhances its binding affinity for LC3 or other autophagy proteins, facilitating the engulfment of damaged mitochondria by autophagosomes.

By utilizing both the PINK1/Parkin (ubiquitin-dependent) and FUNDC1 (receptor-dependent) pathways, the cell ensures that 'leaky' mitochondria, those with mutated mtDNA or inefficient electron transport, are selectively removed. This prevents the energetic failure typically seen in aging and metabolic syndromes, effectively 'rejuvenating' the cellular power supply.

Chaperone-Mediated Autophagy (CMA)[95] is a form of autophagy that selectively degrades soluble cytosolic proteins containing the KFERQ-like pentapeptide motif. Under oxidative stress, oxidized proteins are recognized by chaperones and translocated directly into lysosomes for degradation. This process helps in the removal of oxidatively damaged proteins, thereby maintaining protein quality control.[96] JNK signaling has been implicated in modulating this pathway as it may influence the expression of chaperone proteins under mild oxidative conditions, thereby enhancing the selective degradation of oxidized cytosolic proteins. While the direct involvement of JNK in CMA regulation is less clear, oxidative stress may upregulate the expression of LAMP-2A,[97] the lysosomal receptor essential for CMA substrate translocation. Increased LAMP-2A levels enhance the cell's capacity to degrade oxidized proteins via CMA.[98] In addition, stress conditions can affect the activity of Hsc70,[Error! Bookmark not defined.] the cytosolic chaperone that recognizes and delivers substrates to LAMP-2A. Modulation of Hsc70 activity influences the efficiency of CMA.

Table 5 Specialized Autophagic Pathways Triggered by Oxidative Stress

Autophagy Subtype	Primary Target	Key Mediator/Relay
Macroautophagy	Bulk oxidized proteins & lipids	**Beclin-1 / ASK1**
Mitophagy	Dysfunctional Mitochondria	**JNK → PINK1/Parkin** or **FUNDC1**
CMA	Soluble proteins with KFERQ motif	**Hsc70 / LAMP-2A**

Together, these autophagic pathways (Table 5) offer an orchestrated response that favors selective clearance and functional recovery rather than indiscriminate degradation, a hallmark of the hormetic action of singlet oxygen.

5.3.3. Biological Implications of Autophagy

Autophagy pathway activation has been shown to prevent stress-induced tissue and organ injury. Beyond its immediate cytoprotective function, autophagy contributes to a wide range of systemic adaptations relevant to stress resilience, aging, immunity, and tissue homeostasis (Table 6).

Table 6 Systemic Resilience via the Autophagic Relay

System	Primary Target/Process	Hormetic Outcome
Immune	Xenophagy & DAMP/PAMP regulation	Enhanced pathogen clearance; limited inflammasome activation.
Nervous	Proteostasis (Tau/α-synuclein)	Neuroprotection; prevention of excitotoxicity.
Skin	Keratinocyte/Fibroblast barrier repair	Accelerated wound healing; anti-aging (SIRT6-mediated).
Cardiac	Mitophagy & Vascular NO signaling	Cardioprotection; preservation of vascular tone.
Metabolic	Lipophagy & AT2 regeneration	Hepatic steatosis prevention; lung alveolar repair.

5.3.3.1. Systemic Functions: Immunity, Inflammation, and Aging

Autophagy plays a multifaceted role in immune homeostasis. It mitigates chronic inflammation by degrading damaged organelles and oxidized macromolecules, thereby limiting the passive release of damage-associated molecular patterns (DAMPs)[99] such as mitochondrial DNA, ATP, and oxidized proteins. This suppression of DAMP leakage helps prevent uncontrolled inflammasome activation and cytokine release. Conversely, under certain stress conditions, autophagy may also actively facilitate the secretion of select DAMPs, such as HMGB1, through non-classical pathways- initiating a context-dependent immunomodulatory feedback loop that can further enhance autophagy.[100]

In addition, autophagy functions as a key regulator of immune responses. It plays a crucial role in defending against intracellular pathogens by sequestering and degrading them through a process known as xenophagy,[101] as well as contributing to antigen processing and presentation via MHC class II molecules, supports T cell development and homeostasis, and helps shape adaptive immune responses.

Through these mechanisms, autophagy serves as a multi-layered system that integrates microbial defense, inflammation control, and immune regulation, highlighting its potential as a therapeutic target for infectious, inflammatory, and autoimmune diseases.[102]

In the aging context, basal autophagy levels decline, contributing to the accumulation of cellular damage. The age-related decline in basal autophagy is closely linked to the waning expression of the longevity-associated sirtuin, SIRT6. SIRT6 serves as a vital molecular switch that promotes autophagic flux by modulating the AMPK–mTOR signaling axis and increasing the expression of key autophagy-related genes (ATGs). Under conditions of mild oxidative stress, such as those induced by low-dose singlet oxygen, SIRT6 can be activated to facilitate the clearance of damaged organelles and proteotoxic aggregates that otherwise accumulate during senescence. By transiently restoring SIRT6-mediated autophagy, singlet oxygen may help 'rejuvenate' the cellular clearing apparatus, thereby preserving stem cell function and enhancing systemic resilience against age-related degeneration.[67,69,103] Autophagy also preserves stem cell function across multiple tissues, including muscle, liver, and hematopoietic systems, by maintaining redox and mitochondrial integrity.[104]

5.3.3.2. Nervous System: Maintaining Proteostasis and Synaptic Health

Neuronal cells are especially vulnerable to oxidative damage due to their high metabolic demands and limited regenerative capacity. Autophagy helps remove dysfunctional mitochondria (mitophagy) and protein aggregates, maintaining proteostasis and preventing excitotoxicity. In the context of singlet oxygen exposure, selective autophagy helps prevent the accumulation of neurotoxic proteins such as α-synuclein and phosphorylated tau, processes implicated in neurodegenerative diseases[105,106] including Parkinson's and Alzheimer's[107]. Moreover, autophagy contributes to neural development and synaptic plasticity, influencing learning and memory processes.[106] Dysregulation of autophagy with aging or chronic oxidative stress can exacerbate excitotoxicity and synaptic loss, while controlled activation may confer neuroprotection.[108]

5.3.3.3. Skin: Barrier Maintenance and Oxidative Detoxification

The skin can be viewed as a dynamic immuno-cutaneous ecosystem, where autophagy within skin cells plays a crucial role in preserving immune balance. [109] As the body's largest interface with the environment, the skin is chronically exposed to environmental stressors such as ultraviolet (UV) radiation, pathogens, and oxidants, stressors that can damage keratinocytes, lipids, and extracellular matrix proteins. Autophagy plays a central role in removing harmful intracellular components, maintain cellular homeostasis, and prevent inflammation and premature aging.[110]

A wide range of resident immune cells inhabit the skin, including Langerhans cells, dermal dendritic cells, macrophages, mast cells, and tissue-resident T cells. These immune cells are in ongoing communication with keratinocytes and other structural cells of the skin, collaboratively detecting and responding to pathogens, tumors, allergens, and autoantigens through intercellular signaling involving DAMPs and pathogen-associated molecular patterns (PAMPs) [111].

- Keratinocytes, the predominant cells of the epidermis, are particularly active in this process. In response to UV exposure, oxidative stress, or physical injury, they release DAMPs such as HMGB1, ATP, IL-1α, uric acid, and heat shock proteins. They also express pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and NOD-like receptors,[112] to identify microbial PAMPs like bacterial lipopolysaccharide (LPS), viral RNA, or fungal β-glucans.[111]
- Dermal fibroblasts also serve as key immune modulators. They detect both DAMPs and PAMPs in response to tissue stress, contributing to immune cell recruitment and activation. Importantly, fibroblasts exhibit considerable heterogeneity, with specific subpopulations involved in immune surveillance, epithelial–immune cell communication and sustaining chronic skin inflammation.[113]
- Melanocytes, while less studied in this context, can respond to PAMPs by producing cytokines and chemokines, and may also release DAMPs under oxidative stress, a process implicated in inflammatory skin conditions such as vitiligo.[114]

It has been shown that autophagy supports the function of key skin cells types, including keratinocytes, melanocytes, and immune cells, by regulating inflammation, promoting cell differentiation, and protecting against infection. In dermal fibroblasts, autophagy plays a critical role in modulating responses to DAMPs and PAMPs, limiting excessive immune activation through the degradation of damaged organelles and the regulation of cytokine release.[113] In keratinocytes and epidermal stem cells, autophagy helps preserve skin renewal and barrier function, thereby reducing pathogen penetration and lowering the activation threshold of resident immune cells. In melanocytes, autophagy contributes to pigmentation homeostasis by regulating melanin distribution.[115]

These functions highlight autophagy's essential role in skin wound healing across all key phases: hemostasis, inflammation, proliferation, and remodeling.[116] It promotes keratinocyte proliferation and migration, drives fibroblast activation and differentiation, supports new blood vessel formation (angiogenesis), and helps clear damaged organelles and inflammatory mediators, supporting efficient tissue repair and re-epithelialization. Additionally, autophagy contributes to immune balance by regulating macrophage and neutrophil activity and supporting resolution of inflammation.

When autophagy is disrupted, it can lead to cellular senescence, chronic inflammation, impaired wound healing, and increased risk of pathological scarring or skin cancers. Dysregulated autophagy is also associated with immune-related skin disorders, including atopic dermatitis, psoriasis, and alopecia areata. [109]

It can be concluded that the controlled induction of autophagy may offer a more effective, targeted approach for managing chronic skin conditions. It is also a promising therapeutic target for enhancing wound healing outcomes, treating skin aging and related disorders.

5.3.3.4. Lung: Adaptive Remodeling and Inflammation Control

Autophagy plays a multifaceted role in lung injury and repair by supporting tissue-specific responses such as alveolar regeneration, redox homeostasis, and immune modulation. In particular, autophagy is essential for alveolar type 2 (AT2) progenitor cell–mediated regeneration following lung injury.[117] By promoting glucose, limiting lipid accumulation, and reducing oxidative stress, autophagy supports AT2 proliferation and epithelial barrier restoration.

In acute lung injury (ALI), autophagy interacts with the Nrf2 Nrf2 pathway to enhance antioxidant defense:[118] by degrading the Nrf2 inhibitor Keap1, autophagy facilitates Nrf2 stabilization, contributing to protection against oxidative inflammation and preserving alveolar function. However, as in other tissues, the context and extent of autophagy determine its protective vs. detrimental effects

This balance becomes especially relevant in sepsis-induced lung injury, where autophagy maintains epithelial barrier integrity and regulates immune cell activity. Excessive or prolonged autophagic activation under systemic inflammatory stress may contribute to tissue damage and impaired resolution.[119]

Autophagy also contributes to the pathogenesis of chronic pulmonary diseases:

- In chronic obstructive pulmonary disease (COPD), impaired autophagy disrupts mitochondrial clearance, while excessive autophagy can lead to epithelial cell death and persistent inflammation. Both patterns contribute to tissue destruction and reduced regenerative potential. [120,121]
- In idiopathic pulmonary fibrosis (IPF), deregulated autophagy in epithelial and mesenchymal cells is associated with aberrant fibroblast activation and extracellular matrix accumulation, promoting fibrosis. [122,123]
- In asthma, autophagy modulates immune cell recruitment and cytokine release, influencing airway inflammation and remodeling. Dysregulated autophagy has been linked to enhanced airway hyperresponsiveness and resistance to corticosteroids. [120,124]

Taken together, these findings underscore the context-dependent roles of autophagy in pulmonary health. Targeting autophagic signaling in a cell-type- and disease-specific manner may open new therapeutic avenues for both acute and chronic lung diseases.

5.3.3.5. Cardiovascular System: Cardioprotection and Vascular Homeostasis

Autophagy plays a critical role in maintaining cardiovascular health by supporting the turnover of damaged cellular components, particularly under stress conditions such as ischemia.[125] In cardiac tissues, this process reduces myocardial injury, facilitates tissue remodeling, and promotes recovery after oxidative or mechanical insults. [139]

When autophagy is defective or insufficient, cardiomyocytes accumulate dysfunctional mitochondria, misfolded proteins, and oxidative byproducts, [126] which are hallmarks of cardiac aging and pathology. These impairments contribute to the progression of cardiomyopathies and heart failure. Mitophagy, the targeted removal of damaged mitochondria, is especially vital in the heart, where cells contain a high density of mitochondria and are constantly subjected to high oxidative and metabolic demands. By clearing depolarized mitochondria, mitophagy limits excessive ROS production and protects against ischemia–reperfusion injury. [127]

In the vascular system, autophagy also serves as a key homeostatic mechanism. Endothelial cells rely on basal autophagic activity to preserve nitric oxide signaling, limit vascular inflammation, and prevent atherogenesis. When this regulatory process is impaired, either by aging, chronic inflammation, or external oxidative stimuli such as singlet oxygen, vascular dysfunction and pro-atherogenic changes may ensue. [125]

Importantly, the Nrf2–autophagy axis integrates redox-sensitive signaling with lipid metabolism and immune regulation, offering an additional layer of protection against oxidative and inflammatory stressors. Through this pathway, low-level singlet oxygen may promote adaptive remodeling and preserve vascular tone without triggering damaging oxidative overload. [128]

Together, these findings position autophagy as a central mechanism in cardiovascular resilience, mediating both cardiac and vascular adaptations to oxidative stress, including that induced by singlet oxygen exposure.

5.3.3.6. Skeletal Muscle: Quality Control and Adaptation to Stress

Autophagy maintains skeletal muscle homeostasis by removing dysfunctional proteins and organelles, particularly mitochondria, which is essential for preserving muscle mass, contractile performance, and metabolic adaptability. Mitophagy, the selective degradation of damaged mitochondria, plays a particularly critical role in muscle fibers, where high oxidative load and metabolic turnover necessitate constant mitochondrial quality control. Impairments in this process have been associated with various myopathies, including sarcopenia, muscular dystrophies, and cancer-associated cachexia, as accumulation of dysfunctional mitochondria and protein aggregates leads to fiber atrophy and impaired regeneration.[129,130]

During physiological stress such as endurance exercise or caloric restriction, autophagy is transiently upregulated to promote muscle fiber remodeling, improve mitochondrial efficiency, and mobilize intracellular substrates for energy production. This dynamic regulation involves key redox-sensitive signaling hubs, including AMPK and the Nrf2 pathway, which coordinate the transcriptional and post-translational activation of autophagy machinery in response to oxidative fluctuations.[131] Notably, exercise-induced production of singlet oxygen and other reactive oxygen species may act as a hormetic trigger to fine-tune autophagic activity, enhancing long-term muscle resilience and metabolic health. Understanding the precise balance of autophagic signaling in skeletal muscle may therefore hold therapeutic relevance for age-related muscle decline and metabolic syndromes.

5.3.3.7. Endocrine System: Hormone Regulation and Organelle Turnover

Within endocrine tissues, autophagy plays a dual role in general cellular maintenance and in regulating hormone synthesis and secretion. In peptide-producing cells such as those of the pituitary gland, a specialized autophagic process known as **crinophagy** enables the degradation of excess secretory granules, thus preventing hormone hypersecretion and contributing to hormonal balance. [132]

In steroidogenic cells of the adrenal cortex and testes, autophagy selectively targets mitochondria and smooth endoplasmic reticulum, which are organelles central to steroid biosynthesis. This regulatory role ensures metabolic efficiency and prevents oxidative damage, especially under stress conditions.[133]

Additionally, autophagy in endocrine tissues is modulated by oxidative signals, including ROS such as singlet oxygen, which can trigger redox-sensitive autophagy pathways to adjust hormonal output. Dysfunctional autophagy in endocrine glands has been associated with various pathologies, including diabetes, infertility, and hormone-secreting tumors, due to disrupted secretory or steroidogenic functions.[133,134]

These findings suggest that targeted modulation of autophagy in endocrine tissues could represent a novel therapeutic approach to hormone-related disorders and metabolic diseases.

5.3.3.8. Pregnancy: Placental Development and Immune Tolerance[135]

Autophagy plays a vital role in pregnancy by regulating trophoblast survival, supporting placental development, maintaining immune tolerance, and adapting to the dynamic metabolic demands of both mother and fetus. During early gestation, trophoblasts invade the uterine lining under low-oxygen conditions; here, autophagy facilitates cellular survival and promotes cytotrophoblast differentiation into the invasive phenotype essential for placental formation.

Autophagy also contributes to maternal–fetal immune tolerance by modulating inflammatory cytokine signaling, promoting tolerogenic dendritic cells, and regulating T cell activation. These effects reduce the risk of immune-mediated rejection of the semi-allogeneic fetus and help maintain immunological equilibrium at the maternal-fetal interface. [136]

Additionally, under periods of maternal nutritional stress, autophagy enables intracellular recycling of macromolecules to maintain fetal nutrient supply and energy balance. Dysregulated autophagy, whether insufficient or excessive, has been implicated in various pregnancy complications, including preeclampsia, intrauterine growth restriction (IUGR), and gestational diabetes mellitus (GDM), highlighting its protective function in sustaining placental and fetal health. [137]

5.3.3.9. Liver: Metabolic Regulation and Tissue Regeneration

The liver relies on autophagy for maintaining metabolic balance, detoxification, and redox homeostasis. [130,138] Through lipophagy, autophagy facilitates the degradation of intracellular lipid droplets, contributing to lipid turnover and preventing hepatic steatosis. Simultaneously, mitophagy ensures the removal of dysfunctional mitochondria, protecting hepatocytes from oxidative stress and limiting ROS production. This mitochondrial quality control also supports energy-efficient regeneration of liver tissue following injury, ensuring adequate ATP production while minimizing oxidative damage.[130,139] Dysregulation of hepatic autophagy has been implicated in liver diseases such as non-alcoholic fatty liver disease (NAFLD), alcoholic hepatitis, and fibrosis, underscoring its critical role in hepatocellular protection and regeneration.[140]

5.3.4. Concluding Synthesis: Autophagy as a Hormetic Mediator of Singlet Oxygen Signaling

Across a wide spectrum of tissues and physiological systems, autophagy emerges as a central regulatory process that integrates metabolic signals, oxidative cues, and stress adaptation. The evidence compiled in this chapter reveals a unifying theme: low-level oxidative stress, particularly that induced by singlet oxygen, can serve as a hormetic stimulus, activating autophagic pathways that support cellular renewal, immune modulation, and tissue repair (Figure 5).

In barrier tissues such as the skin and lungs, autophagy preserves epithelial integrity, controls inflammation, and enhances resilience to environmental insults. In skeletal and cardiac muscle, it maintains mitochondrial quality and metabolic homeostasis, particularly during physiological challenges like exercise or ischemia. In the liver, it coordinates lipid turnover and regeneration, while in the endocrine system and placenta, autophagy modulates hormonal synthesis and immune tolerance. Even during pregnancy, autophagy protects the maternal-fetal interface and contributes to placental development.

These diverse functions are governed by overlapping molecular mechanisms, including mitophagy, lipophagy, and redox-sensitive signaling via Nrf2, AMPK, and mTOR, yet are finely tuned to the needs of each tissue context. The dual role of autophagy in both cytoprotection and cell death is especially notable: the intensity and duration of singlet oxygen exposure may dictate whether autophagy serves a survival-promoting or pathological role, reflecting the delicate threshold between adaptive and maladaptive responses.

Understanding this context-dependence and threshold sensitivity is crucial for therapeutic modulation. Pharmacological or photo-induced activation of singlet oxygen may, under controlled conditions, be harnessed to stimulate beneficial autophagy, offering novel treatment avenues in inflammatory, degenerative, metabolic, and fibrotic diseases.

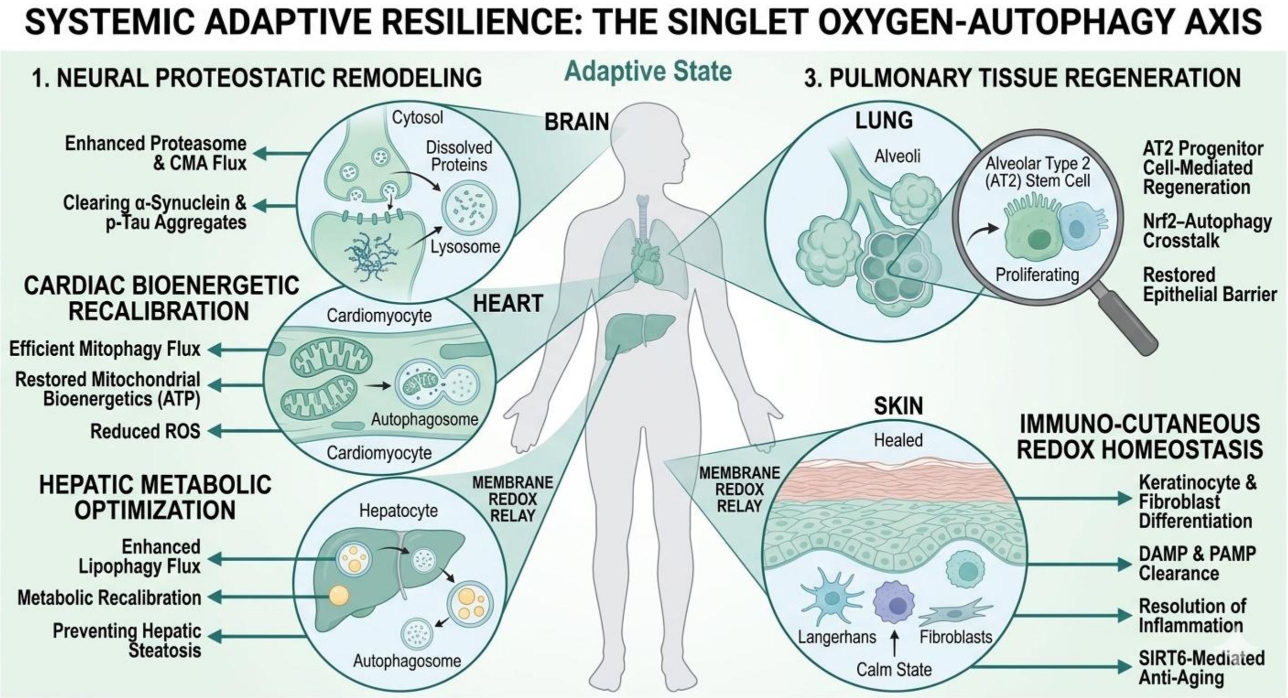

Figure 5 Schematic overview of the systemic adaptive landscape induced by the hormetic singlet oxygen-autophagy relay. The diagram illustrates the transition from a baseline state of cellular stagnation to a state of synchronized systemic recalibration. (1) Neural Proteostasis: Enhancement of autophagic and proteasomal flux facilitates the clearance of neurotoxic protein aggregates (e.g., α-synuclein, p-tau), preserving synaptic health. (2) Cardiac Bioenergetics: Targeted mitophagy eliminates dysfunctional, ROS-leaky mitochondria, restoring ATP production efficiency and myocardial resilience. (3) Pulmonary Regeneration: Activation of the Nrf2-autophagy crosstalk promotes the proliferation of Alveolar Type 2 (AT2) progenitor cells, essential for epithelial barrier restoration and adaptive remodeling. (4) Hepatic Metabolism: Induction of lipophagy optimizes lipid turnover and metabolic flux, mitigating hepatic steatosis and enhancing hepatocellular detoxification. (5) Immuno-Cutaneous Homeostasis: In the skin, the relay coordinates the clearance of DAMPs and PAMPs, facilitating SIRT6-mediated anti-aging effects and resolving chronic inflammatory signals within the dermal-epidermal ecosystem. Collectively, these tissue-specific responses demonstrate how a localized biophysical trigger at the plasma membrane is amplified into a body-wide program of functional rejuvenation and stress resistance.

In summary, autophagy is not merely a stress response- it is a homeostatic amplifier of hormetic signaling. Through its ability to decode singlet oxygen cues into tissue-specific adaptive programs, autophagy bridges environmental sensing with intracellular resilience, affirming its relevance as both a biomarker and target of oxidative medicine.

6. Temporal dynamics of oxidative stress response

The adaptations to oxidative stress unfold in a time-dependent manner[84] and can result in long-lasting physiological benefits (Table 7). Early after oxidative insult, typically within minutes, NF-κB is rapidly activated, leading to a transient pro-inflammatory response that primes the system for defense and cellular recruitment.[141] Within 1–3 hours, these early signals stimulate transcriptional programs, notably via Nrf2, promoting transcription of phase II detoxification enzymes and antioxidant defenses, such as HO-1 and NQO1. As these protective proteins accumulate, they provide an enhanced state of stress resilience lasting up to 48 hours. [84,142,143]

During this intermediate phase, lipid peroxidation by-products like 4-hydroxynonenal (4-HNE) act as secondary messengers that stably modify proteins and influence cell signaling well beyond the initial oxidative event.[142] This extended adaptive phase is further supported by the induction of autophagy, typically induced several hours after exposure, contributing to cellular maintenance by clearing damaged organelles.[141] These processes are complemented by cellular repair mechanisms, activated to restore redox balance and tissue integrity.

Together, these temporally orchestrated responses to moderate oxidative stress, such as that induced by singlet oxygen, foster a sustained hormetic effect that contributes to cellular preconditioning, enhanced metabolic regulation, and long-term resilience to stress.

Table 7 Timing and duration of defense responses to moderate oxidative stress

Response Type	Trigger	Onset (Approx.)	Duration
NF-κB activation	ROS	Minutes	1–3 hours
Nrf2 activation	4-HNE, ROS	1–3 hours	6–48 hours (longer term)
Autophagy induction	Persistent ROS	Several hours	Long-lasting (days)
Cellular repair	Nrf2/ARE genes	After Nrf2 signal	Hours–days

7. Beneficial Physiological Implications of Hormesis induced by Singlet Oxygen-Enriched Air

The transition from cellular signaling to systemic health is mediated by the sustained adaptive responses described previously. By maintaining high levels of cellular integrity and preventing premature apoptosis, low-dose singlet oxygen supports an extended healthspan and enhanced resistance to age-related degeneration.[144] These benefits manifest across several complex physiological systems:

- Systemic Regulation: Hormetic effects contribute to improved blood pressure regulation, cognitive performance, and reproductive success. [28]
- Immune Calibration: Redox homeostasis plays a central role in immune surveillance and pathogen defense while providing a layer of oncological protection.
- Inflammatory Modulation: Specifically, exposure to singlet oxygen-enriched air has been shown to calibrate the activity of monocytes. While these white blood cells require ROS for pathogen defense,[145] excessive production can trigger chronic inflammation.
- Therapeutic Buffering: By moderating this ROS output, singlet oxygen may mitigate collateral tissue damage and prevent hyper-inflammatory states, such as autoimmune responses[146] and cytokine storms[147].

8. From Local External Trigger to Systemic Response: Signal Transduction and Propagation

Given the short lifetime and high reactivity of singlet oxygen, it is unlikely that singlet oxygen itself serves as a long-range traveling messenger within the body. Rather, singlet oxygen is best conceptualized as a localized "biophysical trigger" that initiates secondary messenger cascades capable of propagation through blood, lymphoid trafficking, extracellular vesicle transfer, and neuroimmune reflex arcs. By coordinating these diverse pathways, a localized surface exposure is translated into a widespread, systemic adaptive response.

The therapeutic effects of low-level singlet oxygen-enriched air are initiated primarily through contact with the body's exposed external surfaces,[20] most notably, the skin, respiratory epithelium, sclera, and reproductive tract mucosa. These surfaces act as dynamic biochemical sensors rather than passive barriers.

At the forefront of this sensing are redox-sensitive biomolecules embedded in the plasma membranes of epithelial and immune cells. Upon exposure to singlet oxygen, specific lipids and thiol-containing membrane proteins undergo oxidative modification, which initiates intracellular signalling cascades that regulate gene expression related to antioxidant defenses, inflammation, and cellular repair. [84,148] While resident immune cells are vital mediators, the propagation of the hormetic signal relies on an integrated network of communication involving several pathways:

8.1. Paracrine and Vesicular Signaling: The "Bystander" Relay

While singlet oxygen acts as the initial biophysical trigger, the propagation of its effects beyond the point of contact is driven by the secretion of signaling molecules and membrane-bound packages.

- **The Paracrine Secretome:[149]** Upon exposure to low-level singlet oxygen, epithelial cells and fibroblasts alter their secretome, releasing growth factors such as TGF-β and VEGF, which initiate tissue remodeling and antioxidant defenses in neighboring cells.

- **Extracellular Vesicles (EVs) and Exosomes:**[150] Cells respond to mild oxidative stress by increasing the biogenesis of exosomes, which are nanoscale vesicles that carry "hormetic blueprints," including microRNAs (miRNAs) and protective proteins, to distant sites via the bloodstream.
- **Lipid Peroxidation Products:** Short-lived singlet oxygen can react with membrane lipids to form relatively stable secondary messengers, such as 4-hydroxynonenal (4-HNE), which circulate and act as signaling ligands for distal stress-response pathways.[142]

8.2. Immune Cell Migration

While the skin's immune role is detailed in section 5.3.3.3, it is important to note that similar redox-sensing and signaling occurs in respiratory and ocular surfaces. Resident immune cells, particularly macrophages in the lungs[151] and conjunctiva[152], are responsive to these oxidative cues. These cells not only engage in local tissue maintenance and immune surveillance but also serve as mobile mediators of systemic communication.

Once activated by low-level oxidative stress, macrophages may enter the circulatory system and exert systemic effects, including the regulation of hematopoiesis (the formation of new blood cells) and modulation of inflammation in distant tissues. In the lungs, macrophages help maintain tissue homeostasis during oxidative stress by releasing antioxidant enzymes, engulfing and removing damaged cells, and promoting tissue repair through secretion of growth factors that stimulate epithelial cell proliferation and matrix metalloproteinases (MMPs), which facilitate the breakdown and remodeling of damaged extracellular matrix components. [153]

As oxidative stress often triggers pro-inflammatory signaling,[154] macrophages play a key role in regulating the immune response by releasing anti-inflammatory cytokines that counteract these effects. They also secrete cytokines and chemokines that recruit other immune cells, such as T cells and B cells, to sites of injury, thereby shaping the adaptive immune response, promoting immune tolerance, and supporting the restoration of tissue homeostasis. [155]

Macrophages possess the capacity to migrate throughout the body in response to diverse physiological and pathological signals.[156] During systemic inflammation or disease states, lung-resident macrophages may enter the bloodstream and localize to sites of injury or inflammation, where they contribute to immune regulation and tissue repair. Some may also migrate to the bone marrow, where they influence hematopoiesis and help maintain macrophage populations in organs such as the spleen, liver, and peritoneal cavity.[157]

This migratory behavior is tightly orchestrated by chemokines, cytokines, and other signaling molecules that direct immune cell trafficking and tissue-specific homing.[157] Through this systemic mobility, lung-derived macrophages extend their influence beyond the pulmonary environment, participating in immune surveillance, defense, and the resolution of inflammation throughout the body. These mechanisms support the broader hypothesis that local singlet oxygen exposure may translate into widespread immunomodulatory benefits.

Like pulmonary macrophages, skin and conjunctival macrophages are strategically positioned at external interfaces and respond dynamically to oxidative stress. Upon activation, they release antioxidant enzymes and inflammatory mediators, migrate to lymphoid tissues, or emit systemic signals,[158] contributing to both local defense and broader immune modulation. These properties reinforce the plausibility of systemic effects resulting from surface-level singlet oxygen exposure.

8.3. Neuroimmune Reflex Arcs: The High-Speed Systemic Relay

Because singlet oxygen is a potent "biophysical trigger," it can directly modulate sensory nerve endings at the body's external interfaces (skin and respiratory tract). This initiates a rapid electrical-to-chemical signaling loop that bypasses the need for physical molecule transport.

- **Sensory Transduction at the Interface:[159]** The initial interaction occurs when singlet oxygen-induced lipid peroxidation products or oxidative modifications trigger Transient Receptor Potential (TRP) ion channels on sensory afferent neurons. These neurons act as "oxidative sensors" that convert the chemical stimulus into electrical impulses.
- **The Cholinergic Anti-Inflammatory Pathway:[160]** One of the most well-documented arcs is the Vagus Nerve reflex. Stimulation of peripheral sensory fibers can trigger an efferent signal that leads to the release of acetylcholine (ACh) in distant organs. ACh binds to alpha-7 nicotinic acetylcholine receptors (α7nAChR) on macrophages, effectively "switching off" the production of pro-inflammatory cytokines.
- **Hormetic Signal Amplification:[161]** Through these arcs, a local, low-dose exposure in the lungs can theoretically lead to systemic anti-inflammatory effects in the spleen, gut, or heart within milliseconds.

8.3.1. Genetic Pathways and Central Factors in Neural Signaling

The neural propagation of hormesis involves specific molecular switches that bridge the gap between electrical signals and cellular gene expression:

- **TRPV1 and TRPA1 Channels:[162]** These "redox-sensitive" ion channels in the cell membrane are the primary receptors for oxidative cues. Their activation triggers the influx of calcium (Ca^{+2}), which serves as a second messenger for downstream survival pathways.
- **CREB Activation:[163]** Electrical activity in neurons often leads to the phosphorylation of CREB (cAMP Response Element-Binding protein). This transcription factor promotes the expression of neurotrophic factors like BDNF, which supports neuronal plasticity and stress resistance, a key component of the cognitive benefits reports in the upcoming section.

- **The Adrenergic-Glucocorticoid Axis:**[164] Neuroimmune signals also interface with the hypothalamic–pituitary–adrenal (HPA) axis. Low-level stress can calibrate the release of catecholamines and glucocorticoids, which act on the Glucocorticoid Receptor (GR) to modulate immune cell gene expression, favoring the resolution of inflammation.

8.4. Synthesis: From Localized Trigger to Integrated Systemic Adaption

The multi-channel propagation of the singlet oxygen signal, facilitated by epithelial-vesicular relays, migratory immune cells, and rapid neuroimmune reflex arcs, provides a robust biological framework for the systemic benefits observed in low-dose therapy. This integrated network explains how a short-lived, gas-phase molecule acting on a primary interface (such as the lungs or skin) can induce a state of "systemic hormesis." By simultaneously activating genetic survival pathways (Nrf2/ARE) and calibrating the inflammatory tone via neural and immune signaling, the body transitions into a state of heightened resilience and accelerated repair.

This theoretical foundation is essential for interpreting the clinical and observational data that follow. Whether addressing localized tissue damage or chronic systemic imbalances, the efficacy of singlet oxygen-enriched air relies on this seamless translation of a surface-level biophysical cue into a coordinated physiological response. In the following section, we examine how these mechanisms manifest in specific clinical contexts, ranging from respiratory and dermatological recovery to systemic metabolic and cognitive improvements.

9. Clinical Observations and Applications of Low-Level Ambient Singlet oxygen

Given the systemic reach described above, the potential applications of low-dose singlet oxygen technology span a wide array of physiological systems. The following sections detail the evidence for its role as a supportive adjunct in conventional medical protocols and its impact on recovery, performance, and chronic health management.

This section presents a summary of selected individual patient reports and clinical observations describing subjective or objective functional improvements following low-dose Singlet Oxygen Therapy (SOT), administered via a patented device that generates low-dose singlet oxygen without irradiation.[18]

9.1. Respiratory Health and Pulmonary Homeostasis: Asthma, COPD, and Airway Inflammation

Given that the respiratory epithelium is the most direct interface for gas-phase singlet oxygen, the pulmonary system serves as a primary site for both local repair and the initiation of systemic signals.

9.1.1. Asthma

Asthma is a chronic inflammatory airway disease characterized by bronchial hyperresponsiveness, reversible airway obstruction, and recurrent symptoms such as wheezing, coughing, and breathlessness. Common triggers include allergens, exercise, infections, and environmental irritants. During exacerbations, airway inflammation leads to bronchial constriction, edema, and mucus production, reducing airflow and impairing gas exchange.[165]

Repeated asthma attacks increase the risk of airway remodeling and irreversible airflow limitation. Conventional therapies, including corticosteroids and bronchodilators, are effective but often carry side effects, and many patients remain symptomatic despite optimized pharmacological management.[166] Therefore, there is a growing interest in adjunctive therapies aimed at reducing attack frequency, minimizing reliance on synthetic drugs, and enhancing endogenous healing responses.

Observational Reports of SOT Use in Asthma

Self-reported observations suggest that singlet oxygen-enriched air may confer both acute relief and longer-term benefits for asthma patients. Users have described rapid alleviation of breathlessness during attacks, as well as a gradual reduction in attack frequency and medication dependence. Notably, several individuals who previously required prophylactic steroids for seasonal asthma reported discontinuing their medication after consistent nightly SOT. Some also reported improvements in symptoms associated with airway remodeling.

Preliminary Clinical Study

In a small observational study conducted in Spain by Prof. M. Fegricio,[167] two groups of 25 asthma patients were evaluated over 30 and 60 days. The treatment group used a low-level ambient singlet oxygen generator daily, while the control group received a sham device. Patient-reported outcomes (Figure 6) showed significant improvements in sleep quality and energy in the treatment group, alongside a reduction in weekly asthma attacks (from 1.08 to 0.48 attacks/week). Sixteen patients discontinued all pharmacologic treatment by the study’s end, while no such changes occurred in the control group.

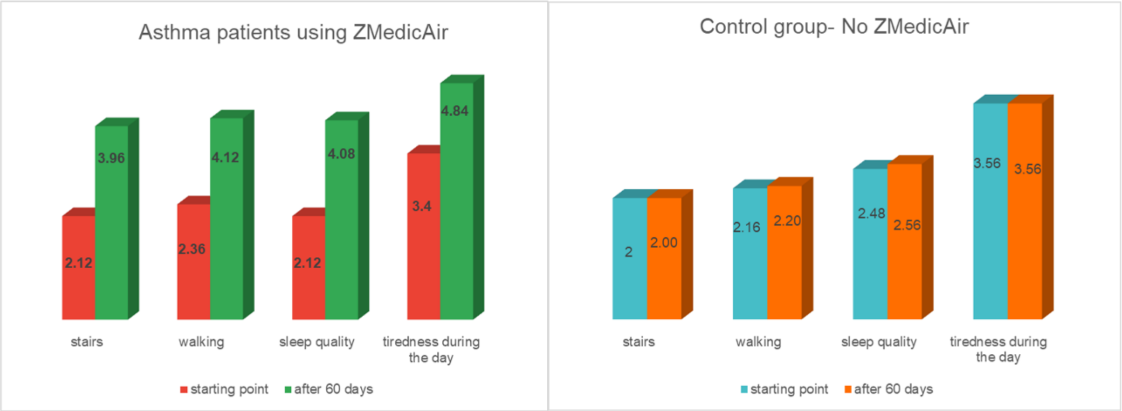

Figure 6 Change in the average rating of energy levels and sleep quality of 25 asthma patients, with (left graph) and without (right graph) daily usage of low-level ambient singlet oxygen generator over a period of 60 days. ***Error! Bookmark not defined.***

Proposed Mechanism: While preliminary and based on observational data, these findings are consistent with the mechanistic rationale discussed in Sections 5 and 7. Specifically, the controlled oxidative signal generated by singlet oxygen may activate redox-sensitive anti-inflammatory and epithelial repair pathways. These processes could improve airway tone and mucosal integrity, thereby lowering susceptibility to bronchoconstriction. However, controlled trials are essential to validate these effects and rule out placebo influences or seasonal fluctuations.

9.1.2. Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD), a progressive respiratory disorder encompassing chronic bronchitis and emphysema, is characterized by persistent airflow limitation, mucus overproduction, and alveolar destruction. As the third leading cause of death in the United States,[168] COPD currently has no cure, only supportive treatments are available, aimed at slowing disease progression and managing symptoms.

Patients with advanced COPD often experience debilitating breathlessness, frequent exacerbations, and, eventually, dependence on supplemental oxygen. Without a lung transplant, this condition ultimately proves fatal. In this context, low-level singlet oxygen exposure has been anecdotally associated with perceived improvements in breathing and function.

Several users have reported enhanced respiratory ease and a reduction in oxygen dependence within days of initiating therapy. A few individuals with advanced disease described regaining the ability to work and travel, improvements that warrant systematic investigation. In some cases, spirometry conducted after a month of use revealed increases in forced expiratory volume (FEV_1) and improved FEV_1/FVC ratios, outcomes not commonly observed in late-stage COPD with non-invasive methods.

These preliminary findings align with earlier observational reports, such as a small, unpublished study in which patients with moderate-to-severe COPD underwent a four-week regimen of singlet oxygen inhalation therapy.[169] Participants demonstrated modest improvements in FEV_1, peak expiratory flow, and a reduction in symptom burden and bronchodilator use. Although the study lacked a control group and peer review, its outcomes parallel known physiological mechanisms described in Sections 5 and 7, including redox-modulated inflammation control, epithelial repair, and enhanced mitochondrial turnover.

The following case observations provide individual examples of patients with moderate to severe COPD who reported respiratory improvements following routine use of SOT.

Case 1: Functional and Spirometric Improvement in a Patient with Severe COPD Following SOT

A 67-year-old male with a 20-year smoking history (approx. 1 pack/day) was diagnosed with severe COPD. Despite smoking cessation, his respiratory condition progressively worsened, with persistent wheezing, dyspnea, and pulmonary congestion that impaired basic activities such as walking and showering.

Initial treatment included corticosteroids (prednisone) and antibiotics (cephalexin), though his lung function continued to deteriorate. FEV_1 declined from 52% to 35% predicted within a year. At this point, physicians recommended long-term oxygen therapy and pulmonary rehabilitation.

In April 2017, the patient initiated daily SOT. Within days, he reported subjective improvement in breathing and energy levels. Over the following weeks, he resumed travel and returned to work.

Spirometry one month into therapy indicated an increase in FEV_1 from 35% to 58% predicted, with further improvement (63%) over the next year. No changes in standard medications were recorded during this time.

Case 2: Remission of COPD With Discontinuation of Inhaled Therapy Following SOT

A 57-year-old female with heavy smoking history was diagnosed in 2020 with moderate COPD, confirmed by spirometry (FEV_1 ~83%; FEV_1/FVC <80%). She experienced progressive dyspnea, wheezing, and exertional fatigue that interfered with her occupation as a children’s entertainer.

In 2021, the patient began nightly SOT. During the first week, she experienced productive coughing with green sputum, possibly reflecting a mucolytic or detoxification response. Over the next two months, she noted substantial improvements in breathing and physical stamina. Wheezing fully resolved within three months.

Initially prescribed four inhaled medications, including corticosteroids and bronchodilators, the patient gradually discontinued them over a six-month period. By year's end, she remained asymptomatic and off all inhalers.

Pulmonary function tests in 2023 and 2025 showed normalized spirometry (FEV_1 >95%; FEV_1/FVC ≥83%). A pulmonologist concluded that the patient no longer met diagnostic criteria for COPD.

The patient has since resumed working and other physical activities, including running and long walks, without any recurrence of respiratory symptoms. She currently reports full respiratory health.

Proposed Mechanism: These cases represent only 2 examples of multiple cases in which users with COPD have experienced long-term COPD remission, both in symptoms and lung function, following SOT, suggesting that singlet oxygen-enriched air may assist in reducing the oxidative burden in the lungs. By triggering the Nrf2-mediated antioxidant response within alveolar macrophages and epithelial cells, the therapy helps neutralize the chronic ROS production characteristic of COPD. Beyond inflammation, the activation of neuroimmune reflex arcs and the potential modulation of nitric oxide (NO) bioavailability may contribute to improved capillary dilation and more efficient oxygen exchange.

9.1.2.1. *Healthcare Cost Implications of Asthma and COPD*

In addition to its profound clinical burden, COPD imposes a substantial financial toll. An analysis done in 2020[170] estimated that respiratory diseases cost the U.S. healthcare system $170.8 billion annually. Asthma accounted for the highest costs, followed by COPD. For asthma, prescription drugs represented the largest share (48%), while for COPD, hospitalizations (28.8%) and prescriptions (28.5%) were primary cost drivers.

Most COPD-related spending was concentrated in adults over 45, with nearly 70% covered by public insurers. In contrast, asthma-related costs were more evenly distributed across age groups.

These data highlight the potential value of adjunct therapies that can reduce exacerbation rates, hospitalizations, and medication use. If low-dose SOT is validated in future clinical studies, it may represent a cost-effective strategy that leverages endogenous repair pathways rather than relying solely on pharmacological suppression.

9.1.3. Pneumonia

Pneumonia remains a significant global health concern, affecting over 500 million individuals annually and accounting for approximately 4 million deaths, which is about 7% of all global mortality. It is the leading infectious cause of death in children under five, particularly in regions with limited access to medical care, such as South Asia and sub-Saharan Africa.[171]

The condition arises when an infection, which can be bacterial, viral, or fungal, triggers inflammation in the lungs, leading to alveolar fluid accumulation, impaired gas exchange, and respiratory distress. Diagnosis and treatment are often complicated by uncertainty around the causative pathogen and the rise in antimicrobial resistance, which can hinder effective, targeted therapy.

Observational Reports of SOT Use in Pneumonia

Several users of singlet oxygen therapy (SOT) have anecdotally reported significant symptomatic relief within **1–3 days** of starting therapy. These effects included:

- Improved breathing comfort
- Reduced coughing and phlegm production
- Relief of chest tightness or discomfort
- Increased physical energy and vitality

Some individuals also noted a shortened recovery timeline, which is typically protracted in pneumonia, often lasting several weeks.

Proposed Mechanism: The reported improvements in respiratory function and recovery following singlet oxygen therapy may be explained by its capacity to modulate redox-sensitive biological pathways. Low-dose oxidative stimulation is known to reduce local inflammation, promote epithelial repair, and enhance mucociliary clearance, key processes in the resolution of pneumonia. Additionally, by supporting immune regulation and restoring redox balance in the lung microenvironment, singlet oxygen may facilitate more efficient pathogen clearance and tissue recovery. These mechanisms, detailed in Section 5, offer a biologically plausible framework for understanding how SOT could accelerate symptom resolution and shorten recovery time in individuals with pneumonia.

9.1.4. Excess Phlegm and Mucociliary Function

Excessive phlegm production is a common and distressing symptom across a broad spectrum of respiratory conditions, including asthma, [172] COPD,[173] pneumonia,[174] allergic rhinitis,[175] chronic exposure to tobacco smoke[176] and other conditions[177]. While mucus is essential for trapping pathogens and particulates,[178] abnormal accumulation or viscosity can impair airflow, reduce oxygenation, and heighten infection risk. In severe cases, it contributes to hypoxemia, atelectasis, and respiratory failure.[179]

Conventional therapies, which include expectorants, mucolytics, bronchodilators, and physical airway clearance techniques, often offer limited relief and may be impractical or burdensome, especially in patients with reduced mobility or chronic illness. Moreover, these treatments do not address upstream dysregulation in inflammatory or redox pathways that often underlie mucus hypersecretion.

Reports on Mucus Reduction Following SOT

Following SOT, users have consistently reported improvements in mucus-related symptoms, including reductions in phlegm volume and viscosity. These reports span a variety of respiratory conditions, including asthma, COPD, pneumonia, allergies, and chronic smoking-related bronchitis. Notably, some individuals described the expulsion of thick, dark mucus during early exposure, interpreted as a "detoxification phase," followed by an enduring sense of airway clearance and improved breathing.

Case: Discontinuation of Airway Suctioning in a Non-Communicative Patient

non-communicative adult with a severe brain injury required routine nightly suctioning to prevent aspiration due to excessive phlegm production. Following SOT, the need for suctioning diminished and ultimately ceased. His mother and caregiver reported improved sleep and overall well-being for both herself and the patient.

Proposed Mechanism: These effects are consistent with redox-modulatory mechanisms described in Section 5. Low-dose singlet oxygen likely reduces local airway inflammation, downregulating the inflammatory pathways that drive excess mucus production.[180] It may also stimulate epithelial repair[117] and enhance ciliary activity[181], both of which are crucial for effective mucociliary clearance. Additionally, redox-sensitive modulation of mucus viscosity may lower its viscosity, facilitating easier expectoration.[182]

Taken together, these effects suggest that singlet oxygen may help restore the mucus production-clearance cycle, particularly in individuals with impaired mucociliary function or chronic inflammation. As a non-invasive, low-burden approach, this therapy could complement existing treatments or offer relief to patients with refractory symptoms.

9.1.5. Biological Basis for Low-Level Singlet Oxygen Beneficial Effect for Respiratory Diseases

The beneficial respiratory effects of low-dose singlet oxygen stem from its ability to induce mild, transient oxidative stress, triggering a hormetic cellular response. This controlled redox perturbation activates protective signaling pathways without overwhelming endogenous antioxidant defenses.

Key mechanisms include the upregulation of antioxidant enzymes,[183] such as superoxide dismutase, catalase, and glutathione peroxidase, modulation of pro- and anti-inflammatory mediators, and promotion of epithelial repair and regeneration.[117] These responses collectively restore redox balance, attenuate tissue inflammation,[184] reduce bronchoconstriction,[185] and enhance mucociliary clearance,[180,181] all of which are essential for resolving respiratory infections and managing chronic airway disorders.

Additionally, singlet oxygen exposure has been proposed to stimulate autophagy and mitochondrial biogenesis, contributing to enhanced metabolic resilience[186] and immune competence within pulmonary tissues. These redox- and autophagy-mediated adaptations, as described in Sections 5 and 7, offer a plausible mechanistic foundation for the observed improvements in respiratory function.

Taken together, these findings support low-dose singlet oxygen as a non-invasive and physiologically adaptive modality for promoting respiratory health, particularly in conditions characterized by chronic inflammation, redox imbalance, and epithelial dysfunction.

9.2.COVID-19 and Related Pulmonary Inflammatory Conditions

The COVID-19 pandemic drew global attention to the devastating consequences of dysregulated immune responses in viral pneumonia, where excessive cytokine release, oxidative stress, and alveolar damage contribute to acute respiratory distress syndrome (ARDS) and long-term pulmonary complications such as fibrosis and reduced oxygen diffusion capacity.[187] In the absence of curative antiviral therapies for severe cases, clinical management has relied primarily on supportive interventions such as mechanical ventilation and ECMO, both of which associated with high morbidity and long-term impairment of lung function.[188]

9.2.1. Reports on COVID-19 Alleviation with SOT

While no controlled clinical trials have yet assessed the efficacy of low-dose SOT in COVID-19 management, a number of anecdotal reports describe apparent improvements in respiratory function, oxygenation, and symptom resolution following its use. The following case summaries are included for observational context:

Case 1: Rapid Symptom Resolution and Functional Recovery

A 15-year-old patient with confirmed COVID-19 presented with high fever (~40 °C), significant labored breathing, and loss of taste and smell. Following the initiation of SOT, the patient reported improved respiratory comfort, restoration of ambulation, and return of olfactory and gustatory function.

Case 2: Recovery from Severe Respiratory Distress

A 36-year-old recording artist experiencing severe respiratory symptoms during acute COVID-19 infection, including significant pulmonary involvement and breathing difficulties, reported progressive respiratory improvement and resumption of full functional capacity after initiating SOT.

Case 3: Prevention of Hospitalization and Respiratory Recovery

A 39-year-old woman with acute deterioration following COVID-19 infection, including loss of taste and smell, nausea, marked weakness, and episodes of respiratory distress with declining oxygen saturation, requiring emergency medical attention. After initiating SOT, she described phlegm expectoration and steady improvement in breathing and energy, with eventual discontinuation of supplemental oxygen and symptom resolution. Her family members, who also began SOT, reported similar improvement.

These reports, while anecdotal and uncontrolled, align mechanistically with the proposed redox-modulating and immunoregulatory effects of low-dose singlet oxygen described in Sections 5 and 7. Their observational consistency underscores the need for rigorous clinical trials to investigate its Physiological potential in acute viral respiratory illnesses.

9.3. Long COVID

Post-acute sequelae of SARS-CoV-2 infection (PASC), or long COVID, is increasingly recognized as a multifactorial syndrome characterized by persistent symptoms lasting weeks to months beyond the resolution of acute illness. According to the World Health Organization, manifestations may include fatigue, dyspnea, cognitive dysfunction ("brain fog"), autonomic instability, and multisystem involvement, often with delayed onset. [189]

Emerging evidence links these symptoms to chronic low-grade inflammation, endothelial dysfunction, and mitochondrial dysregulation,[190] aligning closely with the redox imbalances and impaired energy metabolism described in Section 3. Long COVID pathophysiology includes microvascular injury, immune dysregulation, and altered oxygen delivery, which are all factors contributing to persistent oxidative stress and impaired cellular bioenergetics.

Low-dose singlet oxygen exposure has been anecdotally associated with improvements in these domains. Observational reports describe functional gains in respiratory endurance, cognitive clarity, and fatigue reduction, suggesting that singlet oxygen may support microcirculatory recovery, mitochondrial adaptation, and modulation of chronic inflammation.

These outcomes are consistent with the hormetic mechanisms discussed in Sections 5 and 7, particularly NRF2 activation, mitochondrial biogenesis, and autophagy induction. Although formal validation is required, the absence of systemic toxicity and the feasibility of continuous use make SOT a candidate for further research in post-viral syndromes.

9.4. Dermatological Applications: Skin as a Primary Hormetic Interface

While the lungs serve as an internal gateway, the skin represents the most expansive external interface for singlet oxygen-enriched air. Because the skin is naturally adapted to manage environmental oxidative stressors, such as UV radiation, it is highly sensitive to the low-dose "biophysical trigger" of singlet oxygen. Beyond its role as a physical barrier, the skin functions as an active immuno-cutaneous ecosystem where autophagy and Nrf2-mediated pathways preserve homeostatic balance. Clinical observations suggest that low-dose, ambient singlet oxygen therapy (SOT) may support the resolution of chronic inflammatory and degenerative skin conditions by activating these endogenous repair mechanisms.

Case 1: Alleviating Acne and Reducing Scarring

A female teenager described suffering from Chronic inflammatory acne, significant erythema (redness), pruritus (itchiness), and secondary psychological distress (social anxiety). Previous pharmacological interventions (topical ointments) were reported as ineffective. After utilizing SOT using a fan-like device, rapid resolution of active acne lesions and significant improvement in skin texture (smoothing of scar tissue) was observed. The young woman also reported immediate relief from acute pruritus (itchiness) associated with insect bites and emergent pimples.

Proposed Mechanism: The subject's transition from chronic inflammation to skin clearance and scarring reduction highlights the clinical utility of the pathways established in earlier chapters:

- **Immune Recalibration (Resolution of Erythema):** By shifting skin-resident macrophages toward a pro-resolving phenotype (as established in Section 8.2), SOT halted the cycle of chronic redness and swelling, allowing the tissue to exit the inflammatory phase and begin active repair.
- **Structured Remodeling (Smoothing of Scar Tissue):** The reported smoothing of the skin suggests the activation of fibroblast-led remodeling. Utilizing the Nrf2 and MAPK/ERK pathways (detailed in Section 6), the therapy likely balanced collagen deposition and enzymatic breakdown, preventing disorganized scar formation and promoting healthy re-epithelialization.
- **Neural Desensitization (Rapid Pruritus Relief):** The "immediate relief" from itching (acne and mosquito bites) is a direct application of the Neuroimmune Reflex Arcs (Section 8.3). Localized oxidative cues likely modulated TRP ion channels on sensory nerves,[191] providing near-instantaneous symptomatic relief by dampening the electrical firing of itch-sensing pruriceptors.

Case 2: Relief for Atopic Dermatitis

A male infant, aged 5 months, presented with a history of severe atopic dermatitis (AD) originating at 3 weeks of age. The clinical presentation was characterized by widespread erythematous rashes and inflammatory plaques, localized primarily to the flexural folds (the inner elbows, behind the knees, neck, underarms and so on). The condition was associated with significant pruritus and cutaneous pain, resulting in chronic physical discomfort and sleep disturbances. Initial management included topical corticosteroids; however, the clinical response was transient, with symptomatic relapse occurring within 48–72 hours post-application, indicating a cycle of corticosteroid dependency and recalcitrant inflammation.

Following the introduction of nightly low-dose ambient SOT (generated via non-irradiative gas-phase technology) placed adjacent to the infant's sleeping area, a progressive alleviation of symptoms was observed. Within six weeks of continuous nightly exposure, the inflammatory rashes achieved total clinical resolution. The cutaneous surface returned to a healthy, smooth state with no evidence of residual scaling or erythema. Long-term follow-up indicates that maintenance of nightly SOT has prevented further relapses, suggesting a stabilization of the skin barrier and a potential shift in the local inflammatory cytokine profile.

Case 3: Relief of Severe Dermatitis

A 44-year-old woman suffered for years from severe chronic eczema. Prior to treatment, the patient experienced persistent scaling and pruritus on the elbows and knees, which were only partially managed with topical corticosteroids. Within four weeks of SOT exposure, the patient observed a visible reduction in plaque thickness and redness, alongside a cessation of itching. By the eighth week, the lesions had reached near-total remission, and the patient was able to discontinue topical steroid use.

Proposed Mechanism: The observed clinical benefits in dermatological health are likely mediated by the following hormetic processes described in Sections 5 and 7:

- **Activation of the Nrf2-GSH Axis**: Low-dose singlet oxygen stimulates the synthesis of glutathione, which is essential for maintaining the thiol-disulfide balance in skin proteins and supporting cellular regeneration.
- **Induction of Selective Autophagy**: By removing oxidatively damaged proteins and dysfunctional mitochondria (mitophagy) in keratinocytes, SOT may rejuvenate the cellular clearing apparatus, thereby preserving skin barrier integrity and limiting the release of damage-associated molecular patterns (DAMPs) that drive chronic inflammation.
- **Immune Modulation**: Singlet oxygen-induced redox signaling may recalibrate resident immune cells, such as dermal dendritic cells and macrophages, promoting an anti-inflammatory phenotype that limits tissue overactivation and supports the resolution of inflammatory lesions.

These observations highlight SOT's potential as a non-invasive, drug-free adjunctive therapy for adolescent acne, warranting further investigation into its effects on sebum composition and dermal cytokine profiles.

9.5. Effects on Sleep Quality and Sleep Disorders

One of the earliest and most consistently reported effects by individuals undergoing SOT, including both healthy subjects and those with chronic conditions, is a subjective improvement in sleep quality. These improvements include reports of faster sleep onset, longer uninterrupted sleep, and fewer nocturnal awakenings. Such effects are notable given the central role sleep plays in physiological repair, cognitive functioning, and immune modulation.[192]

Sleep is closely tied to redox biology.[193] During restful sleep, antioxidant systems are restored, and metabolic byproducts, including ROS, are effectively neutralized. Conversely, sleep deprivation has been shown to elevate oxidative stress in the brain and peripheral tissues, disrupt redox-sensitive signaling pathways,[194] and increase the production of pro-inflammatory cytokines such as TNF-α and IL-6. These inflammatory mediators can also impair sleep regulation, potentially reinforcing a feedback loop of oxidative stress, immune dysregulation,[192] and poor restorative capacity[195]. This may contribute to increased risk for chronic diseases such as cardiovascular and neurodegenerative disorders.[196]

Case 1: Remission of Obstructive Sleep Apnea Without CPAP

A 69-year-old male diagnosed with mild-to-moderate obstructive sleep apnea (OSA) in 2018 (AHI 7.0; SpO_2 nadir 86%) was unable to tolerate continuous positive airway pressure (CPAP) therapy. Beginning in 2020–2021, he initiated nightly use of a passive, low-dose singlet oxygen-emitting device during sleep. Over the following years, he experienced a *reported* improvement in sleep quality and energy, coinciding with modest weight loss (BMI decreased from ~29 to 24.7).

A follow-up sleep study in 2025 revealed normalized breathing parameters (AHI 6.8, mean SpO_2 93%, nadir 87%, sleep efficiency 91.4%), and CPAP was deemed unnecessary. Although causality cannot be established, the temporal association raises the possibility that SOT contributed to improved upper airway function and respiratory stability during sleep. This represents a rare instance of OSA remission without CPAP, surgery, or pharmacological intervention.

Proposed Mechanism: Evidence from preclinical and clinical studies suggests that moderate, transient oxidative stimuli, such as those induced by singlet oxygen, can restore redox balance through hormetic mechanisms that recalibrate circadian rhythms[197] and stress responses. This may include the resetting of dysfunctional sleep-wake cycles and attenuation of hyperarousal states commonly associated with insomnia and anxiety. [198,199]

Users commonly describe experiencing noticeable improvements within the first 24 hours of singlet oxygen exposure. These rapid effects may reflect immediate neurophysiological adaptations via redox-sensitive systems involved in melatonin synthesis, hypothalamic signaling, or neuronal hyperexcitability.[200] While speculative, the observed restoration of sleep continuity may suggest an indirect role for singlet oxygen in modulating neuroimmune interactions[201] and systemic stress resilience.

9.6. Snoring alleviation

Snoring and sleep-disordered breathing are widespread issues, affecting over 40% of the population at some point in their lives with varying severity. These conditions disrupt sleep architecture by limiting airflow and preventing entry into deeper, restorative sleep phases. Snoring typically results from partial obstruction of the upper airway, often due to relaxed throat muscles, excess soft tissue, nasal congestion, or tongue positioning, leading to vibratory noise as air passes through narrowed passages.

In otherwise healthy individuals, snoring may present as a benign nuisance, typically impacting bed partners. However, in more severe presentations such as obstructive sleep apnea (OSA) or asthma, repeated airway collapse can result in intermittent hypoxia, oxidative stress, and increased cardiovascular and metabolic risks. [202]

Anecdotal reports from users of SOT have described significant reductions in snoring frequency and intensity, including among individuals not directly using the device. In over 90 reported cases, individuals receiving SOT for unrelated conditions, noted that their bed partners, many of whom were habitual snorers, experienced diminished or absent snoring during the treatment period.

One particularly striking case involved an asthma patient who began nightly SOT; shortly thereafter, his wife, previously a consistent snorer, ceased snoring entirely. This effect occurred without her direct use of the device, raising the possibility that passive exposure to singlet oxygen-enriched air may influence upper airway function.

Proposed Mechanism: Several biological mechanisms could plausibly explain these effects. Low-level oxidative stress induced by singlet oxygen may elicit hormetic responses that promote subtle increases in upper airway muscle tone,[203] thereby reducing the likelihood of collapse during sleep. It may also attenuate inflammation, a key contributor to airway narrowing in conditions such as allergic rhinitis and sinus congestion. Given that OSA and snoring are associated with chronic inflammation and oxidative stress in the upper airway, the redox-balancing effects of singlet oxygen may help reduce tissue swelling, improve airflow, and lower snoring severity.

While these observations are mechanistically consistent with findings described in Sections 5 and 7, they remain preliminary. Controlled clinical studies are needed to determine the extent and reproducibility of SOT's impact on snoring and upper airway physiology.

9.7. Alleviation of Chronic Nightmares and Post-Traumatic Stress Symptoms

Chronic nightmares, that are distressing, recurrent dreams that disrupt sleep, affect approximately 2–6% of adults and are especially common in individuals with posttraumatic stress disorder (PTSD), anxiety, or depression.[204] Despite their impact on sleep quality and mental health, nightmares are frequently underdiagnosed and undertreated. They are rarely spontaneously reported by patients and often overlooked by clinicians, despite well-documented associations with increased risk of suicide, insomnia, and emotional dysregulation.[205,206] This persistent clinical neglect has contributed to diagnostic and therapeutic gaps, leaving many individuals untreated despite significant sleep disruption and psychological distress.

Case: Resolution of Trauma-Associated Nightmares Following SOT

A woman who experienced daily trauma-related nightmares for eight years following an intraoperative awareness event reported immediate and lasting resolution of her symptoms after beginning SOT. Her symptoms, including dissociative aftereffects, reportedly ceased within the first nights of exposure, enabling sustained sleep restoration for the first time in years.

Proposed Mechanism: These effects may be mediated by redox-sensitive neural pathways involved in fear processing and REM regulation. Singlet oxygen-induced low-level oxidative stress may activate antioxidant and anti-inflammatory responses in limbic structures such as the amygdala and prefrontal cortex. These adaptations could stabilize neural activity and reduce hyperarousal, thereby improving REM sleep continuity and reducing nightmare intensity.[207]

Although mechanistically plausible and consistent with preclinical literature on redox-neural interactions, these observations remain anecdotal. Controlled studies are required to confirm therapeutic efficacy in nightmare disorders or trauma-related sleep disturbances.

9.8. Enhancing Exercise Recovery and Performance

A recent study by Hsieh *et al*.[208] reported enhanced exercise performance and physiological resilience following exposure to low-dose singlet oxygen energy (SOE). Participants using a passive, non-invasive singlet oxygen-generating device during exercise showed improvements in cardiorespiratory function, muscle recovery, and subjective vitality.

Rather than attributing these effects solely to SOE, as the writers do, they may reflect generalizable redox-based mechanisms consistent with known physiological adaptations to exercise. Physical activity induces transient oxidative stress that activates hormetic signaling pathways, including Nrf2-mediated antioxidant responses[209] and mitochondrial biogenesis via AMPK and PGC-1α.[210] These responses are part of mitohormesis, a process by which low-level mitochondrial stress improves energy metabolism, mitochondrial quality control (via fusion/fission and mitophagy), and resistance to subsequent challenges.[211]

During recovery, moderate ROS exposure stimulates AMPK signaling, facilitating glucose uptake, fatty acid oxidation, and mitochondrial renewal via upregulation of PGC-1α.[212] In parallel, increased expression of antioxidant enzymes, such as superoxide dismutase and heme oxygenase-1, mitigates inflammation and protects muscle tissue from oxidative damage.[213] These established processes likely underlie the recovery-related benefits observed by Hsieh et al.

Thus, while the SOE device appears to confer tangible benefits, these improvements are interpretable within the broader framework of redox-based adaptive physiology, as discussed in Sections 5 and 7. Future studies comparing singlet oxygen-based delivery to other hormetic interventions, using biomarkers and controlled exercise protocols—could provide a clearer understanding of its relative efficacy.

9.9. Anemia and Blood Disorders

Anemia is a condition in which there is a reduced number of red blood cells or hemoglobin molecules, which are responsible for transporting oxygen throughout the body. Consequently, reduced oxygen supply can impair tissue and organ function. In 2019, around 25% of the global population was affected by anemia (over 1.5 billion people), with the highest prevalence observed in children under five, reaching nearly 50%.[214]

One of the most common forms is anemia of chronic disease, also known as anemia of inflammation.[215] This type arises in the context of chronic illnesses such as autoimmune disorders, cancer, or kidney failure, and is characterized by impaired erythropoiesis and disturbed iron metabolism. The resulting anemia may further impair recovery by limiting oxygen delivery to tissues and suppressing immune competence.

Anecdotal reports suggest that exposure to low-level singlet oxygen may support red blood cell production, including in cases of longstanding or treatment-resistant anemia.

Case: Hematologic Improvement in a Patient with Refractory Anemia

A non-communicative adult patient with dementia, thyroid dysfunction, cardiac disease, and severe anemia (hemoglobin <8 g/dL) had not responded to conventional treatments for several years. After two months of SOT, hemoglobin levels increased to 10 g/dL and reached 10.2 g/dL after six months—levels not previously attained under standard care. Additionally, improvements in thyroid and renal function were also reported.

Proposed Mechanism: Mild oxidative stimulation may activate redox-sensitive transcription factors, supporting hematopoiesis and counteracting inflammation-induced suppression of red blood cell production.[216] In particular, singlet oxygen may influence the hypoxia-inducible factor (HIF) pathway, which regulates erythropoietin (EPO) production in the bone marrow.[217] Ferritin and iron metabolism may also be modulated through oxidative signaling, contributing to more effective erythropoiesis.[218,219] In parallel, the mitigation of chronic inflammation via redox modulation may relieve inhibitory signals that suppress bone marrow activity in anemia of inflammation.

While these mechanisms are theoretically consistent with observed improvements, further research is essential to determine whether low-dose singlet oxygen exposure has a reproducible effect on hematologic parameters, and under which conditions it may be clinically relevant.

9.10. Mitigating Cancer Treatment Side Effects and Enhanced Recovery

Chemotherapy remains one of the most commonly used and effective treatments for various types of cancer, administered in an estimated 50–60% of cases during some phase of treatment.[220] While its efficacy is well established, chemotherapy is frequently accompanied by debilitating side effects, including nausea, fatigue, alopecia, depression, and anemia, which can jeopardize patient compliance and survival. Reducing the severity of these adverse effects is essential to improving both treatment tolerance and outcomes.

Exposure to low levels of singlet oxygen has been anecdotally reported to reduce toxicity and improve treatment tolerance in some individuals. The following clinical observations are presented alongside plausible biological mechanisms, though they require controlled validation.

Case 1: Cancer treatment side-effects: Myelosuppression, Nausea, Fatigue, and Depression

A 50-year-old patient undergoing chemotherapy for lymphoma presented with profound exhaustion, anemia (Hb 11.2 g/dL), breathlessness, and depression. Following the initiation of SOT, the patient reportedly experienced a rapid improvement in energy and his general mood. After one month, hemoglobin levels increased to 12.6 g/dL. Subsequent rounds of chemotherapy were better tolerated, with notably reduced nausea and fatigue.

Proposed Mechanism: These effects may result from hormetic activation of protective cellular pathways, including Nrf2-mediated antioxidant responses,[42] mitochondrial biogenesis,[221] enhanced ATP production and improved redox homeostasis.[222] Modulation of inflammatory signaling,[223] and improved mitochondrial function could account for the observed improvements in fatigue and emotional resilience.

Case 2: Radiation-Induced Neuropathy and Sensory Disturbances

A patient with a history of extensive radiation therapy developed peripheral neuropathy characterized by numbness and an atypical persistent “sharp smell,” consistent with radiation-induced oxidative injury and microvascular compromise, which promote neuronal apoptosis, demyelination, and fibrotic entrapment of nerves.[224] After initiating SOT, the patient reported a complete resolution of both sensory disturbances.

Proposed Mechanism: These outcomes may reflect activation of redox-sensitive neuroprotective pathways, including restoration of mitochondrial redox balance, Nrf2-regulated antioxidant responses, and modulation of glial-driven neuroinflammation (e.g., JNK and ERK signaling). These mechanisms are consistent with those previously discussed in Sections 5 and 7.

9.11. Ocular Surface Health and Relief from Dry Eye Symptoms

Dry eye disease is a chronic disorder characterized by insufficient tear production or excessive tear evaporation, resulting in ocular discomfort, surface inflammation, and visual disturbances. Its pathophysiology often involves immune-mediated processes, including macrophage activation and the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which amplify epithelial damage and perpetuate symptoms.[225]

Conventional therapies, such as artificial tears, corticosteroids, and immunosuppressants like cyclosporine, primarily aim to stabilize the tear film and suppress inflammation. [226] More recently, antioxidant and redox-regulating strategies have emerged as promising adjuncts, given growing evidence that oxidative stress is a key contributor to dry eye pathology. [227]

Anecdotal user reports suggest that exposure to low-level, non-irradiative singlet oxygen may alleviate symptoms of both chronic dry eye and allergic periorbital irritation. Users have described reduced ocular dryness and irritation, as well as rapid relief from itching, redness, and swelling commonly associated with allergic conjunctivitis. These improvements were sometimes observed within hours to days of initiating therapy.

Proposed Mechanisms

These effects may be mediated by the redox-sensitive and immune-modulatory pathways discussed earlier in the review. Singlet oxygen, when delivered at hormetic doses, likely induces mild oxidative preconditioning, which downregulates inflammatory cascades and stabilizes epithelial function. Specifically, suppression of mast cell degranulation and eosinophilic infiltration may reduce the release of histamine, leukotrienes, IL-4, IL-5, and IL-13, thereby lowering vascular permeability and sensory nerve activation.[70] Additionally, SOT may restore epithelial barrier integrity through Nrf2-driven antioxidant responses (Section 5.2), increasing resistance to allergens and environmental irritants. These mechanisms may also contribute to broader immune tolerance at the mucosal surface, as previously observed in respiratory and gastrointestinal contexts (Section 7).

Taken together, these observations support the possibility that singlet oxygen may offer a non-pharmacological, mechanism-based intervention for both dry eye and allergic periorbital conditions. Rather than masking symptoms, it may address underlying biological dysfunction, illustrating a potential translational application of redox-hormetic principles.

9.12. Future Research

In parallel to growing anecdotal observations presented above, academic research into singlet oxygen as a therapeutic agent is also emerging. A 2024 doctoral dissertation by Grimwood at the University of Derby[228] laid the groundwork for a randomized, double-blind controlled trial investigating the physiological and psychological effects of nightly low-dose singlet oxygen exposure in individuals with COPD. While clinical results were not yet reported at the time of submission, the study involved over 180 participants and applied validated tools such as the CAT, ESS, and PSQI. Its rigorous patient-centered design and emphasis on redox-modulating therapies underscore the increasing legitimacy of this research direction and the need for peer-reviewed, controlled evaluations of clinical outcomes.

10. Ruling Out the Placebo Effect: Evidence from Non-Conscious and Indirect Exposure

One of the major challenges in evaluating novel therapeutic interventions, particularly those involving subtle physiological modulation, is distinguishing true biological effects from placebo responses. Placebo responses are mediated through central nervous system circuits involving expectation, emotional modulation, and dopamine-linked reward pathways.[229] These mechanisms can produce transient symptom relief, but do not activate cellular repair pathways, alter redox signaling, or regenerate damaged tissue.[230]

In the case of singlet oxygen-enriched air, several cases presented in this review provide strong evidence that the physiological benefits associated with low-dose singlet oxygen are not merely psychological. These observations, particularly in individuals who were unaware of the intervention or incapable of expectancy-based responses, provide strong evidence for a biological, rather than psychological, basis for the effects.

As previously described in the section on mucociliary function, a severely brain-injured young man, fully bedridden and non-communicative, experienced a sustained and documented reduction in the need for routine suctioning following the introduction of the singlet oxygen-enriched air generator. The cessation of routine suctioning, previously required nightly to prevent choking, occurred without any awareness or behavioral change on the part of the patient, offering compelling support for a direct physiological effect of the therapy on mucociliary function.

A similar conclusion can be drawn from the case reported under the “anemia and blood disorders” section, where an elderly man with dementia and chronic illness exhibited a sustained rise in hemoglobin levels after exposure to singlet oxygen-enriched air. Given his cognitive impairment and lack of knowledge regarding the intervention, the improvement in anemia, thyroid, and renal parameters could not have been driven by expectancy effects.

In the context of oncological support, the case of a terminal lymphoma patient, documented under supporting cancer treatment and recovery, showed an unexpectedly rapid return of verbal communication, appetite, and increased energy shortly after the initiation of low-level ambient singlet oxygen generator use. Although this patient may have been marginally aware of environmental changes, the timing, magnitude, and multifaceted nature of the improvements, including enhanced chemotherapy tolerance and rising hemoglobin levels, suggest physiological mechanisms were at play.

Further support comes from multiple reports involving young children and infants, discussed under respiratory conditions and excess phlegm, who experienced improvements in breathing, mucus clearance, and sleep quality. Given their developmental stage and limited awareness, placebo responses are not a plausible explanation in these cases.

These observations, taken together across multiple populations and physiological systems, indicate that the benefits of singlet oxygen exposure are not the result of suggestion or expectation. Instead, they reflect a pattern of redox-modulated physiological responses consistent with hormetic activation of repair and defense pathways.

11. Singlet Oxygen: A Pathway to Regulated Preventive Therapy

Low-dose exposure to singlet oxygen represents a fundamentally different therapeutic strategy compared to conventional pharmaceuticals. While most drugs act by targeting specific receptors or pathways, singlet oxygen functions mainly through hormesis, which is a mild oxidative stimulus that activates broad, evolutionarily conserved defense systems. These include autophagy, upregulation of antioxidant enzymes, and metabolic adaptation.[106,144]

Such pathways are self-limiting, highly regulated, and sensitive to context. This enables singlet oxygen to maintain physiological balance without the risks of chronic overstimulation or suppression often associated with pharmacological agents.[231] These characteristics make it especially relevant to preventive medicine, where early modulation of redox signaling can reduce inflammation, enhance cellular resilience, and delay disease progression.[124]

Moreover, unlike many drug-based interventions, the protective responses triggered by singlet oxygen are not heavily influenced by individual genetic polymorphisms or metabolic profiles. This broad compatibility increases its potential applicability across diverse populations.[144] Together, these features position singlet oxygen as a novel, non-pharmacological tool for modulating redox-sensitive biological networks to prevent disease onset and maintain long-term physiological equilibrium.

12. Conclusions

This review highlights the emerging role of singlet oxygen as a hormetic agent capable of inducing protective and adaptive cellular responses when delivered at low concentrations. Historically regarded primarily as a cytotoxic species, singlet oxygen is now recognized for its ability to modulate key signaling pathways that regulate antioxidant defenses, autophagy, and inflammation.

By activating regulatory circuits such as the Nrf2-Keap1-SIRT6 axis, MAPK signaling, and JNK-mediated autophagy, mild oxidative stress initiated by singlet oxygen promotes detoxification, cellular repair, and long-term resilience to environmental and physiological challenges. In this context, SIRT6 acts as a vital epigenetic and metabolic switch, amplifying Nrf2-dependent antioxidant transcription while simultaneously maintaining mitochondrial integrity and suppressing pro-inflammatory NF-κB signaling.

These mechanistic insights are supported by case observations presented in this review, which document improvements in a wide array of conditions, including asthma, COPD, sleep disturbances, anemia, and chemotherapy-related fatigue, following exposure to singlet oxygen-enriched air. The singlet oxygen-enriched air generator, which enables safe and non-invasive delivery of singlet oxygen under ambient conditions, represents a promising tool for translating these physiological mechanisms into therapeutic and preventive applications.

Together, the evidence supports the view that low-dose singlet oxygen can serve as a valuable adjunct in regenerative, anti-inflammatory, and resilience-enhancing interventions. The preservation and activation of central longevity proteins like SIRT6 likely underpin the systemic benefits observed, thus laying the groundwork for wider integration of singlet oxygen technology into health-supportive and anti-aging strategies.

13. Data Availability:

The clinical observations and anecdotal reports presented in this review are derived from publicly accessible video and audio testimonials available online across various platforms and languages. These public testimonials have been carefully reviewed and verified by the author for relevance to the discussed topics. While these qualitative accounts are not structured datasets suitable for conventional repository deposition, their public availability enhances transparency. Further formal clinical studies are warranted to systematically validate these observations.

14. Ethical approval and consent statement:

This article is a scientific review and does not present any new research involving human or animal participants requiring ethical approval. All anecdotal reports and observational cases mentioned are derived from publicly accessible video and audio testimonials, described in aggregate, and without any identifying information. The original consent for public dissemination of these testimonials rests with the individuals who provided them. Therefore, no additional ethical approval or individual consent was required for this review.

15. Competing interests:

Dr. Yael Abraham serves as an independent consultant for the patent registration and scientific aspects related to the low-dose singlet oxygen technology (patented in the U.S., South Korea, China, India, Mexico, Europe, and other countries worldwide). She is not involved in the marketing or sales of products derived from this technology and receives no compensation from sales volume. Her current research focuses on the biological effects of low-dose singlet oxygen. This consulting role does not influence the content or conclusions of this review.

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The author was responsible for scientific consulting during the development of the device, gathering clinical observations from users, and interpreting findings through existing biomedical literature. The author also prepared and wrote the review manuscript.

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