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Review

Beauty Begins in the Cell—The Role of Ubiquitination

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Abstract

Skin aging is fundamentally a breakdown in cellular quality control rather than a strictly aesthetic phenomenon. To address this, the present conceptual review provides an interdisciplinary analysis of the biological foundations of skin aging, spotlighting ubiquitination as the master regulator of proteostasis. Complex, interdependent mechanisms are responsible for protecting skin cells, mediating crucial interplay between the ubiquitin-proteasome system (UPS), autophagy, and molecular chaperones. By examining how the UPS governs proliferation, oxidative stress responses, and inflammation, the consequences of its age-related dysregulation become evident. Bridging advanced cell biology with regenerative dermatology, the presented analysis pivots away from direct pharmacological modulation. Instead, it emphasizes biologically grounded strategies to protect and stabilize the cellular environment. In conclusion, the review establishes a "well-aging" paradigm that integrates cutting-edge proteostasis research with practical applications for cosmetic formulation design and proactive skincare.

Keywords: ubiquitination; ubiquitin-proteasome system (UPS); proteostasis; well-aging; skin biology

1. Introduction

Modern cosmetology has decisively shifted away from marketing promises, entering an era of science-backed skincare where the boundary between traditional cosmetics and dermocosmetics is rapidly blurring. Contemporary formulations align closely with pharmacology and cutaneous biology, driven by a preference for evidence-based ingredients such as small-molecule signal peptides [1,2], biomimetic ceramides [3,4], stable forms of vitamins [5], and new-generation retinoids [6]. Their efficacy is further maximized by advanced delivery systems, including liposomes, niosomes, nanoemulsions, and polymer carriers, which safely enhance bioavailability through controlled release [7–10]. The market is increasingly interested in minimal formulation from multifunctional raw materials [11] to generate highly efficient formulas free of unnecessary additives.

Beyond the components of modern cosmetic formulation, the cosmetic industry is being profoundly shaped by EU regulations [12], which emphasize sustainable development. Biotechnological sourcing of active ingredients [13] and AI tools [14] are pioneering the personalization of cosmetics based on lifestyle and skin type. In the context of the discussed topic, a clearly established trend is supporting the skin's microbiota, not by

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bacterial destruction but through developing cosmetics that use pre- and postbiotics [15] to protect the epidermal barrier. Modern daily care aims to be less aggressive, supporting skin physiology and modulating oxidative stress. This shift in the narrative from "anti-aging" to "well-aging" or "pro-aging" (pro-longevity) aims to address the cellular level of skin biology. In this article, the discussed evolution parallels a fundamental paradigm shift in topical care: moving from conventional, invasive "anti-aging" stimulation toward a "well-aging" or "pro-longevity" concept that actively supports skin physiology and modulates oxidative stress [16,17]. Because the structural integrity of the skin, from extracellular matrix collagen to vital cellular enzymes, relies entirely on protein health, modern well-aging strategies must prioritize proteostasis process. As a result, the cellular quality control, particularly the ubiquitin-proteasome system (UPS) responsible for proteostasis, is becoming a key issue in skin biology [18–20]. Efficient ubiquitination mitigates proteostatic decline, providing the biological foundation for tissue regeneration and overall structural balance.

While the molecular pathways of the UPS are well-documented in systemic aging and oncology, their systematic translation into non-pharmacological, preventative dermatology and cosmetic formulation remains fragmented. Therefore, the primary objective of this conceptual review is to bridge this gap by establishing a comprehensive, cell-biology-based framework that links progressive UPS dysregulation directly with skin-layer phenotypes. Furthermore, this paper evaluates the critical crosstalk between the UPS, autophagy, and molecular chaperones under environmental stress, providing cosmetic formulators and dermatologists with biologically grounded, environment-modulating strategies to mitigate proteostatic overload and preserve cutaneous longevity within the framework of cellular quality control.

2. From Superficial Aesthetics to Cellular Homeostasis

For decades, cosmetology and aesthetic dermatology have focused primarily on the superficial signs of skin aging, such as wrinkles (rhytides, creases, or folds), loss of firmness, and uneven skin tone (dyspigmentation). While certain early interventions, most notably topical retinoids [6], successfully targeted cellular turnover, traditional strategies relied heavily on masking symptoms or mechanically resurfacing the skin, offering short-term aesthetic gains without addressing the biological root causes of senescence at the cellular level.

Today, innovative cosmetology is pivoting decisively from surface toward cellular homeostasis [17,21], defined as the ability of skin cells to maintain metabolic, structural, and functional balance. In this approach, youthful skin appearance is no longer an isolated goal but rather a phenotypic reflection of biological processes such as protein quality control, regulation of the inflammatory response, redox balance, and proper cell differentiation.

As a result, skin aging is increasingly defined as a process of gradual loss of cellular balance [22]. The accumulation of damaged proteins, chronic oxidative stress, and persistent low-level inflammation lead to the disorganization of cellular functions, which, in the long term, manifests as structural and aesthetic changes in the skin. The objective is not to artificially "stop time," but to sustain the functional efficiency of skin cells as biological age advances. Consequently, modern cosmetics are now designed to gently but effectively modulate the cellular environment rather than force aggressive, short-term remodeling, treating aesthetic appearance as a natural outcome of long-term biological balance.

This evolution reflects cosmetology's maturation into a functional, interdisciplinary science bridging cell biology, pharmacology, and regenerative medicine [23].

3. Skin Aging as a Cellular and Molecular Process

Skin aging is a complex, multi-stage biological process where clinical aesthetic changes serve as visible manifestations of underlying homeostatic disruption. At the cellular level, the aging process primarily disrupts epidermal keratinocytes and dermal fibroblasts. As we age, their capability to proliferate, differentiate, and regenerate is reduced, which is associated with factors such as telomere shortening, cell cycle disruptions, and accumulating DNA and protein damage. When cellular repair mechanisms are overwhelmed, these damaged cells do not simply undergo apoptosis; instead, many enter a state of cellular senescence. While permanently exiting the cell cycle, these senescent cells remain metabolically active and secrete a potent array of pro-inflammatory cytokines, chemokines, and matrix-degrading enzymes—a phenomenon known as the senescence-associated secretory phenotype (SASP) [24,25]. This chronic, low-grade inflammation further depletes cellular adaptability, leaving the skin highly susceptible to environmental stress.

In young skin, protein quality control systems, including molecular chaperones, the UPS, and autophagy, effectively eliminate damaged, misfolded, or redundant proteins. With age, the efficiency of these mechanisms deteriorates, leading to the toxic accumulation of defective proteins and disruption of cellular function [26,27].

In this context, aging is increasingly defined not merely as the passage of biological time, but as the gradual loss of a cell's ability to maintain its internal molecular balance. Age-related decline of the UPS affects skin layers. In the epidermis, impaired proteostasis in keratinocytes contributes to barrier dysfunction and altered epidermal renewal. In the dermis, reduced protein quality control in fibroblasts diminishes the structural integrity of the extracellular matrix, directly causing the loss of skin firmness and elasticity [28,29] (Figure 1).

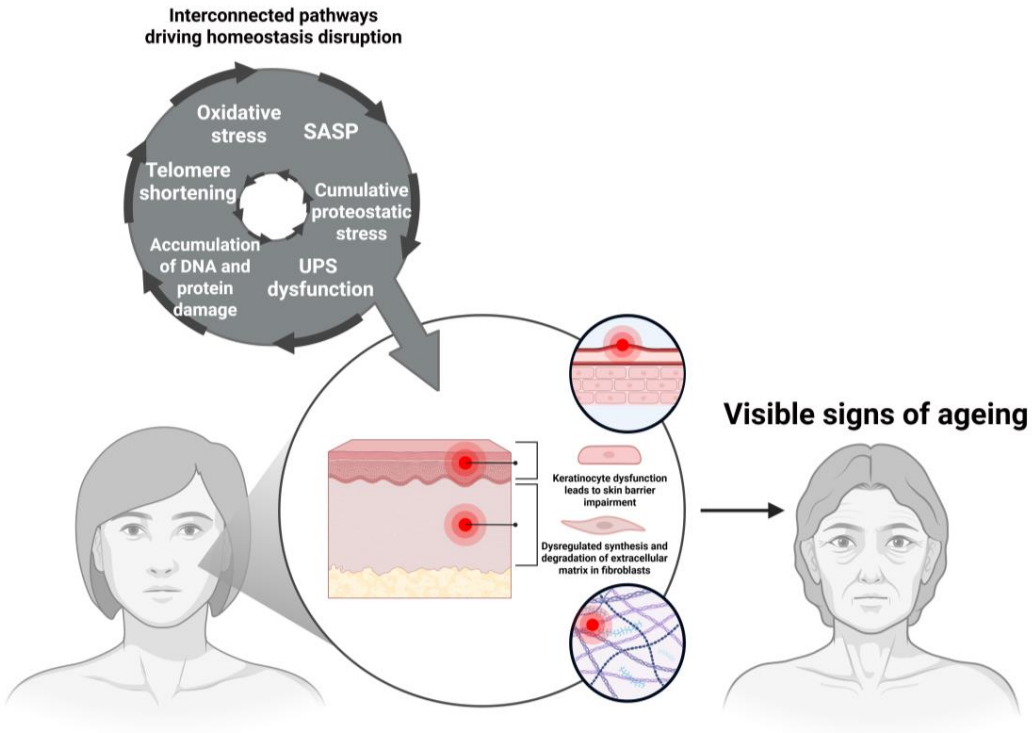


Figure 1. Interconnected cellular mechanisms involved in skin ageing (Skin ageing is associated with a network of processes, including telomere shortening, oxidative stress, accumulation of DNA and protein damage, cellular senescence, and the UPS dysfunction. Together, these changes impair keratinocyte and fibroblast function, contributing to skin barrier dysfunction, extracellular matrix alterations, and visible signs of skin ageing).

4. The Ubiquitin-Proteasome System: Molecular Mechanisms

The UPS is a highly specialized, precisely regulated cellular mechanism that controls the quality, quantity, and function of proteins. As a central element of the proteostasis network, it enables the dynamic adaptation of the cellular proteome to changing physiological and environmental conditions. Unlike non-selective degradation, UPS is characterized by strict substrate specificity, enabling it to act as a regulator of key biological processes rather than merely a degradative system [18,20].

The UPS primarily functions through ubiquitination—an enzymatic, post-translational modification in which ubiquitin, a small 76-amino acid protein, is covalently attached to lysine residues of the target protein. This process occurs via a three-step enzymatic cascade involving a ubiquitin-activating enzyme (E1), a transfer enzyme (E2), and a ubiquitin ligase (E3). Among these, E3 ligases play a key biological role, as they are responsible for substrate recognition and determine the selectivity of the entire system. The wide diversity of E3 ligases in eukaryotic cells enables precise control of the fate of individual proteins, which is fundamental for regulating the cell cycle, stress response, and skin cell differentiation [18].

Ubiquitination is not a uniform process; the way ubiquitin molecules are linked determines the protein's fate. Monoubiquitination typically functions as a regulatory signal, while polyubiquitination can lead to both protein degradation and modulation of its activity. Classic polyubiquitin chains linked by lysine 48 residues act as signals directing proteins for degradation in the proteasome, while other linkages participate in the regulation of signaling pathways, the inflammatory response, and repair mechanisms. In this view, ubiquitin serves as a complex molecular code controlling the fate of proteins in the cell [19,20,30].

The target degradative element of the UPS is the 26S proteasome—a massive, multisubunit protein complex composed of a 20S catalytic core and two 19S regulatory molecules responsible for substrate recognition, unfolding, and translocation. The proteasome degrades the marked proteins into short peptides that can be further utilized in metabolic or immunological processes. A defining feature of the proteasome is its capacity to execute rapid and tightly controlled degradation, enabling the immediate modulation of key regulatory protein levels [18,30,31] (Figure 2).

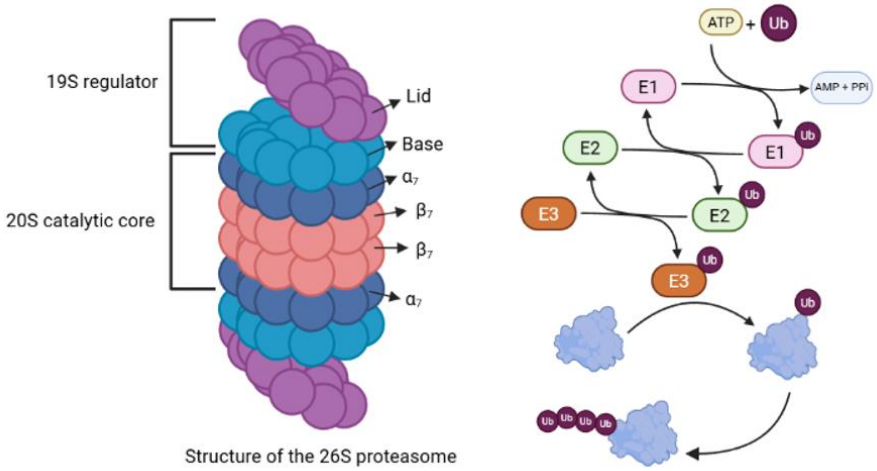


Figure 2. Structure of the 26S proteasome and mechanism of ubiquitination.

The UPS plays a central role in maintaining cellular homeostasis not only by removing damaged proteins, but also by regulating proteins that control cell cycle progression. One of the critical regulatory proteins controlled by the UPS is p53, which, under physiological conditions, is maintained at low levels through its interaction with the E3 ubiquitin ligase Mdm2, which marks it for proteasomal degradation [18,19,32]. In response to cellular stress,

such as oxidative stress, this interaction is disrupted, leading to stabilization and accumulation of p53, followed by activation of signaling pathways involved in cell cycle arrest. When this arrest persists, cells transition into a senescent state characterized by permanent loss of proliferative ability and the development of a distinct secretory phenotype, linked to chronic inflammation. Although UPS does not directly eliminate senescent cells, it plays a crucial role in regulating their formation by controlling regulatory proteins such as p53 [33]. Age-related decline in UPS efficiency impairs the degradation of regulatory and damaged proteins, leading to disrupted cellular signaling and increased proteostatic stress. This dysfunction prolongs p53-dependent signaling activation, facilitating the transition of stressed cells into senescence. Therefore, the correlation between the UPS and cellular senescence is indirect but still significant. Dysregulation of this system promotes the development of senescent cells, linking proteostasis decline with one of the fundamental processes of biological aging [19,32].

In skin cells, the UPS plays a crucial role in regulating the keratinocyte cell cycle, epidermal proliferation and differentiation, response to oxidative stress, and adaptation to UV radiation [19,23,30,34–39]. For instance, recent skin-specific investigations have highlighted that the turnover and processing of highly specialized epidermal barrier proteins, such as profilaggrin, are intimately linked to localized proteasomal activity. The proteasome directly participates in the turnover of profilaggrin through multiple degrons and ubiquitination-prone residues, determining its stability and preventing premature keratinocyte death before keratohyalin granules are properly formed [40]. Precise degradation of short-lived regulatory proteins enables rapid, reversible changes in signaling pathway activity, which is essential for maintaining homeostasis in the dynamically changing skin environment [21,41,42]. Exposure to UV radiation and other physical and chemical factors leads to the formation of damaged or misfolded proteins, which must be efficiently removed to prevent their toxic effects. Under conditions of a properly functioning system, this process is effective, protecting cells from the accumulation of defective protein structures [37]. However, with age, a gradual decline in the UPS efficiency is observed. Reduced proteasome activity, changes in E3 ligase expression, and overload of the system with an increasing number of damaged proteins reduce its regulatory capacity. The consequence of this process is the accumulation of proteins with disturbed structure and function, which is one of the key molecular mechanisms of skin aging [22,34,35,38,39].

UPS dysfunction affects both the epidermis and dermis. In keratinocytes, it impairs epidermal differentiation and renewal, weakening the skin barrier and increasing susceptibility to external factors. In dermal fibroblasts, disruption of protein quality control promotes abnormal synthesis and degradation of extracellular matrix components, exacerbating the loss of skin firmness and elasticity [34,43–45].

The UPS is responsible for selective protein degradation, regulating, among other things, the cell cycle, oxidative stress, and the inflammatory response. Excessive stimulation or disruption can lead to accelerated degradation of structural proteins (e.g., collagen, filaggrin), impaired keratinocyte differentiation, and a weakened epidermal barrier.

This can result in irritation, dry skin, increased sensitivity, and, consequently, accelerated aging [19].

An overactive UPS can modulate the metabolism of cytokines and transcription factors (e.g., NF-κB) by intensifying inflammatory and cytotoxic processes. It potentially exacerbates chronic microinflammation, increases susceptibility to cellular damage, and promotes oxidative stress [46].

Improper regulation of the degradation of proteins controlling cell division can disrupt the balance between proliferation and apoptosis, potentially increasing the risk of abnormal long-term changes. Some cosmetic substances, particularly those with low molec-

ular weight, lipophilic properties, and those used chronically or on damaged skin, may hypothetically modulate the UPS or cellular pathways if they penetrate the body, affect other tissues, influence the protein balance in cells outside the skin, and even cause allergic reactions or hypersensitivity [29]. Peptide-based active ingredients and enzyme modulators may induce biological interactions through non-selective action or by influencing more than one cellular pathway [47].

Viewed through the lens of modern skin biology, the UPS is the central regulator of proteostasis, whose proper functioning maintains the long-term structural and functional integrity of the skin. From this perspective, dermatological and cosmetic strategies that align with the concept of well-aging focus not on directly intervening in degradative mechanisms, but rather on creating an environment conducive to their effective and harmonious functioning [16,48,49]. This approach redefines the concept of skin aesthetics as a consequence of maintained cellular and molecular balance.

5. Proteostasis Network Systems in Skin Cells

Proper skin cell function requires tight control over the quality, quantity, and spatial distribution of proteins. The complex web of mechanisms maintaining this equilibrium is known as the proteostasis network [39,50–52]. This network encompasses the highly coordinated processes of protein synthesis, folding, post-translational modification, transport, and degradation. Contemporary skin biology emphasizes that the UPS does not operate in isolation; rather, it is one pillar of a dynamic triad, interacting continuously with molecular chaperones and autophagy (Figure 3). In skin cells like keratinocytes and fibroblasts, this network must constantly adapt to intense environmental stressors, including UV radiation, oxidative stress, and chemical agents [37,42].

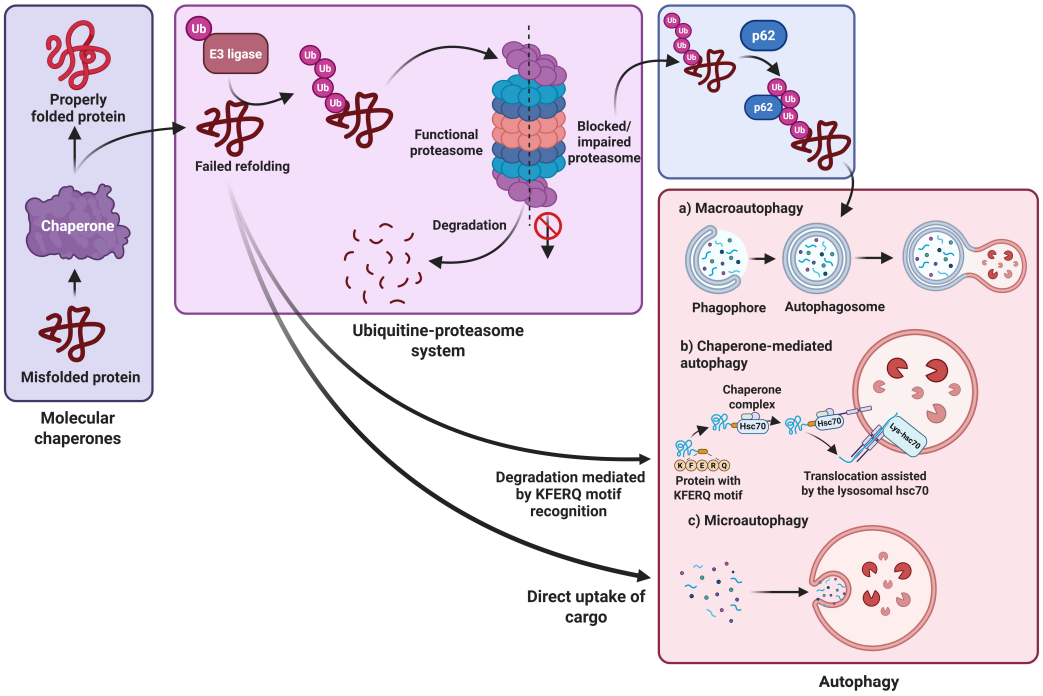


Figure 3. Schematic overview of the cellular proteostasis network (Molecular chaperones, the UPS, and autophagy cooperate to preserve protein quality control. Misfolded proteins are initially subjected to chaperone assisted refolding. If refolding fails, proteins are ubiquitinated and targeted for proteasomal degradation. When proteasomal capacity is exceeded, autophagy provides a complementary degradative pathway through macroautophagy, CMA, and microautophagy. Age-related decline in these mechanisms contributes to protein accumulation and loss of cellular homeostasis during skin ageing).

These proteostasis components (molecular chaperones, the UPS, and autophagy) form a dynamically collaborating network that constantly compensates to maintain cellular equilibrium (Figure 3). Within this network, molecular chaperones serve as the first line of defense [27,52,53], supporting the proper folding of newly synthesized proteins and preventing the formation of toxic aggregates. While chaperone expression temporarily spikes under stressful conditions to help cells adapt, this response weakens with age, promoting the accumulation of misfolded, distorted proteins [54].

When refolding fails, degradation systems take over. A fundamental distinction between these degradative machineries lies in their degree of selectivity. The UPS operates as an exclusively selective mechanism, relying on precise enzymatic tagging to identify and degrade individual, short-lived, or misfolded proteins without disrupting surrounding structures. Conversely, when the burden of defective proteins exceeds UPS capacity, or when the cell must dispose of massive protein aggregates and dysfunctional organelles (such as damaged mitochondria), autophagy provides a critical, large-scale compensatory pathway. Unlike the UPS, autophagy encompasses both non-selective and selective processes. To fully comprehend this compensatory triad, it is essential to distinguish the specific autophagic pathways active in skin cells. Autophagy in the cutaneous environment operates through distinct mechanisms: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) [55,56]. While macroautophagy can function as a non-selective bulk degradation process triggered by acute nutrient starvation, in the context of UV-induced skin aging, it acts as a highly selective clearance mechanism. Specific forms of selective macroautophagy, such as mitophagy and aggrephagy, are crucial for removing UV-damaged mitochondria and toxic protein aggregates in dermal fibroblasts and keratinocytes [57]. In parallel, CMA provides a highly selective, receptor-dependent degradation route where chaperones (e.g., Hsc70) recognize specific KFERQ-like motifs on target proteins, translocating them directly into the lysosome [58]. Furthermore, while its specific cutaneous mechanisms remain less characterized, microautophagy—the direct lysosomal engulfment of cytoplasmic cargo—also contributes to localized protein clearance and organelle turnover. Crucially, the interaction between the UPS and autophagy is physically tethered by specific molecular components, most notably the p62/SQSTM1 adaptor protein [59,60]. When the proteasome becomes overwhelmed by the sheer volume of oxidized proteins, or when ubiquitinated proteins form large aggregates that cannot pass through the narrow 20S proteasome barrel, p62 acts as a vital bridge. It binds to these ubiquitinated cargoes and directly anchors them to LC3 on the autophagosomal membrane, effectively shifting the degradative burden from the UPS to selective macroautophagy [59,60]. Together, this triad ensures the long-term viability of skin cells; however, the age-related decline of these clearance mechanisms disrupts this vital synergy. In aging skin, the gradual decline of both selective macroautophagy and CMA limits the removal of dysfunctional organelles and regulatory proteins. Over time, this progressive imbalance collapses the entire network, resulting in the toxic accumulation of damaged proteins, the exhaustion of cellular energy, and a severe reduction in the skin's regenerative capacity [49,51].

This network collapse is heavily exacerbated by exogenous factors. Reactive oxygen species (ROS), UV radiation, and inflammation induce oxidative protein modifications and impair UPS activity (Figure 4). Specifically, UV exposure generates distinct ROS, including superoxide anion radicals and hydrogen peroxide, which induce severe oxidative modifications, such as protein carbonylation and the generation of oxidized lipids like squalene monohydroperoxide. The oxidation of skin surface squalene is a critical event that directly compromises the stratum corneum integrity, exacerbating inflammation and further overloading the cellular repair machinery [61]. Importantly, these ROS do not merely cause random structural damage; they directly manipulate specific signaling pathways intricately

tied to the UPS. For instance, under moderate oxidative stress, the UPS regulates the Keap1/Nrf2 pathway [62]. Keap1, an adapter for E3 ubiquitin ligase, is oxidized by ROS, halting the ubiquitination and subsequent degradation of the Nrf2 transcription factor. Stabilized Nrf2 then translocates to the nucleus to mount a massive antioxidant response [62]. Conversely, chronic UV-induced ROS trigger the NF-κB inflammatory signaling pathway by stimulating the UPS to rapidly degrade IκB (the inhibitor of NF-κB). Therefore, the UPS acts as a master switch: its efficiency dictates whether the skin cell successfully mounts an antioxidant defense (via Nrf2) or succumbs to chronic inflammation (via NF-κB). Reduced proteasomal function leads to the accumulation of dysfunctional proteins and disruption of proteostasis. This creates a vicious cycle: oxidative stress destabilizes the proteome, leading to an overproduction of damaged proteins right as the UPS and autophagy lose their clearance capacity [63,64]. ROS induce modifications of lipids, proteins, and nucleic acids, further destabilizing the cellular environment and activating proinflammatory pathways. Chronic, low-grade inflammation is a characteristic feature of aging skin and further accelerates the dysfunction of the proteostasis network, creating a chain of mutually exacerbating disorders [65,66].

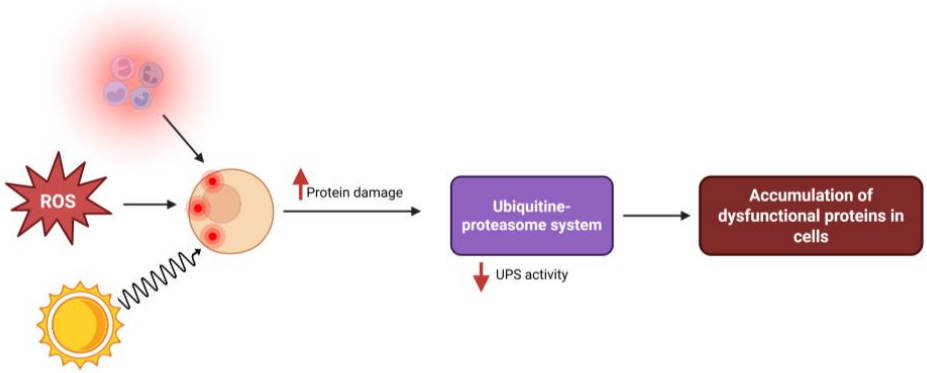


Figure 4. ROS, UV radiation, and inflammation as factors disturbing proteostasis.

Disturbances in proteostasis significantly impair the function of both the epidermis and the dermis. As previously established, this manifests in keratinocytes as impaired differentiation and a compromised epidermal barrier, and in fibroblasts as accelerated degradation of the extracellular matrix, leading to the visible loss of skin firmness [23,34,49].

Understanding skin aging through the lens of proteostasis network dysfunction, rather than viewing it as an inevitable, unalterable degenerative process, provides a profound foundation for modern dermatological and cosmetic strategies [41,67]. Aligned with the concept of well-aging, these strategies focus on protecting holistic cellular homeostasis: mitigating oxidative and inflammatory stress, preventing network overload, and supporting the skin's intrinsic adaptive mechanisms [16,21]. True skin aesthetics, in this paradigm, emerge naturally from the long-term biological resilience of the complete proteostasis network.

6. Role of Ubiquitination in Skin Biology

At the epidermal level, ubiquitination controls the cell cycle, proliferation, and differentiation of keratinocytes. This allows the rate of epidermal renewal to continuously adapt to fluctuating environmental conditions. Selective regulation of the stability of regulatory proteins determines the proper progression of keratinocytes through successive stages of differentiation, which is essential for the formation of the stratum corneum and maintaining the integrity of the epidermal barrier. Disruptions in these mechanisms lead to weakened skin barrier function, increased transepidermal water loss (TEWL), and increased skin reactivity. In the dermis, particularly in fibroblasts, ubiquitination regulates extracellular

matrix homeostasis by controlling the synthesis and degradation of structural and regulatory proteins. This process influences the balance between collagen and elastin production and the activity of metalloproteinases, determining the biomechanical properties of the skin, such as its firmness, elasticity, and regenerative capacity [21,23,36,49].

Beyond structural maintenance, ubiquitination is indispensable for the skin's defense against oxidative stress and UV radiation [37,63,64]. For example, ubiquitination strictly controls the activation of antioxidant defense pathways (such as the Nrf2 pathway), allowing cells to rapidly neutralize ROS [68]. Furthermore, ubiquitination plays a significant role in modulating the skin's inflammatory response [69]. By regulating the stability of key signaling proteins (such as the NF-κB pathway), ubiquitination influences the intensity and duration of the inflammatory response, preventing its pathological prolongation [70]. A properly functioning ubiquitination system protects the skin from the perpetuation of chronic, low-grade inflammation characteristic of the aging process [66,69].

However, as skin ages, the efficiency of ubiquitination mechanisms in skin cells gradually declines. This decline is driven by the impaired expression of E3 ligases and general system overload caused by increasing number of damaged proteins. As the system loses its regulatory precision, signaling pathways become fundamentally deregulated. The subsequent accumulation of defective proteins severely weakens the skin's adaptive capacity [67].

Consequently, it is increasingly recognized that efficient ubiquitination is a molecular determinant of the functional "youthfulness" of skin cells, regardless of chronological age. Its importance extends beyond the process of protein degradation itself to include the regulation of key cellular functions that influence the skin's phenotypic appearance. Understanding the role of ubiquitination in skin biology underpins modern well-aging concepts that aim to support conditions conducive to maintaining molecular balance [21,48].

7. Age-Related Dysfunction of the Ubiquitin–Proteasome System in Skin

The proper functioning of UPS is crucial for maintaining the functional integrity of skin cells. However, with advancing age, individual components of this system gradually become dysregulated, leading to impaired protein quality control and constituting one of the fundamental molecular mechanisms of skin aging. One of the best documented aspects of cellular aging is a decline in proteasome activity, particularly of the 26S complex responsible for the ATP-dependent degradation of ubiquitinated proteins [18,31]. These changes include reduced catalytic efficiency of proteasomal subunits and disturbances in the folding and stability of the entire complex. Consequently, the removal of regulatory and damaged proteins slows dramatically, promoting their toxic accumulation.

At the same time, the ubiquitination process itself falters, particularly in the expression and activity of E3 ligases, which determine UPS selectivity [19,38]. Loss of substrate recognition precision has a twofold impact: it leads to ineffective tagging of defective proteins (allowing them to persist) and to erratic, excessive degradation of functional proteins. This specific dysregulation directly undermines the signaling pathways that govern skin cell proliferation, differentiation, and stress responses [44,51].

UPS dysfunction in aging skin is closely linked to elevated oxidative stress, creating a destructive feedback loop. ROS induce oxidative modifications of proteins, often cross-linking them and rendering them resistant to proteasomal unfolding and degradation. Oxidative stress can also directly damage UPS components, further reducing its efficiency [71]. In turn, the failure to clear these oxidized proteins exacerbates intracellular stress, driving further ROS production and accelerating the aging process [42,63,64] (Figure 5).

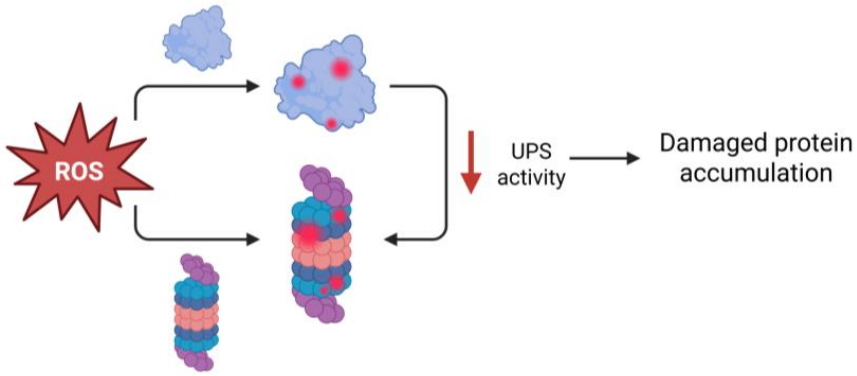


Figure 5. Mechanism of ROS-induced UPS impairment and subsequent damaged protein accumulation.

As these molecular deficits compound, the structural consequences manifest across all skin layers. In the epidermis, UPS dysregulation disrupts the keratinocyte cell cycle, resulting in sluggish renewal and a progressively compromised barrier. In the dermis, proteostasis disruption shifts fibroblast behavior from matrix synthesis to matrix degradation, accelerating the breakdown of collagen and elastin. This compromised cellular environment becomes a catalyst for chronic, low-grade inflammation. The persistence of damaged proteins and the failure to efficiently degrade inflammatory signaling molecules continuously stimulate proinflammatory pathways. This "inflammaging" imposes an even heavier burden on the already exhausted proteasomal system, completely destabilizing the broader proteostasis network [39,44,72].

It is worth emphasizing that UPS dysregulation during aging does not involve a complete loss of function, but rather a loss of regulatory flexibility and adaptive capacity. Aging cells retain some degradative activity but are unable to respond effectively to increased environmental and metabolic stress.

Traditionally, aging is associated with the progressive accumulation of damaged proteins, a decline in the efficiency of degradative systems, and increasing deregulation of signaling pathways. In a healthy proteostasis network, ubiquitination recognizes and removes misfolded or redundant proteins, protecting cellular integrity. However, as this process loses precision and adaptability with age, the proteome destabilizes. The well-aging perspective shifts the focus from the raw degradation rate to regulatory quality.

Consequently, modern aging biology increasingly recognizes that progressive regulatory failure of the UPS, rather than mere accumulation of molecular damage, is a key factor in functional skin aging. Therefore, UPS efficiency is a key determinant of long-term skin homeostasis [21,49]. Understanding this dynamic dictates a specific approach for well-aging strategies. Rather than attempting direct stimulation of the proteasome, modern cosmetic interventions focus on limiting factors that overload the system, such as oxidative and inflammatory stress, and on fostering an environment conducive to its efficient functioning. This perspective frames skin aging as a process that can be modulated at the molecular level, rather than solely as an inevitable consequence of time [71,73].

At this intersection, ubiquitination acts as a molecular decision-maker, fundamentally determining the trajectory of skin aging. When proteostasis is preserved, aging occurs slowly and symmetrically; visible structural changes become a natural, controlled adaptation to time rather than a failure of tissue. Conversely, when the UPS becomes dysregulated, it promotes chronic stress, sustains pro-inflammatory pathways, and rapidly destabilizes the extracellular matrix—manifesting clinically as accelerated, premature skin aging [74].

To integrate the currently available molecular evidence into a mechanistic framework, it is postulated that skin aging is not a sudden failure, but rather a progressive, threshold-dependent collapse of the proteostasis network [26,39]. This can be functionally

understood in three interconnected stages. Initially, youthful skin efficiently neutralizes environmental stressors (e.g., UV, ROS) through a highly responsive UPS and molecular chaperones, predominantly mounting an Nrf2-driven antioxidant defense to clear temporary damage [42,68]. As oxidative damage inevitably accumulates over time, the skin enters a phase of proteostatic overload. In this stage, the UPS becomes saturated with oxidatively cross-linked, degradation-resistant proteins. To survive, the cells undergo a compensatory shift: adaptors actively reroute the excessive degradative burden from the overwhelmed proteasome to selective macroautophagy [50,51]. Eventually, chronic exogenous stress forces the cells past a final threshold where both the UPS and autophagic machinery become profoundly impaired. At this point of network collapse, the molecular regulatory balance critically tips: the dysfunctional UPS sustains NF-κB activation (via impaired regulation of IκB) rather than effective Nrf2-mediated repair [68,70]. This failure locks dermal fibroblasts and epidermal keratinocytes into a chronic state of inflammation, ultimately establishing SASP [24,65].

From a functional skin biology perspective, the goal of well-aging does not involve direct interference with ubiquitination, but rather cultivating a cellular environment that supports proper function. Strategies such as reducing oxidative and inflammatory stress, protecting against UV radiation, and supporting the skin's barrier function help maintain molecular balance [23,42]. Ubiquitination determines the quality of aging. Its role is to maintain a balance between adaptation and degradation, allowing the skin to age in a controlled and biologically consistent manner. Well-aging does not mean delaying aging, but rather supporting the molecular mechanisms that enable skin cells to maintain their capacity for self-regulation and regeneration. Understanding the ubiquitination process underpins modern cosmetology and regenerative dermatology.

8. From Skin Proteostasis to Cosmetic Applications

The growing understanding of the proteostasis network is significantly influencing the design of contemporary cosmetic and dermatological strategies. These mechanisms are no longer viewed solely as elements of housekeeping functions within the cell, but as key determinants of long-term skin functionality and the quality of its aging.

Traditional anti-aging approaches have focused primarily on intensive and aggressive stimulation of cell proliferation, acceleration of epidermal renewal, and enhanced remodeling of the extracellular matrix. While these invasive strategies yield short-term improvements in aesthetic parameters, they often trigger increased oxidative stress, activation of the inflammatory response, and increased burden on protein quality control systems. In the long term, this can promote deregulation of the proteostasis network, including UPS overload and autophagy disorders [71,74].

Consequently, the well-aging paradigm shifts the focus away from maximum stimulation toward regenerative processes and the maintenance of a stable cellular environment conducive to the proper functioning of regulatory mechanisms. While cosmetic formulations cannot directly or pharmacologically activate the UPS, they are becoming an important reference point when designing skincare and therapeutic strategies [75,76]. One key element of innovative skincare strategies is preventing cellular overload. Instead of compensating for the effects of the accumulation of damaged proteins, modern approaches focus on limiting their formation by reducing oxidative stress, providing effective protection from UV radiation, and minimizing chronic skin irritation [48,49,53].

A critical pillar of this protective strategy is the preservation of the epidermal barrier. The stratum corneum acts as the first-line regulator of the cellular environment; its impairment leads to chronic stress and inflammation, thereby drastically increasing the cellular need for protein degradation [29]. By limiting external stressors, barrier-supporting

cosmetics directly reduce the UPS's workload, preserving its reserve capacity for essential regulatory functions [26,54]. In this perspective, the epidermal barrier serves not only a mechanical function but also constitutes a crucial element in regulating molecular homeostasis.

The result of the proteostasis-focused approach is revolutionizing the selection of active ingredients. Their effectiveness is no longer assessed solely on the basis of their stimulating potential, but rather on the basis of long-term cellular tolerance. Consequently, formulators are pivoting toward modulating biocompatible ingredients. This extends to formulation minimalism: reducing the number of potentially reactive additives minimizes unnecessary stress responses. Biocompatible, precision-formulated products designed for long-term use align perfectly with the physiological limits of skin cells [21,29,77,78].

Furthermore, well-aging formulation design increasingly respects the temporal dynamics of cellular biology. The activity of the UPS and autophagy is also deeply intertwined with the circadian rhythm, necessitating a distinction between daytime and nighttime care [79]. Daytime formulas must prioritize environmental shielding to minimize de novo protein damage, while nighttime products should support endogenous regenerative processes without overstimulating degradative mechanisms. By respecting the natural alternation of protective and regenerative phases—and abandoning the concept of continuous 24 h cellular stimulation—these strategies prevent the premature exhaustion of the skin's adaptive capacity [80,81].

Modern anti-aging cosmetics increasingly focus not only on stimulating collagen synthesis but also on supporting proteostasis mechanisms. Examples include active substances capable of activating autophagy, increasing proteasome activity, or inducing the expression of heat shock proteins (HSPs) and activating the Nrf2 pathway. As a consequence, the cosmetics industry offers both well-known and new-generation substances to protect skin balance [82,83]. The concept of proteostatic preventive cosmetology also aims to maintain the effectiveness of protein quality control systems before visible signs of aging appear. This practice means designing multi-targeted preparations that simultaneously have anti-inflammatory, antioxidant, and regenerative effects.

Among them, antioxidant ingredients primarily include sterols, such as triterpenoid saponins; chalcones; diketones; polyunsaturated hydrocarbons; flavonoids; linalool; non-flavonoid polyphenolic organic compounds; natural polysaccharides; and many others [83]. Most of these compounds are naturally derived and pose a lower safety risk.

In addition to well-known molecules such as vitamin C [5] and retinol [6], which perform many important functions and stimulate skin cells to produce collagen and elastin, attention is also being paid to ceramides and other substances that support the skin barrier. Biomimetic ceramides obtained using biotechnological methods are already available on the market. The most popular are NP, AP, EOP, and NS ceramides [84]. Peptide-like substances that enhance vitamin D synthesis in the skin have been shown to effectively counteract inflammation and rebuild the skin barrier, restoring the normal keratinocyte renewal cycle. Vitamin D and its active metabolites also exert a photoprotective effect [85]. Indole-based melatonin also plays a photoprotective role, promoting DNA repair and reducing the inflammatory response [86]. Certain compounds or drugs may exert beneficial effects by promoting collagen synthesis and inhibiting its degradation. A tripeptide derived from collagen (Gly-Pro-Hyp) may prevent the reduction in the skin's extracellular matrix [87]. One of the most versatile ingredients with anti-inflammatory and immunomodulatory properties is niacinamide [88]. By acting at the skin barrier, it supports the synthesis of natural ceramides, free fatty acids, and cholesterol. Recent research confirms its strong antioxidant properties and significant improvement in skin hydration. Natural α-bisabolol has a well-documented anti-inflammatory effect. Ectoine, a natural molecule produced by extremophilic microorganisms, protects cells from environmental stress by stabilizing

proteins and cell membranes. In cosmetics, it works on multiple levels: it improves hydration and long-lasting moisture retention, limits the effects of cellular stress and excessive inflammatory response, strengthens the epidermal barrier, and protects keratinocytes and fibroblasts from UV radiation damage [83,89].

From a scientific and regulatory perspective, precise statements about product compositions are required. Current scientific consensus is that cosmetic products cannot "directly activate" or "modulate" ubiquitination process or the proteasome. However, focusing on protecting the cellular environment, reducing oxidative and inflammatory stress, supporting the barrier, and preserving the skin's natural biological balance are rigorously justified [82]. This perspective draws a firm line between natural regeneration and forced remodeling. Regeneration is treated as an endogenous process that can be supported but never artificially accelerated beyond the cell's physiological capacity.

Modulation of ubiquitination/proteasome, however, involves interference with enzymes (E1, E2, E3, 26S proteasome), altering protein degradation, regulating the cell cycle, and proteotoxic stress. This is a classic pharmacological activity, meaning it belongs to drugs, not cosmetics. Ubiquitination, or the enzymatic cascade, is a cytoplasmic and nuclear process, tightly regulated and requiring high molecular specificity. Direct modulation means binding to the active site of the enzyme or the regulatory domain of the proteasome within a specific range and with high selectivity. Cosmetics are not enzyme ligands, are not selective inhibitors/activator-designed, and are not tested for such activity [18].

Furthermore, there is a physicochemical argument, i.e., skin penetration and lack of adequate bioavailability. The proteasome is located intracellularly, so to modulate it, the substance must penetrate the stratum corneum, enter living cells, reach the appropriate concentration, maintain activity, and specifically interact with the protein complex. This is often extremely difficult, even for drugs. Therefore, cosmetics applied to the skin do not achieve the conditions necessary for direct proteasome modulation [90].

Direct proteasome modulation also disrupts the cell cycle, apoptosis, and stress response. This leads to cytotoxicity and systemic effects. Therefore, proteasome inhibitors are cytotoxic drugs that require strict toxicological monitoring. Adding such a mechanism to a cosmetic would be dangerous and unacceptable. Marketing claims sometimes claim that a cosmetic "affects proteostasis" or "supports protein degradation", in reality, the claimed effect is indirect, such as antioxidant activity, reduction in oxidative stress, or improvement of skin function. Cosmetics do not activate E3 ligase and do not bind directly to the proteasome [91].

However, there is a significant regulatory link between active cosmetic ingredients and ubiquitination. Although most ingredients do not directly affect the UPS, they influence signaling pathways controlled by ubiquitination.

The best-understood mechanism concerns antioxidant substances (e.g., vitamin C, polyphenols, and carotenoids). Under physiological conditions, the Nrf2 protein is constantly ubiquitinated by a complex containing Keap1 and directed for proteasomal degradation. Antioxidant compounds inhibit this process, causing Nrf2 to accumulate in the cell and activate the expression of protective genes [92]. Consequently, cosmetic ingredients reduce oxidative stress, strengthen the skin barrier, and limit photoaging.

Retinol and retinoic acid are among the most important anti-aging ingredients. Their nuclear receptors (RAR and RXR) are regulated by the UPS. Studies on keratinocytes have shown that retinoid receptors are polyubiquitinated and degraded by the proteasome [93].

This indicates that the effectiveness of retinoid signaling depends on the rate of receptor ubiquitination; changes in UPS activity may influence the skin's response to retinoids.

Ubiquitination also regulates the degradation of tyrosinase—a key enzyme in melanogenesis. Some ingredients in depigmenting cosmetics can affect the stability of tyrosinase

by increasing its degradation in the UPS. Additionally, certain fatty acids have been shown to modulate the level of ubiquitinated tyrosinase [43]. This results in reduced melanin synthesis and lightened discolorations.

The NF-κB pathway, responsible for skin inflammation, is also controlled by ubiquitination. Activation of NF-κB requires the ubiquitination and degradation of the IκB protein. Anti-inflammatory substances used in cosmetics (e.g., plant polyphenols) may indirectly affect this mechanism by limiting the expression of inflammatory mediators [94].

Understanding the mechanisms of proteostasis also finds application in dermatology. Increasing evidence indicates that disturbances in protein homeostasis may be involved in the pathogenesis of numerous skin diseases, such as psoriasis [95], atopic dermatitis [95], and wound-healing disorders [96]. Modulation of autophagy and protein degradation processes is therefore becoming a potential therapeutic target, allowing us not only to alleviate disease symptoms but also to address their causes at the cellular level.

From a cosmetology perspective, ubiquitination is therefore a central mechanism regulating the effectiveness of many active ingredients used in anti-aging, photoprotective, anti-inflammatory, and depigmentation therapies. Integrating cellular quality control into skincare redefines the role of cosmetics—transitioning them from superficial tools of aesthetic correction into fundamental components of a long-term biological strategy. True well-aging relies not on the intensity of the intervention, but on a formulation's ability to safeguard the molecular and adaptive equilibrium of the skin.

9. Future Directions and Perspectives

The rapid expansion of knowledge about ubiquitination, UPS, and the interconnected proteostasis networks is opening up new translational perspectives in skin aging research [97]. A deeper molecular understanding of these mechanisms is bridging the gap between basic cell biology and its applications in dermatology and cosmetology, fundamentally redefining how we maintain long-term skin functionality.

Although the direct translation of dynamics into cosmetic applications is still in its early experimental stages, a key direction for future research is the identification of proteostasis biomarkers. Currently, the limited availability of in vivo data highlights the critical need for developing precise, ideally non-invasive tools to monitor proteasomal activity, ubiquitination dynamics, and the accumulation of damaged proteins in vivo. Establishing this foundational knowledge will allow researchers and clinicians to clearly differentiate between chronological age and actual functional (biological) age. This approach lays the foundation for personalized well-aging strategies based on the actual condition of the skin, not solely on chronological age, ensuring that future experimental efforts are methodologically standardized and strictly targeted [98].

To achieve this, the continued development of advanced skin research models that incorporate proteostasis processes remains a significant translational area. Three-dimensional models, organ-on-chip systems, and complex cellular models are enabling increasingly faithful representation of the dynamics of aging tissue [99,100]. Moving forward, these platforms will enable more reliable assessment of the impact of cosmetic and dermatological interventions on the proteostasis network under near-physiological conditions, far surpassing the limitations of traditional 2D cell cultures.

From a cosmetology perspective, a key challenge remains: translating molecular knowledge into biologically sound, safe formulation strategies. The future of cosmetic design lies not in directly modulating processes such as ubiquitination or UPS activity, but in creating an environment conducive to maintaining cellular balance. Integrating biological data, formulation technologies, and analyses of long-term effects of use will be one of the main directions of development in this field [101]. Similarly, in dermatology,

translational perspectives primarily focus on optimizing therapeutic strategies by better accounting for the adaptive constraints of aging skin. Understanding the dynamics of UPS and proteostasis enables more rational planning of the intensity, sequence, and duration of therapy, promoting the integration of regenerative phases with periods of protection and restoration. This approach can increase the long-term effectiveness of dermatological interventions while reducing the risk of overloading control mechanisms [48].

Of particular importance in this area is the fact that UPS dysregulation is associated with cancer [102], immune disorders [103], coronary syndrome [104] and neurodegenerative diseases [105], making it a potential target for new drugs. Numerous natural products targeting the UPS have been discovered and exploited in pharmaceutical development, providing significant insights into the molecular mechanisms of UPS regulation. Manipulating the UPS to achieve targeted protein degradation in cells using chemical and drug-based tools has the potential to transform pharmacological and therapeutic approaches to cancer and other diseases. A better understanding of the molecular mechanism of action of these agents (e.g., thalidomide and its analogues), following their clinical application, has revealed small-molecule modulation of E3 ligase substrate specificity, which in turn has led to the introduction of new immunomodulatory drugs into the clinic. The degradation of many context-specific proteins by these pleiotropic small molecules allows for the discovery of novel cell biology and the development of future drug molecules directed against currently intractable targets [106,107].

As the aging biology shifts its focus from the rate of aging to the quality of aging, industry communication must mature in tandem. Translating these complex molecular mechanisms into clear, scientifically accurate language is essential to separate genuine biological facts from marketing hyperbole. Transparent communication regarding the true role of proteostasis and ubiquitination will be vital for building lasting consumer trust [108]. By respecting the skin's intrinsic adaptive capacity, modern science provides a definitive roadmap for aging in a controlled, biologically harmonious, and functionally resilient, based on supporting natural regenerative processes and tissue homeostasis.

10. Conclusions

Skin aging is a complex biological process fundamentally dictated by cells' capacity to maintain molecular balance. The data presented in this review indicate ubiquitination and the UPS are central to regulating skin proteostasis, integrating protein quality control with processes of proliferation, differentiation, and the endogenous defense against oxidative and inflammatory stress. Dysfunction in these mechanisms constitutes one of the key molecular determinants of skin aging.

This biological reality drives a definitive paradigm shift: moving away from an anti-aging approach focused on correcting external symptoms toward the concept of well-aging, which assumes the preservation of the functional efficiency of skin cells despite the inevitable passage of biological time. Modern cosmetology and dermatology should develop strategies that limit overload of the proteostasis network, support the stability of the cellular environment, and respect the biological rhythms of processes in the skin.

Understanding the deep interdependence of the proteostasis network also establishes clear, scientifically sound boundaries for cosmetic influence. While these complex molecular machineries cannot be directly "activated" by topical formulations, their functional longevity can be profoundly supported by optimizing the external cellular environment. In biological reality, cosmetic products do not act by directly affecting cells in the body. Instead, they act indirectly—by influencing the conditions and environment within the body, which is consistent with scientific research.

The quality of skin aging is dictated by the resilience of the skin's internal regulatory mechanisms. By aligning modern cosmetology and aesthetic dermatology directly with fundamental cell biology, well-aging ceases to be a futile attempt to artificially "delay aging." Instead, it emerges as a robust strategy for maintaining the skin's biological competence—redefining beauty not as the outcome of aggressive, short-term interventions, but as the visible phenotype of long-term, sustained molecular balance.

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