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Proteomics of Human Skin Aging: Molecular and Translational Limits

Niki Tertipi *, Eleni Sfyri, Vasiliki-Sofia Grech, Eleni Andreou, Vassiliki Kefala and Efstathios Rallis *

Department of Biomedical Sciences, School of Health and Care Sciences, University of West Attica, GR-12243 Athens, Greece; elsfiri@uniwa.gr (E.S.); vgkrek@uniwa.gr (V.-S.G.); elandreou@uniwa.gr (E.A.); valiakef@uniwa.gr (V.K.)

* Correspondence: ntertipi@uniwa.gr (N.T.); erallis@uniwa.gr (E.R.)

Abstract

Human skin aging comprises changes in extracellular matrix, epidermal differentiation and barrier function, redox balance, protein homeostasis, inflammation, and senescence. This critical narrative review uses structured descriptive charting of published human skin proteomic evidence relevant to adult aging. Original source identification used non-exhaustive PubMed searches and citation checking through 25 August 2026; revision-time verification searches are documented separately. The source-audited adult corpus comprised 35 reports in 31 report families across direct human skin, explants, and primary cells, with adjacent and contextual sources outside these counts. Findings were grouped post hoc by broad biological domain while retaining specimen, exposure, comparator, analytical endpoint, and validation status. Recurrence concerned broad processes rather than identical proteins, directions, or harmonized pathway statistics. Protein-level comparison was constrained by small cohorts, heterogeneous sampling and inference rules, variable statistical reporting, and scarce external validation. Most bottom-up studies resolved protein groups rather than intact proteoforms; peptide-location and cleavage-susceptibility studies showed why abundance, processing, modification, and structural accessibility are distinct. Direct topical-intervention findings were sparse and formulation-specific. The reviewed literature has not yet established a universal skin-aging signature independently validated across compartments, exposures, and platforms. It supports contextual interpretation and candidate prioritization, while proteomic response alone does not establish biological-age reversal or clinical efficacy.

Keywords: skin aging; photoaging; proteomics; proteoforms; stratum corneum; extracellular matrix; topical interventions; biomarkers

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1. Introduction

The central problem in skin aging proteomics is not a shortage of reported proteins; it is the assumption that all observations refer to the same biological object. Human skin is a spatially heterogeneous organ shaped by intrinsic chronological change and cumulative ultraviolet exposure, air pollution, smoking, hormonal transition, and recent product use. The stratum corneum, viable epidermis, dermis, appendages, and extracellular matrix contribute different protein pools, while comparisons of photoexposed and protected sites and comparisons of older and younger cohorts pose different causal questions [1–

11]. Any proposed aging signature therefore loses meaning when compartment, anatomical site, exposure history, comparator, or sampling protocol is stripped away.

Proteomics is uniquely positioned to interrogate this complexity because proteins embody tissue structure, enzymatic activity, secretion, degradation, accumulated damage, and post-translational processing. It can reveal extracellular matrix organization and features at the peptide level that are not recoverable from transcript abundance alone [1,2,6,11,12]. But the measurement is conditional: tape strips favor terminally differentiated epidermal proteins, biopsies mix cellular and extracellular compartments, biochemical fractionation changes the analyte pool, and cultured primary cells isolate mechanisms while removing the context of intact tissue and the whole organism. The meaningful unit of interpretation is therefore not a protein name by itself, but a protein observation attached to its biological source, contrast, platform, molecular feature, and validation status.

Seen through this lens, the literature is less contradictory than it first appears. Human skin studies and supporting mechanistic reports repeatedly implicate extracellular matrix organization, epidermal differentiation and barrier function, redox balance and protein homeostasis, cytoskeletal remodeling, immune signaling, and secretion associated with senescence [1–20]. Candidate lists nonetheless vary across chronological age and photoexposure [2,3,5–11], changes associated with menopause and dryness [4], and ultraviolet or pollutant stress, clinical and chronological age, and replicative senescence [13–18,20–24]. This asymmetry, in which biological modules converge while individual proteins remain unstable, is the field's most informative pattern, not merely a methodological nuisance.

A second interpretive problem is molecular. A proteoform is a distinct molecular form arising from sequence variation, alternative splicing, post-translational modification, proteolytic processing, or combinations of these events. The distinction is especially consequential in skin, where matrix proteins with long half-lives accumulate oxidation, glycation, crosslinks, and cleavage, and terminal differentiation extensively processes barrier proteins. Most selected studies used bottom-up workflows that infer protein groups from peptides rather than resolve intact proteoforms. Protein group abundance, regional peptide yield, modification at specific sites, processing, and cleavage susceptibility must therefore be treated as different endpoints [11,12,25–27].

The same discipline is required at the translational boundary. A molecular response to an ingredient or formulation may strengthen a mechanism, but it does not establish penetration through intact skin, visible or functional benefit, safety, durability, or equivalence to another product bearing the same ingredient name. In vivo human formulation studies, intact adult human ex vivo skin, and primary skin-cell models occupy different inferential positions [28–39]. Adult provenance is required for the main corpus; the age-unspecified model is discussed as context. Collapsing signature discovery, target validation, mechanistic perturbation, and product testing into one evidence category inflates what the literature can support. Here, 'cosmeceutical' is used descriptively rather than as a regulatory category; prescription all-trans-retinoic acid is retained as a topical comparator with a distinct medical and regulatory context.

This review examines how compartment, exposure, and molecular measurement condition the interpretation of adult skin-aging proteomics. It asks which broad processes recur, when protein-level disagreement concerns different biological or analytical questions, which signals merit harmonized validation, and how topical mechanisms relate to clinical claims. Direct adult human skin forms the primary stream; adult human explants and primary adult skin cells provide separate mechanistic evidence. Animal-only experiments are excluded, while historical, isolated-protein, and age-unspecified reports are explicitly identified outside the adult-corpus denominator.

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2. Materials and Methods

2.1. Study Design and Oversight

This work is a critical narrative review with structured descriptive charting. It does not perform secondary analysis of participant-level data or raw mass spectra. It is neither a systematic nor a scoping review, claims no PRISMA-ScR or JBI compliance, and was not registered [40,41]. MIAPE and its mass-spectrometry module informed analytical reporting checks [25,26]; SANRA domains informed narrative reporting without numerical scoring [42]. No common effect was pooled across incompatible populations, specimens, contrasts, platforms, and interventions.

2.2. Eligibility Criteria

Eligibility followed a population, concept, context structure. Adults aged 18 years or older were the primary population. We prioritized in vivo adult human skin, stratum corneum, or separable skin compartments. Human ex vivo skin and primary human skin cells were retained as distinct mechanistic streams when adult provenance could be verified. For this study, an eligible 'proteomic study' comprised discovery or targeted profiling by mass spectrometry of multiple proteins, or a multiprotein panel driven by a hypothesis for which the source explicitly cited a published prior proteomic discovery report and that was directly evaluated against a phenotype of adult skin aging or clinical age. Assays restricted to a single protein without such a proteomic basis were excluded from the main corpus. Original reports published in peer-reviewed journals were eligible; conference abstracts, preprints, narrative reviews, patents, studies restricted to animals, pediatric studies, evidence limited to neonates, and experiments restricted to established or immortalized models were excluded. Studies covering a mixed life course were used only when an adult comparison was identifiable, and results from pediatric participants were not synthesized.

Sources retained solely for context or molecular interpretation were charted outside the main corpus. These include the isolated-elastin example [11], the antibody-panel report without cited proteomic-discovery provenance [20], the pooled foreskin and mixed-age studies whose adult-only evidence could not be verified [9,18], and primary-cell models whose donor age was not specified in the checked Methods [22,32]. Their retention does not establish adult eligibility or independent replication.

2.3. Information Sources and Search Strategy

Original identification used iterative, purposive PubMed searching and citation checking, with reported coverage through 25 August 2026. Concept blocks concerned skin/compartments; aging, photoexposure, senescence and environmental exposures; proteomic measurement; molecular processing; and topical intervention. Original query logs, retrieval and screening counts are unavailable. Exact Boolean combinations, language/year filters, seed order, and stopping decisions therefore cannot be reconstructed reliably. The retained bibliography cannot recover numbers assessed or excluded.

New verification searches were executed in PubMed on 15 October 2026. Table S1, SearchLog, records their literal queries, dates, limits and returned counts: skin AND aging/senescence AND proteomic measurement AND human text terms (256 hits); skin AND proteomic measurement AND named interventions (61); and selected parent/companion authors AND proteomics AND skin/dermal/fibroblast terms (6). All used a publication-date ceiling of 25 August 2026, without explicit language, adult, species or publication-type filters. These are revision-time source checks, not recovered original searches or a fully screened update. Bounded reference/companion checks examined the driver, GESTALT, hyaluronic-acid, photoexposure and secretome reports identified in

SearchLog, ending at documented reuse or insufficient linkage keys. SearchLog distinguishes these checks from the original, undocumented citation-search sequence and records representative outside-core decisions.

2.4. Selection, Retrieval and Data Charting

Selection followed Table 1: adult provenance, skin or a primary-cell model, a qualifying multiprotein proteomic endpoint, and relevance to aging, exposure, senescence or intervention. The original working charting table is unavailable. Table S1 was reconstructed during revision from the retained bibliography, accessible primary articles, author manuscripts and repository records. Studies preserves all 42 biological reports discussed. MethodsDetails separates enrollment from actual proteomic donor N, biological and technical replication, pooling, age/sex/site, acquisition, quantification, endpoints, statistical thresholds, multiplicity, missingness and validation. Source portions and access limits accompany each record.

Table 1. Operational eligibility criteria and rules for evidence streams.

Domain	Included	Excluded or Restricted
Population/model	Adults ≥18 years; adult human skin; adult human ex vivo skin; primary adult human skin cells; separable adult comparisons in studies spanning the life course	Evidence restricted to animals; pediatric or neonatal evidence; mixed life course evidence without a separable adult subgroup; evidence from established or immortalized models only
Concept	Discovery or targeted profiling by mass spectrometry of multiple proteins; or a multiprotein panel driven by a hypothesis explicitly linked by the source to a published prior proteomic discovery report and directly evaluated against a phenotype of adult skin aging or clinical age	Assays restricted to a single protein without a qualifying proteomic basis; studies without a direct question concerning adult skin aging, exposure, senescence, or topical intervention
Context	In vivo observational or intervention studies; ex vivo tissue; primary fibroblast or keratinocyte models, or matrix produced by cells	Systems unrelated to skin; mixed models without separable results; reports in which predefined adult provenance or provenance of an eligible primary model could not be verified
Translation rule	In vivo intervention evidence interpreted at formulation, concentration, vehicle, and regimen level	No inference of clinical benefit from a proteomic shift alone; mechanistic evidence not treated as clinical efficacy

Eligibility was restricted to evidence supporting the interpretation of adult human skin aging.

The charting unit is a publication with its distinct analytical arms and endpoints; report-family IDs consolidate documented proteomic-data reuse, rather than enumerate independent cohorts or every dataset. ReportMap links each report to its family, parent source, interpretive contribution and overlap assessment. Funding, employment, consultancy and declared conflicts remain separate fields in Studies. NR means not reported in the checked full source or specified section; NV means not verifiable from accessible primary portions; NA means not applicable. Blank numeric N is unknown, not zero. No independent duplicate screening, extraction or appraisal was performed.

Partial overlap was assessed using explicit cross-references/accessions and, where reported, donor identifiers, recruitment/source collection, institution, dates, age/sex/site, experimental arms and commercial model/lot identifiers. Similar age bins or a shared collection citation did not establish identical donors; missing linkage keys did not establish independence. Only documented proteomic reuse was consolidated. ReportMap identifies unresolved pairs. Adult origin was taken from numeric ages in the original publications or an explicitly adult commercial model named there; independent supplier or lot records were not obtained. For the lifespan ECM report, only the 30–50 and >60 year

comparisons inform adult interpretation; separate 5–24 year cultures in the GESTALT follow-up do not add an adult proteomic cohort (source identifiers in MethodsDetails).

2.5. Synthesis and Critical Interpretation

Charting first retained source-reported protein findings, functional annotations and enrichment results with their original context. The authors then assigned these observations post hoc to broad domains: ECM/architecture; epidermal/barrier; oxidative/metabolic stress; proteostasis-related processes; immune signaling; senescence/cytoskeleton; and molecular features. These are interpretive categories, not a new uniform enrichment analysis. Original enrichment tools, backgrounds and thresholds differed, including detected-proteome, secretome, network-expanded and database reference sets; available details are in MethodsDetails. No pooled pathway *p*-values or assumption of comparable enrichment universes was used.

Cross-study comparison was qualitative and restricted to compatible biological questions and molecular endpoints. "Convergence" denotes recurrence of a broad process, not identical subpathways, proteins, effect directions or phenotype associations. Data reuse, unresolved overlap and model-only findings constrain replication claims. ReportMap links selected domains to source findings and counterexamples. Nondetection, nonreporting, nonsignificant comparisons and discordant directions were kept distinct; none was converted into biological absence or silently treated as support. Directionally incompatible observations were described in context rather than averaged or counted as votes. These steps support descriptive conclusions, without a quantitative consistency estimate or exhaustive negative-evidence inventory.

For this review, proteostasis denotes the maintenance of protein homeostasis through protein synthesis; chaperone- and co-chaperone-assisted folding, refolding, assembly, and quality control; and degradation through the ubiquitin–proteasome and autophagy–lysosomal systems [43]. Evidence was classified as proteostasis-related when it addressed these processes or their machinery. Changes in antioxidant/redox enzymes or general metabolism were assigned to oxidative/metabolic stress unless a specific link to protein synthesis, folding, aggregation, or turnover was demonstrated. Protein abundance or pathway enrichment alone was not interpreted as proof of impaired folding, altered degradation flux, or a generalized failure of protein homeostasis.

2.6. Source Verification, Protein Examples, and Critical Appraisal

The protein case studies are deliberately illustrative, not exhaustive, and were verified against the original sources.

An example was retained when it met at least one selection criterion: (a) compatible directional reporting in two or more independent in vivo human reports; (b) orthogonal validation or direct linkage to a clinical phenotype in an adult human study; or (c) clear illustration of lack of equivalence across biological contrasts, compartments, or molecular measurements. Recurrence required compatible context and independent participant sets; linked publications and secondary analyses derived from the same underlying dataset were not counted as independent replication. Protein names and UniProt accessions are reported, and abundance, regional peptide yield, cleavage susceptibility, and intervention response are kept distinct.

The Appraisal worksheet provides a descriptive matrix for every charted report across donor selection/provenance, analytical N, replication/pooling, comparator/specimen, acquisition/quantification, protein inference, differential testing/multiplicity, missingness/exclusions, validation, public data and disclosures. R denotes adequate reporting with an appropriate method for the specified item; L denotes reporting with clear limitations; NR and NV distinguish missing reporting from limited available information. NA

applies where an item is inapplicable. Item-specific notes explain the classification. R is not an overall validity judgment. No validated risk-of-bias tool, numerical score, study-wide grade or independent duplicate appraisal was used. Source-specific sample sizes, effects, uncertainty and model-evaluation settings are retained in Statistics without deriving unreported confidence intervals.

3. Results

3.1. Scope and Organization of the Selected Literature

The source audit retained 35 reports in the adult main corpus, consolidated into 31 report families through documented reuse in [7,14,36,37,44–46]. The main corpus comprises 17 direct human-skin reports in 16 families, one human-explant report, and 17 primary-cell reports in 14 families. Five of the 40 reports originally counted as core were reclassified: [9,18,22,32] as contextual evidence because adult-only provenance or results could not be verified, and [11] as an adjacent isolated-protein molecular-feature example. The antibody panel [20] and the multi-tissue lifespan report discussed in Section 4.2 also remain outside the main corpus. Table S1 preserves every report and the reason for its placement; these counts describe the selected narrative corpus, not all eligible literature, independent cohorts, or experimental datasets.

Lehmann et al. [19] measured cultured primary keratinocytes and belongs to the primary-cell stream. Crabtree et al. [47] contributes adult forearm-biopsy proteomics to the direct human-skin stream; its separate skin-equivalent and HaCaT experiments do not establish in vivo topical efficacy. Schütz et al. [34] is assigned by its fibroblast-secretome endpoint, with clinical and explant outcomes kept as separate arms. The [7,44] family links the driver discovery dataset, while [7] also reports a separate validation cohort. Thus, report-family consolidation prevents double counting of reused data without erasing distinct cohorts within a report.

Possible donor overlap between [8,16,17,47] remains unresolved; separate report-family IDs do not establish independent participants. For [35], three explants per condition came from one 50-year-old woman. For [19], four discovery donors were pooled by age, distinct from an 18-donor source series; inconsistent immunoblot-denominator descriptions are retained in S1 rather than resolved by assumption. Table 2 summarizes the evidence streams, analytical dimensions, and principal interpretive boundaries of the selected literature.

Table 2. Evidence streams, analytical classes, and interpretive boundaries.

Evidence Stream/Analytical Dimension	Reports (Families)	What It Can Inform	Principal Boundary
Directly sampled or in vivo human skin	17 (16)	Signals in adult skin associated with age, exposure, phenotype, or formulation	Site, exposure, specimen, platform, regimen, and commercial context limit generalization
Human ex vivo skin	1 (1)	Local tissue response with multicellular architecture retained	No evidence on delivery, adherence, systemic context, or in vivo tolerability for the whole person
Primary skin cells/cell-derived matrix or secretome	17 (14)	Mechanisms related to donor age and controlled perturbation responses	No evidence of penetration through intact skin or clinical efficacy at the product level; clinical arms reported separately do not convert a proteome measured in the cell secretome into in vivo proteomics
Discovery MS: acquisition mode	Study-dependent	DDA and DIA describe acquisition; [6] uses DDA for its library and DIA for quantification.	Acquisition mode does not specify labels, quantification or validation.

Quantification/labelling	Study-dependent	Label-free or isobaric tags (iTRAQ/TMT) describe quantification strategies.	These may combine with acquisition modes; they are not mutually exclusive platform categories.
Targeted MS (SRM/MRM)	Examples [1,30]	Preselected protein targets; stable-isotope standards may support quantification.	ECM LC-SRM [1] and topical MRM [30] answer specific abundance questions; neither is proteoform resolution.
Adjacent targeted antibody panel (outside core corpus)	1 adjacent report [20]; excluded from core totals	Clinical linkage for five preselected candidates	Not profiling across the proteome; panel provenance is not traceable to a cited proteomic discovery; internal performance is not external validation

The first three rows summarize adult-corpus assignments in Table S1. Report-family counts consolidate documented proteomic reuse and do not count independent participant cohorts; possible donor overlap is recorded separately.

Figure 1 summarizes the study's governing principle: a proteomic signal becomes interpretable only after its biological source, analytical class, molecular feature, comparator, and validation status are carried forward into the claim.

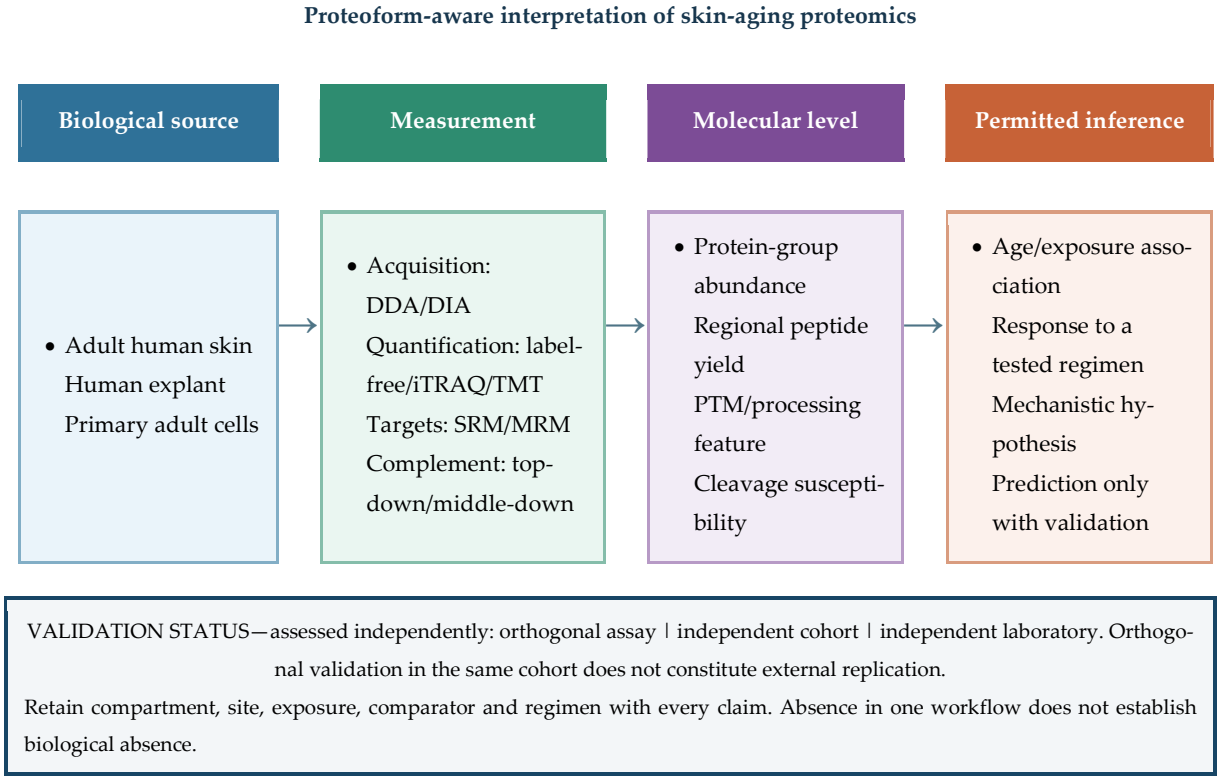


Figure 1. Interpretation from biological source to claim. Acquisition mode and quantification strategy are separate aspects of measurement; validation is an independent dimension. Top-down/middle-down MS are complementary approaches for future characterization; no selected study resolved intact proteoforms.

3.2. Heterogeneity Is a Biological Result, Not Only a Methodological Problem

Heterogeneity followed the biological question. Biopsies, tissue fractionation, and surface sampling measured different layers and protein pools, while cohorts varied in age, sex, skin tone or ethnicity, site, menopausal status, and exposure. Intervention designs also differed: the quinoa study included 61 women across ages 20–80 [28], and the retinoid

trial enrolled 30 women in two active arms [29]. In [47], age-associated biopsy findings and separate skin-equivalent or HaCaT experiments answered different questions.

Primary fibroblast, keratinocyte, and scalp-cell models varied in donor number, passage, dimensionality, and imposed stress [13–19]. They support controlled mechanistic questions; their relation to chronological aging must be tested in tissue.

3.3. The Proteoform Problem: Abundance Is Not Molecular Identity

Most of the selected evidence is unable to resolve proteoforms. Bottom-up workflows digest proteins before analysis and usually report protein groups supported by peptide evidence or canonical gene products. They may detect a modified peptide or a peptide derived from cleavage when it is deliberately searched, but they rarely establish which sequence variant, isoform, processing event, and modification coexist on one intact molecule. Shared peptides can map to several isoforms, while summarization at the protein level can hide opposing peptide behavior. A protein group abundance change assigned to "protein X" may therefore combine several molecular realities.

Skin magnifies this limitation. Keratins and cornified envelope proteins undergo extensive processing; extracellular matrix proteins have long half-lives and may be crosslinked, variably soluble, oxidized, glycated, or proteolyzed; and extraction chemistry determines which pool becomes measurable. Peptide location analysis [12] and controlled analysis of elastin cleavage susceptibility [11] demonstrate why regional peptide yield and structural accessibility cannot be relabeled as bulk abundance. We consequently distinguish protein group abundance, regional peptide yield, modification or processing at specific sites, and experimentally measured cleavage susceptibility. None of the selected studies resolved intact proteoforms or established a validated skin age biomarker based on an intact proteoform.

Interpretation should therefore disclose peptide uniqueness, sequence coverage, isoform databases, modification search space, false-discovery control, protein-inference rules, and the handling of shared peptides [25,26].

Top-down proteomics analyzes intact proteins before their fragmentation in the mass spectrometer, retaining the connection between sequence variants, splice isoforms, proteolytic truncations, and combinations of post-translational modifications (PTMs) on the same precursor. Intact mass together with informative MS/MS fragments can distinguish proteoforms that bottom-up summarization assigns to one protein group; intact mass alone does not necessarily localize every modification or resolve isobaric alternatives [48,49].

Middle-down proteomics uses controlled digestion to generate larger sequence segments than conventional bottom-up peptides. These segments can retain several modification sites and isoform- or processing-specific regions, enabling co-occurring features to be characterized within the same fragment. Combinatorial histone-tail PTMs provide an established example [50]. However, features on separate fragments cannot automatically be linked to one intact molecule, so middle-down measurements provide regional rather than necessarily complete proteoform information.

Application to skin remains technically demanding. Increasing molecular mass complicates intact-protein separation, ion detection, and fragmentation, while complex tissue mixtures and wide abundance ranges favor readily extracted, abundant species. Incomplete fragmentation, difficult modification localization, and demanding data analysis further limit comprehensive characterization [48,49]. These constraints are especially relevant to skin because insoluble or crosslinked matrix proteins may be difficult to recover intact [11,12]. Targeted top-down or middle-down experiments could therefore complement discovery bottom-up data, modification-enriched peptide assays, and orthogonal

methods, with claims restricted to the sequence regions and modification combinations actually resolved.

3.4. Convergence Emerges at the Module Level

Selected findings recurred within broad biological domains (Table 3), without a common enrichment analysis or uniform protein direction. References are unweighted and cannot estimate frequency, consistency or evidentiary strength: design, power, detection opportunity and multiplicity differ, and some reports reuse data. Nonsupportive findings also delimit the synthesis. IL-6 and G-CSF did not correlate significantly with age in the cytokine arm of [16]; UV-exposed fibronectin showed regional peptide changes without altered whole-protein counts [21]; and several barrier proteins were nonsignificant in [30,38]. These results qualify the relevant endpoint rather than refute or confirm an entire module.

Table 3. Descriptive summary at the domain level with selected supporting references.

Module	Reported Domain Signal	Supporting Evidence and Boundary
Dermal extracellular matrix and architecture	Loss, remodeling, insolubility, structural modification, or altered cleavage of collagens, proteoglycans, basement membrane, elastic fiber, and crosslinking components	Selected direct human and primary cell evidence [1,2,6,12,13,16,21,39,51]. Supports a matrix module, not a universal collagen biomarker.
Epidermal differentiation and barrier	Changes in keratins, desmosomal/cornification proteins, protease control, and proteins related to hydration	Observational direct human-skin findings [3–8,10]; in vivo topical-intervention responses [28–30,38]. Site, depth, season, vehicle, and regimen remain influential.
Oxidative and metabolic stress	Age-, exposure-, or intervention-associated changes in redox/antioxidant enzymes, oxidative damage, and metabolic stress responses	Selected direct human and primary cell evidence [2,5,7,14,23,24,39]; in vivo topical-intervention response [28]. Exposure, model, and comparator remain influential. Redox or metabolic changes alone do not establish altered protein homeostasis.
Protein homeostasis and proteostasis-related processes	Focused primary fibroblast evidence for age-associated changes in ribosome biogenesis and autophagy–lysosome pathways	GESTALT primary fibroblasts [14], with LC3 immunoblotting and p62/SQSTM1 measurements supporting the autophagy interpretation. The autophagy–lysosome reanalysis [46] uses the same proteome and adds no independent unit. Measured pathway changes do not by themselves establish a generalized failure of proteostasis.
Inflammaging and immune signaling	Immune, interferon, stress, and protease modules accompany older or photoexposed skin and secretion associated with senescence	Selected direct human and primary cell evidence [2,5,8,14,16,17,23,24,45]. Report [45] reanalyzes [14] and adds no independent proteome. Donor overlap [16,17] is not established. Low-abundance cytokines are inconsistently captured.
Cellular senescence and cytoskeleton	Cytoskeletal, mitotic, lysosomal, and secretory programs vary with donor age or induced senescence	Selected direct human and primary cell evidence [8,13–17,19,21,45,46]. Reports [45,46] reuse [14]. Distinct cell endpoints do not establish independent donor replication; induced senescence is not chronological aging.
Structural change sensitive to proteoforms	Regional peptide yield, processing, and cleavage susceptibility can change without a difference in bulk abundance	Core human skin evidence [12] and an adjacent isolated-elastin example [11]; intact proteoforms were not resolved.

Domains are descriptive author groupings informed by source annotations/enrichment; they do not imply identical subpathways or directions. In vivo topical-intervention references report treatment responses, which answer different questions from age- or exposure-associated observations.

3.5. Protein Candidates as Tests of Context, Not Leaderboard Entries

Table 4 presents five illustrative protein or peptide cases from the adult corpus, an adjacent isolated-elastin case [11], and an adjacent insulin-degrading enzyme (IDE) case

from the targeted-panel report [20]. The seven cases examine recurrence, orthogonal or phenotype linkage, direction across contrasts, and the distinction between abundance, peptide-level information, and cleavage susceptibility.

VTN and CLU recur in older or photoexposed adult skin, but their estimates concern different fractions and workflows [1,2,6]. S100A14 exposure and treatment findings concern different contrasts [7,28]. FBLN1 abundance and regional peptide yield measure different features [1,12]; pooled TUBB3 discovery and culture validation do not provide independent in vivo replication [19]. Elastin cleavage markers remain an adjacent single-protein example [11]. Table 4 gives source-specific N, effects and uncertainty where verifiable; Statistics in S1 retains further details. No common effect estimate is implied.

Table 4. Illustrative case studies at the protein and peptide levels, verified against the original sources.

Protein	UniProt	Specimen/Platform	Effect or Feature	Validation/Independence	Interpretive Limit
Vitronectin (VTN)	P04004	Adult skin; global discovery $n = 6$ (3/age) [1]; second workflow $n =$ 12 women [2].	Global [1]: old/young forearm FC 6.9, $p < 0.05$; CI NR. Ratios in other workflows are not directly comparable.	Separate within-study VTN LC-SRM arm $n = 12$ (6/age) [1]; no external biomarker cohort.	Differential multiplicity correction NR in checked [1,2]; identification FDR is separate.
Clusterin (CLU)	P10909	Adult skin; global discovery $n = 6$ [1], $n = 12$ [2], $n = 20$ [6].	Global [1]: forearm FC 10.1, $p < 0.05$; CI NR. Direction also reported in [2,6], without a common pooled effect.	Different fractions, sites and workflows; no common assay or external threshold.	Source-specific estimates; differential adjustment NR in checked main sources.
Protein S100A14	Q9HCY8	Paired facial discovery: 10 men [7]; separate validation: 7 women. Intervention: 61 women [28].	Higher with solar exposure [7], lower after formulation [28]; comparable effect/CI not established here.	[7,44] share discovery data; [7] has separate female validation.	Exposure and treatment are distinct contrasts; [28] differential proteins use BH-adjusted $p < 0.05$ plus >30% change.
Fibulin 1 (FBLN1)	P23142	Global abundance $n =$ 6 [1]; regional peptide fingerprinting $n = 7$ [12].	Global [1]: FC 4.5, $p < 0.05$, CI NR. Regional peptide yield [12] is a different endpoint.	Separate FBLN1 LC-SRM arm $n = 12$ [1]. Regional [12]: Bonferroni-corrected paired ANOVA.	No shared effect scale; protein-abundance multiplicity adjustment NR in checked [1].
Tubulin beta-3 chain (TUBB3)	Q13509	Primary keratinocytes: 4 discovery donors, pooled 2/age; source series 18 women [19].	Old/young iTRAQ ratio 2.664; CI NR; p_ratio = 4.21 × 10^{-4} and p_sample = 4.87 × 10^{-7} (both <0.05).	Immunoblot/internal culture ROC; exact immunoblot analytic N inconsistent in source; no external in vivo cohort.	Pooled discovery; differential multiplicity correction NR; ID FDR 1% separate.
Elastin (ELN)	P15502	Adjacent isolated-elastin case [11]: 12 adult biopsies, 19–90 y; unique donor N NV.	Controlled-digestion cleavage marker patterns; common abundance effect/CI NA.	Source-specific analytical replication; statistical/uncertainty detail NV from accessible portions.	Single-protein case outside corpus; cleavage susceptibility, not bulk tissue abundance.
Insulin-degrading enzyme (IDE)	P14735	Adjacent five-protein ELISA; reported analysis 351 women; participant flow unreconciled [20].	Age A/D coefficient per 1 SD IDE: β = −1.74 y (95% CI −2.46 to −1.02), $p = 3.29$ × 10^{-6}; Bonferroni criterion.	Internal median AUC: centre 0.611, centre + IDE 0.637, centre + IDE + LCN1 0.641. Target Age A/D > 0; not IDE-only.	Age A/D = clinical–chronological age. Internal resampling percentiles are not external CIs; no external cohort.

These proteins are illustrative candidates, not validated or ranked biomarkers.

The adjacent IDE case is confined here and to Table 4 [20]. Age A/D is operationally clinical age minus chronological age, so a positive value means clinically older

appearance. Clinical age was derived from six clinical signs. The IDE coefficient concerns this difference; the AUC target is Age A/D > 0 and the model includes study centre, rather than IDE alone. Internal resampling is distinct from external validation. The reported analysis N of 351 does not reconcile across the source's participant-flow descriptions, and published proteomic-discovery provenance for the five-protein antibody panel was not identified. The case illustrates clinical association and model interpretation outside the adult-corpus counts.

3.6. Dermal Matrix Remodeling Across Different Endpoints

ECM-related findings recur across biopsies with resolved compartments, decellularized matrix and fibroblast-derived systems, with an adjacent isolated-elastin example [1,2,11,51]. Intrinsic-age and photoexposure contrasts implicate structural matrix, elastic-fiber and crosslinking components but concern different tissue pools and directions. This qualitative recurrence does not rank domains by evidence strength or establish one shared quantitative pathway effect.

Studies of the primary fibroblast proteome, secretome, and matrix produced by cells strengthened the same interpretation at the network level through reduced matrix synthesis, altered fibrillogenesis, and secretory remodeling that depends on age [13,16,17,21]. Protein identities were not fully concordant, and they need not be for the module to remain biologically credible. The robust conclusion is that matrix organization changes with aging and exposure; the unsupported shortcut is that any single collagen, elastin feature, or protein associated with the matrix functions as a universal age marker.

3.7. Epidermal and Barrier Signals Are Defined by Sampling Context

Epidermal evidence is especially relevant to noninvasive sampling and topical research, but it is also unusually sensitive to context. Across stratum corneum and epidermal studies, keratins, differentiation and cornification proteins, pathways related to hydration, protease control, and immune and barrier signaling formed a coherent module. Yet paired sampling of cheek and postauricular sites primarily captured chronic photodamage and site biology [3], comparisons involving postmenopausal or dry skin combined barrier and hormonal context [4], and older epidermis showed a signature associated with interferon gamma [5]. The common biology is barrier remodeling; the observed protein set depends on what, where, and how deeply the skin was sampled.

The fine fiber intervention illustrates both the value and fragility of direct stratum corneum proteomics. In eight women aged 38 to 54 years, lotion plus a fine fiber film was compared with lotion alone for 14 days [38]. Of 172 identified proteins, 163 were analyzed after excluding nine with large baseline differences between sides. The combined regimen improved dryness scores and conductance and was associated with changes in the abundance of proteins related to barrier function and water content, including increased abundance of suprabasin and retroviral-like aspartic protease 1 and decreased abundance of annexin A2. The molecular and instrumental alignment is useful for generating hypotheses, but selection of a small subgroup with dry skin, short duration, baseline filtering, and company employment confine the inference to the tested regimen.

Photoexposure further shows why variability can be biologically informative. Paired facial sampling in professional drivers identified changes involving keratins, S100A14, and the cytoskeleton, with a linked data descriptor rather than independent replication [7,44]. Sampling across multiple decades suggested early senescence associated with photoexposure followed by progressive imbalance in epidermal homeostasis [8]. These patterns argue for separate models of intrinsic aging and photoaging; pooling them would erase the very exposure biology the proteome is detecting.

3.8. Stress, Inflammaging, and Senescence Converge Without Becoming Equivalent

Redox stress, protein homeostasis, inflammatory signaling, and senescence overlapped, but their supporting endpoints were kept distinct. Cigarette smoke condensate and diesel particles altered redox, metabolic, barrier, and inflammatory responses in adult primary keratinocytes [23,24], with additional mechanistic context from the age-unspecified UVA model [22]; those changes alone were not classified as evidence of disrupted proteostasis. Acute ultraviolet exposure of matrix derived from fibroblasts preferentially affected collagen fibrillogenesis [21]. More direct proteostasis-related findings came from the GESTALT fibroblast study: ribosome-biogenesis pathways were less represented with older donor age, whereas autophagy-associated proteins were more represented, with LC3 immunoblotting and lower p62/SQSTM1 abundance supporting the autophagy interpretation [14]. These endpoints do not establish a generalized failure of protein homeostasis. The subsequent autophagy–lysosome analysis [46] reuses the same proteome and supplies pathway-level evidence rather than an independent replication. The other linked analysis [45] connected WTAP, ELF3, and IRF8 to senescence-associated signaling. Computational nomination of hydroxytyrosol [46] still requires experimental testing.

Individual candidates from these domains, including TUBB3, 14-3-3 epsilon, PEBP1, carbonic anhydrase 1, and proteins related to interferon, keratin, or S100, remain specific to individual studies [5,7,9,10,19]. The PEBP1 and carbonic-anhydrase observations from [9] are historical context because adult donor ages could not be verified. These candidates anchor testable mechanisms. Treating them as a ranked biomarker list would ignore the absence of independent validation across compatible in vivo cohorts, sites, and platforms.

3.9. The Translational Bottleneck: Few In Vivo Proteomic Intervention Studies

The intervention corpus exposed the field's largest asymmetry: mechanistic responsiveness is abundant, but direct in vivo human proteomic evidence is scarce. Table 5 contains five intervention arms from four publications [28–30,38]. These studies can establish that a specified formulation, concentration, vehicle, regimen, duration, comparator, and population produced a molecular response. They cannot support a ranking of ingredient classes once those qualifiers are removed.

Table 5. Selected direct in vivo human topical intervention arms with proteomic endpoints.

Intervention and Design	Proteomic Endpoint	Main Observation	Permitted Inference
Quinoa bioester; 61 women, 20–80 y; paired nonrandomized active/vehicle forearms, 30 days [28].	DDA, label-free LC-MS/MS; 61 MS participants, 244 site/visit samples, technical duplicates. Linear SVR: internal MAE 7.17 y, R^2 0.74.	Author-reported score contrasts: 11 model-y (<50, $n = 30$, $p = 0.14$), 16 (≥50, $n = 31$, $p < 0.01$); CIs NR. Protein changes: BH $p < 0.05$ plus >30% change.	Chronological prediction and response score are distinct. No external biological-age validation or direct subgroup interaction test.
Retinol 0.3%; 15 of 30 women, 50–65 y; daily application, 12 months; contralateral control [29].	Stratum-corneum iTRAQ; three pooled subgroups per active/control arm. Donor-level protein variance not available.	Example TGM3 at 3 months: signed FC −1.9608, 3/3 replicates; CI NR. Criterion $\|FC\| \geq 1.5$ in ≥2/3 replicates. Protein-level correction NR.	Negative signed FC means decrease, not log2. Enrichment correction cannot be assigned to protein differences; formulation-specific response.
All-trans-retinoic acid 0.025%; 15 of same 30 women; daily application, 12 months; contralateral control [29].	Same pooled iTRAQ design; separate active arm, not a new independent trial.	Example TGM3 at 3 months: signed FC −2.0408, 3/3 replicates; CI NR. Same replicate/fold criterion; protein-level correction NR.	Source-specific pooled ratios; no donor-level CI inferred. Medical/regulatory and tolerability context remains distinct.
Glycerol 20%; 31 women, 55–75 y, enrolled; randomized double-blind split-face, 4 months; MS day 56 [30].	Targeted MRM with heavy peptides; actual MS analytic N NR separately. Panel size differs in Methods (54/56).	Active/vehicle ratios: KLK5 6.0091 (p = 0.0188), LGALS7 2.7281 (p = 0.0370); CIs NR. Paired t; protein multiplicity adjustment not described.	KLK7/PARK7 not nominally significant. No added wrinkle-score benefit over vehicle; protein changes not established as clinical mediators.

Lotion + fine-fiber film vs. lotion; 8 women, 38–54 y, selected from 17; paired lower legs, 14 days [38].	DDA, label-free normalized PAI; 163 proteins after 9 baseline-imbalance exclusions. Separate biopsy $n = 7$.	Ratio of day-14/baseline fold changes (+film/−film): SBSN 3.5655, ASPRV1 1.5693, ANXA2 0.8167; CIs NR. Wilcoxon/Storey $q < 0.05$.	Response to tested regimen; small selected sample, baseline filtering, no independent proteomic cohort.

The findings support molecular responses specific to the tested formulation, not general clinical efficacy.

The quinoa study illustrates three distinct analytical questions [28]. A linear support-vector model predicted chronological age from pretreatment samples with internal leave-age-out cross-validation (MAE 7.17 years; R^2 0.74). The 122 baseline forearm samples represent 61 women, not 122 independent participants; preprocessing and feature selection were described within training ages. The same cohort's treatment-response score yielded author-reported contrasts of 11 model-years below age 50 ($n = 30$, $p = 0.14$) and 16 at age ≥50 ($n = 31$, $p < 0.01$), with confidence intervals not reported and no direct interaction test. Neither internal prediction accuracy nor score movement establishes externally valid biological age or years of rejuvenation. Hydration did not differ significantly from vehicle ($p = 0.17$).

Table 5 and S1 separate enrolled N from the proteomic analytical denominator in the other trials. Retinoid iTRAQ measurements used pooled subgroups, limiting donor-level uncertainty [29]. In the glycerol study, the actual MS analysis N was not separately stated; only KLK5 and LGALS7 were nominally significant among the highlighted proteins, without described protein-level multiplicity correction [30]. The fine-fiber analysis used eight participants and Storey-adjusted q-values after baseline filtering [38]. These findings concern specified regimens; protein shifts were to predict or mediate clinical benefit.

3.10. Mechanistic Responsiveness Is Not Product Efficacy

Mechanistic intervention studies fill a large space left empty by clinical proteomics, but their abundance can create a false impression of translational depth. Carnosine studies in primary fibroblast spheroids implicated mitochondrial, extracellular matrix, apoptotic, oxidative stress, and UVA response pathways [31,39]; an age-unspecified primary-fibroblast model supplied contextual evidence that Oenothera biennis extract altered peroxide-induced senescence programs [32]; and hydroxystearic acid regioisomers increased the abundance of proteins related to collagen, with ex vivo support [33]. Hydroxystearic acid of biological origin was also associated with changes in the abundance of extracellular matrix and secreted proteins, but its clinical outcomes came from a separate arm rather than the same in vivo proteomic experiment [34]. These findings establish biological responsiveness under defined model conditions, not delivery through intact skin or efficacy at the product level.

The same distinction applies to a marine and maritime ingredient association in human skin explants [35], antioxidant rescue of changes associated with pollutants in primary keratinocytes [23,24], and responses to hyaluronic acid of low molecular weight in adult dermal fibroblasts [36,37]. Ex vivo tissue retains multicellular architecture; primary cells offer experimental control. Neither can supply the penetration, adherence, tolerability, durability, or context of the whole person that a topical clinical claim requires. Their proper output is a mechanism and a prospective hypothesis, not a product recommendation.

3.11. Why the Literature Cannot Yet Support Transportable Biomarkers

The principal limitation was not simply small sample size; it was compound heterogeneity across population, specimen, biological contrast, analytical workflow, and statistical reporting. Small or pooled discovery cohorts, narrow demographic and anatomical

coverage, incomplete preanalytics, inconsistent multiplicity and handling of missing data, and sparse external validation jointly destabilize candidate lists. In the topical studies in Table 5, prespecification of proteomic endpoints, exclusions, multiplicity control, and rules for missing values was not consistent enough for harmonized comparison. Paired designs reduced variation between individuals but could not remove site, exposure, or compartment effects. Findings at the protein level were therefore treated as exploratory unless the source documented stronger controls.

Uneven access to raw data and metadata compounds the problem. A data accession does not guarantee that specimen definitions, covariates, exclusions, and a reproducible workflow for differential analysis are complete; conversely, failure to locate an accession in an accessible abstract is not proof that no data were deposited. The consequence is practical: apparently discordant results often cannot be reanalyzed to determine whether biology, sampling, or computation produced the difference.

Documented industry relationships include funding or acknowledged support [2,3,12,16,21,28,30,33–35] and company affiliations or consultancy [8,13,28,29,33,34,38,47]. Table S1 distinguishes these observations from declared conflicts and identifies disclosure fields that could not be verified. It also preserves the inconsistent funding and conflict statements in [13]. No frequency of commercial involvement is estimated from this purposive inventory. Such relationships do not invalidate results, but complete reporting, formulation transparency, public data, and replication by investigators without a stake in the claim strengthen interpretation.

4. Discussion

4.1. A Coordinate System for Skin Aging Proteomics

Figure 1 identifies the information needed to interpret each observation. Table 6 applies that framework to topical translation, separating in vivo formulation responses, local responses in intact ex vivo tissue, and mechanisms tested in primary cells or their matrix.

Table 6. Evidence ladder developed in this study and informed by proteomics for interpretive use.

Tier	Evidence	What It Can Support	What It Cannot Support
1	In vivo human intervention specific to a formulation with comparator and skin proteomic endpoint	A molecular response specific to the formulation; stronger when the molecular endpoint and analysis are prespecified and linked prospectively to validated clinical outcomes	Universal ingredient efficacy, causal clinical mediation or individualized product matching without replication
2	Human ex vivo skin	Plausibility of pathways at tissue level and local response in intact human tissue	In vivo human efficacy, tolerability, adherence, durability or systemic context
3	Primary adult human skin cells or matrix derived from cells	Mechanistic direction, candidate pathways and hypotheses on responses to exposure	Topical delivery, benefit to whole skin or clinical recommendation at product level

The tiers indicate translational proximity, not methodological quality or product performance.

The tiers describe proximity to clinical inference. Methodological quality must be assessed within each tier through comparator choice, biological replication, analytical validity, statistical control, reporting, and independent validation. A rigorous cell experiment can establish a mechanism while leaving topical delivery and benefit in people unresolved.

4.2. Four Propositions for Interpreting the Field

Proposition 1: context defines the observed aging phenotype. Chronological aging, photoexposure, menopause, dryness, pollution and induced senescence concern distinct specimens and causal questions [1–5,7,8,44,51]. The reviewed literature has not yet

established a universal skin-aging proteomic signature independently validated across compartments, exposures and platforms. This does not rule out a future common signature. Multi-tissue lifespan mapping [52] is contextual rather than direct confirmation of such an adult skin signature.

Proposition 2: broad processes can recur despite variable protein lists; this descriptive convergence does not establish common subpathways, direction or quantitative enrichment [1,2,6,11–13,16,17,21].

Proposition 3: the molecular endpoint defines the claim. Protein-group abundance, regional peptide yield, modification, processing, and cleavage susceptibility cannot substitute for one another [11,12,25,26].

Proposition 4: topical claims require evidence for the tested formulation, concentration, vehicle, regimen, comparator, and population; mechanistic responsiveness alone does not establish clinical efficacy [28–39].

4.3. The Claim Rests on an Observation with Full Provenance

A transportable claim requires a defined endpoint and validation in a compatible external setting. The reviewed reports have not established a universal skin-age classifier, individualized product selection, equivalence among formulations sharing an ingredient, or clinical rejuvenation from proteomic scores. Each remains a distinct validation target.

4.4. Why Apparent Contradictions Are Often Informative

Discordance should be examined against compartment, comparator, extraction, and molecular endpoint before being interpreted as failed replication [1–10,13–18,20]. Low power, incomplete reporting, and platform effects remain alternative explanations; contextual differences do not excuse all disagreement.

For example, higher S100A14 abundance with accumulated solar exposure and lower abundance after a quinoa formulation concern different contrast [7,28]. An elastin cleavage marker likewise measures a different endpoint from elastin abundance [11]. These distinctions define hypotheses that compatible assays and comparators can test.

The main translational gap is prospective linkage between molecular response and clinical benefit. Mechanistic reports [23,24,31–37,39] nominate targets, while in vivo studies [28–30,38] document responses to specific regimens. Whether those changes predict or mediate benefit, persist after treatment, or generalize to another population remains unresolved.

4.5. From Biological Modules to Testable Panels

ECM remodeling offers candidates for panel development across tissue and cell-derived approaches [1,2,6,11–14,16,17,21,51]. The signals concern collagens, elastic fibers, proteoglycans, basement membrane, crosslinking and proteolysis, measured through different extraction and molecular endpoints. They do not constitute an assembled panel or a quantitative ranking above other domain. Panel development must first specify the specimen and whether it measures abundance, regional yield, modification or cleavage susceptibility.

Epidermal and stratum corneum modules offer a more practical route to repeated sampling, centered on keratins, cornification, desmosomal organization, protease control, proteins related to hydration, and immune and barrier signaling [3–5,7–10]. Their accessibility is also their vulnerability: anatomical site, season, recent product use, strip depth, and barrier condition can dominate the measurement. A future panel based on tape strip sampling should therefore be developed as a sampling protocol plus assay, not as an independent list of proteins.

Oxidative/metabolic stress, protein homeostasis, and inflammatory signaling provide connected but distinct candidates for exposure-related panel development. Ultraviolet radiation, smoke condensate, and diesel particles induce overlapping redox, metabolic, keratin-related, and inflammatory responses in primary cells [21–24], while in vivo studies identify related stress and immune signals [2,5,7,8,10]. Proteostasis-related candidates should be selected from defined synthesis, folding, or degradation processes and tested with functional endpoints appropriate to those processes. Acute perturbation responses can nominate mechanisms shared with cumulative exposure and aging, but do not by themselves define the clinical phenotype.

Senescence-related programs depend on donor age, passage, ultraviolet stress and peroxide exposure [8,13–17,19,22,32]. Shared cytoskeletal, lysosomal, mitotic and secretory findings merit tissue validation, but no in vitro signature in this selected corpus has been independently validated to measure an individual's biological skin age. Future panels must distinguish cell state from the route by which it was induced.

4.6. Candidate Proteins as Stress Tests for the Framework

VTN and CLU are reasonable priorities for harmonized replication because they recur in independent reports [1,2,6]. Their importance lies less in their current candidacy than in the experiment they enable: can the same targeted assay reproduce direction and effect in a prespecified specimen, anatomical site, and external cohort? Until that test is passed, recurrence across incompatible workflows supports biological plausibility, not a reference range or classification threshold.

S100A14 tests directionality. The higher abundance of S100A14 in facial skin exposed to chronic sunlight and its lower abundance following application of a quinoa bioester formulation are not opposing estimates of one effect [7,28]. A candidate associated with an adverse exposure state may show lower abundance after treatment, remain unchanged in abundance, or change for reasons unrelated to the proposed mechanism. Direction becomes interpretable only when tissue, comparator, time point, and causal question are specified.

FBLN1, TUBB3, and features derived from elastin test molecular equivalence and validation. FBLN1 abundance and peptide location fingerprints are different endpoints [1,12]; TUBB3 was orthogonally supported within primary keratinocytes but not independently confirmed in compatible in vivo tissue [19]; and elastin marker peptides after controlled digestion reflect cleavage susceptibility rather than abundance [11]. Orthogonal confirmation strengthens measurement credibility inside a study. It does not substitute for biological replication across independent participants and laboratories.

Panel development should specify the specimen, endpoint and clinical use, then test age, site, ultraviolet exposure, sex, menopausal status, skin tone or ethnicity, season and recent product use in an external cohort. VTN, CLU, S100A14, FBLN1, TUBB3 and elastin-derived features remain contextual candidates with different measurements [1,2,6,7,11,12,19,28]. Pathway recurrence does not supply diagnostic thresholds or product-selection rules.

4.7. Heterogeneity Is Structured and Therefore Testable

Molecular heterogeneity can be tested with assays that retain the relevant feature. Different modified, cleaved, or spliced forms can contribute to one bottom-up protein-group signal. Peptide-location fingerprints [12] and elastin cleavage markers [11] motivate regional or processing-specific assays, while the complementary methods in Section 3.3 address the limits of intact-proteoform resolution.

Sampling heterogeneity can be tested by standardizing site, depth, strip number and pressure, barrier condition, and tissue fractionation. Tape strips, whole biopsies, and

isolated or decellularized matrix expose different protein pools [1–5,7,12,44,51]. Harmonization must therefore fix the specimen alongside the biological question.

Analytical heterogeneity requires matched extraction, digestion, acquisition, databases, and inference rules. Targeted MRM measures a predefined panel; discovery workflows provide broader coverage with different missingness [6,25,26,29,30]. A missing signal is interpretable only when detection opportunity is known.

Statistical heterogeneity requires complete quantitative results, the detected background proteome, multiplicity control, and explicit handling of missing data. Pathway enrichment depends on that background and on annotation choices. MIAPE-informed reporting makes biological and computational explanations of discordance assessable [25,26].

Data lineage must be explicit. Reused discovery data [7,44], linked hyaluronic-acid reports [36,37] and GESTALT reanalyses [14,45,46] are not independent proteomic replications. ReportMap in S1 separates documented reuse from unresolved partial donor overlap and records the checked linkage keys. Shared reference materials, participant/specimen metadata and public workflows would enable stronger cross-study comparisons.

4.8. What Evidence Would Change the Conclusion

The current conclusion would change with independent, multicenter in vivo replication. Such studies should prespecify one primary biological contrast and proteomic endpoint, justify sample size, use an appropriate comparator or vehicle, standardize site and sampling depth, and recruit enough diversity to evaluate sex, menopausal status, skin tone or ethnicity, and exposure history. Designs with comparisons within each person can reduce noise between individuals but must still address site effects and carryover. Discovery, model tuning, and external validation require separated cohorts, not repeated splits of one sample [1–7,28–30].

A second threshold is analytical transportability. Consensus preanalytics, shared reference samples, a locked versioned pipeline, transparent rules for protein inference, and reporting complete under MIAPE would make replication across laboratories interpretable [25,26]. Full differential results, background proteomes, strategies for missing data, multiplicity correction, software versions, exclusions, and metadata should accompany public deposition. Recurrent candidates such as VTN and CLU could then be measured by nested targeted assays and challenged in genuinely external cohorts [1,2,6].

A third threshold is prospective linkage between molecular and clinical outcomes. Topical trials should lock formulation, concentration, vehicle, regimen, comparator, and molecular endpoint; measure validated clinical and instrumental outcomes as well as outcomes reported by participants; and test whether molecular change predicts or mediates benefit. Repeated sampling could distinguish early response from later remodeling and determine durability after treatment stops. Safety and tolerability belong in the same causal framework because molecular activity is not beneficial if the regimen damages barrier function or is unacceptable [28–30,38].

Finally, validation must include implementation and equity. Models built in groups narrowly defined by age, sex, ancestry, or skin tone may encode population and exposure imbalance as age. Studies in aesthetic practice should test whether evidence tiers calibrated to claims improve interpretation, referral, and avoidance of diagnostic overreach. Preregistration, protocol publication, complete funding and conflict disclosure, and replication without a commercial stake would materially strengthen both commercial and noncommercial findings [25,26].

4.9. Strengths and Limitations

This review has several strengths. It establishes an explicit adult human boundary, provides an operational definition of eligible multiprotein evidence, treats in vivo human, human ex vivo, and primary cell findings as distinct inferential streams, excludes evidence restricted to animals from synthesis, and recognizes linked reports. It also uses explicit criteria for a protein table that is not exhaustive and preserves formulation, comparator, specimen, and measurement context. This structure supports a defensible distinction between recurring biological domains, preliminary protein candidates, molecular responses specific to a formulation, and claims that remain unsupported.

Selection and availability bias remain. PubMed and purposive citation checking were not supported by a registered protocol or independent duplicate work. Missing original logs prevent reconstruction of the historical candidate/exclusion flow. The dated revision-time verification queries in S1 do not recover that flow or establish an exhaustive update. Source-access limits affect detailed extraction and appraisal; a separate family ID cannot rule out donor overlap. The census describes a selected adult corpus, with age-unspecified/contextual reports outside its denominator.

The evidence base adds further constraints. Discovery cohorts were often small; specimens and platforms were heterogeneous; complete differential protein lists were not uniformly available; and orthogonal or external validation was uncommon. Intact proteoforms were not resolved in the selected studies, so protein group, peptide region, modification, and cleavage findings cannot be interchanged. Table 4 is deliberately illustrative and cannot support protein frequency estimates. No meta-analysis was appropriate because the selected studies did not estimate a common effect across compatible populations, specimens, contrasts, and interventions. Conclusions are therefore restricted to qualitative domains, candidates specific to context, features sensitive to proteoforms, and molecular responses specific to a formulation.

5. Conclusions

The literature reviewed to date has not yet established a universal proteomic signature of adult human skin aging that is consistent across tissue compartments, exposure conditions and analytical platforms and has been independently externally validated. Broad ECM, epidermal/barrier, redox, immune and senescence-related processes recur qualitatively, with more focused proteostasis-related findings. These observations support contextual hypotheses rather than a harmonized pathway effect, intact-proteoform signature, validated biological-age clock or ingredient-class efficacy. A common signature remains a question for future studies.

The practical contribution of proteomics is therefore not to confer molecular authority on a product claim, but to make claims more precise and testable. A signal should travel no farther than its specimen, contrast, molecular endpoint, validation, and, for interventions, its formulation and regimen allow. With harmonized sampling, measurement that accounts for proteoforms, external validation, and prospective linkage to clinical benefit, the field could progress from compelling mechanisms to transportable tools. Until then, proteomics should guide contextual pathway interpretation and candidate prioritization, not diagnosis, individualized product matching, or clinical efficacy inferred from changes in proteomic measurements alone.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/proteomes14040056/s1, Table S1 contains the report inventory (Studies), analytical and adult-provenance details (MethodsDetails), descriptive appraisal matrix (Appraisal), report-family/overlap and domain mapping (ReportMap), source-specific effects

and model metrics (Statistics), and original-search limitations plus dated revision-time verification records (SearchLog). Overview defines counts and codes.

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Abbreviations

Age A/D, clinical age minus chronological age (acceleration/deceleration); AUC, area under the receiver operating characteristic curve; BH, Benjamini–Hochberg; CI, confidence interval; CLU, clusterin; DDA, data-dependent acquisition; DIA, data-independent acquisition; ECM, extracellular matrix; ELN, elastin; FBLN1, fibulin-1; FC, fold change; FDR, false-discovery rate; GESTALT, Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing; IDE, insulin-degrading enzyme; iTRAQ, isobaric tags for relative and absolute quantitation; JBI, Joanna Briggs Institute; LC–MS/MS, liquid chromatography–tandem mass spectrometry; MAE, mean absolute error; MIAPE, Minimum Information About a Proteomics Experiment; MRM, multiple reaction monitoring; NA, not applicable; NR, not reported in the checked source/section; NV, not verifiable from accessible primary portions; PAI, protein amount index; PRISMA-ScR, Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; PTM, post-translational modification; ROC, receiver operating characteristic; SANRA, Scale for the Assessment of Narrative Review Articles; SD, standard deviation; SRM, selected reaction monitoring; SVR, support-vector regression; TMT, tandem mass tag; TUBB3, tubulin beta-3; UVA, ultraviolet A; VTN, vitronectin.

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