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Review Article

Bacopa monnieri (Brahmi) in the Hallmarks of Cutaneous Ageing: An Evidence-Based Rationale for Biotex NIA Cream

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ABSTRACT

Skin ageing is increasingly interpreted through interconnected hallmarks of ageing rather than through oxidative stress alone. Cellular senescence, telomere attrition, mitochondrial dysfunction, loss of proteostasis, disabled autophagy, epigenetic drift, stem-cell dysfunction, altered intercellular communication, and chronic inflammation converge on dermal fibroblast dysfunction and extracellular matrix (ECM) deterioration. This focused review evaluates the anti-ageing rationale of Biotex NIA Cream, a topical formulation built on *Bacopa monnieri* (Brahmi), within this contemporary framework. Bacopa extract protects human fibroblasts from oxidative DNA injury, supports Beclin-1-dependent autophagic protection of human keratinocytes against pollutant-associated mitochondrial stress, drives $\alpha 5 \beta 1$ -integrin/FAK-dependent fibroblast migration, and - in supportive non-cutaneous models - limits pollutant-induced cellular senescence through Parkin-dependent mitophagy and preserves telomere integrity under stress. Two of its phytochemically documented flavonoid constituents extend this biology into further human and experimental anti-ageing endpoints: apigenin reduces UVA-induced senescence and MMP-1, suppresses the senescence-associated secretory phenotype (SASP), promotes type I/III collagen through Smad2/3 signalling, and in a clinical trial produced measurable gains in skin elasticity and dermal density alongside shorter fine wrinkles; luteolin modulates UV- and pollutant-induced oxidative stress, MMP signalling, collagen loss and senescence-associated pathways across multiple human and experimental models. Newer skin-ageing literature also highlights epigenetic dysregulation, epidermal stem-cell exhaustion, glycation-driven collagen damage and age-related microenvironmental communication as important contextual hallmarks. These pathways are used here to define research gaps, not to imply untested NIA-specific effects. Read against the senolytic and partial-reprogramming literature, the available evidence is best characterised as multi-hallmark and predominantly senomorphic - supporting stress resilience, autophagy/mitophagy, SASP control, and matrix homeostasis. Product-specific clinical, analytical, skin-penetration, and biomarker validation remain the essential next steps.

Keywords: *Bacopa monnieri*; NIA Cream; skin ageing; cellular senescence; telomere attrition; mitochondrial dysfunction; loss of proteostasis; epigenetic ageing; stem-cell exhaustion; glycation; senolytic; senomorphic; partial cellular reprogramming; SASP; collagen; photoageing; topical delivery.

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INTRODUCTION:

Antioxidant anti-ageing” to ageing hallmarks

Building on the 2023 update to the Hallmarks of Aging framework, which defines twelve interconnected hallmarks, this review focuses on those most relevant to skin: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, mitochondrial dysfunction and cellular senescence^[1]. Cutaneous ageing expresses many of these hallmarks simultaneously. In aged dermis, fibroblasts show reduced matrix synthesis, altered mechanosignalling and accumulation of senescence-associated phenotypes, while ultraviolet radiation accelerates DNA damage, oxidative stress, mitochondrial injury and inflammatory matrix degradation^[2,3,4].

This review focuses on how the growing evidence base for *Bacopa monnieri* (Brahmi) intersects with specific molecular hallmarks of cutaneous ageing, and what this means for the scientific positioning of Biotex NIA Cream. Two of Brahmi's phytochemically documented flavonoid constituents, apigenin and luteolin, are considered throughout as supporting, constituent-level evidence rather than as independent active ingredients. Ingredient-level biology and finished-product evidence are addressed separately throughout, in keeping with standard practice for botanical-ingredient reviews.

This review addresses three specific questions for pharmacy, cosmetic-science and dermatology readers:

(i) which hallmarks of cutaneous ageing are most directly supported by evidence on *Bacopa monnieri* and its flavonoid constituents apigenin and luteolin; (ii) how far this evidence translates from isolated constituents, non-cutaneous models or oral administration to human, topical, skin-relevant endpoints; and (iii) what this evidence base implies for the scientific positioning of the formulation and for the design of future product-specific studies. Clarifying these questions matters because botanical-ingredient reviews are frequently criticised for blurring ingredient-level pharmacology with finished-product claims; this review is structured throughout to keep that distinction explicit.

Literature approach and evidence rules

We updated the literature appraisal through 2026 using PubMed/MEDLINE and primary publisher records. Search domains included *Bacopa monnieri*/Brahmi, apigenin and luteolin combined with cellular senescence, SASP, telomere attrition, telomerase, mitochondrial dysfunction, mitophagy, autophagy, loss of proteostasis, fibroblast, collagen, MMP, TGF-beta/Smad, photoageing, pollution, senolytic, senomorphic, epigenetic rejuvenation and partial cellular reprogramming. Highest weight was assigned to human topical studies, primary human dermal fibroblast/keratinocyte studies, and human skin/explant evidence.

A transferability framework was applied throughout: evidence from an isolated constituent, oral *Bacopa*, neural cells, animal telomere biology, or experimental reprogramming is used to establish biological plausibility and to guide future research questions, and is reported alongside - rather than substituted for - direct evidence on the finished formulation itself.

This is a narrative (non-systematic) review: literature was appraised and synthesised by the author team rather than through a pre-registered protocol, dual independent screening or formal risk-of-bias scoring, consistent with standard practice for hallmark-based mechanistic reviews of a botanical ingredient. Its structure and reporting follow SANRA (Scale for the Assessment of Narrative Review Articles) principles: an explicit rationale and aims for the review, a transparent description of the literature search, appropriate and verifiable referencing, and consistent separation of mechanistic biological plausibility from direct product-level evidence throughout.

Formulation identity and ingredient boundary

The formulation is considered in this review as a Brahmi-based topical product containing 5% *Bacopa monnieri* (Brahmi) W.P. in a cream base q.s. The declared botanical active is therefore *Bacopa monnieri*. Apigenin, luteolin, bacoside A, and related bacosides are discussed as naturally occurring phytoconstituents reported within the botanical and not as separately added active ingredients. This distinction is important because isolated-constituent studies can support biological plausibility but cannot be assumed to reproduce the concentration, release, penetration, or tissue exposure produced by the finished product. This review is deliberately scoped to biological ageing mechanisms and translational anti-ageing validation,

rather than the formulation's general cutaneous evidence base.

Hallmarks of cutaneous ageing most relevant to *Bacopa monnieri* and its flavonoid constituents

Cellular senescence and SASP

Cellular senescence is a stable stress-associated growth arrest accompanied by resistance to apoptosis and, in many contexts, a pro-inflammatory and matrix-degrading SASP. In skin, senescent fibroblasts can release IL-6, IL-8, IL-1-family signals, chemokines and MMPs, thereby altering neighbouring keratinocytes and fibroblasts and accelerating ECM disorganisation^[3,4,5]. Modern single-cell studies further show that dermal-fibroblast senescence is heterogeneous rather than a single state, an observation relevant to the variable responsiveness of senescent cells to senotherapies^[6].

This makes senescence a more precise anti-ageing target than generic antioxidant activity. Among *Bacopa*'s flavonoid constituents, the senescence-related evidence centres on senomorphic modulation: apigenin dampens several SASP components across human fibroblast senescence models, and luteolin reduces p16/p21 and SASP-associated inflammatory outputs in experimental photoageing^[17,21].

Telomere attrition: an emerging research direction for *Bacopa monnieri*

Telomere attrition contributes to replicative senescence and interacts bidirectionally with mitochondrial dysfunction and oxidative DNA damage^[1,7]. Recent skin-fibroblast reviews specifically identify telomere shortening as one intrinsic driver of dermal-fibroblast senescence^[4]. Topical telomere biology for *Bacopa monnieri* is an emerging research direction rather than an established endpoint, discussed below alongside the supportive non-cutaneous data.

There is supportive, non-cutaneous *Bacopa* evidence: in a maternal-stress rat model, standardized *B. monnieri* extract attenuated stress-associated telomere shortening and changes in TERT and shelterin-related proteins in offspring^[12]. A 2026 randomized human *Bacopa* ageing trial protocol also includes telomere/telomerase biology among its planned endpoints, but results are not yet available^[13]. Together, these findings position telomere maintenance as a promising, biologically plausible research hypothesis for *Bacopa monnieri*.

Mitochondrial dysfunction and mitophagy

Mitochondrial dysfunction is both a hallmark and an amplifier of cellular senescence. Declining membrane potential, impaired oxidative phosphorylation, mtDNA injury, and excess ROS can reinforce DNA-damage responses, SASP, and matrix degradation^[1,8]. Skin-focused reviews increasingly treat mitochondrial quality control - spanning biogenesis, dynamics, and mitophagy - as a single, modifiable axis relevant to both photoageing and chronological skin ageing^[9].

This domain has a meaningful *Bacopa* bridge. In benzo[a]pyrene-challenged human keratinocytes, *B. monnieri* maintained mitochondrial integrity and curtailed

ROS-driven apoptosis, an effect that required Beclin-1-mediated autophagic activity^[15]. In a separate human astrocyte model, Bacopa limited pollutant-triggered senescence and apoptosis through a mechanism dependent on Parkin-mediated mitophagy, since pharmacologically blocking mitophagy removed the protective effect^[11]. The latter is not a skin study, but it strengthens the biological plausibility that Bacopa can influence mitochondrial quality-control machinery upstream of senescence.

Loss of proteostasis and disabled autophagy

Loss of proteostasis describes declining capacity to maintain correctly folded, functional proteins and to remove damaged proteins. In skin, cumulative protein carbonylation and proteotoxic aggregation can impair mitochondrial function, DNA repair, signalling and tissue homeostasis^[10]. Autophagy is one of the major cellular systems that supports proteostasis, and reduced fibroblast autophagy has been linked to dermal ageing^[14].

The Beclin-1-dependent autophagy data in human keratinocytes and the Parkin-dependent mitophagy data in human astrocytes together provide a mechanistic bridge from *Bacopa monnieri* to cellular proteostatic and organellar quality control - the intracellular clearance systems that help maintain protein and organelle integrity as skin ages^[11,15]. This positions Bacopa-derived compounds as candidates for supporting proteostatic and organellar stress resilience in skin.

ECM ageing, fibroblast mechanobiology and senescence-independent decline

Dermal ageing cannot be reduced to cellular senescence alone. A 2024 study comparing neonatal, adult, and experimentally senescent human skin fibroblasts showed that senescent cells produce more MMPs, whereas the age-associated decline in new collagen production also contains substantial senescence-independent components^[22]. Human skin data further demonstrate that aged dermal collagen is rougher, stiffer, and harder, with MMP-1 contributing to fibril fragmentation and advanced glycation contributing to abnormal stiffness^[23].

These findings complement the fibroblast-ECM mechanobiology model in which collagen fragmentation reduces fibroblast spreading and mechanical force, amplifies AP-1/MMP signalling, and weakens TGF-beta-dependent matrix synthesis^[2]. The 2024 Bacopa study showing alpha5beta1-integrin/FAK-mediated focal-adhesion remodelling in primary adult human dermal fibroblasts is therefore particularly relevant, although it was performed in a repair/migration paradigm rather than an ageing trial^[16].

Epigenetic alterations and biological-age readouts

Epigenetic ageing encompasses age-associated shifts in DNA methylation, histone modification, chromatin accessibility and non-coding RNA regulation. Human skin shows age-dependent methylation changes and progressive loss of transcriptional network integrity, while newer skin-specific epigenetic clocks seek to quantify biological age rather than chronological age alone^[35,38]. These changes are attractive anti-ageing endpoints because they sit upstream of many visible phenotypes; however, evidence that

Bacopa monnieri or NIA Cream reverses a validated skin epigenetic clock is currently absent. Accordingly, epigenetic rejuvenation should be treated as a future biomarker domain, not as a present product claim.

Partial cellular reprogramming is conceptually linked to this domain because transient reprogramming can reset aspects of epigenetic age in fibroblasts^[31-33]. The practical implication for this research is methodological: future studies could measure methylation-based skin-age indices, chromatin-associated senescence markers, or transcriptomic age signatures alongside conventional wrinkle and elasticity endpoints. Demonstrating a change in appearance without a corresponding molecular-age signal would still constitute a cosmetic benefit, but would not justify a claim of cellular rejuvenation.

Stem-cell exhaustion, epidermal renewal and intercellular communication

Stem-cell exhaustion or dysregulation is an integrative hallmark of skin ageing. Epidermal stem cells sustain barrier renewal and coordinate responses to wounding, mechanical forces, inflammation and circadian cues; chronic ageing reduces regenerative capacity and can disturb the balance between proliferation and differentiation^[35,36]. Ageing of the hypodermal and dermal adipose niche may further alter paracrine support, adipokine signalling, immune tone and tissue regeneration^[39]. These changes illustrate why skin ageing is a tissue-level process rather than a fibroblast-only disorder.

Altered intercellular communication links these compartments. Senescent fibroblasts release SASP mediators that affect keratinocytes, immune cells and neighbouring fibroblasts; keratinocyte-derived cytokines can in turn modify dermal MMP activity, as illustrated by the IL-20/p38-MAPK axis in luteolin studies^[26]. At present, there is no direct evidence that NIA Cream restores epidermal stem-cell number or reverses stem-cell exhaustion. Nevertheless, the existing Bacopa/apigenin/luteolin data on stress resistance, inflammatory signalling and keratinocyte-fibroblast crosstalk provide a biologically plausible basis for testing this broader microenvironmental hypothesis.

Glycation, Collagen Cross-Linking and Matrix Ageing

Long-lived dermal proteins accumulate non-enzymatic glycation products with age. Advanced glycation end-products can alter collagen triple-helix stability, increase molecular-scale stiffness and impair the ability of collagen molecules to self-assemble into normal fibrillar networks^[37]. In parallel, aged human dermal collagen becomes structurally rougher and mechanically abnormal, while fragmentation and altered cross-linking disturb the forces transmitted to fibroblasts^[23]. This provides an additional senescence-independent explanation for loss of elasticity and matrix resilience.

Direct anti-glycation evidence for topical *Bacopa monnieri* in human skin is not yet established, so glycation should not be presented as a demonstrated mechanism. Instead, it defines an important evidence gap. Future ex vivo or reconstructed-skin studies could quantify fluorescent AGEs, pentosidine or carboxymethyl-lysine, collagen

digestibility and fibril organization after chronic glycation stress. Such experiments would clarify whether the formulation influences matrix ageing beyond the better-supported ROS-MMP-senescence pathways.

Deregulated nutrient sensing: relevant context, not a current claim

Deregulated nutrient sensing is another canonical ageing hallmark involving insulin/IGF signalling, AMPK, mTOR

and sirtuin networks^[1,35]. In skin, these systems interact with autophagy, mitochondrial metabolism, protein turnover and stress resistance. Luteolin's reported SIRT3-associated photoageing effects^[27] provide a limited constituent-level connection to metabolic stress signalling, but they do not establish broad AMPK-mTOR or nutrient-sensing correction by Bacopa or NIA Cream. This domain is therefore best framed as an exploratory mechanistic frontier rather than as an efficacy claim.

Table 1: Ageing hallmarks and the supporting evidence base for *Bacopa monnieri* and its constituents.

Ageing domain	Why it matters in skin	NIA/Bacopa-linked evidence	Evidence-based positioning
Cellular senescence / SASP	Senescent fibroblasts drive chronic inflammation and MMP-rich ECM degradation.	Apigenin suppresses SASP; luteolin reduces p16/p21/SASP-related outputs; whole Bacopa suppresses senescence in a non-skin mitophagy model.	Supports a senomorphic, anti-inflammatory rationale grounded in constituent-level evidence.
Telomere attrition	Critical shortening can trigger persistent DNA-damage signalling and replicative senescence.	Stress-exposed rat model suggests Bacopa-associated telomere maintenance, in a non-cutaneous system.	A promising research direction, supported by non-cutaneous Bacopa data.
Mitochondrial dysfunction	ROS, mtDNA injury, and energetic failure reinforce senescence and ECM breakdown.	Keratinocyte mitochondrial protection; Parkin-dependent mitophagy in human astrocytes.	Mechanistic support for mitochondrial stress resilience via keratinocyte and astrocyte models.
Loss of proteostasis/autophagy	Damaged proteins and impaired clearance compromise cellular homeostasis.	Beclin-1-dependent autophagy and mitophagy evidence.	An indirect but coherent mechanistic bridge to proteostatic and organellar quality control.
ECM / mechanobiology	Collagen fragmentation and altered force signalling reinforce MMP activation and reduce matrix synthesis.	Whole Bacopa α 5 β 1/FAK fibroblast response; apigenin collagen I/III; luteolin MMP regulation.	The strongest and most direct anti-ageing mechanistic domain for Bacopa and its flavonoids.
Epigenetic ageing/reprogramming	Age-associated epigenetic states may be partially reset experimentally.	Demonstrated in general dermal-fibroblast reprogramming research; not yet studied for Bacopa.	A scientific benchmark for future topical geroscience research.
Epigenetic alterations	DNA methylation/chromatin drift can alter biological age and regenerative gene expression.	No direct Bacopa skin-clock reversal data; partial reprogramming literature provides a benchmark.	Important biomarker and future-study domain; not a current product claim.
Stem-cell exhaustion / altered communication	Declining epidermal renewal and paracrine dysregulation reduce barrier and regenerative resilience.	No direct stem-cell restoration data; constituent studies support keratinocyte-fibroblast stress and cytokine modulation.	Contextual hallmark and research gap rather than demonstrated efficacy.
Glycation/matrix cross-linking	AGE accumulation changes collagen stability, fibril assembly, and tissue mechanics.	No direct topical Bacopa anti-glycation evidence in human skin.	Relevant ECM-ageing gap for ex vivo and clinical biomarker testing.
Deregulated nutrient sensing	AMPK/mTOR/sirtuin networks couple metabolism to autophagy, mitochondria, and stress resistance.	Luteolin has SIRT3-linked photoageing evidence; broader Bacopa skin data are insufficient.	Exploratory mechanistic domain, not a current claim.

Bacopa monnieri as a multi-hallmark stress-resilience botanical

The phytochemical argument need not repeat a complete Brahmi profile. The analytically relevant point is that HPLC-based authentication of *B. monnieri* confirms the presence of the flavonoids luteolin and apigenin alongside its characterised bacoside saponin mixture, although their concentrations were not quantified in that analysis^[24].

These constituents provide different, partially complementary links to ageing biology. Whole-Bacopa evidence supplies oxidative-DNA-protection data in human fibroblasts, together with human skin-cell data for mitochondrial/autophagic stress control and fibroblast focal-adhesion behaviour^[15,16,25]. Apigenin and luteolin extend this evidence into human anti-ageing endpoints, collagen homeostasis and senescence-associated signalling.

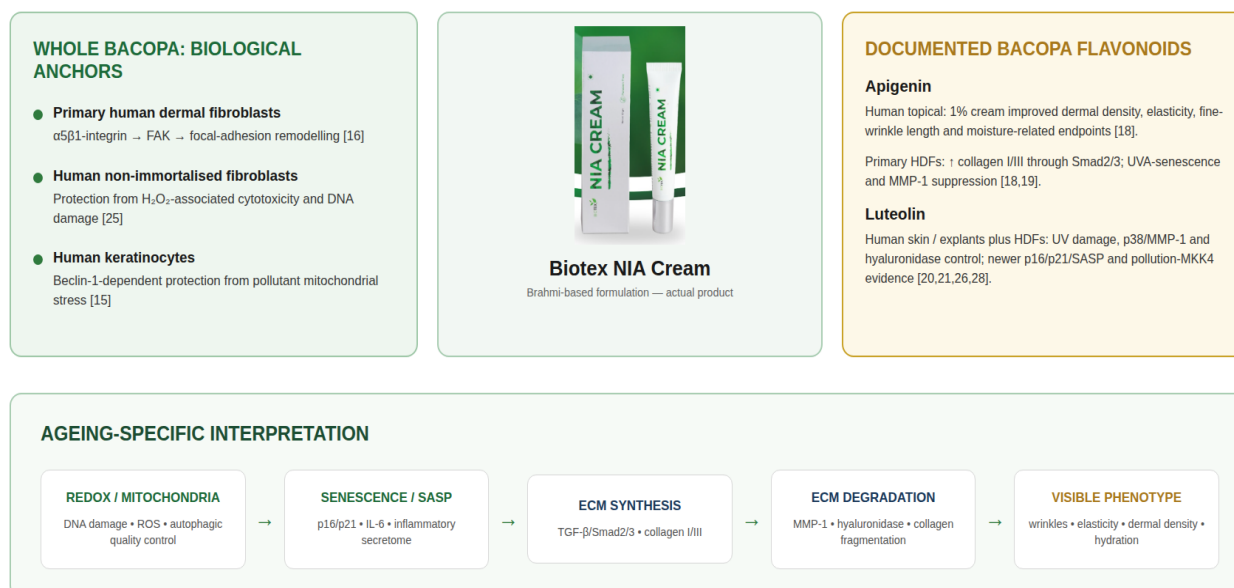


Figure 1: *Bacopa monnieri* phytochemical convergence on dermal-ageing biology, from constituent identification (luteolin, apigenin, bacoside saponins) through to the mechanistic pathways relevant to skin.

Botanical standardization, concentration and active-exposure problem

For a botanical topical, chemical identity is only the first translational step. The biological relevance of apigenin, luteolin and bacoside-related fractions depends on their actual concentration in the extract, stability in the cream, release from the vehicle and penetration into the epidermal or dermal compartment where the proposed target resides. Plant phenolics show highly formulation-dependent skin diffusion, and vehicle composition, partition behaviour, molecular size, skin model, and experimental conditions can materially alter measured delivery^[40]. Consequently, constituent-level efficacy cannot be transferred quantitatively to NIA Cream without analytical and percutaneous-delivery bridging.

A stronger product dossier would therefore characterize authenticated *Bacopa* raw material and the finished cream in parallel. Recommended minimum characterization includes botanical identity, extract ratio and solvent where applicable, HPLC fingerprinting, quantitative marker ranges for bacoside-related components and apigenin/luteolin, total phenolic content, batch-to-batch variability, accelerated and real-time stability, and compatibility with the cream base. Franz-cell or equivalent diffusion studies using appropriate human or validated skin models could then determine whether marker compounds are retained in the stratum corneum, reach viable epidermis, or become detectable in dermal receptor fluid. Such data would substantially strengthen the bridge from phytochemistry to mechanism.

Documented flavonoid constituents of *Bacopa monnieri*: apigenin and luteolin

Apigenin: human translation, senomorphic signalling and collagen synthesis

Apigenin provides the strongest human translational bridge for a documented *Bacopa* constituent. In normal human dermal fibroblasts, apigenin reduced UVA-associated senescence and MMP-1. A four-week, randomized, double-blind trial in human subjects found that a 1% apigenin cream produced measurable gains in dermal density and elasticity, shortened fine-wrinkle length, and improved moisture- and barrier-related measures relative to a matched control formulation^[18]. This clinical evidence establishes apigenin as a well-translated, human-validated anti-ageing constituent.

Apigenin also increased type I and type III collagen in primary human dermal fibroblasts through Smad2/3 signalling, addressing the synthetic side of ECM homeostasis^[19]. Separately, apigenin blunted the SASP in human fibroblast senescence models by dampening IL-1α-driven signalling through IRAK1/4, p38-MAPK and NF-κappaB^[17]. This is best described as senomorphic activity: the senescent secretory phenotype is modulated, rather than senescent cells being selectively killed.

Luteolin: photoageing, pollutant stress and senescence-associated pathways

Luteolin has unusually broad human-skin support. It reduced UVB-induced DNA photoproduct formation, ROS, erythema and COX-2/PGE2 signalling in human keratinocytes and human skin^[20]. Isolated luteolin - a flavonoid also documented in *B. monnieri* extract - blocked solar-radiation-induced MMP-1 and hyaluronidase upregulation in human dermal fibroblasts via p38-MAPK signalling and suppression of keratinocyte-derived IL-20, pointing to a mechanistic, constituent-level link to collagen and hyaluronic-acid preservation rather than direct evidence from *Bacopa* extract itself^[26].

In experimental photoageing, luteolin has reduced ROS and MMP activation and preserved collagen through a SIRT3-ROS-MAPK axis^[27]. A 2025 study in a murine (NIH-3T3/BALB-c) photoageing model further reported reduction of UVA-associated p16, p21, collagen degradation and SASP-related inflammatory factors^[21].

In human keratinocytes exposed to particulate matter, luteolin also suppressed ROS, IL-6, COX-2 and MMP-1 through MKK4/JNK/p38-associated signalling, extending the rationale from ultraviolet photoageing to the pollution exposome^[28].

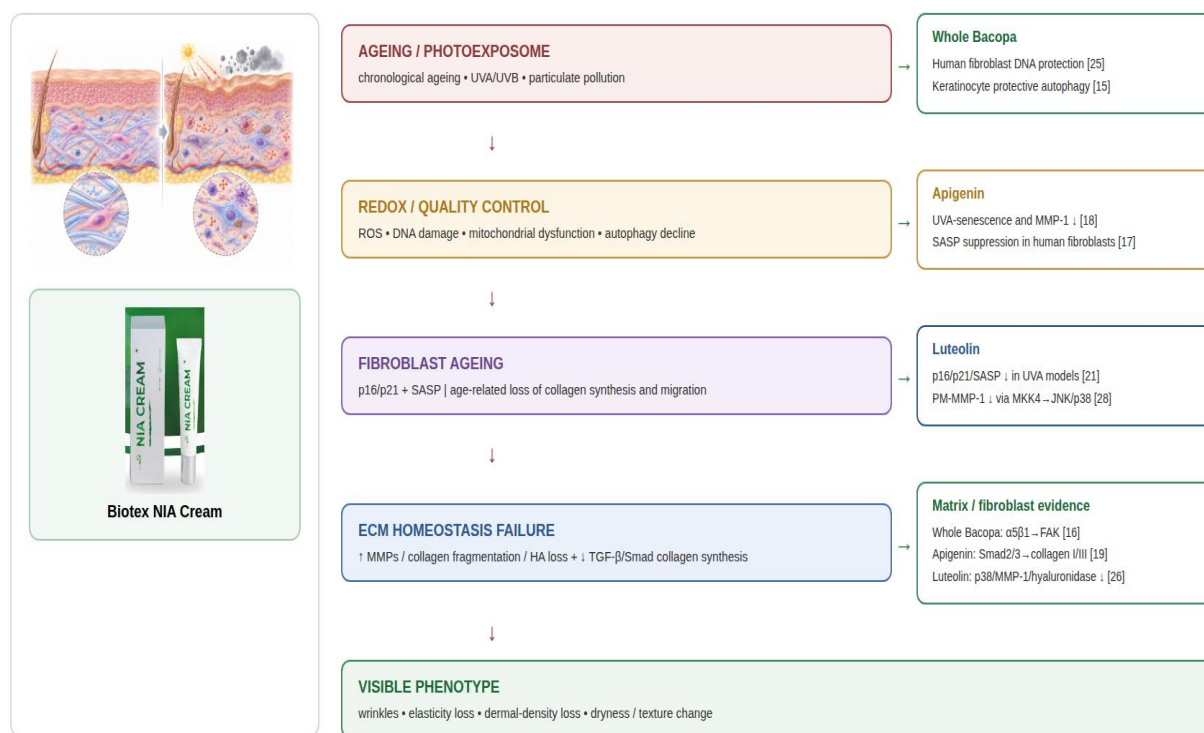


Figure 2: Integrated dermal-ageing circuit. Oxidative and mitochondrial stress, senescence/SASP, and ECM mechanobiology form reinforcing loops, with Bacopa-derived and flavonoid evidence intersecting multiple nodes of this network.

Senolytic versus senomorphic: an important terminology boundary

A senolytic selectively induces death of senescent cells, whereas a senomorphic (or senostatic) intervention suppresses detrimental senescent-cell phenotypes such as the SASP without necessarily eliminating the cells. This distinction is critical for product claims. Skin studies using established senolytic regimens show that selective clearance of senescent dermal fibroblasts can increase collagen density and reduce SASP-associated factors. In mouse skin, the BCL-2-family inhibitors ABT-263 and ABT-737 cleared senescent fibroblasts and raised dermal collagen while lowering SASP output; in a human-skin xenograft model, combined dasatinib and quercetin achieved comparable senescent-cell clearance with parallel gains in collagen density and SASP suppression^[29,30,34].

Bacopa extract, apigenin, and luteolin have not been tested in a selective senescent-cell-clearance (senolytic) paradigm, so their activity is better characterised as senomorphic and cytoprotective: several constituent studies suppress senescence markers or SASP outputs, while whole Bacopa supports autophagy/mitophagy and stress resistance^[11,17,21].

Partial cellular reprogramming: an emerging benchmark for rejuvenation research

The accepted scientific term is partial cellular reprogramming, not “practical cellular reprogramming.” It refers to limited exposure to reprogramming factors or other reprogramming paradigms that aim to reduce cellular age without permanently losing somatic identity. Experimental maturation-phase transient reprogramming of dermal fibroblasts taken from middle-aged human donors reset transcriptomic and epigenetic age by roughly three decades, returned collagen output to youthful levels, and partially restored migratory capacity^[31]. Reviews published in 2024-2025 frame partial reprogramming as a fast-growing rejuvenation strategy, while cautioning that dedifferentiation, loss of cell identity, genomic instability, and tumorigenic risk remain unresolved safety concerns^[32,33].

Partial cellular reprogramming remains a distinct, more advanced rejuvenation paradigm than anything yet tested for *Bacopa monnieri* or its flavonoids. It is nevertheless a useful benchmark for future research: topical geroscience studies of Bacopa-based formulations could examine epigenetic age, chromatin markers, mitochondrial function, proteostasis, and senescence burden alongside

conventional wrinkle and elasticity endpoints, to test whether genuine cellular rejuvenation accompanies cosmetic improvement.

Telomere-proteostasis-mitochondria-senescence crosstalk: an integrated hypothesis for NIA Cream

The hallmarks are not isolated. Telomere dysfunction can amplify p53-dependent stress signalling and mitochondrial decline; mitochondrial ROS can damage nuclear and telomeric DNA; impaired autophagy and proteostasis permit damaged proteins and organelles to accumulate; and persistent damage can stabilize senescence and the SASP^[1,7,8]. In dermal fibroblasts, these processes converge on reduced matrix production, MMP activation, inflammatory crosstalk, and loss of mechanical competence^[3,4].

Within this network, the evidence for *Bacopa monnieri* and its flavonoid constituents is strongest at three points: (1) stress and DNA protection in human fibroblasts; (2) autophagy/mitochondrial quality control in human keratinocytes and supportive non-skin human-cell models; and (3) ECM/senescence modulation by apigenin and luteolin^[11,15,17,18,19,20,21,25,26,27,28]. Direct evidence in human skin is still developing for telomere length, global proteostasis biomarkers, epigenetic-clock reversal, stem-cell exhaustion, and selective senescent-cell clearance - an evidence map this review states explicitly so that Biotex NIA Cream's positioning stays anchored to what the ingredient science currently supports.

Ageing endpoint	Human topical / in vivo	Human skin / explant	Primary human skin cells	Other supportive evidence
Wrinkles / elasticity / dermal density	Apigenin 1% cream: ↑ density and elasticity; ↓ fine-wrinkle length [18]	—	—	Luteolin reduced UVB wrinkling in vivo [27]
UV / photoexposure stress	Luteolin reduced UVB erythema and DNA damage in human skin [20]	Luteolin suppressed SSR-induced IL-6/MMP-1 in human skin explants [26]	Apigenin : UVA-senescence/MMP-1 [18]; Luteolin : UV ROS/MMP pathways [20,21,27]	Luteolin : UVA p16/p21/SASP [21]; ↓ PM-MMP-1 via MKK4 [28]
Collagen synthesis / degradation	—	—	Apigenin : collagen I/III via Smad2/3 [19]; Whole Bacopa supports fibroblast adhesion/migration [16]	Adult human skin fibroblasts show senescence-independent decline in collagen synthesis [22]
Senescence / SASP	—	—	Apigenin suppresses SASP in human fibroblast strains [17]	Senotherapeutic reviews frame senescent-cell clearance and SASP modulation as convergent human-skin anti-ageing strategies [34]
Oxidative / mitochondrial resilience	—	—	Whole Bacopa : oxidative DNA damage [25]; keratinocyte protective autophagy [15]	Modern ageing reviews place redox imbalance and mitochondrial decline upstream of senescence [1,8,9]

Interpretation: Direct anti-ageing evidence is strongest for the documented Bacopa constituents (human topical apigenin; human skin/explant luteolin). Whole-Bacopa studies provide human skin-cell biological anchoring. Finished NIA Cream efficacy remains untested.

Figure 3: Translational map from documented Bacopa biology to human anti-ageing endpoints, showing the directness of evidence at each translational step.

A tissue-network model: beyond single-hallmark interpretation

The expanded hallmark framework suggests that the most realistic anti-ageing model for a botanical topical is network modulation rather than single-target correction. Oxidative and mitochondrial damage can reinforce telomeric DNA-damage signalling; defective autophagy allows damaged proteins and organelles to accumulate; SASP factors alter keratinocyte and immune-cell behaviour; glycation and collagen fragmentation distort the mechanical niche; and reduced regenerative capacity can amplify barrier dysfunction[1,36-40]. These processes are interconnected and may operate at different rates in chronologically aged, photoaged and pollution-exposed skin.

Within this network, the strongest NIA-linked evidence still clusters around stress resilience, mitochondrial/autophagic quality control and ECM regulation. Epigenetic age, stem-cell exhaustion, glycation and broad nutrient-sensing remain important contextual hallmarks but are not yet directly demonstrated product mechanisms. Explicitly preserving this hierarchy makes the review more rigorous: it allows the formulation to be discussed within modern

geroscience without converting every hallmark into an unsupported claim.

Translational priorities for NIA Cream

A product-specific programme should now move beyond generic antioxidant assays. A randomized, blinded, vehicle-controlled 8- to 12-week facial study should combine three-dimensional wrinkle profilometry, Cutometer elasticity, high-frequency ultrasound or optical dermal-density assessment, Corneometer hydration and TEWL with standardized photography. In a mechanistic substudy, minimally invasive tape-strip, suction-blister, or biopsy approaches could examine p16INK4a/p21, selected SASP factors, MMP-1, procollagen, mitochondrial ROS/mitophagy markers, and protein-carbonyl/proteostasis indices.

Telomere measurements may be included exploratorily, but interpretation must be conservative because telomere length in skin is cell-type dependent and short-term topical intervention may not produce detectable change. Similarly, a senolytic claim would require demonstration of selective elimination of senescent cells relative to proliferating cells, while a reprogramming claim would require validated epigenetic-age or cell-identity

evidence. These thresholds are substantially higher than demonstrating improvement in wrinkles or hydration.

Analytical standardization and topical disposition

Before a definitive efficacy trial, the formulation should be analytically locked. A representative clinical batch should be linked to the botanical raw material by a reproducible chromatographic fingerprint and predefined marker specifications. Quantification of bacoside-related components together with apigenin and luteolin would permit later mechanistic studies to report exposure rather than only the nominal percentage of plant material. Stability-indicating assays should confirm that the marker profile is maintained over the intended shelf life.

Skin-delivery work should then determine where the formulation's marker compounds localize after realistic dosing. Because diffusion of plant phenolics is strongly vehicle- and model-dependent^[40], a staged programme could use release testing followed by Franz diffusion with human or validated surrogate skin, tape-stripping for stratum-corneum deposition, and mass-spectrometric or HPLC analysis of viable epidermal/dermal fractions where feasible. These experiments would provide a pharmacological bridge between the 5% botanical declaration and the concentrations used in cell-based apigenin or luteolin studies.

Clinical efficacy design: phenotype first, mechanism second

For a first product-specific study, the primary endpoints should remain clinically interpretable. A randomized, double-blind, vehicle-controlled parallel or split-face design over approximately 8-12 weeks could use three-dimensional optical wrinkle profilometry and Cutometer-based elasticity as primary outcomes, with standardized photography, corneometry, TEWL, and participant-reported tolerability as secondary outcomes. Stratification by age, baseline photoageing severity, Fitzpatrick skin type, sex, smoking, major sun exposure,

and concurrent retinoid/acid use would reduce avoidable heterogeneity. The vehicle control is essential because hydration and occlusion from the cream base can independently improve appearance and barrier metrics.

Mechanistic substudy: testing the hallmark hypothesis

A mechanistic substudy could test whether visible improvement is accompanied by changes in the ageing network proposed here. Minimally invasive sampling could quantify p16INK4a/p21, selected SASP mediators, MMP-1, procollagen-I, oxidative-damage markers, mitochondrial ROS or mitophagy-related proteins and protein-carbonyl indices. Exploratory endpoints could include skin-specific methylation-age measures, but such analyses should be pre-specified and interpreted as biological-age biomarkers rather than cosmetic efficacy endpoints. Telomere length is even more challenging because of cell-type composition, slow kinetics and high inter-individual variability; it is more appropriate for exploratory or longer-duration work than for a short cosmetic trial.

Safety, tolerability and claim thresholds

Anti-ageing positioning also requires a clear safety framework. Patch testing or repeat-insult patch testing, adverse-event surveillance, and, where relevant, phototoxicity/photoallergy assessment should precede broad claims. Botanical authentication and contaminant testing remain essential because microbial load, pesticides, heavy metals, and adulteration can confound both safety and reproducibility. Claims should track evidence tier: improvement in wrinkles or elasticity requires finished-product clinical data; a senomorphic claim requires direct modulation of senescence/SASP endpoints in the relevant skin model; a senolytic claim requires selective clearance of senescent cells; and a reprogramming or epigenetic-rejuvenation claim requires validated biological-age or cell-identity evidence.

Table 2: Proposed validation pathway for Biotex NIA Cream.

Validation domain	Suggested methods	What it would establish	Priority
Identity/quality	Botanical authentication; HPLC fingerprint; marker quantification; contaminants; stability	Locks the tested material and supports batch reproducibility	Before efficacy testing
Topical exposure	In vitro release; Franz diffusion; tape stripping; viable epidermis/dermis marker analysis	Shows whether phytochemical markers reach biologically relevant skin compartments	High priority
Clinical phenotype	3D wrinkle profilometry; Cutometer elasticity; dermal density; corneometry; TEWL; standardized photography	Establishes finished-product anti-ageing efficacy	Primary translational objective
Senescence / ECM	p16/p21; selected SASP factors; MMP-1; procollagen-I; collagen organization	Tests senomorphic and matrix-homeostasis hypothesis	Mechanistic substudy
Mitochondria/proteostasis	Mitochondrial ROS; mitophagy/autophagy markers; protein carbonyls	Tests stress-resilience and quality-control hypothesis	Mechanistic substudy
Epigenetic / telomere	Skin methylation-age measures; exploratory telomere endpoints	Assesses stronger biological-age effects; requires conservative interpretation	Exploratory/longer-term
Safety	Patch testing; irritation; photosafety where relevant; adverse events	Defines tolerability and benefit-risk profile	Mandatory

CONCLUSION

Reframing Biotex NIA Cream through the hallmarks of ageing yields a stronger and more scientifically differentiated anti-ageing review. Cellular senescence, mitochondrial dysfunction, loss of proteostasis and disabled autophagy are directly relevant to the skin-ageing phenotype, while telomere attrition and epigenetic ageing provide important upstream context. The current NIA/Bacopa evidence is strongest for oxidative and mitochondrial stress resilience, autophagy/mitophagy, fibroblast-ECM behaviour and constituent-level modulation of SASP, MMPs and collagen homeostasis. Among its documented flavonoid constituents, apigenin supplies the most direct human cosmetic bridge, while luteolin adds human skin photoprotection and modern senescence/exposome mechanisms.

Biotex NIA Cream is best positioned as a Bacopa-based topical formulation with a multi-hallmark, senomorphic anti-ageing rationale - supporting stress resilience, autophagy/mitophagy, and SASP suppression, mechanisms that stand on a substantial and growing ingredient-level evidence base. Direct, product-specific clinical and biomarker validation is the natural next step to translate this strong ingredient-level foundation into finished-product evidence.

The expanded framework also clarifies what is not yet established. NIA Cream should not presently be described as telomere-lengthening, senolytic, epigenetically reprogramming, stem-cell-restoring, or anti-glycation therapy. Those concepts are scientifically relevant because they define measurable ageing biology and future experimental endpoints, but the current product-linked evidence is not sufficient for such claims. The strongest path forward is therefore sequential: analytically define the 5% Brahmi formulation, demonstrate skin delivery of characteristic markers, establish product-specific clinical benefit, and then test whether that benefit co-occurs with changes in senescence, mitochondrial quality control, proteostasis and ECM biomarkers.

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Cream. This relationship is disclosed as a potential conflict of interest. Ingredient- and constituent-level evidence has been distinguished from finished-product efficacy.

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REFERENCES

1. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. *Cell*. 2023;186(2):243-278. doi:10.1016/j.cell.2022.11.001.
2. Fisher GJ, Wang B, Cui Y, Shi M, Zhao Y, Quan T, Voorhees JJ. Skin aging from the perspective of dermal fibroblasts: the interplay between the adaptation to the extracellular matrix microenvironment and cell autonomous processes. *J Cell Commun Signal*. 2023;17(3):523-529. doi:10.1007/s12079-023-00743-0.
3. Zhang J, Yu H, Man MQ, Hu L. Aging in the dermis: Fibroblast senescence and its significance. *Aging Cell*. 2024;23(2):e14054. doi:10.1111/ace1.14054.
4. Nan L, Guo P, Hui W, Xia F, Yi C. Recent advances in dermal fibroblast senescence and skin aging: unraveling mechanisms and pioneering therapeutic strategies. *Front Pharmacol*. 2025;16:1592596. doi:10.3389/fphar.2025.1592596.
5. Thau H, Gerjol BP, Hahn K, von Gudenberg RW, Knoedler L, Stallcup K, et al. Senescence as a molecular target in skin aging and disease. *Ageing Res Rev*. 2025;105:102686. doi:10.1016/j.arr.2025.102686.
6. Kamat P, Macaluso N, Li Y, Agrawal A, Winston A, Pan L, et al. Single-cell morphology encodes functional subtypes of senescence in aging human dermal fibroblasts. *Sci Adv*. 2025;11(17):eads1875. doi:10.1126/sciadv.ads1875.
7. Gao X, Yu X, Zhang C, Wang Y, Sun Y, Sun H, et al. Telomeres and Mitochondrial Metabolism: Implications for Cellular Senescence and Age-related Diseases. *Stem Cell Rev Rep*. 2022;18(7):2315-2327. doi:10.1007/s12015-022-10370-8. PMID:35460064.
8. Miwa S, Kashyap S, Chini E, von Zglinicki T. Mitochondrial dysfunction in cell senescence and aging. *J Clin Invest*. 2022;132(13):e158447. doi:10.1172/JCI158447.
9. Zhang C, Gao X, Li M, Yu X, Huang F, Wang Y, et al. The role of mitochondrial quality surveillance in skin aging: Focus on mitochondrial dynamics, biogenesis and mitophagy. *Ageing Res Rev*. 2023;87:101917. doi:10.1016/j.arr.2023.101917. PMID:36972842.
10. Dréno B, Benoit I, Perrier E, Radman M. Beyond the genome: protecting the proteome may be the key to preventing skin aging. *Eur J Dermatol*. 2024;34(4):355-360. doi:10.1684/ejd.2024.4739.
11. Saha S, Mahapatra KK, Mishra SR, et al. Bacopa monnieri inhibits apoptosis and senescence through mitophagy in human astrocytes. *Food Chem Toxicol*. 2020;141:111367. doi:10.1016/j.fct.2020.111367.
12. Sivasangari K, Sivamaruthi BS, Chaiyasut C, Rajan KE. Maternal stress-induced changes in adolescent and adult offspring: Neurobehavioural improvement and telomere maintenance. *Heliyon*. 2023;9(10):e20385. doi:10.1016/j.heliyon.2023.e20385.
13. Pradeep HLN, Perera PK, Waratenne PR, Samaranayake N, Dissanayake WDN. Effects of Bacopa monnieri herbal supplement on aging and neurocognitive functions, including neurophysiological assessments, in relation to constitution (Prakriti) in healthy adults: clinical trial protocol. *Front Med (Lausanne)*. 2026;13:1702773. doi:10.3389/fmed.2026.1702773.
14. Lu Y, Pan G, Wei Z, Li Y, Pan X. Role of fibroblast autophagy and proliferation in skin anti-aging. *Exp Gerontol*. 2024;196:112559. doi:10.1016/j.exger.2024.112559.

15. Das DN, Naik PP, Nayak A, et al. Bacopa monnieri-Induced Protective Autophagy Inhibits Benzo[a]pyrene-Mediated Apoptosis. *Phytother Res.* 2016;30(11):1794-1801. doi:10.1002/ptr.5682.
16. Zirmire RK, Saha D, Dey R, et al. Bacopa monnieri phytochemicals regulate fibroblast cell migration via modulation of focal adhesions. *iScience.* 2024;27(4):109489. doi:10.1016/j.isci.2024.109489.
17. Perrott KM, Wiley CD, Desprez PY, Campisi J. Apigenin suppresses the senescence-associated secretory phenotype and paracrine effects on breast cancer cells. *Geroscience.* 2017;39(2):161-173. doi:10.1007/s11357-017-9970-1.
18. Choi S, Youn J, Kim K, et al. Apigenin inhibits UVA-induced cytotoxicity in vitro and prevents signs of skin aging in vivo. *Int J Mol Med.* 2016;38(2):627-634. doi:10.3892/ijmm.2016.2626.
19. Zhang Y, Wang J, Cheng X, Yi B, Zhang X, Li Q. Apigenin induces dermal collagen synthesis via Smad2/3 signaling pathway. *Eur J Histochem.* 2015;59(2):2467. doi:10.4081/ejh.2015.2467.
20. Wölflle U, Esser PR, Simon-Haarhaus B, Martin SF, Lademann J, Schempp CM. UVB-induced DNA damage, generation of reactive oxygen species, and inflammation are effectively attenuated by the flavonoid luteolin in vitro and in vivo. *Free Radic Biol Med.* 2011;50(9):1081-1093. doi:10.1016/j.freeradbiomed.2011.01.027.
21. Yan Y, Huang H, Su T, et al. Luteolin Mitigates Photoaging Caused by UVA-Induced Fibroblast Senescence by Modulating Oxidative Stress Pathways. *Int J Mol Sci.* 2025;26(5):1809. doi:10.3390/ijms26051809.
22. Fullard N, Wordsworth J, Welsh C, et al. Cell Senescence-Independent Changes of Human Skin Fibroblasts with Age. *Cells.* 2024;13(8):659. doi:10.3390/cells13080659.
23. He T, Fisher GJ, Kim AJ, Quan T. Age-related changes in dermal collagen physical properties in human skin. *PLoS One.* 2023;18(12):e0292791. doi:10.1371/journal.pone.0292791.
24. Deepak M, Sangli GK, Arun PC, Amit A. Quantitative determination of the major saponin mixture bacoside A in Bacopa monnieri by HPLC. *Phytochem Anal.* 2005;16(1):24-29. doi:10.1002/pca.805.
25. Russo A, Izzo AA, Borrelli F, Renis M, Vanella A. Free radical scavenging capacity and protective effect of Bacopa monnieri L. on DNA damage. *Phytother Res.* 2003;17(8):870-875. doi:10.1002/ptr.1061.
26. Wölflle U, Heinemann A, Esser PR, Haarhaus B, Martin SF, Schempp CM. Luteolin prevents solar radiation-induced matrix metalloproteinase-1 activation in human fibroblasts: a role for p38 mitogen-activated protein kinase and interleukin-20 released from keratinocytes. *Rejuvenation Res.* 2012;15(5):466-475. doi:10.1089/rej.2011.1309.
27. Mu J, Ma H, Chen H, Zhang X, Ye M. Luteolin Prevents UVB-Induced Skin Photoaging Damage by Modulating SIRT3/ROS/MAPK Signaling: An in vitro and in vivo Study. *Front Pharmacol.* 2021;12:728261. doi:10.3389/fphar.2021.728261.
28. Yun J, Kim JE. Luteolin targets MKK4 to attenuate particulate matter-induced MMP-1 and inflammation in human keratinocytes. *Sci Rep.* 2025;15:16848. doi:10.1038/s41598-025-01090-3.
29. Kim H, Jang J, Song MJ, et al. Attenuation of intrinsic ageing of the skin via elimination of senescent dermal fibroblasts with senolytic drugs. *J Eur Acad Dermatol Venereol.* 2022;36(7):1125-1135. doi:10.1111/jdv.18051.
30. Takaya K, Kishi K. Combined dasatinib and quercetin treatment contributes to skin rejuvenation through selective elimination of senescent cells in vitro and in vivo. *Biogerontology.* 2024;25(4):691-704. doi:10.1007/s10522-024-10103-z.
31. Gill D, Parry A, Santos F, et al. Multi-omic rejuvenation of human cells by maturation phase transient reprogramming. *eLife.* 2022;11:e71624. doi:10.7554/eLife.71624.
32. Paine PT, Nguyen A, Ocampo A. Partial cellular reprogramming: A deep dive into an emerging rejuvenation technology. *Aging Cell.* 2024;23(2):e14039. doi:10.1111/accel.14039.
33. Avelar RA, Palmer D, Kulaga AY, Fuellen G. Conserved biological processes in partial cellular reprogramming: Relevance to aging and rejuvenation. *Ageing Res Rev.* 2025;108:102737. doi:10.1016/j.arr.2025.102737.
34. Wyles SP, Carruthers JD, Dashti P, et al. Cellular Senescence in Human Skin Aging: Leveraging Senotherapeutics. *Gerontology.* 2024;70(1):7-14. doi:10.1159/000534756.
35. Jin S, Li K, Zong X, Eun S, Morimoto N, Guo S. Hallmarks of Skin Aging: Update. *Aging Dis.* 2023;14(6):2167-2176. doi:10.14336/AD.2023.0321.
36. Tang X, Wang J, Chen J, Liu W, Qiao P, Quan H, et al. Epidermal stem cells: skin surveillance and clinical perspective. *J Transl Med.* 2024;22(1):779. doi:10.1186/s12967-024-05600-1.
37. Slosseris D, Forde NR. AGEing of collagen: The effects of glycation on collagen's stability, mechanics and assembly. *Matrix Biol.* 2025;135:153-160. doi:10.1016/j.matbio.2024.12.007.
38. Yang J, Xu M, Duan Y, Yuan Y, Zhang J, Jiang W. Epigenetic Mechanisms, Assessment and Therapeutics of Epidermal Stem Cells in Skin Aging. *Stem Cells Int.* 2025;2025:7575250. doi:10.1155/sci/7575250.
39. Liu M, Lu F, Feng J. Aging and homeostasis of the hypodermis in the age-related deterioration of skin function. *Cell Death Dis.* 2024;15(6):443. doi:10.1038/s41419-024-06818-z.
40. Silva GC, Rodrigues RAF, Bottoli CBG. In vitro diffusion of plant phenolics through the skin: A review update. *Int J Cosmet Sci.* 2024;46(2):239-261. doi:10.1111/ics.12927.