IJPSR (2026), Volume 17, Issue 5 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 November 2025; received in revised form, 30 January 2026; accepted, 12 February 2026; published 01 May 2026

BEYOND BEAUTY: THE MOLECULAR SCIENCE AND CLINICAL EVIDENCE OF ANTI-AGING SKINCARE

Ayesha Siddiqua Gazi *, Umaymah Ahmareen, Aaine Ashfaq and Mehveen Mukaram

Department of Pharmaceutics, Deccan School of Pharmacy, Hyderabad - 500001, Telangana, India.

Keywords:

Anti-aging, Cosmeceuticals

Correspondence to Author:
Dr. Ayesha Siddiqua Gazi

Assistant Professor,
Department of Pharmaceutics, Deccan School of Pharmacy, Hyderabad - 500001, Telangana, India.

E-mail: Umaymahahmareen@gmail.com

ABSTRACT: The anti-aging cosmeceutical industry has transformed from conventional cosmetic applications to biologically active products designed to target the key molecular mechanisms of skin aging itself. The focus of this review is to identify key bioactive ingredients, their mechanisms of action, and delivery systems being used in anti-aging products. The most commonly used bioactives are retinoids, peptides, antioxidants, niacinamide, bakuchiol, glutathione, green tea polyphenols, and hyaluronic acid that provide the anti-aging effect by stimulating collagen, reducing oxidative damage, accelerating epidermal regeneration, and repairing the barrier function of the skin. Recent advances in delivery systems such as liposome delivery systems, nanoparticles, and microneedle delivery systems have greatly increased the stability, bioavailability, and penetration of these bioactive ingredients. The challenges remain regarding the long-term safety efficacy issues, stability of cosmetic formulation, and appropriate regulatory approvals for formulation. The Future research should focus on adopting evidence-based approaches integrating biotechnologies for better skin health and longetivity.

INTRODUCTION: Skin is not simply a cosmetic surface: it is a dynamic, multifunctional organ subject to both intrinsic (biological) and extrinsic (environmental) ageing processes. Recent work demonstrates that ageing of the skin reflects deeper physiological ageing, and that interventions are shifting from merely masking visible signs (wrinkles, laxity, pigmentation) toward preserving and restoring skin's functional biology and longetivity. For example, in one review the skin is described as the "window" into the body's cumulative exposome and biological ageing processes.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.17(5).1375-95

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.17(5).1375-95

Skin as a Mirror of Systemic Ageing: The skin is the body's largest organ and is continuously exposed to internal and external stressors. Recent reviews highlight the bidirectional relationship between skin ageing and systemic biological ageing: The skin records cumulative exposures (for example UV, pollution, metabolic stress) and thus can reflect overall "biological age". Conversely, processes active in systemic ageing (hormonal decline, matrix changes, immune ageing) also manifest in skin structure and function. Understanding this inter-relationship opens potential for skin-targeted interventions not only to improve appearance but possibly to slow systemic ageing or reflect internal health status.

The Choice: From Cosmetics → Cosmeceuticals: Traditional cosmetics (moisturisers, basic serums, make-up) addressed surface appearance with limited claims about altering skin biology.

Cosmeceuticals emerged as formulations incorporating active ingredients (peptides, retinoids, growth factors, botanical extracts) designed to change skin cell behaviour or structure. For example, one article traces the term "cosmeceutical" to early 1990s usage (and earlier) and reports how in countries like Korea dermatologists first used them for skin conditions, later becoming over-the-counter. As scientific understanding of skin ageing advanced (mechanisms, biomarkers, delivery technologies), consumers and brands shifted toward products promising biological benefit, not just beautification. The rise of clinically-oriented skincare lines reflects this.

What are Anti aging Cosmaceuticals: The term "cosmeceutical" (a blend of cosmetic + pharmaceutical) refers to topical products available without prescription that contain biologically active ingredients intended to modulate skin cell function, structure or repair — going beyond purely aesthetic effects. Anti-ageing cosmeceuticals specifically target signs of ageing (fine lines, loss of firmness, uneven tone) and underlying mechanisms (collagen degradation, oxidative stress, reduced cell renewal).

A recent review describes them as a hybrid: "products with therapeutic (medical or drug-like) and cosmetic impact that are intended to enhance the well-being and appearance of the skin. However, it is also emphasised that regulation lags: many are marketed with limited clinical evidence, and the term "cosmeceutical" has no standard legal definition in many jurisdictions.

The Shift from Appearance-Focused Skincare to Mechanism-Targeting Skin:

Longevity: Historically, skincare (especially anti-ageing) focused on visible signs: smoothing wrinkles, evening skin tone, boosting hydration.

But a new paradigm is emerging: Products are increasingly designed to target molecular and cellular mechanisms of skin ageing (e.g., oxidative stress, enzyme inhibition, DNA repair). Reviews argue for "longevity cosmeceuticals" — defined as products that (1) directly modulate skin ageing hallmarks, (2) demonstrably extend functional "skin span", and (3) are validated by clinical biomarker studies.

Dermatology is shifting from reactive correction (post-damages) toward preventive and regenerative strategies that maintain skin health and resilience, not just appearance. Thus, the goal moves from "looking younger" toward "keeping skin younger for longer" — preserving structure, function, response capacity, rather than simply hiding the signs

Global Research and Market Growth of Anti-Ageing Cosmeceuticals:

The anti-ageing cosmeceutical (and broader skincare) market is expanding significantly:

- A 2024 review of anti-ageing cosmeceuticals described how formulation technologies (nanocarriers, liposomes) and bioactive ingredients are increasingly studied to improve penetration and efficacy.
- Several market reports estimate global cosmeceutical market size: is projected to reach USD 84.6 billion by 2030 (CAGR ~3.9 %).
- In terms of trends: the skincare segment (especially anti-ageing) dominates cosmeceuticals, and online/DTC channels are growing fast. Drivers include ageing populations, rising disposable incomes, higher consumer awareness of skin health, demand for evidence based products, and increased access through e-commerce.
- The bottom line: the anti-ageing cosmeceutical market is both large and growing, and research is accelerating to support more mechanistic claims and higher-performance product

The Biology of Skin Aging: Compromised epidermal permeability barrier homeostasis. Aging-associated changes in baseline transepidermal water loss (TEWL) rates, an indicator of epidermal permeability barrier, vary greatly with gender, body sites and pigment types. While some studies have shown that baseline TEWL rates on several body sites are lower in the aging than in young skin, other study demonstrated that TEWL rates on the décolleté region correlated positively with age, but TEWL rates on the neck, forearm and hand were comparable between young and aged women.

Moreover, TEWL rates are higher in aged females than in aged males. Yet, in both aged humans and mice, following acute disruption of permeability barrier function, permeability barrier recovery is significantly delayed in comparison to younger age groups. In addition, stratum corneum integrity also decreases in both aged humans and mice. Taken together, aged epidermis displays defects in permeability barrier homeostasis. Collectively, aged epidermis displays multiple alterations in keratinocyte function, including altered signaling pathways of calcium, cytokine and hyaluronic acid, stratum corneum acidification, keratinocyte proliferation, differentiation, lipid production, as well as decreased epidermal aquaporin 3 expression, consequently leading to compromised epidermal permeability barrier function

Aging in the Dermis:

Fibroblast Senescence: Skin aging is characterized by changes in its structural, cellular, and molecular components in both the epidermis and dermis. Dermal aging is distinguished by reduced dermal thickness, increased wrinkles, and a sagging appearance.

Due to intrinsic or extrinsic factors, accumulation of excessive reactive oxygen species (ROS) triggers a series of aging events, including imbalanced extracellular matrix (ECM) homeostasis, accumulation of senescent fibroblasts, loss of cell identity, and chronic inflammation mediated by senescence-associated secretory phenotype (SASP)

Role of Senescent Dermal Fibroblasts in Skin Aging:

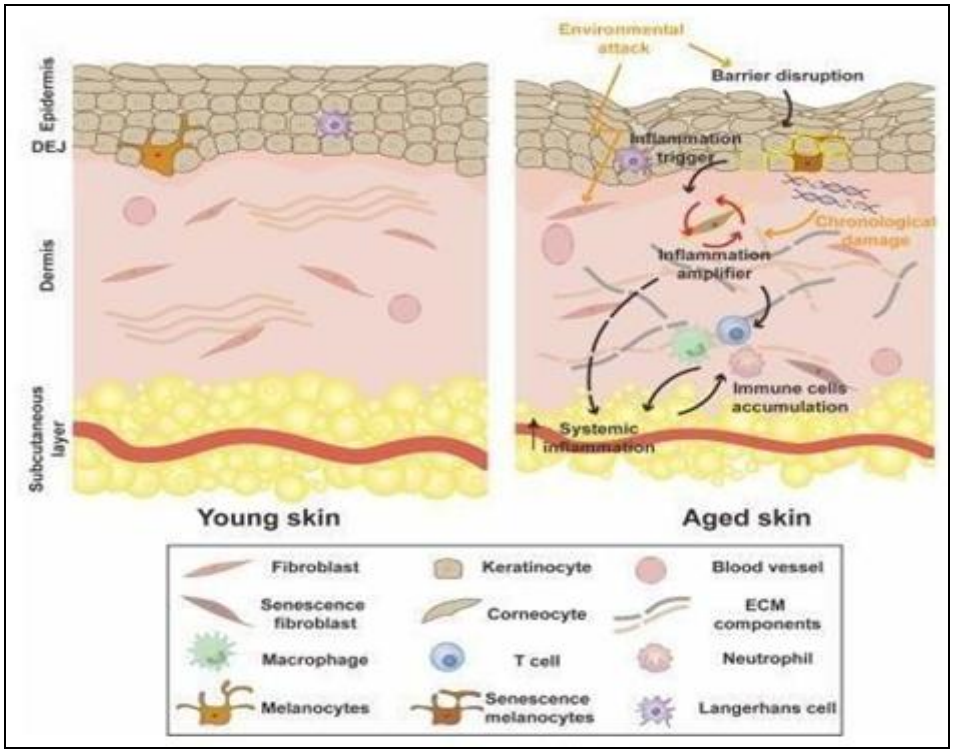

FIG. 1:

Senescence inducers such as reactive oxygen species, DNA damage, irradiation, telomere attrition, and mitochondrial dysfunction increase the activity of cycle-dependent kinase inhibitor proteins. This leads to cell- cycle arrest. An excessive accumulation of senescent fibroblasts significantly contributes to skin aging. These fibroblasts exhibit loss of cell identity, increased secretion of senescence-associated secretory phenotype factors, and impaired extracellular matrix homeostasis. As a result, senescence propagates between cells and accelerates dermal aging.

Dermal SASP in Skin Aging: SASP is a mix of molecules, such as cytokines, matrix metalloproteinases (MMPs), miRNAs, chemokines, growth factors, and small-molecule metabolites,

that are released by senescent cells. These molecules help regulate the immune system and affect how non-senescent cells grow and move. Proteins involved in breaking down the matrix (like MMP1, MMP3, MMP10, and MMP14) and those linked to inflammation (such as interleukin-1β, IL-8, IL-15, and interferon gamma) are found in both skin aging-associated protein (SAASP) and the usual SASP. This suggests that different tissues share similar features when cells become senescent.

Mitochondrial Dysfunction: Age-related changes in hematopoietic stem cells (responsible for life-long production of all blood lineages as well as stem cell pool maintenance, cause predisposition to myeloid malignancies, adaptive immune compromise and anaemia. Functional restoration of ageing tissue-resident stem cells is therefore of high interest. Dr. Els Mansell (Lund University and University College London) showed that mitochondrial membrane potential (ΔΨm) decreases in aged hematopoietic stem cells (HSC) but that a small fraction of ΔΨm high HSCs remain present in the bone marrow of old mice.

Strikingly, her data reveal that ΔΨm is a stronger determinant of the transcriptional state of HSCs than chronological age. In addition, enhancement of ΔΨm through mitoquinol treatment resulted in rescue of metabolic, transcriptional and functional parameters of old HSC. Importantly, mitochondrial treatment of old mice corrected the age-related myeloid bias in the peripheral blood and improved the engraftment potential of old HSCs.

Inflammaging and Immunosenescence:

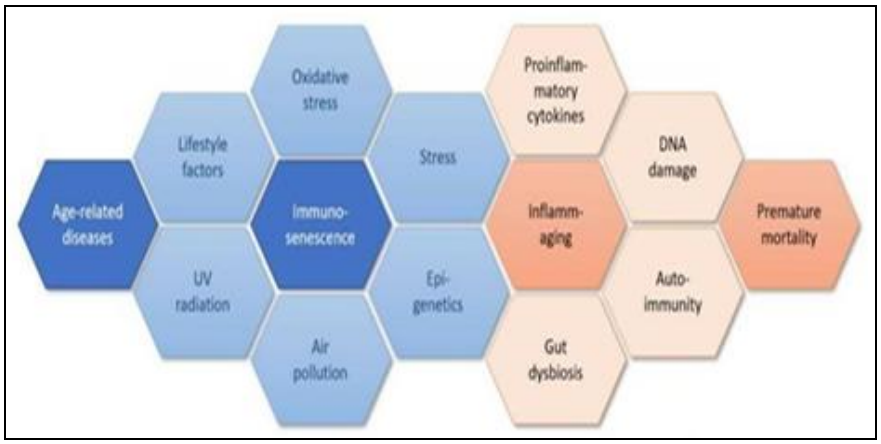

FIG. 2: FACTORS CONTRIBUTING TO IMMUNOSENESCENCE AND INFLAMMAGING

Inflammaging refers to a type of slow, low-level inflammation that naturally occurs as we age. This process is closely linked to changes in the immune system, known as immunosenescence, but it is still unclear which comes first. Inflammaging is not just a result of aging inside the body, such as telomere shortening, genomic instability, mitochondrial problems, or stem cell exhaustion. It is also influenced by outside factors like infections, UV radiation, smoking, and air pollution. Some theories suggest that as the body loses its ability to handle stress, the immune system becomes more reactive, which can speed up aging, cause diseases, damage tissues, and increase the risk of death. Researchers have identified several processes involved in inflammaging, including cellular aging, activation of inflammasomes, mitochondrial dysfunction, autophagy, mitophagy, the ubiquitin proteasome system, and DNA damage. Many signaling pathways help regulate inflammaging, such as the NF-κB, mTOR, RIG-I, NOTCH, TGF-β, RAS pathways, and sirtuin activity.

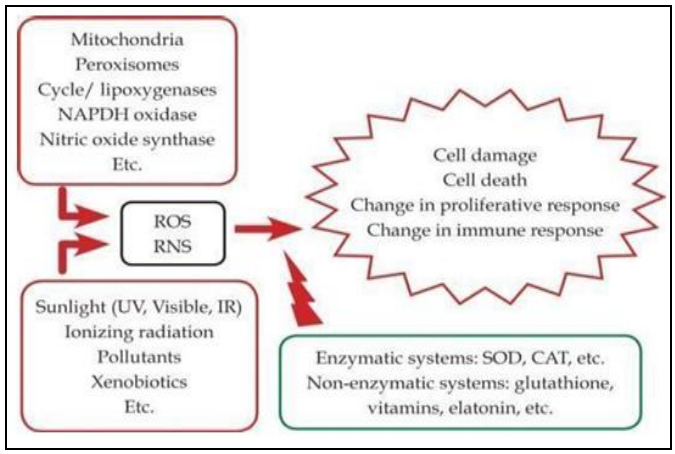

FIG. 3:

What are Anti-aging Cosmeceuticals: The term "cosmeceutical" refers to topical skincare products that include biologically-activeλ ingredients beyond simple cosmetics.

These products aim to reduce visible signs of skin ageing such as wrinkles, loss of elasticity, uneven tone, rough texture, thinning of the skin.

Skin ageing stems from both intrinsic (chronological/genetic) and extrinsic factors (UV radiation/photo-ageing, pollution, lifestyle) that drive oxidative stress, collagen/elastin breakdown, decreased fibroblast activity, and impaired skin barrier.

Key mechanisms by which effective anti-ageing cosmeceuticals act include: stimulating collagen/elastin synthesis; inhibiting matrix metalloproteinases (MMPs) that degrade the extracellular matrix; scavenging reactive oxygen species (ROS); improving epidermal renewal and barrier repair; modulating signalling pathways relevant to ageing.

Some of the most evidence-backed active ingredients: retinol/retinoids (gold standard) and vitamin C earned strong recommendation grades (Grade A) in systematic reviews for anti-ageing efficacy. Other actives such as bakuchiol (a plant-derived retinol-analogue), tetrahydrojasmonic acid, growth factors have some evidence but are rated lower (Grade C) — meaning the evidence is modest and long term data is lacking.

Safety profiles of many cosmeceuticals are favourable overall (few serious adverse events reported), but there remain gaps: small sample sizes, short follow-up durations, and limited long term safety/efficacy data.

Regulatory environment: The term "cosmeceutical" is not formally recognised in many jurisdictions (e.g., the U.S. Food and Drug Administration does not classify it separately) — products must be either cosmetics or drugs depending on claims; this leads to ambiguity in marketing and claims substantiation.

(Practical takeaway: Choosing ingredients with strong evidence (retinol, vitamin C), ensuring proper formulation/delivery, managing expectations (not miracle reversal), and combining with foundational protective habits (e.g., sun protection) yields the best outcomes.

Limitations remain: Surface-only effects for some ingredients, human variability in response, cost/availability, and the fact that topical treatments alone cannot fully reverse deep structural ageing.

Emerging trends: Personalisation, microbiome-friendly formulations, sustainability, more advanced delivery technologies, as well as integrating herbal/biotechnological actives — but these are still in evolution and require more clinical validation.

Mechanism of Cosmeceuticals:

Antioxidant Effect: Antioxidants are substances that interact to counteract reactive oxygen species, thereby preventing oxidative harm to cells and tissues. This antioxidant system is made up of both enzymatic and non- enzymatic components. Regarding enzymatic antioxidants, notable examples include glutathione peroxidase (GPx), catala se (CAT), and superoxide dismutase (SOD). Antioxidants are compound that boost the skin natural antioxidant defense, minimizing free radical damage and inflammation, which can breakdown collagen. They also provide protection against photodamage and skin cancer, aiding in the reversal of the photo aging process.

Collagen Stimulation: One of the most often used ingredients in cosmetics is collagen. With age, the production of natural collagen decreases, which is why producers of cosmetics and cosmeceuticals offer products that allow for replenishment of this ingredient both from the inside and outside. It is a structural protein composed of amino acids that create collagen fibers, characterized by exceptional strength and high elasticity. It inhibits skin aging and improves skin properties like hydration, elasticity, etc. It promotes epithelial cell formation, tissue regeneration, growth factor etc

Prevention of Collagen Breakdown:

- ❖ Collagens are damaged due to UV radiation
- ❖ Hormonal changes
- ❖ Vascular changes

❖ Inflammation

Cellular Rejuvenation: The Rejuvenation refers to giving aged cells or organisms more youthful characteristics through various techniques, such as cellular reprogramming and epigenetic regulation.

The great leaps in cellular rejuvenation prove that aging is not one-way street, and many rejuvenate interventions have appeared to delay and even reverse the aging process.

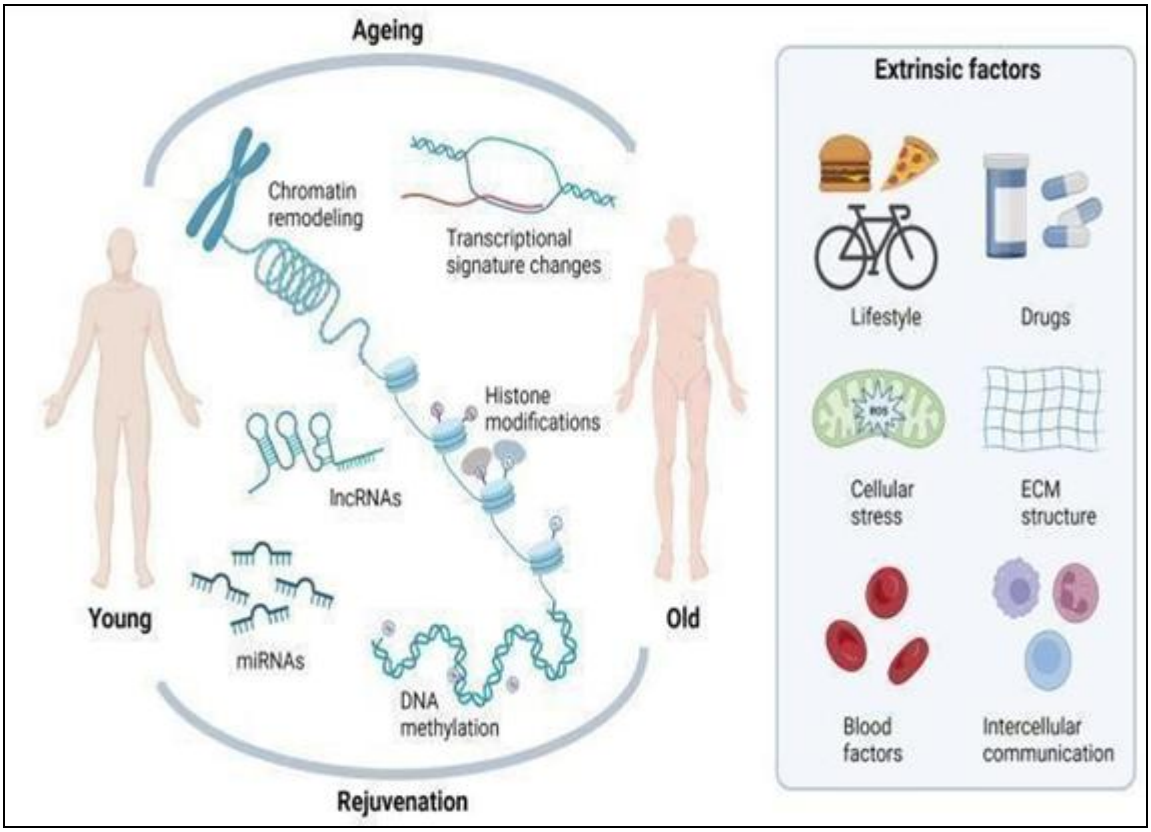

FIG. 4:

The epigenetic states of aging and rejuvenation. Aging and rejuvenation can be affected by intrinsic epigenetic alterations and genetic instability, like DNA methylation and chromatin remodeling. Moreover, many extrinsic factors, like microenvironmental cues, intercellular communication, and systemic factors, can also change the epigenetic states of aging and rejuvenation. miRNAs microRNAs, lncRNAs long noncoding RNAs, ECM extracellular matrix. There are various signaling pathways found in the fields of aging and rejuvenation, such as nutrient-sensing pathways, DNA damage pathways, ROS and mitochondrial unfolded protein response (UPRmt) pathways, inflammation-related pathways, transforming growth factor-β (TGF-β) pathways and Wnt/β-catenin pathways. The known role of these signaling pathways is complex and mutually connected. Given the prominent association of signaling pathways with rejuvenation and aging, targeting these signaling systems pharmacologically and therapeutically has brilliant potential for rejuvenation and human health.

Bioactive Ingredients in Anti aging Cosmaceuticals:

Retinoids: The retinoid family comprises vitamin A (retinol) and its natural derivatives such as retinaldehyde, retinoic acid, and retinyl esters, as well as a large number of synthetic derivatives. Retinoids are natural and synthetic vitamin A derivatives. They are lipophilic molecules and penetrate the epidermis easily.

Mechanism:

Receptor-Mediated Gene Modulation: Retinoids affect gene transcription by binding to nuclearλ retinoic acid receptors (RARs) and retinoid X receptors (RXRs) in skin cells.

Boost Epidermal Turnover and Thickening: For instance they encourage keratinocyte proliferation which results in a thicker viable epidermis and stratum corneum compaction. Increased type I and type III collagen synthesis improved dermal thickness and increased microvasculature (angiogenesis) in the papillary dermis are all effects of retinoids on collagen production and dermal matrix remodeling.

Prevent Collagen Degradation: They prevent matrix metalloproteinases (MMPs) from being activated by UV light which breaks down collagen and preserves dermal structural proteins.

Enhance Skin Texture and Minimize Fine Lines and Wrinkles: Retinoids cause noticeable improvements in photo-aged skin through the aforementioned mechanisms (wrinkles pigmentation texture). Additional effects include improved skin barrier/turnover increased anchoring fibrils decreased melanin transfer (pigmentation) and improved epidermal–dermal junction undulation.

Study / Reference	Concentration & Duration	Mechanisms Observed	Outcomes (Epidermis/Dermis/Clinical)
"Application of retinol to human skin *in-vivo*…" (1995)	1.6%ROL or 0.025% all-trans-RA,4 days occluded, n=10	↑ mRNA/protein CRABP-II, CRBP; epidermalthickening1.5×with1.6% ROL	Epidermal thickness increased 1.5-fold in 4 days; minimal irritation from ROL
"Anti aging action of retinol: from molecular to clinical" (2009)	0.1% ROL, 9-month RCT(48 volunteers)	↑CRABP2, HBEGF;↑ keratinocyte proliferation; ↑ epidermal thickness	Significant improvement in fine lines/tone, epidermal thickening
"Molecular basis of retinol anti- ageing properties innaturally Aged human skin *in-vivo*" (2016)	0.4% ROL, 7 days; sun-protected buttock skin (age ~76±6yrs, n=12)	Epidermis: ↑keratinocyte proliferation (Ki67) up to ~12×, ↑ epidermalthickness~2.1×Dermis:↑ dermal vascularity (endothelial proliferation),↑type I collagen, elastin, fibronectin; activation of TGF- β/CTGF pathway	Histological improvement of dermal matrix in aged human skin; mechanism confirmed
"Improvement of naturally aged skin with vitamin A (Retinol)" (JAMA Dermatology)	0.4%ROL, 24 weeks treatment in intrinsically aged skin (n=36)	↑ GAG (glycosaminoglycans), ↑ procollagen Iindermis; improved matrix molecules	Fine wrinkle effacement seen after 4 weeks; continued improvement through 24 weeks
"Comparative study of effects of retinol and retinoic acid" (2015)	ROL and RA, 4 weeks histology + 12 weeks clinical for ROL	↑epidermal thickness;↑COL1A1, COL3A1 gene expression; ↑ procollagen I & III proteins	Clinical facial wrinkle reduction significant at 12 weeks for ROL; magnitude somewhat smaller vs RA

Peptides: In the cosmetic context, peptides are relatively short chains of amino acids (shorter than proteins, by regulatory definitions often< 40 amino acids) that act as bioactive ingredients. They differ from full-length proteins in that their smaller size (and hence lower molecular weight) may enable better penetration into the upper layers of the skin, and they can act as signalling molecules to interact with skin cells.

Signal Peptides: They work by promoting the production of additional extracellular matrix (ECM) components by the skins own cells particularly fibroblasts in the dermis. A g. collagen fibronectin glycosaminoglycans elastin and proteoglycans. Palmitoyl Oligopeptide (Pal-Tripeptide-1) and Palmitoyl Tetrapeptide-7 are two examples. They either act through TGF-β pathways acting on TGF to stimulate fibrillogenesis or they lower inflammatory cytokines like IL-6 which would otherwise cause ECM degradation. Increased production of collagen and elastin better firmness and elasticity of the skin and a decrease in wrinkle depth are the overall results.

Example: GHK-Cu (glycyl-histidyl-lysine bound to copper) – a copper tripeptide that delivers copper and has been reported to promote collagen synthesis and wound-healing type activity.

Study/Reference	Peptide(s)/ Formulation & Duration	Mechanisms Observed	Outcomes (skin/clinical)
"Topical peptides as cosmeceuticals"(2017)	Review of many peptides (signal peptides: e.g., Pal-KTTKS; Pal-GHK; Other types)	Signal peptides ↑ collagen I & III, fibronectin, elastin, glycosaminoglycan production. Carrier peptides (e.g., copper tripeptide-1) act as cofactors for lysyloxidase; enzyme inhibitor peptides inhibit MMPs.	Supports that peptide scan modulate ECM (extracellular matrix) and may reduce wrinkle formation/firm skin.
"Protective and Anti-Aging Effects of 5 Cosmeceutical Peptide Mixtures on H_2O_2-induced Premature Senescence in Human Skin Fibroblasts" (2021)	*In-vitro*: human skin fibroblasts exposed to oxidative stress; peptides used included carnosine, GHK peptide, acetyl tetrapeptide-5, hexapeptide-11, acetyl hexapeptide-3.	Reduced intracellular free-radical (malondialdehyde, hydroxyl radicals), ↑ hydroxyproline (HYP, marker of collagen), ↑ elastin content, ↑ SOD (superoxide dismutase) & glutathioneperoxidase activities.	Suggests these peptides/mixtures can protect skin fibroblasts from oxidative damage and improve markers of ECM components.
"Effectiveness of a formulation containing peptides and vitamin C in treating signs of facial aging: three clinical studies" (2020)	Clinical: formula with 10% Vitamin C + biopeptides (rice & lupin peptides) + hyaluronic acid; multiple open studies (N≈40-50), duration ~28 days in some parts.	Faster cell turnover (17.1 days vs 19.2 days untreated); improvements in skin texture; reduction in wrinkle grades (crow's-feet −9%; forehead −11%; nasolabial−5%) at 28 days.	Clinical evidence (albeit short term) showing peptide + vitamin C combo improves signs of facial ageing.
"Topical peptides in cosmeceuticals" review (2017)	Review of topical peptide efficacy; summarises various peptides including copper tripeptide, palmitoylpentapeptide-4 etc.	Classifies peptides: signal, carrier, neurotransmitter-inhibitor, enzyme-inhibitor. Notes topical penetration and formulation challenges.	Confirms that some peptides are "well-documented" but underscores that clinical evidence remains less Extensive than for e.g. retinoids.

Antioxidant: Topical antioxidants are agents (often small-molecule or plant-derived) applied to the skin surface, whose primary role is to neutralise or counteract reactive oxygen species (ROS) and other oxidative stressors (such as UV radiation and pollutants) in the skin's outer layers (especially the stratum corneum and epidermis). These agents aim to "maintain physiological balance" of the skin by helping preserve barrier integrity, preventing oxidative damage to lipids, proteins, DNA, and extracellular matrix components.

Study / Reference	Concentration & Duration	Mechanisms Observed	Outcomes (epidermis/dermis/clini cal)
Split-face RCT: 50 women, 30-65 yrs; serum with 20%VitC+ Vit E + raspberry leaf extract, applied for 8 weeks.	20% w/w Vit C+Vit E + plant extract; 4 & 8 weeks	↑skin elasticity, radiance; ↓roughness, scaliness (micro- topography)	Significant improvement in smoothness, wrinkles, tone; well tolerated
RCT: 5% topical ascorbic acid cream vs excipient, 6 months, photo-aged skin.	5%L-ascorbicacid once daily for 6 months	Increased collagen/ precollege synthesis; improved ultrastructure in dermis	Reduction in deep wrinkles, improved texturevs control

Study / Reference	Concentration & Duration	Mechanisms Observed	Outcomes (epidermis/dermis/clinical)
DBRCT: topical antioxidant complex (VitsC + E + ferulic acid) in Chinese women; photo protection trial.	"CEF" – combination appliedfor4daysbefore UV challenge	Reduced UV-induced sunburn cell formation, thymine dimers, p53 expression	Demonstrated photoprotective effects in human skin – less DNA/UV damage
Systematic review: topical Vit C efficacy for wrinkle appearance (7 studies)	Various concentrations(5-20+%) for 12 weeks to 6 months	Ascorbicacidasco- factor in collagen hydroxylation, scavenger of ROS, regenerates Vit E.	4 of 7 studies Level IB evidence; showed wrinkle improvements but many studies combine ding redients - more research needed
Review on antioxidant sin		Oxidative stress drives	

cosmeceuticals	–	collagen degradation, MMP activation; antioxidants (Vit C, CoQ10) → ROS neutralisation, mitochondrial support	Antioxidants are a cornerstone of anti-aging treatments; controlled trials show improvements in photoprotection, skin texture, but many are small/short term
Review of antioxidants for skin health	–	Vitamin C and E, green tea extract, CoQ10, polyphenols– roles in collagen synthesis, photo protection, anti-oxidative, anti- inflammatory	Broad support for antioxidant role in skin health; less strong direct long-term wrinkle reversal data

Alpha-Hydroxy Acids (AHAs) & Beta-Hydroxy Acids (BHAs): AHAs are organic acids with one hydroxyl group attached to the carbon adjacent (alpha position) to the carboxyl group. Examples include glycolic acid, lactic acid, malic acid, tartaric acid, citric acid. They are widely used in cosmetic formulations (creams, peels) for superficial skin resurfacing, treatment of keratoses, photo-aged and rough skin. (Tang & Yang, 2018) BHAs (such as salicylic acid) are somewhat similar structurally but with a hydroxyl at the beta position; though the primary review focuses on AHAs, it remarks on the "dual effects" of AHAs whether beneficial or potentially depending on concentration.

Study / Reference	Formulation / Concentration & Duration	Mechanisms Observed	Outcomes (skin/clinical)
"Clinical efficacy of 10% glycolic acid in the treatment of photo-aged skin" (2001)	10% glycolic acid cream, applied daily for 12 weeks	Exfoliation of stratum corneum; ↑ epidermal thickness; ↑ dermal glycosaminoglycans; stimulation of fibroblast activity	Significant improvement in fine lines, skin texture, hyper pigmentation; subjective skin smoothness improved
"Comparative study of glycolic acid vslactic acid on aged human skin" (2004)	5–10% glycolicor lactic acid cream, 12 weeks, twice daily	Acid-induced desquamation; ↑ epidermal turnover; ↑ collagen content (histology)	Both AHAs improved wrinkle appearance and skin roughness; glycolic acid showed slightly higher improvement
"Beta-hydroxy acid (salicylic acid) peels in photoaged skin" (2008)	20% salicylic acid peel, applied every 2 weeks × 6 sessions	Keratolytic effect; anti-inflammatory; partial induction of epidermal proliferation; some dermal remodeling	Improvement in fine lines, epidermal texture, and pigmentation; well tolerated
"Long-term efficacy and tolerability of glycolic acid peeling sinaging skin"(2010)	30–70% glycolic acid chemical peel every 3–4 weeks × 6–12 months	Controlled epidermal removal → dermal remodeling; ↑ collagen I & III; ↑ glycosaminoglycans	Progressive improvement in deep wrinkles, overall skin rejuvenation; minimal adverse effects with proper neutralization

Study / Reference	Formulation / Concentration & Duration	Mechanisms Observed	Outcomes (skin/clinical)
"Clinical and histologic evaluation of Lactic acid peels" (2013)	50% lactic acid peel, single session	Exfoliation increased epidermal turnover; stimulation of dermal fibroblasts	Histologic thickening of epidermis and dermis; subjective skin smoothness and brightness improved
"Alpha-hydroxy acids: topical applications for skin rejuvenation" (Review, 2015)	Review, topical AHAs5–15%for daily use, or 30–70% peel	↑ Epidermal turnover, ↑ collagen & glycosaminoglycans, improve stratum corneum hydration, reduce MMP activity	Supports use of AHAs for photoaging; clinical evidence shows improved finelines, tone, texture, and pigmentation

Emerging Bioactive Compounds:

Bakuchiol: Outcomes (skin/clinical) Histologic thickening of epidermis and dermis; subjective skin smoothness and brightness improved Supports use of AHAs for photoaging; clinical evidence shows improved fine lines, tone, texture, and pigmentation. Bakuchiol is a natural meroterpene phenolic compound primarily derived from the seeds of the plant *Psoralea corylifolia* (also found in other species) that has attracted significant interest in cosmetic and dermatological formulations for skin-use. In skin-care, it is positioned as a "gentler" alternative to retinol, offering anti-aging, antioxidant, anti-inflammatory and depigmenting effects.

Study/Reference	Formulation / Concentration & Duration	Mechanisms Observed	Outcomes (skin/clinical)
"Prospective, randomised, double- blind assessment of topical bakuchiol and retinol for facial photo-ageing"(2018)	0.5% bakuchiol cream, applied twice daily for 12 weeks vs 0.5% retinol cream once daily	Bakuchiol showed gene-expression changes similar to retinol; stimulation of dermal ECM (extracellular matrix) production, collagen regulation; less irritation.	Both groups showed significant decrease in wrinkle surface area and hyperpig mentation; no statistical difference between compounds; better tolerability (less scaling/stinging) with bakuchiol.
"Clinical Evaluation of a Nature-Based Bakuchiol Anti- Aging Moisturiser for Sensitive Skin" (2020)	Nature-based cleanser + moisturiser containing bakuchiol (unspecified % in abstract) applied twice daily in 60 female subjects age 40-65 for 4 weeks	Improved skin barrier (reduced TEWL, increased corneometry), improved visual smoothness, clarity, radiance in photodamaged sensitive skin.	Statistically significant improvements (P<0.001) in skin smoothness, tactile smoothness, clarity, radiance; ~16% increaseinskin moisture content.
"Multidirectional activity of bakuchiol against cellular mechanisms of skin ageing" (*in-vitro/ex-vivo*)	*In-vitro* & *ex-vivo* human skin/fibroblast studies (not strictly human clinical)	Mechanisms: antioxidative; anti-inflammatory; increasedcellactivity; increased ECM component expression; improved epidermal regeneration.	Demonstrated biologic plausibility: e.g., stimulation of ECM, improved epidermal regeneration, though clinical end point data are indirect.
Comprehensive review: "A comprehensive review of topical bakuchiol for the treatment of photo-aging" (2021)	Review covering 7 articles (in vitro, in vivo, clinical)	Concludes bakuchiol functions as a "retinol-analogue" topically, with additional antioxidant/anti-inflammatory pathways; good tolerability.	Review summary: Bakuchiol was effective in improving signs of photo- aging with minimal side- effects; however, authors emphasise evidence still limited.
Pilot study: "Comparative efficacy of bakuchiol oil and Encapsulated bakuchiol cream on facial skin quality" (2024)	0.5% bakuchiol oil cream vs encapsulated 0.5% bakuchiol cream, applied twice daily for 28 days in 17 subjects split-face	Improvement in moisture, reduced pore size, wrinkle scores; Encapsulated formulation per formed better.	Found enhancement sin skin moisture, wrinkle reduction and pore/ sebum metrics, though short duration (28 days) and small size limit extrapolation.

Glutathione: Glutathione is a tripeptide composed of glutamine, cysteine and glycine. In dermatology and cosmetics it has been widely promoted for its antioxidant, skin-lightening (depigmenting) and anti-aging potentials.

Study / Reference	Formulation / Concentration & Duration	Mechanisms Observed	Outcomes (skin/ clinical)
"Skin-whitening and skin- condition-	2% (w/w) oxidized glutathione (GSSG) lotion,	Inhibition of melanin production (tyrosinase	Significant reduction in melanin index on treated vs

improving effects of topical oxidized glutathione: a double-blind and placebo-controlled clinical trial in healthy women" (2014)	applied twice daily for 10 weeks to one side of face versus placebo side.	inhibition) *via* the glutathione system; antioxidant/thiol protection of proteins from oxidation; measured reduction in melanin index, increase in skin moisture, improvement in smoothness/elasticity.	placebo side (P <0.001 at 10 weeks) increased stratum corneum moisture, improvement in skin smoothness & wrinkle suppression in latter half of study. No major adverse effects reported.
"Combination of topical and oral glutathione as a skin-whitening agent: a double- blind randomized controlled clinical trial" (2021)	Topical glutathione + oral glutathione vs mon other a pies: 46 participants, topical and oral arms, 8 weeks, colourimeter measurements every 2 weeks.	Antimelanogenesis effects, likely *via* combined systemic+topical pathway; improved melanin index, increased L* (lightness) score.	The combination therapy (topical + oral) showed significantly lower melanin index and higher L* score than placebo (P< 0.05) and superior to monotherapy additional.
Systematic review: "The clinical effect of glutathione on skin color and other related skin conditions: A systematic review" (2019)	Reviewed 4 clinical studies (3 RCTs +1 single arm); one used topical 2.0% GSSG, others oral 250-500 mg/day; durations variable.	Trend toward skin colour brigh tening in sun-exposed areas; some evidence for wrinkle / elasticity improvements but limited; mechanisms discussed include antioxidant protection, melanogenesis inhibition.	Evidence was inconclusive: both oral at ~500mg/day and topical 2% oxidized glutathione *could* brighten skin colour in sun-exposed areas as measured by melanin index. No significant reduction in melanin index in sun- protected areas. Trend (but not firm) for wrinkle/elasticity improvements.

Systematic	**Included 5 clinical**	**Findings: improved**	**The review concluded**
Review of topical glutathione: "Systematic Efficacy and Glutathione in (2025)	Trials of topical Glutathione; various formulations (2% creams with actives) with ~8-12 weeks.	GSH/GSSG ratio (marker of Redoxstate), reduction in melanin index (for 2% (trans-epidermal water (P < 0.01) in one trial.	Topical glutathione "Shows promise" for dermatologic applications (pigmentation oxidative damage, TEWL, wrinkles), but Emphasised that there are significant limitations: small sample sizes, short follow-up, lack of long- term data

Niacinamide: Niacinamide acts largely by supporting skin barrier, reducing inflammation/ oxidative stress, modulating pigmentation, maintaining ECM/dermal support, and regulating sebum/antimicrobials rather than by direct exfoliation. It canthus be viewed as a broadly supportive, multifunctional ingredient ratherthana strong "resurfacing" agent like retinol or AHAs. Its gentler profile makes it attractive for many skin types and for incorporation into every day usage, rather than intensive treatment only.

Study / Reference	**Formulation / Concentration & Duration**	**Mechanisms Observed**	**Outcomes (skin/ clinical)**
"Niacinamide: A B vitamin that improves aging facial skin appearance" (2005)	5% niacin amide cream applied twice daily for 12 weeks (split-face, N=50)	Improvement in skin appearance; mechanisms proposed include improved barrier, antioxidant/anti-inflammatory effects.	Significant reductions in fine lines & wrinkles, hyper pigmented spots, red blotchiness, sallowness (yellowing) compared to vehicle.
"Evaluation of anti-wrinkle effects of a novel cosmetic containing niacin amide" (2008)	4% niacin amide cosmetic applied to one side of eye-area for 8 weeks vs control on other side (N=30 Japanese females)	Niacin amide improved the surface roughness (Ra) of skin replicas; presumed increase in epidermal/dermal quality.	64% of subjects showed "marked/moderate" improvement vs control (P <0.001) in wrinkle roughness.
"Topical formulation with Niacin amide combined	Niacin amide- containing formulation (concentration	Mechanisms observed: improved stratum corneum	The niacin amide formulation improved hydration, reduced

with 5 MHz ultrasound for improving skin ageing" (2024)	unspecified in abstract) +weekly unfocused 5-MHz ultrasound, 67 female subjects Age 30-60, 8weekly sessions (so ~8 weeks)	water content, reduced transepidermal water loss (TEWL), sebum reduction; subjective improvements in firmness/elasticity.	sebum, and subjects reported better appearance, firmness, elasticity and reduced wrinkles.
Review "Mechanistic basis and clinical evidence for the applications of nicotinamide to control skin aging and pigmentation" (2021)	Multiple studies summarised (topical niacin amide alone or with others)—typical concentrations 2-5% applied for ~8-12 weeks or more.	Mechanisms: restoration of NAD^+ pool and mitochondrial energetics; attenuation of oxidative stress & inflammation; enhancement of ECM (extracellular matrix) & barrier; inhibition of melanosome transfer (pigmentation)	Review concludes that topical niacin amide "reduces the progression of skin aging and hyper-pigmentation in clinical trials" and is well-tolerated.

Delivery Systems and Formulations:

Liposomes: Liposomes are phospholipid bilayer vesicles capable of encapsulating both hydrophilic and lipophilic bioactives, making them widely used carriers in anti-aging cosmeceutical formulations. In topical applications, liposomes enhance skin penetration, protect unstable ingredients, and enable controlled release within the epidermal and upper dermal layers.

Phosphatidylcholine-based liposomes, often stabilized with cholesterol, are commonly employed due to their biocompatibility and similarity to skin lipids. Liposomal delivery has demonstrated improved efficacy and reduced irritation for actives such as retinoids, antioxidants, peptides, and coenzyme Q10. However, formulation challenges including lipid oxidation, vesicle fusion, and limited long-termstability remain critical considerations for cosmetic products.

Nanoparticles: Nanoparticles typically ranging from 10 to 500 nm, are used in anti-aging skincare to enhance the solubility, stability, and skin localization of bioactive compounds. Lipid-based systems, particularly solid lipid nanoparticles and nanostructured lipid carriers, are preferred for topical use due to their occlusive properties and favorable safety profile. These systems facilitate sustained release and improved skin hydration while limiting systemic absorption.

Polymeric and hybrid nanoparticles have also been explored for the delivery of antioxidants, peptides, and botanical actives. Despite their advantages, nanoparticle penetration across intact skin remains limited, and concerns regarding aggregation, long-term safety, and regulatory acceptance continue to restrict their widespread application.

Microneedles: Microneedle-based delivery systems represent an emerging approach in advanced anti-aging interventions by enabling direct transport of bioactives across the stratum corneum. These minimally invasive devices create transient microchannels that significantly enhance the dermal delivery of high- molecular-weight and poorly permeable compounds, including hyaluronic acid, peptides, and growth factors.

Dissolving and hydrogel-forming microneedles fabricated from biodegradable polymers are particularly suitable for cosmetic applications due to their safety and patient compliance. Nevertheless, limitations related to dose capacity, manufacturing scalability, and regulatory classification as combination products pose challenges for routine cosmeceutical use

Advance Delivery System:

Stimuli-responsive /Smart Delivery Systems: These are carriers (micro- or nano-scale) built to respond to specific stimuli (internal such as pH, enzymes, redox state; or external such as temperature, magnetic field, light, ultrasound) so that drug release is triggered or enhanced at the desired site/time. According to a recent review, modern DDS are expected to have higher precision, automation, and "smart" behaviour.

For example, the review by Ezike *et al.* describes how advanced DDS use nanomaterials or miniaturized devices to accelerate site-specific delivery, maximize therapeutic efficacy, and minimize off-target exposure.

Formulation/Methods: Materials selected to be responsive: pH-sensitive polymers (that swell or degrade in acidic environments), enzyme-sensitive linkers (that cleave in presence of e.g. matrix metalloproteinases), thermosensitive or light-sensitive components. Integration of functional moieties: e.g., ligand attachment for targeting, 'stealth' coatings (PEG) to enhance circulation/stability.

Design of release behaviour: carriers structured to maintain payload until stimulus then release examples include-micro/ nanoparticles with shells that degrade or pores that open under stimulus. Characterisation: as with other systems, important attributes include size, surface charge, loading efficiency, release kinetics, stability, stimulus-sensitivity.

Considerations/Limitations: Complexity in design/manufacture: responsiveness adds layers of design and may complicate scale up. Balance between sensitivity and stability: the system must remain stable during storage/transport and non target circulation, yet respond appropriately once at target.

Biological Variability: target tissues may not present consistent stimulus levels (e.g., pH gradients vary) so triggering may be unreliable. Regulatory and translational hurdles: as with many advanced DDS, fewer have achieved clinical approval.

Relevance for Anti-Aging/Cosmetic Delivery: In a skin/dermal context, stimuli-responsive systems could release actives (e.g., peptides, growth factors) in response to skin barrier damage, enzyme levels associated with aging skin, UV exposure, or temperature changes. This could increase specificity and reduce systemic exposure/unwanted side effects.

Lipid Nanoparticles/Lipid-Based Nano-Carriers (Beyond Classical Liposomes): "Lipid Nanoparticles from Liposomes to mRNA Vaccine" discusses how LNP platforms have evolved to carry complex biologics and stabilize them *in-vivo*. Similarly, the "Engineering precision nanoparticles for drug delivery" review emphasises how advanced NP design can overcome heterogeneous barriers to delivery.

Formulation/Methods: Lipid composition: mixtures of ionizable lipids, phospholipids, cholesterol, PEG- lipids in precisely controlled ratios. These enable encapsulation of hydrophilic payloads (e.g., RNA) and alter endosomal escape.

Microfluidic or Controlled Mixing Methods: To achieve reproducible size, lamellarity, encapsulation and reduce PDI (polydispersity).

Surface Modification: targeting ligands, PEGylation, or biomimetic coatings (e.g., cell-membrane cloaks) to evade clearance and enhance delivery. For example, RBC-membrane camouflaged NPs are described. Payload sophistication: apart from small molecules, these systems carry nucleic acids, proteins, gene editing tools, and thus require carriers that protect from degradation and deliver to intracellular targets.

Considerations/Limitations: Immunogenicity /clearance: lipid carriers may trigger immune responses or be cleared rapidly by the mononuclear phagocyte system.

Stability and Storage: Lipid systems may suffer from leakage, aggregation, changes in composition over time (especially for biologic payloads).

Cost and Scale: Manufacturing with high reproducibility (size, loading, encapsulation) at commercial scale can be challenging.

Translation Gap: Many advanced lipid carriers have shown promise, but translation to approved products (especially in non-viral gene delivery) remains limited.

Relevance for Anti-aging/Cosmetic Delivery: In the context of skin anti-aging, lipid-based nano-carriers could enable delivery of novel actives (e.g., nucleic acid-based therapies, siRNA for MMPs, microRNA, peptides) by improving stability and penetrating skin/matrix barriers. They could also be tailored for topical/transdermal delivery rather than systemic, potentially reducing systemic exposure.

Clinical Evaluation:

***In-vitro* Evaluation:**

Evaluation of the Physical, Chemical and Microbiological Characteristics of the Formulation: In accordance to the current

legislation, the following test were carried out. They are one severity testing of the cosmetic formulation to physical chemical control, organoleptic, characters, and determination of the pH density and viscosity of the developed formulation and microbiological evaluation for the assessment of microbiological, contamination and preservative efficacy test.

TABLE 1: PHYSICOCHEMICAL CHARACTERISTICS OF THE ANTI-AGEING CREAM

Test	Unit	Result
Viscosity at 20 °C (Brookfield DV-III Ultra)	mPa-s	$412.2\times10^3+9\times10^3$
Density at 20 °C (PB-155 ed.I of 2 May 2012)	g/cm³	1.002 +0.003
Organoleptic testing (ISO 6658:2005 p. 5.4.2)		
Appearance		Homogeneous emulsion" Light beige (with gold microcapsules)
Color		Specific Specific of emulsion
Odor		
Consistency		
PH (PB-234 ed. I of 03.10.2013r.)		5.9±0.2

Stability Testing of the Formulation: The stability testing was performed for a period of 30 days under the conditions of product storage at 4°C, 20°C and 40°C

Quality Control of the Cosmetic Formulation: The assessment of quality control of the developed formulation consisted of the following tests;- physicochemical control, organoleptic testing, determination of pH, density, and viscosity of the cosmetic formulation.

Microbiological, Control and Assessment of the Effectiveness of the Preservation of Cosmetic Formulation: We tested the antimicrobial protection of the new formulation using standard procedures.

These included counting and detecting aerobic mesophilic bacteria, yeast and mould, *Staphylococcus aureus*, *Candida albicans*, *Escherichia coli*, and *Pseudomonas aeruginosa*.

We also checked how well the preservative system (phenoxyethanol and ethylhexylglycerin) worked using the international cosmetics challenge test standard.

TABLE 2: MICROBIOLOGICAL ASSAY OF THE ANTI-AGEING CREAM

Parameter	ISO Standard	Result (CFU/g)	Permissible Limits (CFU/g)	Concordance
Enumeration and detection of aerobic mesophilic bacteria	21149:2017	<10	<100	✓
Yeast and mould count	16212:2017	<10	<10	✓
Staphylococcus aureus detection	22718:2016	0	0	✓
Candida albicans detection	18416:2016	0	0	✓
Escherichia coli detection	21150:2016	0	0	✓
Pseudomonas aeruginosa detection	22717:2016	0	0	✓

***In-silico* Approaches for Safety Evaluation of Cosmetic-Related Substances:** A new software tool for integrated hazard and exposure assessment, Sphera Cosmolife v. 0.24, was used to evaluate the cosmetic ingredients in the formulation through computer-based analysis. This software checks its internal database to see if a substance appears in any Annexes of the Cosmetic Regulation (EC) No. 1223/2009. It also estimates both external skin exposure and internal exposure (systemic exposure dose) by modeling the skin permeability coefficient (Kp), and identifies hazards for various toxicological endpoints. The system looks up experimental values for NOAEL (no observed adverse effect level), provides model predictions, and calculates the margin of safety (MoS) and the threshold of toxicological concern (TTC) using a Cramer decision tree. The MoS, which is the ratio of the NOAEL to the systemic exposure dose (SED), should be at least 100. This value accounts for a factor of 10 for interspecies differences (from animal to human) and 10 for intraspecies differences (such as age, gender, body weight, and ethnicity). Both factors can be further divided into toxicokinetic and toxicodynamic components. A cosmetic ingredient is considered safe if the MoS is 100 or higher.

***In-vivo* Evaluation:**

Dermatological Semi-Open Test: The goal of this study was to assess the potential for sensitization or irritation and to evaluate how well the new formulation is tolerated on healthy human skin using a patch test. The test measured redness and swelling after the product was applied. A group of 25 healthy Caucasian volunteers with skin phototypes I to IV on the Fitzpatrick scale, and no history of allergies or skin conditions needing medication, took part in the study. None of the participants had previously reported any sensitivity or negative reactions to the ingredients in the formulation. The product was applied under a patch (12 mm diameter Finn Chamber, SmartPractice, USA) placed on the arm or between the shoulder blades. Two control samples a blind control and a water control were used to help prevent misinterpretation of any skin reactions. The patch was removed after 48 hours, and a dermatologist checked the skin 30 minutes later. The skin was checked again 72 hours after application, and if any irritation appeared or continued for 72 hours, an extra check was done after 96 hours. The results were reported using the Average Irritation Index (Xav), and based on this, the product was rated as "not-irritating," "slightly irritating," "moderately irritating," or "highly irritating."

In use Test Under Dermatological Control: A use test with dermatological supervision was conducted to assess how well the cosmeticλ formulation was tolerated when applied regularly to the skin over 28 days.

The study involved 25 women with various skin types. Each participant applied the product twice a day as they normally would, and a dermatologist evaluated them at the start and end of the study. No irritation or changes requiring medical treatment were observed at the application site [57–60].

Instrumental Assessment of Wrinkle Length and Depth: An instrumental test was also carried out to measure changes in wrinkle length and depth using the Visioline® VL 650 device.

This part of the study included 10 women aged 30 to 70, with different skin types. Measurements were taken at the application site before starting the product (D0) and after 28 days of regular use (D28).

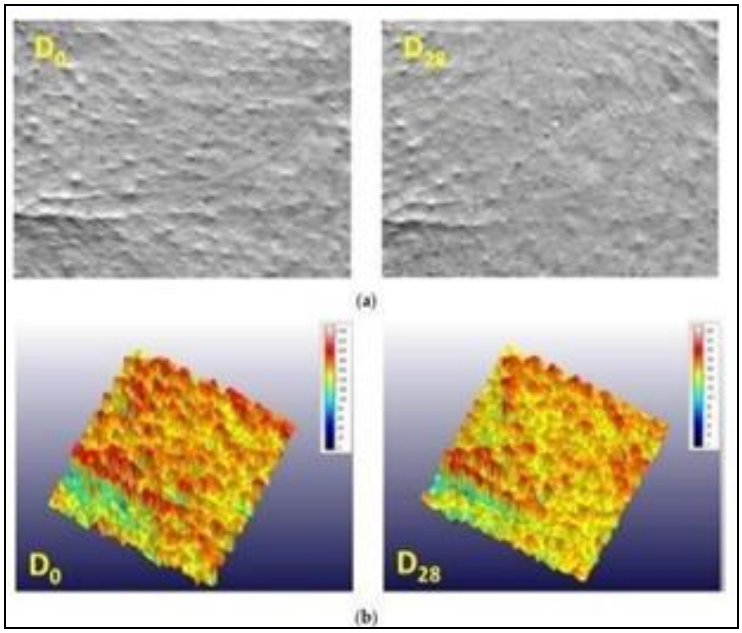

FIG. 5: SKIN SURFACE EVALUATION (SKIN MICRORELIEF) BEFORE (DO) AND AFTER 28 DAYS (D28) OF THE ANTI-AGEING CREAM. IMAGES ARE PRESENTED FOR SUBJECT NO. 10: (A). SKIN REPLICAS AT D0 AND 228 AND (B) 3D PICTURES AT DO AND D28)

***In-vivo* Determination of the Sun Protection Factor:** The sun protection factor assessment represents the method for evaluation of cosmetic products stating that they contain UV filters against erythma which is caused by ultraviolet rays falling on the human skin. It is assessed by using a

simulator with xenon-arc lamp of specific and defined output. The SPF evaluation was tested on 10 healthy subjects, which were Caucasians with photo types I-III, according to the Fitzpatrick scale. A skin area of each subject is exposed to UV without any protection. Another is exposed afterapplication of sun protection product. Third area is exposed after application of SPF reference sunscreen formulation by increasing the UV dose on the skin. Erhythma are conducted. These delayed erythmal responses are then visually assessed for redness intensity, for about 16 to 24 hours after UV radiation, the minimum erythmal dose MED for unprotected skin and the MED obtained after the application of a sun protection. Product must be determined on the same subject on the same day and individual sun protection factor for each subject is tested and calculated as the ratio of MEDP by MEDU. The SPF for the tested formulation is the arythmetic mean of all valid SPF results from each subject in the test and is expressed to one decimal place.

Assessment of the Effect Claimed for the Cosmetic Product: In this assessment, a self assessment study was carried out based on the questionnaire regarding subjects, appreciation of the cosmetic quality and efficacy of the formulation. All 25 subjects received self assessment questionnaire comprising of 12 questions associated with the products characteristics and efficacy, using a 5 grade evaluation. All subjects included in these evaluation test, signed and informed consent form, which included information about the studies, purpose, theology, and potential side-effects. The studies were conducted by an external laboratory according to the most recent recommendations of the regulations of the government.

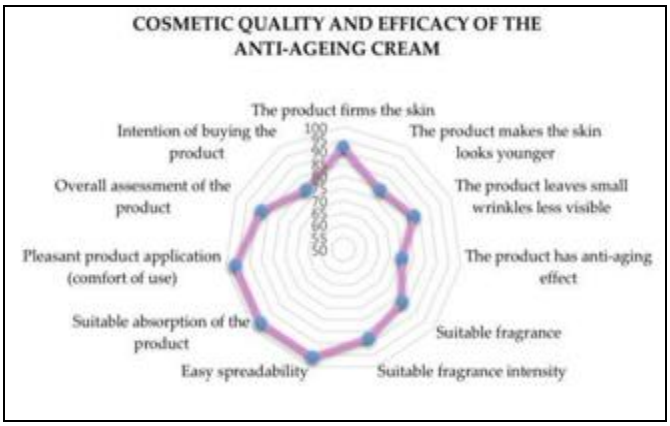

FIG. 6: SELF-ASSESSMENT QUESTIONNAIRE REGARDING THE ANTI-AGEING CREAM'S COSMETIC QUALITY AND EFFICACY (DATA ARE EXPRESSED AS PERCENTAGE OF POSITIVE ANSWERS AT THE END OF THE COSMETIC TREATMENT PERIOD (028)

Safety and Regulation: Numerous regulations have been designed to ensure the safety and efficacy of skincare products for enhanced consumer safety and to minimize risks. The European Regulation mandates that a cosmetic product should be safe for use under normal or foreseeable conditions. To ensure safety, consumption data, such as frequency, amount, and daily use, are necessary to evaluate exposure levels. These regulations are necessary to ensure the safety and efficacy of consumer risks posed by frequent usage of cosmetic products. This exposure is assessed by dividing the daily product use by the consumer's bodyweight, resulting in a systemic exposure dose (SED) for each ingredient. This SED is then compared to a No Observable Adverse Effect Level (NOAEL) to calculate the Margin of Safety (MoS). Early studies in the 2000s provided critical data on cosmetic consumption and exposure across Europe and the United States.

Safety Concerns: Three studies have reported the analysis of ingredients, which revealed that certain ingredients are frequently associated with adverse effects. Among them, the major ingredients were fragrances, preservatives (such as parabens), and colorants. It was reported that fragrances are commonly known to cause allergic reactions and skin sensitivities. While also mentioned that

preservatives can provoke dermatitis and other skin irritations.

Frequency of usage: Five studies have found that the type of personal care product and their usage pattern greatly influences the likelihood of causing adverse effects. Among them, two studies found that skincare products, especially those applied recurrently or left on the skin for longer periods of time are more likely to cause reactions compared to rinse-off products like shampoos.

Marketed Evolution:

DNA Personalized Skincare: Genetic variations that contribute to the unique characteristics of each individual are currently considered to shape the future of clinical and pharmacologic interventions. This is consistent with the idea of treating the person rather than the particular problem, which gains increasing recognition as a more effective approach Based on this, the concept of "personalized medicine" recognizing underlying forms of genetic variations emerges as an exceptional strategy with unique applications in pharmacogenomics and pharmacoproteomics.

This concept can be extended further onto the field of experimental and clinical dermatology and personalized skincare. Recent progress in molecular assays and diagnostic tests facilitates addressing the physiology of skin processes and the pathogenic mechanisms of specific problems including inflammatory and autoimmune skin conditions. Understanding the biology of individual skin structure, sensitivity and hormonal balance and identifying the network of representative genes in the context of specific genetic makeup will drive the design of novel pharmaceuticals and mimetics to modulate appropriate biologic processes. Skin types defined as Caucasian, Oriental, Asian and African origin demonstrate significant differences in the organization and compartmentalized sensitivity to distinct extrinsic factors.

This translates further into different demands regarding preventive measures and relevant cosmetic product applications focusing on distinct aspects of skin damage and regeneration. Personalized skincare is an actively growing area with the biomedical and commercial applications that could provide new generation of skin products. Individual approach to skin, based on the recorded profiles and the in silico modeling of unique characteristics such as structural and biometric measurements, dermal/epidermal biomarkers, hormonal and stress response, could be an effective and affordable treatment of many skin conditions in the future.

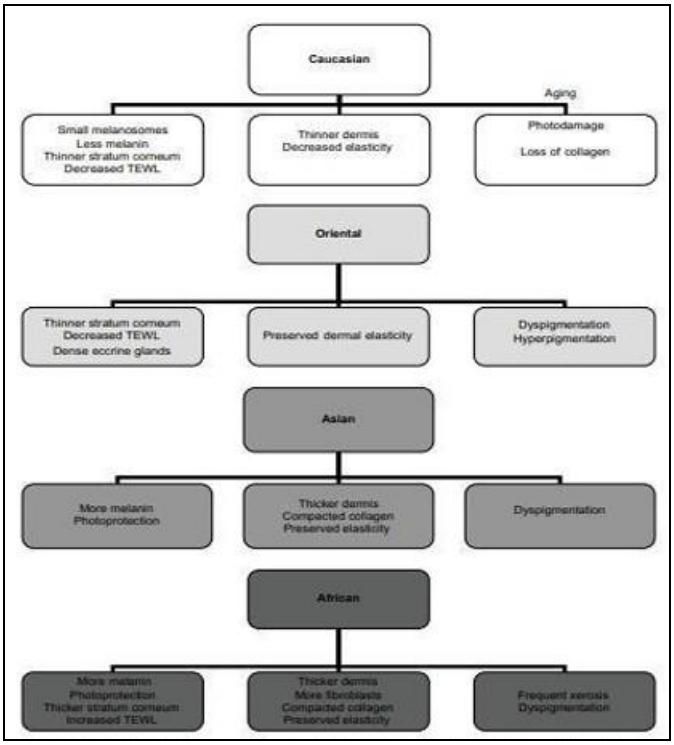

FIG. 7: RAPREZA THE ANGRACAK TYPES THE AGE-CHANGTH DAMAGE ABBREVIATION TV, MADE

AI Integration in Skin Analytics: AI has improved personalized care, leading to more accurate diagnoses, optimized treatments, and better patient management .In dermatology, AI has demonstrated measurable success in enhancing the accuracy of melanoma detection through dermoscopic image analysis, automating histopathological classification of basal cell carcinoma subtypes, and evaluating post-procedural outcomes in laser resurfacing and injectables by quantifying skin texture and symmetry changes This trend is extending into the skincare industry, where personalized solutions are essential for achieving optimal results. AI offers tailored recommendations that enhance patient satisfaction and outcomes through customized skincare regimens. As AI-driven tools become more prevalent in dermatology, they are set to transform the field by providing precise, adaptive,

and personalized skincare solutions tailored to each individual. The integration of AI in skincare addresses the complex interplay of intrinsic and extrinsic factors influencing skin health.

Skin Longevity: In the ever-evolving landscape of beauty and wellness, a notable shift has emerged from the traditional pursuit of decreasing the appearance of skin aging toward a more holistic approach centered around rebuilding skin health. This transition marks a pivotal moment in aesthetic philosophy, in which we move from treating the symptoms to treating the causes of skin aging with the goal of slowing down or reversing skin aging. As we navigate this uncharted territory of skin longevity, a host of considerations come into play. From the mode of delivery, whether topical or injectable, to the frequency of exposure, intermittent versus constant, and other considerations, the nuances of aesthetic practice in the age of skin health span demand careful deliberation. It is no longer sufficient to merely address skin structural concerns; instead, we strive for comprehensive improvements that transcend skin structure and demand skin function.

Emerging Future Trends:

CRISPR-Based Modulation of Collagen Pathways: Recent advances in genome-editing technologies, including CRISPR-Cas9, base editors, and prime editors, have generated interest in their potential to modulate collagen synthesis and extracellular matrix (ECM) regulation. Dermal aging is characterized by reduced type I collagen production, increased matrix metalloproteinase activity, disrupted fibroblast–ECM interactions, and altered TGF-β signaling, all of which contribute to dermal thinning and wrinkle formation.

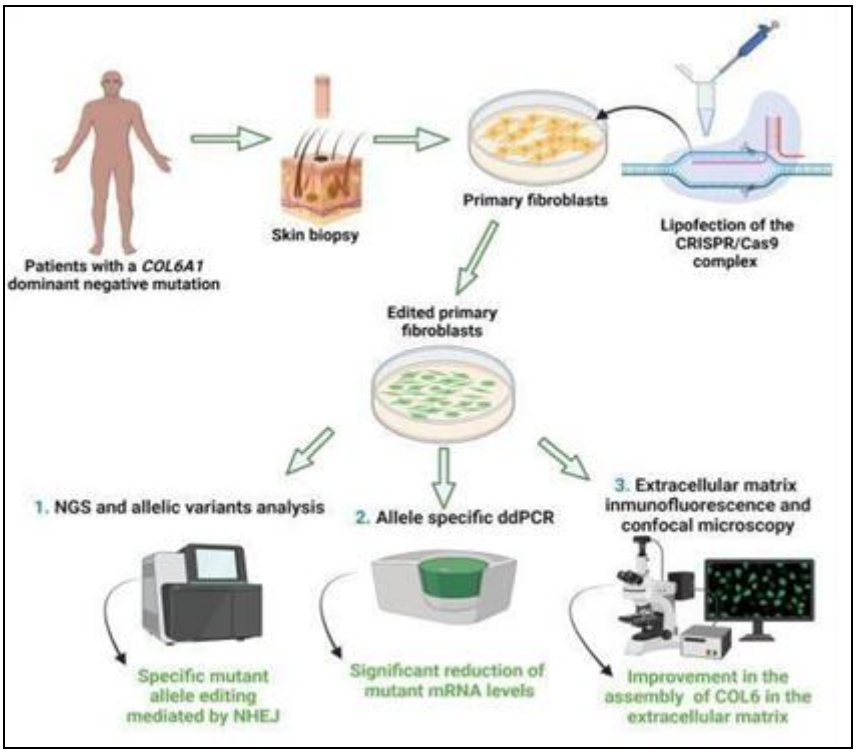

FIG. 8:

Published studies have demonstrated the feasibility of editing collagen-related genes in vitro, including base editing of the COL1A1 promoter in fibroblasts to modulate collagen expression, as well as successful correction of collagen gene mutations in inherited connective tissue disorders. However, current evidence is limited to disease-oriented or experimental models. No published studies have reported CRISPR-based gene editing of dermal fibroblasts in healthy or aging human skin for cosmetic anti-aging purposes. Major challenges include safe and efficient in vivo delivery, long-term safety, off-target effects, and ethical and regulatory constraints. In the foreseeable future, such approaches are more likely to remain within

therapeutic dermatology rather than cosmetic skincare.

Microbiome-Targeted Genetic and Functional Modulation: Growing evidence supports the role of the skin and gut microbiome in skin homeostasis, barrier integrity, inflammation, and aging-related structural changes. Age-associated dysbiosis has been linked to increased inflammation, impaired barrier function, and activation of collagen-degrading enzymes. Recent review articles suggest that microbiome-based interventions, including probiotics and postbiotics, may indirectly improve skin hydration, elasticity, and texture by modulating inflammatory and metabolic pathways.

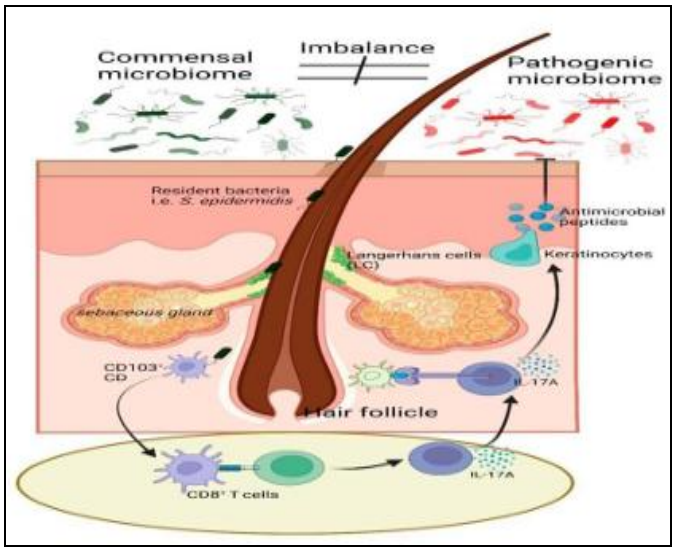

FIG. 9:

Emerging concepts propose the use of genetic engineering tools, such as CRISPR-based microbial editing or engineered bacteriophages, to selectively modulate microbial communities. However, current human evidence is limited to non-genetically modified probiotics or postbiotics, and direct microbiome gene editing for skin anti-aging remains theoretical and preclinical. Challenges include ecosystem complexity, delivery specificity, safety concerns, and regulatory ambiguity. At present, microbiome focused anti-aging strategies are best supported as adjunctive, functional approaches rather than definitive genetic interventions

Challenges and Limitations:

Lack of Unified Regulation / "Grey Zone" Status: The term cosmeceutical is not officially recognised by major regulatory agencies (e.g., U.S. Food & Drug Administration in the U.S.). Products must ultimately be classified either as cosmetics (beautification) or drugs (treatment) depending on claims/ingredients. Because of this, many anti-aging cosmeceuticals "sit in a grey area" — making quasi-therapeutic claims while being regulated only as cosmetics. One article notes: "Anti-aging skincare products often make unrealistic anti-aging claims. Because of the different pre-market testing standards for cosmetics and drugs, companies often classify and market as cosmetics yet emphasise drug-like qualities of the products to consumers." The regulatory frameworks vary significantly by country: e.g., Japan has "quasi drugs," South Korea "functional cosmetics," etc. But there is no global harmonised standard for cosmeceuticals, making cross-market claims and oversight inconsistent. Because of this regulatory ambiguity: Brands may get away with weaker evidence requirements. Consumers may be misled about what is proven vs marketing hype. It may limit the ability of regulators to enforce claims or recall unsafe products. Global launches become more complex (due to varying definitions/standards) and may increase cost.

Misleading or Exaggerated Claims by Brands: Because the regulatory barrier for cosmetics is lower than for drugs, many brands can market "anti-aging" or "collagen boosting" claims without undergoing the rigorous clinical trials required for pharmaceuticals.

One review states: "Cosmeceutical products often lack clinical evidence regarding their efficacy and safety as these products are not regulated by the U.S." The legal classification issue allows a product to be labelled as a cosmetic but marketed with therapeutic-style wording (e.g., "reduces wrinkle depth," "stimulates collagen"). That can confuse consumers. A particular area of concern: the ingredient lists and claims may not always match the evidence. For example, one study of retinoid products found significant instability (see section 4), offering potential for claims to out-pace actual performance. Because of the hype and premium pricing, there's also consumer risk of paying for products whose performance is weak or unsubstantiated. Bottom line: Many anti-aging cosmeceuticals make strong claims, but the level of

substantiating evidence is often weak or absent — consumers and professionals should approach claims with caution.

Limited Long-Term Clinical Evidence: Although many anti-aging cosmeceuticals cite *in-vitro,* animal or short-term human pilot studies, long term, large-scale, randomized controlled trials (RCTs) are rare. One review observes: "Clinical investigations, although generally of modest scale and short duration lack of long-term head-to-head comparisons against established anti-aging actives." Another article highlights that animal studies often suffer from methodological limitations (age of animals, sample size) and that formulation stability or duration of effect are poorly addressed. Because skin aging is a slow, cumulative process, demonstrating meaningful "anti-aging" effect (e.g., structural dermal changes, long-term prevention of wrinkle formation) requires prolonged study — which is rarely done in cosmeceuticals. Some evidence may exist for certain actives (retinoids, vitamin C, peptides) but many newer "anti-aging" ingredients lack robust clinical endpoint data. Bottom line: The evidence base for many anti-aging cosmeceuticals is preliminary; the absence of long-term, rigorous trials limits confidence in claims of durable benefit.

Formulation Stability, Delivery & Consistency Issues: Active ingredients in cosmeceuticals often face significant stability challenges — e.g., oxidation, degradation with temperature/UV, interactions with packaging or other ingredients. One study on retinoids found: "Long-term and accelerated stability testing revealed retinoid instabilities in almost all products 0 %-80 % decline after 6 months at 25 °C and 40-100 % decline at 40 °C."

Another Review States: "The lack of robust stability tests is a recurring limitation physical instability of emulsions containing L-ascorbic acid " In a recent formulation study of multi-active anti-wrinkle creams, one of four formulations showed phase separation during 90-day storage (i.e., physical instability) and authors noted the need for longer-term chemical & microbiological stability data. Other formulation issues: variability in botanical extracts (batch-to-batch), degradation of actives, inadequate penetration/ delivery to dermal layers, and mismatch between claimed active concentration and actual content. Bottom line: Even if the active ingredient is theoretically effective, real-world product performance may be compromised by formulation instability, degradation, poor delivery or inconsistent active levels.

CONCLUSION: Anti-aging skincare has evolved from superficial cosmetic enhancement toward biologically informed strategies targeting the molecular and cellular mechanisms of skin aging, including oxidative stress, collagen degradation, cellular senescence, and barrier dysfunction. Established bioactives such as retinoids, antioxidants (vitamins C and E), peptides, niacinamide, bakuchiol, polyphenols, glutathione, and hyaluronic acid demonstrate anti-aging effects through stimulation of collagen and elastin synthesis, inhibition of matrix metalloproteinases, reduction of reactive oxygen species, and improvement of epidermal barrier function. The efficacy of these actives is closely linked to formulation design, with advanced delivery systems such as liposomes, nanoparticles, and microneedles improving stability, skin penetration, and bioavailability. Emerging trends highlight a shift toward personalized, mechanism-based skincare supported by AI-assisted skin analysis, genetic insights, and microbiome research, alongside a growing focus on skin longevity rather than cosmetic appearance alone. Despite promising in vitro and short-term clinical evidence, substantial gaps remain in long-term safety data, large-scale randomized trials, and regulatory clarity. Addressing formulation stability, safety, and evidence validation will be critical for the translation of advanced anti-aging concepts into reliable and effective products.

ACKNOWLEDGEMENTS: Nil

CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Wyles S, Mehta R, Mannick J & Day D: Skinlongevity:Aparadigmshiftin aesthetics. Journal of Cosmetic Dermatology 2024; 23(9): 2814–2815. https://doi.org/10.1111/jocd.164841.
2. Hash MG, Forsyth A, Coleman BA, Li V, Vinagolu-Baur J & Frasier KM: Artificial Intelligence in the Evolution of Customized Skincare Regimens. Cureus 2025; 17(4): e82510. https://doi.org/10.7759/cureus.82510

3. Markiewicz E & Idowu OC: Personalized skincare: from molecular basis to clinical and commercial applications. Clinical, Cosmetic and Investigational Dermatology 2018; 11: 161–171. https://doi.org/10.2147/CCID.S163799
4. Sami Alyahya R, AlHasson MA & Ali Alhsaon MA: Assessing the Adverse Effects and Safety Concerns Relatedto Cosmetic and Skincare Products: A Systematic Review. Cureus 2025; 17(4): e81759. https://doi.org/10.7759/cureus.81759
5. Pająk J, Nowicka D & Szepietowski JC: Inflammaging and Immunosenescence as Part of Skin Aging-A Narrative Review. International Journal of Molecular Sciences 2023; 24(9): 7784. https://doi.org/10.3390/ijms24097784
6. He X, Liu J, Liu B & Shi J: The use of DNA methylation clock in aging research. Experimental biology and medicine (Maywood, N.J.) 2021; 246(4): 436–446. https://doi.org/10.1177/1535370220968802
7. Wang Z, Man MQ, Li T, Elias PM & Mauro TM: Aging-associated alterations in epidermal function and their clinical significance. Aging 2020; 12(6): 5551– 5565. https://doi.org/10.18632/aging.102946
8. Zhang J, Yu H, Man MQ & Hu L: Aging in the dermis: Fibroblast senescence and its significance. Aging Cell 2024; 23(2): 14054. https://doi.org/10.1111/acel.14054
9. Juncan AM, Morgovan C, Rus LL & Loghin F: Development and Evaluation of a Novel Anti-Ageing Cream Based on Hyaluronic Acid and Other Innovative Cosmetic Actives Polymers 2023; 15(20): 4134. https://doi.org/10.3390/polym15204134
10. Schmauck-Medina T, Molière A, Lautrup S, Zhang J, Chlopicki S, Madsen HB, Cao S, Soendenbroe C, Mansell E, Vestergaard MB, Li Z, Shiloh Y, Opresko PL, Egly JM, Kirkwood T, Verdin E, Bohr VA, Cox LS, Stevnsner T, Rasmussen LJ and Fang EF: New hallmarks of ageing: a 2022 Copenhagen ageing meeting summary. Aging, 2022; 14(16): 6829–6839. https://doi.org/10.18632/aging.204248
11. Draelos ZD: Cosmeceuticals: undefined, unclassified, and unregulated. Clinicsin Dermatology 2009; 27(5): 431–434. https://doi.org/10.1016/j.clindermatol.2009.05.005
12. Devvanshi, Nitesh, Rai, Kakli, Gupta, Ashish, Singh, Sarita, Chauhan, Ashirvad, Chauhan, Ankit and Abdul A: Cosmeceutical: their role as anti-aging and their future aspects 2025. https://www.researchgate.net/publication/392136220_COSMECEUTICAL_THEIRRO
13. Addor F and AS: Antioxidants in dermatology. Anais Brasileiros De Dermatologia 2017; 92(3): 356–362. https://doi.org/10.1590/abd1806-4841.20175697
14. Glass GE: Cosmeceuticals: The Principles and Practice of Skin Rejuvenation by Nonprescription Topical Therapy. Aesthetic Surgery Journal. Open forum 2020; 2(4): ojaa038. https://doi.org/10.1093/asjof/ojaa038
15. Jadach B, Mielcarek Z & Osmałek T: Use of Collagen in Cosmetic Products. Current Issues in Molecular Biology 2024; 46(3): 2043–2070. https://doi.org/10.3390/cimb46030132
16. Ji MS, Xiong M, Chen H, Liu Y, Zhou L, Hong Y, Wang M, Wang C, Fu X & Sun X: Cellular rejuvenation: molecular mechanisms and potential therapeutic interventions for diseases. Signal Transduction and Targeted Therapy 2023; 8(1): 116. https://doi.org/10.1038/s41392-023-01343-5
17. Orsola Crespi, François Rosset, Valentina Pala, Cristina Sarda, Martina Accorinti, Pietro Quaglino and Simone Ribero Cosmetics 2025; 12(5): 209; Cosmeceuticals for Anti-Aging: Mechanisms, Clinical Evidence, and Regulatory Insights A Comprehensive Review https://doi.org/10.3390/cosmetics12050209
18. Juncan AM, Morgovan C, Rus LL & Loghin F: Development and evaluation of a novel anti-ageing cream based on hyaluronic acid and other innovative cosmetic actives. Polymers 2023; 15(20): 4134. https://doi.org/10.3390/polym15204134
19. Cosmeceuticals for Anti-Aging: Mechanisms, Clinical Evidence, and Regulatory Insights—A Comprehensive Review by Orsola Crespi François Rosset Valentina Pala Cristina Sarda Martina Accorinti Pietro Quaglinoand Simone Ribero https://doi.org/10.3390/cosmetics12050209
20. Cosmeceuticals for antiaging: a systematic review of safety and efficacy Megan Lau, Jessica Mineroff Gollogly, Jennifer Y Wang, Jared Jagdeohttps://pubmed.ncbi.nlm.nih.gov/38758222/

How to cite this article:
Gazi AS, Ahmareen U, Ashfaq A and Mukaram M: Beyond beauty: the molecular science and clinical evidence of anti-aging skincare. Int J Pharm Sci & Res 2026; 17(5): 1375-95. doi: 10.13040/IJPSR.0975-8232.17(5).1375-95.