Review

Epigenetic Modulators in Anti-Aging Skincare: Unraveling Molecular Mechanisms and Advancing Patient Applications

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Epigenetic Modulators in Anti-Aging Skincare: Unraveling Molecular Mechanisms and Advancing Patient Applications

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Abstract: Background: The aging of skin is a multifaceted process influenced by both internal (chronological) and external (environmental) factors, which leads to the formation of wrinkles, a decline in elasticity, and alterations in pigmentation. Epigenetics, involving heritable changes in gene expression that do not modify the DNA sequence, is crucial in governing skin homeostasis and its reaction to environmental influences. Various epigenetic modifications, including DNA methylation, histone changes, and non-coding RNAs, play a significant role in modulating gene activity that is essential to aging characteristics. This review consolidates the molecular mechanisms and practical applications of epigenetic agents in anti-aging skincare, while also addressing challenges such as variability in studies and the requirement for extensive safety data over the long term. **Methods**: A comprehensive literature search was performed on PubMed, Scopus, and Web of Science, focusing on peer-reviewed research articles published between 2015 and 2025. The search utilized keywords such as "epigenetics," "anti-aging skincare," "DNA methylation," "histone modification," "non-coding RNA," and "clinical trials," which were combined using Boolean operators. The inclusion criteria emphasized studies that examined epigenetic processes related to skin aging, along with both natural and synthetic modulators, and clinical outcomes, while excluding non-peer-reviewed literature and studies on non-human subjects lacking translational relevance. The data extraction concentrated on molecular mechanisms, profiles of modulators, designs of clinical trials, and outcomes reported by patients. **Results**: Epigenetic alterations related to aging, such as hypermethylation of the COL1A1 promoter and changes in histone acetylation, play a role in the characteristics of aging skin. Both natural substances (like resveratrol, EGCG, quercetin, and dihydromyricetin) and synthetic compounds (including retinoids, senolytic peptides such as OS-01 and GHK-Cu, NAD+ precursors, and HDAC/DNMT inhibitors) have been found to influence epigenetic modifications. Clinical trials indicate that these agents are effective in decreasing biological skin age while enhancing hydration (by 20.37% to 44%), elasticity (by 5.3% to 25.6%), and reducing wrinkle depth (by 6.2% to 55.8%), often outperforming traditional methods. Outcomes reported by patients show a high level of satisfaction (for instance, 70% satisfaction with OS-01), albeit with some**. Conclusions**: Epigenetic modulators present a groundbreaking method for anti-aging skincare by focusing on reversible molecular processes. Their combination with personalized dermatological care, microbiome management, and innovative delivery systems shows potential for extending skin vitality. Rigorous, long-term clinical trials are essential to confirm their effectiveness and safety, paving the way for a transition to precision, expert-driven anti-aging approaches.

Keywords: epigenetic; anti-aging; histone modification

1. Introduction

The skin, which is the body's most extensive organ, undertakes essential protective, immune, and metabolic roles. Its look and overall condition are significantly affected by aging, which is caused by intrinsic factors (like genetic, hormonal, and metabolic influences) and extrinsic factors (such as

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UV exposure, pollution, and lifestyle choices) [1]. Intrinsic aging results in a thinning of the epidermis and a decrease in elasticity in areas shielded from the sun, while extrinsic aging contributes to the development of coarse wrinkles, skin discoloration, and solar elastosis in areas exposed to sunlight[2]. The interplay of these factors accelerates structural and functional decline, diminishing skin resilience and aesthetic appeal [3].

Historically, aging of the skin was considered an unchangeable process influenced by genetics. Nevertheless, the field of epigenetics—referring to heritable modifications in gene expression that do not involve changes in the DNA sequence—has transformed this viewpoint [4]. Epigenetic processes, such as DNA methylation, modifications of histones, and non-coding RNAs, control gene expression that is essential for maintaining skin stability and adapting to environmental changes [5]. Their reversibility offers a novel therapeutic avenue, enabling interventions that rejuvenate skin cells at a molecular level [6]. This review compiles existing insights into epigenetic modifiers in anti-aging skincare, with the goal of clarifying molecular processes, assessing clinical effectiveness, and investigating personalized applications in dermatology.

2. Methodology

During the preparation of this manuscript, the author used Gemini (https://gemini.google.com/) and Grok (https://grok.com/) to collect information and write articles. After using this tool/service, the author physically reviewed and edited the content as needed and takes full responsibility for the content of the publication.

A systematic review of the literature was carried out to maintain rigor and reproducibility, adhering to established standards for academic reviews. An extensive search was conducted across PubMed, Scopus, and Web of Science, chosen for their broad coverage of peer-reviewed articles in medicine and dermatology. The search utilized keywords such as “Epigenetic Modulators,” “Anti-Aging Skincare,” “DNA Methylation,” “Histone Modification,” “Non-coding RNA,” and “Clinical Trials,” which were combined using Boolean operators (e.g., “Epigenetic Modulators AND Skin Aging”). The searches covered the years 2015–2025, while also incorporating important older studies for historical perspective.

Inclusion Criteria: Priority was given to peer-reviewed studies, reviews, and clinical trials that examine epigenetic mechanisms involved in the aging of skin, as well as both natural and synthetic modulators and their clinical implications. Only English-language research with strong methodologies and safety information was included .

Exclusion Criteria: Non-peer-reviewed materials, studies not about skin aging or epigenetics, and animal research lacking relevance to human conditions were excluded. Articles that did not provide sufficient methodological details or clinical findings were also left out.

Titles and abstracts were evaluated for their relevance, after which a full-text review was conducted based on inclusion criteria. The reference lists of significant articles were examined to find additional studies. Data extraction focused on molecular mechanisms, modulator profiles, clinical trial methodologies, outcomes, and safety issues, ensuring an organized synthesis.

3. Molecular Mechanisms of Epigenetic Regulation in Skin Aging

Epigenetic processes regulate gene expression without changing the DNA sequence, playing a crucial role in the aging of skin. This part describes DNA methylation, histone modifications, non-coding RNAs, and their functions in cellular aging and the skin barrier's integrity [7].

3.1. DNA Methylation

DNA methylation involves adding methyl groups to cytosine residues at CpG sites, catalyzed by DNA methyltransferases (DNMT1, DNMT3A/B) [8]. Promoter hypermethylation typically silences genes, impacting skin integrity [9]. Age-related hypermethylation of the COL1A1 gene, encoding type I collagen, reduces collagen synthesis, contributing to wrinkles and reduced firmness

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[10]. Systemic conditions like diabetes exacerbate this by inducing COL1A1 and TERT promoter hypermethylation, accelerating telomere shortening [11]. The "epigenetic clock," which relies on patterns of CpG methylation, measures biological age and acts as a biomarker for interventions aimed at anti-aging [12].

3.2. Histone Modifications

Histone modifications, including acetylation and methylation, regulate chromatin accessibility [13]. Histone acetyltransferases (HATs) promote open chromatin, while histone deacetylases (HDACs) compact it, repressing transcription [14]. Aged and UV-exposed skin shows increased histone H3 acetylation and reduced HDAC4/11 expression, upregulating matrix metalloproteinases (MMPs) that degrade collagen [15]. Sirtuin 1 (SIRT1), which is a deacetylase dependent on NAD+, decreases as we age, leading to heightened MMP activity and oxidative stress [16].

3.3. Non-coding RNAs

MicroRNAs (miRNAs) such as miR-146a control gene expression after transcription, influencing collagen production and inflammatory responses [17]. Reduced levels of miR-146a in aging fibroblasts correlate with decreased proliferation and increased DNA damage [18]. Long non-coding RNAs (lncRNAs) play a role in senescence and wound healing, and are becoming important targets for therapy [19].

3.4. Cellular Senescence and SASP

Cellular senescence, marked by cell cycle arrest, accumulates in aged skin, driven by epigenetic changes [20]. The senescence-associated secretory phenotype (SASP) promotes inflammation ("inflammaging"), exacerbating aging [21]. Epigenetic regulators aimed at senescence present an opportunity to mitigate the impacts of the senescence-associated secretory phenotype (SASP) [22].

3.5. Skin Barrier and Inflammation

Epigenetic regulation affects barrier proteins (e.g., filaggrin) and inflammatory cytokines [23]. The methylation process of the FLG gene disrupts barrier function, whereas modifications to histones influence inflammation, playing a role in inflammaging [24].

Table 1. Key Epigenetic Mechanisms and Their Role in Skin Aging.

Mechanism	Process	Enzymes/Molecules	Impact	Role in Aging
DNA Methylation	Methyl group addition to CpG sites	DNMT1, DNMT3A/B	Gene silencing	COL1A1 hypermethylation; epigenetic clock [12]
Histone Modifications	Acetylation/methylation of histones	HATs, HDACs, SIRT1	Gene activation/repression	Increased H3 acetylation; SIRT1 decline [15, 16]
Non-coding RNAs	Post-transcriptional regulation	miRNAs (e.g., miR-146a), lncRNAs	mRNA degradation	Dysregulated miR-146a; lncRNAs in senescence [17, 19]
Senescence & SASP	Cell cycle arrest; inflammatory secretion	p16INK4a, cytokines	Inflammation	Senescent cell accumulation; inflammaging [21]
Barrier & Inflammation	Barrier protein/cytokine regulation	DNMTs, miRNAs	Barrier dysfunction	FLG methylation; inflammatory dysregulation [24]

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4. Epigenetic Modulators in Anti-Aging Skincare

Epigenetic modulators, both natural and synthetic, target molecular pathways to rejuvenate skin [25]. This part classifies these compounds along with their uses.

4.1. Natural Compounds

- **Polyphenols**: Resveratrol activates SIRT1, enhancing collagen synthesis and reducing UV-induced damage [26]. EGCG upregulates filaggrin and nc886, mitigating senescence [27]. Quercetin targets SIRT1, reducing oxidative stress [28].
- **Dihydromyricetin (DHM)**: Inhibits DNMT1, reducing DNA methylation age and reactivating silenced genes [29]. Clinical trials show increased epidermal thickness and fibroblast proliferation [30].
- **Vitamins/Minerals**: Vitamin B12, zinc, and selenium decrease epigenetic age, supporting DNA repair and telomere stability [31].

4.2. Synthetic Compounds and Peptides

- **Retinoids:** such as tretinoin and retinol, promote collagen production through retinoic acid receptors, functioning as epigenetic-like modulators [32]. Nanoformulations improve tolerability [33].
- **Senolytic Peptides**: OS-01 reduces senescence and biological age, improving hydration (+32.49%), firmness (+10.19%), and elasticity (+25.58%) [34]. GHK-Cu modulates over 4,000 genes, reducing wrinkle volume (-55.8%) [35].
- **NAD+ Precursors**: NMN and NR replenish NAD+, activating sirtuins and reducing epigenetic age [36].
- **HDAC/DNMT Inhibitors**: Remetinostat (HDAC inhibitor) and DHM (DNMT inhibitor) reverse epigenetic changes, showing dermatological promise [37, 29].

4.3. Emerging Therapies

Microbiome-focused treatments (such as probiotics, prebiotics, synbiotics, and bacteriophages) affect epigenetic mechanisms indirectly by lowering inflammation [38]. Combination therapies and nanoparticle delivery techniques enhance efficacy [39].

Table 2. Selected Epigenetic Modulators.

Category	Modulator	Type	Targets	Reference
Natural	Resveratrol	Polyphenol	SIRT1, collagen synthesis	[26]
Natural	EGCG	Polyphenol	nc886, filaggrin	[27]
Natural	DHM	Flavonoid	DNMT1 inhibition	[29]
Synthetic	Retinoids	Vitamin A derivative	Retinoic acid receptors	[32]
Synthetic	OS-01	Peptide	Senescence reduction	[34]
Synthetic	NMN	NAD+ precursor	Sirtuin activation	[36]
Microbiome	Probiotics	Microorganisms	Inflammation reduction	[38]

5. Patient Applications and Clinical Efficacy

Clinical studies confirm the effectiveness of epigenetic modulators in skincare aimed at reducing aging [40].

Clinical Outcomes:

- **DHM**: Reduced biological age by 2 years and wrinkle grade by 3.7 years [30].
- **OS-01**: Improved hydration (+32.49%), elasticity (+25.58%), and reduced TEWL (-17.33%) [34].
- **GHK-Cu**: Reduced wrinkle volume (-55.8%) and depth (-32.8%) [35].

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- **Resveratrol**: Enhanced elasticity (+5.3%), density (+10.7%), and reduced roughness (-6.4%) [26].
- **NAD+ Precursors**: Reduced biological age by up to 12 years [36].

Patient satisfaction is high (e.g., 70% for OS-01), though standardized PROMs are needed [41].

6. Discussion

Epigenetic modulators engage with reversible processes, presenting significant possibilities for anti-aging interventions. There are challenges such as variability in studies and a lack of extensive safety data over time. Upcoming research should prioritize tailored strategies, improved delivery mechanisms, and long-term clinical studies [42, 43, 44].

7. Conclusion

Epigenetics transforms our understanding of skin aging, showing it can be reversed. Compounds such as resveratrol, OS-01, and NAD+ precursors have exhibited notable effectiveness, as evidenced by epigenetic clocks. The progression of dermatological practices will be enhanced through standardized trials and individualized approaches, fostering healthy aging [45].

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