cosmetics

MDPI

Review

Dehydroepiandrosterone and Skin: Sex- and Age-Related Mechanisms of Action

Tatiana A. Fedotcheva * and Nikolay L. Shimanovsky

Laboratory of Molecular Pharmacology, Pirogov Russian National Research Medical University, 1 Ostrovityanova St., Moscow 117997, Russia; shimannn@yandex.ru

* Correspondence: tfedotcheva@mail.ru; Tel.: +7-916-935-3196

Abstract

Geroprotective molecules are currently being actively investigated for the prevention of skin aging. An overview of geroprotectors in dermatology encompasses agents such as antioxidants, ultraviolet (UV) photoprotective agents, chemical peels, and carbon dioxide (CO_2) lasers, each with inherent limitations, including poor tolerability in individuals with sensitive skin. Regarding biostimulators, high-molecular-weight peptides (exceeding 500 Da) exhibit limited cutaneous bioavailability, underscoring the need for low-molecular-weight geroprotective compounds. One such candidate is dehydroepiandrosterone DHEA, a neurosteroid with anti-aging and anti-stress properties, which also serves as a precursor to sex steroids. Although topical hormone replacement therapy with estrogens and androgens is being utilized, it remains confined to formal hormone replacement regimens and is associated with a significant adverse effect profile. The aim of this review was to analyze the key molecular mechanisms underlying the effects of DHEA on the skin, with particular emphasis on its metabolism and sex- and age-dependent mechanisms of action. Additionally, this review seeks to elucidate the factors contributing to the absence of approved topical DHEA formulations and to outline the potential of DHEA as an anti-aging agent in dermatological applications. DHEA has demonstrated significant skin-improving effects in several studies; its investigation has been predominantly confined to postmenopausal women. Furthermore, the outcome measures employed in these studies lacked specificity. DHEA is not permitted for use in cosmetic products within the European Union due to its hormonal activity. Its use is only allowed as an extemporaneous formulation under the established regulatory frameworks of individual countries. The indications for its use and the appropriate dosage for men and women must be clearly defined based on the results of future clinical studies. Promising research directions include the pharmacogenetic characterization of steroidogenic enzymes and sex hormone receptors, as well as the evaluation of DHEA in both sexes, specifically in premenopausal women and in men presenting with late-onset hypogonadism. Additionally, the biological effects of the primary metabolites of DHEA, androstenedione, and 5-androstenediol, on the cutaneous function remain unexplored, including their potential anti-aging activity mediated through retinoid receptor activation.

Keywords: skin; DHEA; age; sex; estrogens; androgens; steroidogenic enzymes; polymorphism; hormone; geroprotector; extemporaneous formulations

Check for updates

Academic Editor: Enzo Berardesca

Received: 20 April 2026
Revised: 18 May 2026
Accepted: 20 May 2026
Published: 22 May 2026
Corrected: 12 August 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

Skin aging, the loss of muscle mass, and decreased bone mineral density, as well as a decline in sexual function, cognitive performance, and mood, are all associated with the age-related reduction in hormone production, primarily DHEA and the sex hormones androgens and estrogens. The marked reduction in the formation of the sulfate form of DHEA (DHEA-S) by the adrenals during aging results in a dramatic fall in the formation of androgens and estrogens in peripheral target tissues, a situation that has been proposed to be associated with age-related diseases, including skin atrophy, insulin resistance, and obesity. Androgens and estrogens are used as hormonal replacement therapy, HRT (oral forms, injections, implants, transdermal patches, gels, and creams), whereas DHEA is only used as intravaginal suppositories (Prasterone) for the treatment of dyspareunia in postmenopause. DHEA is also used off-label as a dietary supplement to improve sexual and cognitive function in tablet form and for aging skin care in gels. A clinical trial of DHEA gels was conducted in 2017 in Canada in postmenopausal women as an anti-aging medication for skin for one year with 0.3% DHEA gel, but the results have not been published [1].

The use of DHEA as a geroprotector as part of HRT has been debated for many years. DHEA is classified as a hormonally active substance and is prohibited for use in cosmetic products in most countries; however, its use may be permitted for therapeutic purposes with a prescription, not as a cosmetic agent. For more effective use in dermatological practice, the indications for its prescription need to be clearly defined. Approximately every five years, a narrative review or meta-analysis is published, reporting the positive effects of DHEA for alleviating the menopausal symptoms [2–5], an increase in ovarian reserve [6], and its neuroprotective effect on the central and peripheral nervous system [7,8]. Although there is substantial evidence on the beneficial effect of DHEA on aging skin, the molecular mechanisms of its action have not been adequately studied. As a rule, small clinical trials were conducted in which the endpoints assessed general signs—wrinkle length, hydration, sebum production—and pharmacodynamics at the molecular level were not evaluated, nor were the results interpreted according to the sex and age of the subjects and their pharmacogenetic profile [9,10].

Meta-analyses of conducted clinical trials do not allow for a definitive conclusion and are insufficient; those that were conducted were performed exclusively on postmenopausal women. The use of transdermal DHEA should be evaluated in perimenopausal women and men with age-related androgen deficiency, i.e., aged 40–55 years. Considering that during this period of life, the expression of sex hormone receptors reaches a plateau and has not yet sharply declined, DHEA is capable of exerting positive pharmacological effects by compensating for insufficient levels of estrogens and androgens.

With transdermal application, DHEA is more bioavailable, and local anti-aging effects can be achieved without pronounced systemic action. Therefore, the creation of dosage forms with improved skin penetration through novel delivery systems (e.g., liposomes, microneedles) is under investigation to enhance effectiveness, and there are already publications on increased permeability due to nanoencapsulation with poly lactic-co-glycolic acid (PLGA)-based NCs [11] and the use of alpha-cyclodextrin [12].

In this review, we have attempted to examine the molecular mechanisms of age- and sex-related features of transdermal DHEA anti-aging action and the ability to prevent skin senescence in men using DHEA. The fact that DHEA is an endogenous anti-aging steroid with cytoprotective action and a neurosteroid suggests that personalization, considering age and sex, the expression of sex hormone receptors and steroidogenic enzymes, as well as pharmacogenetic analysis of these proteins, will contribute to obtaining more definitive results. We also focus on the creation of new DHEA dosage forms with various enhancers

and on the application of DHEA to the facial and neck skin in men, including those on long-term finasteride therapy.

2. The Biosynthesis of DHEA

The main site of the synthesis of DHEA and DHEA-S is the adrenal glands (70–85%). Only 10% of DHEA is synthesized in the gonads—testes and ovaries. A small amount is also synthesized in the brain from pregnenolone [13].

DHEA-S has the highest concentration in peripheral blood throughout the entire spectrum of steroids, including cortisol. The concentration of DHEA-S is thousands of times higher than the blood testosterone content in healthy men and tens of thousands of times higher than the level of 17β-estradiol in women. The age-related dynamics of free DHEA are similar to those of its sulfated form. While at a young age, the concentration of DHEA in the blood can reach 10 μM, by the age of 80, its level usually does not exceed 5 nM [14].

The main inducer of DHEA synthesis is ACTH (AdrenoCorticoTropic Hormone): it stimulates DHEA production via cortisol. Cortisol, produced in response to stress, by the mechanisms of biofeedback, increases DHEA and DHEA-S levels, whereas insulin administration, conversely, reduces the levels of these hormones. The cortisol/DHEA-S ratio is a marker of stress and premature aging, a so-called marker of epigenetic clocks, and a predictor of epigenetic clocks [15].

The biosynthesis of DHEA at the local level is regulated by cholesterol availability and the activity of specific intracellular proteins (such as POU3F2 and CYB5A), capable of finely tuning the DHEA production depending on age and the body's metabolic needs. A local lack of substrate can directly influence the cell's "profile," initiating the DHEA production program. Cholesterol deficiency reduces the transcriptional activity of *POU3F2*, which normally stimulates *HSD3B2* (a gene that encodes the enzyme 3βHSD2 or 3β-HSD or 3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4 isomerase). Cholesterol deficiency increases DHEA synthesis, decreases HSD3B2, and increases CYB5A [16].

The transcription factor POU3F2 (also known as N-Oct3 or BRN2) regulates the activity of the enzyme 3β-HSD, which can switch steroid production from cortisol to DHEA—this is a fine self-regulating system. The role of the POU3F2 factor in sexual behavior and maternal instinct has recently been confirmed, underscoring its exceptional role in steroid production [17]. In peripheral tissues, like skin and placenta, type 1 of 3-beta-hydroxysteroid dehydrogenase (3βHSD1) is responsible for the local conversion of DHEA into androgens.

At the cellular level, the main rate-limiting step in DHEA biosynthesis is the transport of cholesterol across the mitochondrial membrane, mediated by the StAR protein (steroidogenic acute regulatory protein), which determines the overall rate of steroidogenesis and is the main regulatory point under the influence of tropic hormones. Cholesterol cannot penetrate the inner mitochondrial membrane on its own. Its transport is ensured by the StAR protein. ACTH activates StAR and rapidly stimulates DHEA synthesis.

The second critical stage is the 17,20-lyase activity of the CYP17A1 enzyme, the efficiency of which depends on the availability of oxidoreductase POR and cytochrome b5, determining the ratio between DHEA and glucocorticoid production. Furthermore, an important factor limiting DHEA output is the activity of the competing enzyme 3βHSD2, which, when high, shifts the precursor metabolism towards progestins and active androgens, reducing the DHEA formation [18].

Recently, another regulatory mechanism for DHEA and cortisol biosynthesis has been identified, which involves the protein SVIP (small VCP-interacting protein). SVIP is an endogenous inhibitor of endoplasmic reticulum-associated degradation (ERAD). SVIP overexpression mainly increases the biosynthesis of cortisol as well as DHEA by enhancing

the expression of key steroidogenic proteins; excessive overexpression diminishes adrenal steroid hormone biosynthesis [19].

3. Sex- and Age-Related Differences in DHEA Biosynthesis

The concentration of DHEA in both sexes changes significantly throughout life. During pregnancy, the synthesis and consumption of DHEA increase: fetal DHEA-S production (200 mg/day) is significantly higher than in adults (up to 30 mg/day). Pregnenolone entering the fetal organism is used for the synthesis of DHEA-S, which is converted into 16-hydroxy-DHEA-S in the fetal liver and adrenal glands. Then, in the placenta, 16-hydroxy-DHEA-S undergoes hydrolysis by steroid sulfatase and, together with DHEA, is utilized for the formation of estrone, estradiol, and estriol in the placenta. Estriol is conjugated in the maternal liver and then excreted in the urine. It is the main marker of fetoplacental system function [20].

After birth, the fetal zone regresses within 3 months, concurrently with a decrease in the blood DHEA level, which remains low until approximately 6 years of age. Later, some unidentified factors "switch on" DHEA production, which gradually increases and peaks around age 30, and then begins to steadily decline at a rate of 60 ng/mL per year. These metabolic and hormonal changes lead to aging progressively. This mechanism is referred to as intrinsic aging, which is also known as endogenous aging. Another type is exogenous aging, which is caused by different kinds of radiation, chemicals, and environmental factors. By age 75, humans exhibit very low amounts of DHEA, i.e., only 10 to 20% of young-adult DHEA levels [21].

The importance of DHEA in steroid hormone production increases with age. In addition to the decline in estrogen and testosterone production by the gonads, the adrenal production of their precursors DHEA and DHEA-S decreases with age in both sexes (adrenopause). In women, DHEA declines faster than in men [22]. In women with ovarian failure, adrenal DHEA becomes the main source of sex hormones. In men, testosterone secretion by the testes continues for a longer period than estradiol secretion by the ovaries in women.

In both sexes, equally low DHEA levels are associated with increased risks of developing atherosclerosis and a decline in neurophysiological parameters, bone mineral density, and glucose tolerance. Its decline also similarly affects erectile function and female receptivity [22]. Changes in the biosynthesis and metabolism of sex hormones affect virtually all body systems. Estrogens and androgens act through their specific receptors in the skin, whose expression also decreases with age. It has been shown that the level of estrogen receptors (ERs) declines faster than that of androgen receptors (ARs) [23].

In women, DHEA, testosterone, estradiol, and estrone gradually decline, whereas the more active androgen dihydrotestosterone (DHT), the metabolite of testosterone, does not change significantly with age. In men, during aging, DHEA and testosterone decline, while DHT and estrogens do not change. This underscores the unique role of DHEA compared to other steroids, since its age-related decline is observed in both sexes, making it a central focus for studying the aging process. It turns out that already low estrogen levels in women have nothing to bind to, whereas even with low levels of androgens, there are sufficient receptors available for binding. The preserved AR expression in men is one reason for slower aging and thinning of skin in men, and the second reason is more stable DHEA levels. There is great variability among women of the same age; DHEA levels can differ almost tenfold.

In men, the decrease in plasma levels is curvilinear; in women, it is stepwise: the concentrations fall by 40% between ages 50 and 60 and then remain constant to about age 80. The same sharp decline occurs with estrogen levels during the menopausal transition:

circulating levels of estradiol decline from over 300 pool/L to about 20 pool/L and estrone becomes the predominant form of estrogen in postmenopausal women. Estrone derives principally from tissue androstenedione by aromatization, with 20% secreted directly by the adrenals [23].

In men, 80% of plasma estradiol is produced by peripheral aromatization of testosterone. In younger men, 5–10 μg/day of estradiol is produced by Leydig cells, 20 μg/day derives from the peripheral conversion of plasma testosterone, and 5 μg/day from androstenedione. Despite the age-associated decline in testosterone, it has been postulated that plasma estradiol levels remain relatively unchanged because of a rise in aromatase activity, which is coincident with the age-associated increase in body mass fat. As a result, plasma estradiol levels in older men are significantly higher than in postmenopausal women [23].

The influence of ACTH on DHEA biosynthesis in both sexes is very important, but not exclusive. Possibly, the dissociation in the dynamics of ACTH, cortisol, and sex hormone production during adrenarche and aging is also explained by changes in the activity of enzyme systems responsible for steroid synthesis via the Δ^4- and Δ^5-pathways. These changes in enzyme system activity occur both within the adrenals themselves and in peripheral tissues. There are at least two pathways for steroid production from cholesterol:

- Delta-4 Pathway: this pathway leads to the production of cortisol and aldosterone.
- Delta-5 Pathway: this pathway leads to the production of DHEA [24]

The enzymatic activity also changes in peripheral tissues, which affects the subsequent pharmacodynamics of DHEA.

The oral administration of DHEA, despite its poor bioavailability, causes a similar increase in blood DHEA, but a stronger increase in DHEA-S in women, as shown in a single-blind, placebo-controlled trial with a single dose of 200 mg of DHEA, which revealed a sex difference: DHEA concentrations increased five- to sixfold in both genders, while DHEA-S levels rose fivefold in men and 21-fold in women compared to the baseline [25]. This sex difference is most likely influenced by the steroid sulfatase STS. This enzyme is widely distributed in various peripheral target tissues (e.g., adipose tissue, skin, prostate, liver), where DHEA is needed for further synthesis of active sex hormones.

It is known that, in prepubertal children (2–7 years), the enzyme activity in leukocytes is significantly higher, more than twice, than in adults (15–40 years). After puberty, STS activity decreases in both men and women; however, the ratio of activities between the sexes is maintained: in women, the enzyme activity on average is higher than in men. This is because the STS gene is located on the X chromosome and is only partially subject to inactivation, leading to a gene dosage effect—in women with two X chromosomes, the enzyme level can be higher. The human STS gene is located in the pseudoautosomal region of the short arm of the X-chromosome that escapes X-inactivation. Females are carriers of two functional alleles. Males carry one functional and a nonfunctional STS pseudogene on their Y-chromosome [26]. Regarding changes in old age, there are few studies on STS enzyme activity in people over 40 years of age, or, to be more precise, there are no statistical data.

Thus, there are differences in the biosynthesis of DHEA between men and women at all stages of the process. This is related to the activity of enzymes and transport proteins. Furthermore, their polymorphisms play a role; this topic is currently being actively researched, and significant single-nucleotide polymorphisms (SNPs) have been found. A completely unexplored question is how epigenetic factors influence DHEA biosynthesis and how DHEA itself affects DNA methylation. Most likely, the diversity of DHEA's effects on the reproductive system is precisely related to these processes. The search for specific "epigenetic signatures" (DNA methylation patterns) that correlate with DHEA levels is a direct way to understand which genes and processes this hormone influences most strongly.

The elevated levels of this hormone at the prepubertal stage are associated with earlier puberty onset and a predisposition to developing the polycystic ovary syndrome. Does a DNA methylation signature reflecting the process of adrenarche exist? It has recently been discovered that higher childhood DHEA-S concentrations are associated with the methylation of specific CpG sites, which may influence the activity of genes controlling the pubertal development [27]. New discoveries in this direction are anticipated.

4. Direct and Metabolism-Mediated Mechanisms of DHEA Action: The Role of Conversion into Sex Hormones

The skin is one of the most important target organs for sex steroids, which contains sex steroid receptors. This is the largest organ that performs several main functions: protective (barrier against external influences), thermoregulatory (maintenance of body temperature), excretory (removal of sweat and metabolic products), receptor (perception of touch, pain, and temperature), and synthetic (production of vitamin D, collagen, and elastin), as well as absorptive, respiratory, and immune functions. DHEA is able to regulate all of the listed functions through several mechanisms: through direct binding to CAR, PPAR, PXR, LXR, FXR, and RXR [28] or through ER and AR after its conversion in the skin to A4, 5-AED, estradiol, and testosterone (Figure 1).

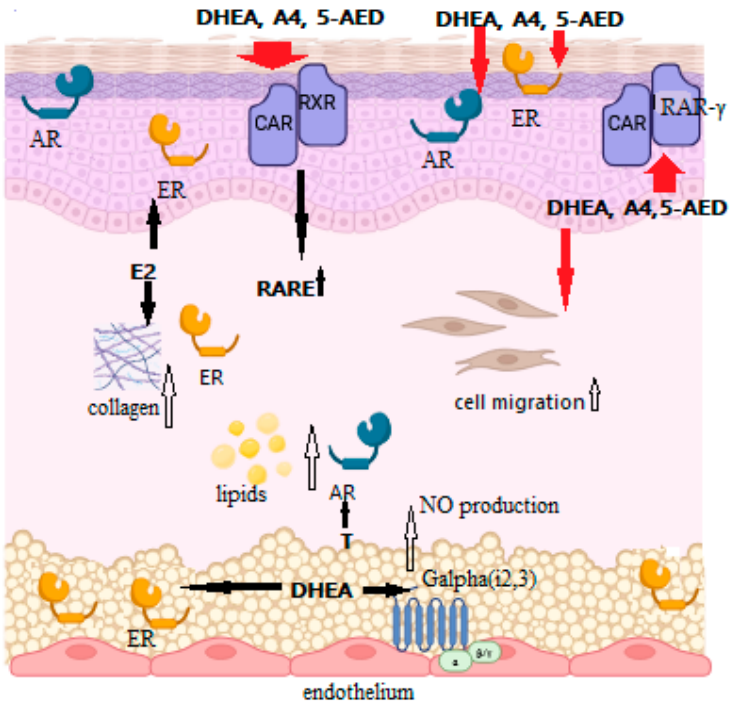


Figure 1. The main mechanisms of DHEA action on aging skin. Note: DHEA and its metabolites A4 and 5-AED can bind not only to ER and AR but also to CAR and RXR or RAR-γ, which form heterodimers and activate RARE, thereby mediating the anti-aging regenerative effects of RA. In skin endothelial cells, DHEA binds to its specialized membrane-bound receptors Gα(i2) and Gα(i3), promoting endothelial cell proliferation, migration, and angiogenesis. Through local conversion into testosterone and estradiol (T and E2) at homeostatic levels, DHEA exerts AR- and ER-mediated effects on the skin. Created with Biorender.com.

The biosynthesis of DHEA at the first stage depends on the activity of STS and SULT2A1. Subsequently, DHEA metabolism proceeds with the participation of 3β-HSD, the activity of which declines with age in both sexes, while 17β-HSD activity remains unchanged, and aromatase (CYP19) activity increases. The intermediate metabolites A4, 5-AED, and DHEA itself can bind not only to ER and AR but also to CAR and RAR-γ,

which form heterodimers and activate RARE, leading to the anti-aging regenerative effects of RA—Figure 1. In skin endothelial cells, DHEA binds to its specialized membrane-bound receptors Galpha(i2) and Galpha(i3) to promote endothelial cell proliferation, migration, and angiogenesis. DHEA and its metabolites can be produced in peripheral tissues such as cardiac tissue, immune cells, nervous system tissues, adipose tissue, and skin [29].

Indeed, de novo synthesis of DHEA from cholesterol occurs in the skin, and the skin also actively metabolizes precursors coming from the blood or external sources. The skin expresses the key steroidogenesis genes: CYP11A1 (the enzyme converting cholesterol to pregnenolone—the first step in DHEA biosynthesis) and CYP17A1 (converts pregnenolone to DHEA) [30,31]. Subsequently, the metabolism of DHEA itself occurs, and which pathway DHEA conversion in the skin will take, with the formation of which final effector steroids, depends on steroidogenic enzymes. And what effects DHEA metabolites will exert depends on receptor expression.

4.1. Steroidogenic Enzymes in the Skin

The skin expresses enzymes that regulate the interconversion of DHEA: steroid sulfatase (STS) and sulfotransferase (SULT). These enzymes manage the interconversion between DHEA and its inactive storage form, DHEA-S:

(1) STS converts DHEA-S → DHEA.
(2) SULT2A1 (DHEA-ST) converts DHEA → DHEA-S.

Human steroid sulfatase STS is an enzyme that catalyzes the hydrolysis of not only DHEA-S, but also estrone sulfate (E1S) and cholesterol sulfate. Abnormal expression of STS causes several diseases, including colorectal, breast, and prostate cancers, and refractory skin disease XLI. XLI is a disease that causes excessive keratinization and occurs more often in males than in females because it results from a deletion or mutation of the STS gene on the X chromosome [32].

Furthermore, STS plays a role in maintaining the skin barrier, since in the skin, in lamellar bodies and the intercellular space, STS converts cholesterol sulfate into cholesterol. So, STS in the skin is expressed in keratinocytes, dermal papilla cells, sebaceous glands, and as part of lamellar bodies, participating in the maintenance of the barrier function and normal skin renewal. After being secreted from lamellar bodies, STS enters the space between epidermal cells. Excessive accumulation of cholesterol sulfate inhibits enzymes that break down the bonds between dead cells of the stratum corneum. By removing excess cholesterol sulfate, STS allows these cells to detach in a timely manner, ensuring imperceptible skin renewal [33].

The enzyme SULT2A1 (DHEA-ST) is expressed mainly in keratinocytes. SULT2A1 has a higher affinity toward DHEA, while SULT2B1a and SULT2B1b have a higher affinity toward pregnenolone and cholesterol, respectively. Overall, sulfotransferases play an important detoxifying role in the skin and participate in the wound healing process [34].

Polymorphisms in sulfotransferase genes lead to an imbalance in cholesterol metabolism in the skin. It has recently been shown that SNPs in the SULT1A1 and SULT2A1 genes lead to an increase in the level of active DHEA [35]. The inhibitors of SULT1A1 and SULT2A1 also increase the concentration of active DHEA, i.e., they slow down its sulfation. Potent inhibitors include glycyrrhetinic acid, flavones, quercetin, and kaempferol [36].

The expression of this enzyme in various skin cells has not been studied, and polymorphisms are currently being evaluated primarily in the brain. It has been established that SULT2A1 (rs2637125) polymorphism was not associated with cognitive decline, but reduced concentration of the product of this enzyme—DHEA-S—was associated with cognitive disorders [37].

The next stage of DHEA metabolism in the skin is the formation of androstenedione (A4), 5-androstenediol (5-AED), estrone, estradiol, and testosterone—Figure 2.

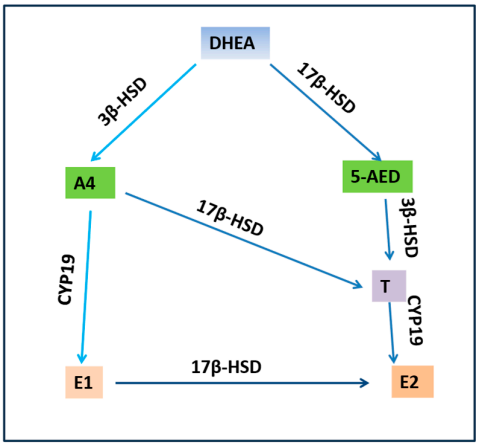


Figure 2. The formation of androstenedione (A4), 5-androstenediol (5-AED), estrone (E1), estradiol (E2), and testosterone (T) from DHEA.

In this stage of DHEA metabolism in the skin, the rate-limiting enzyme is 3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4 isomerase (3β-HSD), the expression of which occurs in the sebaceous glands, an organ of the skin that produces sex steroids. The expression levels of this enzyme change throughout the day and throughout life. 3β-HSD activity varies in different areas of the skin: it is highest in the skin of the shoulders and lower in the axilla and thigh. 3β-HSD activity declines with age (Figure 3), while 17β-HSD activity remains unchanged.

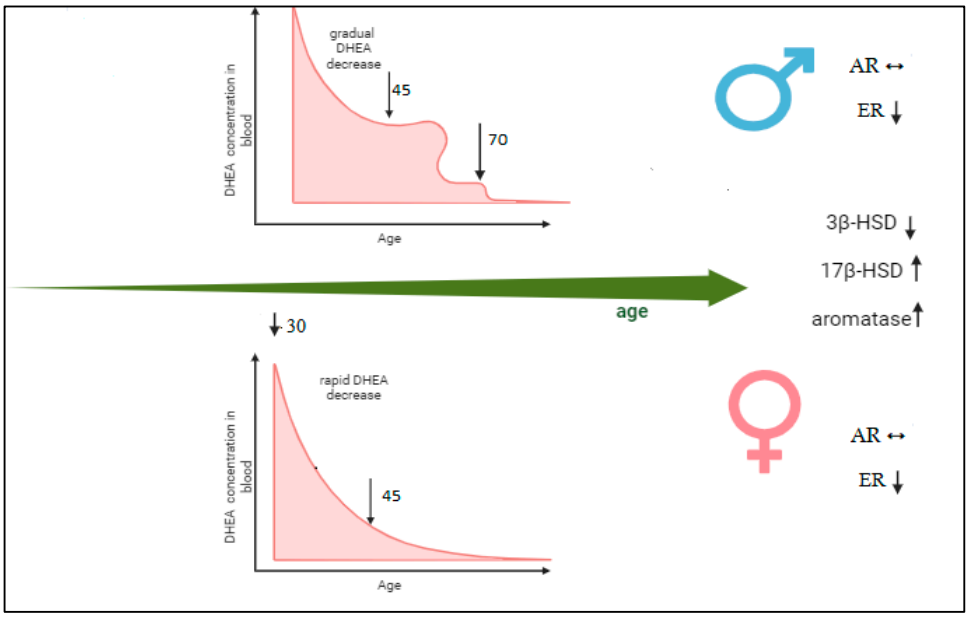


Figure 3. Stepwise (in men) and sharp, rapid (in women) decline in DHEA levels with age. Note: arrows indicate the key milestones of the decrease in blood DHEA concentration (at 30, 45, and 70 years). Created in BioRender. Fedotcheva, T. (2026). https://app.biorender.com/profile/template/details/t-6a140e8829fe8ac76a070c33-stepwise-concentration-decline (accessed on 19 May 2026).

Spatial and age-related differences in 3β-HSD activity in the human skin determine the variable local production of sex steroids from DHEA. This factor, combined with the potential individual characteristics of further androstenedione metabolism to testosterone, may contribute to the pathogenesis of acne [38].

As in other steroidogenic organs, the following enzymes are involved in the metabolism of DHEA in the skin to produce androgens and estrogens:

1. 3β-HSD (3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4 isomerase): converts DHEA into androstenedione.
2. 17β-HSD (17β-hydroxysteroid dehydrogenase): converts androstenedione into the potent androgen testosterone.
3. Steroid 5α-reductase: transforms testosterone into the more potent androgen dihydrotestosterone (DHT), which is crucial for processes like androgenetic alopecia.
4. Aromatase (CYP19): converts androgens (testosterone/androstenedione) into estrogens (17β-estradiol/estrone).

Throughout the day, the activity of the enzymes of DHEA metabolism undergoes changes as a result of the integration of signals from the central circadian clock (via ACTH), the functioning of intracellular "clocks" within the adrenal tissue itself, as well as the complex interaction of transcription factors (SF-1 and DAX-1) [39] and the availability of specific cofactors (cytochrome b5, and NAD+) [40].

Other hormones of the hypothalamic–pituitary–adrenal axis participate in DHEA metabolism in the skin. In response to stress (e.g., UV exposure), the skin synthesizes corticotropin-releasing hormone, urocortins, proopiomelanocortin, and its derivatives—ACTH, α-MSH, and β-endorphin [31]. Thus, the activation of the HPA axis increases the pool of precursors for DHEA synthesis.

The main skin structure where DHEA metabolism occurs most intensively is the sebaceous gland: it is a key player in the balance of the synthesis of sex hormones from DHEA. Cutaneously produced steroids are an important source of sex steroids for postmenopausal women. Sebaceous glands produce sebum, a lipid-rich substance composed of triglycerides, wax esters, squalene, cholesterol, and free fatty acids. Sebum secretion is primarily regulated by dihydrotestosterone, acting as a stimulant; estrogens, glucocorticoids, growth hormone, or insulin-like growth factor-1 modulate sebaceous gland function in different ways. Sebum production is low in infancy, increases during puberty due to rising androgen levels, and decreases with age. DHEA can stimulate its production and therefore cause anti-aging effects.

Sebocytes express little cytochrome P450c17 (steroid 17-alpha-hydroxylase/17,20-lyase), which is necessary for the synthesis of DHEA and androstenedione from cholesterol; they selectively use DHEA to produce active androgens. Sebocytes are the only cells that express all three types of 5α-reductases in the skin. The type 1 isotype of 5α-reductase converts testosterone to the highly potent androgen, DHT. The type 2 isotype is active in beard hair follicles. The type 3 isotype, sensitive to finasteride, a 5α-reductase inhibitor, is strongly expressed in sebaceous gland cells. The sebaceous glands also express aromatases that convert testosterone and androstenedione into estrogens [23].

Regarding DHEA metabolism, it is important to note that 3β-HSD activity decreases with age, while 17β-HSD activity remains unchanged [23]. The activity of this enzyme determines androgen synthesis, since according to histochemical studies, skin areas prone to acne exhibit higher 3β-HSD activity than areas without acne, despite the comparable concentrations of sebaceous glands in these areas [23]. The age-related decline in 3β-HSD activity may be the reason for the decrease in acne incidence with age.

The localization of enzymes is presented in Table 1.

The expression and activity of enzymes play an important role in DHEA metabolism in the skin. However, the expression of sex hormone receptors plays an equally important role. Undoubtedly, DHEA metabolism in the skin varies depending on sex and age. Therefore, future studies need to evaluate all these factors, including the SNPs of steroidogenic

enzymes, and to narrow the inclusion criteria in clinical trials in such a way as to understand the effects of DHEA in a homogeneous sample and obtain clear results.

Table 1. Distribution of Steroidogenic Enzymes and Receptors in Human Skin Layers and Cell Types.

Layer	Cell Type	Expression of Enzymes	Expression of Receptors	Refs.
Epidermis	Keratinocytes	17β-HSD, 3β-HSD1, 5α-reductase 1,2; STS; StAR	AR, ERβ, ERα, GPER; GR, MR	[41–43]
	Melanocytes	17β-HSD, 3β-HSD1, 5α-reductase 1,2	AR, ERβ, ERα, GPER	[44–46]
Dermis	Fibroblasts	17β-HSD, 3β-HSD1, 5α-reductase 1,2	AR, ERβ, ERα, GPER, GR	[46,47]
Sebaceous glands	Sebocytes	17β-HSD (isotypes 3 and 5), 3β-HSD1, 5α-reductase (1,2,3); aromatase; STS; StAR	AR, ERβ, ERα, MR	[48]
Sweat glands	Epithelial cells (eccrine and apocrine)	17β-HSD, 3β-HSD; aromatase; 5α-reductase	AR, ERβ, ERα, GPER	[44,49]
Endothelium	Endothelial cells	5α-reductase type 5, 17β-HSD, 3β-HSD, 5α-reductase 1,2; StAR	AR, ERβ; DHEA-specific GPCR (Gαi)	[45,47,50]

4.2. DHEA Receptors in the Skin

All the skin structures—keratinocytes in the epidermis, fibroblasts in the dermis, and sebocytes in sebaceous glands—express nuclear and membrane receptors capable of binding steroid, thyroid, and peptide hormones [51].

To date, specific DHEA receptors have not been identified, including in the skin [8,28]. It is generally accepted that DHEA exerts effects through its metabolites—androgens and estrogens, which, in turn, bind to their respective receptors, mediating genomic and non-genomic effects. The only specific receptor for DHEA may be localized in the endothelium [52].

ER and AR are considered to be the final target receptors for DHEA action. DHEA does not bind to glucocorticoid or mineralocorticoid receptors [28,53]. In addition to these well-established targets, direct ligand binding to nuclear receptors PPAR, PXR, and CAR has been actively discussed in the last decade [53]. Recent studies have established the occurrence of cross-signaling between PXRs, CARs, and RXRs [54]. After binding with DHEA, CAR dimerizes with RXR and, thereby, may induce the effects of retinoic acid [53,55]. This hypothesis has been developing recently.

DHEA enhances the metabolic/mitochondrial function by inducing GLUT4 (Glucose Transporter Type 4) and mediates its anti-obesity and health-promoting effects in living organisms [56].

Specific receptors for DHEA have not yet been identified. The well-documented effects of DHEA are realized through its metabolites—estrogens and androgens. Estrogen receptors (ERα and ERβ) in dermal fibroblasts promote collagen synthesis and vascularization, while androgen receptors in sebocytes stimulate sebum production. The distribution and density of these receptors can vary depending on anatomical site, age, sex, and hormonal status [57].

ERs are present in almost all skin structures: keratinocytes, Langerhans cells, melanocytes, fibroblasts, sebaceous glands, hair follicles, endocrine glands, and blood

vessels. ER expression in the facial skin is higher than, for example, in the skin of the breasts or thighs. In the pilosebaceous unit, ERα are located separately from ERβ and androgen receptors [58].

The local use of estrogens for androgenetic alopecia has proven quite successful [59], as has the topical application of 5-alpha-reductase inhibitors in the treatment of acne [60]. This demonstrates the important physiological role not only of sex hormone receptors but also of steroidogenic enzymes in the skin.

4.3. Expression of Sex Hormone Receptors in the Skin

The skin contains the steroid hormone receptors ER, AR, MR, and GR. The expression of ERα, ERβ, and AR in the human skin decreases with age, with this decline being most pronounced in areas exposed to the sun (extrinsic aging). The highest level of ERβ is observed in young age (20–35 years), after which it significantly decreases, whereas AR levels decline gradually and slightly in both sexes, indicating that the level of ER decreases more strongly, while the level of AR remains unchanged [23].

While ERβ is present in virtually all skin cells, ERα is found only in melanocytes, sebaceous glands, and dermal fibroblasts. ERβ is the predominant receptor in adult human scalp skin and is strongly expressed in the stratum basale and stratum spinosum of the epidermis. Both ERα and ERβ are expressed in the sebaceous gland. ERβ is the main mediator of estrogen effects on the skin and hair. ERβ is also highly expressed in blood vessels and dermal fibroblasts (Table 1).

Sebocytes express the highest number of AR in the skin [49]. They also express the corticotropin-releasing hormone (CRH) receptor, melanocortin receptors (MC1-5R), and PPARs [61]. Only 1–2% of circulating testosterone is free, 32% is bound to albumin, and 66% is bound to sex hormone binding globulin (SHBG). Free and albumin-bound testosterone is bioavailable to tissues and acts through AR in the skin. The main source of testosterone in men aged 60–75 is adrenal DHEA, which contributes about 40% to the total pool of androgens [23].

GR and MR are widely expressed in the skin. Their activity is regulated by the enzyme 11-beta-hydroxy-steroid dehydrogenase type 2 (11β-HSD2), which inactivates cortisol and activates inactive cortisone in humans. Recent studies demonstrate that MR antagonists have anti-age effects and might improve skin elasticity in mice [62].

In conclusion, it should be noted that almost all types of receptors and all enzymes are present in keratinocytes. For example, according to the Human Protein Atlas, 60% of ERs are expressed in keratinocytes, with the remaining 40% in melanocytes, fibroblasts, smooth muscle cells, and pericytes. Keratinocyte cell models, such as the HaCat cell line, represent a standard cellular model for studying various pharmacological effects of anti-aging molecules and drug formulations in vitro [63].

4.4. Limitations and Future Prospects in DHEA Metabolism Studies

The difficulty in studying DHEA metabolism in the skin lies in the fact that it is extremely challenging to obtain biopsy material with separate layers and preserve its integrity. Since the skin consists of multiple layers, we cannot investigate each layer individually. Another problem is obtaining biopsy material from healthy volunteers. The punch biopsy technique is used for this purpose. As a rule, the procedure is minimally invasive. Skin samples from patients are collected by punch biopsy with a diameter of 6 mm in the suprascapular region on the right side and 3 cm above the upper corner of the scapula. Samples of unchanged skin of apparently healthy individuals are taken during scheduled plastic surgeries for figure correction [64]. Nevertheless, most studies

on DHEA metabolism in the skin and its skin permeation have been conducted on animal skin, particularly pig ear skin sections [65].

Investigations along this line require highly sensitive equipment, since the concentrations of DHEA metabolite hormones in the skin are extremely low, in the picomolar range, and vary depending on the skin layer. A recent German study investigated DHEA metabolism in different cell cultures. It was shown that HaCat keratinocytes synthesize the widest spectrum of steroids—A4, testosterone, DHT, and estradiol. In dermal fibroblast and preadipocyte cells, DHEA-S was converted only to DHEA and A4 during 72 h of incubation [66].

The effects of the intermediate DHEA metabolites androstenedione A4 and 5-androstenediol (5-AED) also raise many intriguing questions. Binding data showed that 5-AED is a weak competitor for cytosolic ER (IC50 range: 0.14–0.34 μM) [28]. These results suggest a direct estrogenic activity for 5-AED. The action of A4 on its own also needs further study, since there is evidence that up to 25% of women with a normal serum testosterone who had clinical features of androgen excess had an elevated level of serum A4 [67]. The steroids 5-AED and DHEA are considered to be immunomodulators and radioprotectors; their effect on the skin immune system needs further research.

5. Anti-Age Hormonal Therapy for Skin

Anti-age therapy for skin is primarily aimed at increasing the production of lipids and collagen. Lipids in the composition of sebum are synthesized exclusively in the sebaceous glands. Sebocytes are responsible for this; as they mature, they fill with lipids, disintegrate, and release sebum onto the skin surface. This process is directly regulated by AR. Collagen (the main structural protein of the dermis) is produced by fibroblasts, the main cells of the connective tissue located in the dermis. It is fibroblasts that synthesize and secrete the extracellular matrix, including collagen types I and III, elastin, and other components responsible for skin firmness and strength; their regulation is carried out predominantly by ERs. Thus, ARs are primarily responsible for lipids, while ERs are responsible for collagen synthesis.

In women, DHEA, as well as estrogens and androgens, decline faster than in men. Therefore, much more research is devoted to HRT in women than in men.

5.1. Systemic HRT

It is well known that estrogens significantly influence skin physiology and aging. Postmenopausal women with estrogen insufficiency experience increased oxidative stress in the skin, atrophic skin changes, accelerated skin aging, and impaired wound healing. DHEA-S and DHEA have a vital role in skin physiology and diseases since they are precursors of E2 in elderly women, but they are still not officially approved for anti-aging therapy. HRT based on estrogens or a combination of estrogens with progesterone, where progesterone acts as an endometrial protector against the mitogenic action of estrogens, has been widely developed [68].

Not only do esthetic problems reduce the quality of active longevity, but also a number of diseases manifest themselves with the onset of menopause. Studies have shown that the strongest association with the postmenopausal period occurs in the case of alopecia, especially frontal fibrosing alopecia (FFA) and female androgenetic alopecia: most cases manifested themselves after menopause, with early or surgical menopause increasing the risk. Psoriasis and melasma also often worsen after menopause, although objective assessments are limited, and the response to hormone therapy is unpredictable. HRT use was often associated with an increased risk of FFA and rosacea [69].

Despite decades of research, clinical guidelines do not support the use of HRT solely for the treatment of estrogen-deficient skin due to the lack of robust clinical trials dedicated to specific skin therapy [70].

Systemic menopausal HRT is the first-line and most effective treatment for menopausal symptoms. The most important limitation of HRT is that it cannot be applied to everyone, and the benefit-risk profile must be considered. The goal of such therapy is systemic action. It is associated with risks, especially when taking medications orally.

The key approach to minimizing risks when prescribing HRT to women, especially those with systemic comorbidities, is the choice of the transdermal route of administration (gels, patches), which reduces the risk of thrombosis, since hormones are absorbed directly into the bloodstream, bypassing the liver and not causing excessive production of clotting factors. In addition, the number of gastrointestinal diseases increases with age, and for patients with inflammatory bowel diseases, the transdermal route becomes the optimal way to bypass problems with drug absorption in the gastrointestinal tract, guaranteeing stable hormone delivery [71]. However, regarding the skin, clinical outcomes have not correlated with histological findings, and most controlled trials have failed to demonstrate reproducible improvements in visible signs of aging with estrogen therapy [72]. It is difficult to speak about the benefits of systemic (oral) DHEA therapy, which compensates for the deficiency of both sex hormones, estrogens and androgens, but a number of studies indicate that DHEA 50 mg after four months increases sex hormone concentrations when administered orally and may be an alternative to estrogen HRT, especially in adrenal insufficiency [73]. In the first ever double-blind, placebo controlled clinical study, oral administration of DHEA at 50 mg/day over a year in 280 healthy women and men aged 60–79 years has been documented to lead to a significant attenuation of the bone degradation activity, an increase in libido parameters and improved skin status, particularly in women, in terms of hydration, epidermal thickness, sebum production and pigmentation [10]. Systematic reviews on HRT using DHEA are scarce; much more is known about local therapy with either estrogens or androgens.

5.2. Topical Estrogen Therapy

Estrogen decline accelerates many skin changes often characterized as exogenous aging, including dryness, atrophy, wrinkle formation, and impaired wound healing [74].

Among topical estrogens, estradiol (E2) and estriol (E3) are the most studied for their effects on skin aging. E2, as the predominant premenopausal estrogen, exhibits the highest potency, while E3, a weaker metabolite, is considered to have a more favorable safety profile due to its lower systemic activity and shorter half-life [75].

Most prescription compounded anti-aging creams contain E3 0.3% and demonstrate collagen stimulation, epidermal thickening, and fibroblast activation, supported by findings of increased procollagen and transforming growth factor-β1 signaling with suppression of collagen-degrading enzymes. Increases in elastin density and dermal vascularity have also been reported, though the results are inconsistent [72].

Recently, esthetic treatment considerations for the perimenopausal and menopausal patients were discussed in a roundtable. In addition to the prospects of using various geroprotective procedures in dermatology, the importance of hormonal balance for skin health was emphasized. It was summarized that topical estrogens directly address hormonal deficiency, while regenerative procedures complement hormone action by providing tissue remodeling and collagen stimulation. Future research may focus on randomized clinical trials in postmenopausal women to more accurately assess the efficacy of therapy in estrogen-deficient skin [76].

The role of topical estrogen therapy was analyzed in 23 clinical studies by Rzepecki A.K. et al. [77]. The studies differed in various parameters, such as study design, method of topical steroid application, concentration of estrogen in the product, etc. Based on this rather approximate but systematic analysis, as well as the analyses by Roster, 2026 [69], it

was summarized that the topical application of 0.01% estradiol or 0.3% estriol in the form of a cream to the face and neck produced the following anti-aging effects:

- Type I and III collagen significantly increased in the skin by the end of treatment.
- Epidermal thickness increased by 23% compared to the control group.
- Markers of skin aging (rete peg pattern, epidermal thinning) significantly improved/were reversed.
- Wound healing improved due to increased fibronectin in the wound area.
- Hyaluronic acid concentration significantly increased.
- Skin texture improved in the application area on the cheeks (measured using a digital microscope).

Despite the positive effects, neither estrogen nor testosterone is used as a local geroprotector for the skin. Their use was discontinued back in the 1950s, partly due to uncontrolled use. In one described case, a 93-year-old woman was diagnosed with breast cancer and endometrial hyperplasia, which was linked to the use of an ethinyl estradiol cream three times daily for 75 years [78].

Estradiol and testosterone exist in the form of medicinal products (gels, creams—Divigel, Estrogel, Androgel, Androfeme), approved for application to the skin, but with clear indications in the instructions, among which there is no indication as an anti-aging agent for skin aging or for wound healing.

Although there are no direct indications for treating menopausal skin aging, the use of extemporaneous and off-label topical estrogen formulations (0.3% estriol, 0.01% estradiol) has increased rapidly in recent years, despite limited clinical data; however, broader acceptance continues to be limited by safety concerns.

Limitations of local estrogen therapy include changes in the vascularization index (VMI), seborrhea, breast tenderness; transient increase in erythema/telangiectasia, increased blood prolactin levels, and rare side effects such as itching, facial redness, and increased pigmentation have been noted [77]. Nevertheless, dermatologists may prescribe such gels off-label for the treatment of facial skin aging. This is discussed in professional circles: some doctors consider it promising, while others caution against it due to the risks of systemic absorption and irritation [75,76].

Phytoestrogens, particularly genistein, are considered to be an alternative to topical estrogens. However, genistein has weak activity and is also not particularly effective (about 0.2% of the estrogenic effect of estradiol) when taken orally. When applied transdermally, it acts as an antioxidant. In other words, it is effective when the extrinsic pathway of premature aging, caused by aggressive environmental factors, is triggered, rather than the intrinsic aging pathway associated with the depletion of sex hormones [72].

5.3. Topical Androgen Therapy

Various gels (Androgel, Testogel) with different testosterone concentrations have been developed for transdermal testosterone application. These are applied to the skin of the upper arm, shoulder, or abdomen. Such formulations have a prolonged action, are well-absorbed, and cause a slight, gradual increase in blood testosterone concentration.

According to the Russian Association of Endocrinologists guidelines, a total testosterone level of 12.1 nmol/L is accepted as the threshold distinguishing the normal status from potential deficiency. When total testosterone is in the range of 8–12 nmol/L, SHBG should be measured to calculate free testosterone, whose lower normal limit is 243 pool/L. Screening and subsequent treatment are also recommended for men over 65 years [79].

Currently, androgen therapy is not approved by the FDA (Food and Drug Administration) for treating sexual dysfunction in women. Since the testosterone level ratio in women versus men is 1:10, there is a high risk of supraphysiological doses in women.

Before prescribing it, the free androgen index (FAI) should be calculated using the formula: FAI = total testosterone/SHBG × 100. If the value is in the lowest quartile (<1%), a trial of testosterone may be considered [80].

A cream containing 1% testosterone is currently approved in only a few countries, for example, Australia, where the recommended dose is 0.5 g/day [81]. According to the instructions, the cream should be applied to the upper outer thigh or lower torso/buttock, avoiding the application to the upper body or arms. This precaution is necessary because the application to these areas could lead to undesirable lymphatic drainage of the drug to the mammary glands and also increase the risk of transfer to other people. The application of the preparation to the vulva or vaginally often causes irritation and uneven absorption [82].

A testosterone cream for women exists, but it is indicated for treating sexual dysfunction, not for skin conditions. However, the development of these formulations for women supports the role of DHEA as an androgen precursor in menopausal women.

Thus, topical skin therapy with androgens for dermatological issues is not yet approved. In this context, DHEA, as a precursor to testosterone, may be successful in treating hypogonadism and acne, as well as in cases of finasteride use in men (finasteride reduces scalp skin DHT levels by 60–70% even at a dose of 1 mg/day). The approval of testosterone for women holds considerable promise: clinical trials in women with low libido and depression have already commenced [83].

Transdermal testosterone application can influence all androgen-dependent processes in the skin and potentially alleviate skin dryness or pigmentation. However, the effects of topical testosterone application are yet to be studied in clinical research.

5.4. Topical DHEA Therapy: The Effects of DHEA on the Skin

Unlike transdermal formulations of testosterone and estrogens, clinical studies using transdermal DHEA are no thorough clinical studies have been virtually performed. Those that were conducted showed good results on aging skin; however, for unknown reasons, they were not developed further. The peak of publications occurred between 2000 and 2010; even L'Oréal conducted research, as did the research group of Baulieu [9,10]. During that same period, gels, patches, and sprays containing DHEA as an active ingredient were patented.

Currently, the investigations of DHEA as a neurosteroid for preventing and treating depression, cognitive decline, and neuroinflammation are being continued [7,8].

Nevertheless, a vast number of transdermal DHEA formulations are used off-label, especially in the USA. In 1994, DHEA was approved as a dietary supplement, but the quality of DHEA and the wide dosage range are not regulated at the governmental level [84].

The main effects of DHEA on the skin are presented in Table 2.

Table 2. The main effects of DHEA on the skin.

Skin Process	Target Cells	Molecular Mechanism	Key Results	Refs.
sebum production	sebocytes	stimulation of activity: the effect is completely blocked by a pure antiandrogen (flutamide), but is not blocked by an antiestrogen (EM-800, a prodrug of the antiestrogen acolbifene).	DHEA, by being locally converted into androgens (specifically into DHT), increases sebum production and may cause an increase in the size of the glands.	[85]

Table 2. *Cont.*

Skin Process	Target Cells	Molecular Mechanism	Key Results	Refs.
collagen synthesis	epidermis and dermis	dose-dependent increase in the expression of collagen-synthesizing genes in the skin	1% and 2% DHEA cream treatment twice daily for 13 weeks in postmenopausal women caused a dose-dependent increase in the expression of COL1, COL3, and COL5; secreted protein acidic and rich in cysteine (SPARC).	[86]
collagen synthesis	cultured human skin fibroblasts	regulation of production and degradation in the extracellular matrix	DHEA decreases the expression of collagen-metabolizing enzymes (collagenase mRNA decreased in response to DHEA by 40%, whereas stromelysin-1 mRNA increased up to 2.4-fold); increased collagen production α1(I) (procollagen mRNA increased 1.6-fold).	[87]
keratinocyte proliferation and differentiation	epidermis	DHEA stimulates epidermal renewal and remodeling.	1% and 2% DHEA cream treatment twice daily for 13 weeks in postmenopausal women caused an increase in the expression of serine (or cysteine) proteinase inhibitor, clade B, member 3 (SERPINB3), SERPINB4, calgranulin A, B, and decreased corneodesmosin, claudin 8, and keratin.	[86]
cell viability	human fibroblasts	extension of replicative lifespan; stimulation of proliferation.	DHEA suppresses p21 levels, which normally increase as these cells enter senescence; DHEA increases DNA synthesis in fibroblasts; it increases viability after UV irradiation up to 45% during 24 h of incubation.	[88,89]
viability and regeneration	cultured human skin fibroblasts (NCUF8)	stimulates the proliferation and viability of fibroblasts; prevents UV damage.	up to 45% increase in cell viability during 24 h of incubation with DHEA before and after UV exposure.	[90]

Table 2. *Cont.*

Skin Process	Target Cells	Molecular Mechanism	Key Results	Refs.
wound healing	keratinocytes, fibroblasts	DHEA stimulates cell migration and synthesis of extracellular matrix components.	DHEA, through conversion to estrogens, improves wound healing by enhancing fibroblast migration, suppressing excessive inflammation, and increasing DNA synthesis in fibroblasts to a greater extent than ERα and ERβ agonists	[91–94]
reduction in proteolysis	epidermis, dermis	prevents degradation of ECM proteins; prevents frequent tears in atrophic skin.	DHEA increases procollagen synthesis, inhibits MMP-1 (collagenase) activity, activates TIMP-1 (metalloproteinase inhibitor), reduces stromelysin-1 (MMP-3) production.	[95,96]
age-related atrophy	whole skin *	DHEA prevents skin atrophy	DHEA has strong anti-cortisol action, thus preventing catabolic corticosteroid changes	[97]
age-related atrophy	whole skin *	DHEA modulates SIRT1, Nrf2/ARE, NF-κB, ERβ, AR.	DHEA exerts anti-aging and antioxidant effects via SIRT1 and Nrf2 and reduces inflammation via NF-κB.	[98]
age-related atrophy	fibroblasts	TGFβ normalization (of excessive production)	DHEA inhibits the TGF-β1/Smad signaling pathway	[99]
age-related atrophy	epidermis and dermis	RXR dimerization	DHEA activates GPER1 (G protein-coupled estrogen receptor 1), CAR, and PPARα by indirect dephosphorylation; RXR and RAR-γ form heterodimers with them, leading to the well-known anti-aging effects of RA.	[53,100]
antioxidant defense	epidermis, dermis (keratinocytes, fibroblasts)	protects from oxidative damage	DHEA increases SOD, reduces ROS, increases protein expression of NADPH oxidase.	[101]
estrogen synthesis activation	keratinocytes, fibroblasts, adipocytes	DHEA increases aromatase activity, which converts testosterone to estradiol.	DHEA increases aromatase activity by acting directly on the classic estrogen response element.	[102]

Table 2. *Cont.*

Skin Process	Target Cells	Molecular Mechanism	Key Results	Refs.
age-related repair	keratinocytes, fibroblasts (primary cultures of human skin epidermal keratinocytes and dermal fibroblasts)	regulation of gene expression involved in repair and aging.	DHEA up-regulates the genes ANGPTL4, CXCL1, LMNB1, and TXNIP, which play key roles in angiogenesis, inflammation, nuclear structure organization, and cellular stress.	[94]
cell migration	keratinocytes, fibroblasts	stimulation of cell migration (key process for wound healing).	DHEA activates classical nuclear receptors (ERα and ERβ) and the membrane receptor GPER1; biphasic effect: stimulation of migration is observed both at early (4 h, non-genomic mechanisms) and late (24–48 h, genomic mechanisms) stages.	[93,94]
inflammation	macrophages (immune cells)	modulation of the inflammatory response: DHEA suppresses the production of pro-inflammatory cytokines by macrophages.	DHEA acts through its conversion to estrogens on MAP kinase and PI3 kinase signaling pathways, reducing excessive inflammation characteristic of chronic wounds and decreasing excessive TGFβ; reduces eosinophil and mast cell infiltration by decreasing the production of Th2-associated cytokines and chemokines.	[91,92,103, 104]
microcirculation	skin endothelium	DHEA promotes endothelial cell proliferation, migration, and angiogenesis.	DHEA activates specific receptors Galpha(i2) and Galpha(i3).	[52,105]

* The effects of DHEA assumed to occur in the whole body and particularly in the skin.

In addition to the ability of DHEA to restore hormonal homeostasis in the skin, it has a regenerative effect on fibroblasts, as demonstrated in cell cultures [89]. The mechanism of the stimulating action of DHEA on fibroblasts may be related to the specific suppression of p21 protein levels, which increase during cellular aging, indicating that it suppresses the signs of senescence, as shown in the Wi-38 lung fibroblast cell culture [88].

DHEA, at relatively high but physiologically achievable concentrations of around 10 μM, increases the collagen production and reduces the expression of collagen-metabolizing enzymes. In cultured human skin fibroblasts, the level of collagenase mRNA in response to treatment with 10 μM DHEA decreased by 40%, and the activity of the collagenase promoter decreased by 70%, while the mRNA level of stromelysin-1 increased up to 2.4 times compared to the control. The maximal activation of the gene encoding stromelysin-1 occurred at a DHEA concentration of 1 μM and was 4.5 times higher than in the control [87].

The regenerative effect of DHEA was demonstrated by Dr. Shin and co-authors. A 5% DHEA formulation was tested on 12 volunteers, both old and young men. The cream was applied three times a week for 4 weeks. A significant increase in the expression of procollagen α1(I) protein and its mRNA was noted in both aged and young skin. Topical DHEA application significantly reduced the basal expression of matrix metalloproteinase 1 (MMP-1) and increased the expression of the TIMP-1 protein (tissue inhibitor of matrix metalloproteinase 1) in aging skin [95]. Similar effects were observed in cultured human fibroblasts exposed to ultraviolet radiation. DHEA prevented UV-induced changes in MMP-1 and type I procollagen expression and inhibited UV-induced AP-1 binding activity in human dermal fibroblasts [95].

New data from recent years have shown that DHEA inhibits excessive TGF-β production, preventing accelerated keratinization [99]. Through TGF-β signaling in dermal fibroblasts, DHEA can locally increase skin thickness, while via AKT signaling, it may promote elastin synthesis. However, the molecular mechanisms by which DHEA acts on these pathways remain largely unexplored. DHEA also exhibits significant anti-inflammatory and antioxidant properties in the skin [102,103].

Thus, one can definitively speak of the cytoprotective, antioxidant, and regenerative effects of DHEA on the skin. Further research into the geroprotective effects of DHEA on the skin is required to provide molecular and epigenetic evidence at the level of senescence markers such as p16 and p21.

Future prospects are linked to identifying specific DHEA receptors in the skin, as well as receptors for its metabolites, 5-AED and A4. The anti-aging effect may be mediated by its metabolites and also by its potential ability to activate retinoic acid receptors (RARα, β) through dimerization with CAR, which is activated by DHEA [100].

6. Current DHEA Formulations

With the market release of DHEA as an over-the-counter supplement in 1994, promising research emerged, including randomized controlled trials and subsequent meta-analyses, investigating the potential benefits of DHEA for various conditions [106].

DHEA is widely used as an “anti-aging” hormone in the USA and Western Europe. The oral form of DHEA (25–50 mg/day) is sold in the USA as a dietary supplement, despite the fact that high doses may have androgenic effects, particularly acne and hirsutism. It slows down aging processes, improves metabolism in obesity, stimulates the immune system, and possesses anti-cancer properties. Consequently, an improvement in health-related quality of life is observed in the elderly, which is especially important for postmenopausal women, providing them with deficient estradiol that can be converted “intracrinally” into estradiol in target tissues outside the gonads.

Dietary supplements are minimally regulated by the FDA; these products exhibit highly variable quality, purity, and dosage. Intravaginal DHEA (Prasterone, 6.5 mg) has been approved for treating dyspareunia and vulvovaginal atrophy in postmenopausal women [28]. The approval of a topical gel indicates that for DHEA formulations, the route of administration is crucial, significantly affecting DHEA bioavailability and metabolism. Studies in rats have shown that DHEA bioavailability is much higher with topical application, almost 10 times greater: oral DHEA bioavailability is approximately 3%, while transdermal bioavailability reaches 30% [107].

Considering the receptor status, sex, lifestyle, and the activity of steroidogenic enzymes, the effectiveness of transdermal DHEA can be enhanced. To improve the efficacy and penetration of DHEA, research into novel transdermal DHEA formulations with various enhancers should be initiated. Based on the successful experience with transdermal estradiol (e.g., Divigel) and testosterone formulations, including gels (Androgel, Testim),

patches (Vivelle), and sprays (Evamist), which are applied to the skin for systemic effects, investigating similar formulations for DHEA—for both systemic action and local geroprotective effects on the skin—appears highly relevant.

For personalized and targeted action, the question of dosage is critical and complex. Dosages in transdermal sex steroid formulations vary significantly: for example, Divigel contains 1 mg of estradiol per 1 g of gel, Androgel contains 10 mg of testosterone per 1 g, Testim provides 50 mg of testosterone per 5 g, and Evamist spray delivers 1.53 mg of estradiol per actuation. For achieving geroprotective and wound-healing effects of DHEA on the skin, it is necessary to create micromolar local concentrations, meaning a sufficiently high percentage in the formulation, of around 1%, which is equivalent to 5 to 10 mg per 1 mL [108].

A limitation in developing the formulations of DHEA is its poor water solubility: DHEA is a fat-soluble compound with very low aqueous solubility. For a patch or gel to work, a high concentration of the substance must be created within it to facilitate diffusion into the skin. The partition coefficient of the substance between the vehicle and the skin is crucial for transdermal delivery. Based on its molecular structure, DHEA presents more challenges in this regard compared to estradiol.

This problem can potentially be overcome by modifying the molecular structure of DHEA itself—for example, using ester derivatives [90]—and by employing specific excipients, such as complexes with alpha-cyclodextrins, phosphatidylcholine, and others that improve DHEA solubility and skin penetration. Some of these have already been investigated, including Transcutol, peppermint essential oil, Lauroglycol, Brij 58, and propylene glycol [109,110], Span®, Carbopol®, and chitosan [111]. Penetration enhancers being explored include Azone® (laurocapram), oleic acid, and terpenes (menthol, cineole, limonene) [112].

Promising directions for topical steroid application involve modern delivery systems based on carbopol or Transcutan. Carriers such as cyclodextrin (improving solubility), phosphatidylcholine (enabling deep skin penetration), and chitosan (offering biocompatibility and prolonged release) are already being actively researched and utilized. Linoleic acid and oleic acid could be used as enhancers of both lipid synthesis and penetration. Encapsulation strategies such as lipid nanoparticles and polymeric nanocarriers can enhance stability, control release, and improve penetration through the stratum corneum, while reducing irritancy by allowing more gradual delivery to target sites in the epidermis and dermis [113].

Optimizing the transdermal delivery of DHEA will improve its bioavailability and significantly enhance its anti-aging efficacy.

7. Limitations

To date, there have been only a few clinical studies on the topical application of DHEA as an anti-aging cream that, however, have shown good results. The topical application of DHEA induces the expression of the transforming growth factor-β1 and connective tissue growth factor mRNA in cultured fibroblasts and aged skin, stimulates procollagen production, and reduces metalloproteinase activity [114]. Only a limited number of DHEA studies have been conducted in postmenopausal women, and data on its effects on the skin in men are completely lacking.

As these studies were conducted in the 2000s, the outcome measures were too common, and analytical and molecular-genetic methods were not sufficiently implemented. The fact that androstenedione and 5-androstenediol, being the main metabolites isolated from skin incubates, may exert immunomodulatory anti-aging effects on the skin without being

converted into androgens or estrogens has not been investigated at all. Their action on the skin remains incompletely understood.

The composition of DHEA formulations used in clinical studies has varied, differing in both the percentage concentration of the active pharmaceutical ingredient and the excipients used. Clinical studies on the topical application of DHEA in men are lacking. Furthermore, it remains unclear which factors influence the activity of enzymes involved in DHEA biosynthesis and metabolism, as well as the frequency of gene polymorphisms of these enzymes in men and women. Inducers and inhibitors of steroidogenic enzymes need to be clearly identified.

Finally, an important limitation is the lack of comprehensive clinical studies on dermal pharmacokinetics, the results of which would clearly demonstrate whether DHEA exerts systemic effects following transdermal application. The extent to which DHEA can be introduced into dermatological practice depends on the results of dermal pharmacokinetic studies, since DHEA is classified as a hormonally active substance.

8. Future Prospects

DHEA as a geroprotector has long attracted attention due to its intracrine action, the ability to replenish the deficiency of sex hormones up to homeostatic levels, and the fact that it is not considered a hormone per se, since it lacks its own precisely identified receptors.

Modern dermatology and esthetic medicine are moving towards preventive biostimulation and regeneration (a trend for 2026). Therefore, the improvement of transdermal delivery systems for the endogenous steroid DHEA, with its high lipophilicity, may find a translational intersection: the therapy of age-related tissue changes through endogenous mechanisms.

A promising approach in anti-aging skin therapy, in our view, is the search for common molecular targets of DHEA and retinoic acid (RA). Just as substances and formulations based on RA are being improved, the same could be performed for DHEA. Retinoids remain the gold standard in topical anti-aging cosmetics. RA is the most biologically active form, binding directly to nuclear retinoic acid receptors (RARs) to regulate gene transcription involved in extracellular matrix remodeling. However, the potent clinical efficacy of RA is often offset by adverse effects such as erythema, dryness, and peeling, prompting cosmetic formulations to rely on precursors—including retinol, retinaldehyde, and retinyl esters—which must undergo enzymatic conversion within the skin.

The benefits of optimized delivery have been confirmed for the anti-age molecule retinol. Emerging research has also begun to evaluate next-generation retinoids, including retinyl retinoate and hydroxypinacolone retinoate (also marketed as granactive retinoid) [115].

DHEA and RA may act synergistically. DHEA and its metabolites activate CARβ; CARβ, in turn, forms a complex with the retinoid X receptor (RXR). It is this complex (CARβ-RXR) that binds to the retinoic acid-responsive element in DNA, mimicking the effect of RA. DHEA can trigger the transcription of genes typically activated by retinoic acid, but through a "proxy"—the CARβ receptor.

Furthermore, DHEA suppresses the activity of enzymes critical for retinol metabolism, such as beta-carotene monooxygenase and lecithin-retinol acyltransferase. This means that DHEA can influence how much retinol is converted into active retinoic acid, which then activates RAR [63,116].

The advancement of pharmacogenomics, genomic profiling, and microbiome mapping allows for the identification of predisposition to conditions such as hyperpigmentation, premature aging, or impaired barrier function. This enables the selection of active ingredients that specifically target the skin microbiome. In this context, it appears important to monitor the polymorphism and expression of genes in the skin responsible for the conversion of

DHEA into sex hormones within the skin –3β-HSD and aromatase. A new approach could involve the use of inducers and inhibitors of these enzymes. Good results are already being shown by 5-alpha reductase inhibitors against acne [117,118] and SOD in the treatment of vitiligo [119–121].

Monitoring senescence markers and senescent cells could be one of the outcome measures when testing DHEA [122]. To date, there is evidence of Senescence-Associated Secretory Phenotype (SASP) marker suppression by DHEA in nerve cells [8], but no such data are available for the skin. The standardization of clinical studies with DHEA could also reduce the risk of misleading claims that undermine confidence in the prospects of using this steroid in general [115].

First, it is necessary to investigate the dermal pharmacokinetics and dosing regimen of DHEA in order to determine the dose at which DHEA exerts no systemic effects while still producing an anti-aging effect. To demonstrate the efficacy of DHEA as a topical anti-aging agent in both men and women, a randomized, double-blind, placebo-controlled trial of at least six months' duration is required. It is essential to measure not only DHEA and its sulfate form but also its metabolites (5-AED, A4, E2, T) in both skin and serum.

Inclusion criteria: Men aged 50–70 years with late-onset hypogonadism and women aged 40–55 years, with skin phototypes II–IV and clinical signs of photoaging (wrinkles, dryness, thinning).

Exclusion criteria: History of hormone-dependent tumors (breast cancer, prostate cancer), acne or hyperandrogenism, pregnancy or lactation, as well as use of systemic or topical hormone replacement therapy within 6 months prior to the study.

Efficacy should be assessed using clinical scales (Glogau wrinkle scale, elasticity, and hydration), biochemical markers (COL1A1, MMP-1, ELN), and pharmacogenetic profiling (STS, SULT2A1, CYP19, 3β-HSD, 17β-HSD, aromatase).

In conclusion, the use of DHEA in men becomes particularly relevant in several clinical situations: during finasteride therapy, in cases of premature age-related testosterone decline, and in androgenetic alopecia, since DHEA is capable of locally and gently compensating for androgen deficiency in the skin without sharp systemic hormonal fluctuations.

9. Conclusions

With age, the absorptive function of the gastrointestinal tract changes, prompting modern pharmaceutics to focus on creating more convenient dosage forms for the elderly. The absorptive function of the skin also declines with age. It is important to note that the activity of steroidogenic enzymes and sex hormone receptors decreases as well. Therefore, it is advisable to study DHEA in individuals aged 40–55, when these functions have not yet sharply declined but are at a relatively stable plateau phase.

Research on the effects of DHEA on the skin has at least four promising directions: the creation of esters and conjugates to increase lipophilicity and provide prolonged action; the development of modern formulations with enhancers and through nanoencapsulation; the use of combinations with retinol to reduce the concentration of each active molecule; and the designing of combinations with inducers and inhibitors of biosynthesis and enzyme activity. The pharmacogenetic typing of patients before the prescription of DHEA—to assess the expression of sex hormone receptors and steroidogenic enzymes (including determining the levels of the metabolites 5-AED and A4)— would also expand the possibilities for the topical application of DHEA not only as a geroprotective agent but also to combat skin problems caused by hypo- or hyperproduction of sex hormones.

AI-based diagnostic tools, accessible via mobile applications, connected devices, or clinical imaging systems, can now assess wrinkle depth, pigmentation patterns, hydration levels, and pore size in real time. Gene expression analysis in the skin using tape stripping

will help personalize and improve the anti-aging effects of DHEA. This modern, minimally invasive, rapid method will allow identification of DHEA's targets and dose optimization. These tools will facilitate the implementation of personalized DHEA application regimens, opening unprecedented opportunities for customization.

We hypothesize that DHEA esters and conjugates with amino acid residues could significantly increase DHEA lipophilicity, enhance skin penetration, and ensure a prolonged effect. Testosterone propionate and, in particular, decanoate are significantly more lipophilic than testosterone itself, which allows for a prolonged release profile. Consequently, these esters exhibit a markedly extended duration of action compared to non-esterified testosterone. The same should apply to DHEA esters. Using DHEA in combination with retinol could also allow for a reduction in the concentration of the active pharmaceutical ingredient in the final formulation, because they act synergistically.

Author Contributions: Conceptualization, T.A.F. and N.L.S.; formal analysis, T.A.F. and N.L.S.; and writing—original draft preparation, T.A.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the state assignment of the Ministry of Health of the Russian Federation No. 124020900031-0.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study.

Acknowledgments: We thank the BioRender team for the free version of the web resource.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. ClinicalTrials.gov. Effect of DHEA on Skin Aging in Postmenopausal Women. National Library of Medicine (US). 2005. Available online: https://clinicaltrials.gov/study/NCT00248989 (accessed on 14 March 2026).
2. He, S.; Lu, K.; Zhang, L.; Cao, H.; Tang, X.; Zhang, X. Impact of DHEA supplementation on testosterone and estradiol levels in postmenopausal women: A meta-analysis of randomized controlled trials assessing dose and duration effects. *Diabetol. Metab. Syndr.* **2025**, *17*, 258. [CrossRef]
3. Li, Y.; Ren, J.; Li, N.; Liu, J.; Tan, S.C.; Low, T.Y.; Ma, Z. A dose-response and meta-analysis of dehydroepiandrosterone (DHEA) supplementation on testosterone levels: Perinatal prediction of randomized clinical trials. *Exp. Gerontol.* **2020**, *141*, 111110. [CrossRef] [PubMed]
4. Zhu, Y.; Qiu, L.; Jiang, F.; Găman, M.A.; Abudoraehem, O.S.; Okunade, K.S.; Zhang, M. The effect of dehydroepiandrosterone (DHEA) supplementation on estradiol levels in women: A dose-response and meta-analysis of randomized clinical trials. *Steroids* **2021**, *173*, 108889. [CrossRef] [PubMed]
5. Stomati, M.; Monteleone, P.; Casarosa, E.; Quirici, B.; Puccetti, S.; Bernardi, F.; Genazzani, A.D.; Rovati, L.; Luisi, M.; Genazzani, A.R. Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. *Gynecol. Endocrinol.* **2000**, *14*, 342–363. [CrossRef] [PubMed]
6. Yuan, W.S.; Abu, M.A.; Ahmad, M.F.; Elias, M.H.; Abdul Karim, A.K. Effects of Dehydroepiandrosterone (DHEA) Supplementation on Ovarian Cumulus Cells following In Vitro Fertilization (IVF)/Intra-Cytoplasmic Sperm Injection (ICSI) Treatment—A Systematic Review. *Life* **2023**, *13*, 1237. [CrossRef] [PubMed]
7. Fedotcheva, T.A.; Shimanovsky, N.L. Current State of the Neurotrophin-Based Pharmaceutics in the Treatment of Neurodegenerative Diseases and Neuroinflammation. *Med. Sci.* **2025**, *14*, 15. [CrossRef]
8. Fedotcheva, T.A.; Shimanovsky, N.L. Neurosteroids Progesterone and Dehydroepiandrosterone: Molecular Mechanisms of Action in Neuroprotection and Neuroinflammation. *Pharmaceuticals* **2025**, *18*, 945. [CrossRef]
9. Nouveau, S.; Bastien, P.; Baldo, F.; de Lacharriere, O. Effects of topical DHEA on aging skin: A pilot study. *Maturitas* **2008**, *59*, 174–181. [CrossRef]
10. Baulieu, E.E.; Thomas, G.; Legrain, S.; Lahlou, N.; Roger, M.; Debuire, B.; Faucounau, V.; Girard, L.; Hervy, M.P.; Latour, F.; et al. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: Contribution of the DHEAge Study to a sociobiomedical issue. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 4279–4284. [CrossRef]

11. Badihi, A.; Debotton, N.; Frušić-Zlotkin, M.; Soroka, Y.; Neuman, R.; Benita, S. Enhanced cutaneous bioavailability of dehydroepiandrosterone mediated by nano-encapsulation. *J. Control. Release* **2014**, *189*, 65–71. [CrossRef]
12. Ceschel, G.; Bergamante, V.; Maffei, P.; Borgia, S.L.; Calabrese, V.; Biserni, S.; Ronchi, C. Solubility and Transdermal Permeation Properties of a Dehydroepiandrosterone Cyclodextrin Complex from Hydrophilic and Lipophilic Vehicles. *Drug Deliv.* **2005**, *12*, 275–280. [CrossRef]
13. Rozhivanov, P.V.; Vaks, V.V. Dehydroepiandrosterone: Physiological role and possibilities of use as a drug. *Probl. Endocrinol.* **2005**, *51*, 46–51. (In Russian)
14. Schwartz, A.G. Dehydroepiandrosterone, Cancer, and Aging. *Aging Dis.* **2022**, *13*, 423–432. [CrossRef] [PubMed]
15. Takeshita, R.S.C.; Nguyen, A.T.; Auger, A.P.; Chung, W.C.J. Cortisol, DHEAS, and the cortisol/DHEAS ratio as predictors of epigenetic age acceleration. *Biogerontology* **2025**, *26*, 164. [CrossRef] [PubMed]
16. Pignatti, E.; Altinkilic, E.M.; Bräutigam, K.; Grössl, M.; Perren, A.; Zavolan, M.; Flück, C.E. Cholesterol Deprivation Drives DHEA Biosynthesis in Human Adrenals. *Endocrinology* **2022**, *163*, bqac076. [CrossRef]
17. Nasu, M.; Abe, Y.; Matsushima, A.; Yamanaka, M.; Kozuki, N.; Ueda, S. Deficient maternal behavior in multiparous Pou3f2⊿ mice is associated with an impaired exploratory activity. *Behav. Brain Res.* **2022**, *427*, 113846. [CrossRef]
18. Im, S.C.; Peng, H.M.; Waskell, L.; Auchus, R.J. Similar Rates of Second Electron Transfer and Single-Turnover Dehydroepiandrosterone Formation for Oxyferrous Human Cytochrome P450 17A1 (Steroid 17-Hydroxylase/17,20-lyase)-17-hydroxypregnenolone Complex with Either Human Cytochrome P450-Oxidoreductase or Human Cytochrome b5. *Biochemistry* **2025**, *64*, 2306–2317. [CrossRef] [PubMed]
19. Ilhan, R.; Üner, G.; Yilmaz, S.; Sahar, E.A.; Cayli, S.; Erzurumlu, Y.; Gozen, O.; Kirmizibayrak, P.B. Novel regulation mechanism of adrenal cortisol and DHEA biosynthesis via the endogen ERAD inhibitor small VCP-interacting protein. *Sci. Rep.* **2022**, *12*, 869. [CrossRef]
20. Ana-Elena, M.; Bohiltea, L.-C.; Gheorghe, P.L.; Nicolae, S. Development and Clinical Significance of the Human Fetal Adrenal Gland as a Key Component of the Feto-Placental System: A Systematic Review. *Reprod. Med.* **2025**, *6*, 31. [CrossRef]
21. Gupta, A.; Saraf, S.; Kaur, C.D.; Saraf, S. The Potentials of Dehydroepiandrosterone (DHEA) in Skin ageing process. *Res. J. Top. Cosmet. Sci.* **2013**, *4*, 29–35. Available online: https://rjtcsonline.com/HTML_Papers/Research%20Journal%20of%20Topical%20and%20Cosmetic%20Sciences__PID__2013-4-2-1.html (accessed on 14 April 2026).
22. Samaras, N.; Papadopoulou, M.A.; Samaras, D.; Ongaro, F. Off-label use of hormones as an antiaging strategy: A review. *Clin. Interv. Aging* **2014**, *9*, 1175–1186. [CrossRef] [PubMed]
23. Farage, M.A.; Miller, K.W.; Zouboulis, C.C.; Piérard, G.E.; Maibach, H.I. Gender Differences in Skin Aging and the Changing Profile of the Sex Hormones with Age. *J. Steroids Horm. Sci.* **2012**, *3*, 109. [CrossRef]
24. Powrie, Y.S.L.; Smith, C. Central intracrine DHEA synthesis in ageing-related neuroinflammation and neurodegeneration: Therapeutic potential? *J. Neuroinflammation* **2018**, *15*, 289. [CrossRef]
25. Frye, R.F.; Kroboth, P.D.; Kroboth, F.J.; Stone, R.A.; Folan, M.; Salek, F.S.; Pollock, B.G.; Linares, A.M.; Hakala, C. Sex differences in the pharmacokinetics of dehydroepiandrosterone (DHEA) after single- and multiple-dose administration in healthy older adults. *J. Clin. Pharmacol.* **2000**, *40*, 596–605. [CrossRef]
26. Iliev, D.I.; Braun, R.; Sánchez-Guijo, A.; Hartmann, M.; Wudy, S.A.; Heckmann, D.; Bruchelt, G.; Rösner, A.; Grosser, G.; Geyer, J.; et al. Very High Dehydroepiandrosterone Sulfate (DHEAS) in Serum of an Overweight Female Adolescent Without a Tumor. *Front. Endocrinol.* **2020**, *11*, 240. [CrossRef]
27. Sudman, M.; Stöger, R.; Bentley, G.R.; Melamed, P. Association of childhood dehydroepiandrosterone sulfate concentration, pubertal development, and DNA methylation at puberty-related genes. *Eur. J. Endocrinol.* **2024**, *191*, 623–635. [CrossRef]
28. Fedotcheva, T.A.; Uspenskaya, M.E.; Ulchenko, D.N.; Shimanovsky, N.L. Dehydroepiandrosterone and Its Metabolite 5-Androstenediol: New Therapeutic Targets and Possibilities for Clinical Application. *Pharmaceuticals* **2024**, *17*, 1186. [CrossRef]
29. Sturges, C.I.; Jain, S.; Velasquez, M.; Gedamu, H.; Komarovsky, J.; McDonald, J.; Harris-Tryon, T. Cutaneous Hormone Sampling and Analysis for Dermatologic Research. *J. Investig. Dermatol.* **2025**, *145*, 1850–1857. [CrossRef]
30. Luu-The, V.; Ferraris, C.; Duche, D.; Bélanger, P.; Leclaire, J.; Labrie, F. Steroid metabolism and profile of steroidogenic gene expression in Episkin: High similarity with human epidermis. *J. Steroid Biochem. Mol. Biol.* **2007**, *107*, 30–36. [CrossRef] [PubMed]
31. Bocheva, G.; Slominski, R.M.; Slominski, A.T. Neuroendocrine Aspects of Skin Aging. *Int. J. Mol. Sci.* **2019**, *20*, 2798. [CrossRef]
32. Baek, H.S.; Kwon, T.U.; Shin, S.; Kwon, Y.J.; Chun, Y.J. Steroid sulfatase deficiency causes cellular senescence and abnormal differentiation by inducing Yippee-like 3 expression in human keratinocytes. *Sci. Rep.* **2021**, *11*, 20867. [CrossRef]
33. Kwon, T.-U.; Kwon, Y.-J.; Park, H.; Kang, Y.-J.; Chun, Y.-J. Dysregulation of STS in keratinocytes promotes calcium signaling and differentiation. *Sci. Rep.* **2025**, *15*, 662. [CrossRef]
34. Ogawa, M.; Isobe, Y.; Uchino, H.; Hirayama, M.; Kato, T.; Negishi, K.; Arita, M. The Microbiome Modulates Corneal Wound Healing via the Induction of Cholesterol Sulfotransferase Pathway. *FASEB J.* **2026**, *40*, e71429. [CrossRef]

35. Kurogi, K.; Cao, Y.; Segawa, K.; Sakakibara, Y.; Suiko, M.; Uetrecht, J.; Liu, M.C. Sulfation of 12-hydroxy-nevirapine by human SULTs and the effects of genetic polymorphisms of SULT1A1 and SULT2A1. *Biochem. Pharmacol.* **2022**, *204*, 115243. [CrossRef] [PubMed]
36. James, M.O.; Ambadapadi, S. Interactions of cytosolic sulfotransferases with xenobiotics. *Drug Metab. Rev.* **2013**, *45*, 401–414. [CrossRef]
37. Konjevod, M.; Balic, N.; Tudor, L.; Uzun, S.; Nikolac Perkovic, M.; Vuic, B.; Milos, T.; Nedic Erjavec, G.; Mimica, N.; Pivac, N.; et al. Lower plasma DHEAS and BDNF levels as indicators of cognitive decline. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2026**, *144*, 111605. [CrossRef]
38. Chakraborty, J.; Thomson, J.; MacSween, M.; Muir, A.; Calman, K.; Grant, J.; Milne, J. The In Vitro Metabolism of 7α-3H dehydroepiandrosterone by Human Skin. *Br. J. Dermatol.* **1970**, *83*, 477–482. [CrossRef] [PubMed]
39. Campbell, A.N.; Choi, W.J.; Chi, E.S.; Orun, A.R.; Poland, J.C.; Stivison, E.A.; Kubina, J.N.; Hudson, K.L.; Loi, M.N.C.; Bhatia, J.N.; et al. Steroidogenic Factor-1 form and function: From phospholipids to physiology. *Adv. Biol. Regul.* **2024**, *91*, 100991. [CrossRef]
40. Sasaki, L.; Hamada, Y.; Yarimizu, D.; Suzuki, T.; Nakamura, H.; Shimada, A.; Pham, K.T.N.; Shao, X.; Yamamura, K.; Inatomi, T.; et al. Intracrine activity involving NAD-dependent circadian steroidogenic activity governs age-associated meibomian gland dysfunction. *Nat. Aging* **2022**, *2*, 105–114. [CrossRef]
41. Thiboutot, D.; Knaggs, H.; Gilliland, K.; Lin, G. Activity of 5-alpha-reductase and 17-beta-hydroxysteroid dehydrogenase in the infrainfundibulum of subjects with and without acne vulgaris. *Dermatology* **1998**, *196*, 38–42. [CrossRef] [PubMed]
42. Peržeľová, V.; Sabol, F.; Vasilenko, T.; Novotný, M.; Kováč, I.; Slezák, M.; Ďurkáč, J.; Hollý, M.; Pilátová, M.; Szabo, P.; et al. Pharmacological activation of estrogen receptors-α and -β differentially modulates keratinocyte differentiation with functional impact on wound healing. *Int. J. Mol. Med.* **2016**, *37*, 21–28. [CrossRef]
43. Amuzescu, A.; Tampa, M.; Matei, C.; Georgescu, S.R. Adult Female Acne: Recent Advances in Pathophysiology and Therapeutic Approaches. *Cosmetics* **2024**, *11*, 74. [CrossRef]
44. Spałkowska, M.; Dyduch, G.; Broniatowska, E.; Damiani, G.; Wojas-Pelc, A. Molecular Proof of a Clinical Concept: Expression of Estrogen Alpha-, Beta-Receptors and G Protein-Coupled Estrogen Receptor 1 (GPER) in Histologically Assessed Common Nevi, Dysplastic Nevi and Melanomas. *Medicina* **2021**, *57*, 1228. [CrossRef] [PubMed]
45. Chen, W.; Zouboulis, C.C.; Fritsch, M.; Blume-Peytavi, U.; Kodelja, V.; Goerdt, S.; Luu-The, V.; Orfanos, C.E. Evidence of heterogeneity and quantitative differences of the type 1 5alpha-reductase expression in cultured human skin cells—Evidence of its presence in melanocytes. *J. Investig. Dermatol.* **1998**, *110*, 84–89. [CrossRef] [PubMed]
46. Tang, J.; Chen, P.; Huang, C.; Wang, W.; Wang, B.; Shi, W.; Tang, Y.; Deng, Z.; Zhang, Y.; Li, J.; et al. 17β-Estradiol promotes LL37-induced rosacea-like skin inflammation via G protein-coupled estrogen receptor 30. *J. Dermatol. Sci.* **2025**, *119*, 101–111. [CrossRef]
47. Slominski, A.; Zbytek, B.; Nikolakis, G.; Manna, P.R.; Skobowiat, C.; Zmijewski, M.; Li, W.; Janjetovic, Z.; Postlethwaite, A.; Zouboulis, C.C.; et al. Steroidogenesis in the skin: Implications for local immune functions. *J. Steroid Biochem. Mol. Biol.* **2013**, *137*, 107–123. [CrossRef]
48. Zouboulis, C.C.; Coenye, T.; He, L.; Kabashima, K.; Kobayashi, T.; Niemann, C.; Nomura, T.; Oláh, A.; Picardo, M.; Quist, S.R.; et al. Sebaceous immunobiology—Skin homeostasis, pathophysiology, coordination of innate immunity and inflammatory response and disease associations. *Front. Immunol.* **2022**, *13*, 1029818. [CrossRef]
49. Choudhry, R.; Hodgins, M.B.; Van der Kwast, T.H.; Brinkmann, A.O.; Boersma, W.J. Localization of androgen receptors in human skin by immunohistochemistry: Implications for the hormonal regulation of hair growth, sebaceous glands and sweat glands. *J. Endocrinol.* **1992**, *133*, 467–475. [CrossRef]
50. Savineau, J.P.; Marthan, R.; Dumas de la Roque, E. Role of DHEA in cardiovascular diseases. *Biochem. Pharmacol.* **2013**, *85*, 718–726. [CrossRef]
51. Gratton, R.; Del Vecchio, C.; Zupin, L.; Crovella, S. Unraveling the Role of Sex Hormones on Keratinocyte Functions in Human Inflammatory Skin Diseases. *Int. J. Mol. Sci.* **2022**, *23*, 3132. [CrossRef]
52. Liu, D.; Dillon, J.S. Dehydroepiandrosterone activates endothelial cell nitric-oxide synthase by a specific plasma membrane receptor coupled to Galpha(i2,3). *J. Biol. Chem.* **2002**, *277*, 21379–21388. [CrossRef]
53. Prough, R.A.; Clark, B.J.; Klinge, C.M. Novel mechanisms for DHEA action. *J. Mol. Endocrinol.* **2016**, *56*, R139–R155. [CrossRef]
54. Bwayi, M.N.; Garcia-Maldonado, E.; Chai, S.C.; Xie, B.; Chodankar, S.; Huber, A.D.; Wu, J.; Annu, K.; Wright, W.C.; Lee, H.-M.; et al. Molecular basis of crosstalk in nuclear receptors: Heterodimerization between PXR and CAR and the implication in gene regulation. *Nucleic Acids Res.* **2022**, *50*, 3254–3275. [CrossRef]
55. Petrova, S.Y.; Albanova, V.I.; Nozdrin, K.V.; Guzev, K.S. Main effects of retinol palmitate on skin structures and the technology of its use in dermatological practice. *Vestn. Dermatol. Venerol.* **2023**, *99*, 6–17. [CrossRef]
56. Yokokawa, T.; Sato, K.; Iwanaka, N.; Honda, H.; Higashida, K.; Iemitsu, M.; Hayashi, T.; Hashimoto, T. Dehydroepiandrosterone activates AMP kinase and regulates GLUT4 and PGC-1α expression in C2C12 myotubes. *Biochem. Biophys. Res. Commun.* **2015**, *463*, 42–47. [CrossRef]

57. Rosset, F.; Marino, M.; Mastorino, L.; Pala, V.; Santaniello, U.; Sciamarrelli, N.; Giunipero di Corteranzo, I.; Aquino, C.; Ribero, S.; Quaglino, P. Hormonal Therapies in Cosmetic Dermatology: Mechanisms, Clinical Applications, and Future Perspectives. *Cosmetics* **2025**, *12*, 207. [CrossRef]
58. Thornton, M.; Taylor, A.H.; Mulligan, K.; Al-Azzawi, F.; Lyon, C.C.; O'DRiscoll, J.; Messenger, A.G. The distribution of estrogen receptor beta is distinct to that of estrogen receptor alpha and the androgen receptor in human skin and the pilosebaceous unit. *J. Investig. Dermatol. Symp. Proc.* **2003**, *8*, 100–103. [CrossRef] [PubMed]
59. Devjani, S.; Ezemma, O.; Kelley, K.J.; Stratton, E.; Senna, M. Androgenetic Alopecia: Therapy Update. *Drugs* **2023**, *83*, 701–715. [CrossRef] [PubMed]
60. Sekhavat, H.; Bar Yehuda, S.; Asotra, S. Using the Mechanisms of Action Involved in the Pathogenesis of Androgenetic Alopecia to Treat Hair Loss. *Int. J. Mol. Sci.* **2025**, *26*, 10712. [CrossRef] [PubMed]
61. Mosca, S.; Ottaviani, M.; Briganti, S.; Di Nardo, A.; Flori, E. The Sebaceous Gland: A Key Player in the Balance Between Homeostasis and Inflammatory Skin Diseases. *Cells* **2025**, *14*, 747. [CrossRef]
62. Ali, A.; Fossas De Mello, N.; Luo, Y.; Bensreti, H.; Melynk, S.; Shaver, J.C.; Choudhary, V.; McGee-Lawrence, M.E.; Bollag, W.B. The Effect of Glucocorticoid and Mineralocorticoid Receptor Antagonists in the Skin of Aged Female Mice. *Int. J. Mol. Sci.* **2025**, *26*, 8346. [CrossRef]
63. Tan, L.; Wu, J.; Wang, J.; Zhang, H.; Zhang, W.; Gao, A.; Zhong, Z.; Chen, T.G.; Zhou, B.; Han, T.; et al. The anti-aging potential of VA'S new derivatives through metabolomic profiling. *Sci. Rep.* **2025**, *15*, 42581. [CrossRef]
64. Demina, O.M. Expression of Androgen, Estrogen, and Progesterone Receptors in the Skin of Patients with Severe Acne and the Assessment of Their Predictive Potential Using Artificial Intelligence Methods. *Int. J. Biomed.* **2024**, *14*, 595–601. [CrossRef]
65. Ceschel, G.C.; Mora, P.C.; Lombardi Borgia, S.; Maffei, P.; Ronchi, C. Skin permeation study of dehydroepiandrosterone (DHEA) compared with its alpha-cyclodextrin complex form. *J. Pharm. Sci.* **2002**, *91*, 2399–2407. [CrossRef]
66. Karakus, E.; Schmid, A.; Schäffler, A.; Wudy, S.A.; Geyer, J. Intracrine Formation of Steroid Hormones in Breast Cancer, Epidermal Keratinocyte, Dermal Fibroblast, and Adipocyte Cell Lines Measured by LC-MS/MS. *Int. J. Mol. Sci.* **2025**, *26*, 1188. [CrossRef]
67. Cussen, L.; McDonnell, T.; Bennett, G.; Thompson, C.J.; Sherlock, M.; O'Reilly, M.W. Approach to androgen excess in women: Clinical and biochemical insights. *Clin. Endocrinol.* **2022**, *97*, 174–186. [CrossRef]
68. Fedotcheva, T.A.; Fedotcheva, N.I.; Shimanovsky, N.L. Progestins as Anticancer Drugs and Chemosensitizers, New Targets and Applications. *Pharmaceutics* **2021**, *13*, 1616. [CrossRef]
69. Roster, K.; Fleshner, L.; Karatas, T.B.; Ecanow, A.; Sayegh, A.; Farabi, B.; Marmon, S. Menopause and Common Dermatoses: A Systematic Review. *Am. J. Clin. Dermatol.* **2026**, *27*, 67–84. [CrossRef]
70. Viscomi, B.; Muniz, M.; Sattler, S. Managing Menopausal Skin Changes: A Narrative Review of Skin Quality Changes, Their Aesthetic Impact, and the Actual Role of Hormone Replacement Therapy in Improvement. *J. Cosmet. Dermatol.* **2025**, *24*, e70393. [CrossRef]
71. Mukherjee, A.; Davis, S.R. Update on Menopause Hormone Therapy; Current Indications and Unanswered Questions. *Clin. Endocrinol.* 2025, *online ahead of print*. [CrossRef]
72. Troxel, J.; Correa Ferrer, L.; Iwamoto, A.; Van Voorhis, B.J.; Powers, J.G. Topical estrogen therapy for aging skin: Current evidence and clinical considerations. *JAAD Rev.* **2026**, *7*, 73–80. [CrossRef]
73. Arlt, W.; Callies, F.; van Vlijmen, J.C.; Koehler, I.; Reincke, M.; Bidlingmaier, M.; Huebler, D.; Oettel, M.; Ernst, M.; Schulte, H.M.; et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N. Engl. J. Med.* **1999**, *341*, 1013–1020. [CrossRef]
74. Lephart, E.D.; Draelos, Z.D. Overview of Aging, Skin Health, Estrogen, Menopause and HRT. *Life* **2026**, *16*, 401. [CrossRef]
75. Farkas, E.; Goldblatt, A.; Nehorayan, I.; Lefkowitz, R.B.; Fleshner, L.; Tepper, K.; Marmon, S. Topical estrogen for skin aging: A systematic review of safety and efficacy. *J. Am. Acad. Dermatol.* **2026**, *94*, 212–215. [CrossRef]
76. Fabi, S.G.; Firsowicz, M.; Kamrani, P.; Draelos, Z.D.; Dayan, S.H. Round Table Discussion: Aesthetic Treatment Considerations for the Perimenopausal & Menopausal Patient. *J. Cosmet. Dermatol.* **2026**, *25*, e70626. [CrossRef]
77. Rzepecki, A.K.; Murase, J.E.; Juran, R.; Fabi, S.G.; McLellan, B.N. Estrogen-deficient skin: The role of topical therapy. *Int. J. Womens Dermatol.* **2019**, *5*, 85–90. [CrossRef]
78. Komori, S.; Ito, Y.; Nakamura, Y.; Aoki, M.; Takashi, T.; Kinuta, T.; Tanaka, H.; Koyama, K. A long-term user of cosmetic cream containing estrogen developed breast cancer and endometrial hyperplasia. *Menopause* **2008**, *15*, 1191–1192. [CrossRef]
79. Volkova, N.I.; Safronenko, A.V.; Gantsgorn, E.V.; Degtyareva, Y.S. Clinical and pharmacological basis of the use of testosterone drugs for hormonal replacement therapy for hypogonadism in men. *Obes. Metab.* **2022**, *19*, 233–241. [CrossRef]
80. Scott, A.; Newson, L. Should we be prescribing testosterone to perimenopausal and menopausal women? A guide to prescribing testosterone for women in primary care. *Br. J. Gen. Pract.* **2020**, *70*, 203–204. [CrossRef]
81. Nácul, A.P.; Rezende, G.P.; Gomes, D.A.Y.; Maranhão, T.; Costa, L.O.B.F.; Reis, F.M.D.; Maciel, G.A.R.; Damásio, L.C.V.D.C.; Rosa e Silva, A.C.J.S.; Lopes, V.M.; et al. Use of androgens at different stages of life: Climacterium. *Rev. Bras. Ginecol. Obstet.* **2022**, *44*, 83–88. [CrossRef]

82. Balan, V.E.; Zaidieva, Y.Z.; Tsarkova, A.V. Androgens in postmenopausal women. *Akusherstvo I Ginekol.* **2019**, *6*, 34–39. (In Russian) [CrossRef]
83. Glynne, S.; Kamal, A.; Kamel, A.M.; Reisel, D.; Newson, L. Effect of transdermal testosterone therapy on mood and cognitive symptoms in peri- and postmenopausal women: A pilot study. *Arch. Womens Ment. Health* **2025**, *28*, 541–550. [CrossRef]
84. Lin, H.Y.; Chen, J.H.; Chen, K.H. The Sex Hormone Precursors Dehydroepiandrosterone (DHEA) and Its Sulfate Ester Form (DHEAS): Molecular Mechanisms and Actions on Human Body. *Int. J. Mol. Sci.* **2025**, *26*, 8568. [CrossRef]
85. Labrie, F.; Luu-The, V.; Labrie, C.; Simard, J. DHEA and its transformation into androgens and estrogens in peripheral target tissues: Intracrinology. *Front. Neuroendocrinol.* **2001**, *22*, 185–212. [CrossRef]
86. Calvo, E.; Luu-The, V.; Morissette, J.; Martel, C.; Labrie, C.; Bernard, B.; Bernerd, F.; Deloche, C.; Chaussade, V.; Leclaire, J.; et al. Pangenomic changes induced by DHEA in the skin of postmenopausal women. *J. Steroid Biochem. Mol. Biol.* **2008**, *112*, 186–193. [CrossRef]
87. Lee, K.S.; Oh, K.Y.; Kim, B.C. Effects of dehydroepiandrosterone on collagen and collagenase gene expression by skin fibroblasts in culture. *J. Dermatol. Sci.* **2000**, *23*, 103–110. [CrossRef]
88. Mawal-Dewan, M.; Frisoni, L.; Cristofalo, V.J.; Sell, C. Extension of replicative lifespan in WI-38 human fibroblasts by dexamethasone treatment is accompanied by suppression of p21Waf1/Cip1/Sdi1 levels. *Exp. Cell Res.* **2003**, *285*, 91–98. [CrossRef]
89. Sokolov, M.N.; Rozhkov, V.V.; Uspenskaya, M.E.; Ulchenko, D.N.; Shmygarev, V.I.; Trukhan, V.M.; Churakov, A.V.; Shimanovsky, N.L.; Fedotcheva, T.A. The Effects of the Steroids 5-Androstenediol and Dehydroepiandrosterone and Their Synthetic Derivatives on the Viability of K562, HeLa, and Wi-38 Cells and the Luminol-Stimulated Chemiluminescence of Peripheral Blood Mononuclear Cells from Healthy Volunteers. *Biomolecules* **2024**, *14*, 373. [CrossRef]
90. Matyushin, A.I.; Semeikin, A.V.; Fedotcheva, T.A.; Antipova, A.V.; Grishina, E.D.; Uspenskaya, M.E.; Golounina, A.V.; Molkanov, N.N.; Shimanovsky, N.L. Influence of Combined Effect of Dehydroepiandrosterone Derivatives and Electromagnetic Irradiation on the Viability of Human Tumor and Normal Cells. *Pharm. Chem. J.* **2025**, *58*, 1685–1689. [CrossRef]
91. Mills, S.J.; Ashworth, J.J.; Gilliver, S.C.; Hardman, M.J.; Ashcroft, G.S. The sex steroid precursor DHEA accelerates cutaneous wound healing via the estrogen receptors. *J. Investig. Dermatol.* **2005**, *125*, 1053–1062. [CrossRef]
92. Zomer, H.D.; Cooke, P.S. Targeting estrogen signaling and biosynthesis for aged skin repair. *Front. Physiol.* **2023**, *14*, 1281071. [CrossRef]
93. Stevenson, S.; Sharpe, D.T.; Thornton, M.J. Effects of oestrogen agonists on human dermal fibroblasts in an in vitro wounding assay. *Exp. Dermatol.* **2009**, *18*, 988–990. [CrossRef]
94. Pomari, E.; Dalla Valle, L.; Pertile, P.; Colombo, L.; Thornton, M.J. Intracrine sex steroid synthesis and signaling in human epidermal keratinocytes and dermal fibroblasts. *FASEB J.* **2015**, *29*, 508–524. [CrossRef]
95. Shin, M.H.; Rhie, G.E.; Park, C.H.; Kim, K.H.; Cho, K.H.; Eun, H.C.; Chung, J.H. Modulation of collagen metabolism by the topical application of dehydroepiandrosterone to human skin. *J. Investig. Dermatol.* **2005**, *124*, 315–323. [CrossRef]
96. Daniell, H.W. Oral dehydroepiandrosterone might prevent frequent tears in atrophic skin: A case report. *JAAD Case Rep.* **2017**, *3*, 534–535. [CrossRef]
97. Kennedy, E.K.C.; Janz, D.M. Chronic stress causes cortisol, cortisone and DHEA elevations in scales but not serum in rainbow trout. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **2023**, *276*, 111352. [CrossRef]
98. Naguib, Y.M.; Rizk, M.S.; Abo-Elsoud, R.A.A. Dehydroepiandrosterone opposes cardiac aging via NFκB/IL-10/Sirt1/Nrf2 mediated pathway in aged rats. *Exp. Gerontol.* **2025**, *212*, 112968. [CrossRef]
99. Quan, X.; Zhao, L.; Jin, J.; Jing, C.; Yang, K.; Jin, S.; Jin, Z. Dehydroepiandrosterone Suppresses Keloid Fibroblasts Fibrosis by Inhibiting the TGF-β1/Smad Signaling Pathway. *J. Craniofac. Surg.* **2025**, *36*, 2904–2908. [CrossRef]
100. Clark, B.J.; Klinge, C.M. Structure-function of DHEA binding proteins. *Vitam. Horm.* **2023**, *123*, 587–617. [CrossRef]
101. Budzianowska, A.; Banaś, K.; Budzianowski, J.; Kikowska, M. Antioxidants to Defend Healthy and Youthful Skin—Current Trends and Future Directions in Cosmetology. *Appl. Sci.* **2025**, *15*, 2571. [CrossRef]
102. Erceg, N.; Micic, M.; Forouzan, E.; Knezevic, N.N. The Role of Cortisol and Dehydroepiandrosterone in Obesity, Pain, and Aging. *Diseases* **2025**, *13*, 42. [CrossRef] [PubMed]
103. Cao, J.; Li, Q.; Shen, X.; Yao, Y.; Li, L.; Ma, H. Dehydroepiandrosterone Attenuates LPS-Induced Inflammatory Responses via Activation of Nrf2 in RAW264.7 Macrophages. *Mol. Immunol.* **2021**, *131*, 97–111. [CrossRef] [PubMed]
104. Chan, C.C.; Liou, C.J.; Xu, P.Y.; Shen, J.J.; Kuo, M.L.; Len, W.B.; Chang, L.E.; Huang, W.C. Effect of dehydroepiandrosterone on atopic dermatitis-like skin lesions induced by 1-chloro-2,4-dinitrobenzene in mouse. *J. Dermatol. Sci.* **2013**, *72*, 149–157. [CrossRef]
105. Cai, J.J.; Wen, J.; Jiang, W.H.; Lin, J.; Hong, Y.; Zhu, Y.S. Androgen actions on endothelium functions and cardiovascular diseases. *J. Geriatr. Cardiol.* **2016**, *13*, 183–196. [CrossRef]
106. Mohamad, N.V.; Razali, N.C.; Shamsuddin, N.M. Dehydroepiandrosterone and Bone Health: Mechanisms and Insights. *Biomedicines* **2024**, *12*, 2780. [CrossRef]
107. Labrie, C.; Flamand, M.; Bélanger, A.; Labrie, F. High bioavailability of dehydroepiandrosterone administered percutaneously in the rat. *J. Endocrinol.* **1996**, *150*, S107–S118.

108. Kurakov, V.V.; Goncharov, N.P.; Katsiya, G.V. Composition Based on Dehydroepiandrosterone, Method for Its Application. RU Patent 2,592,370 C9, 20 July 2016.
109. Minghetti, P.; Cilurzo, F.; Casiraghi, A.; Montanari, L.; Santoro, A. Development of patches for the controlled release of dehydroepiandrosterone. *Drug Dev. Ind. Pharm.* **2001**, *27*, 711–717. [CrossRef]
110. Mauriège, P.; Langin, D.; Montminy, V.; Martel, C.; Després, J.P.; Bélanger, A.; Labrie, F.; Deshaies, Y. Effect of a long-term percu-taneous adrenal steroid treatment on rat adipose tissue metabolism. *Int. J. Obes. Relat. Metab. Disord.* **2000**, *24*, S148–S150. [CrossRef]
111. Fard, A.S.; Sabouri, Z.; Darroudi, M.; Arezumand, R. Application of chitosan-based nanogels for dermal and transdermal delivery systems. *J. Mater. Sci. Mater. Med.* **2026**, *37*, 10. [CrossRef] [PubMed]
112. Hmingthansanga, V.; Singh, N.; Banerjee, S.; Manickam, S.; Velayutham, R.; Natesan, S. Improved Topical Drug Delivery: Role of Permeation Enhancers and Advanced Approaches. *Pharmaceutics* **2022**, *14*, 2818. [CrossRef]
113. Stefanov, S.R.; Andonova, V.Y. Lipid Nanoparticulate Drug Delivery Systems: Recent Advances in the Treatment of Skin Disorders. *Pharmaceuticals* **2021**, *14*, 1083. [CrossRef] [PubMed]
114. Makrantonaki, E.; Zouboulis, C.C. Androgens and ageing of the skin. *Curr. Opin. Endocrinol. Diabetes Obes.* **2009**, *16*, 240–245. [CrossRef]
115. Crespi, O.; Rosset, F.; Pala, V.; Sarda, C.; Accorinti, M.; Quaglino, P.; Ribero, S. Cosmeceuticals for Anti-Aging: Mechanisms, Clinical Evidence, and Regulatory Insights—A Comprehensive Review. *Cosmetics* **2025**, *12*, 209. [CrossRef]
116. Naharro-Rodriguez, J.; Bacci, S.; Hernandez-Bule, M.L.; Perez-Gonzalez, A.; Fernandez-Guarino, M. Decoding Skin Aging: A Review of Mechanisms, Markers, and Modern Therapies. *Cosmetics* **2025**, *12*, 144. [CrossRef]
117. Escamilla-Cruz, M.; Magaña, M.; Escandón-Perez, S.; Bello-Chavolla, O.Y. Use of 5-Alpha Reductase Inhibitors in Dermatology: A Narrative Review. *Dermatol. Ther.* **2023**, *13*, 1721–1731. [CrossRef]
118. Dragicevic, N.; Maibach, H.I. Liposomes and Other Nanocarriers for the Treatment of Acne Vulgaris: Improved Therapeutic Efficacy and Skin Tolerability. *Pharmaceutics* **2024**, *16*, 309. [CrossRef]
119. Al-Smadi, K.; Imran, M.; Leite-Silva, V.R.; Mohammed, Y. Vitiligo: A Review of Aetiology, Pathogenesis, Treatment, and Psychosocial Impact. *Cosmetics* **2023**, *10*, 84. [CrossRef]
120. Guarneri, F.; Bertino, L.; Pioggia, G.; Casciaro, M.; Gangemi, S. Therapies with Antioxidant Potential in Psoriasis, Vitiligo, and Lichen Planus. *Antioxidants* **2021**, *10*, 1087. [CrossRef]
121. Salazar-Formoso, V.; Morales-Sánchez, M.A. Efficacy of Superoxide Dismutase in the Treatment of Vitiligo: A Systematic Review. *Cureus* **2025**, *17*, e88335. [CrossRef] [PubMed]
122. Dorf, N.; Maciejczyk, M. Skin senescence—From basic research to clinical practice. *Front. Med.* **2024**, *11*, 1484345. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.