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Androgens/Androgen Receptor in the Management of Skin Diseases

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Abstract

Beyond regulation of male sexual function, the increasing evidence shows that androgens and androgen receptor (AR) have a variety of physiological and pathological effects on the skin. Skin cells express all androgen metabolizing enzymes that are required for independent skin androgen synthesis and the development of hyperandrogenic related disorders such as acne, hirsutism and androgenetic alopecia. Targeting various elements of androgen function and metabolism is the major goal of medication design for the treatment of androgen-related diseases. Antiandrogen drugs such as clascoterone, flutamide could improve conditions. Even though the involvement of androgens and AR in skin diseases has been investigated for a long time, their molecular mechanisms in skin disorders remain largely insufficient. In this review, recent studies and advances on the role of androgens/AR in several skin-related diseases and their therapeutics are systematically summarized.

Keywords

Androgens, Androgen Receptor, Skin Diseases

1. Androgens and Androgen Receptor

Androgens are 19-carbon (C19) steroids, including testosterone (T), dehydroepiandrosterone (DHEA), androstenedione, and its metabolite 5α-dihydrotestosterone (DHT) [1]. Androgens are primarily synthesized and secreted by the testes, with a small amount also produced by the ovaries and adrenal glands. Some functions of the human skin, such as wound healing, hair growth, sebaceous gland growth and differentiation, and epidermal barrier homeostasis, appear to be heavily reliant on physiologically active androgens [2]. Androstenedione and DHEA have been shown to stimulate sebum production in humans, while the less potent DHEA sulfate (DHEA-S) has been associated with

prepubertal sebum production and cystic acne in adults [3]. Key sex hormone production genes expressed in human skin include CYP11A1, CYP17A1, 3-hydroxysteroid dehydrogenase, and CYP19A1 (aromatase), indicating that the skin has all the synthetic mechanisms for the complete production of androgens [3]. Five main enzymes are involved in androgen activation and inactivation [4]. Figure 1 illustrates pathways of cutaneous androgen metabolism and the converting enzymes.

AR is a member of the nuclear receptor subfamily 3 (NR3), which is a ligand-dependent transcription factor found mainly in the cytoplasm. It is activated by androgens, endogenous hormones or xenobiotic endocrine disruptors

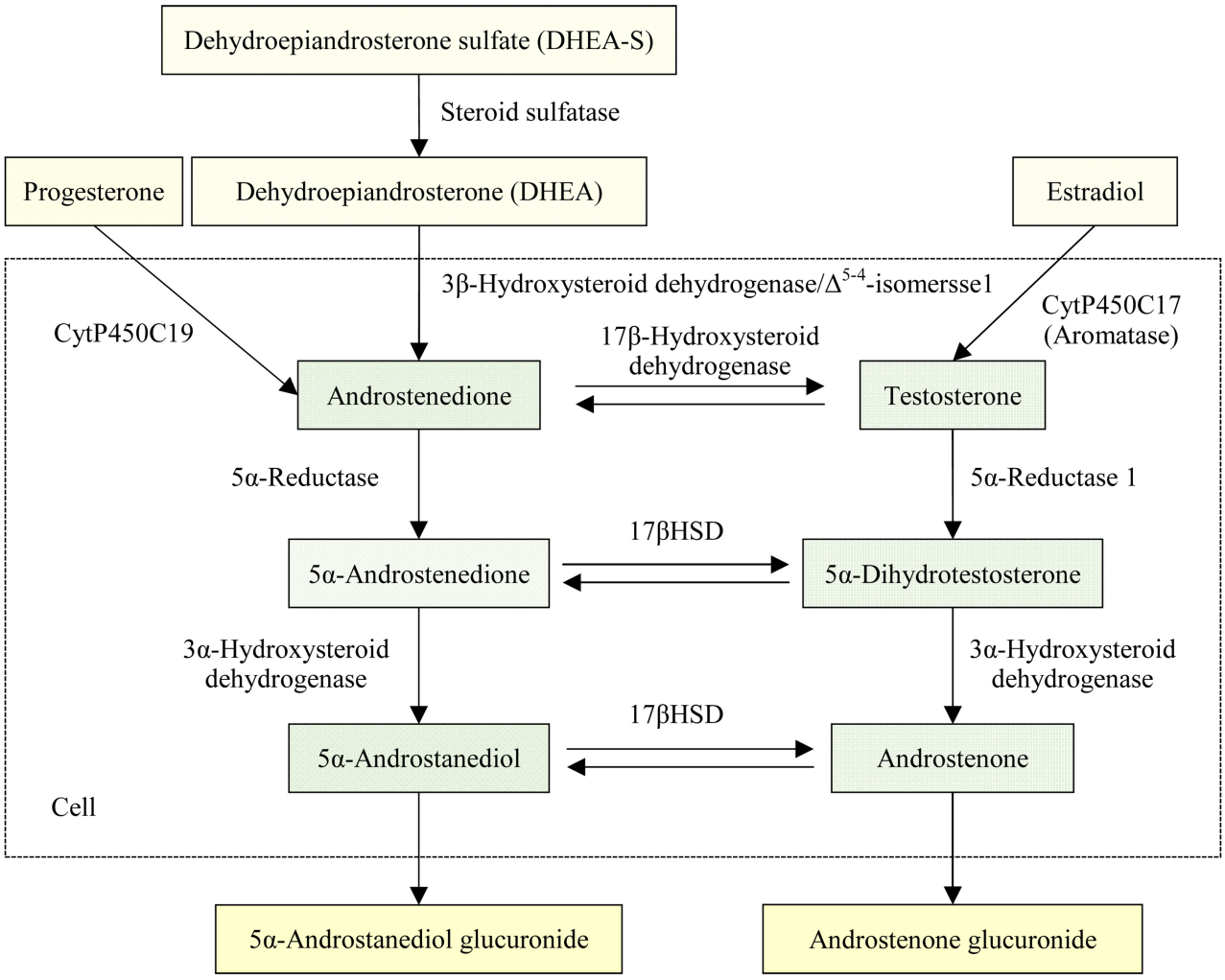

Figure 1. Pathways of cutaneous androgen metabolism and the converting enzymes. In the first step, steroid sulfatase which is express both in sebaceous glands and dermal papilla cells of the terminal hair follicle hydrolyze DHEA-S to dehydroepiandrosterone. Subsequently, DHEA is changed into androstenedione by 3β-hydroxysteroid dehydrogenase (3β-HSD). In a further step, androstenedione is activated by conversion to testosterone through 17β-HSD. The cutaneous expression of 17β-HSD is mainly concentrated in the pilosebaceous unit and epidermal keratinocytes. 5α-reductase irreversibly converts testosterone to DHT, the most potent naturally occurring androgen in tissue. Finally, 3α-HSD, an enzyme existing in three isoforms, converts active androgens to compounds that do not bind the androgen receptor [5]. By glucuronidation, the water-soluble compounds are excreted through the kidney. Alternatively, aromatase can convert testosterone and androstenedione to estrogens in certain cell types.

(EDs) and controls the expression of specific genes [6]. The ligand binding domain (LBD) consists of 11 α-helices (helix 1 and helix 3 - 12) and two antiparallel β-sheets. H12, the most dynamic helix in AR, forms the core of the activity function-2(AF2) domain, which acts as a lid to close the ligand-binding pocket (LBP) upon agonist binding. Activation function 1 (AF1) and activation function 5 (AF5) are two defined transactivation areas found in the N-terminal domain (NTD). The AR-AF1 contains two units: the ligand-dependent TAU-1 and ligand-independent TAU-5. Synergistic interactions between Tau-1 and Tau-5 have been shown to be necessary for the full activity of AR and sufficient to explain transaction activation [7]. The DNA binding domain (DBD) is composed of two zinc finger regions that are necessary for receptor dimerization and binding DNA elements in androgen-responsive gene promoter and enhancer regions [8]. Hinge region plays crucial and partly receptor-specific roles in nuclear receptor (NR) functioning by influencing DNA binding, nuclear translocation, receptor mobility and transactivation [9]. However, its potential as a drug target remains unknown. **Figure 2** shows the structural organization of AR gene and AR Protein. As shown in **Figure 3**, AR exerts its function in both androgen-dependent and androgen-independent mechanisms [10].

2. Androgens/Androgen Receptor and Skin

Aristotle recognized a link between androgenetic alopecia and sexual/gender maturity as far back as the fourth century BC. The binding to AR plays a key role in how androgens affect the skin [2]. Keratinocytes, fibroblasts, endothelial cells, eccrine sweat glands, the external root sheath of hair follicles, dermal papilla, sebocytes, and vaginal melanocytes all contain the androgen receptor [11]. A piliary component and a sebaceous component make up the pilosebaceous unit (PSU). In the majority of body regions, androgens are crucial to the development of the PSU. Before puberty, the hair is vellus, and the sebaceous glands are

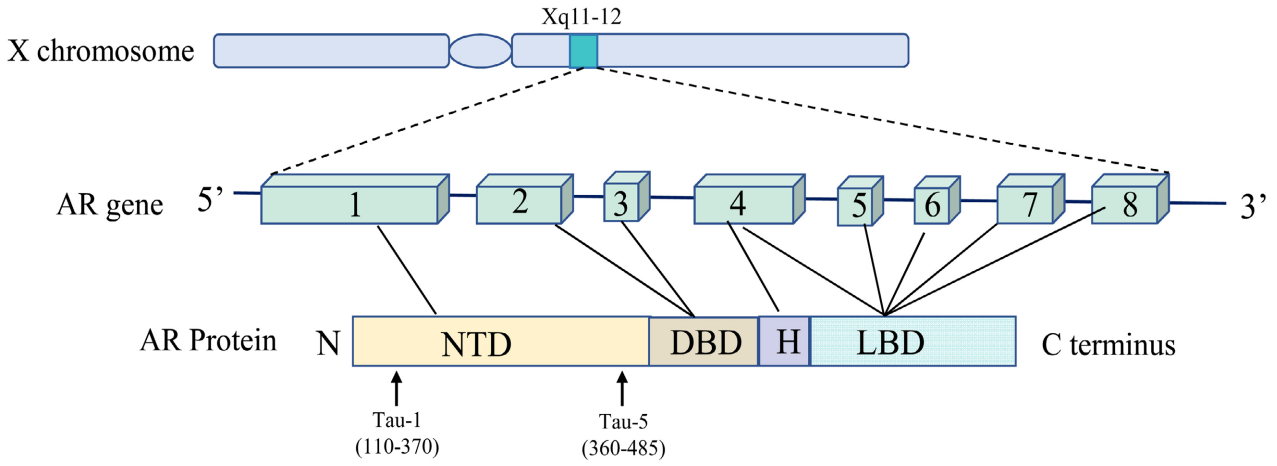

Figure 2. Structural organization of AR gene and AR Protein. The human AR gene is located on the X chromosome at the locus Xq11-Xq12, and encodes eight exons that are transcribed and translated into a 110 kDa protein. The full-length AR consists of four main structural domains: NTD, DBD, H, LBD. H, the hinge region.

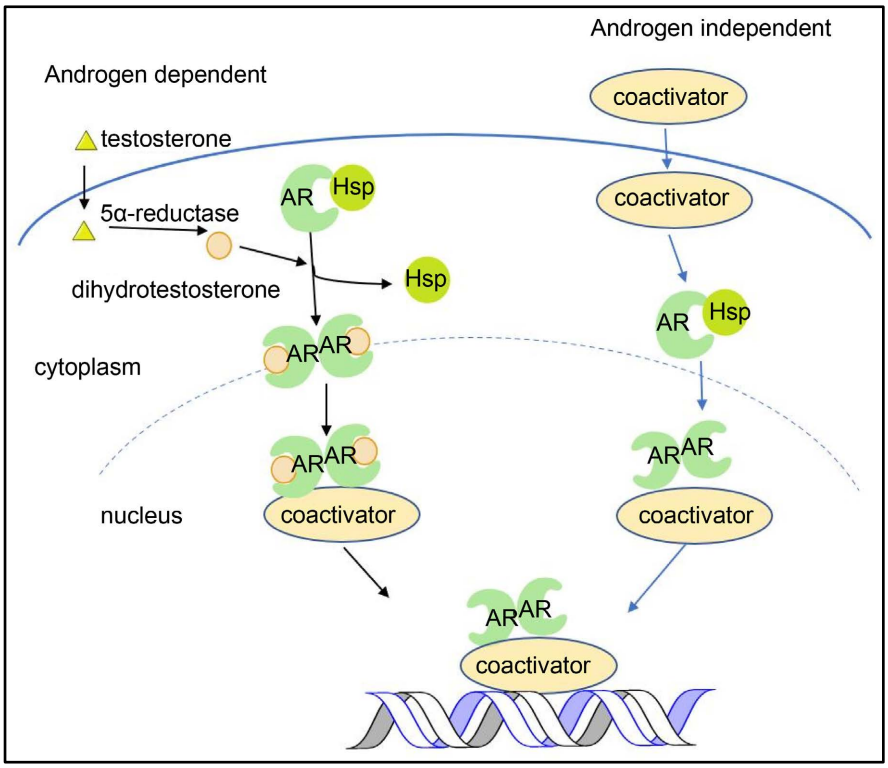

Figure 3. Androgen-dependent and androgen-independent gene expression pathways. In the androgen-dependent pathway, AR that is not bound to ligands is inactive and forms complexes with heat shock protein 90 (Hsp90) in the cytoplasm. These androgens are converted in a series of biochemical reactions by the enzyme 5*α*-reductase to DHT, and activates the AR mainly in the form of DHT. The activated AR is then transferred to the nucleus, where it binds to the AR response sequence, initiates transcription and interacts with a series of transcriptional cofactors to regulate target gene expression. High-level expression of coactivators could offer a mechanism for AR activation through other ligands including the adrenal androgens or by ligand-independent mechanisms. It has been demonstrated that AR can be activated in the androgen-independent AR pathway.

tiny in androgen-sensitive areas. PSUs transform into large terminal hair follicles (sexual hairs) in places with sexual hairs in response to rising testosterone levels, or into sebaceous follicles (sebaceous glands) in areas with sebaceous tissue [12]. The generation of pheromones in the apocrine glands of the human axilla is directly correlated with androgen activity. The nucleus of the apocrine epithelium exhibits a strong AR immune response [13]. In human hair follicles, AR expression is restricted to dermal papilla cells (DPCs). DPCs, which are located in the hair bulb of hair follicles, are regarded as a significant target cell of androgen in hair follicles and play a key role in maintaining and triggering the periodic cycling of hair follicles. DPCs derived from beard and balding scalp contain high affinity AR, than those derived from relatively androgen-insensitive non-balding scalp follicles. This fact suggests that androgens act on hair follicles through the dermal papillae in the body [14].

A polymorphic CAG repeats that codes for a polyglutamine tract can be found in the modulatory domain of the human androgen receptor gene. *In vitro* studies

show that the transcriptional activity of the AR is inversely associated with CAG tract length [15]. The CAG polymorphism of the AR gene may be a candidate genetic marker for diseases such as acne in men. According to a recent linkage study, the AR gene's shorter GGN repeat has a larger gene effect due to genetic variability [16].

Before the conditional AR-deficient mice became accessible, it was difficult to comprehend the precise involvement of AR in the linked pathogenic functions due to the lack of an appropriate animal model. The development of the conditional AR knockout (ARKO) mouse model may offer an effective method for analyzing the role of AR in various cell or tissue types involved in skin pathogenesis and may provide new knowledge or mechanistic explanations for these disorders [17]. Male ARKO mice were sterile, had 80% fewer testes than wild-type males, had decreased testosterone levels, and had abnormal prostate development. For instance, ARKO mice with a background in rhino mice might be used to examine the effects of androgens/AR on the activity of the sebaceous glands associated with acneic comedones, while ARKO mice with a background in B6CBAF1 could be used to study androgenetic alopecia [18].

3. Androgens/AR and Acne

3.1. Acne

Acne is a chronic inflammatory disease of the pilosebaceous unit in the upper trunk, face, and neck. 15% - 20% of young people suffer from moderate to severe acne [11]. Infection by propinobacterium acnes is one of the main pathogenic causes contributing to acne. It promotes hyper keratinization that provokes obstruction of the infundibulum, perifollicular inflammation, seborrhea, stimulation of sebum production, and excessive presence of androgens from local or systemic origin [13].

Numerous experimental and clinical studies have shown that androgens play a significant role in the etiology of acne, and the increased sensitivity of hair follicle sebaceous gland unit to androgen is one of the most important pathogenic factors. Androgen can cause enlargement of sebaceous glands and increase of sebum secretion [19] even if there is no association between the severity of acne and indicators of androgenicity [15]. DHT has also been demonstrated to play a role in sebocytes' secretion of proinflammatory cytokines, in addition to sebum production [17]. The 17-HSD reduction process is necessary for the synthesis of the more potent androgens [20]. In comparison to non-acne-prone areas, the sebaceous glands from acne-prone areas like facial skin displayed a stronger reductive activity of 17-HSD, indicating a higher testosterone production [15]. The gene encoding the AR has been a leading candidate for the assessment of acne risk due to the role of androgen in the etiology of acne. The AR gene has a glutamine repeat polymorphism within exon 1. Shorter CAG-repeat lengths may contribute to the emergence of androgen-mediated skin diseases in both men and women, according to research. There have been various hypothesized ways

by which androgens/AR control sebocyte activity in acne vulgaris. For instance, AR may promote lipogenesis in sebocytes by enhancing the production of proteins that bind to sterol-regulatory element-binding proteins (SREBPs) [18]. Second, it has been demonstrated that fibroblast growth factor receptor 2 (FGFR2) is essential for the development and homeostasis of the sebaceous gland. Third, in regulating acne development, androgens and insulin-like growth factor-1 (IGF-1) interactions may occur. It has been demonstrated that IGF-1 can stimulate SREBP-1 expression and lipogenesis in sebocytes.

3.2. Therapies

The U.S. Food and Drug Administration (FDA) has approved topical retinoids for the treatment of acne vulgaris [21]. These include adapalene, retinoic acid, and tazarotene, which control keratinocyte proliferation and differentiation and have anti-inflammatory properties to prevent acne from forming [22]. Retinoids also change the expression of the HOX genes, which are probably involved in PSU morphogenesis. The systemic retinoid oral isotretinoin (**1**) is generally safe and well tolerated. It is FDA-approved for the management of pain recalcitrant acne vulgaris and is also advised for the treatment of moderate acne that is treatment-resistant, causes significant psychological distress, or leaves scars. Despite being widely regarded as safe, isotretinoin obviously has teratogenic and embryotoxic effects [21]. Although topical antibiotics offer additional anti-inflammatory benefits and can be used as the first line of treatment for acne vulgaris, they shouldn't be used as a stand-alone therapy due to the high rates of antibiotic resistance that quickly emerge after a few weeks or months [23]. Oral antibiotics combined with topical retinoic acid and/or benzoyl peroxide are recommended for the treatment of moderate to severe inflammatory acne or inflammatory acne where topical treatment alone has failed.

The combination oral contraceptives (COCs) traditionally used to treat acne contain Cyproterone acetate (CPA) (**2**), chlormadinone, drospirenone together with an oestrogen, almost always ethinyl estradiol (EE). The combination of ethinyl estradiol and a progestin in COC has an overall anti-androgenic effect, which eventually causes the size and functionality of the sebaceous glands to reduce [23]. A recently marketed progestin, drospirenone (a derivative of 17-alpha spironolactone), first marketed by Fuji Pharma, shows no androgenic effects with anti-androgenic and antimineralocorticoid activity, which makes it effective in acne and hirsutism. In 1978, Schering AG first introduced the use of cyproterone acetate in the treatment of acne. CPA is a progestin that works as an anti-androgen and its primary action is directly blocking androgen receptors [19]. Due to the limited permeability of the skin, researchers studied different diameter nano-lipid carriers through the skin penetration ability. The results show that the accumulation ability of 300 nM lipid carrons in the hair follicles is the best [24]. A COC with CPA 2 mg and EE 35 μg is approved for acne in Italy but not for contraception. In the UK, this prescription is used to treat women with se-

vere acne who have failed to respond to long-term antibiotic treatment. Only three COCs with the progestins norethindrone, norgestimate, and drospirenone are now FDA-approved for the treatment of moderate acne in the United States [19].

Clascoterone (**3**) is an androgen receptor inhibitor. In terms of molecular structure, the molecule resembles DHT and spironolactone. The FDA approved clascoterone as the first topical antiandrogen to treat hormonal acne in August 2020. It reduces androgen-receptor binding and competes with androgens, particularly dihydrotestosterone, for binding, preventing downstream signaling of pathways involved in the etiology of acne. Clascoterone is commercially accessible as 1% (10 mg/g) cream in patients 12 years of age and older [25]. The AR degradation enhancer, ASC-J9 (**4**), was co-developed by Orient Europharma and Andro Science for use in clinical trials and for sale in Australia [26]. ASC-J9 is currently being studied in phase II clinical trial for acne vulgaris [17]. For its antiandrogenic properties, the potassium-saving diuretic spironolactone (**5**) is used in females with moderate to severe hormonal acne, and it is typically well tolerated at low dosages (50 - 200 mg daily). Spironolactone, a synthetic steroidal aldosterone derivative, functions as an aldosterone antagonist. It acts on acne through an anti-androgenic action, mainly targeting the blocking of androgen receptors; it decreases the amount of sebum production induced by androgens by competing with testosterone and DHT. It also raises the level of SHBG, inhibits testosterone synthesis by lowering liver 17β-hydroxylase activity, reducing the conversion of androstenedione to testosterone, influences the LH/FSH ratio by lowering the response of LH to GnRH, and lowers 5α-reductase activity [27]. Despite being often used by dermatologists, it is not an FDA-approved acne therapy [21]. Flutamide (**6**) is a competitive antagonist of the androgen receptor. It was first marketed by Schering-Plough in 1984. Although flutamide has been given FDA approval to treat prostate cancer, it is also used off-label to treat acne. Acne can improve about 80% with the typical acne dosage, which is between 62.5 and 500 mg per day. The main drawback of this medication is hepatic toxicity, which appears to be dose- and age-related [28]. **Figure 4** shows the structures of some compounds used in the treatment of acne.

4. Androgens/AR and AGA

4.1. AGA

Androgenetic alopecia (AGA) is the most prevalent type of progressive hair loss illness in men. AGA involves a gradual shrinkage of the hair follicle that results in the terminal hair becoming vellus. Endocrine variables and genetic predisposition combine to determine the prevalence and progression of androgenetic alopecia. The most significant regulator of human hair growth is androgen, which can increase the size of hair follicles in androgen-dependent regions (such as the beard, axilla, and pubic hair). However, paradoxically, in the scalp follicles of susceptible men suppress hair growth and encourage miniaturization of and

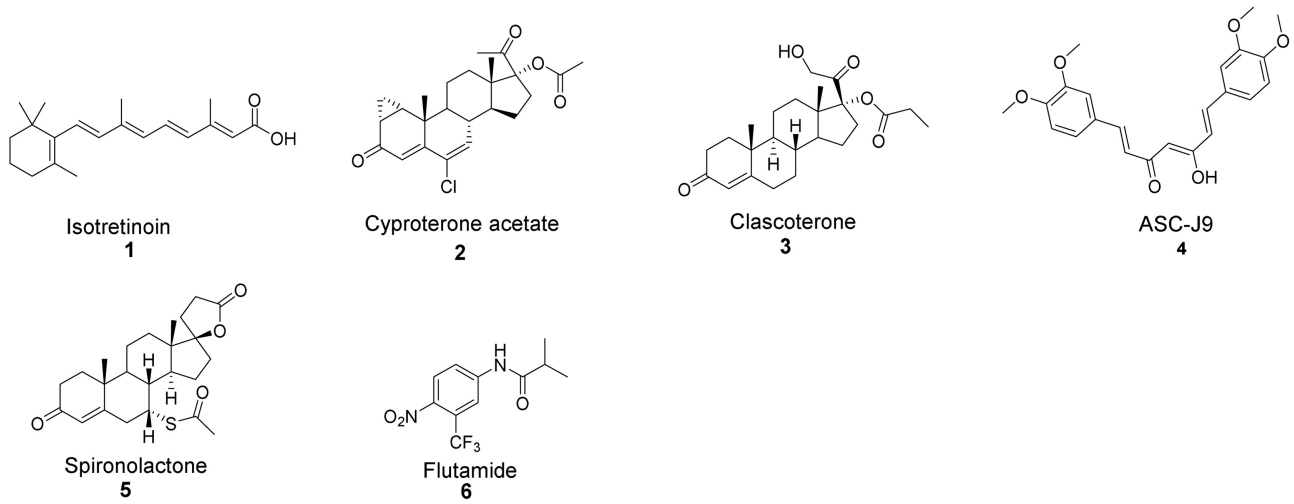

Figure 4. Structures of compounds for acne.

shorter hair in the anagen stage, which results in common baldness. Similar to acne, the majority of men with AGA have normal levels of androgen; therefore a mechanism of cutaneous hyperandrogenism involving *in situ* hyperproduction of androgens in the pilosebaceous unit or overexpression and/or hyperresponsiveness of androgen receptors should once again be hypothesized. Two facts have been used to support the idea that AR plays a role in AGA disorder: 1) people without a functional AR do not bald, such as patients with androgen insensitivity syndrome; 2) the expression of AR in the scalp of AGA patients is site-specific and elevated in the frontal and vertex regions, but normal in the parietal and occipital regions. Numerous studies have conclusively determined that the X-chromosome AR EDA2R locus and the chromosome 20p11 locus are the two main genetic risk loci for androgenetic alopecia [16]. It has been recognized that AR gene variants cause abnormal expression of AR proteins in scalp hair follicles, leading to AGA. In an effort to clarify the mechanisms involved in the etiology of AGA, a recent study found that balding DPCs experience premature senescence *in vitro*, which is indicated by the production of the proteins p16INK4a and senescence-associated-galactosidase (SA-gal), as well as markers of oxidative and DNA damage [29]. According to a paper, androgen/AR signaling, in conjunction with DNA damage, speeds up the premature senescence of human DPCs from the frontal scalp [30]. The biological characteristics of DPC are positively regulated by Tcf4. Recent research has demonstrated that AR reduces DPC proliferation and may cooperate with Tcf4 to control DPC growth [31]. AGA might be treated by concentrating on the AR/Tcf4 complex.

4.2. Therapies

4.2.1. Antiandrogen Therapies

Finasteride (**7**) is the first type 2 5α-reduction enzyme inhibitor applied to the clinical. It was developed by Merck in the United States and was first launched in July 1992. It belongs to the 4-nitrogen miscellaneous body hormone compounds.

Finasteride could decrease the conversion of testosterone to dihydrotestosterone (DHT), which is responsible for the miniaturization of the hair follicle seen in Male AGA (MAGA). The side effects of finasteride include decreased libido, erectile dysfunction and decreased ejaculated volume [32]. Since discontinuing finasteride therapy results in slow hair loss and a return to the pre-treatment condition within a year, finasteride therapy should be lifelong. Among more than 3000 AGA-afflicted men in a major Japanese trial, finasteride caused significant hair growth in 11.1% of participants, moderate growth in 36.5%, and minimal growth in 39.5% of patients over the course of three years [33]. It exists in tablets of 1 mg and 5 mg, with the lesser dose being recommended for male pattern baldness. It is not recommended for usage in women and is classified as pregnancy category X because it may result in a male fetus having ambiguous genitalia. Since this medication may be acquired over the counter, patients can much more easily afford it.

Finasteride's replacement, dutasteride (**8**), is a selective competitive inhibitor of type 1 and type 2 5*α*-reductase as well as a second-generation 5*α*-reductase inhibitor. According to reports, dutasteride has 100 times the ability of finasteride to inhibit the type II enzyme and is three times as effective at inhibiting the type I enzyme. The medication is available in dosages of 2.5 and 5 mg, both of which have demonstrated more efficacy than finasteride 5 mg. [34] In Japan and South Korea, oral dutasteride has already been authorized for the treatment of AGA. However, adverse effects of dutasteride include decreased libido, erectile dysfunction and ejaculatory dysfunction [35].

Spironolactone (**5**), a potassium-saving diuretic, is regarded as an antiandrogen since it lowers testosterone levels and inhibits the androgen receptors in the tissues it is intended to treat [36]. For female pattern hair loss (FPHL), spirolactone is the antiandrogen most frequently used, and the recommended dosage ranges from 100 to 200 mg per day. Oral minoxidil 0.25 mg and spironolactone 25 mg were initially described by Sinclair as a secure and reliable treatment for female pattern hair loss [37]. Spironolactone's side effects include electrolyte imbalance, deterioration of renal function, and hypotension despite being well-tolerated and available for decades [36].

Cyproterone acetate (**2**) is an androgen receptor antagonist. In addition to lowering testosterone levels through reducing the release of follicle-stimulating and luteinizing hormone, it may directly inhibit DHT from binding to its receptors. Cyproterone therapy, either alone or in combination with ethinylestradiol or spironolactone, can increase hair growth in FPHL patients [38]. It is permitted for usage in Europe and Canada to treat female alopecia, acne, and hirsutism. Hepatotoxicity, weight gain, decreased libido, breast tenderness, and feminization of the male fetus are some of the drug's side effects.

Clascoterone (**3**) is a corticosterone ester derivative. In vitro, it has a high affinity for androgen receptors and inhibits DHT-stimulated signal transduction. It is an effective anti-androgen with selective local activity [39]. In a randomized, double-blind, dose-ranging clinical trial (EudraCT2016-003733-23), Clascote-

rone solution was shown to be effective in treating androgenetic alopecia in male subjects (18 - 55 years of age) with mild to moderate disease in the temple and vertex region [39]. Clascoterone external cream developed by Cassiopea is in phase II of clinical treatment for androgen alopecia. The most frequent (incidence > 5%) new or worsening local skin reactions with clascoterone were erythema/redness, scaling/dryness and pruritus.

Flutamide (**6**) is an oral antiandrogen that is hardly used in clinical settings. It was initially discovered that oral flutamide was a suitable treatment for hyperandrogenic alopecia by Enrico Carmina in 2003. Anosha Yazdabadi reported a woman whose hair loss progressed while using spironolactone and topical minoxidil in combination, but reversed with flutamide [40]. Flutamide has a risk of liver damage and other common side effects include hot flushes.

Pyrilutamide (**9**), a topical androgen receptor antagonist, has successfully completed Phase I and Phase II clinical trials [41]. Suzhou Kintor Pharmaceuticals Inc advanced it to clinical phase III trials in China and the United States in 2022. Unlike finasteride, which systematically inhibits the synthesis of androgen DHT and thus stimulates hair growth, pyrilutamide binds androgen receptor by competing with androgen, thereby locally inhibiting the transmission of androgen and its receptor-mediated signaling pathway. Direct androgen receptor antagonists could be used in men if it is proven to be safe and efficient to apply topically. GT-20029 was the first topical drug used PROTAC (Proteolysis Targeting Chimera) in the treatment of androgenic alopecia. It captures the androgen receptor and induces its degradation through ubiquitin-mediated proteolysis [42]. It is being developed by Suzhou Kintor Pharmaceuticals for a Phase 1 clinical trial in the US in 2022.

4.2.2. Androgen-Independent Therapies

Minoxidil (**10**) was the first topical drug approved by the FDA to treat AGA. The 2% solution, 5% solution, and 5% foam were all approved for use on males in 1988, 1991, and 2016, respectively. The 2% solution for women was authorized in 1991, while the 5% foam was approved in 2014. Minoxidil is a potassium channel opener. Active metabolite of minoxidil sulfate binds ATP-sensitive potassium channels and relaxes the surrounding smooth muscle, increasing the width of existing hairs but not as significantly as hair count [43]. According to some research, it may also enhance hair growth by boosting prostaglandin E2 (PGE2) production via stimulating prostaglandin endoperoxide synthase-1. The most frequent side effects of minoxidil include face hypertrichosis and contact dermatitis.

Ketoconazole (**11**) is an antifungal agent that can be used topically as a 2% shampoo for the treatment of seborrhoeic dermatitis. Ketoconazole has antiandrogenic activities with DHT inhibition since it can interfere with steroidogenesis in addition to its antifungal and anti-inflammatory properties for the treatment of seborrheic dermatitis [44]. Ketoconazole used topically has no negative side effects. AGA can be treated with shampoos containing 2% ketoconazole,

which is a promising adjuvant or alternative therapy [45].

Figure 5 shows the structures of some compounds used in the treatment of AGA.

5. Androgens/AR with Hirsutism

5.1. Hirsutism

Hirsutism is the excessive growth of terminal hair in a masculine pattern distribution on a female's face and body. The degree of hirsutism in women is evaluated using the Ferriman-Gallwey score [46]. The majority of women who have testosterone levels that are twice the upper limit of the normal range or above have some degree of hirsutism. Notably, the degree of hirsutism does not exactly match androgen levels. In addition to androgen levels, the sensitivity of hair follicles to androgens is one of several factors that contribute to hirsutism. Some women with excess androgen have no skin manifestations, or they may have seborrhea, acne, or alopecia without hirsutism. Most hirsute women have an androgen excess disease, such as hyperandrogenic insulin-resistant acanthosis nigricans (HAIRAN) syndrome, nonclassical adrenal hyperplasia (NCAH), polycystic ovary syndrome (PCOS), or in very rare cases, androgen-secreting neoplasms [47].

5.2. Management

5.2.1. Physical and Cosmetic Measures

In the control of hirsutism, cosmetic measures are essential. These physical procedures, such as hair removal or bleaching to eliminate hair pigmentation, are efficient and ought to be suggested either in place of or in addition to pharmacological treatment. Hydrogen peroxide is usually the main element in bleaching hair colour removal products, and a solution with a 6% concentration is suitable.

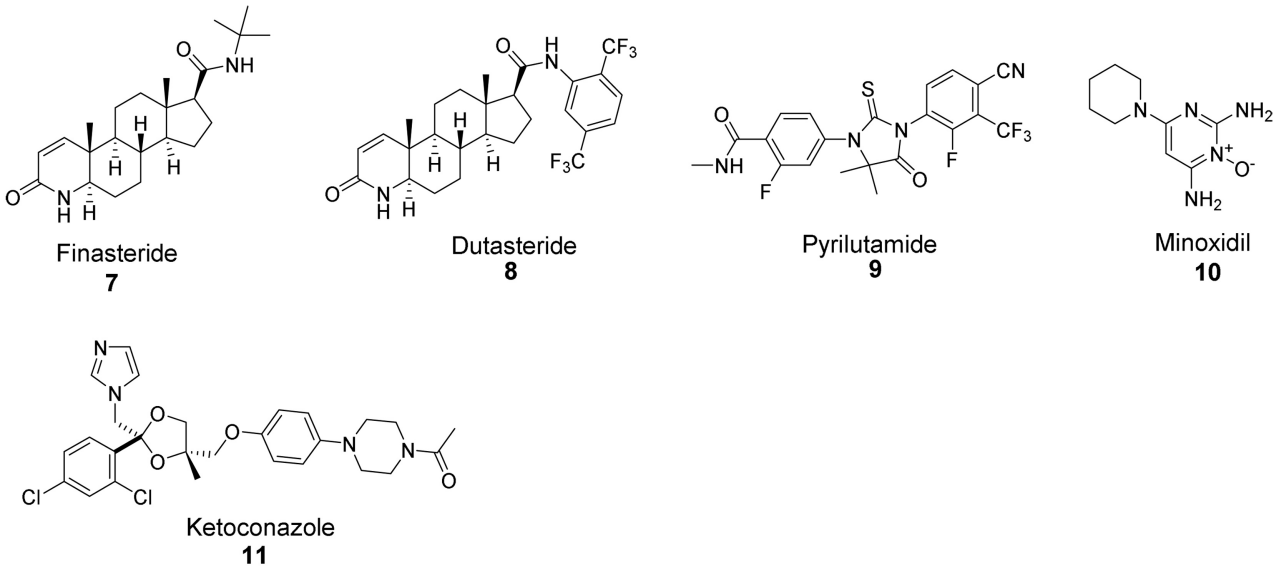

Figure 5. Structures of compounds for AGA.

Shaving is a reliable, safe, and quick fix for facial hair, but most patients find it unattractive. Chemical hair removal products work similarly to shaving as they remove hair by hydrolyzing disulfide bonds. Electrolysis and pyrolysis are slow processes that can be used on people of any skin or hair color, but they need a number of sessions to be effective [48]. Faster than pyrolysis or electrolysis, lasers can treat bigger regions. Additionally, they have a skin cooling mechanism that helps prevent injury to the epidermis throughout the procedure.

The FDA has given the topical drug Eflornithine (**12**) hydrochloride cream 13.9% (Vaniqa) approval for the treatment of female facial hair that is undesirable as well as for the treatment of hair that does not respond to laser therapy. Ornithine decarboxylase, the rate-limiting enzyme in polyamine production, appears to be crucial for the formation of stromal cells in the hair follicle and, consequently, important for hair development. Ornithine decarboxylase is permanently inhibited by eflornithine. Although eflornithine does not eliminate hair, it does slow the growth of new hair. When compared to controls, eflornithine-treated patients had 26% less thick hair and 23% less hair length. Local drug tolerance was high, and eflornithine hydrochloride 13.9% adverse effects during studies were often modest, with about 8.0%, 3.6%, and 2.8% of patients reporting stinging, tingling skin, or a rash, respectively [49].

5.2.2. Pharmacologic Therapy

In roughly 60% - 100% of hyperandrogenic women, combined estrogen-progestin oral contraceptives reduce hair development and are recommended as the first line of treatment. The mechanisms by which oral contraceptives reduce hirsutism include: 1) Contraceptives inhibit luteinizing hormone secretion, thereby suppressing luteinizing hormone-dependent ovarian androgen production. 2) The estrogenic effects of contraceptives stimulate the liver to produce sex hormone-binding globulin, which reduces serum concentrations of free testosterone and other sex hormone-binding globulin-binding androgens, and inhibits adrenal androgen secretion. Doctors usually recommend that treatment should begin with preparations containing low doses of estrogens and non-androgenic progestins [50]. Potent orally active progestins include chlormadinone acetate (CMA), CPA, and dienogest [51]. They primarily work by inhibiting androgen receptors in the target organs, while they can also lower skin 5α-reductase activity. Because CMA and CPA block the release of gonadotropins, less ovarian and adrenal androgen is produced.

Spironolactone (**5**) acts as both an androgen receptor antagonist and aldosterone antagonist, inhibits both the activity of the androgen receptor in a dose-dependent competitive manner. Spironolactone is used orally at doses between 50 and 200 mg daily to treat androgen-dependent hirsutism [51]. Dyspepsia, nausea, polyuria, nocturia, exhaustion, headaches, ovulatory changes, breast tenderness, decreased libido, sun hypersensitivity, and atopic responses are the side effects most frequently linked to spironolactone use. Spironolactone and OCPs work better together than OCPs alone [52].

Flutamide (**6**) is an androgen receptor blocker approved by the FDA as adjuvant treatment for prostate cancer. Use a dose of 500 mg per day in the treatment of hirsutism, although a single dose of 250 mg per day may be effective in some patients [48]. Hepatotoxicity makes flutamide unadvisable. Bicalutamide (**13**) is a well-tolerated non-steroidal pure anti-androgen drug with a half-life of 7 - 10 days. A recommended dose of 50 mg per day has been determined for the treatment of prostate cancer. 25 mg/day of bicalutamide has been shown to be effective in the treatment of patients with hirsutism, and in patients with idiopathic hirsutism without significant side effects or menstrual cycle changes [51].

A 5α-inhibitor named finasteride (**7**) has been granted by the FDA to treat benign prostatic hyperplasia. It is helpful in the treatment of female hirsutism [53]. Finasteride is given to hirsutized female patients in doses ranging from 1 mg to 5 mg daily. After 6 months of therapy, finasteride reduced the FG score and hair diameter more than flutamide (250 mg twice/day), but flutamide was more efficient at 12 months [54]. When compared to other hirsutism medications, it has the fewest side effects. Finasteride use, however, can result in congenital abnormalities in males due to the crucial part DHT plays in embryonic development. Considering the half-lives of finasteride, it would appear safe for women to become pregnant 10 days after finishing therapy.

Figure 6 shows the structures of some compounds used in the treatment of hirsutism.

6. Androgens/AR with Atopic Dermatitis (AD)

Atopic dermatitis, commonly called as atopic eczema, is a chronic inflammatory skin disease with a complex etiology [55]. Eczematous, oozing, or weeping pruritic sores over dry skin are acutely recurrent symptoms of AD. Chronic lesions involve prurigo nodules, and red or brownish patches of dry, cracked or scaly skin. Skin itchiness contributes to weariness and disrupts sleep, especially at night [56]. Genetic differences, immunological dysregulation, and environmental variables all play a role in the complex etiology of AD.

Both the immune response of the skin and the permeability of the skin are influenced by sex hormones, and the balance between the immune response and the regulatory role of the skin barrier may regulate the course of AD. Androgens diminish skin permeability while estrogens strengthen it [57]. Women may be

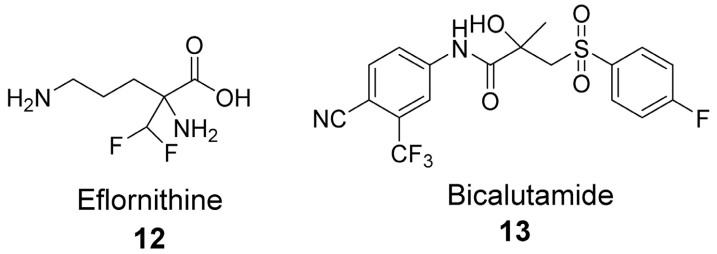

Figure 6. Structures of compounds for hirsutism.

more sensitive to the effects of DHEA because they have larger levels of the enzyme steroid sulfatase, which converts dehydroepiandrosterone sulfate to dehydroepiandrosterone. DHT decreased the amount of peroxisome proliferator-activated receptor (PPAR), a receptor that inhibits the transcription of IFN, in mouse CD4+T cells. Androgens suppress Th1 differentiation: testosterone inhibited IL-12-induced phosphorylation of STAT4 in murine CD4+T cells by upregulating the expression of protein tyrosine phosphatase nonreceptor 1, which inactivates the Jak2 and Tyk2 kinases [58]. Androgens also prevent Th2 and Th17 from differentiating. On another side, androgens bind androgen response elements on the Foxp3 promoter via activated AR, enhancing acetylation of histone H4 on the promoter and allowing binding of additional transcription factors, thus enhancing Foxp3 expression in human T cells and inducing Tregs [59].

7. Conclusions and Perspectives

Androgens and AR are key participants in a variety of skin problems, according to recent research. Androgens may be produced by skin, and it has the ability to locally transform weaker androgens into strong ones. Androgens/AR is one of the key parameters of skin physiology and is involved in numerous skin diseases, such as acne, androgenetic alopecia, hirsutism, and atopic dermatitis. Clascoterone, cyproterone acetate, flutamide and other antiandrogen drugs are widely used in hormonal therapies for these skin conditions. Current treatments targeting androgens (such as in patients with prostate cancer) usually result in undesirable side effects that are not acceptable in skin disorders. Creating topical medicines that can be effectively delivered to skin target cells and destroyed before entering the circulatory system is a smart way to reduce adverse effects. According to conventional thinking, androgens and AR depend on one another to complete their physiological tasks; nevertheless, a new concept has recently emerged that differentiates between androgens' and AR's functions. [60] Both basal cells and sebocytes in the sebaceous glands exhibit AR. Discoveries and mechanistic explanations about these illnesses may result from the development of the conditional ARKO mouse model, which could serve as a useful tool for dissecting AR function in the various cells or tissue types involved in skin pathogenesis. The use of compounds that target AR in treatments has benefited from a clinical perspective. Pyrilutamide and GT20029, which developed in the last few years, are being studied as topical antagonists of the androgen receptor. Direct androgen receptor antagonists could be used in men if they are proven to be safe and efficacious when applied topically.

Even though many therapies for androgen-dependent skin disorders are efficient and tolerated, understanding the various functions of androgens, AR, or their downstream pathways in each skin condition could contribute to the creation of better treatments. To treat various skin conditions, these medicines may specifically target AR (rather than androgens).

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Tobiansky, D.J., Wallin-Miller, K.G., Floresco, S.B., Wood, R.I. and Soma, K.K. (2018) Androgen Regulation of the Mesocorticolimbic System and Executive Function. *Frontiers in Endocrinology* (*Lausanne*), **9**, Article 279. https://doi.org/10.3389/fendo.2018.00279

[2] Zouboulis, C.C. and Degitz, K. (2004) Androgen Action on Human Skin-From Basic Research to Clinical Significance. *Experimental Dermatology*, **13**, 5-10. https://doi.org/10.1111/j.1600-0625.2004.00255.x

[3] Zouboulis, C.C., Chen, W.-C., Thornton, M.J., Qin, K. and Rosenfield, R. (2007) Sexual Hormones in Human Skin. *Hormone and Metabolic Research*, **39**, 85-95. https://doi.org/10.1055/s-2007-961807

[4] Chen, W., Thiboutot, D. and Zouboulis, C.C. (2002) Cutaneous Androgen Metabolism: Basic Research and Clinical Perspectives. *Journal of Investigative Dermatology*, **119**, 992-1007. https://doi.org/10.1046/j.1523-1747.2002.00613.x

[5] Fritsch, M., Orfanos, C.E. and Zouboulis, C.C. (2001) Sebocytes Are the Key Regulators of Androgen Homeostasis in Human Skin. *Journal of Investigative Dermatology*, **116**, 793-800. https://doi.org/10.1046/j.1523-1747.2001.01312.x

[6] Tan, M.H., Li, J., Xu, H.E., Melcher, K. and Yong, E.L. (2015) Androgen Receptor: Structure, Role in Prostate Cancer and Drug Discovery. *Acta Pharmacologica Sinica*, **36**, 3-23. https://doi.org/10.1038/aps.2014.18

[7] Callewaert, L., Van Tilborgh, N. and Claessens, F. (2006) Interplay between Two Hormone-Independent Activation Domains in the Androgen Receptor. *Cancer Research*, **66**, 543-553. https://doi.org/10.1158/0008-5472.CAN-05-2389

[8] Jakob, M., Kolodziejczyk, R., Orlowski, M., Krzywda, S., Kowalska, A., Dutko-Gwozdz, J., *et al*. (2007) Novel DNA-Binding Element within the C-Terminal Extension of the Nuclear Receptor DNA-Binding Domain. *Nucleic Acids Research*, **35**, 2705-2718. https://doi.org/10.1093/nar/gkm162

[9] Clinckemalie, L., Vanderschueren, D., Boonen, S. and Claessens, F. (2012) The Hinge Region in Androgen Receptor Control. *Molecular and Cellular Endocrinology*, **358**, 1-8. https://doi.org/10.1016/j.mce.2012.02.019

[10] Gaba, A., Mairhofer, M., Zhegu, Z., Leditznig, N., Szabo, L., Tschugguel, W., *et al*. (2018) Testosterone Induced Downregulation of Migration and Proliferation in Human Umbilical Vein Endothelial Cells by Androgen Receptor Dependent and Independent Mechanisms. *Molecular and Cellular Endocrinology*, **476**, 173-184. https://doi.org/10.1016/j.mce.2018.05.007

[11] Datta, D., Madke, B. and Das, A. (2022) Skin as an Endocrine Organ: A Narrative Review. *Indian Journal of Dermatology, Venereology and Leprology*, **88**, 590-597. https://doi.org/10.25259/IJDVL_533_2021

[12] Deplewski, D. and Rosenfield, R.L. (2000) Role of Hormones in Pilosebaceous Unit Development. *Endocrine Reviews*, **21**, 363-392. https://doi.org/10.1210/edrv.21.4.0404

[13] Beier, K., Ginez, I. and Schaller, H. (2005) Localization of Steroid Hormone Receptors in the Apocrine Sweat Glands of the Human Axilla. *Histochemistry and Cell*

Biology, **123**, 61-65. https://doi.org/10.1007/s00418-004-0736-3

[14] Inui, S. and Itami, S. (2011) Molecular Basis of Androgenetic Alopecia: From Androgen to Paracrine Mediators through Dermal Papilla. *Journal of Dermatological Science*, **61**, 1-6. https://doi.org/10.1016/j.jdermsci.2010.10.015

[15] Yang, Z., Yu, H., Cheng, B., Tang, W., Dong, Y., Xiao, C., *et al*. (2009) Relationship between the CAG Repeat Polymorphism in the Androgen Receptor Gene and Acne in the Han Ethnic Group. *Dermatology*, **218**, 302-306. https://doi.org/10.1159/000202983

[16] Lolli, F., Pallotti, F., Rossi, A., Fortuna, M.C., Caro, G., Lenzi, A., *et al*. (2017) Androgenetic Alopecia: A Review. *Endocrine*, **57**, 9-17. https://doi.org/10.1007/s12020-017-1280-y

[17] Lai, J.J., Chang, P., Lai, K.P., Chen, L. and Chang, C. (2012) The Role of Androgen and Androgen Receptor in Skin-Related Disorders. *Archives of Dermatological Research*, **304**, 499-510. https://doi.org/10.1007/s00403-012-1265-x

[18] Bernerd, F., Schweizer, J. and Demarchez, R. (1996) Dermal Cysts of the Rhino Mouse Develop into Unopened Sebaceous Glands. *Archives of Dermatological Research*, **288**, 586-595. https://doi.org/10.1007/BF02505261

[19] Bettoli, V., Zauli, S. and Virgili, A. (2015) Is Hormonal Treatment Still an Option in Acne Today? *British Journal of Dermatology*, **172**, 37-46. https://doi.org/10.1111/bjd.13681

[20] Liao, D.J. and Dickson, R.B. (2002) Steroid Hormone-Growth Factor Interactions in Proliferative Controls of the Mammary Gland and Breast Cancer: A Rapidly Evolving Perspective. *Journal of Steroid Biochemistry and Molecular Biology*, **80**, 135-136. https://doi.org/10.1016/S0960-0760(01)00181-9

[21] Habeshian, K.A. and Cohen, B.A. (2020) Current Issues in the Treatment of Acne Vulgaris. *Pediatrics*, **145**, S225-S30. https://doi.org/10.1542/peds.2019-2056L

[22] Leyden, J., Stein-Gold, L. and Weiss, J. (2017) Why Topical Retinoids Are Mainstay of Therapy for Acne. *Dermatologic and Therapy*, **7**, 293-304. https://doi.org/10.1007/s13555-017-0185-2

[23] Thiboutot, D.M., Dreno, B., Abanmi, A., Alexis, A.F., Araviiskaia, E., Barona Cabal, M.I., *et al*. (2018) Practical Management of Acne for Clinicians: An International Consensus from the Global Alliance to Improve Outcomes in Acne. *Journal of the American Academy of Dermatology*, **78**, S1-S23. https://doi.org/10.1016/j.jaad.2017.09.078

[24] Ghasemiyeh, P., Azadi, A., Daneshamouz, S., Heidari, R., Azarpira, N. and Mohammadi-Samani, S. (2019) Cyproterone Acetate-Loaded Nanostructured Lipid Carriers: Effect of Particle Size on Skin Penetration and Follicular Targeting. *Pharmaceutical Development and Technology*, **24**, 812-823. https://doi.org/10.1080/10837450.2019.1596133

[25] Santhosh, P. and George, M. (2021) Clascoterone: A New Topical Anti-Androgen for Acne Management. *International Journal of Dermatology*, **60**, 1561-1565. https://doi.org/10.1111/ijd.15752

[26] Lai, J.J., Lai, K.-P., Chuang, K.-H., Chang, P., Yu, I.-C., Lin, W.-J., *et al*. (2009) Monocyte/Macrophage Androgen Receptor Suppresses Cutaneous Wound Healing in Mice by Enhancing Local TNF-α Expression. *Journal of Clinical Investigation*, **119**, 3739-3751. https://doi.org/10.1172/JCI39335

[27] Kim, G.K. and Del Rosso, J.Q. (2012) Oral Spironolactone in Post-teenage Female Patients with Acne Vulgaris: Practical Considerations for the Clinician Based on Current Data and Clinical Experience. *The Journal of Clinical and Aesthetic Der-*

matology, **5**, 37-50.

[28] Dikensoy, E., Balat, O., Pence, S., Akcali, C. and Cicek, H. (2009) The Risk of Hepatotoxicity during Long-Term and Low-Dose Flutamide Treatment in Hirsutism. *Archives of Gynecology and Obstetrics*, **279**, 321-327. https://doi.org/10.1007/s00404-008-0719-z

[29] Bahta, A.W., Farjo, N., Farjo, B. and Philpott, M.P. (2008) Premature Senescence of Balding Dermal Papilla Cells *in Vitro* Is Associated with $p16^{INK4a}$ Expression. *Journal of Investigative Dermatology*, **128**, 1088-1094. https://doi.org/10.1038/sj.jid.5701147

[30] Yang, Y.C., Fu, H.C., Wu, C.Y., Wei, K.T., Huang, K.E. and Kang, H.Y. (2013) Androgen Receptor Accelerates Premature Senescence of Human Dermal Papilla Cells in Association with DNA Damage. *PLOS ONE*, **8**, e79434. https://doi.org/10.1371/journal.pone.0079434

[31] Yu, N., Hu, T., Yang, H., Zhang, L., Zhu, L., Zhou, X., *et al*. (2022) Androgen Receptor Inhibits the Hair Follicle Induction Potential of Dermal Papilla Cells by Binding with Tcf4 at the A574 Binding Site. *Genes & Diseases*. https://doi.org/10.1016/j.gendis.2022.04.015

[32] Irwig, M.S. and Kolukula, S. (2011) Persistent Sexual Side Effects of Finasteride for Male Pattern Hair Loss. *The Journal of Sexual Medicine*, **8**, 1747-1753. https://doi.org/10.1111/j.1743-6109.2011.02255.x

[33] Sato, A. and Takeda, A. (2012) Evaluation of Efficacy and Safety of Finasteride 1 mg in 3177 Japanese Men with Androgenetic Alopecia. *Journal of Dermatological Science*, **39**, 27-32. https://doi.org/10.1111/j.1346-8138.2011.01378.x

[34] Olsen, E.A., Hordinsky, M., Whiting, D., Stough, D., Hobbs, S., Ellis, M.L., *et al*. (2006) The Importance of Dual 5α-Reductase Inhibition in the Treatment of Male Pattern Hair Loss: Results of a Randomized Placebo-Controlled Study of Dutasteride versus Finasteride. *Journal of the American Academy of Dermatology*, **55**, 1014-1023. https://doi.org/10.1016/j.jaad.2006.05.007

[35] Kelly, Y., Blanco, A. and Tosti, A. (2016) Androgenetic Alopecia: An Update of Treatment Options. *Drugs*, **76**, 1349-1364. https://doi.org/10.1007/s40265-016-0629-5

[36] Nestor, M.S., Ablon, G., Gade, A., Han, H. and Fischer, D.L. (2021) Treatment Options for Androgenetic Alopecia: Efficacy, Side Effects, Compliance, Financial Considerations, and Ethics. *Journal of Cosmetic Dermatology*, **20**, 3759-3781. https://doi.org/10.1111/jocd.14537

[37] Sinclair, R.D. (2018) Female Pattern Hair Loss: A Pilot Study Investigating Combination Therapy with Low-Dose Oral Minoxidil and Spironolactone. *International Journal of Cosmetic Dermatology*, **57**, 104-109. https://doi.org/10.1111/ijd.13838

[38] Coneac, A., Muresan, A. and Orasan, M.S. (2014) Antiandrogenic Therapy with Ciproterone Acetate in Female Patients Who Suffer from Both Androgenetic Alopecia and Acne Vulgaris. *Clujul Medical*, **87**, 226-234. https://doi.org/10.15386/cjmed-386

[39] Dhillon, S. (2020) Clascoterone: First Approval. *Drugs*, **80**, 1745-1750. https://doi.org/10.1007/s40265-020-01417-6

[40] Yazdabadi, A. and Sinclair, R. (2011) Treatment of Female Pattern Hair Loss with the Androgen Receptor Antagonist Flutamide. *Australasian Journal of Dermatology*, **52**, 132-134. https://doi.org/10.1111/j.1440-0960.2010.00735.x

[41] Dominguez-Santas, M., Diaz-Guimaraens, B., Saceda-Corralo, D., Hermosa-Gelbard, A., Arrones, O.M.M., Pindado-Ortega, C., *et al*. (2022) The State-of-the-Art in the

Management of Androgenetic Alopecia: A Review of New Therapies and Treatment Algorithms. *JEADV Clinical Practice*, **1**, 176-185. https://doi.org/10.1002/jvc2.53

[42] Saceda-Corralo, D., Dominguez-Santas, M., Vano-Galvan, S. and Grimalt, R. (2022) What's New in Therapy for Male Androgenetic Alopecia? *American Journal of Clinical Dermatology*. https://doi.org/10.1007/s40257-022-00730-y

[43] Li, M., Marubayashi, A., Nakaya, Y., Fukui, K. and Arase, S. (2001) Minoxidil-Induced Hair Growth Is Mediated by Adenosine in Cultured Dermal Papilla Cells: Possible Involvement of Sulfonylurea Receptor 2B as a Target of Minoxidil. *Journal of Investigative Dermatology*, **117**, 1594-1600. https://doi.org/10.1046/j.0022-202x.2001.01570.x

[44] Inui, S. and Itami, S. (2007) Reversal of Androgenetic Alopecia by Topical Ketoconzole: Relevance of Anti-Androgenic Activity. *Journal of Dermatological Science*, **45**, 66-68. https://doi.org/10.1016/j.jdermsci.2006.08.011

[45] Fields, J.R., Vonu, P.M., Monir, R.L. and Schoch, J.J. (2020) Topical Ketoconazole for the Treatment of Androgenetic Alopecia: A Systematic Review. *Dermatologic Therapy*, **33**, e13202. https://doi.org/10.1111/dth.13202

[46] Bienenfeld, A., Azarchi, S., Lo Sicco, K., Marchbein, S., Shapiro, J. and Nagler, A.R. (2019) Androgens in Women: Androgen-Mediated Skin Disease and Patient Evaluation. *Journal of the American Academy of Dermatology*, **80**, 1497-1506. https://doi.org/10.1016/j.jaad.2018.08.062

[47] Souter, I., Sanchez, L.A., Perez, M., Bartolucci, A.A. and Azziz, R. (2004) The Prevalence of Androgen Excess among Patients with Minimal Unwanted Hair Growth. *American Journal of Obstetrics and Gynecology*, **191**, 1914-1920. https://doi.org/10.1016/j.ajog.2004.06.064

[48] Hussein, R.S. and Abdelbasset, W.K. (2022) Updates on Hirsutism: A Narrative Review. *International Journal of Biomedicine*, **12**, 193-198. https://doi.org/10.21103/Article12(2)_RA4

[49] Wolf Jr., J.E., Shander, D., Huber, F., Jackson, J., Lin, C.-S., Mathes, B.M., *et al*. (2007) Randomized, Double-Blind Clinical Evaluation of the Efficacy and Safety of Topical Eflornithine HCl 13.9% Cream in the Treatment of Women with Facial Hair. *International Journal of Dermatology*, **46**, 94-98. https://doi.org/10.1111/j.1365-4632.2006.03079.x

[50] Mastorakos, G., Koliopoulos, C. and Creatsas, G. (2002) Androgen and Lipid Profiles in Adolescents with Polycystic Ovary Syndrome Who Were Treated with Two Forms of Combined Oral Contraceptives. *Fertility and Sterility*, **77**, 919-927. https://doi.org/10.1016/S0015-0282(02)02993-X

[51] Mofid, A., Seyyed Alinaghi, S.A., Zandieh, S. and Yazdani, T. (2008) Hirsutism. *International Journal of Clinical Practice*, **62**, 433-443. https://doi.org/10.1111/j.1742-1241.2007.01621.x

[52] Swiglo, B.A., Cosma, M., Flynn, D.N., Kurtz, D.M., Labella, M.L., Mullan, R.J., *et al*. (2008) Clinical Review: Antiandrogens for the Treatment of Hirsutism: A Systematic Review and Metaanalyses of Randomized Controlled Trials. *Journal of Clinical Endocrinology & Metabolism*, **93**, 1153-1160. https://doi.org/10.1210/jc.2007-2430

[53] Mimoto, M.S., Oyler, J.L. and Davis, A.M. (2018) Evaluation and Treatment of Hirsutism in Premenopausal Women. *JAMA*, **319**, 1613-1614. https://doi.org/10.1001/jama.2018.2611

[54] Hu, A.C., Chapman, L.W. and Mesinkovska, N.A. (2019) The Efficacy and Use of Finasteride in Women: A Systematic Review. *International Journal of Dermatology*, **58**, 759-776. https://doi.org/10.1111/ijd.14370

[55] Chiesa Fuxench, Z.C., Block, J.K., Boguniewicz, M., Boyle, J., Fonacier, L., Gelfand, J.M., *et al*. (2019) Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. *Journal of Investigative Dermatology*, **139**, 583-590. https://doi.org/10.1016/j.jid.2018.08.028

[56] Torres, T., Ferreira, E.O., Goncalo, M., Mendes-Bastos, P., Selores, M. and Filipe, P. (2019) Update on Atopic Dermatitis. *Acta Medica Portuguesa*, **32**, 606-613. https://doi.org/10.20344/amp.11963

[57] Gratton, R., Del Vecchio, C., Zupin, L. and Crovella, S. (2022) Unraveling the Role of Sex Hormones on Keratinocyte Functions in Human Inflammatory Skin Diseases. *International Journal of Molecular Sciences*, **23**, Article 3132. https://doi.org/10.3390/ijms23063132

[58] Kissick, H.T., Sanda, M.G., Dunn, L.K., Pellegrini, K.L., On, S.T., Noel, J.K., *et al*. (2014) Androgens Alter T-Cell Immunity by Inhibiting T-Helper 1 Differentiation. *Proceedings of the National Academy of Sciences of the United States of America*, **111**, 9887-9892. https://doi.org/10.1073/pnas.1402468111

[59] Walecki, M., Eisel, F., Klug, J., Baal, N., Paradowska-Dogan, A., Wahle, E., *et al*. (2015) Androgen Receptor Modulates Foxp3 Expression in CD4+CD25+Foxp3+ Regulatory T-Cells. *Molecular Biology of the Cell*, **26**, 2845-2857. https://doi.org/10.1091/mbc.E14-08-1323

[60] Chuang, K.H., Altuwaijri, S., Li, G., Lai, J.J., Chu, C.Y., Lai, K.P., *et al*. (2009) Neutropenia with Impaired Host Defense against Microbial Infection in Mice Lacking Androgen Receptor. *Journal of Experimental Medicine*, **206**, 1181-1199. https://doi.org/10.1084/jem.20082521

Questions (Answers Provided after Questions)

1) (True/False) The ligand binding domain (LBD) consists of 11 α-helices.

A. True

B. False

2) (True/False)AR only works through androgens.

A. True

B. False

3) Which enzyme is the most common cutaneous symptom of PCOS?

A. Hirsutism

B. Alopecia

C. Acne

4) Which enzyme irreversibly converts testosterone to DHT?

A. Steroid sulfatase

B. 5α-reductase

C. 3β-HSD

5) DHT is the most potent naturally occurring androgen in tissue.

A. True

B. False

6) Flutamide is a competitive antagonist of the androgen receptor.

A. True

B. False

7) Topical retinoids are the treatment of choice for all acne.

A. True

B. False

8) Finasteride is a more potent 5α-reductase inhibitor than dutasteride.

A. True

B. False

9) Which of the following drugs is used in the androgen-independent therapies of AGA?

A. Pyrilutamide

B. Flutamide

C. Minoxidil

10) GT-20029 first topical drug used PROTAC in the treatment of androgenic alopecia.

A. True

B. False

Answers

1) A

2) B

3) A

4) B

5) A

6) A
7) A
8) B
9) C
10) A