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Review

Adult Female Acne: Recent Advances in Pathophysiology and Therapeutic Approaches

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Abstract: Adult acne is a chronic inflammatory disease of the pilosebaceous unit characterized by the excessive production of abnormal sebum favoring an imbalance of the skin microbiota and the hyperproliferation of *Cutibacterium acnes* and other virulent microbial strains, leading to an inflammatory environment, innate immunity overactivation, and keratinocyte hyperproliferation in hair follicles pores. Degraded keratinocytes plug the pores, consequently forming microcomedons, which can later evolve to papules, nodules, pustules and scars. Distinct from juvenile acne, in adult female acne (AFA) the symptomatology occurs or persists in postadolescence (after age 25). Although hyperandrogenism or the excessive sensitivity of androgen receptors are the main causes, AFA can be triggered by multiple factors, either including or not including androgen disturbances. The prevalence in adult women is 15–20%. Hyperandrogenism is present in 50% of cases; 70% of hyperandrogenism cases feature polycystic ovary syndrome (PCOS), a complex endocrine and metabolic condition. Genetic susceptibility occurs in 80% of acne cases, often with familial inheritance. Beyond classical stepwise therapeutic protocols (topical agents, isotretinoin, antibiotics, hormonal therapy with estrogens, progestins, spironolactone), novel approaches include the highly effective topical antiandrogen clascoterone, the management of insulin resistance by diet, exercise, stress avoidance, and adjuvant therapies such as berberine. Vaccines against the pathogenic proinflammatory *C. acnes* hyaluronidase A are in development.

Keywords: adult female acne; hormonal acne; hyperandrogenism; polycystic ovary syndrome; insulin resistance; genetic studies; antiandrogens

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1. Introduction

Considering the increasing number of acne cases after puberty, this pathology cannot be considered a disease of adolescence anymore, as it significantly affects sufferer's quality of life, possibly leading to depression and social anxiety [1].

The worldwide occurrence of acne among women across all age brackets stands at approximately 10% [2,3], with large variations across age groups [4]. Among adult women, the prevalence of acne ranges from 15 to 20% [5], with 20 to 30% of these cases exhibiting hirsutism [6], while a proportion varying between 18 and 88% demonstrate elevated androgen levels [7]. This suggests that the primary etiological factor lies in either heightened androgen secretion or the increased sensitivity of androgen receptors [8].

The majority of authors define acne as a chronic inflammatory illness affecting the pilosebaceous gland, resulting in increased sebum production. Although patients have a polymorphic clinical picture similar to *acne vulgaris*, adult female acne (AFA), also named postadolescent acne or hormonal acne, is defined as a chronic inflammatory disease of the pilo-sebaceous follicle predominantly distributed in the lower third of the face, appearing especially in adult women over 25 years of age [9].

So far, two clinical forms of AFA have been described: 1. the inflammatory form (accounting for 58% of cases), presenting papulopustular lesions and nodules that often result in residual hyperpigmentation; hyperseborrhea may not always be evident with this form, mainly located at the mandible level, and 2. the retention form, manifested by open comedones and microcystic lesions, with a reduced number of inflammatory lesions; hyperseborrhea is consistently present, affecting not only the jawline but also the upper facial areas, particularly the forehead [10]. In terms of evolutionary progression, AFA can be categorized into three groups: persistent acne (the most prevalent type), late-onset acne (developing for the first time after age 25), and recurrent acne (emerging during adolescence, disappearing for several years, then resurfacing in adulthood) [1,10].

Multiple factors contribute to the development of hormonal acne in adult women, including genetic predispositions, hormonal fluctuations, and external influences such as diet, smoking, heightened stress levels, skincare products, and use of medication. Chronic inflammation is particularly significant in this process. The scientific literature supports the hormonal hypothesis regarding the origin of AFA, which stems from the increased activity in androgen hormone metabolism and related enzymes like 5α-reductase. These enzymes are expressed in the skin hair follicles keratinocytes and sebaceous glands, as well as in the gonads (ovaries and testicles). They catalyze the conversion of testosterone to its active form, dihydrotestosterone (DHT), which exhibits a stronger binding affinity to human androgen receptors (AR) than testosterone. Consequently, the DHT-androgen receptor complex is considerably more stable [4,11].

Although the general pathophysiology of acne is exquisitely complex, most authors consider four fundamental processes at hair follicle level (Figure 1), interconnected by a large and variable network of feedback loops. The main triggers of the disease are androgens, particularly dehydroepiandrosterone sulfate (DHEAS) reconverted to active androgens like testosterone and DHT by steroid-metabolizing enzymes of follicular keratinocytes. Androgens stimulate keratinocyte proliferation and sebaceous glands secretion, producing the comedo plug, which is rapidly colonized by pathogenic *C. acnes* strains. These bacteria convert sebum lipids into free fatty acids, further promoting bacterial growth, while sebum lipoperoxides and bacterial factors trigger innate immunity and inflammatory mechanisms [12]. However, *C. acnes* is ubiquitous in sebaceous glands-containing skin after puberty, therefore the model stating its hyperproliferation in comedo-plugged follicles seems outdated; it seems rather that highly pathogenic and virulent variants contribute to acne dysbiosis [13–15].

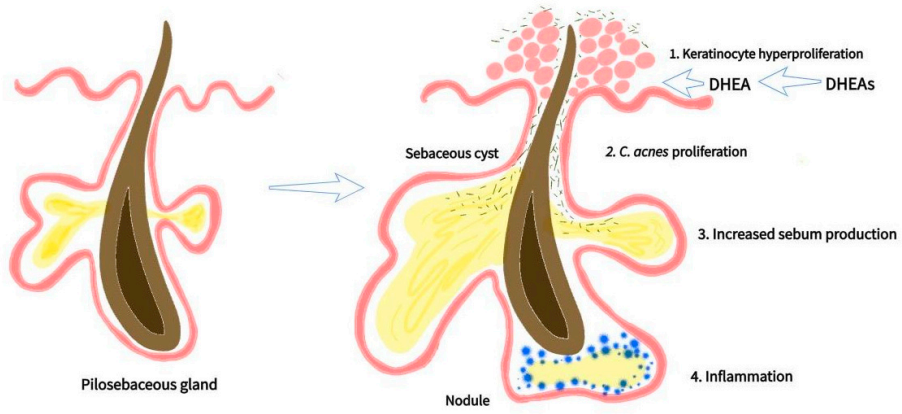

Figure 1. The main four pathophysiological processes involved in cutaneous acne lesions.

The distention of microcomedones eventually results in their rupture in the surrounding skin, inoculating the dermis with cell debris, keratin, sebum and bacteria, which trigger an acute inflammatory reaction [16]. Perifollicular CD4+ lymphocytes quickly invade the lesions during the first day, followed after 24 h by neutrophils, but the former play an essential role by activating specific pathways, such as the following: TLR2 and IFN-γ

signaling in Th1 cells with IL-12 secretion, TGF-β, IL-1β and IL-6 signaling in Th17 cells with the inhibition of Treg (Foxp3^{+}) cells [17], and TLR2,4 and NLRP3 inflammasome activation in macrophages with signal transmission along NF-κB, MAPK and caspase-1 pathways, resulting in increased IL-1β, TNF-α, IL-8 and IL-12 secretion [14] and many other molecular events. Both the innate and adaptive immune system play a role in acne, and there is a temporal and stage-dependent succession in perilesional cell infiltration and inflammatory signals [18]. The neurogenic component of inflammation is also important, and a remarkable electron microscopy study proved the existence of ultrastructural changes induced in sebaceous gland cells by neuropeptides such as substance P [19].

The aim of this study was to perform a systematic review focused on the pathophysiology of AFA and a related condition, polycystic ovary syndrome (PCOS), particularly on novel discoveries and genetic/epigenetic findings, as well as to highlight new therapeutic approaches. The relevant literature was retrieved by performing searches of the PubMed database with the keyword combination "adult female acne", "hormonal acne", and the same terms combined with "AND treatment".

2. New Insights into the Pathophysiology of AFA and PCOS

2.1. Hyperandrogenism and Increased AR Sensitivity

Hyperandrogenism was for a long time suspected to play a major role in the etiopathogenesis of AFA, hence the alternate name hormonal acne. The variation in acne prevalence with age is an indirect proof, with values ranging from 50 to 55% in high school or college students which are related to puberty-induced hormonal changes, to 40% in master/PhD students, and to negligible frequencies during menopause [4]. The overall prevalence in women of all ages amounts to 10–15% [2,3]. AFA prevalence in adult women varies between 15 and 20% [5]; within this patient group, approximately 20–30% also present hirsutism [6], and over 50% on the average feature high levels of circulating androgens [7]. Overall, these data suggest that the major cause of AFA is the increased secretion of androgens and/or an excessively high sensitivity to androgen receptors (AR) [8]. Thus, AFA pertains to the larger group of **hyperandrogenism disorders**, which can present as clinical features *acne*, *seborrhea*, hair loss on the scalp with a specific pattern—*androgenetic alopecia* (AGA)—*hirsutism* at face or body level, and *oligo/amenorrhea*. A total of 70% of hyperandrogenism states are caused by **polycystic ovary syndrome** (PCOS), and the rest by other conditions such as congenital adrenal hyperplasia (CAH), Cushing's syndrome, hyperprolactinemia, insulin resistance (IR), and certain malignant tumors or treatments [20]. The consensus document that established the Rotterdam PCOS diagnosis criteria defined hyperandrogenism based on *clinical criteria*, the most important one being hirsutism, as well as *biochemical criteria* such as circulating androgens levels [21]. Total and free testosterone levels are the most sensitive markers, but a few patients can feature isolated increases in DHEAS (dehydroepiandrosterone sulphate). Another useful marker is androstenedione, which can be moderately increased in non-classic adrenal hyperplasia (NCAH), an autosomal recessive disorder produced by a 21-hydroxylase deficit. Measuring matinal basal levels of 17-hydroxyprogesterone is useful to exclude this condition. Thyroid-stimulating hormone (TSH) levels measurement is of limited utility, while serum follicle-stimulating hormone (FSH) and estradiol (E2) levels are useful to exclude hypogonadotropic hypogonadism, and the endocrine disorder caused by central hypothalamo-hypophyseal conditions. PCOS was characterized as belonging to normoestrogenic normogonadotropic anovulatory states (group 2 according to the WHO classification). Also, serum prolactin level measurements are useful to exclude hyperprolactinemia, although many hyperandrogenism patients feature prolactin levels trending to the upper limit of normal or slightly increased.

The steroid hormones synthesis pathway (Figure 2) features several enzymes located in different organs and tissues, including gonads (ovary/testis), cortical adrenal glands and the epidermis (Figure 2). Starting from cholesterol, we can distinguish a **progestagens** (21 carbon atoms) **synthesis pathway**, continued with the **corticosteroid synthesis pathway**, which features two enzymes (11-β-hydroxylase and aldosterone synthase) and three prod-

ucts (cortisol, corticosterone and aldosterone). The prostagens pathway is coupled with the **androgens** (19 carbon atoms) **synthesis pathway** continued with the **estrogens** (18 carbon atoms) **synthesis pathway** by the enzyme 17–20 lyase acting on two progestagen intermediates, 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, and transforming them into dehydroepiandrosterone (DHEA) and androstenedione, respectively. One enzyme is common for all pathways: 3-β-hydroxysteroid dehydrogenase (3β-HSD); 17α-hydroxylase and 21-hydroxylase are specific for the progestagens synthesis pathway, and 17β-HSD and 5α-reductase are specific for the androgens synthesis pathway. Aromatase converts androgens into estrogens: androstenedione into estrone, which is later converted into estriol (E3) by the liver and placenta enzymes, and testosterone into estradiol (E2), later also converted into E3. A majority of these enzymes are located in the smooth endoplasmic reticulum, except for 11β-hydroxylase (11β-HSD), aldosterone synthase and cholesterol side-chain cleavage enzymes, which are mitochondrial. In women, androgen- and estrogen-producing enzymes are located in the thecal and granulosa cells of maturating ovarian follicles, being controlled by the hypophyseal gonadotropic hormones FSH and LH. In the cortical adrenal glands, 17α-hydroxypregnenolone is converted into 17α-hydroxyprogesterone, and further into androgens (androstenedione and testosterone) and corticosteroids (11-deoxycortisol and cortisol); however, small amounts of 17α-hydroxypregnenolone are also converted into DHEA, which is transported at skin level as an inert sulphated derivative (DHEAS). This compound can be easily reconverted into DHEA and further processed into androstenedione, testosterone and dihydrotestosterone (DHT) by active hair follicle keratinocytes, which feature higher expression levels of 17β-HSD and 5α-reductase compared to epidermal keratinocytes [12]. This augmented androgen synthesis by follicular keratinocytes also increases their proliferation rate. Increased local androgen levels stimulate sebocyte activity, resulting in increased sebum secretion.

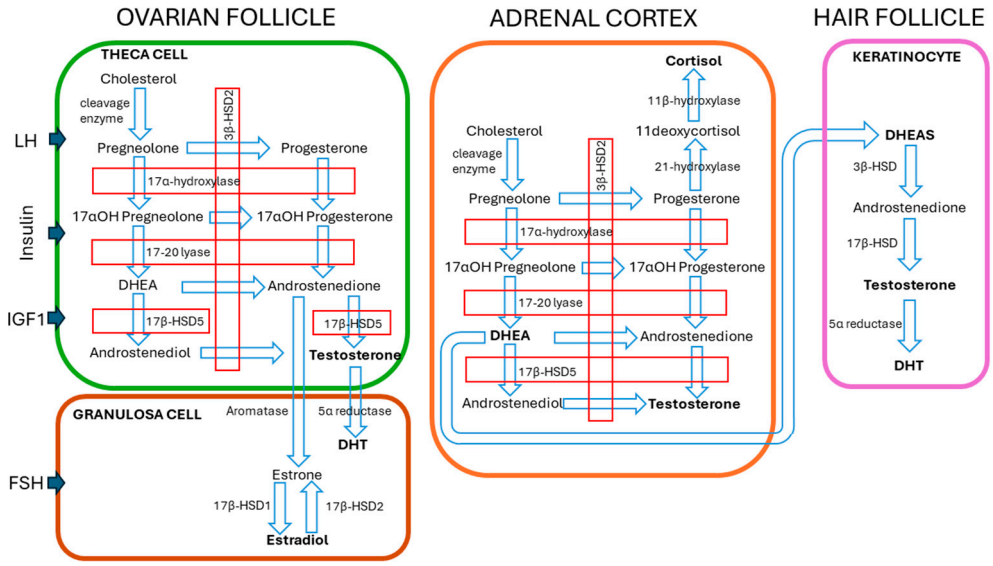

Figure 2. Steroid hormones synthesis pathways active in ovarian follicles (theca and granulosa cells), adrenal cortex and hair follicle keratinocytes, leading to androgen production.

2.2. Endocrine Disturbances Affecting Follicle Maturation and Ovulation

In humans, oocytes are formed during embryogenesis, when oogonia enter the gonadal ridge and proliferate by mitosis until the second or third trimester of pregnancy. They become surrounded by pregranulosa cells, forming primordial follicles. Thereafter, oogonia stop dividing and enter the prophase of the first meiotic division, remaining dormant in the dictyotene stage for decades, until follicular maturation and ovulation driven by the preovulatory LH peak. During each menstrual cycle, one or a few dominant follicles increase in size, become mature and undergo ovulation. Dominant follicles receive a

stronger FSH stimulus for maturation in their granulosa cells due to a larger size, better vascularization and a higher density of FSH receptors, and also start to express LH receptors; therefore they can survive falling FSH levels occurring by a feedback mechanism when granulosa aromatase activity increases, resulting in increased estrogen and inhibin secretion. Meanwhile, the FSH drop will drive the non-dominant follicles into an atretic state, with a regression in size followed by deterioration.

Some researchers hypothesized that PCOS is primarily the result of fetal exposure to increased levels of androgens that inhibit folliculogenesis, as suggested by finding polycystic ovaries in girls before puberty [22]. Fetal ovarian androgens may be produced in response to increased maternal human chorionic gonadotropin (HCG) in subjects with genetic susceptibility, and excessive testosterone secretion may be accompanied by pregnancy hyperglycemia and fetal hyperinsulinemia, resulting in epigenetic reprogramming disturbances in fetal primordial follicles leading to PCOS [23]. The progestagens and androgens synthesis pathways are primarily active in follicular thecal cells, under hormonal control exerted by LH, insulin and insulin-like growth factor (IGF) receptors, while dihydrotestosterone (DHT), estrone and estradiol (E2) are produced in granulosa cells by 5α-reductase, aromatase, and 17β-HSD following the activation of FSH receptors [11]. In PCOS thecal cells feature increased sensitivity to LH receptors due to the dysfunction of inhibitory feedback resulting in receptor downregulation, as well as IR and hyperinsulinemia. Increased androgen secretion by PCOS thecal cells results from an increased expression of 17α-hydroxylase, 17–20 lyase and cholesterol side-chain cleavage enzymes, as proved by in vitro experiments [24].

Altered follicular LH sensitivity in PCOS produces multiple endocrine feedback imbalances, resulting in GnRH (gonadotropin-releasing hormone) hyperpulsatility and a resistance to progesterone-induced negative feedback. Subsequently, the amplitude and frequency of preovulatory LH peaks increase, a phenomenon that can be alleviated by antiandrogens such as flutamide which can restore hypothalamic sensitivity to estrogens and progesterone [25]. In total, 55% to 75% of PCOS patients feature an excessive hypophyseal LH secretion and altered LH/FSH ratios upon hyperstimulation by GnRH, but it is not yet clear if the hypothalamus-hypophyseal dysfunction primarily appears or if it is subsequent to androgens/estrogens imbalance [26]. LH hypersecretion and/or increased LH receptor sensitivity may induce early granulosa cells' luteinization, stopping antral follicle growth, as well as activating premature oocyte progression through meiosis, resulting in aneuploidies [27].

Another factor playing a key role in ovarian folliculogenesis is the anti-müllerian hormone (AMH), a member of the GFRβ family (growth factor receptor), secreted by granulosa cells of growing preantral follicles smaller than 4 mm in diameter which inhibits granulosa cell sensitivity to FSH until follicles exceed 8 mm in diameter; after this stage, FSH produces accelerated follicle growth and estrogen secretion resulting in feedback inhibition, dominant follicle selection and ovulation. In PCOS patients, AMH secretion can exceed normal levels up to 75-fold, resulting in the increased recruitment of antral follicles featuring premature differentiation and growth stop [28]. These increased AMH levels are associated with increased LH or androgens levels, and may impede oocyte maturation, fertilization rates, as well as result in low embryo quality during in vitro fertilization procedures [29]. Other signaling factors that may impede follicle growth and maturation are TGF-β family members like bone morphogenetic (BMP) factors, activin, follistatin, β inhibins, the vascular endothelial growth factor (VEGF), other cytokines like interleukins (IL), tumor necrosis factor alpha (TNF-α), FS-7 associated surface antigen (FAS receptor), also known as TNF receptor superfamily member 6 (TNFRSF6) or CD95 and its ligand FASL, miRNAs, etc. [11,23].

Hyperinsulinemia can activate ovarian steroidogenesis by acting on both theca and granulosa cells, stimulating thecal cell proliferation, LH receptor-mediated androgens synthesis, and LH and IGF receptors expression [30], and similar effects can occur at the cortical adrenal level [31]. Insulin also promotes hyperandrogenism via inhibiting the syn-

thesis by hepatocytes of the sex hormone-binding globulin (SHBG) and insulin-like growth factor-binding protein 1 (IGFBP1), also known as placental protein 12 (PP12). Insulin action on follicular cells occurs via the inositol glycan system, which may explain the increased urinary inositol found in some PCOS patients [32]. A rare autosomal recessive disorder first described in the 1950s [33] is the Rabson–Mendenhall syndrome, caused by mutations in the insulin receptor gene leading to hyperinsulinemia, head, face (prognathism and senile-like face), teeth and nails abnormalities, *acanthosis nigricans*, enlarged genitalia and early puberty, as well as extreme hirsutism. The condition is commonly associated with Donohue syndrome (leprechaunism) [34]. It was proved that these diseases result from a combination of reduced insulin receptor sensitivity and a defective autophosphorylation [35]. The first proof of hyperinsulinemia and altered glucose tolerance in PCOS patients was brought in 1980, including the intriguing finding that some patients with classical PCOS featured *acanthosis nigricans* [36]. Insulin resistance in PCOS is not ubiquitous, occurring at muscle and adipose tissue level but not in ovarian follicles. Therefore, at this level, in theca cells, insulin signaling can activate androgen production by stimulating 17α-hydroxylase and 3β-HSD isoform 2 [37].

2.3. Genetic Insights in AFA and PCOS

Acne in general and particularly AFA have for a long time been considered diseases with associated genetic susceptibility. In an extensive review of acne histopathology, Albert Kligman stated that, in spite of the fact that the genetics of acne is poorly understood, it definitely presents features of a polygenic condition without a clear Mendelian inheritance pattern, whereby multiple susceptibility genes exert moderate but synergic predisposing effects, none of them playing a decisive role by itself [38]. Indeed, numerous epidemiology studies have confirmed the hypothesis of hereditary predisposition. A large cohort study on British subjects with "persistent acne" with ages between 26 and 78 years proved that a positive family history of acne increased the individual risk between 2.3 and 4.69-fold [39,40]. A retrospective study performed on British monozygote and dizygote twin pairs revealed that 41% of acne patients transmitted the disease to the progeny, 47% of them had affected first degree relatives, and for 25% of them their parents were affected by the same condition [41]. A very important study was performed in China on a group of 238 patients with *acne vulgaris* and 207 control subjects [42]. The authors found a variable number of CAG/GGN repeats in the N-terminal transcription activation domain (TAD) of the first exon of the AR gene, encoding polyglutamine/polyglycine sequences of variable length associated with different gene transcription transactivation efficiencies; they proved that acne patients presented shorter triplet repeats than controls (CAG<23/GGN $\leq$23, odds ratio OR = 3.33, $p < 0.05$), resulting in higher AR expression levels and increased androgen sensitivity. This finding explains acne susceptibility in subjects with an increased sensitivity of AR, who do not necessarily feature increased androgen levels, and can account for the approximately 50% of AFA cases not associated with increased androgen levels [7]. Other single-nucleotide polymorphysms (SNP) generally associated with *acne vulgaris* were identified in genes of innate immune system components: the 308 G/A polymorphism in the TNF gene [43], M196R in the TNFR2 gene and R753N in the TLR2 gene [44], 4845 G>T in the IL-1α gene [45], and several others; a comprehensive review on this topic is that of Zhang and Zhang 2023 [46]. Unsurprisingly, significant associations with acne were found for SNPs in genes of steroid synthesis pathways, such as 34 T/C in cytP450c17α (CYP17), encoding an enzyme with the function of both 17α-hydroxylase and 17–20 lyase [47]; T>C at −34 bp in the promoter of the same gene and T>C (W/R) in the codon 39 of CYP19A1 encoding aromatase (SNP code: rss2236722) [48]; several haplotypes of CYP21A2 encoding 21-hydroxylase [49]; as well as SNPs in CYP1A1, encoding aryl hydrocarbon hydroxylase (AHH), an enzyme converting polyunsaturated fatty acids into proinflammatory signaling molecules like epoxides [50]. We should add that gene mutations leading to 21-hydroxylase deficiency are the main cause of non-classic congenital adrenal hyperplasia (NCAH), a condition that has to be excluded in the differential diagnosis of hyperandrogenism [51].

Similar findings occurred in genetic susceptibility studies on patients with AFA and PCOS. For example, an epidemiology study on a group of 93 PCOS patients retrieved the disease in significant proportions of their first degree relatives: 35% of mothers prior to menopause and without hormone therapy, and 40% of sisters [52]. Another cohort study on 1332 monozygotic twin sisters and 1873 dizygotic twin sisters or singleton sisters of twins found PCOS occurrence correlation coefficients of 0.71 for monozygotic twin pairs and only 0.38 for dizygotic twins/singletons [53]. Some researchers consider that PCOS-associated mutations offered some selective advantages such as a decrease in the number of descendants, resulting in better maternal outcomes and children thriving, therefore they spread especially across Asian populations [23]. Hypophyseal tropic hormones, particularly the adrenocorticotropic hormone (ACTH), may produce an excessive stimulation of the inner *zona reticularis* of the adrenal cortex in PCOS patients, resulting in the increased conversion of 17α-hydroxyprogesterone into cortisol but also testosterone, and 17α-hydroxypregnenolone conversion into DHEA and further into DHEAS. However, certain gene variants of sulfotransferase 2A1 (SULT2A1) with augmented activity can easily reconvert DHEAS, an inert androgen, into the active DHEA [54]. Similarly, gene variants of cytP450c17α (CYP17) resulting in high enzyme activities can also increase adrenal androgen synthesis, a condition estimated to occur in up to 30% of PCOS patients [55]. Another interesting and complex gene disorder occurs via mutations in 11β-HSD1 and hexose-6-phosphate dehydrogenase, transmitted in a digenic triallelic manner, resulting in decreased cortisol levels and activation via the ACTH feedback of adrenal androgen steroidogenesis [56].

Folliculogenesis and its hormonal modulation are also the main factors of genetic susceptibility in AFA and PCOS. An interesting study performed on 80 PCOS subjects and 24 normal controls identified via whole-genome sequencing (WGS) 24 rare variants (allele frequency < 0.01) in the AMH gene, 18 of them in the PCOS group. When reproduced in pcDNA3.1 plasmids containing the AMH gene transfected into COS-7 simian fibroblasts, only the 18 PCOS-associated variants resulted in signaling deficiencies, as proved by a luciferin–luciferase assay [57]. A related study showed that AMH synthesis in the granulosa cells of PCOS patients with amenorrhea is increased by up to 75-fold [58]. Altered AMH signaling in PCOS may weaken its inhibitory effects on cytP450c17α activity and androgen synthesis, possibly leading to excessive follicular androgen secretion [57]. Many other genetic factors associated with ovarian folliculogenesis have been identified, for example the primordial follicles inhibitory transcriptional factors, such as liver kinase B1-serine/threonine kinase 11 (LKB1/STK11), the expression of which is inhibited by androgens like testosterone and DHT and activated by 17β-estradiol via the estrogen receptor α (ERα), proapoptotic FOX factors secreted by oocytes, some local follicular factors regulating follicle recruitment, growth and development, e.g., growth differentiation factor 9 (GDF9), and bone morphogenetic factors (BMP) 4, 6, 9 and 15, which are members of the transforming growth factor β (TGF-β) family, β inhibins, miRNAs, etc. [11]. Oocyte-secreted GDF9 is the main stimulus for early follicular development, activating the proliferation and differentiation of granulosa cells via a signaling chain represented by BMP receptor 2 followed by TGF-β receptor 1 (ALK-5), and the phosphorylation of SMAD2 and 3, which form a complex with SMAD4 that undergoes nuclear translocation, activating the transcription of specific gene sets [59].

The review by Han Zhao et al. 2016 [60] summarizes the results of several genome-wide association studies (GWAS) performed on groups of PCOS patients of different ethnicities. Thus, a study on a Chinese Han population [61] explored a group of 744 PCOS patients and 895 control healthy women; another study [62] explored an even larger Chinese Han population with 10480 cases in the PCOS group and 10,489 cases in the control group. Furthermore, a study was performed on the Korean population with a group of 976 PCOS cases and 946 control subjects [63], and two studies were performed on European Caucasian populations: one on 984 PCOS patients and 2964 control subjects [64], and another one on 5184 self-reported PCOS patients and 82,759 controls [65]. The results of these wide-scale

studies were significant and there were some overlapping results. Chen et al. 2011 [61] found several SNPs (rs13429458 and rs12478601) located close to the THADA gene (thyroid adenoma associated, or ARMC13—armadillo repeat containing), one SNP (rs13405728) associated with LHCGR (LH/choriogonadotropin receptor), and two SNPs (rs2479106 and rs10818854) close to the DENND1A gene (differentially expressed in normal and neoplastic development isoform A1), encoding a protein named connecdenn 1, expressed on chlatrin-coated membrane invaginations of theca cells where membrane receptors are located. Interestingly, the DENND1A SNP rs2479106 was also found by the other Chinese Han population study [62], as well as the THADA SNP rs13429458 and the LHCGR SNP rs13429458, while the European population study of Day et al. 2015 [65] retrieved the THADA SNP rs7563201 and the YAP1 (yes-associated protein 1, a transcription coregulator of cell proliferation/apoptosis genes) SNP rs11225154, and Shi et al. 2012 [62] retrieved another YAP1 SNP, rs1894116. The Korean population study of Lee et al. 2015 [63] validated one single SNP related to the KHDRBS3 gene. Other PCOS SNPs-related genes found in the European studies were c9orf3/FANCC (Fanconi anemia group C protein), GATA4/NEIL2, KCNA4/FSHB, ERBB4/HER4, FSHB, RAD50 and KRR1. The Chinese Han population study of Shi et al. 2012 [62] retrieved the most PCOS SNPs, related to genes RAB5B/SUOX, HMGA2, C9orf3, FSHR, TOX3, SUMO1P1, INSR, plus the above-mentioned ones. These findings are highly relevant, since DENND1A expression was found in the cortical adrenal gland *zona reticularis*, and other genes encode hormone receptors like the FSH receptor (FSHR), LH receptor (LHCGR), or the insulin receptor (INSR), associated with IR, THADA and HMGA2 involved in type 2 diabetes mellitus, and RAB5B and SUOX located in a susceptibility site for type 1 diabetes [11]. However, a search on the National Cancer Biology Institute (NCBI) gene database with the keyword combination "androgenic acne" retrieved only six entries, listed in Table 1, while a similar search in the OMIM (Online Mendelian Inheritance in Man) database retrieved 57 entries using the "Gene map" display mode; a NCBI Gene database search for "adult female acne" retrieved 52 entries, and a search of the same database for "hormonal acne" retrieved 19 entries (Figure 3). Similar findings are reported in the review by Heng et al. on genetic variability in *acne vulgaris* [66].

Table 1. Entries retrieved from the NCBI Gene database by search with keyword combination "androgenic acne". (MIM—gene identifier in the Online Mendelian Inheritance in Man (OMIM) database.)

Name	Gene ID	Description	Location	Aliases	MIM
FST	10468	Follistatin (*Homo sapiens*)	Chromosome 12, NC_000012.12 (102395874..102481839, complement)	IGF, IGF-I, IGFI, MGF	14,440
IL1B	3553	Interleukin 1 beta (*Homo sapiens*)	Chromosome 2, NC_000002.12 (112829751..112836779, complement)	IL-1, IL1-BETA, IL1F2, IL1beta	147,720
AR	367	Androgen receptor (*Homo sapiens*)	Chromosome X, NC_000023.11 (67544021..67730619)	AIS8, DHTR, HUMARA, HYSP1, KD, NR3C4, SBMA, SMAX1, TFM, AR	313,700
VDR	7421	Vitamin D receptor (*Homo sapiens*)	Chromosome 12, NC_000012.12 (47841537..47904994, complement)	NR1I1, PPP1R163	601,769
CYP17A1	1586	Cytochrome P450 family 17 subfamily A member 1 (*Homo sapiens*)	Chromosome 10, NC_000010.11 (102830531..102837413, complement)	CPT7, CYP17, P450C17, S17AH	609,300
IGF1	24482	Insulin-like growth factor 1 (*Rattus norvegicus*)	Chromosome 7, NC_086025.1 (24169608..24249446)	IGF	

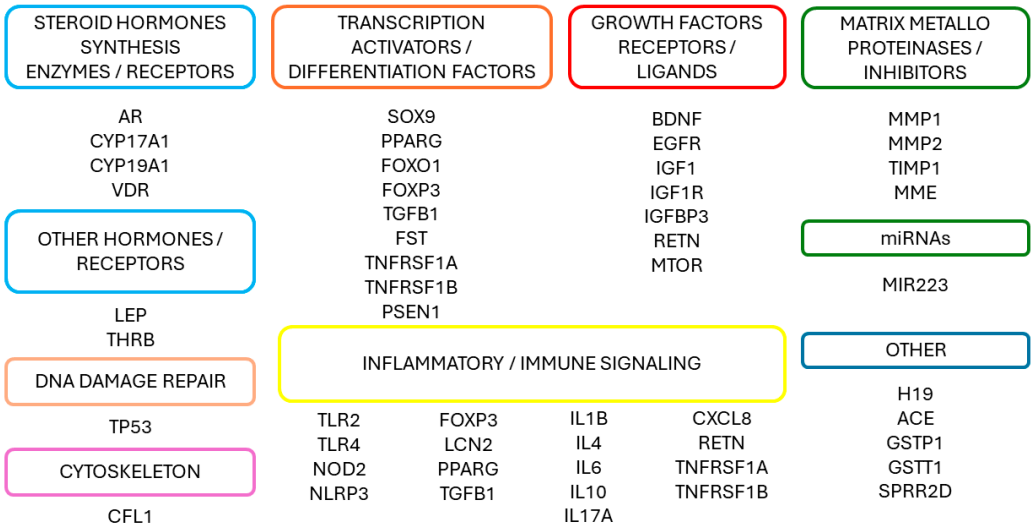

Figure 3. Functional groups of genes retrieved from the NCBI Gene database with the keyword combination "adult female acne".

Somatic mutations and segmental or nonsegmental somatic mosaicism have been involved in a variety of acne-related genetic syndromes such as the Apert syndrome (acrocephalosyndactyly) and *nevus comedonicus*, associated with FGFR2 (fibroblast growth factor receptor 2) mutations, and the autoinflammatory syndromes PAPA (pyogenic arthritis, *pyoderma gangrenosum*, acne), PASH (*pyoderma gangrenosum*, acne, suppurative hidradenitis), PAPASH (pyogenic arthritis, *pyoderma gangrenosum*, acne, suppurative hidradenitis), PsAPASH (pustular psoriasis, arthritis, *pyoderma gangrenosum*, synovitis, acne, suppurative hidradenitis), PASS (*pyoderma gangrenosum*, acne, suppurative hidradenitis, ankylosing spondylitis) and SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis), with most mutations associated with the IL-1β pathway and matrix metalloproteinases such as MMP 2 and 9 [67].

Recent studies have also documented the important roles of epigenetic changes in the etiopathogeny of PCOS. These mechanisms include DNA methylation, histone acetylation, protein phosphorylation, non-coding RNAs (ncRNA), and RNA processing (methylation, editing and splicing). Xu et al. 2010 found a decrease in DNA methylation in peripheral leukocytes in 20 PCOS patients relative to a control group [68]. Fetal exposure to testosterone is assumed to alter DNA methylation for the group of TGF-β regulatory genes [23]. Differentially methylated CpG islands of PPARG1 and NCOR1 genes were identified in granulosa cells, and they may lead to hyperandrogenism [69]. Decreased methylation levels of AMH receptor gene at follicular level and the increased methylation of INSR gene in the endometrium in PCOS patients have been associated with increased and decreased expression of these genes, respectively [70]. Even more complex transcriptomic changes associated with retinoids treatments in PCOS patients with acne have been described [71]. Thus, androgens and IGF-1 signaling in follicular keratinocytes activates via the AKT and mTOR phosphorylation of nuclear factors FoxO1 and FoxO3, enhancing the transactivation of proinflammatory and lipogenesis factors like AR, SREBF1, PPARγ, STAT3, while reducing the expression of GATA6, the main regulator of follicular keratinocytes homeostasis. The phosphorylation by AKT of the p53-binding factor MDM2 promotes p53 degradation, whereas isotretinoin treatment enhances the expression of p53, FoxO1 and FoxO3 in sebaceous glands of acne patients. A recent Chinese epigenetics study identified 23 differentially methylated sites related to severe acne, involving multiple genes such as PDGFD (platelet-derived growth factor D), ARHGEF10 (rho guanine nucleotide exchange factor 10), IL1R1 (IL-1 receptor), PARP8 (poly ADP-ribose polymerase 8), MAPKAPK2 (MAP kinase-activated protein kinase 2), MUC8 (mucin isoform secreted in the endometrium and endocervix), NAV1 (neuron navigator 1), KCNT2 (Na^+-activated K^+ channel T2 or slick

channel), and Wnt9A (an embryogenetic differentiation and patterning factor of the Wnt family) [72]. Another recent study performed a DNA methylation and multi-omics analysis of acne skin samples, finding 31,134 differentially methylated sites and 770 differentially methylated genes with changes in expression [73].

3. Classical and Novel Therapeutic Approaches in AFA

Adult female acne typically follows a chronic course, often marked by frequent relapses that necessitate ongoing maintenance therapy. Notably, postadolescent acne often proves challenging to effectively treat with all available medication options. For instance, Goulden et al. [74] found that up to 82% of postadolescent patients did not show improvement after undergoing multiple courses of oral antibiotics. Additionally, approximately 33% of patients experienced a recurrence of symptoms following one or more courses of oral isotretinoin. Many patients seem to endure unnecessary suffering because they are unaware of the alternative therapies that are available to them. Because adult female acne commonly presents with mild to moderate symptoms, it can typically be managed effectively with a well tolerated topical monotherapy, such as azelaic acid or retinoids [75], but in some cases topical treatments are not efficient and new strategies that approach the problem at molecular level are needed.

3.1. Topical Therapy

Azelaic acid (20% cream or 15% gel) has anti-inflammatory, antibacterial and comedolytic properties and is advantageous because it inhibits cellular protein synthesis in *C. acnes* without inducing bacterial resistance [76]. During two decades of clinical experience, no harmful effects on fetuses have been reported with the use of topical azelaic acid [77].

Retinoids for topical use are an essential component of acne therapy, due to their diverse beneficial effects, which include the control of keratinocyte maturation, a decrease in sebum secretion, comedolysis, anti-inflammatory actions, epithelial regeneration with scar and hyperpigmentation healing, and side effects such as dryness and skin irritation [78,79]. Commercial preparations include tretinoin gel 0.025%, deemed to provide similar efficiency to the third generation retinoid adaptalene 0.1% or 0.3%, alone or in combination with benzoyl peroxide 2.5% gel, but the latter is better tolerated [79]. Tazarotene 0.1% gel is even more efficient, and is the only topical retinoid completely forbidden during pregnancy or lactation, although in these conditions all retinoids should be avoided due to risk of teratogenic effects [75].

Benzoyl peroxide is widely used, alone or in combination, due to bactericidal, keratolytic and anti-inflammatory effects. The antimicrobial spectrum is large, because it acts by producing reactive oxygen species [79]. Side effects include dryness of skin, irritation, itching, photosensitivity, redness or peeling, and the bleaching of clothes, which limit applied concentrations to 5% [75,78].

Topical antibiotics include primarily erythromycin and clindamycin, both of them being effective in reducing skin and hair follicles colonization with *C. acnes* and related inflammation. They can be associated with topical retinoids and benzoyl peroxide, and combined therapy is recommended due to widespread microbial resistance [78,79].

Salicylic acid is a classical drug with anti-inflammatory and keratolytic effects, available in a variety of preparations for topical use such as solutions, lotions, gels, creams, shampoos, soaps, cotton pads and plasters. Its side effects include skin dryness, irritation and itching [78]. The related compound methyl salicylate should not be used for acne treatment.

Niacinamide (nicotinamide) may exert beneficial preventive and curative effects in acne, such as a reduction in sebum secretion, increased ceramides synthesis in keratinocytes, an increase in epidermal permeability [80], the prevention of *C. acnes*-induced TLR2 activation [81], and a decrease in risk of non-melanoma skin cancers [82]. It is present in a large number of cosmetic products such as creams, face sera, gels, lotions, etc., and has few side effects.

Dapsone was originally developed as an antibiotic for leprosy. However, it emerged as a useful first-line therapy in patients with inflammatory acne, particularly those with darker skin [79]. It can be applied as a 5% gel low-cost therapy [78], but it may produce irritation, dryness, an itching or burning sensation, yellow/orange skin discoloration, and sometimes severe hypersensitivity reactions [83].

Clascoterone is an AR inhibitor for topical use. The US Food and Drug Administration (FDA) has recently granted approval for clascoterone cream 1% for treating acne in individuals aged 12 and above. Clinical trials have demonstrated its superior effectiveness compared to a placebo, resulting in significant reductions in both non-inflammatory and inflammatory acne lesions after 12 weeks of treatment [84]. It has been demonstrated to specifically bind to ARs solely at the site of application on the skin, without inducing any systemic anti-androgenic effects. This targeted action makes it safe for use in both male and female patients. By binding to ARs in the sebaceous glands and hair follicles upon topical application, clascoterone effectively inhibits the binding of DHT [85].

3.2. Systemic Therapy

Systemic antibiotics include, according to the therapeutic guidelines and expert opinion, top choice compounds used for moderate-to-severe papulo-pustular or nodular/conglobate acne [76] such as tetracyclines (doxycycline, tetracycline, minocycline), macrolides (erythromycin, roxithromycin, clarithromycin, azithromycin), lincosamides (clindamycin), sulfonamides (co-trimoxazole) and fluoroquinolones (e.g., levofloxacin) [78]. Although tetracyclines are included in the first line of treatment, second-generation agents like limecycline and doxycycline are linked to fewer interactions with food and enhanced patient compliance, primarily because they are administered once daily [86]. Minocycline and doxycycline are superior to tetracycline due to anti-inflammatory and immunosuppressive effects [87]. Minocycline is advised as a secondary treatment option for females experiencing severe seborrhea and erythromycin should be given only during pregnancy for less than one month due to the frequent occurrence of *C. acnes* resistance [88]. Systemic antibiotic therapy duration should not be longer than 3 months [79], and they should be administered in combination with topical agents due to synergistic effects, not in monotherapy [89].

Isotretinoin is the preferred retinoid for oral administration in moderate-to-severe acne, when topical agents alone or other drugs are ineffective, or as first line treatment for nodular-cystic acne [90]. Isotretinoin is effective against all four pathophysiology mechanisms of acne: hyperseborrhea, *C. acnes* proliferation, inflammation and hyperkeratosis/comedogenesis [91]. Besides the above-mentioned teratogenic risk, the side effects of the drug include skin/mucosa dryness, biochemical disturbances (lipid profile, aminotransferases), an increased risk to develop inflammatory bowel diseases, depression and suicide [79]. A detailed description of the effects of isotretinoin on the complex molecular signaling pathways and gene regulation mechanisms in acne is provided by [71]. A consensus recommendation of the Global Alliance to Improve Outcomes in Acne is to administer oral isotretinoin as a first line therapy in nodular as well as cystic or conglobate acne (considered the most severe varieties), due to its high efficiency and lowest rate of recurrence. The recommended doses are 0.5–1 mg/kg body weight/day for 4 to 6 months, achieving a cumulative dose of 120–150 mg/kg. However, there is no consensus yet on the criteria and doses required to maintain remission [92].

Hormonal therapy can be applied using a number of compounds targeting mainly hyperandrogenism or increased AR sensitivity, such as AR inhibitors, oral contraceptives limiting ovarian androgen production, or glucocorticoids to inhibit adrenal androgen production. Hormonal therapy targets primarily sebum production, therefore it should be supplemented with other agents such as antibiotics or topical therapy [75]. Moreover, oral contraceptives are also the main therapy for PCOS, along with diet, exercise and drugs to limit IR, and pregnancy-inducing methods like laparoscopic ovarian drilling and assisted reproduction techniques [93].

Androgen receptor inhibitors (antiandrogens) include cyproterone acetate (CPA), spironolactone (SPL), its analog drospirenone, and flutamide. CPA (the first antiandrogen in medical use) and drospirenone were developed as progestatives with antiandrogen effects, combined with estrogens in birth control pills, while flutamide is a nonsteroidal antiandrogen. Flutamide use, even at the minimally active dose of 125 mg/day, alters liver enzyme levels [94]. SPL and drospirenone exert strong antialdosterone effects and act as K^+-sparing diuretics, requiring kalemia control. All AR inhibitors are prohibited during pregnancy due to the risk of feminization of male fetuses [79].

Spironolactone, which acts as an aldosterone antagonist with antiandrogenic properties, has emerged as a promising option for treating acne in females. In a randomized, double-blind, placebo-controlled trial involving sixty-three women, participants were equally divided into three groups: placebo, SPL25, and SPL50. The study found that SPL was effective in reducing both objective acne counts and improving subjective clinical grading and showed that utilizing a low dose of SPL (25–50 mg/day) in AFA led to a high success rate with minimal side effects such as menstrual irregularities in 13–33%, breast tenderness in 2–4%, and dizziness in 2–3%. The onset of spironolactone's action is typically slower compared to other systemic acne treatments, taking approximately 12 weeks (with a range of 8–20 weeks). However, a potential pharmacokinetic advantage is in that its effects last for at least 1 month after discontinuation, particularly when continuing topical medication maintenance [95]. Spironolactone may be combined with a third or fourth generation oral contraceptive to alleviate side effects.

Inhibitors of ovarian androgen production are oral contraceptive pills containing a combination of estradiol and a progestin with antiandrogen activity, such as CPA or drospirenone. These combinations seem to be more effective compared to those containing modern progestatives (levonorgestrel, desogestrel, norgestimate, gestodene) [96]. The medications are effective in both inflammatory and non-inflammatory acne, but the effects occur upon prolonged treatment, with a 62% reduction in inflammatory lesions at 6 months [97]. Paradoxically, in some cases acne can be triggered or aggravated by this treatment, requiring a substitution with a combination containing a less androgenic progestin or a lower estradiol dose [98]. Other compounds, such as 5α-reductase inhibitors finasteride and dutasteride, are not particularly effective in acne.

Zinc salts in oral preparations containing 200 mg elemental zinc/day may be effective in the treatment of acne-induced inflammatory lesions [99].

Probiotics. Some authors associated emotions like fear, anxiety, and depression with alterations in gut microorganisms, suggesting that these changes could lead to localized and systemic inflammation, known as *the brain–gut–skin theory.* Both animal and human studies have demonstrated that stress disrupts the balance of normal gut microflora, particularly affecting *Lactobacillus* and *Bifidobacterium* species [100]. Psychological stressors induce intestinal microbes to generate neurotransmitters (acetylcholine, serotonin, norepinephrine), that can traverse the intestinal mucosa and enter the bloodstream, ultimately leading to systemic inflammation [14]. Kazandjieva J et al. have shown that combining a prebiotic with an anti-inflammatory food supplement (prebiotic molecules: fructooligosaccharides—FOS and galactooligosaccharides—GOS, zinc, lactoferrin, and niacinamide) as part of the treatment regimen provides an additional clinical benefit, particularly in reducing inflammatory lesions and improving the severity of acne scores [101]. Clinical trials have investigated the impact of probiotics on acne. Kang et al. found that after 8 weeks of topical *Enterococcus faecalis* treatment, there was a statistically significant 50% reduction in inflammatory acne lesions count (specifically pustules) compared to placebo, as well as a decrease in non-inflammatory lesions such as comedones [102].

3.3. Therapeutic Guidelines for Acne

Although it is impossible to reach a universal agreement concerning the best methods and therapeutic protocols for acne in general (and for AFA in particular), the Global Alliance to Improve Outcomes in Acne formulated in 2018 ten consensus recommendations based

on a Delphi panel and questionnaire [92]. A major impediment in assessing effectiveness of different therapies is the lack of a standardized scale or grading system for acne severity. The high efficiency of modern topic treatments also tends to distort traditional classifications and therapy guidelines. For AFA some important principles are to apply early treatment in order to minimize acne scarring (consensus recommendation 10) and to use topical retionoids alone or in combination with benzoyl peroxide in AFA (consensus recommendation 9). Gollnick et al. 2016 established a number of specific therapeutic protocols for different clinical varieties of acne [76]. Thus, for *comedonal facial acne* the recommended therapy is topical (in the sequence topical retinoid > azelaic acid > salicylic acid) for 12 weeks, followed by topical maintenance therapy in case of success or more radical measures in case of no response or increase in severity. For *papulo-pustular facial acne,* the therapy is topic in mild cases (benzoyl peroxide, topical retinoid, azelaic acid or combination), while in moderate cases it is based on a fixed topical combination, and in moderate-to-severe cases this combination can be supplemented with oral isotretinoin, oral zinc, or oral antiandrogens. In the case of therapeutic success after 12 weeks, the maintenance therapy is based on topical retinoids > azelaic acid, while in the case of failure a careful analysis and more intensive therapies are required. For the most severe forms, *nodular/conglobate acne*, the treatment is different for males vs. females. The former group requires oral isotretinoin or fixed combination topic therapy plus high-dose oral antibiotics, while for females these therapies have to be supplemented or replaced with oral antiandrogens. In the case of success after 12 weeks, the maintenance therapy includes topic retinoids > azelaic acid or topic retinoid and benzoyl peroxide combinations, but never benzoyl peroxide or topic antibiotic monotherapy. In the case of a lack of response, updated and more aggressive therapies are required. It will be interesting to see how novel, deemed game-changing therapies, such as topic clascoterone, will impact these guidelines. However, alternative or adjunctive therapies and particularly lifestyle and diet changes are of utmost importance and may bring an essential contribution to success in controlling the disease.

3.4. Alternative Holistic Theraphy (Herbal Medicines)

Spearmint tea, a species of mint scientifically classified as *Mentha spicata*, also known as garden mint or common mint, is native to Europe and southern temperate Asia, and has confirmed antiandrogen properties. Peter Grant conducted a study with 41 patients completing the full 30-day treatment period. Following the 30-day treatment with herbal teas, the results showed significant reductions in both free and total testosterone levels in the spearmint tea group ($p < 0.05$). Additionally, LH and FSH levels increased ($p < 0.05$). Subjective assessments of hirsutism, as scored by the modified DQLI, showed significant reductions in the spearmint tea group ($p < 0.05$) [103]. Another study was made on 21 patients who consumed a cup of tea twice a day for 5 days during the follicular phase of their menstrual cycles. Following treatment with spearmint tea, there was a noteworthy reduction in free testosterone levels and an increase in luteinizing hormone, follicle-stimulating hormone, and estradiol levels. However, there were no significant decreases in total testosterone or DHEAS levels [104].

Fenugreek seeds. Trigonella foenum-graecum, commonly known as fenugreek, is an annual plant belonging to the family *Fabaceae*, originating from the Mediterranean region, southern Europe, and western Asia, with anti-diabetic and cholesterol-lowering properties. Additionally, it has been observed to reduce insulin resistance in women with PCOS. Hassanzadeh et al. conducted a study to examine the impact of fenugreek seed extract on insulin resistance among women with PCOS. The intervention group received three tablets of 500 mg metformin along with two tablets of 500 mg fenugreek, while the control group received three tablets of 500 mg metformin and two tablets of a placebo for a duration of 2 months. The study observed a significant reduction in ovarian cysts after the 2-month period. However, there were no notable changes observed in fasting glucose levels, insulin sensitivity, or hormonal concentrations between the intervention and control groups [105].

Berberine belongs to the protoberberine group of benzylisoquinoline alkaloids and is classified as a quaternary ammonium salt, and has been shown to modulate the diversity of gut microbes effectively at a daily dose of 500 mg. Moreover, it has been found to positively influence gene regulation related to cholesterol absorption when administered at a daily dose of 300 mg in humans. Additionally, it is an effective insulin sensitizer and improvements in glucose metabolism have been observed with a daily dose of 1.0 g, as outlined in a recent systematic review [106]. Also, a review study from 2023 indicated that berberine might enhance lipid concentrations [107]. Studies have indicated that berberine supplementation may have a positive role in reducing insulin resistance, acne, androgen, and inflammation, in regulating lipid metabolism, and in improving body composition, and therefore can represent a novel clinical supplementation strategy for PCOS, although the results are demonstrated only in a specific population, namely normal or overweight women with PCOS who exhibit normal menses [108].

Licorice, known as *Glycyrrhiza glabra* in botanical terms, is a flowering plant belonging to the bean family *Fabaceae*. It is commonly used for its sweet and aromatic flavoring, which is extracted from the plant's root. Yang et al. discovered that licorice extract mitigates the symptoms of PCOS by regulating serum FSH levels, LH/FSH ratio, and irregular ovarian [109]. Licorice inhibits the activity of 17-hydroxyl esterase dehydrogenase and 17,20-lyase activity, while stimulating aromatase activity, due to its estrogen-like effects [110].

Many other complementary and alternative medicines of the same type are discussed by Fox et al. 2016 [111].

3.5. Adjunctive Therapy

Adjunctive therapies are used less frequently compared to the main topic or systemic therapies; however, in selected cases they can provide supplementary effectiveness and boost healing or prevent relapse.

Light therapy with red or blue light could improve acne by reshaping the skin microbiota and lowering *C. acnes* counts within the lesions, as well as by limiting sebum secretion. Blue light should be used cautiously and with well-defined timing protocols due to higher energy of photons compared to red or near infrared light, to avoid skin irritation or lesions.

Photodynamic therapy (PDT) consists of a combination of phototherapy and a photosensitizing chemical agent such as aminolevulinic acid or its methyl derivative. Light can be produced by high-intensity light-emitting diodes (LED) or lasers, in a continuous or pulsed regime. Red light PDT can produce up to a 68% reduction in inflammatory acne lesions [112,113]. Caution in applying PDT is also recommended, to avoid frequent side effects such as pain and a flare-up of the acne when high doses are used.

Ultraviolet (UV) phototherapy is a widely recognized bactericidal therapy known to inhibit the release of lipotheichoic acid, lipopolysaccharides, and other bacterial metabolites associated with pro-inflammatory effects [14]. The time of application and intensity should be limited to avoid actinic lesions.

Chemical peels containing compounds such as glycolic acid (30–70%), salicylic acid (20–30%), Jessner's solution (a combination of salicylic acid, lactic acid and resorcinol) included by Dr. Max Jessner in his patented Jessner peels, or trichloroacetic acid (10–35% for superficial peels, 40–50% for medium peels, and >50% for deep peels) can be successfully applied in mild-to-moderate acne [75].

Microneedling with radiofrequency was successfully applied in four clinical trials, according to Pathmarajah et al. [114], resulting in a decrease in both inflammatory and non-inflammatory lesions counts (pustules, papules, comedones).

Physical therapies include mechanical procedures such as comedone extraction, microdermabrasion, electrocauterization, cryotherapy, cryoslush therapy, and intralesional injection of corticosteroids [75,111].

3.6. Lifestyle (Diet and Exercise)

Recently, there has been increased attention to the role of environmental factors, particularly the Western diet, in the development of acne. The Western diet typically comprises red meat, dairy products, high glycemic index foods such as refined carbohydrates, chocolate, and saturated fat, which have been suggested to exacerbate acne by triggering metabolic signals derived from nutrients. An optimal "anti-acne diet" would resemble a Paleolithic-style nutrition plan, emphasizing the consumption of vegetables and fruits with a low glycemic index, as well as sea fish rich in anti-inflammatory omega-3 fatty acids [115]. It was postulated that high-protein diets, based on meat, eggs or dairy products, predispose to acne due to their rich leucine content, resulting in the activation of mTOR (mechanistic target of rapamycin) complexes 1 or 2 with excessive lipogenesis and swelling of the pilosebaceous unit [116]. A good proof in this respect is the fact that populations that traditionally have diets low in meat, grains and dairy products never develop acne [117].

3.7. Novel Therapeutic Approaches

The progress in exploring the complex pathophysiology of acne, including a variety of molecular players, signaling pathways and genomic or epigenomic features, opened the perspective of new therapeutic approaches aiming to exploit these recently added elements of knowledge. A review of the advances in acne therapy identified several relevant topics and areas of interest in acne, such as the complex inflammatory and innate immunity pathways, peculiarities of the skin microbiome, genetic susceptibility, or diets and nutrition principles [78]. This study presents a relatively large list of compounds included in recent clinical trials, some of them completely new, e.g., B244 (nitric oxide-producing agent), S6G5T-3 (encapsulated benzoyl peroxide and tretinoin cream), GK530G (fixed-dose adaptalene-benzoyl peroxide combination gel, compared to adaptalene 0.1% gel-CD0271 and benzoyl peroxide 2.5% gel-CD1579), P005672-HCl (a novel tetracycline derivative for oral administration), CJM112 (an anti-IL-17A antibody), calcipotriene (a vitamin D3 analog for topical therapy), olumacostat glasaretil 5% gel (an acetyl-CoA carboxylase inhibitor of fatty acid synthesis), CD5789 (trifarotene—a fourth-generation selective retinoic acid receptor-γ agonist for topical use), cortexolone 17α-propionate (clascoterone), and afamelanotide (synthetic analog of α-melanocyte-stimulating hormone- αMSH), FMX-101 (4% minocycline foam). The list of recently available brand products for acne tratment presented in the same study includes Winlevi (Clascoterone topical cream), Solodyn (minocycline-tetracycline for oral use), Vibramycin (tetracyclines-antimalarials for oral use), Differin (adaptalene-retinoids topical gel), Absorica and Accutane (isotretinoin for oral use).

Karolina Chilicka et al. discuss the therapeutic potential for acne of cosmetic acids (such as pyruvic, lactic, glycolic, phytic, salicylic, azelaic, mandelic, ferulic acid), and of alkaline water with a pH of 8–10, produced by electrolysis in the cathode region and containing active molecular hydrogen, capable to neutralize free oxygen radicals with antioxidant, anti-inflammatory and antiapoptotic effects [118].

A recent study [119] describes the development of an in vivo acne model in double knockout C57BL/6 mice (TLR2$^{-/-}$ TLR4$^{-/-}$) injected intradermally with various *C. acnes* strains and treated topically with artificial sebum. The pathogenicity of each strain was estimated by collecting the inoculated skin after 48h, followed by homogenization, the seeding of bacterial cultures and counting the colony forming units (CFU). The most pathogenic acne-associated strain (HL043PA1, Clade IA-2, RT5) and the least pathogenic strain (HL110PA3, Clade II, RT6) expressed hyaluronidase A (proinflammatory acne-associated hylA) and hyaluronidase B (moderately anti-inflammatory hylB), respectively. Via in silico studies, a small peptide hylA inhibitor and a multiepitope hylA vaccine were produced and administered intraperitoneally to CD1 mice, showing the effectiveness against pathogenic *C. acnes* inoculated intradermally post-vaccination and the specificity of effect for pathogenic strains. These pioneering studies open the way for creating efficient *C. acnes* hylA vaccines for clinical use.

Another recent review [120] explores the complex molecular pathways triggered in acne by pathogenic *C. acnes* strains via TLR and the activation by PAMPs and DAMPs (pattern/damage-associated molecular patterns) of PRRs (pattern recognition receptors) such as NOD (nucleotide-binding oligomerization domain) receptors and NLR (NOD-like receptors), with the subsequent assembly of the NLRP3 inflammasome, the activation of caspase-1 and the subsequent cascade of proinflammatory cytokines like IL-1β and IL-8. Some potentially useful inhibitors of this pathway, including NLRP3 inhibitors baicalein, eucalyptol extracted from *Laurus nobilis*, superoxide dismutases, auranofin (an antirheumatic colloidal gold compound), or ROS production inhibitor polyphyllin I may be successfully used in future therapeutic protocols for acne. Cong et al. [121] recapitulate the pathophysiology of acne and explore new emerging treatments. Thus, increased sebum secretion may be limited by melanocortin receptor antagonist JNJ-10229570 and peroxisome proliferator-activated receptor-γ (PPARγ) modulator N-acetyl-GED-0507-34-LEVO (NAC-GED). A multicentric randomized controlled clinical trial performed on 450 patients with moderate or severe facial acne tested the effects of topical NAC-GED applied at 2% or 5% concentration, concluding the product is effective and devoid of adverse effects [122]. IGF-induced lipogenesis and the AMPK-SREBP-1 signaling pathway are inhibited by epigallocatechin-3-gallate (EGCG); isotretinoin, metformin, olumacostat glasaretil and XEN103 exert similar effects. IL-1β-induced signaling and subsequent IL-8 release are inhibited by αMSH analogs afamelanotide and K_DPT (a tripeptide derivative of the αMSH C terminal), and by the phosphodiesterase 4 inhibitor apremilast. Other options are monoclonal antibodies against IL-1, IL-17, or IL-1β, for example gevokizumab (XOMA 052) [123]. Recently proposed non-conventional acne therapies are Rhizoma Paridis saponins (extracted from *Paris polyphylla*), which inhibit Nrf2 and MAPK inflammatory pathways via KEAP1 binding [124], the promotion of keratinocyte apoptosis via the PI3K/Akt pathway by bacteriophage φPaP11-13 [125], a reduction in *C. acnes*-triggered inflammation via the MAPK and NF-κB pathways by ethanol extracts of the harebell poppy (*Meconopsis quintuplinervia*) [126], or the inhibition of mechanisms associated with neutrophil extracellular traps by adipose-derived stem cells via Nrf2 signaling pathways [127].

4. Conclusions

AFA and PCOS as an underlying condition are diseases with a complex pathophysiology that is still incompletely understood, although during the last decades significant progress has occurred through establishing precise quantitative diagnosis criteria and protocols, and by exploring a large variety of signaling pathways and mechanisms with the methods of molecular biology and genomics. The treatment should be individualized, using an ever enlarging array of therapeutic options, and application of alternative or non-conventional methods such as dietary restrictions, exercise, stress avoidance, natural products, probiotics, etc. may bring important contributions to the induction and maintenance of remission in these difficult-to-treat diseases.

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