



Endocrine Disorders and Hormonal Therapy for Adolescent Acne

Chittinan Assawaruangsin

Assumption University of Thailand, Bang Sao Thong, Samut Prakan, Thailand 10570

ABSTRACT: Acne vulgaris is a worldwide disease which is mostly found in teenagers. This has a crucial impact on their life's quality, particularly when endocrine disorders have been implicated. Current consideration regarding antibiotic stewardship, failing with antibiotic utilization, and the improvement of antibiotic-resistant *Propionibacterium acnes*, there are many treatment alternatives for pimple therapy have been acknowledged. A following analysis investigates hormonal treatments for the therapy of acne vulgaris.

KEYWORDS: Acne, Consensus Recommendation, Treatment.

INTRODUCTION

One of the most frequently treated skin conditions by dermatologists is acne vulgaris which adolescents are primarily affected. Pimple, a chronic inflammatory affliction, forms from the pilosebaceous parts that is multifactorial [1]. It is possible to have seborrhea and other skin lesions such as nodules and erythematous and pustular lesions [1]. In some cases, scarring can be seen due to these lesions, but this is extremely rare. Four distinct pathogenetic mechanisms cause acne: raised sebum creation, follicular hyperkeratinisation, *Propionibacterium acnes* (*P. acnes*) colonization, and inflammatory results. In current years, as our knowledge of acne's pathogenesis has improved, new therapeutic options have been developed [2, 3]. As more and better acne treatment options become available to patients, it will be easier to meet their needs and expectations when it comes to treating their condition. Acne management success requires a meticulous anti-acne

A. Topical therapy recommended for Acne vulgaris

Topical medicine is efficacious for minor and temperate acne when used alone, in combination, or as maintenance therapy.

1. Benzoyl peroxide

In addition to being an effective topical agent, it is available in various forms and concentrations (2.5–10%), making it a versatile product [4]. Stability is highly vehicle-dependent. To compare with gels, creams and lotions, gel is more stable and active than others, however, oil base gels are more irritant than water-based [5]. Benzoyl peroxide is a potent bactericidal mediator with a broad spectrum of activity due to its oxidizing activity [6]. In addition to having anti-inflammatory, keratolytic, and comedolytic properties, minor-to-temperate acne vulgaris is required to treat by the medication [7]. Physicians must balance the appropriate concentration, the vehicle base, and the risk of antagonistic effects, as greater concentrations are not usually effective. Benzoyl peroxide has been known to cause irritant dermatitis [8]. However, the initiating therapy is occurred in a short period and diminished with persistent use [9, 10].

B. Topical retinoids

For more than 30 years, retinoids have been used. Topical retinoids are used to treat acne's microcomedo-precursor lesion [11]. When treating mild-to-moderate acne, there has been a lot of agreement recently that topical retinoids should be the first thing people try. They can be used alone or in combination, and they are the most popular option in long-term care [6].

Its efficacy is well established, since it represses aberrant follicular epithelial hyperproliferation, follicular plugging, and the production of microcomedones and non-inflammatory as well as inflammatory acne lesions [9]. Nuclear hormone receptors (retinoic acid receptor RAR and retinoids X receptor RXR, each of which has three subtypes) and cytosolic binding proteins modulate their biological functions [9]. RAMBAs, such as liarozole, have been discovered and studied to treat all-trans-retinoic acid resistance [5, 11].

Topical retinoids currently include tretinoin, adapalene, tazarotene, isotretinoin, metretinide, retinaldehyde, and retinoyl glucuronide. Tretinoin and adapalene are the most extensively investigated topical retinoids for broad global application [10, 12]. There is no concurrence regarding the relative beneficial effects of the topical retinoids presently available (tretinoin, adapalene,



tazarotene, and isotretinoin). Tolerability may be affected by the carrier in which a retinoid is administered [5, 7]. Adapalene was commonly more well-tolerated than all other retinoids studied. Tretinoin is now available in novel formulations with improved tolerability. One such product that includes tretinoin ambushed inside the porous copolymer microspheres is Retin-A Micro (0.1% gel) [5, 13, 14]. Avita contains tretinoin encapsulated in a polyoylprepolymer (PP-2). These formulations gradually release tretinoin into the pore and onto the epithelium's covering, effectively reducing irritancy. The initial irritate inflammation, which manifests as erythema, scaling, and a searing perception and varies according to skin type, sensitivity, and formulation is topical retinoids' most common adverse effect [15, 16].

2. Topical antibiotics

There are numerous formulations of topical antibiotics, which are alone or in conjugation. The increase of *Propionibacterium acnes* and alleviate inflammation are restrained [17]. The topical antibiotics, for instance, erythromycin and clindamycin, which will be feasible in various vehicles and packaging are the antibiotics commonly used in the acne's therapy [18]. In order to resist inflammatory acne, using clindamycin and erythromycin in topical doses of 1–4% with or without zinc were efficient [19]. For acne treatment, a placebo is more effective than a combination of topical 2% zinc sulfate and nicotinamide [20]. Although minor, adverse reactions are consist of erythema, peeling, itching, dryness, and burning, as well as pseudomembranous colitis, which is infrequent, nonetheless, it is accounted with clindamycin [21]. The contemporary antibiotics have a significant adverse result, which is bacterial antagonism incident and cross-antagonism; consequently, they might not be applied in isolation [22].

3. Other topical/new agents

Preventing and eliminating *P. acne* resistance is a major advantage of using benzoyl peroxide with other antifungal medications [23, 24]. As a result, it is more frequently used in combination therapy [25]. As demonstrated in multiple trials, it is efficient and tolerable when used in conjunction with contemporary erythromycin or clindamycin [26]. Benzoyl peroxide has been shown to be superior to tretinoin monotherapy when combined with it. Both molecules might not be used concurrently, since benzoyl peroxide can oxidize tretinoin [8]. The topical retinoid and topical antimicrobial conjugation have had more efficacious than either agent alone in lessening inflammatory and noninflammatory acne lesions [5]. Both topical clindamycin and benzoyl peroxide were used one time a day, and definite clindamycin phosphate 1.2% and tretinoin 0.025% in an aqueous-based gel type applied one time a day was considered be an efficient acne treatment [27, 28]. Zinc acetate added to clindamycin and erythromycin gel demonstrated comparable effectiveness, however, it likely reduced microbial opposition. Salicylic acid is applied as a comedolytic agent in acne for many years, however, it is less effective than thematic retinoids [29, 30]. Azelaic acid: There is a thematic lotion containing 10%–20% azelaic acid which is illustrated to be efficient in treating inflammatory and comedonal acne [31, 32]. Picolinic acid gel 10%: It is an amino acid intermediate metabolite. It is antiviral, antibacterial, and immunostimulating [33]. When used two times a day for 3 months, it was efficient in treating these types of acne injuries, nevertheless, the additional experiments are necessary to strengthen its security and potency [34–36]. Dapsone 5% gel is a sulfone with antimicrobial and anti-inflammatory features [37, 38]. The experiments established that topical dapsone gel 5% is efficient and harmless in minor-to-temperate acne vulgaris when used separately or in accumulation with other thematic agents [39, 40].

B. Connection between Acne's Hormones and the Pathogenesis

The discharge of provocative intermediary, modified Keratinization, acne evolution, modified sebum formation, and follicular duplication related to bacterium *P. acnes* have increased multifactorial acne's pathogenesis [41, 42].

Hormones and the Sebaceous Gland

The sebaceous gland is a significant component of acne. The usual function of the sebaceous gland is to produce sebum, a mixture of triglycerides, fatty acids, and esters that lubricates the skin, transports anti-oxidants, protect against ultra-violet (UV) rays, and promote anti-bacterial activity [43]. Excess sebum production or changes in its fatty acid composition can disrupt follicular keratinization, resulting in pore obstruction and the onset of acne [44]. Additionally, a sebum-rich environment promotes *P. acnes* proliferation [45].

1. Androgens

Excess sebum is ascribed to the powerful androgen 5 α -dihydrotestosterone (5 α -DHT), which is produced when testosterone is metabolised by 5 α -reductase type 1, an enzyme mainly found in the skin, particularly in facial sebocytes and sweat glands [46, 47]. The action of 5-DHT on the sebaceous gland is mediated by the nuclear androgen receptor (AR). Genetic researches have revealed that severe acne patients have dysregulation of the AR [45]. Additionally, in vivo topographic evaluation demonstrated an



analytically vital rise in AR manifestation in the face's T-zones, which are realized to produce more sebum than the face's U-zones [48]. It also found that people who had acne had more sebum production in both of these areas than people who didn't have acne [48]. Nonetheless, there is no relationship between sebum production and acne wound identified in the majority of spaces, implying that the acne's pathogenesis is complex [49]. *In vitro* trials have shown that androgens such as testosterone and 5-DHT do not completely inhibit sebum synthesis [50]. They almost certainly need vivo cofactors, for example, peroxisome proliferator-activated receptor (PPAR) ligands, to exert their impact on the sebaceous gland [6,10]. Indeed, testimony recommends that other PPAR ligands, for instance, leukotriene B4 (LTB4), may also play a role in the progression of inflammatory acne wounds [51, 52].

2. *Insulin-like growth factor-1 (IGF-1)*

The AR's end organ receptor irritability is especially relevant to the manners that contribute to comedone. One hormone that has gotten a lot of attention recently is insulin-like growth factor 1 (IGF-1) [53, 54]. During adolescence, growth hormone (GH) levels rise dramatically, followed by the release of IGF-1. IGF-1 stimulates the secretion of androgens by the adrenal and gonadal glands and also affects the sebaceous gland by the GF-1/AKT/mTORC1/SREBP1 signaling pathway [55]. This pathway leads to an increase in testosterone conversion to 5-DHT (which has a higher affinity for AR), an increase in end-organ receptor irritability to androgens, and an increase in PPAR expression [56]. As a result of interaction between insulin-like growth factor-1 and androgens, as well as their impacts on the sebaceous gland, researchers have questioned whether high glycemic loads can lead to an increase in the secretion of IGF-1, consequently, a greater chance of acne [54].

3. *Estrogens*

By countering androgens, estrogens inhibit sebaceous gland performance. Estrogens may also play a role in lesion recuperation and anti-inflammatory methods via their complicated interplay with IGF-1 [57-59]. According to a standardized evaluation of over 1,000 researches, cases with acne vulgaris were reduced serum estrogen degrees than controls [60]. It indicates that estrogen can also play a role in the acne's pathogenesis [61].

4. *Corticotrophin-releasing hormone (CRH) and Cortisol*

Corticotrophin-releasing hormone (CRH) and cortisol are hormones associated with tension which regulate sebaceous activity [62]. When acne-affected skin is compared to unaffected skin, extremely high levels of CRH expression are detected in the sebaceous glands [63]. CRH suppresses sebocyte proliferation, activates sebum formation, and enhances the appearance of the enzyme 5-hydroxysteroid dehydrogenase, which stimulates androgens [64]. CRH and cortisol have been classified as strain hormones since the body releases them during periods of psychological tension. Numerous researches reveal a crucial link between tension levels and the severity of acne [65]. Increases in cortisol and CRH during stressful periods may play a role in developing acne lesions through the sebaceous gland's mechanisms, which have already been discussed. However, no studies have directly examined this. Indeed, while one research of 94 teenage pupils in Singapore discovered a vital correlation between examination-related tension and pimple asperity, there was no crucial distinction in sebum assessments between the high- and low-stress environments [66]. This assumes that stress, mechanisms other than a rise in sebum activation lead to the pimple wounds' growth [67, 68].

C. *Cytokines and Inflammation*

Previously, it had been believed that inflammation played a role only in the late phases of pimple wounds (i.e., papules, pustules, cysts) [69, 70]. On the other hand, histological and immunological proof illustrate that subclinical inflammation occurs during the earliest stages of acne. The upregulation of inflammatory mediators (IL-1, CD3+, CD4+, macrophages) in uninvolved skin and the activity of IL-1 in the open, previously considered "non-inflammatory," acne provides evidence for this [71]. It is known that these inflammatory procedures are involved before the hyperkeratinization procedure in pimples, proving that pimples are eventually a chronic, inflammatory disease [72]. Numerous factors and the bacterium *P. acnes* stimulating toll-like receptor 2 (TLR2), varied sebum component, and disturbance of the oxidant/antioxidant ratio in skin surface lipids are thought to activate inflammatory mediators [10,20]. *P. acnes* is not required to develop acne inflammation, implying that sebaceous glands play a critical role in initiating inflammatory events in pimples [73].

Acne lesions are thought to form due to changes in the lipid component of sebum. Lipoperoxides, especially those made when squalene breaks down, may be condemned [74]. According to one study, lipoperoxides are found in essentially higher combinations in the pimples of acne patients than in vigorous dermis [75]. Lipoperoxides inhibit keratinocyte proliferation and increase pro-inflammatory cytokine release [76]. They are also ligands for PPAR γ , a nuclear hormone receptor that, as previously referred, simplifies androgen-induced comedone evolution [75]. A cytokine mRNA study exposed significantly increased degrees of tumour



necrosis factor- (TNF-) and interleukins in facial acne lesions. IL-8 levels, in particular, were found to be 3000-fold higher in acne lesions than in uninvolved skin [76]. Eventually, another research discovered that DHT could increase TNF- and IL-6 levels in initial scalp sebocyte cultures [76]. This indicates that androgens have direct inflammatory effects in addition to influencing sebogenesis [69, 70, 76].

D. Extracellular Dopamine and Retinoids

Retinoids are vitamin A-derived retinoic acid receptors agonists (RAR-, RAR-, RAR-) [77]. Retinoic acid receptors form a homo/hetero-dimer when the ligand is bound. To initiate gene transcription, this dimer complex interacts with nuclear responsive elements RARE (retinoic acid response element) or RXRE (retinoid X receptor response element). As previously noted, EDCs are implicated in every aspect of nuclear hormone receptor activation [78]. Certain EDCs may act as an agonist, antagonist, or recruiter of retinoic acid receptor coregulators, either boosting or interfering with acne treatment. Because the efficacy of topical retinoids is dose-dependent, the possibility of exogenous chemicals interfering with the therapeutic reaction exists [79].

E. Endocrine Disrupting Compounds (EDCs) and Hormonal Therapies

Owing to their anti-androgenic and anti-inflammatory effects, combined oral contraceptives (COCs), including estrogen, are advised as an acne's second-line therapy for women [80-82]. COCs inhibit androgen synthesis, inhibit the AR, inhibit 5-alpha reductase activity, and increase sex-hormone-binding globulin (SHBG) levels— result in decreased androgen levels in the blood [80]. Spironolactone, an AR antagonist, is likewise occasionally taken off-label and is helpful for woman acne individuals and teenagers with polycystic ovarian syndrome [83]. As previously noted, various EDCs have been shown to connect with various hormonal pathways, containing those involving androgens, estrogens, IGF-1, and CRH/cortisol [84]. Oral contraceptives and testosterone antagonists both target these similar mechanisms [80]. This is critical to keep in mind when discussing acne treatment, as there may be direct antagonistic consequences between androgenic EDCs and Spironolactone, for instance, which could jeopardize therapy efficacy [85].

F. Conclusion

Over the last century, the continuous industrialisation of civilisation has increased human exposure to a diverse array of exogenous substances. As previously stated, several of these chemicals are endocrine disruptors and bioaccumulate to such a degree in humans that they impair endogenous hormone signalling. EDC exposure has been connected with the aetiology of cancer, reproducing problems, cardiovascular and pulmonary illness, metabolic disorder, and other tumours in many experimental, clinical, and epidemiological research. Thus, risk evaluation of EDC exposure is crucial for disease burden reduction, particularly during critical developmental periods.

Hormones have a crucial role in the pathogenesis of acne vulgaris, and this assessment looked at the relationship between EDC exposure and acne. Indeed, as previously demonstrated, EDCs alter various critical endogenous hormonal pathways in acne, including those mediated by androgens, estrogens, IGF-1, and CRH/cortisol. A significant component of convergence is the lipogenic and inflammatory mediators released by hormones and cytokines implicated in acne and observed in response to EDC exposure. EDCs are also likely to interact with hormonal acne medicines, making it crucial to evaluate if chronic EDC exposure hinders the efficacy of androgen and retinoid-based therapy in acne cases.

Examining the link between EDCs and acne vulgaris will reveal novel therapeutic approaches. The finding that phytoestrogens (genistein and resveratrol) can counteract the lipogenic and sebocyte growth-advocating effects of androgens and PPARy advocates that plant-rich diets will aid acne cases and will have capability for a condition control strategy. There are numerous researches demonstrated that a low-glycemic, plant-rich diet can alleviate inflammatory acne [89,90,91,92], and it has been postulated that the therapeutic benefits of food are considered by changes in PPARy, IGF-1, and androgen signalling [90].

Provided the proof establishing a link between EDCs' hormone signalling pathways and acne, there is adequate factor for concern to justify confining these agents' risk to patients with acne. The mounting proof that even low dose individual risk may be hazardous, strategies for acne care should address minimising thematic and systemic risk to drugs realized to react with estrogen, androgen, and cortisol signalling. Clinicians and acne patients must communicate effectively, which may involve various ways to prevent exposure and promote lifestyle modifications. The following section contains specific guidelines for physicians to assist them in counselling patients on how to abstain from EDCs in daily life.



Further elucidation of the link between EDC exposure and the development of acne vulgaris will require examining EDC exposure in individuals with acne vulgaris. Additional genomic studies studying the genes involved in acne progression and their interactions with EDC pathways may aid in elucidating the molecular mechanisms. This should be crucial in determining the efficacy of hormonal acne therapy in terms of EDCs to provide the best advice to acne patients regarding exposure minimization. Finally, because humans are constantly exposed to mixtures of EDCs that can have additive or synergistic effects, the relationship between multi-chemical interactions and acne vulgaris remains uncertain. Nonetheless, the association between acne vulgaris and EDCs in this study is expected to promote awareness, stimulate future clinical research, and educate possible protection strategies.

REFERENCES

1. M. H. Gold, H. Baldwin, and T. Lin, "Management of comedonal acne vulgaris with fixed-combination topical therapy," *Journal of cosmetic dermatology*, vol. 17, no. 2, pp. 227-231, 2018.
2. C. S. K. Fuchs, V. K. Ortner, F. S. Hansen, P. A. Philipsen, and M. Haedersdal, "Subclinical effects of adapalene-benzoyl peroxide: a prospective in vivo imaging study on acne micromorphology and transfollicular delivery," *Journal of the European Academy of Dermatology and Venereology*, vol. 35, no. 6, pp. 1377-1385, 2021.
3. D. Z. Eichenfield, J. Sprague, and L. F. Eichenfield, "Management of Acne Vulgaris: A Review," *JAMA*, vol. 326, no. 20, pp. 2055-2067, 2021.
4. B. Dréno *et al.*, "Prevention and reduction of atrophic acne scars with adapalene 0.3%/benzoyl peroxide 2.5% gel in subjects with moderate or severe facial acne: results of a 6-month randomized, vehicle-controlled trial using intra-individual comparison," *American journal of clinical dermatology*, vol. 19, no. 2, pp. 275-286, 2018.
5. V. K. Emmerich, C. G. Purvis, and S. R. Feldman, "An overview of adapalene and benzoyl peroxide once-daily topical gel as a therapeutic option for acne," *Expert Opinion on Pharmacotherapy*, no. just-accepted, 2021.
6. V. D. Callender, H. Baldwin, F. E. Cook-Bolden, A. F. Alexis, L. Stein Gold, and E. Guenin, "Effects of Topical Retinoids on Acne and Post-inflammatory Hyperpigmentation in Patients with Skin of Color: A Clinical Review and Implications for Practice," *American journal of clinical dermatology*, pp. 1-13, 2021.
7. A. K. C. Leung, B. Barankin, J. M. Lam, K. F. Leong, and K. L. Hon, "Dermatology: how to manage acne vulgaris," *Drugs in context*, vol. 10, 2021.
8. E. C. N. Kaminska, "Treatment of acne and acne-related scarring with fixed combination clindamycin phosphate and benzoyl peroxide gel (1.2%/3.75%) and tretinoin gel microsphere 0.06% in an Asian American transgender female," *SAGE Open Medical Case Reports*, vol. 8, p. 2050313X20984038, 2020.
9. G. Latter, J. E. Grice, Y. Mohammed, M. S. Roberts, and H. A. E. Benson, "Targeted topical delivery of retinoids in the management of acne vulgaris: current formulations and novel delivery systems," *Pharmaceutics*, vol. 11, no. 10, p. 490, 2019.
10. J. A. See, C. L. Goh, N. Hayashi, D. H. Suh, and F. A. Casintahan, "Optimizing the use of topical retinoids in Asian acne patients," *The Journal of dermatology*, vol. 45, no. 5, pp. 522-528, 2018.
11. S. S. Kolli, D. Pecone, A. Pona, A. Cline, and S. R. Feldman, "Topical retinoids in acne vulgaris: a systematic review," *American journal of clinical dermatology*, pp. 1-21, 2019.
12. A. Samadi *et al.*, "Efficacy assessments of tretinoin-loaded nano lipid carriers in acne vulgaris: a double blind, split-face randomized clinical study," *Archives of Dermatological Research*, pp. 1-9, 2021.
13. S. Dogra *et al.*, "Efficacy and safety comparison of combination of 0.04% tretinoin microspheres plus 1% clindamycin versus their monotherapy in patients with acne vulgaris: a phase 3, randomized, double-blind study," *Journal of Dermatological Treatment*, vol. 32, no. 8, pp. 925-933, 2021.
14. S. K. Tying, L. H. Kircik, D. M. Pariser, E. Guenin, V. Bhatt, and R. Pillai, "Novel Tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: Assessment of efficacy and safety in patients aged 9 years and older," *Journal of drugs in dermatology: JDD*, vol. 17, no. 10, pp. 1084-1091, 2018.
15. H. F. Salem, R. M. Kharshoum, S. M. Awad, M. A. Mostafa, and H. A. Abou-Taleb, "Tailoring of retinyl palmitate-based ethosomal hydrogel as a novel nanoplatfrom for acne vulgaris management: Fabrication, optimization, and clinical evaluation employing a split-face comparative study," *International Journal of Nanomedicine*, vol. 16, p. 4251, 2021.



16. V. Mazzeo et al., "Clinical assessment of new topical cream containing two essential oils combined with tretinoin in the treatment of acne," *Clinical, cosmetic and investigational dermatology*, vol. 13, p. 233, 2020.
17. J. S. Barbieri, N. Spaccarelli, D. J. Margolis, and W. D. James, "Approaches to limit systemic antibiotic use in acne: systemic alternatives, emerging topical therapies, dietary modification, and laser and light-based treatments," *Journal of the American Academy of Dermatology*, vol. 80, no. 2, pp. 538-549, 2019.
18. B. Dreno, E. Bagatin, U. Blume-Peytavi, M. Rocha, and H. Gollnick, "Female type of adult acne: Physiological and psychological considerations and management," *JDDG: Journal Der Deutschen Dermatologischen Gesellschaft*, vol. 16, no. 10, pp. 1185-1194, 2018.
19. J. W. Marson and H. E. Baldwin, "An overview of acne therapy, part 1: topical therapy, oral antibiotics, laser and light therapy, and dietary interventions," *Dermatologic clinics*, vol. 37, no. 2, pp. 183-193, 2019.
20. M. Mwanthi and A. L. Zaenglein, "Update in the management of acne in adolescence," *Current opinion in pediatrics*, vol. 30, no. 4, pp. 492-498, 2018.
21. M. Santer, N. A. Francis, D. Platt, E. A. Eady, and A. M. Layton, "Stemming the tide of antimicrobial resistance: implications for management of acne vulgaris," vol. 68, ed: British Journal of General Practice, 2018, pp. 64-65.
22. P. S. Reddy, L. C. DeBord, R. Gupta, P. Kapadia, A. Mohanty, and H. Dao Jr, "Antibiotics for acne vulgaris: using instagram to seek insight into the patient perspective," *Journal of Dermatological Treatment*, 2019.
23. M. K. Trivedi, S. S. Bosanac, R. K. Sivamani, and L. N. Larsen, "Emerging therapies for acne vulgaris," *American journal of clinical dermatology*, vol. 19, no. 4, pp. 505-516, 2018.
24. R. Dursun, M. Daye, and K. Durmaz, "Acne and rosacea: What's new for treatment?," *Dermatologic therapy*, vol. 32, no. 5, p. e13020, 2019.
25. S. Deyno et al., "Essential oils as topical anti-infective agents: A systematic review and meta-analysis," *Complementary therapies in medicine*, vol. 47, p. 102224, 2019.
26. L. Drake, S. Reyes-Hadsall, J. S. Barbieri, and A. Mostaghimi, "New Developments in Topical Acne Therapy," *American Journal of Clinical Dermatology*, pp. 1-12, 2022.
27. E. Alshammari, "Efficacy of Generic vs. branded Isotretinoin for Acne treatment: a case report," *Journal of Advanced Pharmacy Education & Research| Jan-Mar*, vol. 11, no. 1, 2021.
28. E. N. Olsufyeva and V. S. Yankovskaya, "Main trends in the design of semi-synthetic antibiotics of a new generation," *Russian Chemical Reviews*, vol. 89, no. 3, p. 339, 2020.
29. M. A. Kayiran, A. S. Karadag, S. Al-Khuzaei, W. Chen, and L. C. Parish, "Antibiotic resistance in acne: mechanisms, complications and management," *American Journal of Clinical Dermatology*, pp. 1-7, 2020.
30. R. Abdel Hay, R. Hegazy, M. Abdel Hady, and N. Saleh, "Clinical and dermoscopic evaluation of combined (salicylic acid 20% and azelaic acid 20%) versus trichloroacetic acid 25% chemical peel in acne: an RCT," *Journal of Dermatological Treatment*, vol. 30, no. 6, pp. 572-577, 2019.
31. A. Szymańska, E. Budzisz, and A. Erkiert-Polguj, "Efficacy of 30% azelaic acid peel in the nonpharmacological treatment of facial acne," *Journal of Dermatological Treatment*, vol. 32, no. 3, pp. 291-296, 2021.
32. A. Bisht et al., "Azelaic acid and Melaleuca alternifolia essential oil co-loaded vesicular carrier for combinational therapy of acne," *Therapeutic Delivery*, no. 0, 2021.
33. J. Liang, D. Sun, Y. Yang, M. Li, H. Li, and L. Chen, "Discovery of metal-based complexes as promising antimicrobial agents," *European Journal of Medicinal Chemistry*, vol. 224, p. 113696, 2021.
34. F. Khatoon et al., "A comprehensive Review on Buthūr Labaniyya (Acne vulgaris) with special references of Unani System of Medicine," *seed*, vol. 28, p. 31, 2021.
35. M. Li et al., "The Prebiotic Effect of Triple Biotic Technology on Skin Health," *Journal of Cosmetics, Dermatological Sciences and Applications*, vol. 11, no. 4, pp. 304-319, 2021.
36. K. Kameswararao, C. Sujani, N. V. N. Koteswararao, A. Rajarao, and P. N. S. Satyanarayanamma, "A Brief Review on Acne Vulgaris," *Research Journal of Pharmacology and Pharmacodynamics*, vol. 11, no. 3, pp. 109-119, 2019.
37. J. Q. Del Rosso, L. Kircik, and E. Tanghetti, "Management of truncal acne vulgaris with topical dapsone 7.5% gel," *The Journal of clinical and aesthetic dermatology*, vol. 11, no. 8, p. 45, 2018.



38. S. A. Temiz and M. Daye, "Dapsone for the treatment of acne vulgaris: do the risks outweigh the benefits?," *Cutaneous and Ocular Toxicology*, no. just-accepted, pp. 1-17, 2021.
39. S. Jakhar, V. Kadian, and R. Rao, "Dapsone-Loaded Microsponge Gel for Acne Management: Preparation, Characterization and Anti-Microbial Activity," *Micro and Nanosystems*, vol. 13, no. 2, pp. 211-222, 2021.
40. A. Y. Moore *et al.*, "Once-daily Dapsone 7.5% Gel for the Treatment of Acne Vulgaris in Preadolescent Patients: A Phase IV, Open-label, 12-week Study," *The Journal of Clinical and Aesthetic Dermatology*, vol. 14, no. 4, p. 43, 2021.
41. S. Bharti and H. C. Vadlamudi, "A strategic review on the involvement of receptors, transcription factors and hormones in acne pathogenesis," *Journal of Receptors and Signal Transduction*, vol. 41, no. 2, pp. 105-116, 2021.
42. T.-X. Cong, D. Hao, X. Wen, X.-H. Li, G. He, and X. Jiang, "From pathogenesis of acne vulgaris to anti-acne agents," *Archives of dermatological research*, vol. 311, no. 5, pp. 337-349, 2019.
43. R. W. Clayton, K. Göbel, C. M. Niessen, R. Paus, M. A. M. Van Steensel, and X. Lim, "Homeostasis of the sebaceous gland and mechanisms of acne pathogenesis," *British Journal of Dermatology*, vol. 181, no. 4, pp. 677-690, 2019.
44. I. L. Kanwar, T. Haider, A. Kumari, S. Dubey, P. Jain, and V. Soni, "Models for acne: A comprehensive study," *Drug discoveries & therapeutics*, vol. 12, no. 6, pp. 329-340, 2018.
45. S. Briganti, E. Flori, A. Mastrofrancesco, and M. Ottaviani, "Acne as an altered dermato-endocrine response problem," *Experimental Dermatology*, vol. 29, no. 9, pp. 833-839, 2020.
46. M. A. Rocha and E. Bagatin, "Adult-onset acne: prevalence, impact, and management challenges," *Clinical, cosmetic and investigational dermatology*, vol. 11, p. 59, 2018.
47. U. Iftikhar and N. Choudhry, "Serum levels of androgens in acne & their role in acne severity," *Pakistan journal of medical sciences*, vol. 35, no. 1, p. 146, 2019.
48. A. Bienenfeld, S. Azarchi, K. L. Sicco, S. Marchbein, J. Shapiro, and A. R. Nagler, "Androgens in women: Androgen-mediated skin disease and patient evaluation," *Journal of the American Academy of Dermatology*, vol. 80, no. 6, pp. 1497-1506, 2019.
49. C. Kumtornrut, T. Yamauchi, S. Koike, S. Aiba, and K. Yamasaki, "Androgens modulate keratinocyte differentiation indirectly through enhancing growth factor production from dermal fibroblasts," *Journal of dermatological science*, vol. 93, no. 3, pp. 150-158, 2019.
50. C. March and S. Witchel, "Acne, Hirsutism, and Other Signs of Increased Androgens," in *Endocrine Conditions in Pediatrics*: Springer, 2021, pp. 85-94.
51. J. E. A. Common, J. N. Barker, and M. A. M. van Steensel, "What does acne genetics teach us about disease pathogenesis?," *British Journal of Dermatology*, vol. 181, no. 4, pp. 665-676, 2019.
52. C. C. Zouboulis, A. Nogueira da Costa, S. Fimmel, and K. C. Zouboulis, "Apocrine glands are bystanders in hidradenitis suppurativa and their involvement is gender specific," *Journal of the European Academy of Dermatology and Venereology*, vol. 34, no. 7, pp. 1555-1563, 2020.
53. V. G. Clatici, C. Voicu, C. Voaides, A. Roseanu, M. Icriverzi, and S. Jurcoane, "Diseases of Civilization—Cancer, Diabetes, Obesity and Acne—the Implication of Milk, IGF-1 and mTORC1," *Mædica*, vol. 13, no. 4, p. 273, 2018.
54. M. Wardhana, R. Vebryanti, G. A. Karmila, G. A. Praharsini, and R. S. Tallo, "Association between Psychological Stress and Insulin like Growth Factor-1 (IGF-1) with Acne Vulgaris," 2021.
55. E. Aktaş Karabay, Z. A. Saltık, and Ö. Unay Demirel, "Evaluation of serum FoxO1, mTORC1, IGF-1, IGFBP-3 levels, and metabolic syndrome components in patients with acne vulgaris: A prospective case-control study," *Dermatologic therapy*, vol. 33, no. 6, p. e13887, 2020.
56. E. Rodighiero *et al.*, "Do acne treatments affect insulin-like growth factor-1 serum levels? A clinical and laboratory study on patients with acne vulgaris," *Dermatologic therapy*, vol. 33, no. 3, p. e13439, 2020.
57. V. Magri *et al.*, "Multidisciplinary approach to prostatitis," (in eng), *Arch Ital Urol Androl*, vol. 90, no. 4, pp. 227-248, Jan 18 2019, doi: 10.4081/aiua.2018.4.227.
58. A. Ebrahimi *et al.*, "Association between CYP19A< G rs700518 Polymorphism with Acne Vulgaris and its severity: influence on sex hormones level," *International journal of molecular and cellular medicine*, vol. 8, no. 2, p. 162, 2019.



59. N. Akdoğan, S. Doğan, N. Atakan, and B. Yalçın, "Association of serum hormone levels with acne vulgaris: Low estradiol level can be a pathogenetic factor in female acne," *Our Dermatology Online/Nasza Dermatologia Online*, vol. 9, no. 3, 2018.
60. T. M. DeGrazia, R. Rolader, D. M. Thiboutot, and H. Yeung, "Eligibility criteria related to hormone therapy in acne clinical trials: a systematic review," *The Journal of Investigative Dermatology*, no. 1, pp. 189-191, 2020.
61. R. E. Ashton *et al.*, "Antiandrogen treatment in women with acne: a controlled trial," in *Antiandrogen-Estrogen Therapy for Signs of Androgenization*: De Gruyter, 2019, pp. 117-130.
62. U. Singh, A. Chaudhary, M. M. P. Singh, M. P. S. Sawhney, B. Karunanand, and B. K. Anand, "A Study of Hormonal Profile (Luteinizing Hormone, Estrogen, Follicle Stimulating Hormone and Prolactin) In the Women Suffering From Acne Vulgaris," *Annals of International Medical and Dental Research*, vol. 4, no. 4, p. 22, 2018.
63. B.-P. Wang *et al.*, "An unusual case of ectopic corticotrophin-releasing hormone syndrome caused by an adrenal noncatecholamine-secreting pheochromocytoma: a case report," *BMC endocrine disorders*, vol. 18, no. 1, pp. 1-5, 2018.
64. P. Bansal, K. Sardana, G. Vats, L. Sharma, U. C. Garga, and A. Khurana, "A prospective study examining trigger factors and hormonal abnormalities in adult female acne," *Indian Dermatology Online Journal*, vol. 11, no. 4, p. 544, 2020.
65. D. Azanbayeva, G. Batpenova, T. Tarkina, T. Algazina, and T. Kotlyarova, "CLINICAL AND LABORATORY CHARACTERISTICS OF PATIENTS WITH ADOLESCENCE ACNE AND ACNE TARDA," *Georgian medical news*, no. 282, pp. 103-106, 2018.
66. F. Kelestimur and K. Unluhizarci, "Congenital Adrenal Hyperplasia (CAH): Definition and Enzymatic Defects in Various Forms," in *Fertility and Reproductive Outcomes in Different Forms of Congenital Adrenal Hyperplasia*: Springer, 2021, pp. 1-18.
67. B. Chen, Y. Zheng, and Y. Liang, "Analysis of potential genes and pathways involved in the pathogenesis of acne by bioinformatics," *BioMed research international*, vol. 2019, 2019.
68. S. Soleymani, M. H. Farzaei, A. Zargar, S. Niknam, and R. Rahimi, "Promising plant-derived secondary metabolites for treatment of acne vulgaris: a mechanistic review," *Archives of dermatological research*, vol. 312, no. 1, pp. 5-23, 2020.
69. B. Zhang *et al.*, "Toll-like receptor 2 plays a critical role in pathogenesis of acne vulgaris," *Biomedical Dermatology*, vol. 3, no. 1, pp. 1-6, 2019.
70. S. Zhang *et al.*, "Serum levels of proinflammatory, anti-inflammatory cytokines, and RANKL/OPG in synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome," *Modern rheumatology*, vol. 29, no. 3, pp. 523-530, 2019.
71. Y. Wang *et al.*, "The anti-inflammatory activities of *Propionibacterium acnes* CAMP factor-targeted acne vaccines," *Journal of Investigative Dermatology*, vol. 138, no. 11, pp. 2355-2364, 2018.
72. G. W. Agak *et al.*, "Phenotype and antimicrobial activity of Th17 cells induced by *Propionibacterium acnes* strains associated with healthy and acne skin," *Journal of Investigative Dermatology*, vol. 138, no. 2, pp. 316-324, 2018.
73. C. Rosette, F. J. Agan, A. Mazzetti, L. Moro, and M. Gerloni, "Cortexolone 17 α -propionate (clascoterone) is a novel androgen receptor antagonist that inhibits production of lipids and inflammatory cytokines from sebocytes in vitro," *Journal of drugs in dermatology: JDD*, vol. 18, no. 5, pp. 412-418, 2019.
74. H.-y. He *et al.*, "Association of brain-derived neurotrophic factor levels and depressive symptoms in young adults with acne vulgaris," *BMC psychiatry*, vol. 19, no. 1, pp. 1-8, 2019.
75. M. Shan, F. Meng, C. Tang, L. Zhou, Z. Lu, and Y. Lu, "Surfactin-oleogel with therapeutic potential for inflammatory acne vulgaris induced by *Propionibacterium acnes*," *Applied microbiology and biotechnology*, pp. 1-14, 2021.
76. C. C. Zouboulis *et al.*, "Adalimumab dose intensification in recalcitrant hidradenitis suppurativa/acne inversa," *Dermatology*, vol. 236, no. 1, pp. 25-30, 2020.
77. J. N. Clark, A. Whiting, and P. McCaffery, "Retinoic acid receptor-targeted drugs in neurodegenerative disease," *Expert Opinion on Drug Metabolism & Toxicology*, vol. 16, no. 11, pp. 1097-1108, 2020.
78. C. Yavuz and M. Ozcimen, "An evaluation of peripapillary choroidal thickness in patients receiving systemic isotretinoin treatment," *Cutaneous and ocular toxicology*, vol. 38, no. 1, pp. 25-28, 2019.
79. R. Ferreira, J. Napoli, T. Enver, L. Bernardino, and L. Ferreira, "Advances and challenges in retinoid delivery systems in regenerative and therapeutic medicine," *Nature Communications*, vol. 11, no. 1, pp. 1-14, 2020.



80. A. Rao, S. C. Douglas, and J. M. Hall, "Endocrine Disrupting Chemicals, Hormone Receptors, and Acne Vulgaris: A Connecting Hypothesis," *Cells*, vol. 10, no. 6, p. 1439, 2021.
81. N. Stefanovic, A. D. Irvine, and C. Flohr, "The Role of the Environment and Exposome in Atopic Dermatitis," (in eng), *Curr Treat Options Allergy*, pp. 1-20, May 21 2021, doi: 10.1007/s40521-021-00289-9.
82. T. Passeron, J. Krutmann, M. L. Andersen, R. Katta, and C. C. Zouboulis, "Clinical and biological impact of the exposome on the skin," *Journal of the European Academy of Dermatology and Venereology*, vol. 34, pp. 4-25, 2020.
83. H. Kaya Ozden and A. S. Karadag, "Could endocrine disruptors be a new player for acne pathogenesis? The effect of bisphenol A on the formation and severity of acne vulgaris: A prospective, case-controlled study," *Journal of Cosmetic Dermatology*, vol. 20, no. 11, pp. 3573-3579, 2021.
84. M. FitzPatrick, "Endocrine Disrupting Chemicals and Personal Care Products: Risk Awareness and Exposure Assessment for Women's Reproductive Health," 2021.
85. A. Dzimitrowicz *et al.*, "Cold atmospheric pressure plasmas as versatile tools for effective degradation of a mixture of hazardous and endocrine disturbing compounds from liquid wastes," *Journal of Environmental Chemical Engineering*, vol. 9, no. 6, p. 106718, 2021.