Proceedings of CONF-MCEE 2026 Symposium: Advances in Sustainable Aviation and Aerospace Vehicle Automation
DOI: 10.54254/2755-2721/2026.KA27046

Cutibacterium Acnes and Acne Vulgaris: Pathogenesis, Antimicrobial Resistance, and Therapeutic Strategies

Jixuan Li

School of Chemical and Material Engineering, Jiangnan University, Wuxi, China
1051230315@stu.jiangnan.edu.cn

Abstract. Acne vulgaris is a common chronic inflammatory skin disorder affecting pilosebaceous units, characterized by non-inflammatory (comedones) and inflammatory (papules, pustules, nodules) lesions, with a global prevalence of approximately 240 million individuals in 2021. This review focuses on the role of Cutibacterium acnes (C. acnes) in acne pathogenesis, its antimicrobial resistance, and therapeutic strategies. C. acnes, a gram-positive anaerobic bacterium resident in sebaceous follicles, contributes to acne through mechanisms including excessive sebum production, follicular hyperkeratinization, and induction of inflammation via toll-like receptors and complement pathways. Key therapeutic agents (clindamycin, tretinoin, benzoyl peroxide, and azelaic acid) are discussed in terms of their chemical properties and mechanisms, targeting bacterial growth, follicular function, and inflammation. A critical challenge is the rising antimicrobial resistance of C. acnes, with over 50% of strains resistant to erythromycin and clindamycin globally, and rates exceeding 90% in some regions. Strategic combination therapies, such as antibiotics with BPO or triple combinations (e.g., clindamycin/BPO/adapalene), have shown efficacy in reducing resistance and enhancing lesion clearance, highlighting their importance in managing resistant strains. This review underscores the need for targeted approaches to address C. acnes pathogenesis and resistance, improving acne management and patient outcomes.

Keywords: Acne vulgaris, Cutibacterium acnes, Antimicrobial resistance

1. Introduction

Acne vulgaris is a common chronic inflammatory skin disorder affecting the pilosebaceous units [1], characterized by both non-inflammatory and inflammatory lesions [2]. Non-inflammatory lesions include closed comedones (whiteheads) and open comedones (blackheads), arising from sebum and keratin buildup in hair follicles. Inflammatory lesions, such as papules, pustules, nodules, and cysts, develop when blocked follicles rupture, triggering immune responses. These lesions usually occur on the face, chest, or upper back [3]. Untreated acne can lead to permanent scarring, while its impact extends beyond physical symptoms, affecting patients' mental health and quality of life through issues like poor self-esteem and disrupted social interactions.

Epidemiological data from the Global Burden of Disease (GBD) highlight acne's widespread prevalence: in 2021, approximately 240 million individuals were affected globally, with 67% aged 15–49 year. Its prevalence increased steadily from 2010 to 2021, ranking 8th among all diseases

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2755-2721/2026.KA27046

worldwide and 2nd among global skin diseases [4]. This data underscores acne as a significant public health concern, affecting diverse age groups and populations across regions [5].

A key clinical challenge in acne management is the rising antimicrobial resistance of Cutibacterium acnes (C. acnes), the primary bacterium involved in pathogenesis. Resistance to antibiotics like erythromycin and clindamycin was first reported in 1979 and is now globally prevalent, with at least 50% of acne patients colonized by resistant strains [6]. Existing treatment regimens also face limitations, including variable efficacy, skin irritation, and the need for long-term adherence. These challenges highlight the urgent need for innovative therapeutic strategies to address resistance and improve patient outcomes.

2. Biological characteristics and pathogenic mechanisms of cutibacterium acnes

Propionibacterium acnes(P. acnes) was the original name of C. acnes and Genomic and metagenomic investigations in 2016 led to this name change [7]. There are many different kinds of bacteria on the healthy skin of humans and C. acnes is one of them, which is gram-positive and anaerobic, mainly lives deep in the hair follicles[7]. As the major resident of the normal human skin, C. acnes can break down sebum and then produce free fatty acids which can inhibit growth of other bacteria and then protect the bacterial balance of the skin [8]. However, when skin environment changes and becomes conducive for the growth of C. acnes, for example, when the sebum secretion of the skin suddenly increases, these bacteria will start to cause disease. The factors for sebum overproduction may include environmental and climate changes, alterations in lifestyle habits, fluctuations in hormone levels, the impact of diseases or medications, etc.

3. Pathogenic mechanisms of C. acnes

Although free fatty acids produced by C. acnes can help maintain the pH value and protect the bacterial balance of the skin, they can also induce abnormal keratinocyte growth and break the balance of hair follicles [4]. C. acnes also enhances sebum production via increasing diacylglycerol acyltransferase activity, exacerbating androgen-driven sebum overproduction and creating a lipid-rich skin environment that promotes its growth [4]. Additionally, porphyrins secreted by C. acnes can catalyze squalene oxidation, which is an abundant sebum component. Free fatty acids and oxidized squalene can both contribute to comedone formation by changing keratinocyte differentiation [7,9]. Besides, C. acnes can also induce inflammation through multiple mechanisms including engagement with toll-like receptors like TLR2 and TLR4 on keratinocytes and sebocytes to trigger secretion of pro-inflammatory factors such as IL-1α, IL-6 and TNF-α; activation of classical and alternative complement pathways, generating C3a and C5a to enhance the permeability ability of blood vessels and the aggregation of white blood cells7,10. Inflammation caused by C. acnes will damage the structure of human skin and increased vascular permeability and leukocyte infiltration impair the stratum corneum, lessening the skin's barrier strength and its ability to hold moisture, showing up as dry skin, red patches, and increased sensitivity to the environment [11].

Beyond acne vulgaris, C. acnes can also cause other health problems when given the chance, and different types of it are linked to specific diseases. For example, sarcoidosis, a condition where small lumps form in organs like the lungs and skin, is connected to C. acnes subsp. acnes (phylotype I). This type is found in 64–80% of these lumps and probably triggers immune reactions by activating TLR2. Prostate cancer might be related to C. acnes subsp. defendens (phylotype II); this type is more common in cancerous prostate tissues, often has a special structure that helps it stick and form biofilms, and studies even link severe acne in teens to a higher risk of dying from prostate cancer

DOI: 10.54254/2755-2721/2026.KA27046

later. Progressive macular hypomelanosis, a skin condition with light-colored spots on the trunk, is strongly tied to C. acnes subsp. elongatum (phylotype III); this type is rarely on the face, which matches why the spots usually don't appear there. Prosthetic joint infections (PJIs), especially in the shoulder, hip, and knee, are often caused by specific types: IA1 (CC18) and IA2 (CC28) in spinal implant infections, and IB (CC36) and II (CC53) in joint replacements. These types form biofilms, which make the infections last longer and harder to treat with antibiotics. Additionally, C. acnes, especially types IC and II that form lots of biofilms, can cause other infections, like blood infections, infections linked to heart devices, and infections from catheters, where biofilms help the germ stick around and keep causing problems [12].

4. Mechanisms and properties of acne therapeutic agents

Nowadays many kinds of drugs have been used for treating acne vulgaris and they are grouped by how they are applied (topically or systemically) or what they do in the body. For mild to moderate acne, topical treatments are usually tried first. These include retinoids like tretinoin and adapalene, which help normalize how skin cells grow and shed in hair follicles, preventing clogged pores. There are also antimicrobials: benzoyl peroxide (BPO) kills the bacteria Cutibacterium acnes and reduces redness, while clindamycin works similarly but is often paired with BPO to avoid resistance. Azelaic acid is another option, fighting bacteria and calming inflammation at the same time [7,13]. For more severe or stubborn acne, oral drugs come into play. Antibiotics like doxycycline or minocycline can tamp down bacterial overgrowth and swelling, though they're not used long-term to prevent resistance. Isotretinoin, a strong retinoid taken by mouth, stands out because it targets all parts of acne's cause: too much oil, clogged follicles, bacteria, and inflammation [11]. Recently, doctors often combine drugs to work better and lower the chance of bacteria becoming resistant [4]. While topicals are go-to for starting treatment, isotretinoin remains key for severe cases, though it needs careful monitoring due to risks like birth defects. Overall, the goal is to pick the right mix to clear acne without causing new problems.

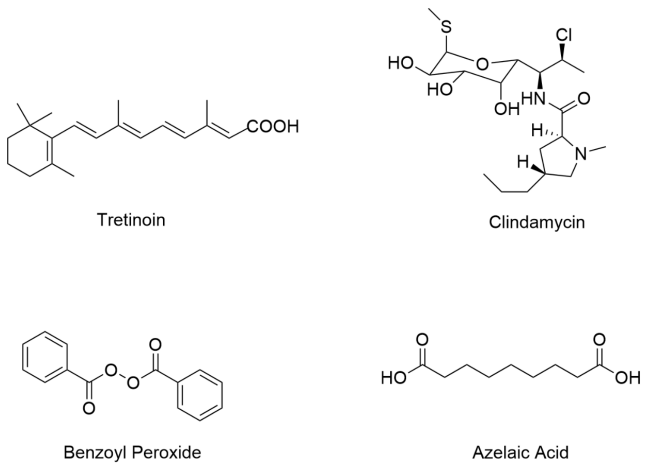

Figure 1. The chemical structures of four drugs

In this work, four drugs will be introduced in terms of their chemical structures, chemical properties, and mechanisms of action. They are clindamycin, tretinoin, benzoyl peroxide (BPO) and azelaic acid (AzA). You can see their chemical structures in Figure 1. And only topical treatments of these drugs will be introduced in this article.

DOI: 10.54254/2755-2721/2026.KA27046

4.1. Clindamycin

Clindamycin, a lincosamide antibiotic, has a chemical structure (see Figure 1) derived from lincomycin, with a key modification: a chlorine atom replaces the hydroxyl group at the 7-position of the lincomycin molecule. Clindamycin contains two key cyclic structures: the methylthiolincosamide ring and the L-threo-α-D-galacto-octopyranoside ring. These rings, with their non-polar substituents and hydrophobic moieties, enhance the molecule's lipophilicity, aiding its penetration of bacterial membranes and skin barriers [12,14].

Clindamycin can irreversibly binds to the peptidyl transferase center of the 50S ribosomal subunit in bacteria, specifically interacting with nucleotides A2451 and G2505 within the 23S rRNA to block peptide bond formation and disrupt protein synthesis [15]. This mechanism selectively targets bacterial ribosomes over mammalian ones, making it effective against Gram-positive anaerobes like C. acnes by inhibiting the production of essential proteins. Beyond protein synthesis inhibition, clindamycin demonstrates bacteriostatic effects against Gram-positive anaerobes like C. acnes by disrupting essential metabolic pathways and cell wall integrity. Its lipophilic nature allows penetration into pilosebaceous follicles, making it effective for topical acne treatment by reducing bacterial load and modulating inflammation. Notably, clindamycin's structural similarity to macrolides can lead to cross-resistance via erm gene-mediated rRNA methylation, which alters the ribosomal binding site. However, its resistance profile remains distinct due to unique binding determinants [16].

4.2. Tretinoin

Tretinoin, an active form of vitamin A, has a simple but key chemical structure (see Figure 1): a water-repelling ring, a long chain with double bonds, and an acidic end group, all of which make it part of the retinoid family. This structure gives it useful properties: the ring and chain let it slip through cell membranes and into oil-producing skin follicles, while the acidic end helps it stick to special "retinoid receptors" in cells that control skin cell behavior [11].

Over time, retinoids have gotten improved, with different types each having their own upsides. Early ones, like tretinoin (all-trans retinoic acid), work by helping skin cells shed normally and keeping pores from clogging, but they break down easily in light or air, so they're not super stable. Then came stronger ones, like isotretinoin, which are great for ssevere acne because they cut down oil production and fix messed-up pore linings1. But they're risky for pregnant people, so strict birth control is a must. Newer retinoids, such as adapalene and tazarotene, have tweaked structures: adapalene, for example, sticks better to the skin's retinoid receptors and doesn't break down as easily. This means less irritation, making them good for long-term use on the skin. All these changes show how retinoids have gotten better at clearing acne while being safer and easier to use [11].

Tretinoin treats acne through several key ways, all working together to tackle the root causes. First, it helps skin cells (called keratinocytes) in hair follicles shed normally, stopping them from piling up and clogging pores, which is one of the first steps in acne formation. By normalizing this "cell turnover," it prevents the tiny plugs that trap oil and bacteria like C. acnes inside follicles [1,11]. Then, it cuts down on sebum production by shrinking overactive sebaceous glands, since excess sebum feeds bacteria and makes acne worse [17]. And also, it eases inflammation: it calms down the red, swollen bumps by reducing the release of pro-inflammatory chemicals that the body sends to fight the trapped bacteria. These combined effects of unclogging pores, reducing oil, and quieting inflammation make tretinoin the first choice of acne treatment, whether used topically for mild cases or orally (like isotretinoin) for severe, stubborn acne [13].

DOI: 10.54254/2755-2721/2026.KA27046

4.3. Benzoyl peroxide

Benzoyl peroxide (BPO) has a distinct chemical structure (see Figure 1) and properties that support its efficacy. Structurally, it consists of two benzoyl groups linked by an unstable peroxide bond, forming the molecular formula $C_{14}H_{10}O_4$ [18]. This arrangement creates a symmetrical molecule with a rigid benzene ring on each end and a reactive oxygen-oxygen bridge in the center. The benzene rings provide hydrophobicity, allowing BPO to enter oily follicles where acne-causing bacteria like C. acnes thrive. Chemically, BPO is classified as an organic peroxide, characterized by its strong oxidizing properties. When applied to the skin, it decomposes upon contact with moisture or heat, breaking the peroxide bond to release free radicals. These radicals disrupt bacterial cell membranes and denature proteins, exerting a broad-spectrum bactericidal effect against C. acnes. Additionally, BPO's oxidizing activity reduces free fatty acids in sebum, which are known to stimulate follicles and exacerbate inflammation. Notably, BPO does not rely on antibiotic mechanisms, making it resistant to bacterial resistance, which is a critical advantage over other acne treatments [13].

4.4. Azelaic acid

Azelaic acid (AzA), a naturally occurring dicarboxylic acid, boasts a chemical structure (see Figure 1) and properties that make it effective for acne management. Structurally, it features a straight nine-carbon chain with carboxylic acid groups at both ends, giving it the molecular formula $C_9H_{16}O_4$ [13]. This symmetrical design, hydrophobic hydrocarbon chain flanked by polar carboxyl groups, makes AzA amphiphilic, allowing it to enter both oily pilosebaceous follicles and aqueous skin layer [11]. Chemically, it is a weak acid (pKa ≈ 4.5) with modest solubility in wate but better solubility in alcohols, which helps stabilize it in topical formulations. Its stability ensures it remains effective in creams or gels during storage. When applied to the skin, AzA's structure supports its dual actions: the carboxyl groups aid in disrupting bacterial membranes and inhibiting C. acnes growth, while the hydrocarbon chain helps reduce excess keratinocyte growth, preventing pore clogging [13]. Unlike some antibiotics, it does not induce bacterial resistance, adding to its appeal for long-term use in acne [19].

AzA fights acne through several key mechanisms that work together to tackle the condition at multiple stages. First, it directly targets C. acnes, disrupting their cell membranes and slowing their growth which helps reduce the bacterial overgrowth that fuels inflammatio[11,13]. Second, it calms overactive skin cells in hair follicles, preventing them from clumping together and clogging pores, which stops the formation of blackheads and whiteheads. Additionally, it eases redness and swelling by lowering levels of pro-inflammatory chemicals like interleukin-8, which are released when the body reacts to trapped bacteria [11]. It also has a mild lightening effect on dark spots left by acne, which is an extra benefit for people with darker skin tones. These combined actions of fighting bacteria, unclogging pores, reducing inflammation, and improving post-acne discoloration make it a multifunctional option for mild to moderate acne [11,13].

5. Antibacterial resistance and strategies

5.1. Antibacterial resistance in cutibacterium acnes

C. acnes have shown alarming antibiotic resistance, driven largely by long-term use of topical antibiotics. Globally, at least 50% of acne patients are colonized with C. acnes strains resistant to

DOI: 10.54254/2755-2721/2026.KA27046

erythromycin and clindamycin [6], with resistance rates reaching as high as 91% for combined erythromycin and clindamycin resistance in regions like Spain[20]. Erythromycin resistance, first reported in 197 [6], has become so prevalent that its topical use for acne has nearly ceased, while clindamycin use has risen over the past two decades [20]. This shift aligns with the increasing number of studies on clindamycin resistance, publications on the topic surpassed 100 per year by 2003, roughly 30 years after its first use in acne, mirroring the timeline of erythromycin resistance emergence [20].

5.2. Strategies for combined drug use

Combating antibiotic resistance in C. acnes relies heavily on strategic combination therapies that target bacterial survival mechanisms while minimizing selective pressure. A key strategy is pairing topical antibiotics with BPO, as BPO's bactericidal action (via free radical release) bypasses resistance pathways and suppresses resistant strains. For example, clindamycin combined with BPO reduces the risk of clindamycin resistance, with studies showing that this combination lowers the emergence of resistant C. acnes by 52% compared to clindamycin monotherapy [7,20]. This is critical given that clindamycin resistance rates have reached 90.4% in some regions[7], and erythromycin resistance exceeds 50% globally [6].

Triple combinations, such as clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15% gel, further enhance efficacy by targeting multiple pathogenic factors: antibiotics address bacteria, BPO counteracts resistance, and adapalene normalizes follicular excessive keratinization. In clinical trials, this triple therapy reduced inflammatory lesions by 55.8% in pediatric patients, outperforming dual combinations and limiting resistance development [21].

6. Conclusion

Acne vulgaris remains a significant global health concern, driven by the complex interplay between C. acnes and host factors. The pathogenic mechanisms of C. acnes, including its role in sebum metabolism, follicular occlusion, and inflammation, provide critical targets for therapeutic intervention. While topical and systemic agents effectively address these pathways, the escalating antimicrobial resistance of C. acne poses a major clinical challenge, with resistance rates exceeding 50% globally and reaching 91% in specific regions.

Looking forward, future advances in acne care will likely focus on novel non-antibiotic approaches to avoid resistance. These include targeted inhibitors of C. acnes virulence factors, personalized treatments based on strain-specific traits of C. acnes, and microbiome-modulating strategies to restore skin microbial balance. Such innovations could boost efficacy while reducing resistance, improving long-term acne management.

References

[1] Reynolds, R. V.; Yeung, H.; Cheng, C. E.; Cook-Bolden, F.; Desai, S. R.; Druby, K. M.; Freeman, E. E.; Keri, J. E.; Stein Gold, L. F.; Tan, J. K. L.; Tollefson, M. M.; Weiss, J. S.; Wu, P. A.; Zaenglein, A. L.; Han, J. M.; Barbieri, J. S. Guidelines of Care for the Management of Acne Vulgaris. J. Am. Acad. Dermatol. 2024, 90 (5), 1006.e1-1006.e30. https: //doi.org/10.1016/j.jaad.2023.12.017.

[2] Tuchayi, S. M.; Makrantonaki, E.; Ganceviciene, R.; Dessinioti, C.; Feldman, S. R.; Zouboulis, C. C. Acne Vulgaris. Nat. Rev. Dis. Primers 2015, 1, 15029. https: //doi.org/10.1038/nrdp.2015.29.

[3] Ogé, L. K.; Broussard, A.; Marshall, M. D. Acne Vulgaris: Diagnosis and Treatment. Acne Vulgaris 2019. https: //doi.org/2019; 100(8): 475-484.

DOI: 10.54254/2755-2721/2026.KA27046

[4] Xu, H.; Li, H. Acne, the Skin Microbiome, and Antibiotic Treatment. Am. J. Clin. Dermatol. 2019, 20 (3), 335–344. https: //doi.org/10.1007/s40257-018-00417-3.
[5] Acne vulgaris - level 3 cause | institute for health metrics and evaluation. https: //www.healthdata.org/research-analysis/diseases-injuries-risks/factsheets/2021-acne-vulgaris-level-3-disease (accessed 2025-07-31).
[6] Valente Duarte De Sousa, I. C. An Update on the Pharmacological Management of Acne Vulgaris: The State of the Art. Expert Opin. Pharmacother. 2024, 25 (16), 2177–2190. https: //doi.org/10.1080/14656566.2024.2418986.
[7] Dréno, B.; Pécastaings, S.; Corvec, S.; Veraldi, S.; Khammari, A.; Roques, C. Cutibacterium Acnes (Propionibacterium Acnes) and Acne Vulgaris: A Brief Look at the Latest Updates. J. Eur. Acad. Dermatol. Venereol. 2018, 32 (S2), 5–14. https: //doi.org/10.1111/jdv.15043.
[8] McLaughlin, J.; Watterson, S.; Layton, A. M.; Bjourson, A. J.; Barnard, E.; McDowell, A. Propionibacterium Acnes and Acne Vulgaris: New Insights from the Integration of Population Genetic, Multi-Omic, Biochemical and Host-Microbe Studies. Microorganisms 2019, 7 (5), 128. https: //doi.org/10.3390/microorganisms7050128.
[9] Gerami, P.; Paller, A. S. Making a Mountain out of a Molehill: NRAS, Mosaicism, and Large Congenital Nevi. J. Invest. Dermatol. 2013, 133 (9), 2127–2130. https: //doi.org/10.1038/jid.2013.146.
[10] Lheure, C.; Grange, P. A.; Ollagnier, G.; Morand, P.; Désiré, N.; Sayon, S.; Corvec, S.; Raingeaud, J.; Marcelin, A.-G.; Calvez, V.; Khammari, A.; Batteux, F.; Dréno, B.; Dupin, N. TLR-2 Recognizes Propionibacterium Acnes CAMP Factor 1 from Highly Inflammatory Strains. PLOS One 2016, 11 (11), e0167237. https: //doi.org/10.1371/journal.pone.0167237.
[11] Khalil, S.; Bardawil, T.; Stephan, C.; Darwiche, N.; Abbas, O.; Kibbi, A. G.; Nemer, G.; Kurban, M. Retinoids: A Journey from the Molecular Structures and Mechanisms of Action to Clinical Uses in Dermatology and Adverse Effects. J. Dermatol. Treat. 2017, 28 (8), 684–696. https: //doi.org/10.1080/09546634.2017.1309349.
[12] Boyanova, L. Cutibacterium Acnes (Formerly Propionibacterium Acnes): Friend or Foe? Future Microbiol. 2023, 18 (4), 235–244. https: //doi.org/10.2217/fmb-2022-0191.
[13] Zaenglein, A. L.; Pathy, A. L.; Schlosser, B. J.; Alikhan, A.; Baldwin, H. E.; Berson, D. S.; Bowe, W. P.; Graber, E. M.; Harper, J. C.; Kang, S.; Keri, J. E.; Leyden, J. J.; Reynolds, R. V.; Silverberg, N. B.; Stein Gold, L. F.; Tollefson, M. M.; Weiss, J. S.; Dolan, N. C.; Sagan, A. A.; Stern, M.; Boyer, K. M.; Bhushan, R. Guidelines of Care for the Management of Acne Vulgaris. J. Am. Acad. Dermatol. 2016, 74 (5), 945-973.e33. https: //doi.org/10.1016/j.jaad.2015.12.037.
[14] Pelet Del Toro, N. M.; Strunk, A.; Wu, J. J.; Stein Gold, L.; Del Rosso, J. Q.; Brodell, R. T.; Han, G. Topical Clindamycin for Acne Vulgaris: Analysis of Gastrointestinal Events. J. Dermatol. Treat. 2024, 35 (1), 2325603. https: //doi.org/10.1080/09546634.2024.2325603.
[15] Tenson, T.; Lovmar, M.; Ehrenberg, M. The Mechanism of Action of Macrolides, Lincosamides and Streptogramin B Reveals the Nascent Peptide Exit Path in the Ribosome. J. Mol. Biol. 2003, 330 (5), 1005–1014. https: //doi.org/10.1016/S0022-2836(03)00662-4.
[16] Warner, G. T.; Plosker, G. L. Clindamycin/Benzoyl Peroxide Gel: A Review of Its Use in the Management of Acne. Am. J. Clin. Dermatol. 2002, 3 (5), 349–360. https: //doi.org/10.2165/00128071-200203050-00007.
[17] Greydanus, D. E.; Azmeh, R.; Cabral, M. D.; Dickson, C. A.; Patel, D. R. Acne in the First Three Decades of Life: An Update of a Disorder with Profound Implications for All Decades of Life. Dis. Mon. 2021, 67 (4), 101103. https: //doi.org/10.1016/j.disamonth.2020.101103.
[18] Sagransky, M.; Yentzer, B. A.; Feldman, S. R. Benzoyl Peroxide: A Review of Its Current Use in the Treatment of Acne Vulgaris. Expert Opin. Pharmacother. 2009, 10 (15), 2555–2562. https: //doi.org/10.1517/14656560903277228.
[19] Borch, J.; Andersen, K.; Bindslev-Jensen, C. The Prevalence of Acute Cutaneous Drug Reactions in a Scandinavian University Hospital. Acta Derm. Venereol. 2006, 86 (6), 518–522. https: //doi.org/10.2340/00015555-0143.
[20] Austin, B. A.; Fleischer, A. B. The Extinction of Topical Erythromycin Therapy for Acne Vulgaris and Concern for the Future of Topical Clindamycin. J. Dermatol. Treat. 2017, 28 (2), 145–148. https: //doi.org/10.1080/09546634.2016.1214234.
[21] Podwojniak, A.; Tan, I. J.; Sauer, J.; Parikh, A.; Cohen, B. A.; Heath, C. Updates on Topical Dyad and Triple Combination Therapies Approved for Acne Vulgaris. Cureus 2024. https: //doi.org/10.7759/cureus.61413.