

## Topical treatments for acne: a bibliographic review

### Tratamentos tópicos para acne: uma revisão bibliográfica

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#### **ABSTRACT**

**Objective:** To relate the existing topical therapeutic approaches to combat acne and their mechanisms of action and particularities through bibliographic review. We shall analyze the antibacterial, anti-inflammatory and anti-seborrheic activities of these substances. **Methods:** The bibliographic review was based on research of published and unpublished articles, in English or Portuguese, in the Cochrane, Pubmed and Scopus databases, *in vitro*, *in vivo* and bibliographic reviews demonstrating the topical treatment methods in the fight against *Acne vulgaris*, considering data from 2010 to August 2020. **Results:** Topical therapy is based on the type and severity of acne. Despite the severity, it is often treated with topical retinoids or a variety of different substances, such as antibiotics, azelaic acid, salicylic acid, benzoyl peroxide, niacinamide and others, in addition to complementary and alternative medicines (CAM), such as resveratrol, vitamin C, tea tree oil, among others. Topical treatment has the advantage of reducing systemic absorption and increasing exposure of pilosebaceous follicles to treatment. **Conclusions:** Topical retinoids have been used in acne therapy for over forty years, due to both their efficacy (demonstrated in several clinical trials) and the development of third generation retinoids,

which allowed for the reduction of side effects, better chemical compatibility and better stability of formulations. Other topical treatments adopted sought to complement the retinoids and antibiotics with mechanisms of antiseptic, anti-inflammatory, comedolytic and keratolytic action. They are often used as a second line of treatment; and in some special cases for sensitive patients and pregnant women. *Acne vulgaris* is a chronic disease that affects not only the skin; it has a great psychological and financial factor in affected patients. Clinical follow-up is important because it is an exclusive long-term treatment, and awareness of this fact is important.

**Keywords:** *Propionibacterium acnes*, skin health, therapy, comedolytics, antimicrobials, antiseptics.

## RESUMO

**Objetivo:** Relacionar as abordagens terapêuticas tópicas existentes no combate à acne e seus mecanismos de ação e particularidades por meio de revisão bibliográfica. Analisaremos as atividades antibacteriana, antiinflamatória e anti-seborréica dessas substâncias. **Métodos:** A revisão bibliográfica baseou-se em pesquisa de artigos publicados e não publicados, em inglês ou português, nas bases de dados Cochrane, Pubmed e Scopus, *in vitro*, *in vivo* e em revisões bibliográficas que demonstrem os métodos de tratamento tópico no combate à *Acne vulgaris*, considerando dados de 2010 a agosto de 2020. **Resultados:** A terapia tópica é baseada no tipo e gravidade da acne. Apesar da gravidade, muitas vezes é tratada com retinóides tópicos ou uma variedade de substâncias diferentes, como antibióticos, ácido azelaico, ácido salicílico, peróxido de benzoíla, niacinamida e outros, além de medicamentos complementares e alternativos (CAM), como o resveratrol, vitamina C, óleo da árvore do chá, entre outros. O tratamento tópico tem a vantagem de reduzir a absorção sistêmica e aumentar a exposição dos folículos pilosebáceos ao tratamento. **Conclusões:** Os retinóides tópicos têm sido utilizados na terapia da acne há mais de quarenta anos, tanto pela eficácia (demonstrada em diversos ensaios clínicos) quanto pelo desenvolvimento de retinóides de terceira geração, que possibilitaram a redução dos efeitos colaterais, melhor compatibilidade química e melhor estabilidade de formulações. Outros tratamentos tópicos adotados buscaram complementar os retinóides e antibióticos com mecanismos de ação anti-séptica, antiinflamatória, comedolítica e ceratolítica. Eles são frequentemente usados como uma segunda linha de tratamento; e em alguns casos especiais para pacientes sensíveis e mulheres grávidas. *Acne vulgaris* é uma doença crônica que afeta não apenas a pele; tem um grande fator psicológico e financeiro nos pacientes afetados. O acompanhamento clínico é importante por se tratar de um tratamento exclusivo de longa duração e o conhecimento desse fato é importante.

**Palavras-chave:** *Propionibacterium acnes*, saúde da pele, terapia, comedolíticos, antimicrobianos, anti-sépticos.

## 1 INTRODUCTION

Acne vulgaris (AV) is a chronic disease that settles in the polysaccharic follicles, caused by multiple factors, including sebaceous hypersecretion, keratinization of the follicular canal and bacterial colonization by *Propionibacterium acnes* (*P. acnes*).<sup>1,2</sup>

The multiplication of *P. acnes* in the skin results in an increase of reactive oxygen species (ROS) and this process together with protease enzymes leads to the rupture of sebaceous glands and alteration of the composition of sebum.<sup>3,4</sup> Hyperkeratinization is initiated together with the reduction in peeling skin. Subsequently, pro-inflammatory cytokines are released, causing microcomponents that may evolve into comedones and inflammatory lesions.<sup>1</sup>

Although the main targets are adolescents, there is data on the presence of acne in adulthood, about 8% between 25 and 34 years old and 3% between 35 and 44 years old.<sup>5</sup> Current treatments seek to cover all factors involved in the disease and, according to the degree of acne, the appropriate algorithm is chosen.

Topical treatment has the advantage in reducing systemic absorption and increasing exposure of pilosebaceous follicles to treatment. Despite this, a consequence of using anti-acne products topically is skin irritation. Preparations for topical application are available in various formulations, including creams, gels, lotions, solutions and soaps.<sup>5-7</sup>

In this work we seek to relate the existing topical therapies to combat acne, their mechanisms of action and the particularities of each active through a bibliographic review, analyzing the antibacterial, anti-inflammatory and anti-seborrheic activities of these substances.

## 2 CLASSIFICATION OF ACNE

Acne consists of a set of lesions, which, alone or together, define its type and severity.<sup>8</sup>

- Comedones - it arises as a result of sebaceous hypersecretion and retention of the pilo-sebaceous follicle. It is the elementary and primary lesion of acne, known as blackhead;
- Wheal - appears as an area of redness and swelling around the comedones, with small dimensions (up to 3 mm);
- Pustule - inflammation of the pustule with purulent content;
- Nodule - has a structure identical to the wheal, but is larger, up to 2 cm;
- Cyst - large comedone that undergoes several ruptures and recapsulations;
- Scar - irregular depression covered with red and atrophic skin, resulting from the destruction of the pilo-sebaceous follicle by an inflammatory reaction.

The number of lesions, the affected areas and the severity of the condition allow acne to be classified as mild, moderate or severe, serving as a basis for an algorithm for its treatment (Figure 1).<sup>8</sup>

Figure 1. Treatment algorithm for acne.

Mild acne	Comedonal	Topical retinoid and physical removal of comedones	OR • Another topical retinoid • Azelaic acid • A-hydroxy acid • B-hydroxy acid • Combinations	Maintenance with a topical retinoid	--
	Papulo-postulate	Topical retinoids and / or benzoyl peroxide	OR • Another topical retinoid Topical antimicrobial • Azelaic acid	Maintenance with a topical retinoid	--
Moderate acne	Papulo-postulate	Oral antibiotic and topical retinoid / benzoyl peroxide	OR Oral Isotretinoin	Maintenance with a topical retinoid +/- benzoyl peroxide	Women: hormone treatment and a topical retinoid +/- benzoyl peroxide
	Nodular	Oral antibiotic and a topical retinoid and benzoyl peroxide	OR Oral Isotretinoin	Maintenance with a topical retinoid +/- benzoyl peroxide	Women: hormone treatment and a topical retinoid +/- oral antibiotic
Severe Acne		Oral Isotretinoin	High-dose oral antibiotic and topical retinoid and benzoyl peroxide	Maintenance with a topical retinoid +/- benzoyl peroxide	Women: hormonal treatment and a topical retinoid +/- oral antibiotic

Source: Katsambas *et al.* (2004).

## 2 METHOD

### SEARCH STRATEGY

The bibliographic review was based on a search in published articles, in English or Portuguese. The active search was carried out through a database (Cochrane, Pubmed and Scopus), in manual searches, and articles published until May 2020 were considered. To facilitate the virtual search, strategic terms were used (“topical treatment” and “acne”). The evaluation of the studies was carried out from December 2019 to May 2020, with the help of a second reviewer (S.E.S), and the results are presented below.

### 3 RESULTS

Topical therapy is based on the type and severity of acne. In mild to moderate cases, it is often treated with topical retinoids or a variety of different treatments, such as azelaic acid, salicylic acid, benzoyl peroxide, among others, in addition to anti-inflammatory agents and topical antibiotics.<sup>2,4,7</sup> In severe cases, there is a need for an

association between oral and topical treatment to ensure that superficial skin treatment will be effective. Below we will look at the main anti-acne active principles available in the topical treatment of the disease.

### **Retinoids**

Topical retinoids can be used as monotherapy for inflammatory acne, in combination with more severe forms of acne or as a maintenance treatment.<sup>9</sup> They act as comedolytics and anticomedogenic agents, can have anti-inflammatory effects and facilitate the penetration of other topical agents. The most common are adapalene, tretinoin and tazarotene.<sup>10,11</sup>

All retinoids are contraindicated in cases of pregnancy and breastfeeding. Effective contraception must be used by women of child-bearing potential.<sup>8</sup>

### **Tretinoin**

Tretinoin is a form of vitamin A. It is a standard comedolytic agent used in the treatment of acne to regulate the peeling of the epithelium, which prevents the blockage of pilosebaceous units.<sup>2</sup> It also appears to have anti-inflammatory properties. As potential adverse effects, irritation, sun intolerance and skin dryness, needing to be applied at night.<sup>3,4,7</sup>

### **Adapalene**

Adapalene is a synthetic retinoid analog that is more frequent in first-line treatment for AV. It normalizes the cell differentiation of the follicular epithelium and prevents the formation of comedones. It also shows anti-inflammatory action on acne lesions.<sup>2,4</sup>

Adapalene is associated with less irritating potential, is more stable to light and can be applied in the morning.<sup>10</sup>

### **Tazarotene**

Tazarotene is an acetylenic retinoid from which the body converts tazarotenic acid. Its active metabolite has the same level of keratinocytes.<sup>2,10</sup> It affects the differentiation and proliferation of keratinocytes in epithelial tissue and may also show anti-inflammatory properties.<sup>2,12</sup> It becomes the drug of choice after the ineffectiveness of treatment with tretinoin or adapalene. It can cause more intense irritation than the other retinoids.<sup>10,13</sup>

## Antibiotics

Topical antibiotics are generally used for mild to moderate inflammatory acne.<sup>4</sup> The most popular are erythromycin and clindamycin, but in recent years, the continued use of these antibiotics has led to the development of resistance to the *P. acnes* strains.<sup>14,15</sup>

Therefore, the best indication for the use of topical antibiotics is for a maximum of 12 weeks, and in combination with other topical alternatives such as benzoyl peroxide, zinc or retinoids to avoid bacterial resistance. The use of oral and topical antibiotics in combination in the treatment of acne should be avoided.<sup>16</sup>

## Erythromycin

Erythromycin is a macrolide antibiotic that binds to the bacterial 50S ribosomal unit and prevents translocation, which is necessary for the protein synthesis of bacteria.<sup>14</sup> It is active against *P. acnes* and reduces the colony on the skin surface and in the follicles. It has been found to be very effective in acne therapy, but *P. acnes* resistance of up to 60% has recently been discovered<sup>17</sup>

## Clindamycin

Clindamycin is classified as a lincosamide antibiotic. It is a semi-synthetic derivative of the antimicrobial agent, lincomycin. Its mechanism of action is the same as that of erythromycin.<sup>11,17</sup>

## Miscellaneous treatments

The other topical treatments adopted seek to complement the retinoids and antibiotics with mechanisms of antiseptic, anti-inflammatory, comedolytic and keratolytic action.

## Salicylic Acid

It is an exfoliant, with keratolytic characteristics capable of dissolving the intercellular cement, and can be associated with topical retinoids in the treatment of comedonic acne or as a second-line treatment.<sup>18,19</sup> It has a minor anti-inflammatory effect, improves the penetration of other topical drugs and, in low concentrations, is also both a fungistatic and a bacteriostatic. Salicylic acid is found in several over-the-counter acne products.<sup>19</sup>

## Chemical peel with hydroxy acids

Chemical peels involve the removal of skin layers, causing a controlled inflammatory reaction, followed by tissue repair and reepithelization.<sup>20</sup> This therapy can be divided into different groups according to the depth of penetration and destruction. Alpha-hydroxy acids (AHA) were developed for more superficial peels, indicated for the treatment of hyperkeratosis. They are divided into alpha-hydroxy acids (ie, glycolic acid and lactic acid), beta-hydroxy acids (ie, salicylic acid) and polyhydroxy acids. Concentrations range from 10 to 30%, depending on the acid and frequency of treatment.<sup>20,21</sup> Chemical peeling should be a complementary treatment and not a treatment of first choice.<sup>4</sup>

## Benzoyl Peroxide

It is a comedolytic and antimicrobial agent and can be used alone or in combination with topical retinoids or topical or oral antibiotics.<sup>5,11,20</sup> Most retinoids undergo oxidation by benzoyl peroxide (BP), so one is meant to apply BP in the morning and retinoids in the evening. An exception is adapalene, which is more stable and can be applied with other substances.<sup>18</sup>

The association between BP and antibiotics creates synergism in the fight against *P. acnes*, given to the fact the bactericidal action of BP hampers the development of bacterial resistance and provides better tolerability of treatment.<sup>17,18</sup> Its adverse reaction is skin peeling and irritation and use in low concentrations (2.5% or 5%) is indicated.<sup>18</sup>

## Azelaic acid

It has bacteriostatic, comedolytic, antioxidant and anti-inflammatory properties. It is used as a second line. It is a natural dicarboxylic acid that inhibits the protein synthesis of *P. acnes* species.<sup>12</sup> Can be used during pregnancy and can be used in the summer because it does not have photosensitivity. The initial application should be nocturnal and later it can be increased up to 2 to 3 times a day.<sup>5,19</sup> Azelaic acid helps in the uniformity of skin tone.<sup>18</sup>

## Sulfur

Sulfur is a chemical that has been shown to have mild keratolytic, astringent and bacteriostatic properties.<sup>22,23</sup> When used in conjunction with benzoyl peroxide or sodium sulfacetamide, sulfur shows a better therapeutic effect on AV.<sup>24</sup> Its use can cause allergy

in people with sensitivity to the mineral and should be used 1 to 2 times a day. Use in pregnant women is not recommended due to its excretion in breast milk.<sup>23</sup>

### **Niacinamide**

Niacinamide, also known as nicotinamide, is the active amide form of vitamin B3 associated with nicotinic acid. It has anti-inflammatory properties due to its inhibitory effect on the production of interleukin-8 (IL-8).<sup>20</sup>

Some studies suggest inhibition of sebaceous secretions, which results in less skin oiliness. Topical application of 4% niacinamide led to significant improvements in the disease.<sup>4,20,22</sup>

### **Triclosan**

Triclosan is an antibacterial (antiseptic) agent that can be used to treat acne. It was determined that bacterial populations did not develop resistance to triclosan under clinical conditions. It is used in soaps and lotions in the process of cleaning acneic skin.<sup>4,25</sup>

### **Sodium sulfacetamide**

This agent belongs to the antibacterial sulfonamide group.<sup>24</sup> It is bacteriostatic by inhibiting the synthesis of deoxyribonucleic acid (DNA) through competitive antagonism of para-aminobenzoic acid (PABA).<sup>4</sup> It is often combined with sulfur to treat acne rosacea and seborrheic dermatitis in addition to AV.<sup>24,26</sup>

### **Dapsone**

Dapsone has antibacterial and anti-inflammatory activity. It has been traditionally used as a drug against *Mycobacterium leprae*.<sup>27</sup> The suggested mechanism of action for its action against acne would be the inhibition of leukocyte migration, subsequent release of cytokines and alteration of the action of *P. acnes* in the hair follicle.<sup>11</sup> The dapsone gel (5%) can be used to reduce inflammatory and non-inflammatory acne lesions.<sup>28</sup> It is used as a second treatment line.

### **Resveratrol**

There are different treatment options for acne, including topical, systemic treatments and use of complementary and alternative medicines (CAM). RSV is considered to be a CAM because it is effective against pro-inflammatory cytokines and antimicrobial activity.<sup>4,18</sup> Due to its antioxidant action, it has the capacity to transport



reactive oxygen species and, by interrupting the oxidative chain, there is a decrease in the disintegration of keratinocytes and a decrease in the inflammatory reaction.<sup>29,30</sup> There are studies on the negative regulation of the rapamycin complex 1 mechanistic target gene (mTORC1), resulting in decreased skin oiliness<sup>31</sup> and positively regulates the nuclear transcription factor FoxO1, which is related to androgen receptor suppression and other important receptors for cell proliferation, lipid biosynthesis and inflammatory cytokines.<sup>32</sup>

### **Vitamin C**

Ascorbic acid or vitamin C, the most well-known antioxidant, has anti-inflammatory properties, preventing the oxidation of sebum which contributes to the reduction of inflammation and follicular keratinization. Vitamin C has been shown to prevent UVA-induced sebum oxidation by up to 40%<sup>20</sup>. It is used as complementary therapy.

### **Green tea**

Green tea is derived from the plant *Cammelia sinensis* and contains potent polyphenolic compounds called catechins, which have antioxidants and anti-inflammatory properties.<sup>12,20</sup>

### **Melaleuca oil**

It is produced from the leaves of the *Melaleuca alternifolia tree*, a plant originally from Australia and is traditionally used to treat infections. It also has antiseptic properties.<sup>4</sup> Numerous studies have shown that tea melaleuca oil reduces the number of lesions in patients with mild to moderate acne.<sup>33</sup>

### **Conclusion**

Topical retinoids have been used in acne therapy for over forty years, due to their effectiveness demonstrated in several clinical trials, despite presenting some disadvantages such as skin irritation, chemical instability and photosensitivity. The development of third generation retinoids, adapalene and tazarotene allowed the reduction in side effects, in addition to chemical compatibility and stability that allowed the combination with other drugs that help in the treatment of acne.

Other topical treatments adopted seek to complement the retinoids and antibiotics with mechanisms of antiseptic, anti-inflammatory, comedolytic and keratolytic action.

They are often used as a second line of treatment and especially in sensitive patients and pregnant women.

Acne vulgaris is a chronic disease that affects not only the skin; it also has a great psychological and financial factor in affected patients. Despite being more prevalent in adolescence, it can continue into adulthood. There are a variety of products available for free sale on the market, but without the proper guidance there are not always positive results. Clinical follow-up is important, because in more severe cases monotherapy is unsatisfactory, in addition to being an exclusive long-term treatment that requires awareness of the patient.

## REFERENCES

1. Melnik BC. Linking diet to acne metabolomics, inflammation, and comedogenesis: An update. *Clinical, Cosmetic and Investigational Dermatology*. 2015;8:371-388.
2. Muizzuddin N, Giacomoni P, Maes D. Acne - a multifaceted problem. *Drug Discovery Today: Disease Mechanisms*. 2008;5(2).
3. Tan AU, Schlosser BJ, Paller AS. A review of diagnosis and treatment of acne in adult female patients. *International Journal of Women's Dermatology*. 2018;4(2):56-71.
4. Fox L, Csongradi C, Aucamp M, du Plessis J, Gerber M. Treatment Modalities for Acne. *Molecules*. 2016;21(8).
5. Silva AMF da, Costa FP da, Moreira M. Acne vulgar: diagnóstico e manejo pelo médico de família e comunidade. *Revista Brasileira de Medicina de Família e Comunidade*. 2014;9(30):54-63.
6. Soleymani S, Farzaei MH, Zargaran A, Niknam S, Rahimi R. Promising plant-derived secondary metabolites for treatment of acne vulgaris: a mechanistic review. *Archives of Dermatological Research*. 2020;312(1):5-23.
7. Gollnick, H. Current concepts of the pathogenesis of acne: Implications for drug treatment. *Drugs* 63, 1579–1596 (2003).
8. Figueiredo A, Massa A, Picoto A. Avaliação e tratamento do doente com acne - ParteII. *Revista Portuguesa de Clínica Geral*. 2011;27(1):66-76.
9. RANG, H. P.; DALE, M. M.; RITTER, J. M. **Farmacologia**. 8. ed. Rio de Janeiro: Elsevier, 2016.
10. Oliveira RF de. Adapaleno e Tazaroteno: uma revisão sobre o uso destes retinóides de terceira geração Trabalho. 2011;(3).
11. James KA, Burkhart CN, Morrell DS. Emerging drugs for acne. *Expert Opinion on Emerging Drugs*. 2009;14(4):649-659.
12. Kanlayavattanukul M, Lourith N. Therapeutic agents and herbs in topical application for acne treatment. *International Journal of Cosmetic Science*. 2011;33(4):289-297.
13. Bergler-Czop B. The aetiopathogenesis of acne vulgaris - What's new? *International Journal of Cosmetic Science*. 2014;36(3):187-194.
14. Shaw, Lindsay & Kennedy, Cameron. (2003). The treatment of acne. *Paediatrics and Child Health*. 2007

15. Coenye T, Brackman G, Rigole P, *et al.* Eradication of *Propionibacterium acnes* biofilms by plant extracts and putative identification of icariin, resveratrol and salidroside as active compounds. *Phytomedicine*. 2012;19(5):409-412.
16. Lavers I. Clinical Focus Diagnosis and Management of Acne Vulgaris.; 2014. [www.pcids.org.uk](http://www.pcids.org.uk)
17. Scheinfeld NS, Tutrone WD, Torres O, Weinberg JM. Macrolides in dermatology. *Disease-a-month : DM*. 2004;50(7):350-368.
18. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *The Lancet*. 2012;379:361-372.
19. Katsambas AD, Stefanaki C, Cunliffe WJ. Guidelines for treating acne. *Clinics in Dermatology*. 2004;22(5):439-444.
20. Zeichner JA. Practical Applications for Cosmeceuticals Cosmeceuticals for the Treatment of Acne Vulgaris.; 2014.
21. Kim RH AA. Current state of acne treatment: highlighting lasers, photodynamic therapy, and chemical peels. *Dermatol Online J*. 2011;17.
22. Liu H, Yu H, Xia J, *et al.* Topical azelaic acid, salicylic acid, nicotinamide, sulphur, zinc and fruit acid (alpha-hydroxy acid) for acne. *Cochrane Database of Systematic Reviews*. 2020;2020(5).
23. Akhavan, A., & Bershada, S. (2003). Topical acne drugs: review of clinical properties, systemic exposure, and safety. *American journal of clinical dermatology*, 4(7), 473–492.
24. Del Rosso J. The Use of Sodium Sulfacetamide 10% -Sulfur 5% Emollient Foamin the Treatment of Acne Vulgaris. *Clinical and aesthetic Dermatology*. 2009;2.
25. Domínguez-Delgado CL, Rodríguez-Cruz IM, Escobar-Chávez JJ, Calderón-Lojero IO, Quintanar-Guerrero D, Ganem A. Preparation and characterization of triclosan nanoparticles intended to be used for the treatment of acne. *European Journal of Pharmaceutics and Biopharmaceutics*. 2011;79(1):102-107.
26. Well D, Levine SR. Acne vulgaris: A review of causes and treatment options. *Journal of the Dermatology Nurses' Association*. 2014;6(6):302-309.
27. Wozel G, Blasum C. Dapsone in dermatology and beyond. *Archives of Dermatological Research*. 2014;306(2):103-124.
28. Draelos ZD, Carter E, Maloney JM, *et al.* Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. *Journal of the American Academy of Dermatology*. 2007;56(3):439.e1-439.e10.
29. Baxter RA. Anti-aging properties of resveratrol: Review and report of a potent new antioxidant skin care formulation. *Journal of Cosmetic Dermatology*. 2008;7(1):2-7.

30. Chachay et al. 2011. Resveratrol – pills to replace a healthy diet ? Published online 2011.
31. Melnik BC. Dietary intervention in acne: Attenuation of increased mTORC1 signaling promoted by Western diet. *Dermato-Endocrinology*. 2012;4(1):20-32.
32. Melnik BC. FoxO1 - The key for the pathogenesis and therapy of acne? *JDDG - Journal of the German Society of Dermatology*. 2010;8(2):105-114.
33. Hammer KA. Treatment of acne with tea tree oil (melaleuca) products: A review of efficacy, tolerability and potential modes of action. *International Journal of Antimicrobial Agents*. 2015;45(2):106-110.