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The Role of Different Factors in Pathophysiology of Acne and Potential Therapeutic Options :A Brief Review

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Abstract

Acne vulgaris is a chronic multifactorial skin disease that millions of people around the world of suffering from that. Pathophysiology of acne consists of several mechanisms including hyper-seborrhea, hyperkeratinization of pilosebaceous units, increased bacterial proliferation, hyperandrogenism, alteration in sebum contents, and inflammatory processes. In this regard, consideration of the main causes of acne development and severity of acne lesions in the selection of suitable pharmacologic agents is essential. In this review, among the other factors, the role of the different lipids in pathophysiology of acne were considered. The common sources of skin lipids have been categorized into two main categories including endogenous and exogenous sources. Furthermore, the role of different factors including lipids and fatty acids, androgens, microorganisms, cosmeceuticals, and lipids oxidation and peroxides in acne vulgaris development have been summarized. In the end, the necessity of the choice of appropriate pharmacotherapy regimens and recruitment of novel drug delivery systems in acne management have been mentioned.

Keywords: Acne, Pathophysiology, Lipids, Microorganisms, Androgens, Cosmeceuticals

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1. Introduction

Acne vulgaris is a chronic multifactorial skin disease that affects millions of people around the world. Pathogenesis of acne consists of several mechanisms including excess production of sebum (hyper-seborrhea), alteration in sebum composition, increased proliferation of *Cutibacterium acnes* (*C. acnes*), hyperkeratinization of pilosebaceous units of the skin, inflammatory processes, immune dysfunction, and hormonal dysregulation (1, 2).

Sebum has a complex composition that is released from the sebaceous glands and finally reaches to the surface of the stratum corneum via hair follicles (3). Pilosebaceous glands are not real excitatory glands and they release their contents within the hair canal after the cells rupture human sebum which consists of a mixture of diglycerides, triglycerides (TG), wax esters (WE), squa-

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lene (SQ), free fatty acids (FFAs), cholesterol, and cholesterol esters (ChoE) (3-5). Sebum secretion alterations include a) hyper seborrhoea which is due to sebaceous lipogenesis and overproduction of sebum caused by epidermal growth factor receptor (EGFR), Perilipins, and peroxisome proliferator-activated receptor gamma (PPARγ) which is more important in men, b) alterations of sebum fatty acids such as decreased linoleic acid and other essential free fatty acids, c) pro-inflammatory sebum lipid fractions including lipoperoxides and monounsaturated fatty acids (MUFAs) leading to follicular hyperkeratinization by changing the oxidant to antioxidants ratio and stimulating proliferation and differentiation of keratinocytes (5). Insulin-like growth factor-1 (IGF-1) which is a product of insulin can downregulate the nuclear levels of FoxO-1 resulting in activation of mTORC-1 which leads to both hyper-seborrhoea and hyperkeratinization of follicles (6). IGF-1 can also upregulate androgens such as sex steroids, DHEA, testosterone, progesterone, estradiol, cholesterol, pregnenolone, and glucocorticoids which directly increase sebum production (6). From another perspective, leucine can increase the activity of mTORC-1 leading to acne formation (6). Fatty acids and omega-3 can inhibit leukotriene B4 and IGF-1 affecting the processes of inflammation, sebum production, and hyperkeratinization (6). In recent years, several studies were conducted to investigate the role of sebum compartments such as free fatty acids in the development and progression of acne vulgaris. Furthermore, some studies have compared the sebum of individuals with and without acne to investigate the differences in the sebum composition of these two groups.

The main purpose of this review is to focus on the role of lipids especially FFAs in the pathophysiology of acne vulgaris. Also, the beneficial and/or harmful effects of each of endogenous and exogenous lipids in acne vulgaris initiation and progression are summarized. In addition, the role of essential FFAs, cosmeceuticals, androgens, microorganisms, and oxidative stress in acne pathophysiology have been considered. Finally, the importance of acne pharmacotherapy as a multifactorial skin disease and the importance of nanotechnology and targeted drug delivery has been discussed briefly.

2. Lipid sources

The common sources of skin lipids can be divided into two main categories including endogenous and exogenous lipids. Exogenous lipids are those produced by resident bacteria and also lipids derived from dietary sources. While the endogenous lipids are those secreted by the sebaceous glands and also those synthesized through the keratinizing process of the epidermis (7). In this focused review, lipids are classified into three main categories based on their source including endogenous (epidermal and sebaceous lipids) and exogenous lipids.

2.1. Epidermal lipids (Stratum corneum lipids)

The surface of the skin has been covered with endogenous lipids of epidermal keratinocytes and sebaceous glands origin. Lipids of the epidermal source act as a mortar or cement and fill the intercellular spaces. They are mainly consisting of a mixture of FFAs, cholesterol, and ceramides (8). The epidermal lipids have an essential role to construct the skin barrier characteristics. This barrier, also known as the stratum corneum (SC) layer, can protect the body against microbial invasion. The SC layer which is a mixture of FFAs, cholesterol, and ceramides can be terminally differentiated into keratinocytes (8).

2.2. Sebaceous glands

Lipids of sebaceous glands origin are mainly consisting of non-polar lipids including wax esters, squalene, and triglycerides (TGs) (8). The elevated sebaceous glands secretion (sebum) is considered as an important risk factor in acne pathophysiology. Sebaceous lipids are mainly constructed from triglycerides which can be hydrolyzed via bacteria to FFAs and glycerol. In general, the composition of the sebum are 45% TGs, 25% wax esters, 12% squalene, 10% FFAs, 4% cholesterol and sterol esters, and 2% diglycerides (8).

2.2.1. Sapienic acid

Sapienic acid (16:1, Δ6) is a predominant and unique FFA in sebum which cannot be found anywhere else. The role of sapienic acid in acne

pathophysiology is still controversial as it has been reported that the presence of sapienic acid in sebum is associated with higher sebum levels and higher incidence of acne accordingly (9). Also, it has been reported that sapienic acid showed beneficial effects against bacteria that are the main cause of acne (8, 10). Akaza *et al.* showed that women with acne have more sebum and TG than women without acne. The amount of sapienic acid in TG and FFA of acne patients was higher in women with acne than those without acne. This study suggests that the amount of TG determines the composition of sebum and there is no difference in fatty acid composition based on the presence or absence of acne (11).

2.2.2. Wax esters

Wax esters are another common and unique composition of sebum. It has been reported that there is a significant association between the amounts of wax esters and the sebaceous glands' differentiation (8, 12). Wax esters can act as protective layers on the skin. Also, they are capable of coating microorganisms including bacteria, fungi, and algae. Furthermore, they showed higher resistance against hydrolysis, thermolysis, and oxidation in comparison to TGs and phospholipids. In addition, they act as a lubricant on the skin surface (8).

2.2.3. Squalene

Squalene, a precursor of cholesterol, is synthesized via squalene synthase and metabolized via squalene epoxidase and squalene monooxygenase. The percentage of squalene accumulation within sebaceous lipids is correlated with the amount of these enzymes expression. Squalene can act as a strong lubricant with high permeation efficiency (8). Squalene is a long unsaturated hydrocarbon that is mostly seen in sebocytes (13). Pappas et al showed that patients with acne had 2.2-fold more squalene in their sebum than those without acne. Squalene and its products can induce comedogenic properties (13). Ottaviani *et al*. investigated the effect of squalene peroxides in acne pathogenesis and showed that squalene peroxides can initiate the inflammatory process along with an increase in the lipoxygenase (LOX) activity, interleukin-6 (IL-6), and nuclear factor kappa B (NF-kB) levels (14). Motoyoshi *et al.* investigated the effect of squalene and oleic acid and their peroxides products as comedogenic compound in rabbit ear skin and showed that squalene was scarcely comedogenic; however, squalene peroxides were highly comedogenic. Squalene peroxides caused hyperplasia and hyperkeratosis of the infundibular epithelium (15).

2.2.4. Stearic acid

Stearic acid (18:0) is a fully saturated free fatty acid. Katsuta *et al*. showed that application of stearic acid and palmitic acid on hairless mice skin did not induce abnormal epidermal differentiation, not increase keratinocyte proliferation, not alter the skin barrier function, and not increase the calcium in the keratinocytes (16). Akaza *et al*. showed that the amount of stearic acid in TG and FFA in the sebum of women with acne was lower than that of women without acne (11).

2.2.5. Oleic acid

Oleic acid (18:1, Δ9) is a monounsaturated free fatty acid that could induce calcium influx into the keratinocytes. Also, there are several reports on its activity against *P. acnes* (17). Furthermore, oleic acid and palmitoleic acid were effective against Staphylococcus aureus and Streptococcus pyogenes (18).

Li *et al.* showed that sebum contents of patients with acne had higher saturated free fatty acids (SFFAs), higher unsaturated free fatty acids (UFFAs), and lower SFFAs/UFFAs ratio. Therefore, it could be concluded that the UFFAs were enhanced more than the SFFAs in the sebum of patients with acne in comparison to the control group. This study also investigated the effect of oleic acid on the human epidermal equivalent (HEE) and the results revealed that oleic acid could induce a dose-dependent SC thickening. Also, the release of IL-1 from epidermal cells was enhanced in the treatment group in comparison to the control one (19). Furthermore, Motoyoshi et al showed that oleic acid peroxides had a higher comedogenic effect than oleic acid (15). In addition, Katsuta *et al.* showed that application of oleic acid and palmitoleic acid on hairless mice skin re-

sulted in enhanced scales on the surface, abnormal epidermal differentiation, enhanced proliferation of keratinocytes, reduced barrier function, and increased calcium content in keratinocytes (16).

2.2.6. Palmitoleic acid

Palmitoleic acid (C16:1, Δ9) is an unsaturated FFA with anti-bacterial potential. It has been shown that palmitoleic acid is effective against *S. aureus* and *Pseudomonas aeroginasa* while ineffective against *P. acnes*. The application of topical palmitoleic acid was accompanied by keratinocyte hyper-proliferation and comedogenesis due to the calcium influx into the keratinocyte cells that can lead to skin barrier disturbance (17, 20).

2.3. Exogenous lipids

Cholesterol, ceramides, and FFAs are essential in skin barrier homeostasis. It has been reported that topical application of each of these lipids including ceramides, cholesterol, linoleic acid, and other FFAs alone or as an incomplete mixture can interfere with barrier homeostasis and might delay skin barrier recovery due to worsening of transcutaneous water loss. However, topical application of a complete mixture of FFAs, ceramides, and cholesterol can accelerate normal skin barrier recovery (21).

3. The role of essential fatty acids in acne

There are two types of essential fatty acids including n-6 series and n-3 series that are derived from dietary linoleic and α-linolenic acid, respectively (22). Linoleic acid (18:2, Δ9,12) and α-linolenic acid (18:2, Δ9,12,15) are among the most important essential fatty acids that are commonly derived from diet and cannot be produced in the human body. Results of previous studies demonstrated that the essential fatty acids comprises only a small amount of skin surface lipids (8).

3.1. Linoleic acid

Linoleic acid (18:2, Δ9,12) is an essential free fatty acid, not produced in the body and should be obtained from the diet. Downing et al showed that a reduction in essential FFAs especially linoleic acid can play a significant role in acne formation. Linoleic acid and its metabolites can affect the water barrier function of the skin layer. Linoleic acid deficiency in humans' diet can result in scaly skin with diminished skin barrier potential (3). It has been reported that an increase in sebum production can decrease the concentration of linoleic acid in sebum which can result in hyperkeratosis and decreased skin barrier function against microorganisms. So, bacterial overgrowth would be predicted in conditions with decreased linoleic acid composition (23). In addition, results of previous studies revealed that acne treatment with anti-androgenic agents including cyproterone acetate or treatment with retinoic acid can result in the enhanced linoleic acid content of the sebaceous lipids (3, 24). Furthermore, Wertz et al showed that the linoleic acid content of ceramides obtained from normal human stratum corneum was 41%, while the counterpart amount in comedones was reduced to 6%. Therefore, it seems that linoleic acid deficiency in the follicular epithelium region would be a significant precipitating factor in acne pathophysiology (25).

3.2. α-Linolenic acid

It seems that the n-3 essential fatty acid series that are derived from α-linolenic acid is less important in the skin than the n-6 series. It is difficult to attribute a specific dermal effect to α-linolenic acid alone. Furthermore, it has been reported that administration of α-linolenic acid alone without linoleic acid not only ineffective, but also harmful to the skin. This harmful effect can be attributed to the weakened cutaneous capillaries that are prone to rupture (22). Another study revealed that linolenic acid and n-3 series might act as a modulator of the n-6 series' function and metabolism (26). Therefore, it can be concluded that α-linolenic in combination with linoleic acid would be beneficial in acne management.

4. The role of cosmeceuticals in acne

Cosmeceuticals are skin products that are placed somewhere between prescribed medications and conventional cosmetic products. In this regard, there are several cosmeceuticals available in the market for acne management including retinoids, niacinamide, α-hydroxy acids, β-hydroxy

acids, and fatty acids such as linoleic acid and α-linolenic acid (27).

4.1. Retinoids

Cosmeceutical retinoids including retinol and retinaldehyde are widely used in acne management. While retinoic acid and its synthetic derivatives are prescribed drugs that are available in systemic dosage forms. Application of topical retinol was accompanied by enhanced skin thickness and also activation of transcription factors. Results of previous studies revealed that topical retinol and retinoic acid had similar biologic effects while retinol had less skin irritation and erythemal potential (28).

4.2. Niacinamide

Niacinamide is the active form of niacin or vitamin B3. Niacinamide has several beneficial skin effects including antimicrobial effects, sebostatic effects, anti-inflammatory effects, enhanced ceramide synthesis, melanosome transfer inhibition, and nitric oxide inhibition which inhibits the capillary permeability changes. Previous studies revealed that topical niacinamide was effective in the reduction of acne severity and lesion counts (28). Therefore, it was concluded that niacinamide 4% was as effective as clindamycin 1% in the management of moderate inflammatory acne (29).

4.3. Glycolic acid

The role of glycolic acid, as an α-hydroxy acid, in cosmeceuticals is the enhancement of skin roughness and scaling. Glycolic acid can induce corneocyte deadhesion through penetration into the stratum corneum and epidermis layer. The efficacy of glycolic acid has been proved in the management of mild acne at day 45 (28).

4.4. Salicylic acid

Salicylic acid is a type of β-hydroxy acid that is widely used in acne management. Salicyclic acid showed comedolytic properties through the regulation of SC turnover. Therefore, a reduction in the number of acne lesions would be predictable after topical application of salicylic acid (27). α-hydroxy acids and β-hydroxy acids can induce pH-dependent skin irritation. So, pH adjustment and optimized formulation design are crucial to avoid further skin irritation during acne treatment (27).

4.5. Fatty acids

Linoleic acid (omega-6), α-linolenic acid, and lauric acid as a medium-chain free fatty acid are among the commonly used fatty acids in cosmeceuticals in acne management. The possible mechanisms attributed to the anti-acne potential of these fatty acids and their wound healing capability, conservation of SC permeability, and inhibition of pro-inflammatory cytokines (27). Furthermore, it has been reported that lauric acid showed some anti-microbial properties against Propionibacterium acnes (*P. acnes*), which is currently known as *C. acnes* (30).

5. The role of androgens in enhanced lipid secretion

Since patients with acne have higher levels of testosterone and 5α-dihydrotestosterone, a direct correlation between androgen level and acne occurrence has been suggested. The possible mechanism of androgens in acne development can be attributed to the enhanced sebum secretion in response to higher androgen levels (31). However, results of some other previous studies revealed that although the free testosterone, total testosterone, progesterone, and sex hormone-binding globulin levels were increased in acne patients in comparison to the healthy patients without acne, the sebum levels were the same. Therefore, this study emphasized that the androgens' effect on acne development is independent of sebum secretion (32).

Androgens can regulate the performance of the pilosebaceous units. So, hyperandrogenemia due to the enhanced adrenal and/or ovarian androgen production is obvious in patients with severe acne. Treatment strategies in hyperandrogenemia conditions in patients with acne are: 1) the inhibition of androgenic receptors via antiandrogen medications, and 2) the inhibition of pituitary luteinizing hormone (LH) secretion to block the ovarian source of androgen production (33).

6. The role of microorganisms in acne

C. acnes (formerly known as *P. acnes*),

an opportunistic pathogen also known as Corynebacterium parvum, is one of the main contributing factors in acne pathogenesis. The possible mechanisms of *P. acnes* in acne development are attributed to enhanced inflammation of the pilosebaceous unit, pro-inflammatory cytokines induction, and comedogenesis potential due to keratinocyte hyper-proliferation (34). Other microorganisms that are considered as potential causes of acne vulgaris initiation are *S. aureus*, *S. epidermidis*, *S. pyogenes*, *S. agalactiae*, and *Klebsiella pneumonia* (35). The virulence genes are the main cause of the pathogenic pathway of microorganisms in acne development. In this regard, virulence genes, including camp5, tly, gehA, neuraminidases, lipases, hemolysins, endoglycoceramidases, and sialidases, are capable of producing toxins. They are also the main cause of adhesions and invasions of the causative microorganisms (35). *P. acnes* colonization and accumulation can clog the hair follicles. After that, they can secrete some degrading enzymes that can lead to hair follicle rupture (36). In addition, *P. acnes* can affect keratinocytes and macrophages. Therefore, it can induce the production of pro-inflammatory cytokines including IL-1, IL-8, IL-12, and tumor necrosis factor-α (TNF-α) which are the main causes of inflammatory acne vulgaris (37).

7. The role of oxidation in acne

The main components of oxidative stress including reactive oxygen species (ROS) and lipid peroxide (LPO) are considered as important causative factors in acne pathophysiology. Free radicals can lead to oxidative skin damage through lipid peroxidation and the production of inflammatory cytokines. ROS-associated oxidative damage can be derived from both endogenous and exogenous origins (38). Endogenous sources of ROS are enzymatic oxidation and auto-oxidation. While photo-oxidation through ultraviolet (UV) light and environmental/pollutant oxidants are considered as exogenous sources (38). ROS and LPO have an important role in the induction of epithelial cell inflammation in the pilosebaceous unit which can be considered as crucial factors in pathophysiology of acne vulgaris initiation and progression (38).

Vitamin E or α-tocopherol as a natural lipophilic anti-oxidant can neutralize the oxidative damage associated with ROS. Therefore, it seems that targeted delivery of vitamin E to the pilosebaceous unit can alleviate oxidative damage to the skin surface (39).

The main pathophysiologic factors in acne vulgaris initiation and progression are shown in Figure 1.

8. Pharmacotherapy

Acne vulgaris is a multi-factorial skin disorder with various simple and complicated pathogenesis pathways. Therefore, pharmacotherapy of acne includes consideration of various possible causes of acne initiation and progression and a clinical approach to each of them. In this regard, various treatment options including cosmeceuticals, anti-microbials, anti-inflammatory agents, and anti-androgens medications are available and would be considered according to the causative factors. Different topical and systemic therapeutic agents used in acne vulgaris treatment are summa-

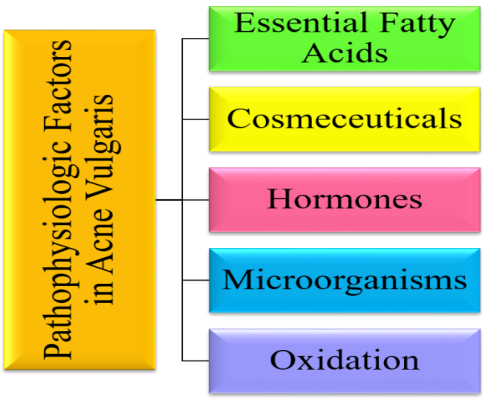

Figure 1. The main pathophysiologic factors in acne vulgaris initiation and progression.

Table 1. Different topical and systemic therapeutic agents used in acne vulgaris treatment.

Route of administration	Pharmacologic category	Drugs
Topical	Topical antimicrobials	Benzoyl peroxide
		Topical antibiotics: Erythromycin,
		Clindamycin
		Sulfacetamide
		Dapsone
		Minocycline
	Topical retinoids	Tretinoin
		A dapalene
		Tazarotene
	Antibacterial, comedolytic, and anti-inflammatory	Azelaic acid
	Comedolytic	Salicylic acid
Oral	Oral antibiotics	Tetracylines: Tetracycline
		Doxycycline
		Minocycline
		Macrolides: Erythromycin
		Azithromysin
		Other antibiotics: Trimetoprim-Sulfamethoxazole
		Clindamycin
		Cephalexin
	Hormonal therapy	Oral contraceptives
		Spironolactone
		Systemic glucocorticoids
		Flutamide
	Oral retinoids	Isotretinoin

rized in Table 1. In addition, the potential investigational agents considered in acne management are presented in Table 2. The role of nanotechnology in enhanced skin permeation (40) and targeted drug delivery to skin organelles (41) would be highly beneficial to improve drug efficacy and improve patients' compliance in acne management. In this regard, various novel topical drug delivery systems including solid lipid nanoparticles, nanostructured lipid carriers (41-44), hydrogels (45), polymeric nanoparticles (46), vesicular nanocarriers including liposome, noisome, ethosome, etc. (47) have been extensively considered.

9. Conclusion

In conclusion, it seems that due to the multifactorial origin of acne vulgaris, various pharmacologic agents including antibiotics, anti-androgenic agents, anti-inflammatory agents, and cosmeceuticals can be considered in acne management based on the severity and acne lesion stages. In addition, the selection of suitable excipients and ingredients is crucial in the fabrication of topical anti-acne formulations. Furthermore, it would be essential to avoid further oxidation processes during formulation preparation and storage. Also, the harmful and/or beneficial role of different lipids in acne pathophysiology should be considered in the selection of suitable lipids in topical formulations design and preparation. Finally, recruitment of novel topical drug delivery systems in acne management is of high importance in order to obtain enhanced drug penetration through skin layers and dermal deposition and also to obtain targeted

Table 2. Potential investigational agents considered in acne management (48).

Route of administration	Pharmacologic category	Drugs
Topical	Sebosuppressive agents	Spironolactone in microemulsion
		Olumacostat glasaretil
		Cortexolone 17-α propionate
		Stearoyl-CoA desaturase 1 (SCD1) enzyme
		Melanocortin (MC) receptor antagonist
		Peroxisome proliferator activated receptor (PPAR) γ modulator; N-Acetyl-GED0507–34-LEVO
		Botulinum neurotoxin type A
		Calcipotriene
		Retinoic acid receptor-γ agonist
	Antimicrobial agents	Omiganan pentahydrochloride
		Minocycline
		Neramexane
		Kanuka honey 90%/glycerin 10%
		tyrothrycin
	Anti-inflammatory agents	sodium 3-(ethyl(3-methoxyphenyl) amino) propane-1- sulfonate (ADPS)
		Ammonia-oxidizing bacteria-basedcompound
		Polymer-based nitric oxide-releasing compound SB204
		The alcoholic, pentacyclic triterpenoid lupeol
		A modulator of NF-κB and PI(3)
		K/Akt pathways
		Protein kinase
		C activator ingenol disoxate
		Timolol
Oral	5α-reductase inhibitors	Finasteride
	Antimicrobials	Levamisole
		Serratia peptidase
	Biological agents	Anti-interleukin-1 (IL-1) monoclonal antibodies (Gevokizumab)
		Anti-IL-17A monoclonal antibody
	Anti-inflammatory agents	Doxycycline
		Lymecycline
		Phosphodiesterase 4-inhibitor apremilast
		Leukotriene B4 (LTB4)
		15- hydroxyeicosatetraenoic acids
		12-hydroxyeicosatetraenoic acids
		Zileuton
		Acebilustat
	Micellaneous	Talarozole

drug delivery to skin organelles especially pilo-sebaceous units and hair follicles to enhance the clinical efficacy of acne pharmacotherapy and to reduce or eliminate systemic adverse drug reaction encountered during the oral therapy using different pharmacological agent including antiandrogens or oral retinoids.

Conflict of Interest

None declared

References

1. Moradi Tuchayi S, Makrantonaki E, Ganceviciene R, Dessinioti C, Feldman SR, Zouboulis CC. Acne vulgaris. *Nat Rev Dis Primers*. 2015 Sep 17;1:15029. doi: 10.1038/nrdp.2015.29. PMID: 27189872.
2. Oge' LK, Broussard A, Marshall MD. Acne Vulgaris: Diagnosis and Treatment. *Am Fam Physician.* 2019 Oct 15;100(8):475-484. PMID: 31613567.
3. Downing DT, Stewart ME, Wertz PW, Strauss JS. Essential fatty acids and acne. *J Am Acad Dermatol*. 1986 Feb;14(2 Pt 1):221-5. doi: 10.1016/s0190-9622(86)70025-x. PMID: 2936775.
4. Downing DT, Strauss JS, Pochi PE. Variability in the chemical composition of human skin surface lipids. *J Invest Dermatol.* 1969 Nov;53(5):322-7. doi: 10.1038/jid.1969.157. PMID: 5347411.
5. Zouboulis CC, Jourdan E, Picardo M. Acne is an inflammatory disease and alterations of sebum composition initiate acne lesions. *J Eur Acad Dermatol Venereol.* 2014 May;28(5):527-32. doi: 10.1111/jdv.12298. Epub 2013 Oct 18. PMID: 24134468.
6. Baldwin H, Tan J. Effects of Diet on Acne and Its Response to Treatment. Am J Clin Dermatol. 2021 Jan;22(1):55-65. doi: 10.1007/s40257-020-00542-y. *Erratum in: Am J Clin Dermatol.* 2020 Dec 26;: PMID: 32748305; PMCID: PMC7847434.
7. Nicolaides, N. and T. Ray, Skin lipids. III. Fatty chains in skin lipids. The use ofvernix caseosa to differentiate between endogenous and exogenous components in human skin surface lipid. *J Am Oil Chem Soc*. 1965 Aug;42:702-7. doi: 10.1007/BF02540043. PMID: 14343880.
8. Pappas A. Epidermal surface lipids. *Dermatoendocrinol.* 2009 Mar;1(2):72-6. doi: 10.4161/derm.1.2.7811. PMID: 20224687; PMCID: PMC2835894.
9. Smith RN, Braue A, Varigos GA, Mann NJ. The effect of a low glycemic load diet on acne vulgaris and the fatty acid composition of skin surface triglycerides. *J Dermatol Sci.* 2008 Apr;50(1):41-52. doi: 10.1016/j.jdermsci.2007.11.005. Epub 2008 Jan 4. PMID: 18178063.
10. Wille JJ, Kydonieus A. Palmitoleic acid isomer (C16:1delta6) in human skin sebum is effective against gram-positive bacteria. *Skin Pharmacol Appl Skin Physiol*. 2003 May-Jun;16(3):176-87. doi: 10.1159/000069757. PMID: 12677098.
11. Akaza N, Akamatsu H, Numata S, Matsusue M, Mashima Y, Miyawaki M, Yamada S, Yagami A, Nakata S, Matsunaga K. Fatty acid compositions of triglycerides and free fatty acids in sebum depend on amount of triglycerides, and do not differ in presence or absence of acne vulgaris. *J Dermatol*. 2014 Dec;41(12):1069-76. doi: 10.1111/1346-8138.12699. Epub 2014 Nov 12. PMID: 25388081.
12. Stewart ME, Quinn MA, Downing DT. Variability in the fatty acid composition of wax esters from vernix caseosa and its possible relation to sebaceous gland activity. *J Invest Dermatol.* 1982 Apr;78(4):291-5. doi: 10.1111/1523-1747.ep12507228. PMID: 7069207.
13. Pappas A, Johnsen S, Liu JC, Eisinger M. Sebum analysis of individuals with and without acne. *Dermatoendocrinol.* 2009 May;1(3):157-61. doi: 10.4161/derm.1.3.8473. PMID: 20436883; PMCID: PMC2835908.
14. Ottaviani M, Alestas T, Flori E, Mastrofrancesco A, Zouboulis CC, Picardo M. Peroxidated squalene induces the production of inflammatory mediators in HaCaT keratinocytes: a possible role in acne vulgaris. *J Invest Dermatol*. 2006 Nov;126(11):2430-7. doi: 10.1038/sj.jid.5700434. Epub 2006 Jun 15. PMID: 16778793.
15. Motoyoshi K. Enhanced comedo formation in rabbit ear skin by squalene and oleic acid peroxides. *Br J Dermatol*. 1983 Aug;109(2):191-8. doi: 10.1111/j.1365-2133.1983.tb07080.x. PMID: 6223652.
16. Katsuta Y, Iida T, Inomata S, Denda M. Unsaturated fatty acids induce calcium influx into keratinocytes and cause abnormal differentiation of epidermis. *J Invest Dermatol.* 2005 May;124(5):1008-13. doi: 10.1111/j.0022-202X.2005.23682.x. PMID: 15854043.
17. Costa A, Siqueira Talarico A, Parra Duarte Cde O, Silva Pereira C, de Souza Weimann ET, Sabino de Matos L, Della Coletta LC, Fidelis MC, Tannous TS, Vasconcellos C. Evaluation of the Quantitative and Qualitative Alterations in the Fatty Acid Contents of the Sebum of Patients with Inflammatory Acne during Treatment with Systemic Lymecycline and/or Oral Fatty Acid Supplementa-

tion. *Dermatol Res Pract.* 2013;2013:120475. doi: 10.1155/2013/120475. Epub 2013 Sep 26. PMID: 24191156; PMCID: PMC3803126.
18. Smith KR, Thiboutot DM. Thematic review series: skin lipids. Sebaceous gland lipids: friend or foe? *J Lipid Res.* 2008 Feb;49(2):271-81. doi: 10.1194/jlr.R700015-JLR200. Epub 2007 Nov 1. PMID: 17975220.
19. Li WH, Zhang Q, Flach CR, Mendelsohn R, Southall MD, Parsa R. In vitro modeling of unsaturated free fatty acid-mediated tissue impairments seen in acne lesions. *Arch Dermatol Res.* 2017 Sep;309(7):529-540. doi: 10.1007/s00403-017-1747-y. Epub 2017 May 31. PMID: 28567492.
20. Melnik BC. Linking diet to acne metabolomics, inflammation, and comedogenesis: an update. *Clin Cosmet Investig Dermatol.* 2015 Jul 15;8:371-88. doi: 10.2147/CCID.S69135. PMID: 26203267; PMCID: PMC4507494.
21. Man MQ, Feingold KR, Elias PM. Exogenous lipids influence permeability barrier recovery in acetone-treated murine skin. *Arch Dermatol.* 1993 Jun;129(6):728-38. PMID: 8507075.
22. Horrobin DF. Essential fatty acids in clinical dermatology. *J Am Acad Dermatol.* 1989 Jun;20(6):1045-53. doi: 10.1016/s0190-9622(89)70130-4. PMID: 2526823.
23. Downing DT, Stewart ME, Wertz PW, Strauss JS. Essential fatty acids and acne. *J Am Acad Dermatol.* 1986 Feb;14(2 Pt 1):221-5. doi: 10.1016/s0190-9622(86)70025-x. PMID: 2936775.
24. Stewart ME, Greenwood R, Cunliffe WJ, Strauss JS, Downing DT. Effect of cyproterone acetate-ethinyl estradiol treatment on the proportions of linoleic and sebaleic acids in various skin surface lipid classes. *Arch Dermatol Res.* 1986;278(6):481-5. doi: 10.1007/BF00455168. PMID: 2947544.
25. Wertz PW, Miethke MC, Long SA, Strauss JS, Downing DT. The composition of the ceramides from human stratum corneum and from comedones. *J Invest Dermatol.* 1985 May;84(5):410-2. doi: 10.1111/1523-1747.ep12265510. PMID: 3158712.
26. Ziboh VA, Chapkin RS. Biologic significance of polyunsaturated fatty acids in the skin. *Arch Dermatol*. 1987 Dec;123(12):1686a-1690. PMID: 3688908.
27. Boxley S. Role of cosmeceutical skincare in the management of acne. *J Aesthet Nurs.* 2018. 7(Sup1): p. 8-12.
28. Barros BS, Zaenglein AL. The Use of Cosmeceuticals in Acne: Help or Hoax? *Am J Clin Dermatol*. 2017 Apr;18(2):159-163. doi: 10.1007/s40257-016-0249-6. PMID: 28063095.
29. Shalita AR, Smith JG, Parish LC, Sofman MS, Chalker DK. Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol.* 1995 Jun;34(6):434-7. doi: 10.1111/j.1365-4362.1995.tb04449.x. PMID: 7657446.
30. Araviiskaia E, Dréno B. The role of topical dermocosmetics in acne vulgaris. J *Eur Acad Dermatol Venereol*. 2016 Jun;30(6):926-35. doi: 10.1111/jdv.13579. Epub 2016 Feb 24. PMID: 26916232.
31. Li X, He C, Chen Z, Zhou C, Gan Y, Jia Y. A review of the role of sebum in the mechanism of acne pathogenesis. *J Cosmet Dermatol.* 2017 Jun;16(2):168-173. doi: 10.1111/jocd.12345. Epub 2017 May 29. PMID: 28556292.
32. Bakry OA, El Shazly RM, El Farargy SM, Kotb D. Role of hormones and blood lipids in the pathogenesis of acne vulgaris in non-obese, non-hirsute females. *Indian Dermatol Online J.* 2014 Nov;5(Suppl 1):S9-S16. doi: 10.4103/2229-5178.144506. PMID: 25506579; PMCID: PMC4252966.
33. Henze C, Hinney B, Wuttke W. Incidence of increased androgen levels in patients suffering from acne. *Dermatology*. 1998;196(1):53-4. doi: 10.1159/000017867. PMID: 9557226.
34. Dessinioti C, Katsambas AD. The role of Propionibacterium acnes in acne pathogenesis: facts and controversies. *Clin Dermatol.* 2010 Jan-Feb;28(1):2-7. doi: 10.1016/j.clindermatol.2009.03.012. PMID: 20082942..
35. Kumar B, Pathak R, Mary BP, Jha D, Sardana K, Gautam HK. New insights into acne pathogenesis: Exploring the role of acne-associated microbial populations. *Dermatologica sin.* 2016. 34(2): p. 67-73.
36. Minegishi K, Aikawa C, Furukawa A, Watanabe T, Nakano T, Ogura Y, Ohtsubo Y, Kurokawa K, Hayashi T, Maruyama F, Nakagawa I, Eishi Y. Complete Genome Sequence of a Propionibacterium acnes Isolate from a Sarcoidosis Patient. *Genome Announc*. 2013 Jan;1(1):e00016-12. doi: 10.1128/genomeA.00016-12. Epub 2013 Jan

15. PMID: 23405284; PMCID: PMC3556827.
37. Nakatsuji T, Tang DC, Zhang L, Gallo RL, Huang CM. Propionibacterium acnes CAMP factor and host acid sphingomyelinase contribute to bacterial virulence: potential targets for inflammatory acne treatment. *PLoS One.* 2011 Apr 12;6(4):e14797. doi: 10.1371/journal.pone.0014797. PMID: 21533261; PMCID: PMC3075254.
38. Mills OH, Criscito MC, Schlesinger TE, Verdicchio R, Szoke E. Addressing Free Radical Oxidation in Acne Vulgaris. *J Clin Aesthet Dermatol*. 2016 Jan;9(1):25-30. PMID: 26962389; PMCID: PMC4756869.
39. Konger RL. A new wrinkle on topical vitamin E and photo-inflammation: Mechanistic studies of a hydrophilic gamma-tocopherol derivative compared with alpha-tocopherol. *J Invest Dermatol*. 2006 Jul;126(7):1447-9. doi: 10.1038/sj.jid.5700308. PMID: 16778813.
40. Ghasemiyeh P, Mohammadi-Samani S. Potential of Nanoparticles as Permeation Enhancers and Targeted Delivery Options for Skin: Advantages and Disadvantages. *Drug Des Devel Ther.* 2020 Aug 12;14:3271-3289. doi: 10.2147/DDDT.S264648. PMID: 32848366; PMCID: PMC7429187.
41. Ghasemiyeh P, Azadi A, Daneshamouz S, Heidari R, Azarpira N, Mohammadi-Samani S. Cyproterone acetate-loaded nanostructured lipid carriers: effect of particle size on skin penetration and follicular targeting. *Pharm Dev Technol.* 2019 Sep;24(7):812-823. doi: 10.1080/10837450.2019.1596133. Epub 2019 Apr 26. PMID: 30889371.
42. Ghasemiyeh P, Azadi A, Daneshamouz S, Mohammadi Samani S. Cyproterone acetate-loaded solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs): preparation and optimization. *Trends in Pharmaceutical Sciences.* 2017;3(4):275-86.
43. Ghasemiyeh P, Mohammadi-Samani S. Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: applications, advantages and disadvantages. *Res Pharm Sci.* 2018 Aug;13(4):288-303. doi: 10.4103/1735-5362.235156. PMID: 30065762; PMCID: PMC6040163.
44. Rahnama V, Motazedian MH, Mohammadi-Samani S, Asgari Q, Ghasemiyeh P, Khazaei M. Artemether-loaded nanostructured lipid carriers: preparation, characterization, and evaluation of in vitro effect on Leishmania major. *Res Pharm Sci.* 2021 Oct 15;16(6):623-633. doi: 10.4103/1735-5362.327508. PMID: 34760010; PMCID: PMC8562414.
45. Ghasemiyeh P, Mohammadi-Samani S. Hydrogels as drug delivery systems; pros and cons. *Trends in Pharmaceutical Sciences*. 2019;5(1):7-24.
46. Ghasemiyeh P, Mohammadi-Samani S. Polymers Blending as Release Modulating Tool in Drug Delivery. *Front Mater*. 2021;8:752813. doi: 10.3389/fmats.2021.752813
47. Castro GA, Ferreira LA. Novel vesicular and particulate drug delivery systems for topical treatment of acne. *Expert Opin Drug Deliv*. 2008 Jun;5(6):665-79. doi: 10.1517/17425247.5.6.665. PMID: 18532922.
48. Zouboulis CC, Dessinioti C, Tsatsou F, Gollnick HPM. Anti-acne drugs in phase 1 and 2 clinical trials. *Expert Opin Investig Drugs.* 2017 Jul;26(7):813-823. doi: 10.1080/13543784.2017.1337745. Epub 2017 Jun 19. PMID: 28627277.