Review: Delivery of Pharmaceutical Agents to Treat Acne Vulgaris: Current Status and Perspectives

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Abstract

Acne vulgaris is one of the most common dermatological disorders that afflict people in their adolescence. Although it is not life-threatening, severe acne can greatly burden a patient's psychological status, thereby reduces their participation in social activities. The present review focuses on a pathogenic bacterium, *Propionibacterium acnes*, in the human skin and summarizes the therapeutic modalities of acne vulgaris, including the pharmaceutical dosage forms of oral and topical administrations. Furthermore, this paper also reviews state-of-the-art in particle-based drug delivery systems and light-based therapy for acne treatment from *in vitro* and *in vivo* studies.

Keywords: *Propionibacterium acnes*, Photodynamic therapy, Acne vulgaris, Drug delivery system, Antimicrobial

1. General considerations for acne and its therapy

Acne vulgaris, one of the most common skin disorders, is the result of a chronic inflammation of a sebaceous follicle and is characterized by tender inflammatory papules and nodules mainly scattered on the face, chest, and upper back. It may be caused by cutaneous micro-organisms such as *Propioni-bacterium acnes* (*P. acnes*) and usually appears in adolescence and early adulthood [1]. The premature form of acne vulgaris is characterized by non-inflammatory comedones in the midline region of the face, where no *P. acnes* is found. [2]. At this stage of the disease, depositions of desquamated follicular corneocytes (commonly referred to as blackheads) are found on the forehead, nose, and chin. *P. acnes* is a gram-positive and propionic acid-producing bacterium that colonizes anaerobically within the hair follicles of the skin [1]. For the inflammation reactions associated with acne virulence, the pathogenesis of the disease has been found to be multi-factorial and the syndromes, such as increased sebum, epidermal hyperproliferation, and hormonal changes, are recognized as non-inflammatory factors [3]. However, the pathogenic role of *P. acnes* in acne has not been completely identified because it resides in normal skin as a harmless commensal [4]. In a recent study, *P. acnes* secretome obtained from five different strains displayed hydrolytic enzymes and immunoreactive adhesins in the secreted fraction of *P. acnes*, which results to acne virulence [5,6].

Traditional therapy for acne-suffering patients involves the administration of antibiotics and retinoids. Although isotretinoin, a kind of retinoid, has the highest bioavailability, it is potentially teratogenic [7,8]. New technologies for safe and effective acne treatment, such as light and laser therapy, photodynamic therapy, chemical pills and the development of oral drugs, have satisfied numerous patients. Such technologies are the novel drugs that modulate the metabolism of endogenous retinoids [9]; topical gels; micro-sponge vehicles [10], and physical therapies such as laser irradiation at various wavelengths [11].

2. Cutaneous bacterial microflora

The human skin can harbor several types of microbe, such as gram-positive species, because physical skin conditions (stable pH, oxygen, ions, etc.) provide an excellent habitat for bacteria. Resident micro-organisms include cutaneous *Propionibacterium*, *Staphylococcus*, *Micrococcus*, *Corynebacterium*, and *Acinetobacterium*. Among these bacteria, cutaneous *Propionibacterium* is commensal on the surface of the skin and keratinized epithelia underneath the surface of the skin [12]. Cutaneous *Propionibacterium* has five species, namely *P. acnes*, *P. avidum*, *P. granulosum*, *P. propionicum*, and *P. lymphophilum*, with *P. acnes* being the most studied strain. It is a non-classical strain of an anaerobe and tolerates oxygen [13]. The cell wall of cutaneous *Propionibacterium* is resistant to various skin conditions, such as drying, osmotic shock, and mechanical stress.

Optical microscopic observation of *P. acnes* shows a coryneform appearance with irregular and short branches. *P. acnes* is commonly found in sebum-rich skin, indicating that sebum is essential for the growth [2]. Its population is about one half of the cutaneous micro-organisms, e.g., 10^2 - 10^6

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bacteria per cm^2 [14]. However, there is no direct relationship between the density of *P. acnes* and the severity of acne [15]. The cutaneous microflora of human skin can greatly vary from person to person. Nutrient availability is critical to the expressed phenotype of *P. acnes*. It has been reported that skin micro-organisms can secrete several enzymes such as lipase and protease that harvest the nutrients to produce energy and biomass. The composition and density of skin microflora thus vary significantly [12].

3. Pathogenesis of acne vulgaris

Facial acne is described as a uniform disorder in many dermatology textbooks, as it onsets in the adolescence period. It can also start in any post-adolescence period [16]. The pathophysiology of acne vulgaris can be classified into several subtypes [1], including increased sebum secretion [16], ductal keratinocyte hyperproliferation, excess growth of acne-associated bacteria, and host inflammatory response [17]. In lesion initiation [17], abnormal proliferation and differentiation leads to the occurrence of microcomedone in the initial lesion. This is followed by (1) the accumulation of sebum in the follicle lumen, causing a plug, either open or closed, of a clinical comedone; (2) inflammatory components leaking from a follicle to the dermis. An acne lesion thus forms. A patient's immune sensitivity toward acne-associated antigens and skin integrity can affect the initiation of acne lesions.

According to the genomic data of *P. acnes* publicly released in 2004 [18], acne virulence factors encoded in the genome can degrade host tissue and trigger inflammation [19]. There are several molecular cues that cause the progression of acne virulence. One is the presence of Christie, Atkins, Munch-Peterson (CAMP) factor of *P. acnes*, a secretory protein with its co-hemolytic activity of the host acid sphingomyelinase (ASMase). These two, CAMP and ASMase can be utilized for the development of drugs to inhibit the progression of acne or even eradicate bacterial overgrowth. The synergistic lysis of erythrocytes via the CAMP reaction has been found in *P. acnes* [6,22]. The CAMP reaction was originally described as a synergistic lysis of sheep erythrocytes by *Staphylococcus aureus* sphingomyelinase C and CAMP factor (extracellular protein) produced by some streptococcal species. The constituents of the plasma membrane, sphingomyelin and phospholipids, are first hydrolyzed by the enzyme, followed by cell lysis [23]. A recent study showed that the *P. acnes* CAMP factor can be utilized by *Staphylococcus aureus* to enhance hemolysis in an acne lesion [24]. A mutagenesis method has been developed to knock out the genes encoding CAMP factors in *P. acnes* [25].

One development to prevent acne virulence is the sialidase, a bacterial cell-wall anchoring factor produced by *P. acnes* [18]. It can catalyze the hydrolysis of sialic acid from the surface of mammalian cells and lead to cell death. The immunization of sebocytes with recombinant sialidase has been found to neutralize *P. acne*-induced toxicity in sebocytes, and sialidase-vaccinated ICR mice showed reduced erythema on the ears [20,21]. Therefore, this innovative medicine could be developed into an effective acne-preventing medication. The *P. acnes* genome encodes several extracellular hydrolases, such as hyaluronate lyase, endoglycoceramidases, and sialidase.

Looking at the micro-environment of acne lesions, e.g., free fatty acids hydrolyzed by the gene product, *P. acnes* lipase plays a role in the colonization of bacteria in sebaceous follicles [22]. Other inflammatory reactions localized in the acne lesion include chemoattractant molecules that recruit polymorphonuclear leukocytes and lymphocytes, the production of the inflammatory cytokines, and the complement activation [2].

The pathogenesis of acne can also be triggered through the toll-like receptor 2 (TLR2), which regulates many immune response genes. *P. acnes* activates the pilosebaceous unit and induces the production of IL-12 and IL-8 of monocytes via the TLR2 pathway. TLR2 and TLR4 expression is increased in the acne lesions of the epidermis. This inflammation, in turn, can lead to hyperproliferation of the ductal epidermis. IL-8 can recruit neutrophils to the pilosebaceuous unit, in which degradative enzymes lead to the rapture of the follicular epithelium [3].

To summarize the above-mentioned inflammatory factors, the complex behavior of acne lesions leads to the clinical symptoms of acne. The interplay of non-inflammatory factors, such as endocrine disorders, stress, insufficient sleep, genetic disorders, diet, and ultraviolet radiation, and inflammatory factors makes acne occurrence spatially and temporally diverse among patients. Figure 1 shows the role of *P. acnes* in the pathogenesis of acne virulence.

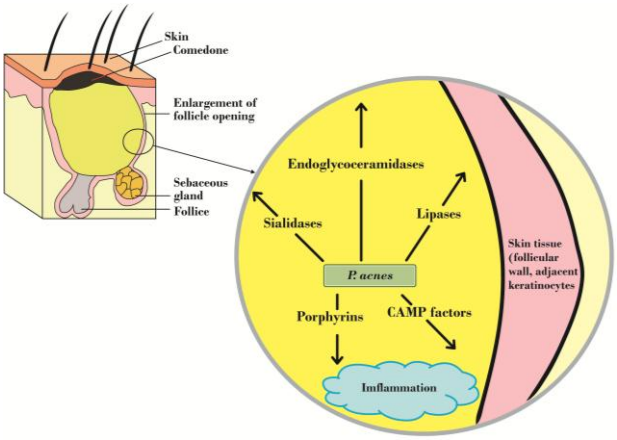

Figure 1. Roles of *P. acnes* in the pathogenesis of acne.

4. Biomedical studies of propionibacterium acnes

Acne vulgaris is associated with the overgrowth of *P. acnes* in sebum-rich skin, where keratinocytes and sebocytes are located. For laboratory study, pathogenic *P. acnes* is available from the American Type Culture Collection (ATCC). Many strains of *P. acnes* have been deposited at the ATCC for research purposes. However, the strain numbered 6919 or equivalent strains deposited in professional laboratories other than ATCC are the most researched [19,25-27]. The first report to characterize *Propionibacteria* was published by Johnson and

Table 1. Current medical treatments of acne vulgaris.

Administration method	Drug or dosage form*	Feature of the treatment	References
Oral	Doxycycline, Tetracycline, Minocycline, Isotretinoin (13-cis-retinoic acid)	1. Several hundred mg of drugs should be taken daily 2. High patient complience 3. Adverse reactions limit the therapeutic window of the drugs	[8,7,35-41]
Topical	Benzoyl peroxide (BPO), Clindamycin, Erythromycin, Tetracycline, Tretinoin, Tazarotene, Green tea extracts	1. Locally administration of drugs 2. Ease of termination of drug action 3. Adverse reactions limit the long-term use of topical drugs	[43-53]
Particle-based DDS	Liposomes, Solid lipid nanoparticles, Nanostructured lipid carriers, Microemulsions	1. Sustained release of the drugs 2. More effective than topical gel 3. Higher flux of drug across the skin 4. Effective for follicular targeting	[54-68]
Light-based therapy**	Endogenous porphyrins (coproporphyrin III), 5-aminolevulinic acid (5-ALA)	1. Fewer adverse reactions than those systemic/topical administration and DDSs 2. Light therapy alone or along with liposomal drugs has been reported. 3. Not a first-line therapy for acne vulgaris	[69-134]

***** for particle-based DDSs; ** this emerging therapy utilizes either topical drugs or particle-based DDSs along with light irradiation.

Cumins, who compared the cell-wall composition and DNA similarities among 80 strains of anaerobic coryneform bacteria with many classical strains [28]. *P. acnes* is generally cultured in an anaerobic jar at 37 ℃.

In a vaccination study, sialidase anchored on a bacterial cell wall was molecularly cloned for the over-expression of recombinant protein in competent *E. coli* [20]. To inactivate the CAMP factor of *P. acnes*, Sörensen et al. knocked out specific genes (*camp2* and *camp4*) to disrupt its hemolytic activity [25]. To illustrate the initiation of the inflammation reaction, *P. acnes* (10^7 colony forming units/mL) was injected in the tissue chamber installed in the abdominal skin of ICR mice. The results indicated that the host cells of neutrophils and macrophages in the chamber were infiltrated after the injection of the bacteria [29]. It has been reported that the innate immune system produces antimicrobial proteins (AMPs) to defend the skin against any microbial infection. It has been found that neutrophils in the skin biopsies of patients bearing acne vulgaris express antimicrobial human neutrophil proteins (HNP 1-3) [30]. This class of AMP was originally identified as the expressed proteins from mammalian cells, such as keratinocytes and sebocytes, when skin is infected by susceptible bacteria [31]. Although the *in vivo* experiments employed some strains of rodents, researchers should bear in mind that not all laboratory animals are suitable for the study of acne therapy. The skin of animals might not produce the right composition of sebum to harbor *P. acnes* [29], or the inflammation of the induced acne may be insufficient to represent the acne of human skin [32]. For example, the ears of rhino mice have large follicles for comedogenicity, but these immune-deficient mice are not suitable for vaccination purposes [33].

5. Dosage forms for the treatment of acne vulgaris

Although acne is not a life-threatening disease, its medical and psychological implications can be significant. Symptoms of acne can range from mild comedones in an early facial lesion to severe inflammation of acne with scarring. Clinical guidelines for treating the various stages of acne vulgaris have been proposed [34,35]. Clinically approved medications, which are divided into oral-administered (systemic) drugs, topical drugs, novel dosage forms of particle drug delivery systems, and light-based therapy, are reviewed below. Table 1 summarizes the medical treatments discussed in this article and their associated features.

5.1 Oral administration of antibiotics and retinoids

The systemic administration of antibiotics to pediatric patients, aged 8 to 11, is accepted by most clinicians [35]. However, warnings of bacterial resistance have triggered the development of alternative drugs. The main oral antibiotics used for treating acne are doxycycline, tetracycline, and minocycline. Among them, tetracycline has been prescribed the longest to treat acne. Oral doxycycline is usually prescribed at a dosage of 100 mg twice daily, which may be taken with food [36]. Oral tetracycline is usually prescribed at a dosage of 500 mg twice daily and taken on an empty stomach because food reduces its absorption [37]. On the other hand, minocycline is taken orally with food. This is the preferred anti-acne drug due to its greater oral bioavailability and antimicrobial effects against *P. acnes* compared to those of other antibiotics as a result of its higher lipid solubility [37]. Furthermore, it has been reported that minocycline can reduce sebum free fatty acids and bacterial lipases [38]. Based on a golden standard of 1 mg/kg/day of minocycline for acne treatment, extended-release formulations using either cellulose derivatives or synthetics polymers have

been thoroughly investigated [38-41]. The long-time use of tetracycline can cause adverse reactions such as photo-sensitivity, gastrointestinal tract dyspepsia, and the risk of developing vaginal candidiasis in women. Children under the age of 10 can develop enamel hypoplasia and a yellowish discoloration of forming teeth [42].

For patients with severe acne irresponsive to antibiotic treatments for a certain period of time, the systemic application of retinoids is generally considered. The retinoid drug isotretinoin (13-cis-retinoic acid) is regarded as a first-line defense therapy for acne. This vitamin A derivative is usually quite effective for most symptoms of acne, such as keratinization abnormality, sebum over-production, and inflammation [7]. Though this drug is not antimicrobial, it modifies the follicular micro-environment, thereby effectively inhibiting the growth of *P. acnes* [43]. The European Directive has harmonized the systemic prescription of isotretinoin throughout Europe [8]. However, it should be noted that systemic retinoids are contraindicated during pregnancy, and lactation [7].

5.2 Topical administration of antibiotics and retinoids

The topical delivery of medication has certain advantages over systemic administration. For example, the local action of drugs in skin can eliminate systemic adverse effects. In addition, the ease of drug action termination is superior to those of oral and parenteral drug delivery systems. The drug interaction with topical administration is minor compared to that with a systemic route. Currently available topical antimicrobials include benzoyl peroxide (BPO), clindamycin, erythromycin, and tetracycline. BPO is a cheap and powerful *P. acnes*-destroying antimicrobial agent. At present, the combination of BPO and topical antibiotics has been confirmed to be more powerful and medically tolerated than the use of BPO alone [44].

Topical clindamycin monotherapy can lead to more resistant strains of *P. acnes*. Formulations of clindamycin phosphate 1.2% or tretinoin (all-trans retinoic acid) 0.025% gel have achieved superior clinical outcomes with fewer acne lesions [45]. Erythromycin is also considered as an effective topical antibiotic for treating acne [46]. Adapalene is a third-generation retinoid. The cutaneous tolerance of adapalene is greater than that of retinoic acid, and many clinical trials have confirmed its efficacy in acne therapy [47]. A Japanese clinical trial with 238 participants showed that 0.1% adapalene gel is effective and optimal for reducing acne lesion counts [48]. Other retinoids are being developed for acne therapy, such as tretinoin [49,50] and tazarotene [51].

It should be noted that the use of topical tretinoin has dose-related adverse effects, such as erythema, pruritus, burning, and stinging. Long-term administration can increase the occurrence of certain adverse effects. Many studies have also shown that green tea extracts have good anti-oxidantive and anti-inflammatory properties for skin. Topical 2% green tea lotion has been found to treat mild-to-moderate acne vulgaris [52]. In addition, the use of green tea extracts has been found to have no dose-related adverse effects [53], and the extracts have been reported to have a steady release pattern for 48 hours [54].

5.3 Partcle drug delivery systems

Particle-based drug delivery system (DDS) are based on the phase separation between a continuous phase of solvent, usually water or an isotonic solution, and a semi-solid phase where drugs are encapsulated by surfactants or amphiphilic molecules [55]. Particle DDSs such as liposomes (spherical vesicles consisting of natural phospholipids) [56,57], solid lipid nanoparticles [58], and nanostructured lipid carriers [59] have been extensively investigated for biomedical applications [60]. For sebaceous tissue drug targeting, such as follicular drug targeting, some concerns should be taken into account, including size selectivity, and sebum and hair cycles [61]. Two particle size ranges are effective for drug transport to follicles, namely 1.5-7.0 μm and 20-40 nm. The flux of sebum toward the skin surface can hinder the transport of drug-loaded particles. Therefore, a lipophilic drug or sebum-miscible carrier is preferred. Based on the relative dimensions of the structure of skin and drug-loaded nanoparticles, a review article indicated that the stratum corneum, furrow (dermatoglyph), and hair follicles are likely sites on intact skin for nanoparticle penetration [62]. Among these routes, lipophilic stratum corneum is a natural particle barrier to the penetration of hydrophilic drugs. Conversely, the follicular route is considered to target and accumulate drugs to the sebaceous glands because of complex vascularization and thin stratum corneum in the hair follicles [63].

In general, liposomal delivery can alter the pharmacokinetics and biodistribution of free drugs to decrease systemic toxicity [64]. The outer membrane of liposomes is composed of biocompatible phospholipids. Commonly used phospholipids include egg phosphatidylcholine, phosphatidyl-choline, dipalmitoyl-phosphatidylcholine, dipalmitoyl-phosphatidylglycerol, and distearoylphosphatidylethanol-amine.

Tretinoin is widely used in the topical delivery of acne. The efficacy and local tolerability of liposomal tretinoin have been investigated clinically. In a double-blind study, 20 patients with uncomplicated acne vulgaris received 0.01% liposomal tretinoin on one side of the body, whereas a commercial gel preparation with either 0.025% or 0.05% tretinoin was applied on the other side once daily over a period of 10 weeks [65]. The results indicated that liposomal tretinoin is better tolerated than commercial tretinoin gel. Reports have clearly indicated that liposomal tretinoin can stay chemically stable for at least 3 months [66]. In addition, the encapsulation of antibiotic clindamycin in liposome has been proven to be very effective in reducing the total number of comedones, papules, and pustules [67].

In an *in vitro* study, free fatty acids such as lauric acid (LA), oleic acid, and palmitic acid encapsulated in liposome mainly made of egg phosphatidylcholine showed antimicrobial activity against *P. acnes*. A concentration of 51 μg/mL of LA in liposome exhibited an bactericidal effect, whereas free LA of the same concentration was ineffective against *P. acnes*. Free fatty acids have been found to have a toxicity effect on *P. acnes* [57]. Liposomal oleic acid has been found to have a very

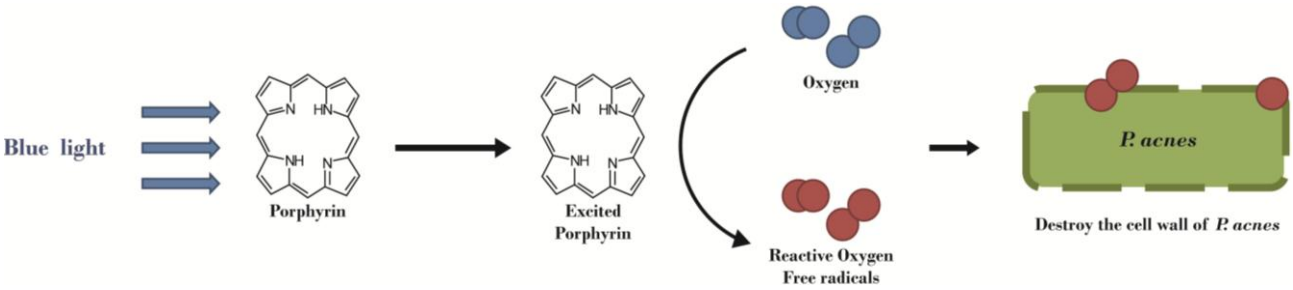

Figure 2. Mechanisms of blue light interaction with porphyrins that destroy *P. acnes*.

similar bactericidal effect on drug resistant *Staphylococcus aureus* [58]. Fatty acids encapsulated in liposome enhancing the membrane permeability of bacteria has been suggested as a possible mechanism for the antimicrobial activity.

In addition to cellular toxicity, a recent review indicated three mechanisms of liposomal delivery through skin [68]. First, the lipid components of liposome are believed to exchange with endogenous skin lipids in the topmost layer of skin, the stratum corneum. Second, the osmotic gradient and hydration force suck the liposome into the epidermis. Third, liposome transports via pilosebaceous units. The third pathway could serve as the most effective treatment against acne virulence.

Microemulsions are clear, stable, isotropic liquid mixtures. This physical system is very different from liposomes in that its single layer of surfactant acts as a diffusion barrier for drugs encapsulated inside the microemulsion particles. The system is a dispersion of oil and water interfaced with surfactant and co-surfactant molecules. Microemulsions have been used as drug carriers for topical and transdermal administration [69]. The bioactive azelaic acid has been approved for treating acne and associated skin disorders [70]. The transport of azelaic acid from a microemulsion and a gel through the full thickness of abdominal skin has been reported. A lag time was evident when the microemulsion or gel was applied on the skin. The percentage of azelaic acid permeated from the microemulsion was several times higher than that from the gel. In conjunction with microemulsions, the effect of 1% and 2% dimethyl sulfoxide, chosen as a penetration enhancer, on the efficiency of transport has been investigated. In 8-hour transdermal experiments, 43% and 64% of the total amount of drug dose passed through hairless skin for microemulsions with 1% and 2% dimethyl sulfoxide, respectively, illustrating the potential of microemulsions in acne therapy [71].

5.4 Light-based therapy

Intense pulsed light (IPL) has been used to treat human disorders [72,73]. Even though the use of drugs, either antibiotics or retinoids, has reached satisfactory levels of the tolerance and response of patients, lasers and other light sources have been developed for the treatment of skin disorders [74]. This kind of therapeutic modality is an alternative option for curing acne vulgaris with a lower incidence of adverse effects. IPL is generally composed of multiple pulses of high-intensity light, whose selected wavelength can penetrate through the dermis. When light reaches a certain distance from the surface of skin, its energy is absorbed and converted into heat, with the diseased part of the skin undergoing photothermolysis [75,76]. Physically, IPL can irradiate diseased sites in a localized manner and thereby reduce the risk of the adverse effects often seen in systemic/topical DDSs [77,78]. IPL therapy has been utilized for the treatment of inflammatory and non-inflammatory acne lesions [76-86]. Photodynamic therapy (PDT) utilizes organic compounds, such as 5-aminolevulinic acid (5-ALA), methyl-aminolevulinic acid (MAL), or other photosensitizing agents to enhance the effect of subsequent light or laser therapy. Photosensitizers can be used with IPL to provide a more aggressive therapy for acne vulgaris. Light-emitting diodes (LEDs) with various wavelengths, including red and blue, are used in phototherapy. Polychromatic therapy with LEDs have been clinically proven to be cost-effective, convenient, low-risk, and well tolerated [87-89].

The bactericidal effect of light on *P. acnes* depends on the wavelength of the irradiating light, which can correspond to chromophores such as coporporphyrin, which is the major porphyrin secreted by *P. acnes* [90-94]. The endogenous porphyrins (coproporphyrin III) in the cell body of *P. acnes* are the key photosensitizer enabling the eradication of acne virulence upon irradiation with blue and/or red light [91,94]. The mechanism of blue light interaction with porphyrins destroying *P. acnes* is illustrated in Fig. 2. The photo-inactivation of *P. acnes* starts with light with a wavelength in the range of 400-420 nm being absorbed by porphyrins, followed by singlet oxygen production. An *in vitro* study found that a combination of blue and red light along with 5-ALA can effectively kill *P. acnes* [92]. Although red light (centered at 635 nm) does not directly contribute to the production of endogenous porphyrins, it is believed that red light is effective in acne therapy. The disadvantage of using red light is the occurrence of erythema and hyperpigmentation. The administration of 5-ALA prior to the irradiation of red light allowed the exposure dose of the light to be reduced, thereby reducing the possibility of potential side effects [92]. In the *in vivo* study of Lee et al., it was found that an array of LEDs for PDT can reduce the numbers of inflammatory and non-inflammatory lesions by up to 77.93% and 34.38%, respectively [95]. Combined blue-red light therapy causes less skin irritation and seems to reduce the number of inflammatory lesions [96,97].

In mammalian cells such as colon-26 tumor cells, the photosensitizer 5-ALA is converted into proporphyrin IX to

produce photo-damage upon irradiation with a 633-nm laser [98]. The limitation of PDT is the penetration depth of light through the tissues or organs to be treated. Therefore, PDT for cancers is mainly restricted to anatomical regions that are easily accessible to light or an endoscope, such as oral cancer [99], esophageal cancer [100], breast cancer [101], and skin cancer [102]. Furthermore, the hydrophilic nature of 5-ALA leads to poor penetration through tumors. The conjugation of eighteen 5-ALAs with a second-generation dendrimer led to a satisfactory *in vitro* production of porphyrin in the murine mammary adenocarcinoma M3 [103]. In animal experiments, the peak production of porphyrin was observed at 3-4 hours after the administration of free 5-ALA, and sustained porphyrin production was observed for a period of 24 hours. The enzymatic cleavage of the ester linkage between a dendrimer and 5-ALA results in the sustained release of 5-ALA. For PDT applied to acne, exogenous 5-ALA was found to penetrate from the stratum corneum to the sebaceous gland and follicles when 10% 5-ALA cream was applied on the skin [104]. 5-ALA and some photosensitizing agents such as MAL and indocyanine green can enhance the effect of therapy [105,106].

Kosaka et al. reported a targeting method for selectively accumulating 5-ALA in the sebaceous gland. They found that a contact time of 1-2 hours for the topical administration of 2.5% or 5% ALA hydrochloride was optimal for acne therapy in rhino mice [107]. A higher dose of ALA hydrochloride damaged the sebaceous gland and epidermis. However, a lower dose and shorter contact time may only exert physical therapy, instead of PDT. However, compared to cancer therapy, treatment using light-based therapy for dermatological disorders is not restricted, because of the ease of the light irradiation on the surface of skin.

The available types of light source for the light-based therapy of acne vulgaris include IPL, infrared diode lasers and continuous visible lights (blue/red light). Haedersdal et al. found that many controlled clinical studies of acne vulgaris and other dermatological infections using various light sources achieved suboptimal treatment quality [108]. This is due to a variety of intrinsic and extrinsic factors such as individual variation and the settings of lasers and the operating parameters of the light source. Even though there are successful clinical reports of treating acne vulgaris using light-based therapy, patients should be informed that PDT is not a first-line therapy in current dermatological practice.

6. Summary and perspectives

The pathophysiology of acne vulgaris was discovered when the complete sequence of the genome of the pathogenic bacterium *P. acnes* was published [18]. Therapeutic approaches can be divided into drug administration via systemic or topical routes and PDT. The recent development of particle-based DDS, especially liposomes, has led to more effective and safer acne therapy. The enhancement of the transdermal delivery of drugs to the skin can be attributed to the lipophilic molecules of the stratum corneum of the skin being exchanged with the lipid component of liposomes. A retrospective investigation of preclinical and clinical studies revealed that naturally occurring molecules such as fatty acids can be encapsulated in liposomes. This development could eventually lead to a broadly accepted dosage form of acne therapy. Although the adverse effects of light-based therapy are lower than those of pharmaceutical agents, the first-line therapy agreed upon by most clinicians for managing acne virulence is the topical administration of antibiotics or retinoids. The combination of PDT and potent photosensitizers, delivered by sophisticated drug vehicles, might prove to be much more effective than traditional methodologies, such as topical therapy. Medical practitioners should pay attention to new findings in the biochemistry and pathogenesis of *P. acnes*, which may lead to the development of new medications or vaccines.

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