基于药物递送技术的痤疮治疗

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摘要: 寻常痤疮是一种慢性炎症性皮肤病, 主要由毛囊堵塞和炎症引起, 是全球第八大最常见疾病, 严重影响人们的生活质量。尽管现有多种治疗选择, 如药物治疗和物理治疗, 但多数药物存在不良反应显著、化学稳定性差和靶向效果低等不足。药物递送系统 (drug delivery systems, DDS) 在痤疮治疗中展现出潜在的应用前景, 特别是在提高药物疗效和减少不良反应方面具有显著优势。因此, 开发新型DDS成为当前研究的重点。本综述首先分析了寻常痤疮的病理机制及其治疗目标, 其次系统概述了现有的治疗方法, 最后重点探讨了DDS在痤疮治疗中的潜在应用, 旨在为未来的痤疮治疗提供新的视角和方案。

关键词: 寻常痤疮; 药物递送系统; 病理机制; 治疗方法; 纳米载体; 靶向递送; 深共熔溶剂; 透皮给药

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Acne treatment based on drug delivery technology

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Abstract: Acne vulgaris is a chronic inflammatory skin disease, mainly caused by clogged and inflamed hair follicles, and is the eighth most common disease worldwide, severely affecting people's quality of life. Although several treatment options are available, such as pharmacotherapy and physiotherapy, most medications suffer from significant side effects, poor chemical stability, and low targeting efficacy. Drug delivery systems (DDS) have potential applications in acne treatment, particularly in enhancing drug efficacy and minimizing side effects. Therefore, the development of novel DDS has become the focus of current research. This review firstly analyzes the pathological mechanisms of acne vulgaris and its therapeutic targets, secondly systematically outlines the existing therapeutic approaches, and finally focuses on the potential applications of DDS in acne treatment, aiming to provide new perspectives and options for future acne treatment.

Key words: acne vulgaris; drug delivery system; pathomechanism; therapeutic approach; nanocarrier; targeted delivery; deep eutectic solvent; transdermal drug delivery

寻常痤疮是一种由皮肤毛囊皮脂腺单位引起的慢性炎症性疾病, 常见于面部和躯干等部位, 影响着世界各地的人们[1]。根据全球疾病负担研究, 寻常痤疮是全球第八大常见疾病, 患病率为20.5%。其中, 在16～24岁的群体中患病率最高, 达到28.3%[2]。然而, 该疾病可于儿童期发病, 并可能持续至青春期后[3]。此外, 因其高发病率和较长的病程, 患者可能会面临社会问题和心理障碍[4]。如内向、社交焦虑和社会孤立感增

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加等[5]。

寻常痤疮的病变形式主要表现为: 非炎症性闭合性粉刺 (毛囊内皮脂或角蛋白积聚形成的丘疹; 也被称为白头粉刺); 开放性粉刺 (即角蛋白扩张毛囊, 从而导致毛囊开放、脂质氧化和黑色素沉积; 也称为黑头); 以及炎性丘疹、脓疱和囊肿等[6], 尽管临床实践中多数医生采用基于简化主观量表的分类 (轻度、中度、重度) 评估痤疮, 但在临床诊疗及评价潜在疗效的研究中, 应用可靠方法评估其严重程度至关重要。目前已提出多种痤疮分级工具, 然而多数临床应用受限, 且关于优选量表尚未达成共识[7]。

尽管痤疮的发病机制已被充分研究, 且临床上广泛使用过氧化苯甲酰 (benzoyl peroxide, BPO)、阿达帕林 (adapalene, AD) 等治疗方案, 但这些传统方法常常存在疗效有限、化学稳定性差、无法靶向病理生理途径以及不良反应显著等缺陷[8]。随着纳米技术和材料科学的快速发展, 药物递送系统 (drug delivery systems, DDS) 在克服这些缺陷方面展现出巨大的潜力。DDS 通过改善药物的稳定性、提高靶向性和控制释放速率, 显著增强了药物的疗效并减少了不良反应。本文旨在探讨基于药物递送技术的痤疮治疗方法, 首先分析痤疮的病理机制和现有治疗手段, 然后重点讨论 DDS 在痤疮治疗中的应用及其未来发展前景。通过整合最新的研究成果, 期望为痤疮治疗提供新的思路和方法, 改善患者的治疗体验和生活质量。

1 寻常痤疮的病理机制与治疗目标

寻常痤疮的发病机制涉及多种因素的协同作用[8] (图 1)。传统理论认为其发病环节包括: 雄激素介导的皮脂分泌增加、毛囊导管角化异常、痤疮丙酸杆菌定植伴随菌群多样性下降, 以及炎症介质释放等过程[9]。然而, 导致痤疮病变发展的确切机制目前尚不完全明确[10]。

1.1 皮脂分泌增加

Wnt 信号通路调控连接 LRIG1$^+$细胞的增殖和特异性, 而雄激素可能促进皮脂细胞分化并抑制 Wnt 信号, 导致 LRIG1$^+$细胞发生转变, 从而导致寻常痤疮的发病[11], 同时皮脂中的角鲨烯在紫外线 (ultraviolet, UV) 辐射下发生过氧化反应, 通过刺激脂氧合酶和 IL-6 的产生, 在炎症级联反应和粉刺形成起着关键作用[12]。因此, 在寻常痤疮治疗过程中, 应将其作为考虑因素[13]。

1.2 皮脂腺毛囊内导管角化过度

毛囊基底层及皮脂腺毛囊导管内的过度角化, 是痤疮病变发展的关键初始环节。过度的角质形成细胞的异常增殖致使毛囊皮脂腺导管上皮层增厚、管腔缩窄[14], 进而促使角质细胞在毛囊漏斗部滞留堆积, 最终形成角质栓塞及粉刺[15]。微粉刺主要由扩张的毛囊组成, 其中充满角蛋白鳞片、细菌和肉眼难以辨识的皮脂。微粉刺被认为是所有寻常痤疮病变 (例如粉刺和炎性丘疹) 的前驱病变, 但其演变成其他痤疮病变的确切机制尚不清楚。此外, 角蛋白 (K6、K16 和 K17) 和基底层中丝聚蛋白的异常高表达与痤疮病变密切相关[16]。

1.3 痤疮丙酸杆菌过度增殖

痤疮丙酸杆菌是定植于人体皮肤的厌氧革兰阳性杆菌。研究表明, 寻常痤疮的发病具有个体差异性, 其

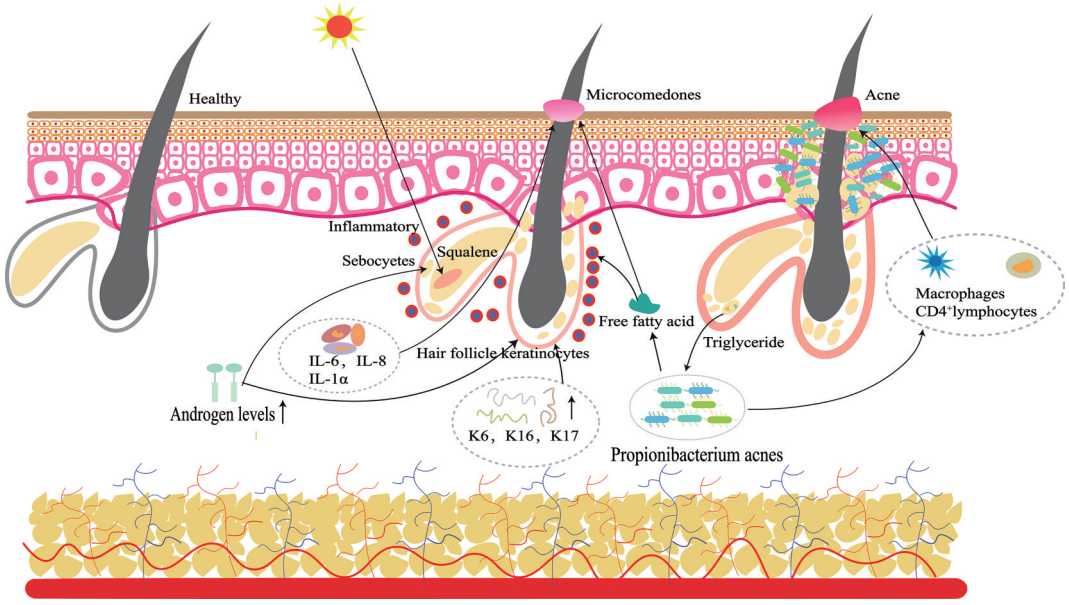


Figure 1 Diagram of the pathogenesis of acne. Acne: Acne vulgaris

严重程度与宿主免疫应答强度密切相关[17]。痤疮丙酸杆菌在毛囊内过度增殖时, 可分泌脂肪酶分解甘油三酯, 产生具有刺激性的游离脂肪酸, 进而诱导粉刺形成并促进炎症反应[18]。因此, 痤疮丙酸杆菌毒力因子在痤疮关键病理过程中发挥着关键作用[19]。

从信号通路机制分析, 痤疮丙酸杆菌可激活皮脂腺及角质形成细胞上的Toll样受体2 (toll-like receptor 2, TLR-2) 和TLR-4, 通过受体介导的信号转导诱导单核细胞释放白细胞介素-6 (IL-6)、白细胞介素-8 (IL-8) 及白细胞介素-12 (IL-12) 等促炎细胞因子, 从而加剧局部炎症反应[20]。

1.4　炎症

痤疮的病理进程中, 先天性与适应性免疫系统均被激活。研究表明, 患者毛囊周围真皮中$CD3^+/CD4^+$ T细胞、巨噬细胞及IL-1α水平显著升高, 提示炎症是痤疮病变的早期特征[21]。此外, 组织学观察发现的痤疮皮肤亚临床炎症进一步证实, 炎症是痤疮发病机制的关键因素[22,23]。

1.5　寻常痤疮的病理机制新发现

1.5.1　全基因组与痤疮　近期关于寻常痤疮病理机制研究取得了显著进展。Teder-Laving等[23]通过整合全基因组关联研究 (genome-wide association study, GWAS) 及跨群体荟萃分析, 新鉴定出4个痤疮风险基因位点 (*11q12.2*、*12q21.1*、*17q25.3* 和 *22q12.1*), 将已知痤疮易感位点总数增至50个。该研究揭示了Wnt信号通路与丝裂原活化蛋白激酶通路在毛囊稳态失衡中的关键作用。荟萃分析进一步发现, 调控炎症反应 (如tumor necrosis factor, TNF) 及影响皮脂腺功能与活性 (如 *CYP17A1*、*follistatin*) 的基因存在与痤疮发生及严重程度相关的潜在风险变异[24], 此外, 胰岛素样生长因子-1 (insulin-like growth factor 1, IGF-1) 多态性研究证实, 其水平升高与皮脂分泌过多和痤疮发生显著相关[25], 这些为痤疮分子机制研究提供了新的理论视角。

然而, 遗传因素与痤疮严重程度的关联性仍需深入探究。Du等[26]通过孟德尔随机化 (mendelian randomization, MR)、共定位和全转录组关联研究 (基因座transcriptome-wide association study, TWAS) 分析发现, 痤疮易感性与严重程度的遗传重叠较低 (仅26%风险相关), 并鉴定出6个严重程度特异性新基因。同时, Liu等[27]在耐药痤疮丙酸杆菌大鼠模型中证实, 噬菌体φPaP11-13通过裂解病原体显著抑制IGF-1/IGF-1R通路异常激活 (IGF-1水平与炎症程度呈正相关)。上述研究不仅深化了对痤疮多基因遗传架构的理解, 也为开发靶向干预策略提供了分子靶点和理论依据。

1.5.2　肠道微生物组与痤疮　近年来, 微生物组在皮肤病发病机制中的作用受到广泛关注, 特别是肠道微生物群通过“肠–皮肤轴”对宿主免疫与代谢的调控机制。肠道菌群通过免疫调节及代谢产物 (如短链脂肪酸) 的生成维持肠道屏障完整性, 而其失调则会通过免疫激活、神经内分泌及代谢途径破坏皮肤稳态平衡[28,29]。这一机制已在酒渣鼻等炎症性皮肤病的研究中得到验证[30]。

针对痤疮这一多因素致病的皮肤疾病, Wang等[31]采用双向孟德尔随机化分析, 首次揭示特定肠道菌群 [拟杆菌科 *Bacteroidaceae*, odds ratio (OR) = 2.25; *Allisonella*, OR = 1.42] 与痤疮风险之间存在显著因果关联 ($P_{FDR} < 0.05$), 而反向分析未显示痤疮对菌群的因果效应。这提示肠道菌群可能通过调节全身炎症或脂质代谢过程参与痤疮发病, 为痤疮的靶向干预提供了分子流行病学依据。

目前, 对痤疮复杂病理机制的新认识为痤疮治疗开辟了一系列新的可能性。

2　传统治疗痤疮的方法

痤疮的治疗主要是在已有病变的基础上进行干预, 旨在控制症状并防止病情进一步恶化[32]。在制定治疗方案时, 需要综合考虑患者的自身因素, 如病变的严重程度、瘢痕是否存在以及患者对治疗方法 (口服或外用) 的偏好; 同时, 还需考虑外在因素, 如治疗费用和药物的不良反应[1]。只有综合这些因素, 才能制定出有效且个性化的治疗方案。

2.1　药物疗法

2.1.1　传统药物　在寻常痤疮治疗过程中, 药物疗法扮演着至关重要的角色, 多种药物已被广泛应用于控制和治疗痤疮。表1[2,6,33-52]总结了当前临床用于治疗寻常痤疮的药物。

2.1.2　新型药物JAK抑制剂　JAK/STAT (janus kinase/signal transducer and activator of transcription) 信号通路在炎症性皮肤病发病中起关键作用, 其成员 (JAK1、JAK2、JAK3、tyrosine kinase 2) 的特异性激活模式可能决定不同疾病的病理特征。

在寻常痤疮的研究中, Awad等[53]首次发现炎性皮损中JAK1与JAK3蛋白呈现特异性过表达 ($P < 0.05$), 且其表达水平与痤疮严重程度 (采用global acne grading system, GAGS评分) 及人口学特征无显著性相关性。这一发现提示, JAK1/3可能通过调控局部炎症反应参与痤疮发病过程。值得注意的是, 尽管JAK抑制剂在某些免疫性皮肤病的治疗中显示出有效性, 但其可诱发痤疮样皮疹 (非典型痤疮), 这表明JAK通路在不同皮病中存在调控异质性[54]。

在临床转化方面, Sun等[55]开展的21例玫瑰痤疮

Table 1 Current medications used in acne treatment. ROS: Reactive oxygen species

Classification	Therapeutic drug	Therapeutic mechanism	Negative effect	Ref.
Vitamin A analogues	Isotretinoin	Isotretinoin inhibits sebaceous gland function, reducing sebum secretion and promoting acne resolution; it also decreases TLR-2 expression on monocytes, thereby attenuating inflammatory responses	Dose-dependent effects, dryness, cheilitis, acne flare-ups	[33,34]
	Adapalene	Normalizes keratinocyte proliferation and blocks multiple inflammatory pathways to promote acne dissolution and inhibit micro-acne formation	Tingling, pruritus, redness, dryness of the skin	[35,36]
	Tazarotene	Tazarotene is metabolized to active tazarotenic acid in skin, normalizing follicular keratinization and sebaceous gland proliferation while exhibiting anti-inflammatory effects	Irritation and skin redness	[2,37,38]
Antibiotics	Erythromycin	Erythromycin inhibits cutibacterium acnes growth and reduces inflammation by suppressing neutrophil chemotaxis and reactive oxygen species production	Dryness, irritation	[6,39]
	Clindamycin	Beyond antibacterial protein synthesis inhibition, clindamycin reduces inflammation *via* lipase suppression (decreasing free fatty acids) and inhibition of leukocyte/cytokine chemotaxis	Pruritus, erythema, dryness, photosensitivity	[40]
	Minocycline	Minocycline inhibits bacterial protein synthesis *via* 30S ribosomal binding and exerts anti-inflammatory effects by suppressing pro-inflammatory cytokines, neutrophil chemotaxis, phagocytosis, and superoxide dismutase activation	Yellowing and irritation of the skin	[41,42]
Oral contraceptives	Denogestrel + ethinylestradiol	Elevates sex hormone-binding globulin synthesis, thereby reducing bioactive free testosterone levels in women	Gastrointestinal discomfort, mood changes, headache, high blood pressure	[43,44]
Hormones	Spironolactone	Spironolactone, an aldosterone receptor antagonist, reduces sebum production by inhibiting ovarian androgen production and blocking the effects of androgens on the sebaceous glands	Dizziness, hyperkalemia	[45]
	Clasterone	As a topical androgen receptor antagonist, clascoterone competitively inhibits dihydrotestosterone binding, diminishing inflammatory cytokines and sebum production	Erythema	[46,47]
Other classes	Benzoyl peroxide	Can release ROS and has a bacteriolytic effect	Pruritus, peeling, irritation and redness of the skin	[48,49]
	Azelaic acid	Inhibits microbial energy metabolism and reduces pro-inflammatory factor production regulates keratinocyte differentiation	Skin redness, burning sensation, dyspnea and pruritus	[50,51]
	Salicylic acid	Salicylic acid is a beta hydroxyl compound that reduces acne formation by exfoliating the skin and keeping pores open; it also has anti-inflammatory and antibacterial properties	Irritation, pruritus and dryness	[52]

患者回顾性研究显示, 口服JAK1/3抑制剂托法替布可使71.4%的患者 (n = 21) 实现皮损完全或近完全清除, 且研究者整体评分 (investigator global assessment, IGA) 平均下降2.2分 (P < 0.001), 证实了该药物对丘疹脓疱型及红斑毛细血管扩张型玫瑰痤疮的有效性。上述研究结果表明, JAK亚型特异性调控是炎症性皮肤病精准治疗的潜在方向。然而, JAK通路在不同皮肤病中的激活模式、治疗应答差异及潜在不良反应, 仍需通过更大样本量的研究进一步阐明。

2.2 补充或替代疗法

天然产物疗法通过具备抗菌、抗炎或油脂调节作用的植物提取物、精油等活性成分, 被开发为痤疮的外用/口服制剂或传统治疗的辅助手段[56]。传统药用植物正逐步转化为痤疮治疗相关药妆产品 (如茶树油凝胶等), 尽管基础实验研究已证实其具有显著的治疗潜力, 但其临床循证证据仍显匮乏, 需通过更深入的研究明确其作为常规治疗替代或辅助方案的有效性与安全性[57,58](表2[59-70])。

2.3 物理疗法

物理疗法通过物理手段治疗痤疮, 可有效减轻症状并改善皮肤状态。该疗法常与药物等其他治疗联用以增强疗效, 实施时需在皮肤科医师或专业美容师指导下进行, 确保治疗安全有效。

2.3.1 光学疗法 光学疗法是一种通过特定波长来治疗疾病或改善皮肤状况的方法, 其中红光和蓝光已被证实具有抗菌和抗炎作用, 常用于痤疮的治疗[71]。表3[72-75]是目前关于光学疗法的常见类型。

2.3.2 射频疗法 射频疗法 (radiofrequency, RF) 作为一种基于电磁辐射能量的皮肤治疗技术[76], 其作用机制为通过电磁辐射产生的能量在真皮等高阻抗组织中转化为热能, 进而用于深层组织。根据技术原理可划分单极射频 (monopolar radiofrequency, MRF)、多极射

Table 2　Natural products for acne treatment and their mechanisms of action. NADPH: Nicotinamide adenine dinucleotide phosphate hydrogen

Plant	Family	Medicinal part	Mechanism of action	Ref.
Cannabis	Cannabaceae	Cannabis extract (cannabidiol)	Suppresses cutibacterium acnes-induced inflammation and downregulates TNF-α mRNA/cytokine expression in sebocytes	[59]
Greentea	Camelliaceae	Green tea extract (catechin)	Apoptotic, inhibitory and anti-inflammatory effects on human sebocytes	[60]
Psoralen	Leguminosae	Psoralen extract (psoralen)	Inhibits the growth of propionibacterium acnes and reduces the secretion of inflammatory cytokines IL-8 and TNFα in the skin	[61]
Centella asiatica	Umbelliferae	Centella asiatica extract (asiaticoside)	Inhibits the production of pro-inflammatory cytokine IL-1β and TLR2 expression and nuclear translocation of NF-κB in propionibacterium acnes-stimulated THP-1 human monocytes	[62]
Turmeric	Zingiberaceae	Turmeric rhizome (curcumin)	Inhibits the production of propionibacterium acnes and inflammation	[63]
Mangosteen	Garciniacam bogia	Mangosteen extract (α-mangosteen)	Reduces inflammation by inhibiting the proliferation of propionibacterium acnes and blocking the activation of the TAK1-NF-κB pathway	[64,65]
Teatree oil	Camelliaceae		Inhibits the growth of acne-associated bacteria (propionibacterium acnes and staphylococcus aureus) and reduces acne-induced inflammation, thereby reducing acne formation	[66]
Oreganoessential oil	Labiatae		Causes structural and functional damage to bacterial cell membranes and reduces the release of inflammatory factors such as TNF-α, IL-1β, and IL-6; and inhibits NADPH oxidase	[67]
Thyme essential oil	Labiatae		Disrupts acne-associated bacterial cell membranes, leading to the release of their cytoplasmic components and inhibiting inflammation	[68]
Rosemaryessential oil	Labiatae		Inhibits lipid peroxidation and the secretion and mRNA expression of pro-inflammatory cytokines IL-8, IL-1β and TNF-α in propionibacterium acnes-stimulated monocyte THP-1 cells	[69,70]

Table 3　Optical therapy for acne treatment and its mechanism of action. PDT: Photodynamic therapy; ALA: 5-Aminolevulinic acid; NR4A1: Nuclear receptor subfamily 4 group A member 1

Classification	Mechanism of action	Ref.
Blue light therapy	Blue light penetrates the skin and is absorbed by porphyrins produced by propionibacterium acnes. this absorption causes porphyrin photoexcitation, generating oxygen radicals that exert a bactericidal effect within the sebaceous glands	[72]
Red light therapy	Red light activates bacterial porphyrins and exhibits greater tissue penetration than blue light. it inhibits propionibacterium acnes growth and possesses anti-inflammatory properties	[73]
PDT	PDT often utilizes topical photosensitizers, such as ALA, to enhance efficacy. ALA-PDT inhibits the Akt signaling pathway, activating JunD. this subsequently induces *NR4A1* transcription, leading to lipogenesis inhibition	[74,75]

频 (multi-polar radiofrequency, Multi-RF)、射频微针 (micro needle radio frequency, MNRF) 和分数射频等类型。该疗法的热能效应可通过破坏过度活跃的皮脂腺以减少皮脂分泌, 同时通过高温抑制痤疮丙酸杆菌的活性, 并通过促进局部血液循环加速炎症介质清除, 从而减轻炎症[77]。此外, 射频能量产生的热刺激可诱导真皮层胶原蛋白合成, 促进皮肤修复和组织再生, 并降低表皮损伤所致的炎症后色素沉着和红斑[78]。

作为一种非剥脱性的治疗方式, 射频疗法具有术后恢复周期短的优势, 且在多种皮肤疾病的临床治疗中表现出极低的严重不良反应发生率。综上所述, 射频疗法凭借其独特的作用机制及安全高效的治疗特性, 有望成为痤疮治疗领域的创新选择[79]。

2.3.3　冷冻疗法　冷冻疗法通过低温作用降低组织温度, 减轻疼痛并抑制继发性损伤与炎症反应, 并促进伤口愈合[80]。其治疗痤疮机制主要是: ① 诱导痤疮丙酸杆菌细胞内/外冰晶形成, 破坏细胞结构与功能, 导致细菌灭亡[81]; ② 调节炎性因子表达 (降低 TNF-α、增加 IL-10 释放), 以缓解炎症[82]。

尽管冷冻疗法能迅速缓解症状, 但可能引发疼痛、暂时性红斑和色素沉着等不良反应[83], 因此该疗法需要在专业医生的指导下进行, 以确保治疗的安全性和有效性。

3　潜在的治疗前景

痤疮丙酸杆菌是寻常痤疮的关键病原体, 也是口服抗生素的主要靶标。然而临床应用中, 抗生素疗法面临双重挑战: 一方面存在诱发肠道菌群失调及致畸性等潜在风险; 另一方面, 体外研究证实该菌在毛囊内形成的生物膜结构会显著阻碍抗生素渗透, 因此提升药物对生物膜的穿透能力成为增强疗效的关键环

节[84]。针对皮肤给药屏障, 角质层 (主要由神经酰胺、游离脂肪酸和胆固醇等脂质构成) 不仅是机体抵御外界侵害和防止水分流失的物理屏障, 也是药物透皮吸收的主要障碍, 尤其对大分子质量药物的渗透具有显著阻滞作用[85]。基于此, 与内源性脂质结构相似的合成脂质载体系统, 因其可增强角质层黏附性与水合性, 已成为促进药物向表皮和真皮层渗透的首选策略[86]。

在透皮给药途径中, 药物吸收主要通过表皮途径和附属器途径 (毛囊、皮脂腺等) 实现。尽管表皮途径的局部药物递送研究更为广泛, 但针对痤疮这一毛囊皮脂腺单位慢性炎症性疾病, 毛囊结构展现出独特的治疗靶向优势: 一方面, 毛囊直接穿透富含脂质的角质层屏障, 为水溶性药物提供高效渗透通道; 另一方面, 深入真皮的毛囊显著增加了有效吸收表面积, 并可形成药物储库[87]。研究表明, 聚合物纳米载体系统可优先通过毛囊等附属器途径进入皮肤深层, 发挥缓释作用, 从而达到治疗痤疮的效果[88]。

因此, 针对目前痤疮药物治疗方法面临如药物在储存期间稳定性差、皮肤渗透性不足以及局部刺激性强等诸多问题[89]。新型药物递送系统通过提升药物稳定性、渗透性及耐受性, 实现可控释放, 有效突破传统治疗局限, 可以为痤疮治疗提供新方向[90]。

3.1 基于脂质载体药物递送系统

1965年, Bangham等首次报道了关于脂质体生物结构, 已成为代表性药物递送纳米载体。目前, 全球已有13款脂质体载药制剂获得临床批准并实现商业化应用, 另有多项改良型脂质体新药处于I～II期临床研究阶段[91]。为克服传统脂质体在透皮效率上的限制, 研究者开发了转移体和立方体等新型脂质载体系统。这些新型脂质系统通过改善药物在皮下组织的渗透性, 有效提高了透皮给药的生物利用度, 适用于局部及全身性治疗。新型脂质体载体类型如图2所示。

3.1.1 脂质体 脂质体是由磷脂、胆固醇及活性成分形成的超分子聚集体, 在水性环境中, 疏水性脂质尾部自我定向, 形成由亲脂性双层膜包围的水性核心组成的双层球形结构。这种两亲特性使脂质体成为不同极性分子的理想药物载体[92]。

Bhardwaj等[93]采用薄膜水化法制备他扎罗汀脂质体, 体外释放实验表明, 12 h后药物累积释放率达98.12%, 其抗菌活性显著优于市售制剂。体内实验进一步证实, 该脂质体制剂疗效显著优于传统市售制剂。目前, 除抗菌药物外, 外用视黄酸 (retinoic acid, RA) 是痤疮治疗的一线选择, 但局部RA递送常伴随皮肤刺激等不良反应。Tsai等[94]设计了负载蛋白酶K与视黄酸的阳离子脂质体作为痤疮的联合治疗体系。体外研究表明, 多功能脂质体对正常角质形成细胞无明显细胞毒性, 但能有效抑制痤疮皮肤中的角质形成细胞过度增殖。与负载RA的单一脂质体相比, 多功能脂质体显著改善了由RA可能引起的皮肤刺激性等问题。

3.1.2 固体脂质纳米粒子 固体脂质纳米粒子 (solid lipid nanoparticles, SLN) 是由生物相容性成分 (如生理脂质) 分散在表面活性剂水溶液或水中组成的亚微米胶体系统, 但在体内环境以固体形式存在[95]。SLN能有效保护负载的活性药物成分在恶劣的生物环境中免受化学降解, 并控制药物的释放速率, 从而减少重复性给药的需求[96]。与传统的脂质体相比, SLN具有低毒

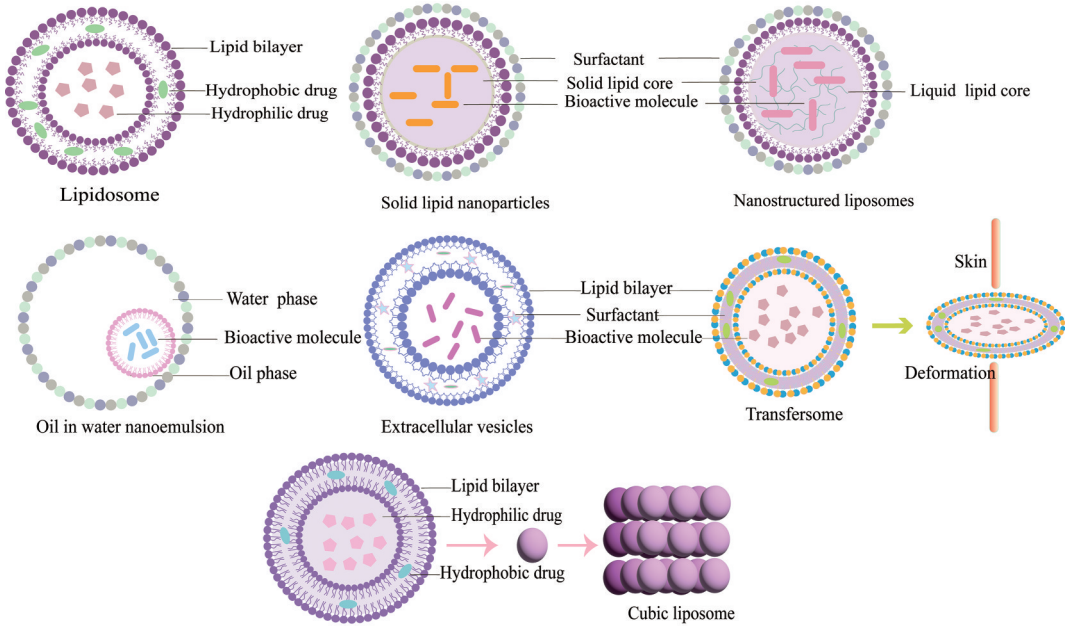


Figure 2 Liposome-based drug carriers

性、延长药物释放、提高药物溶解度以及促进药物在胃肠道的渗透和改善药物的跨细胞吸收等优势[97]。

Kelidari等[98]通过采用乳液–溶剂蒸发法结合超声制备螺内酯 (spironolactone, SP) 固体脂质纳米粒 (SP-SLN)。体外皮肤渗透实验证实, SP-SLN的皮肤渗透性显著优于普通SP。因此, SLN可以显著提升SP的皮肤渗透性, 其双相释放模式可实现痤疮的高效靶向治疗, 表明SLN可作为痤疮局部治疗的高效载体。

AD作为临床常用的合成类视黄醇痤疮治疗药物, 在治疗过程中可能会出现干燥、脱皮、红斑和刺激等不良反应, 并且呈浓度依赖性[99], 进而影响患者的依从性和治疗效果, 且AD几乎不溶于水性介质。为了克服这些局限性, Rodrigues等[100]通过离子对策略构建了具有高包封率和稳定性的SLN-AD凝胶。与市售传统AD凝胶相比, SLN-AD凝胶具有可控的药物释放、表皮靶向性和更低的皮肤刺激性。SLN-AD凝胶的成功开发为痤疮治疗提供了一种更为有效且安全的选择, 进一步展示了SLN在药物递送系统中的广泛应用潜力。

3.1.3　纳米结构脂质载体　固体脂质纳米粒子 (SLN) 作为第一代脂质纳米载体, 其固体脂质形成了高度有序的晶体结构。然而, 这种结构导致药物包合空间有限, 导致载体载药能力下降, 并可能引发储存过程中的药物泄漏问题[101]。为了克服这些局限性, 纳米结构脂质载体 (nanostructured lipid carriers, NLC) 应运而生。NLC由分散在含有表面活性剂的水溶液中的固体和液体脂质的混合物组成, 这种脂质组合形成了有序度较低的脂质基质, 有效结合和保护生物活性化合物, 从而增加载药能力, 减小载体粒径, 并避免在储存过程中生物活性化合物释放的风险[102,103]。

姜黄素是从姜黄根茎中提取的主要酚类生物活性物质, 具有抗菌、抗肿瘤、抗氧化、抗糖尿病等多种药理作用, 同时已被用于治疗皮肤老化、感染、痤疮、皮肤炎症和皮肤癌等疾病[104]。由于其溶解度低、渗透性差和理化性质不稳定, 姜黄素的临床应用受到了限制。为了改善难溶性姜黄素对局部皮肤层的渗透, Rapalli等[105]采用热乳化后探针超声处理制备了姜黄素-NLC。体外研究显示, 与游离药物相比, 姜黄素-NLC表现出良好的控释效果。体内外药物释放和皮肤刺激性研究表明, 姜黄素在皮肤层中的渗透和滞留得到了显著改善, 使其可以安全应用于痤疮或其他局部皮肤感染的治疗。

3.1.4　纳米乳液　纳米乳液, 又称为超细乳液、亚微米乳液或微型乳液, 是借助表面活性剂等乳化剂将水性和油性两种不混溶液体混合后, 形成直径为20～500 nm的微小液滴, 这种乳液具有生物相容性和可生物降解性等特点[106]。此外, 纳米乳液不仅具备流体性质、高效渗透能力和高生物利用度, 还可以有效保护具有刺激性、挥发性及高分子量的分子, 使其在药物递送系统中成为一种极具应用前景的载体[107,108]。

Hosny等[109]开发了负载异维A酸 (isotretinoin, ITT) 的纳米乳液 (ITT-SNEDDS), 通过引入白藜芦醇以减少异维A酸肝毒性等不良反应。体内研究表明, 与其他异维A酸制剂相比, 这种新型纳米乳液具有优越的肝保护活性和较低的毒性, 可以作为痤疮治疗药物的递送载体选择。

3.1.5　细胞外囊泡　细胞外囊泡 (extracellular vesicles, EV) 是由脂质和其他成分组装而成的纳米级球形单层囊泡, 其中一些成分可以减少囊泡与非目标组织的非特异性作用, 从而提高其治疗效率[110]。根据其大小、性质、生物发生途径以及生物学功能, EV主要分为3种亚型: 微囊泡 (microvesicles, MV)、外泌体和凋亡体[111]。随着研究的进展, 其他亚型如外体和嗜酸体等也被发现[112]。尽管脂质体制剂在药物治疗递送方面具有优势, 但在将药物递送至靶器官方面仍然遇到许多生物障碍, 如网状内皮系统限制和触发先天免疫反应[113]。EV作为药物递送载体, 有望克服脂质体和其他合成药物递送系统相关问题。

RA, 又称维生素A酸, 是维生素A的衍生物, 已被证明可有效治疗轻度至中度痤疮。然而, 由于水溶性低、对光和热不稳定、口服生物利用度低、血浆清除率低等缺陷, 限制了其在临床上的利用[114]。囊泡的亲脂性使它们能够在水中掺入难溶性药物, 同时改善药物在皮肤中的渗透性能[115]。

Shamma等[116]采用薄膜水合技术合成了负载RA纳米囊泡, 将Span 60和Tween 20作为囊泡双层成分, 确保其安全性和有效性。临床研究表明, 负载视黄酸的纳米囊泡能够增强视黄酸通过角质层的渗透性, 在治疗痤疮等深层皮肤病方面, 相比传统治疗药物, 在皮肤安全性和患者依从性方面具有明显的优势。

3.1.6　转移体　为了克服脂质体在皮肤渗透方面的不足, 20世纪90年代, Cevc和Blume等设计了可变形囊泡—转移体 (transfersomes)。转移体由磷脂、表面活性剂、乙醇和水等关键成分组成, 具有弹性、超可变形和应激反应等特性[117]。在体温作用下, 皮肤表面水分蒸发形成渗透梯度, 促使药物从应用部位转移到目标区域。结合其超变形和弹性特性, 转移体能够穿透皮肤中的微小孔隙, 从而抵达真皮层并发挥作用[118]。转移体不仅可以经皮递送低分子量和高分子量药物, 还能容纳各种溶解度的药物分子, 保护封装药物免受代谢酶降解, 提高其稳定性, 但是在不损害其变形和弹性性

能的前提条件下, 将疏水性药物嵌入转移体存在一定的挑战性[119]。

维生素C在消除AD常规单一疗法相关的不良反应 (脱皮, 刺激等) 方面具有显著效果, 并已广泛用于抗衰老化妆品中。Vasanth等[120]开发了含有维生素C的AD负载转移体凝胶, 作为治疗寻常痤疮的联合疗法。与单一AD凝胶相比, 转移体凝胶不仅提高了疗效, 还改善了AD治疗的整体局限性, 同时具有更好的递送效果和抗炎作用。

克林霉素磷酸盐作为林可酰胺类抗生素, 被广泛用于寻常痤疮等皮肤病治疗。然而, 传统剂型存在皮肤刺激性和生物利用度低 (仅5%～8%有效) 等问题。为克服这些局限性, Abdellatif等[121]通过薄膜水合技术成功制备了克林霉素磷酸盐转移体。体外皮肤渗透实验结果表明, 该转移体在24 h内的药物累积释放率显著高于传统克林霉素磷酸盐制剂。此外, 在人类志愿者中进行的皮肤刺激性评估证实了该转移体制剂的无刺激性。综上所述, 该研究证明, 克林霉素磷酸盐转移体能够有效减少传统剂型相关的皮肤不良反应, 同时维持药物的安全性和治疗有效性。

3.1.7 立方体 立方体是由两亲性脂质和表面活性剂在具有立方晶体对称性的液晶相中自组装而产生的具有热力学稳定性质的连续立方液晶体系[122]。立方体连续重复和复杂的三维结构使其可以有效结合亲水性、亲脂性和两亲性成分, 并同时掩盖药物的刺激性气味[123]。与其他脂质纳米载体相比, 立方体不仅具有生物相容性、提高药物的稳定性和封装效率等特性[124], 还因其独特的液晶排列结构, 可以长时间提供药物的连续释放, 从而减少给药频率并提高患者的依从性[125]。

氨苯砜 (dapsone, DAP) 在生物药剂学分类系统 (biopharmaceutics classification system, BCS) 中被归为II类, 具有高渗透性和低溶解度特性。尽管在正常剂量下DAP耐受性良好, 但仍可能引发溶血和高铁血红蛋白血症等不良反应[126], 这限制了其临床使用。

Nithya等[127]通过对含有单油酸甘油酯和泊洛沙姆407的立方凝胶基质的水分散液进行超声处理, 成功制备负载有DAP的立方体, 体外皮肤渗透性研究发现, 氨苯砜立方体制剂的透皮率分别比市售制剂和对照溶液 (PBS缓冲液中DAP) 高1.28和1.58倍, 可能是与皮肤脂质相互作用形成了能够促进药物渗透的通道。

Khan等[128]通过乳化法并优化甘油单油酸酯和泊洛沙姆407的比例, 成功制备了红霉素立方体。体外释放实验结果表明, 红霉素立方体显著优于普通红霉素凝胶, 在24 h累积释放量更高, 并且36 h仍维持高释放水平。上述研究结果证实, 红霉素立方体可实现药物的局部持续释放, 为痤疮治疗与预防提供了一种有效的非侵入性给药策略。

3.2 基于聚合物载体药物递送系统

聚合物系统可分为天然聚合物 (如壳聚糖、纤维素) 和人工合成聚合物 (如环氧树脂), 这些系统可以根据物理和化学性能的要求设计成不同的结构和形态。由于其灵活性和可控性, 聚合物系统被认为是极具前景的药物递送系统之一。通过精准控制药物释放, 聚合物系统不仅可以提高患者的依从性, 还能降低毒性, 延长治疗效果[129]。聚合物类型的药物载体如图3所示。

3.2.1 微针 微针 (microneedles, MN) 是一种基于微米级针头阵列构建的新型透皮给药系统, 由聚合物、金属和生物材料等多种材料制成。该系统结合了皮下注射针的有效性和非侵入性贴剂的优势[130], 可以以无痛的方式穿过皮肤屏障, 在降低给药不适感的同时, 绕过生理屏障将治疗药物精准输送至靶位点, 显著提升药物生物利用度与患者依从性[131]。然而, 微针技术仍面临若干挑战: 敏感皮肤在受到刺激后可能导致过敏现象; 微针尖端在皮肤内断裂并长时间停留可能引起炎症反应等不良事件[132]。为了解决上述问题, 研究人员设计了可溶解微针[133]。

Zhang等[134]通过将聚离子液体 (poly ionic liquid, PIL) 与微针结合起来, 构建了负载水杨酸 (salicylic acid, SA) 的给药系统用于痤疮感染治疗。该微针体系可显著提高水杨酸的透皮效率, 强化治疗效果。体外试验表明, SA-PIL-MN贴剂结合了阳离子聚合物的抗菌特性和水杨酸阴离子的抗炎作用, 在治疗皮肤痤疮感染方面表现出独特的协同优势。

3.2.2 聚合物胶束 在水性介质中, 当两亲性嵌段共聚物 (由亲水链和疏水链组成) 的浓度超过临界胶束浓度 (critical micelle concentration, CMC) 和临界温度 (critical temperature, CMT) 时, 会自组装形成纳米级胶束结构, 即聚合物胶束[135]。这种胶束具有疏水核心和亲水外壳的独特纳米结构, 不仅能延长药物滞留时间, 还能通过减少药物与内源性物质的非特异性相互作用以及抑制光解、化学分解等降解过程, 最终有效提高药物的生物利用度[136]。

Rao等[137]开发了负载DAP的混合胶束凝胶用于痤疮治疗。研究结果表明, 与游离DAP相比, 该混合胶束凝胶显著提高了DAP的溶解度, 并表现出高释放性、高渗透率和良好的安全性, 有望成为痤疮治疗的潜在新型疗法。

Dahmana等[138]利用可生物降解共聚物成功制备了负载SP的聚合物胶束。为评估其皮脂腺靶向递送能力, 研究者比较了含皮脂腺与不含皮脂腺皮肤活检

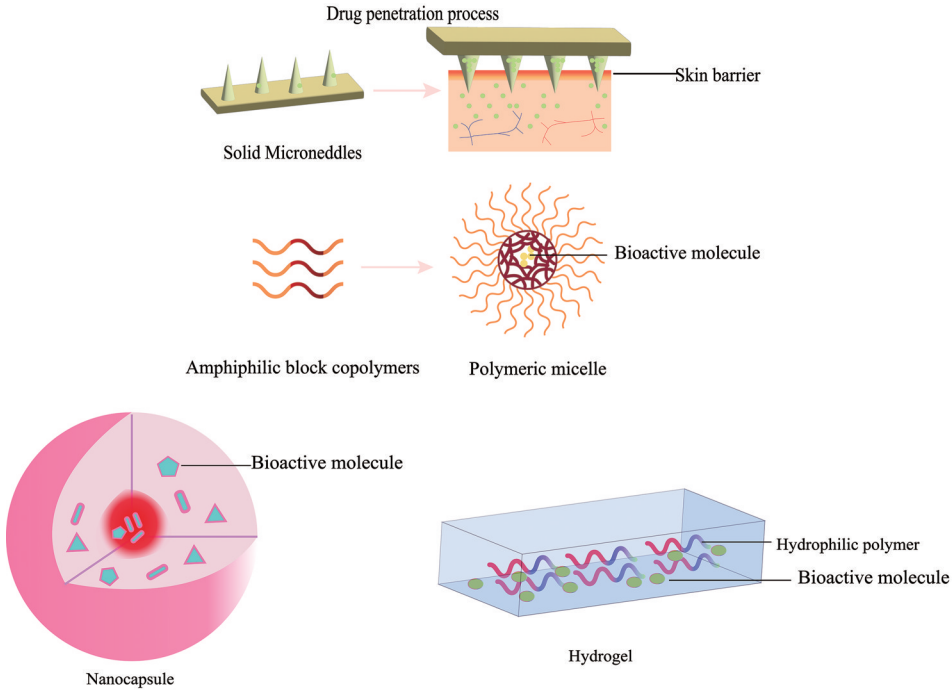


Figure 3　Polymer-based drug carriers

组织中的SP含量。结果显示, 含皮脂腺活检组织中的SP递送量较不含皮脂腺组织显著高出5倍。这表明该聚合物胶束不仅能作为SP的有效纳米载体, 更能实现对皮脂腺的选择性靶向, 为痤疮治疗提供了一种新途径。

3.2.3　纳米胶囊　纳米胶囊 (nanocapsules, NCs) 是一种球形微观结构, 其核心空腔可以包裹药物并由外壳保护。由于具备高载药能力、粒径分布可调、制备工艺简单及储存稳定性高等特点, 纳米胶囊在生物医药、食品等领域展现出广泛的应用前景[139]。

壳聚糖 (chitosan, Ch) 作为仅次于纤维素的天然多糖, 来源于甲壳类动物和真菌细胞壁, 兼具生物相容性和抗菌活性[140]。da Silva 等[141]通过将茶树油 (tea tree oil, TTO) 负载于壳聚糖–聚己内酯核壳纳米胶囊 (NC-TTO-Ch), 成功应用于局部痤疮治疗。研究表明: 与单纯TTO纳米胶囊相比, NC-TTO-Ch对痤疮丙酸杆菌的抑制活性显著增强。这种增效作用可能是TTO和Ch的协同效应, 既能提高治疗效果, 又可有效降低细菌耐药性风险。

Ivanova等[142]利用具有高度亲脂性与生物降解的玉米醇溶蛋白, 结合丙二醇, 通过自组装技术制备了负载牛至精油 (essential oil, EO) 的纳米胶囊 (NCs)。体外试验显示, 在人体皮肤细胞安全浓度范围内, 该EO-NCs可显著促进EO的透皮渗透, 使其能有效递送并富集于痤疮丙酸杆菌定植的炎症区域。同时, EO-NCs展现出清除活性氧的能力, 进而保护皮肤细胞免受氧化损伤。与传统抗痤疮产品相比, 含EO-NCs的配方在增强皮肤渗透性和抗菌功效方面更具优势, 并有望缓解抗生素耐药性 (antimicrobial resistance, AMR) 的选择压力。

3.2.4　水凝胶　水凝胶是由亲水性聚合物通过物理或化学方法交联形成的三维网络结构, 其释放机制涵盖扩散、溶胀及环境响应性等多重模式。该类材料能够长时间维持活性药物成分浓度, 有效延长药物在给药部位的滞留时间, 促进皮肤水合作用, 从而加速透皮吸收, 同时实现多药共同递送[143]。

Zeng等[144]采用热交联方法, 将甘草酸 (glycyrrhizic acid, GA) 与隐丹参酮–肽缀合物 (cryptotanshinone-peptide conjugate, CTS-G-GLU, CU) 共组装, 成功制备了CU-GA水凝胶。皮肤刺激性评估表明, 该水凝胶具备优异的透皮渗透性和无刺激性。更重要的是, 两种活性分子的结合在抑制NF-κB通路方面表现出显著的协同效应, 从而最大化地发挥了抗炎与抗菌活性, 为痤疮治疗提供了一种新策略。

此外, Tomić 等[145]开发的壬二酸 (azelaic acid, AZA) 纳米 (AZA-NC) 水凝胶相比传统AZA乳膏, 能够显著减少痤疮病变数量, 且安全性更高。针对AZA在临床应用中可能引发的瘙痒、红斑等不良反应问题, Bisht等[146]进一步设计含茶树精油的壬二酸复合水凝胶, 体内研究证实该体系生物耐受性更优、抗痤疮活性更强, 为寻常痤疮的局部治疗提供一种高效安全的药物递送系统。

3.2.5 乳凝胶 乳凝胶作为一种新型药物递送载体，由分散在连续相中的乳液和形成三维网络结构的凝胶结合而形成的复合材料，有效整合了两者的优势特性[147]。乳液可以保护药物免受酶降解和水解的影响，并改善渗透性和延长药物作用时间；凝胶则提高了黏度和铺展性，降低了表面张力，从而提高了热力学稳定性[148]。

在透皮给药领域，乳凝胶展现出多重技术优势。与软膏、贴剂等传统剂型相比，乳凝胶具有便捷清除、易于涂展、无油腻感、半透明外观及其保质期较长等特点，显著提高了患者依从性[149]。

Malavi 等[150]制备了负载维甲酸 (tretinoin, TRT) 的外用乳凝胶制剂。该 TRT 乳凝胶表现出良好的延展性，抗痤疮活性与市售 TRT 凝胶相当，且具有显著的抗炎活性，同时也表现出更高的安全性和稳定性。

3.3 其他类型药物载体药物递送系统

当前研究人员正致力于开发新型药物载体 (图 4)，在脂质体及聚合物载体基础上进一步通过提高药物稳定性、实现精准靶向递送及突破生物屏障等策略，为痤疮的治疗提供更有效的治疗方案。

3.3.1 金属有机框架 金属有机框架 (metal organic framework, MOF) 是一种以无机金属离子/团簇为节点、有机配体作为支柱，通过自组装而形成的多孔配位聚合物 (porous coordination polymer, PCP)，其结构具有高热稳定性和机械稳定性[151]。部分 MOF 复合物还具有抗菌和自清洁特性[152]。如在特定刺激下 (如降低 pH 值和超声)，MOF 能够产生活性氧，通过诱导细菌细胞损伤与功能失活实现抑菌效果[153]。

Xiang 等[154]通过将复合 MOF (ZnTCPP@ZnO) 装载到透明质酸钠合成的微针中。研究表明，该超声反应微针贴片不仅具有优异的生物安全性，还能够抑制痤疮相关因子表达并促进皮肤修复等，验证了 MOF 在生物医学领域的潜力。

Taherzade 等[155]开发了一种适用于皮肤给药的复合贴剂。该贴剂基于 MOF 材料，其孔道内共负载了抗炎药物烟酰胺和抗生素 AZA 药物，并进一步与聚乙烯醇 (polyvinyl alcohol, PVA) 聚合物复合制备得到 PVA-MOF 复合皮肤贴剂。该 PVA-MOF 复合贴剂表现出良好的生物相容性和较高的药物载量。体外释放研究表明，两种药物在 24 h 内可实现近乎完全的释放，符合皮肤给药的时效需求。药物释放动力学研究表明，MOF 孔道结构可有效调控药物释放行为，促进药物渗透至皮肤活性靶部位。体外皮肤渗透实验结果证实，该贴剂递送至皮肤各层药物总量，均达到或优于相应市售制剂的水平。

3.3.2 自乳化药物递送系统 自乳化药物递送系统 (self-emulsifying drug delivery system, SEDDS) 是由油相、表面活性剂、助表面活性剂和药物组成的各向同性混合物。当与胃肠液等水性介质接触时，SEDDS 在胃肠道蠕动作用下可自发形成水包油纳米乳液[156]。其吸收机制主要通过淋巴途径转运，从而有效规避肝脏首过效应。相较于传统乳液，SEDDS 因不含水相而形成均相体系，展现出更优的物理稳定性。同时，该系统具有能够降低给药频率、提高系统载药量以及剂型选择灵活等特性[157]，成为难溶性药物递送的重要策略。

与其他纳米递送系统 (如脂质体) 相比，SEDDS 通常含有更高浓度的表面活性剂，在一定程度上可以提高药物吸收速率，但也会引发胃肠道刺激及潜在毒性[158]。Eid 等[159]采用自纳米乳化技术制备 BPO 纳米乳液，实验表明该制剂比市售药具有更高的药物释放速率和抗菌活性，并显著减少药物不良反应。

3.3.3 介孔二氧化硅纳米颗粒 介孔二氧化硅纳米颗粒 (mesoporous silica nanoparticles, MSN) 是一种具有规则孔道结构的无机纳米材料，其孔径范围在 2～50 nm

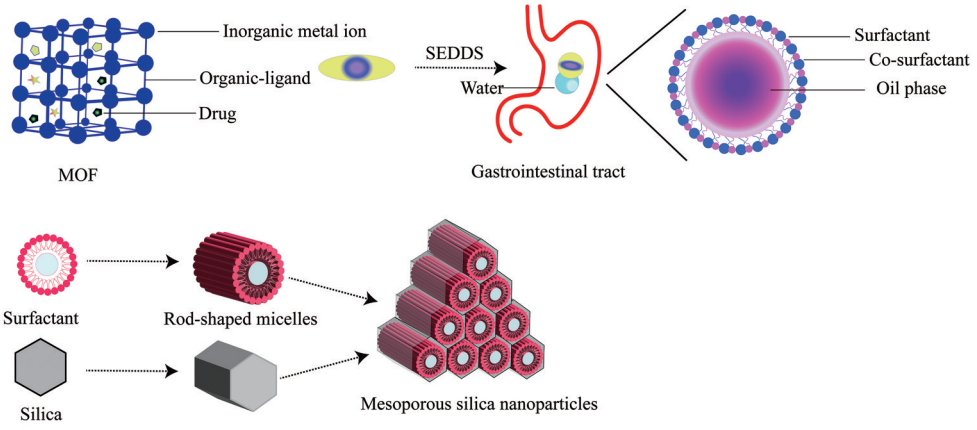


Figure 4 Other types of drug carriers. MOF: Metal organic framework; SEDDS: Self-emulsifying drug delivery system

之间[160]。作为药物递送系统, MSN的显著优势在于其表面可修饰性, 可以通过物理改性和化学改性等方式实现功能化修饰[161], 并结合光、pH等刺激响应分子实现空间和时间上的可控释放, 从而降低全身毒性[162]。然而, MSN的临床应用仍面临较大挑战: 其一, 制备过程中难以实现纳米颗粒的尺寸均一性; 其二, 长期生物安全性数据尚不完善[163]。

近期突破性研究显示, Ain等[164]开发了负载甘草多糖 (glycyrrhiza glabra polysaccharide, GGP) 的介孔二氧化硅纳米递药系统, 用于局部痤疮治疗。研究表明, MSN-NH_2-GGP@PDA通过阻断痤疮丙酸杆菌激活的TLR2-MAPK和NF-κB信号通路, 来调控炎症反应, 从而有效治疗痤疮。

3.3.4　深共熔溶剂　深共熔溶剂 (deep eutectic solvent, DES) 是由氢键受体 (hydrogen-bond acceptor, HBA) 和氢键供体 (hydrogen-bond donor, HBD) 按一定摩尔比相互作用形成的低熔点混合物[165], 近年来在透皮给药领域展现出显著的应用价值。研究表明, DES不仅能增强药物透皮渗透效率, 其细胞毒性较乙醇等传统化学促渗剂降低30%～50%, 有效缓解皮肤刺激问题[166]。其中, 胆碱–香叶酸盐DES (choline and geranic acid, CAGE) 因独特的双功能和安全性成为研究热点: 其分子结构中的季铵盐基团通过破坏角质层紧密结构促进药物旁细胞转运, 而香叶酸衍生物则增强上皮细胞膜通透性[167,168]。实验证实, 在不依赖外源促渗剂条件下, CAGE可使牛血清白蛋白、胰岛素等大分子药物的透皮渗透率较50%化学促渗剂体系提高2.3～3.8倍[169], 且在角质形成细胞或小鼠模型中均未表现出显著毒性。这种优异的生物相容性与促渗能力的平衡, 使得CAGE成为首个进入人体临床试验的DES药物递送系统[170]。

值得注意的是, Luhaibi等[171]基于胆碱类DES开发的一种壬二酸局部递送系统在痤疮治疗中展现出良好效果。研究结果表明, DES作为壬二酸的增溶和递送载体, 在痤疮治疗领域具有显著的应用潜力。进一步研究发现, 纯胆碱–香叶酸盐DES制剂能够深入真皮层, 对定植于皮肤深层的痤疮丙酸杆菌产生有效抑制作用, 这一发现为开发新型痤疮治疗策略提供了重要依据[172]。

3.4　临床转化现状

近年来, 纳米递送载体技术 (如脂质体、聚合物纳米粒及微针) 在痤疮治疗领域展现出显著的转化潜力。传统疗法中, 局部类视黄醇 (如维A酸) 虽能有效改善痤疮, 但其引发的灼热、脱皮、干燥等局部不良反应常导致患者依从性下降。新型载体通过改善药物溶解度、增强皮肤渗透性及靶向递送特性, 能够优化药物吸收效率并降低刺激性。例如, II期临床试验 (NCT04080869)[173]采用脂质体封装技术, 对比研究了视黄醇棕榈酸酯囊泡制剂与传统制剂的耐受性差异, 通过载体介导的控制释放机制显著降低皮肤刺激, 验证了载体技术对疗效和耐受性的双重提升。可实现药物吸收效率的优化及皮肤刺激性的显著降低。

然而, 纳米药物的临床转化仍面临三大核心挑战: ① 靶向递送效率欠佳, 部分药物无法精准到达毛囊或皮脂腺靶点; ② 长期生物安全性存疑, 载体材料在皮肤内的代谢途径尚未完全明确; ③ 潜在系统毒性风险, 纳米颗粒可能通过血液循环引发全身性毒副作用。

为推进该领域发展, 建议重点开展以下研究方向: ① 完善药物载体材料的药效动力学机制研究; ② 系统解析纳米材料的结构–功能关系及其代谢途径; ③ 加强跨学科协同创新, 建立标准化评价体系[174]。

4　结语与展望

随着现代生活水平的提高以及环境因素的影响, 青少年痤疮的发病率持续处于高位。为减少痤疮的发病率, 目前多采取综合性措施进行治疗和预防, 如: ① 调整饮食结构, 避免高糖和高脂食物的摄入, 以控制皮脂分泌并降低痤疮风险; ② 采用科学有效的压力管理和改善睡眠策略, 以维持体内激素水平的稳定, 从而缓解痤疮症状; ③ 进行相应药物治疗, 以对痤疮进行根源性干预。然而, 痤疮药物治疗仍面临多种挑战。局部用药存在皮肤屏障穿透力弱、疗效波动及局部刺激等问题; 系统性药物虽然能有效减轻症状, 但长期使用可能导致抗生素耐药等, 从而导致某些患者的治疗效果不佳。

新型药物递送系统在解决这些问题方面展现了巨大潜力。如, 纳米载体可以有效携带药物穿透皮肤屏障, 将药物输送至皮脂腺或毛囊, 从而有效抑制痤疮的发生; 微针技术则能通过微创方式实现药物的深层传递, 显著提升药物的稳定性和生物利用度。这些技术为痤疮药物的递送带来了革命性的进展, 但其临床开发仍面临诸多挑战。首先, 相关技术的复杂性和高成本使得这些系统的临床应用受到限制; 其次, 许多药物递送载体仍处于实验阶段, 需要更多的临床试验来验证其安全性和有效性。此外, 个体差异也是影响药物递送效果的重要因素, 需要进一步研究以优化个性化治疗方案。

随着科技的发展和临床研究的深入, 加强对药物递送系统的研究显得尤为重要。通过克服成本、临床方面应用和个体差异等挑战, 新型药物递送系统有望在实际治疗中得到更广泛的应用, 从而更好地满足患

者的个性化需求, 推动精准医疗的发展。

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利益冲突: 本文所有作者声明不存在利益冲突关系。

References

[1] Eichenfield DZ, Sprague J, Eichenfield LF. Management of acne vulgaris: a review [J]. JAMA, 2021, 326: 2055-2067.

[2] Vasam M, Korutla S, Bohara RA. Acne vulgaris: a review of the pathophysiology, treatment, and recent nanotechnology based advances [J]. Biochem Biophys Rep, 2023, 36: 101578.

[3] Balić A, Vlašić D, Žužul K, et al. Omega-3 versus omega-6 polyunsaturated fatty acids in the prevention and treatment of inflammatory skin diseases [J]. Int J Mol Sci, 2020, 21: 741.

[4] Almutawa YM, Bhattarai E, AlGhareeb M, et al. Evaluation of psychiatric comorbidities and quality of life as well as brain-derived neurotrophic factor (BDNF) concentrations among patients suffering from acne vulgaris: a systematic review and meta-analysis [J]. Cureus, 2023, 15: e33357.

[5] Darji K, Varade R, West D, et al. Psychosocial impact of postinflammatory hyperpigmentation in patients with acne vulgaris [J]. J Clin Aesthet Dermatol, 2017, 10: 18.

[6] Ogé LK, Broussard A, Marshall MD. Acne vulgaris: diagnosis and treatment [J]. Am Fam Physician, 2019, 100: 475-484.

[7] Carmina E, Dreno B, Lucky WA, et al. Female adult acne and androgen excess: a report from the multidisciplinary androgen excess and PCOS committee [J]. J Endocr Soc, 2022, 6: bvac003.

[8] Peng X, Li X, Xie B, et al. Gout therapeutics and drug delivery [J]. J Control Release, 2023, 362: 728-754.

[9] Yang J, Yang H, Xu A, et al. A review of advancement on influencing factors of acne: an emphasis on environment characteristics [J]. Front Public Health, 2020, 8: 450.

[10] Gollnick HP. From new findings in acne pathogenesis to new approaches in treatment [J]. J Eur Acad Dermatol Venereol, 2015, 29(Suppl 5): 1-7.

[11] Clayton RW, Göbel K, Niessen CM, et al. Homeostasis of the sebaceous gland and mechanisms of acne pathogenesis [J]. Br J Dermatol, 2019, 181: 677-690.

[12] Cruz S, Vecerek N, Elbuluk N. Targeting inflammation in acne: current treatments and future prospects [J]. Am J Clin Dermatol, 2023, 24: 681-694.

[13] ShamLoul G, Khachemoune A. An updated review of the sebaceous gland and its role in health and diseases Part 1: Embryology, evolution, structure, and function of sebaceous glands [J]. Dermatol Ther, 2021, 34: e14695.

[14] Li L, Zhang J, Cheng W, et al. Saponins of Paris polyphylla for the improvement of acne: anti-inflammatory, antibacterial, antioxidant and immunomodulatory effects [J]. Molecules, 2024, 29: 1793.

[15] O′Neill AM, Gallo RL. Host-microbiome interactions and recent progress into understanding the biology of acne vulgaris [J]. Microbiome, 2018, 6: 177.

[16] Kurokawa I, Nakase K. Recent advances in understanding and managing acne [J]. F1000Res, 2020, 9: F1000 Faculty Rev-792.

[17] Turan Ç, Coşansu NC, Yüksekal G. The SII reflects inflammation in acne vulgaris, but fails to determine categorical severity [J]. J Cosmet Dermatol, 2022, 21: 6385-6392.

[18] Tax G, Urbán E, Palotás Z, et al. Propionic acid produced by propionibacterium acnes strains contri-butes to their pathogenicity [J]. Acta Derm Venereol, 2016, 96: 43-49.

[19] Lomholt HB, Scholz CFP, Brüggemann H, et al. A comparative study of cutibacterium (propionibacterium) acnes clones from acne patients and healthy controls [J]. Anaerobe, 2017, 47: 57-63.

[20] Kim HJ, Kim YH. Exploring acne treatments: from pathophysiological mechanisms to emerging therapies [J]. Int J Mol Sci, 2024, 25: 5302.

[21] Dréno B. What is new in the pathophysiology of acne, an overview [J]. J Eur Acad Dermatol Venereol, 2017, 31: 8-12.

[22] Layton AM, Ravenscroft J. Adolescent acne vulgaris: current and emerging treatments [J]. Lancet Child Adolesc Health, 2023, 7: 136-144.

[23] Teder-Laving M, Kals M, Reigo A, et al. Genome-wide meta-analysis identifies novel loci conferring risk of acne vulgaris [J]. Eur J Hum Genet, 2024, 32: 1136-1143.

[24] Heng AHS, Say YH, Sio YY, et al. Gene variants associated with acne vulgaris presentation and severity: a systematic review and meta-analysis [J]. BMC Med Genomics, 2021, 14: 103.

[25] Conforti C, Agozzino M, Emendato G, et al. Acne and diet: a review [J]. Int J Dermatol, 2022, 61: 930-934.

[26] Du Z, Iyyanki T, Lessard S, et al. Genome-wide association study analysis of disease severity in acne reveals novel biological insights [J]. medRxiv, 2023. DOI: 10.1101/2023.11.13.23298473.

[27] Liu Y, Zhen N, Liao D, et al. Application of bacteriophage *φ*PaP11-13 attenuates rat cutibacterium acnes infection lesions by promoting keratinocytes apoptosis *via* inhibiting PI3K/Akt pathway [J]. Microbiol Spectr, 2024, 12: e02838-23.

[28] Ilari S, Nucera S, Morabito L, et al. A systematic review of the effect of polyphenols on alterations of the intestinal microbiota and shared bacterial profiles between metabolic syndrome and acne [J]. Nutrients, 2024, 16: 3591.

[29] Radaschin DS, Iancu AV, Ionescu AM, et al. Comparative analysis of the cutaneous microbiome in psoriasis patients and healthy individuals-insights into microbial dysbiosis: final results [J]. Int J Mol Sci, 2024, 25: 10583.

[30] Searle T, Ali FR, Carolides S, et al. Rosacea and the gastrointestinal system [J]. Australas J Dermatol, 2020, 61: 307-311.

[31] Wang Y, Yao T, Lin Y, et al. Association between gut microbiota

and pan-dermatological diseases: a bidirectional mendelian randomization research [J]. Front Cell Infect Microbiol, 2024, 14: 1327083.

[32] Fox L, Csongradi C, Aucamp M, et al. Treatment modalities for acne [J]. Molecules, 2016, 21: 1063.

[33] Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris [J]. J Am Acad Dermatol, 2016, 74: 945-973.

[34] Paichitrojjana A, Paichitrojjana A. Oral isotretinoin and its uses in dermatology: a review [J]. Drug Des Devel Ther, 2023, 17: 2573-2591.

[35] Stein GL, Baldwin H, Kircik LH, et al. Efficacy and safety of a fixed-dose clindamycin phosphate 1.2 % , benzoyl peroxide 3.1 %, and adapalene 0.1 5% gel for moderate-to-severe acne: a randomized phase II study of the first triple-combination drug [J]. Am J Clin Dermatol, 2022, 23: 93-104.

[36] Kim SY, Ochsendorf FR. New developments in acne treatment: role of combination adapalene – benzoylperoxide [J]. Ther Clin Risk Manag, 2016, 12: 1497-1506.

[37] Zip C. Tazarotene lotion 0. 045% for the treatment of acne [J]. Skin Therapy Lett, 2022, 27: 1-3.

[38] Han JJ, Faletsky A, Barbieri JS, et al. New acne therapies and updates on use of spironolactone and isotretinoin: a narrative review [J]. Dermatol Ther, 2021, 11: 79-91.

[39] Sayyafan MS, Ramzi M, Salmanpour R. Clinical assessment of topical erythromycin gel with and without zinc acetate for treating mild-to-moderate acne vulgaris [J]. J Dermatolog Treat, 2020, 31: 730-733.

[40] Mohammadi S, Pardakhty A, Khalili M, et al. Niosomal benzoyl peroxide and clindamycin lotion *versus* niosomal clindamycin lotion in treatment of acne vulgaris: a randomized clinical trial [J]. Adv Pharm Bull, 2019, 9: 578.

[41] Wafae BGO, Barbieri JS. Innovations in acne [J]. Dermatol Clin, 2025, 43: 11-25.

[42] Auffret N, Claudel JP, Leccia MT, et al. Novel and emerging treatment options for acne vulgaris [J]. Eur J Dermatol, 2022, 32: 451-458.

[43] Forslund M, Melin J, Alesi S, et al. Different kinds of oral contraceptive pills in polycystic ovary syndrome: a systematic review and meta-analysis [J]. Eur J Endocrinol, 2023, 189: S1-S16.

[44] Curtis KM. US medical eligibility criteria for contraceptive use, 2016 [J]. MMWR Recomm Rep, 2016, 65: 1-103.

[45] Dhurat R, Shukla D, Lim RK, et al. Spironolactone in adolescent acne vulgaris [J]. Dermatol Ther, 2021, 34: e14680.

[46] Hebert A, Thiboutot D, Gold LS, et al. Efficacy and safety of topical clascoterone cream, 1%, for treatment in patients with facial acne: two phase 3 randomized clinical trials [J]. JAMA Dermatol, 2020, 156: 621-630.

[47] Kalabalik-Hoganson J, Frey KM, Ozdener-Poyraz AE, et al. Clascoterone: a novel topical androgen receptor inhibitor for the treatment of acne [J]. Ann Pharmacother, 2021, 55: 1290-1296.

[48] Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris [J]. J Am Acad Dermatol, 2024, 90: 1006.e1-1006.e30.

[49] Thiboutot DM, Dréno B, Abanmi A, et al. Practical management of acne for clinicians: an international consensus from the global alliance to improve outcomes in acne [J]. J Am Acad Dermatol, 2018, 78: S1-S23.e1.

[50] Dallo M, Patel K, Hebert AA. Topical antibiotic treatment in dermatology [J]. Antibiotics (Basel), 2023, 12: 188.

[51] Feng X, Shang J, Gu Z, et al. Azelaic acid: mechanisms of action and clinical applications [J]. Clin Cosmet Investig Dermatol, 2024, 17: 2359-2371.

[52] Calvisi L. Efficacy of a combined chemical peel and topical salicylic acid - based gel combination in the treatment of active acne [J]. J Cosmet Dermatol, 2021, 20: 2-6.

[53] Awad SM, Tawfik YM, El - Mokhtar MA, et al. Activation of Janus kinase signaling pathway in acne lesions [J]. Dermatol Ther, 2021, 34: e14563.

[54] Ballanger F, Auffret N, Leccia MT, et al. Acneiform lesions but not acne after treatment with janus kinase inhibitors: diagnosis and management of janus kinase-acne [J]. Acta Derm Venereol, 2023, 103: adv11657.

[55] Sun Y, Man X, Xuan X, et al. Tofacitinib for the treatment of erythematotelangiectatic and papulopustular rosacea: a retrospective case series [J]. Dermatol Ther, 2022, 35: e15848.

[56] Peyravian N, Deo S, Daunert S, et al. The anti-inflammatory effects of cannabidiol (CBD) on acne [J]. J Inflamm Res, 2022, 15: 2795-2801.

[57] Hoffmann J, Gendrisch F, Schempp CM, et al. New herbal biomedicines for the topical treatment of dermatological disorders [J]. Biomedicines, 2020, 8: 27.

[58] Mansoor K, Aburjai T, Al-Mamoori F, et al. Plants with cosmetic uses [J]. Phytother Res, 2023, 37: 5755-5768.

[59] Goyal A, Sharma A, Kaur J, et al. Bioactive-based cosmeceuticals: an update on emerging trends [J]. Molecules, 2022, 27: 828.

[60] Ansong JA, Asante E, Johnson R, et al. Formulation and evaluation of herbal - based antiacne gel preparations [J]. Biomed Res Int, 2023, 2023: 7838299.

[61] Puyana C, Chandan N, Tsoukas M. Applications of bakuchiol in dermatology: systematic review of the literature [J]. J Cosmet Dermatol, 2022, 21: 6636-6643.

[62] Park KS. Pharmacological effects of Centella asiatica on skin diseases: evidence and possible mechanisms [J]. Evid Based Complement Alternat Med, 2021, 2021: 5462633.

[63] Qadir A, Ullah SNMN, Gupta DK, et al. Phytoconstituents - loaded nanomedicines for the management of acne [J]. J Cosmet Dermatol, 2022, 21: 3240-3255.

[64] Yahyazadeh R, Rahimi VB, Yahyazadeh A, et al. A mechanistic review on protective effects of mangosteen and its xanthones

against hazardous materials and toxins [J]. Curr Neuropharmacol, 2024, 22: 1986-20152.

[65] Zou WS, Yin P, Shi YR, et al. A novel biological role of α-mangostin *via* TAK1-NF-κB pathway against inflammatory [J]. Inflammation, 2019, 42: 103-112.

[66] Nurzyńska-Wierdak R, Pietrasik D, Walasek-Janusz M. Essential oils in the treatment of various types of acne—a review [J]. Plants (Basel), 2022, 12: 90.

[67] Bora L, Avram S, Pavel IZ, et al. An up-to-date review regarding cutaneous benefits of Origanum vulgare L. essential oil [J]. Antibiotics (Basel), 2022, 11: 549.

[68] Abdelhamed FM, Abdeltawab NF, ElRakaiby MT, et al. Antibacterial and anti-inflammatory activities of Thymus vulgaris essential oil nanoemulsion on acne vulgaris [J]. Microorganisms, 2022, 10: 1874.

[69] Bungau AF, Radu AF, Bungau SG, et al. Emerging insights into the applicability of essential oils in the management of acne vulgaris [J]. Molecules, 2023, 28: 6395.

[70] Kiokias S, Proestos C, Oreopoulou V. Phenolic acids of plant origin-a review on their antioxidant activity *in vitro* (o/w emulsion systems) along with their *in vivo* health biochemical properties [J]. Foods, 2020, 9: 534.

[71] Austin E, Geisler AN, Nguyen J, et al. Visible light. Part I: Properties and cutaneous effects of visible light [J]. J Am Acad Dermatol, 2021, 84: 1219-1231.

[72] Diogo MLG, Campos TM, Fonseca ESR, et al. Effect of blue light on acne vulgaris: a systematic review [J]. Sensors (Basel), 2021, 21: 6943.

[73] Kharazi L, Dadkhahfar S, Rahimi H, et al. The efficacy of blue light versus the combination of blue and red light therapy in the treatment of acne vulgaris [J]. Photodermatol Photoimmunol Photomed, 2021, 37: 564-566.

[74] Wang P, Wang B, Zhang L, et al. Clinical practice guidelines for 5-aminolevulinic acid photodynamic therapy for acne vulgaris in China [J]. Photodiagn Photodyn Ther, 2023, 41: 103261.

[75] Wu Y, Liu X, Zhang L, et al. 5-Aminolevulinic acid photodynamic therapy modulates lipid production by akt/jund-mediated NR4A1 activation in the treatment of acne vulgaris [J]. J Invest Dermatol, 2025. DOI: 10.1016/j.jid.2025.01.018.

[76] Toledano-Macías E, Martínez-Pascual MA, Hernández-Bule ML. Electric currents of 448 kHz upregulate anti-senescence pathways in human dermal fibroblasts [J]. J Cosmet Dermatol, 2024, 23: 687-700.

[77] Zhang X, Zhou M, Liu Y, et al. Recent advances in the treatment of acne using radiofrequency techniques [J]. Lasers Med Sci, 2024, 39: 92.

[78] Salameh F, Shumaker PR, Goodman GJ, et al. Energy-based devices for the treatment of acne scars: 2022 international consensus recommendations [J]. Lasers Surg Med, 2022, 54: 10-26.

[79] Ekelem C, Thomas L, Van Hal M, et al. Radiofrequency therapy and noncosmetic cutaneous conditions [J]. Dermatol Surg, 2019, 45: 908-930.

[80] Racinais S, Dablainville V, Rousse Y, et al. Cryotherapy for treating soft tissue injuries in sport medicine: a critical review [J]. Br J Sports Med, 2024, 58: 1215-1223.

[81] Atashzar MR, Hamblin MR, Maleki F, et al. Tumor cryotherapy using ice-producing bacteria [J]. Med Hypotheses, 2020, 144: 110101.

[82] Garcia C, Karri J, Zacharias NA, et al. Use of cryotherapy for managing chronic pain: an evidence-based narrative [J]. Pain Ther, 2021, 10: 81-100.

[83] Rho NK. Revisiting the role of local cryotherapy for acne treatment: a review and update [J]. J Clin Med, 2022, 12: 26.

[84] Zhang Y, Feng P, Yu J, et al. Ros-responsive microneedle patch for acne vulgaris treatment [J]. Adv Ther, 2018, 1: 1800035.

[85] Jeong WY, Kwon M, Choi HE, et al. Recent advances in transdermal drug delivery systems: a review [J]. Biomater Res, 2021, 25: 24.

[86] Dudhat S, Singh P, Pimple P. Insights of lipid vesicular and particulate carrier mediated approach for acne management [J]. Curr Drug Deliv, 2023, 20: 57-74.

[87] Lei Y, Jiang W, Peng C, et al. Advances in polymeric nanodelivery systems targeting hair follicles for the treatment of acne [J]. Drug Deliv, 2024, 31: 2372269.

[88] Kahraman E, Güngör S. Polymeric micellar nanocarriers of benzoyl peroxide as potential follicular targeting approach for acne treatment [J]. Colloids Surf B Biointerfaces, 2016, 146: 692-699.

[89] Green LJ, Lain E, Prunty T, et al. Enhancing topical pharmacotherapy for acne and rosacea: vehicle choices and outcomes [J]. J Clin Aesthet Dermatol, 2022, 15: 36.

[90] Verma S, Utreja P, Kumar L. Nanotechnological carriers for treatment of acne [J]. Recent Pat Antiinfect Drug Discov, 2018, 13: 105-126.

[91] Shahsavari S, Rad MB, Hajiaghajani A, et al. Magnetoresponsive liposomes applications in nanomedicine: a comprehensive review [J]. Biomed Pharmacother, 2024, 181: 117665.

[92] De Leo V, Maurelli AM, Giotta L, et al. Liposomes containing nanoparticles: preparation and applications [J]. Colloids Surf B Biointerfaces, 2022, 218: 112737.

[93] Bhardwaj A, Kori ML. Evaluation of tazarotene loaded topical liposomal gel for management of acne [J]. AJPER, 2018, 7: 105-114.

[94] Tsai MJ, Lin CY, Trousil J, et al. Proteinase K/retinoic acid-loaded cationic liposomes as multifunctional anti-acne therapy to disorganize biofilm and regulate keratinocyte proliferation [J]. Int J Nanomedicine, 2023, 18: 3879-3896.

[95] Sivadasan D, Ramakrishnan K, Mahendran J, et al. Solid lipid nanoparticles: applications and prospects in cancer treatment [J].

Int J Mol Sci, 2023, 24: 6199.

[96] Ganesan P, Narayanasamy D. Lipid nanoparticles: different preparation techniques, characterization, hurdles, and strategies for the production of solid lipid nanoparticles and nanostructured lipid carriers for oral drug delivery [J]. Sustain Chem Pharm, 2017, 6: 37-56.

[97] Salah E, Abouelfetouh MM, Pan Y, et al. Solid lipid nanoparticles for enhanced oral absorption: a review [J]. Colloids Surf B Biointerfaces, 2020, 196: 111305.

[98] Kelidari HR, Saeedi M, Akbari J, et al. Formulation optimization and *in vitro* skin penetration of spironolactone loaded solid lipid nanoparticles [J]. Colloids Surf B Biointerfaces, 2015, 128: 473-479.

[99] Sadick N, Pannu S, Abidi Z, et al. Topical treatments for photoaged skin [J]. J Drugs Dermatol, 2023, 22: 867-873.

[100] Rodrigues LBO, Lima FA, Alves CPB, et al. Ion pair strategy in solid lipid nanoparticles: a targeted approach to improve epidermal targeting with controlled adapalene release, resulting reduced skin irritation [J]. Pharm Res, 2020, 37: 148.

[101] Gomaa E, Fathi HA, Eissa NG, et al. Methods for preparation of nanostructured lipid carriers [J]. Methods, 2022, 199: 3-8.

[102] Gu L, Sun R, Wang W, et al. Nanostructured lipid carriers for the encapsulation of phloretin: preparation and *in vitro* characterization studies [J]. Chem Phys Lipids, 2022, 242: 105150.

[103] da Silva MG, de Godoi KRR, Gigante ML, et al. Developed and characterization of nanostructured lipid carriers containing food-grade interesterified lipid phase for food application [J]. Food Res Int, 2022, 155: 111119.

[104] Kouhpeikar H, Butler AE, Bamian F, et al. Curcumin as a therapeutic agent in leukemia [J]. J Cell Physiol, 2019, 234: 12404-12414.

[105] Rapalli VK, Kaul V, Waghule T, et al. Curcumin loaded nanostructured lipid carriers for enhanced skin retained topical delivery: optimization, scale-up, *in-vitro* characterization and assessment of *ex-vivo* skin deposition [J]. Eur J Pharm Sci, 2020, 152: 105438.

[106] Mushtaq A, Wani SM, Malik AR, et al. Recent insights into nanoemulsions: their preparation, properties and applications [J]. Food Chem X, 2023, 18: 100684.

[107] Rai VK, Mishra N, Yadav KS, et al. Nanoemulsion as pharmaceutical carrier for dermal and transdermal drug delivery: formulation development, stability issues, basic considerations and applications [J]. J Control Release, 2018, 270: 203-225.

[108] Ozogul Y, Karsli GT, Durmuş M, et al. Recent developments in industrial applications of nanoemulsions [J]. Adv Colloid Interface Sci, 2022, 304: 102685.

[109] Hosny KM, Alhakamy NA, Al Nahyah KS. The relevance of nanotechnology, hepato-protective agents in reducing the toxicity and augmenting the bioavailability of isotretinoin [J]. Drug Deliv, 2021, 28: 115-125.

[110] Herrmann IK, Wood MJA, Fuhrmann G. Extracellular vesicles as a next-generation drug delivery platform [J]. Nat Nanotechnol, 2021, 16: 748-759.

[111] Gupta D, Zickler AM, El Andaloussi S. Dosing extracellular vesicles [J]. Adv Drug Deliv Rev, 2021, 178: 113961.

[112] Gurunathan S, Kang MH, Qasim M, et al. Biogenesis, membrane trafficking, functions, and next generation nanotherapeutics medicine of extracellular vesicles [J]. Int J Nanomedicine, 2021, 16: 3357-3383.

[113] Elsharkasy OM, Nordin JZ, Hagey DW, et al. Extracellular vesicles as drug delivery systems: why and how? [J]. Adv Drug Deliv Rev, 2020, 159: 332-343.

[114] Na K, Liu K, Yu J, et al. A solvent-assisted active loading technology to prepare gambogic acid and all-trans retinoic acid co-encapsulated liposomes for synergistic anticancer therapy [J]. Drug Deliv Transl Res, 2020, 10: 146-158.

[115] Guillot AJ, Martínez-Navarrete M, Garrigues TM, et al. Skin drug delivery using lipid vesicles: a starting guideline for their development [J]. J Control Release, 2023, 355: 624-654.

[116] Shamma RN, Sayed S, Sabry NA, et al. Enhanced skin targeting of retinoic acid spanlastics: *in vitro* characterization and clinical evaluation in acne patients [J]. J Liposome Res, 2019, 29: 283-290.

[117] Phatale V, Vaiphei KK, Jha S, et al. Overcoming skin barriers through advanced transdermal drug delivery approaches [J]. J Control Release, 2022, 351: 361-380.

[118] Chen RP, Chavda VP, Patel AB, et al. Phytochemical delivery through transferosome (phytosome): an advanced transdermal drug delivery for complementary medicines [J]. Front Pharmacol, 2022, 13: 850862.

[119] Raj A, Dua K, Nair RS, et al. Transethosome: an ultra-deformable ethanolic vesicle for enhanced transdermal drug delivery [J]. Chem Phys Lipids, 2023, 255: 105315.

[120] Vasanth S, Dubey A, Gs R, et al. Development and investigation of vitamin C-enriched adapalene-loaded transfersome gel: a collegial approach for the treatment of acne vulgaris [J]. AAPS PharmSciTech, 2020, 21: 61.

[121] Abdellatif AA, Tawfeek HM. Transfersomal nanoparticles for enhanced transdermal delivery of clindamycin [J]. AAPS PharmSciTech, 2016, 17: 1067-1074.

[122] Umar H, Wahab HA, Gazzali AM, et al. Cubosomes: design, development, and tumor-targeted drug delivery applications [J]. Polymers (Basel), 2022, 14: 3118.

[123] Zaker H, Taymouri S, Mostafavi A. Formulation and physicochemical characterization of azithromycin-loaded cubosomes [J]. Res Pharm Sci, 2023, 18: 49-58.

[124] Nguyen TT, Nguyen TTD, Tran NM, et al. Lipid-based nanocarriers via nose-to-brain pathway for central nervous system disorders [J]. Neurochem Res, 2022, 47: 552-573.

[125] Palma AS, Casadei BR, Lotierzo MC, et al. A short review

on the applicability and use of cubosomes as nanocarriers [J]. Biophys Rev, 2023, 15: 553-567.

[126] Reunala T, Hervonen K, Salmi T. Dermatitis herpetiformis: an update on diagnosis and management [J]. Am J Clin Dermatol, 2021, 22: 329-338.

[127] Nithya R, Jerold P, Siram K. Cubosomes of dapsone enhanced permeation across the skin [J]. J Drug Deliv Sci Technol, 2018, 48: 75-81.

[128] Khan S, Jain P, Jain S, et al. Topical delivery of erythromycin through cubosomes for acne [J]. Pharm Nanotechnol, 2018, 6: 38-47.

[129] Marriott R, Spiridonova TI, Tverdokhlebov SI, et al. Using compartments to model drug delivery from biodegradable polymers [J]. J Pharm Sci, 2022, 111: 3096-3107.

[130] Liu TT, Chen K, Wang Q. Skin drug permeability and safety through a vibrating solid micro-needle system [J]. Drug Deliv Transl Res, 2018, 8: 1025-1033.

[131] Long L, Ji D, Hu C, et al. Microneedles for in situ tissue regeneration [J]. Mater Today Bio, 2023, 19: 100579.

[132] Waghule T, Singhvi G, Dubey SK, et al. Microneedles: a smart approach and increasing potential for transdermal drug delivery system [J]. Biomed Pharmacother, 2019, 109: 1249-1258.

[133] Sartawi Z, Blackshields C, Faisal W. Dissolving microneedles: applications and growing therapeutic potential [J]. J Control Release, 2022, 348: 186-205.

[134] Zhang T, Sun B, Guo J, et al. Active pharmaceutical ingredient poly (ionic liquid)-based microneedles for the treatment of skin acne infection [J]. Acta Biomater, 2020, 115: 136-147.

[135] Gupta A, Costa AP, Xu X, et al. Continuous processing of paclitaxel polymeric micelles [J]. Int J Pharm, 2021, 607: 120946.

[136] Yang C, Yin L, Yuan C, et al. DPD simulations and experimental study on reduction-sensitive polymeric micelles self-assembled from PCL-SS-PPEGMA for doxorubicin controlled release [J]. Colloids Surf B Biointerfaces, 2021, 204: 111797.

[137] Rao MR, Deshpande S, Deshpande P. Dapsone-loaded mixed micellar gel for treatment OF acne vulgaris [J]. AAPS PharmSciTech, 2023, 24: 109.

[138] Dahmana N, Mugnier T, Gabriel D, et al. Polymeric micelle mediated follicular delivery of spironolactone: targeting the mineralocorticoid receptor to prevent glucocorticoid-induced activation and delayed cutaneous wound healing [J]. Int J Pharm, 2021, 604: 120773.

[139] Meng Q, Zhong S, Gao Y, et al. Advances in polysaccharide-based nano/microcapsules for biomedical applications: a review [J]. Int J Biol Macromol, 2022, 220: 878-891.

[140] Khubiev OM, Egorov AR, Kirichuk AA, et al. Chitosan-based antibacterial films for biomedical and food applications [J]. Int J Mol Sci, 2023, 24: 10738.

[141] da Silva NP, Carmo Rapozo Lavinas Pereira ED, Duarte LM, et al. Improved anti-Cutibacterium acnes activity of tea tree oil-loaded chitosan-poly (*ε* -caprolactone) core-shell nanocapsules [J]. Colloids Surf B Biointerfaces, 2020, 196: 111371.

[142] Ivanova K, Ramon E, Ivanova A, et al. Bio-based nano-enabled cosmetic formulations for the treatment of cutibacterium acnes-associated skin infections [J]. Antioxidants (Basel), 2023, 12: 432.

[143] Fang G, Yang X, Wang Q, et al. Hydrogels-based ophthalmic drug delivery systems for treatment of ocular diseases [J]. Mater Sci Eng C Mater Biol Appl, 2021, 127: 112212.

[144] Zeng Q, Liang T, Liu M, et al. Co-assembled cryptotanshinone derivative and glycyrrhizic acid carrier-free hydrogel: a synergistic approach to acne treatment [J]. Nano Lett, 2025, 25: 8814-8824.

[145] Tomić I, Miočić S, Pepić I, et al. Efficacy and safety of azelaic acid nanocrystal-loaded *in situ* hydrogel in the treatment of acne vulgaris [J]. Pharmaceutics, 2021, 13: 567.

[146] Bisht A, Hemrajani C, Rathore C, et al. Hydrogel composite containing azelaic acid and tea tree essential oil as a therapeutic strategy for propionibacterium and testosterone-induced acne [J]. Drug Deliv Transl Res, 2022, 12: 2501-2517.

[147] Afzal A, Shah SNH, Javed H, et al. Spilanthes acmella extract-based natural oils loaded emulgel for anti-microbial action against dermatitis [J]. Gels, 2023, 9: 832.

[148] Donthi MR, Munnangi SR, Krishna KV, et al. Nanoemulgel: a novel nano carrier as a tool for topical drug delivery [J]. Pharmaceutics, 2023, 15: 164.

[149] Milutinov J, Krstonošić V, Ćirin D, et al. Emulgels: promising carrier systems for food ingredients and drugs [J]. Polymers (Basel), 2023, 15: 2302.

[150] Malavi S, Kumbhar P, Manjappa A, et al. Emulgel for improved topical delivery of tretinoin: formulation design and characterization [J]. Ann Pharm Fr, 2022, 80: 157-168.

[151] Sun Y, Zheng L, Yang Y, et al. Metal-organic framework nanocarriers for drug delivery in biomedical applications [J]. Nano-micro Lett, 2020, 12: 103.

[152] Seidi F, Jouyandeh M, Taghizadeh M, et al. Metal-organic framework (MOF)/epoxy coatings: a review [J]. Materials (Basel), 2020, 13: 2881.

[153] Li R, Chen T, Pan X. Metal-organic-framework-based materials for antimicrobial applications [J]. ACS Nano, 2021, 15: 3808-3848.

[154] Xiang Y, Lu J, Mao C, et al. Ultrasound-triggered interfacial engineering-based microneedle for bacterial infection acne treatment [J]. Sci Adv, 2023, 9: eadf0854.

[155] Taherzade SD, Rojas S, Soleimannejad J, et al. Combined cutaneous therapy using biocompatible metal-organic frameworks [J]. Nanomaterials (Basel), 2020, 10: 2296.

[156] Jianxian C, Saleem K, Ijaz M, et al. Development and *in vitro* evaluation of gastro-protective aceclofenac-loaded self-emulsifying drug delivery system [J]. Int J Nanomedicine, 2020, 15:

5217-5226.

[157] Maji I, Mahajan S, Sriram A, et al. Solid self emulsifying drug delivery system: superior mode for oral delivery of hydrophobic cargos [J]. J Control Release, 2021, 337: 646-660.

[158] de Oliveira MC, Bruschi ML. Self-emulsifying systems for delivery of bioactive compounds from natural origin [J]. AAPS PharmSciTech, 2022, 23: 134.

[159] Eid AM, Naseef H, Jaradat N, et al. Antibacterial and anti-acne activity of benzoyl peroxide nanoparticles incorporated in lemon-grass oil nanoemulgel [J]. Gels, 2023, 9: 186.

[160] Limongi T, Susa F, Allione M, et al. Drug delivery applications of three-dimensional printed (3DP) mesoporous scaffolds [J]. Pharmaceutics, 2020, 12: 851.

[161] Li Q, Wang W, Hu G, et al. Evaluation of chitosan derivatives modified mesoporous silica nanoparticles as delivery carrier [J]. Molecules, 2021, 26: 2490.

[162] Hussein HA, Nazir MS, Azra N, et al. Novel drug and gene delivery system and imaging agent based on marine diatom biosilica nanoparticles [J]. Mar Drugs, 2022, 20: 480.

[163] Castillo RR, Vallet-Regí M. Functional mesoporous silica nanocomposites: biomedical applications and biosafety [J]. Int J Mol Sci, 2019, 20: 929.

[164] Ain NU, Khan B, Zhu K, et al. Fabrication of mesoporous silica nanoparticles for releasable delivery of licorice polysaccharide at the acne site in topical application [J]. Carbohydr Polym, 2024, 339: 122250.

[165] Svigelj R, Zanette F, Toniolo R. Electrochemical evaluation of tyrosinase enzymatic activity in deep eutectic solvent and aqueous deep eutectic solvent [J]. Sensors (Basel), 2023, 23: 3915.

[166] Li X, Ma N, Zhang L, et al. Applications of choline-based ionic liquids in drug delivery [J]. Int J Pharm, 2022, 612: 121366.

[167] Tanner EEL, Curreri AM, Balkaran JPR, et al. Design principles of ionic liquids for transdermal drug delivery [J]. Adv Mater, 2019, 31: e1901103.

[168] Liu Y, Wang D, Lai Y, et al. Deep eutectic solvents for essential-oil delivery and bacterial-infected wound Healing [J]. Langmuir, 2024, 40: 23766-23779.

[169] Banerjee A, Ibsen K, Iwao Y, et al. Transdermal protein delivery using choline and geranate (CAGE) deep eutectic solvent [J]. Adv Healthc Mater, 2017, 6: 1601411.

[170] Mitragotri S. Choline geranate (CAGE): a multifaceted ionic liquid for drug delivery [J]. J Control Release, 2024, 376: 593-600.

[171] Luhaibi DK, Ali HHM, Al-Ani I, et al. The formulation and evaluation of deep eutectic vehicles for the topical delivery of azelaic acid for acne treatment [J]. Molecules, 2023, 28: 6927.

[172] Zakrewsky M, Banerjee A, Apte S, et al. Choline and geranate deep eutectic solvent as a broad-spectrum antiseptic agent for preventive and therapeutic applications [J]. Adv Healthc Mater, 2016, 5: 1282-1289.

[173] Patel HA, Guo L, Feldman SR. The impact of current investigational drugs for acne on future treatment strategies [J]. Expert Opin Investig Drugs, 2024, 33: 127-132.

[174] Li XT, Lai YY, Wan GH, et al. Approved natural products-derived nanomedicines for disease treatment [J]. Chin J Nat Med, 2024, 22: 1100-1116.