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REVIEW

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Seeking new acne treatment from natural products, devices and synthetic drug discovery

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ABSTRACT

Despite lots of research on the pathogenesis of acne, the development of new therapeutic agents is still stagnant. Conventional agents which target multiple pathological processes have some serious side effects and this makes seeking new treatment options important for treating acne. As new therapeutic options, researchers are focusing on natural products, synthetic drugs and devices. From natural products, epigallocatechin-3 gallate, lupeol, cannabidiol and Lactobacillus fermented *Chamaecyperis obtusa* were reported to be possible candidates for novel drugs, targeting multiple pathogenic factors. Synthetic anti-*P.acnes* agent, nitric oxide nanoparticles and α-mangostin nanoparticles are shown to be effective in acne treatment. Device or procedural methods such as fractional microneedling radiofrequency, cryolysis, photothermolysis and daylight photodynamic therapy have potential as new treatment options for acne. Further large clinical trials comparing these new treatments with existing agents will be necessary in the future.

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Introduction

Acne is the most universal sebaceous gland related skin disease characterized by 4 major pathogenic factors; excessive sebum production, inflammation, follicular hyperkeratinization and overgrowth of *Propionibacterium acnes*.[1,2] To function as a treatment option for acne, it should block at least one of these pathogenic factors. However, only a few drugs are known to target multiple pathological processes, and use of such drugs can be accompanied by some serious side effects. For example, isotretinoin, one of the most commonly used drugs in acne treatment, is known for teratogenicity, liver enzyme abnormalities and dyslipidemia.[2] Topical retinoid may evoke burning and irritation, and antibiotics can cause bacterial resistance. Therefore, new drugs that target multiple pathological processes of acne with few side effects are urgently needed.

Natural product

Natural products have received a lot of attention as candidates for novel drugs due to their relative safety and abundancy in nature. Yoon et al. reported that epigallocatechin-3 gallate, a constituent of green tea, improved acne by modulating intracellular molecular targets and inhibiting *P. acnes*.[3] The same group also published that lupeol, a kind of pentacyclic triterpene, acts as a therapeutic agent by targeting multiple pathogenic factors of acne. They conducted activity-guided purification after a series of screenings from several medicinal plants to find out a novel anti-acne component.[4] They applied a series of instrumental analysis to isolate a single functional molecule and conducted cellular and histological analysis to find out mechanisms of this molecule on acne treatment.

To explore anti-acne ingredients from natural compounds, they screened 5 candidate medicinal plants that are known to be effective for acne from the literature or complementary medicine. Botanical fractions dissolved in various organic solvents were tested for biologic activities such as toxicity, anti-lipogenesis, anti-inflammation, and anti-microbial activities. Among various fractions, the acidic hexane fraction of

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Solanum melongena (SM) showed the most desired result. It demonstrated selective anti-proliferative effects on SEB-1 sebocytes with no direct cytotoxicity for other cells, suppression of intracellular lipid contents, and anti-inflammatory activities. To identify a single constituent with anti-acne traits, they separated acidic hexane fraction of SM extracts by open-column chromatography and following HPLC steps. Then, each sub-fraction was evaluated by serial anti-acne screening steps, and the final sub-fraction showing the most desired effects was purified. A molecular structure of this final fraction was identified after analyzing data from GC-MS, FT-IR, and NMR. Lupeol, which is the final purified molecule, presents in several plant species, and has been reported to possess wide-spectrum pharmacological activities.[4]

In cellular model, lupeol significantly decreased lipid production in SEB-1 sebocytes (Fig. 1). Specific fatty acid components were also reduced as the lupeol concentration increased. Decreased ^{14}C acetate incorportation into fatty acids, cholesterol, and squalene further confirmed lupeol induced reduction of intracellular lipid synthesis. As a possible mechanism of this sebosuppression, lupeol significantly decreased expressions of both precursor and mature SREBPs, major transcription factors responsible for the regulation of cholesterol and fatty acid metabolisms. Downstream targets of all SREBPs such as fatty acid synthase, acetyl-CoA carboxylase, HMG-CoA reductase and HMG-CoA synthase were also decreased. As upstream regulators responsible for suppression of the SREBP pathway, lupeol decreased IGF-1R/IRS-1/PI3K/Akt pathway in SEB-1 sebocytes in a dose dependent manner. Co-treatment with lupeol and PI3K/Akt inhibitor LY294002 did not synergistically decrease SREBP-1 and intraceullar lipid content, strongly suggesting that lupeol suppressed sebum mainly through the inhibition of the IGF-1R/IRS-1/PI3K/Akt/SREBP-1 pathway in SEB-1 sebocytes. In sebocytes, lupeol decreased levels of proinflammatory cytokines induced by heat-inactivated *P. acnes* in a dose dependent manner (Fig. 1). Protein expressions of NF-κB and phospho-IκB were decreased accordingly indicating that mitigation of NF-κB would be the major anti-inflammatory mechanisms of lupeol. Almost parallel patterns were observed in HaCaT keratinocytes. In addition, lupeol significantly suppressed protein and mRNA expressions of IL-1α, a strong inducer of hypercornification of the infundibulum, TLR-2, a key molecule in IL-1α release during comedogenesis, and keratin 16, a marker of abnormal differentiation in HaCaT keratinocytes. These data provide strong evidence that lupeol can potentially modulate epidermal dyskeratosis (Fig. 1). Lupeol also demonstrated anti-microbial effects against *P. acnes* although the growth of *P. acnes* was effectively inhibited at rather higher concentrations of lupeol. Nevertheless, lupeol may also partly contribute to suppress

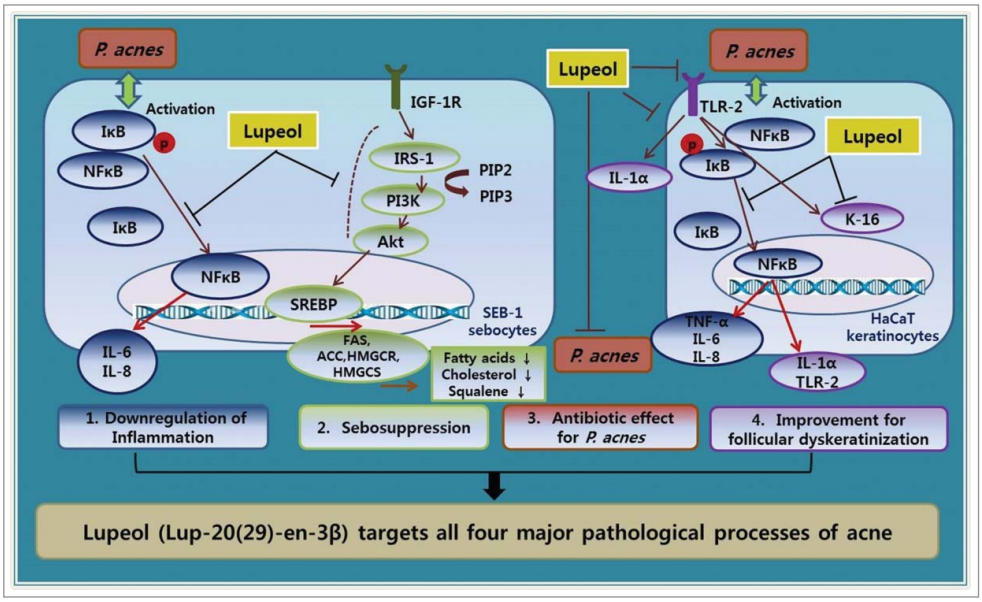

Figure 1. Possible therapeutic mechanisms of lupeol on pathogenetic factors of acne (from Figure 5 h of reference 4. © Elsevier. Reproduced by permission of Elsevier. Permission to reuse must be obtained from the rightsholder.

abnormal colonization of *P. acnes* for acne development *in vivo* because it can be highly concentrated in sebaceous duct.[4]

In histologic analysis from skin biopsy specimens, all pathogenic target molecules decreased accordingly, and histopathologic changes confirmed proposed therapeutic mechanisms *in vivo*, suggesting that lupeol has possible therapeutic roles against acne.[4] In addition to these anti-acne traits, this molecule is lipophilic, has no ionizable moiety in the physiologic pH, and is chemically stable.[5] These accumulated evidences would make lupeol a novel effective treatment option for acne.

Several studies about other natural products possessing anti-acne traits were reported. Gao et al. demonstrated that Aspidin BB, phloroglucinol derivatives from ferns, has strong antibacterial activity against *P. acnes*.[6] Also, there was an article about sebostatic, anti-proliferative and anti-inflammatory effects of cannabidiol on human sebocytes.[7] Cannabidiol is a promising therapeutic agent of acne because multiple physiologic processes are regulated by the endocannabionoid system. It has already been applied in clinical practice without any significant side effects. Authors of this group proved cannabidiol can act against major pathogenic factors of acne; lipogenesis, proliferation and inflammation through distinct molecular pathways.[7]

Kwon et al. studied Lactobacillus fermented *Chamaecyparis obtusa* (LFCO) and compared it with tea tree oil (TTO), one of the most widely used anti-acne botanical ingredients,[8] for the treatment of acne in double blind randomized controlled split face study.[9] *C. obtusa* is a species of cypress commonly found in Korea and widely used as perfume, cosmetics and disinfectant. Many component molecules of *C. obtusa* have anti-microbial, anti-inflammatory and anti-proliferative properties, and effects of *C. obtusa* on the development of atopic dermatitis-like skin lesion were demonstrated.[10] 34 patients were instructed to apply LFCO to the randomly allocated side and TTO to the other side of their faces for 8 weeks. Inflammatory and non-inflammatory acne lesions on LFCO treated side decreased by 65% and 53% respectively at week 8, showing significant difference from tea tree oil treated side which only showed 38% and 24% decrease respectively. Acne severity evaluated by Leeds grading also showed significant difference between LFCO and TTO side. In histological and molecular analysis, inflammatory cytokines such as IL-8, NF-κB, IL-1α were decreased on LFCO treated side, and the degree of reduction in these cytokines was greater than TTO treated side. SREBP-1 and IGF-1 which are associated with sebum production were also decreased on LFCO treated side while there was no change on TTO treated side. RT-PCR data was consistent with immunohistochemistry data. UPLC-HRMS showed that specific molecules were increased after the fermentation of *C. obtusa* and they were found out to be dihydroxybenzoic acid, taxifolin 3-O-β-D-xylopyranoside and quercetin 3-rhamnoside.[9] *Lactobacillus* fermentation can induce biochemical conversions of metabolites with enhanced antimicrobial or antioxidant activities, and many of them would be useful in healthcare and cosmetic industries.

Not only have the studies so far demonstrated therapeutic potentials of natural products, but they also suggested how to find new drugs from nature in the future. Many of them will come to market and might replace existing treatments. Still, more research about natural products needs to be done.

Synthesized anti *P. acnes* and anti-acne agents

Several synthetic agents are developed as new therapeutic options for acne. Schmidt et al. engineered Pentobra, a peptide-aminoglycoside which combines the potent ribosomal activity of aminoglycosides with the bacteria-selective membrane permeabilizing abilities of antimicrobial peptides.[11] Pentobra showed much more powerful antibacterial effect against *P. acnes* than tobramycin and it was non-toxic for human skin cells. Electron microscopy showed pentobra induced cell lysis of *P. acnes* with externalization of cytoplasmic contents. It maintained bactericidal effect in sebaceous microcomedones which are obtained from donor's faces. Pentobra suppressed *P. acnes* induced chemokines indicating that it may have anti-inflammatory properties. This group showed that aminoglycosides equipped with cell-penetrating abilities can have antibiotic activity against slow growing bacteria like *P. acnes*, providing viable approach for developing antibiotics.

Qin et al. reported that nitric oxide releasing nanoparticles cleared *P. acnes* itself and inhibited *P. acnes* induced immune response.[12] Nitric oxide, a potent biologic messenger, has been demonstrated to have broad-spectrum antimicrobial and immunomodulatory

properties. They established nanoparticles capable of generating and releasing NO over-time whose average radius was about 108nm. *P. acnes* were found to be highly sensitive to these nanoparticles but they were nontoxic for human cells such as HaCaT cells and peripheral blood mononuclear cells (PBMC). The effect of these nanoparticles on inflammasome, a cytoplasmic molecular complex which can rapidly initiate inflammation,[13] was investigated. NO releasing nanoparticles inhibited PBMC IL-1β secretion via the inflammasome pathway. It seems to work by inhibiting caspase-1 and IL-1β gene expression not affecting NLRP3 and ASC gene expression.[12]

Pan-In et al. reported α-mangostin nanoparticles which can be pushed into hair follicles to deliver drugs to nearby sites such as sebaceous gland. Mangostin, the major component of *Gacinia mangostana* extract, has both anti-inflammatory and anti-*P acnes* activity.[14] In this study, its anti-acne and skin irritation potential was tested, and patients showed improvement in acne severity score and inflammatory acne lesion counts.[15]

Although there are not many studies because of the difficulties in synthesis of new drugs, these studies have shown the way to develop novel therapeutic agents.

Devices and procedures

Fractional microneedling radiofrequency (FMR) had been mainly used in the treatment of acne scar. On account of insulated microneedle, only the tip of FMR is active, making no electrothermal epidermal damage and no cooling is required. The advantages of FMR include deeper tissue effect, quick recovery and specific targeting.

Min et al. reported FMR treatment of acne-related post-inflammatory erythema (PIE) which is very common with acne scar and cosmetically unacceptable.[16] Usually PIE persists or improves very slowly over time. They treated 25 patients with 2 sessions of FMR with 4 week interval. Results showed that clinical improvement was noted only in FMR treated group. Erythema index and a^* values were significantly decreased in FMR treated group compared to control group. In histopathology, inflammatory cells in H&E staining, and microvessels in α-SMA staining were greatly decreased in FMR treated group. In immunohistochemistry, IL-8, NF-κB, VEGF were also significantly decreased in FMR treated group compared to the control group after 2 sessions of FMR treatment. FMR can be a safe and effective method for PIE treatment by reducing inflammation and abnormal vessel proliferation. They suggested FMR may reduce inflammation by decreasing expression of NF-κB, resulting in downregulation of VEGF via direct or indirect pathway.[16]

Jalian et al. reported about selective cryolysis of sebaceous gland.[17] Cryolipolysis is widely used for local reduction of unwanted subcutaneous fat.[18] Due to the preferential susceptibility of lipid containing cells to cold, they hypothesized that controlled local skin cooling can cause preferential injury to sebaceous gland. In human study, they used either single 20-minute cycle or two 10-minute cycles at temperature from -15 to -10 °C. Both methods reduced sebum production significantly for 2 weeks but it had a tendency to return to baseline value at week 4. Cooling disrupted sebocyte membranes, alkaline phosphatase activity, and significantly reduced sebocyte lipid content.[17] The results strongly suggest that acne treatment with modern controlled cooling device is worth investigating.

Selective photothermolysis of sebaceous follicles was tried with topically delivered light absorbing gold microparticles. A suspension of these microparticles was delivered into human pre-auricular and swine sebaceous glands in vivo, using mechanical vibration. Laser exposure after that procedure caused selective thermal damage to sebaceous gland and hyperkeratinizing cells of the infundibulum. This local heating of the microenvironment might also reduce *P. acnes* in the follicles. In clinical trials, patients received this treatment 3 times with 2 week interval and inflammatory acne lesions decreased by 61% at week 28.[19]

Daylight photodynamic therapy was used for photoaged skin and actinic keratosis before.[20] Kwon et al. published an article about the daylight photodynamic therapy (PDT) in acne treatment.[21] They used variant of 5-aminolevulinate (ALA)-ester, 1.5% 3-butenyl ALA gel, using daylight only as the potential visible light source. Fluorescence image after UV exposure showed absorption of this photosensitizer but it was not strong compared to conventional photosensitizer because of low concentration. Inflammatory and non-inflammatory acne lesions decreased by 58% and 34% respectively at week 12, showing significant improvement compared with control group. IGA score also decreased and patients' subjective assessment for efficacy was good. Although there were some cutaneous side effects in 22%, all of them were mild symptoms such as transient erythema and dryness.

In skin biopsy specimens, inflammation severity in H&E staining and associated inflammatory markers such as IL-8, IL-1β, MMP-9 and NF-κB were also significantly reduced after PDT. As experimental results well correlate with clinical results, daylight PDT for acne can be effective for both inflammatory and non-inflammatory acne lesions. Moreover, in view of less frequency and degree of side effects compared to conventional PDT, this ambulatory PDT may provide good compliance and acceptability by acne patients.[21]

Because acne is a disease of complex pathomechanism, devices and procedures which affect pathogenetic factors can be options for treatment. Such devices and procedures may be additively applied to patients with drugs or may be used as an alternative to drugs.

Conclusion

Various therapeutic approaches from natural products, medications, novel anti-*P.acnes* agents, and procedural methods have been applied to overcome limitations of conventional anti-acne treatment. Further large scale clinical trials comparing with existing agents should be followed in the near future.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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