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Research progress on the role of macrophages in acne and regulation by natural plant products

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Acne vulgaris is one of the most common skin diseases. The current understanding of acne primarily revolves around inflammatory responses, sebum metabolism disorders, aberrant hormone and receptor expression, colonization by *Cutibacterium acnes*, and abnormal keratinization of follicular sebaceous glands. Although the precise mechanism of action remains incompletely understood, it is plausible that macrophages exert an influence on these pathological features. Macrophages, as a constituent of the human innate immune system, typically manifest distinct phenotypes across various diseases. It has been observed that the polarization of macrophages toward the M1 phenotype plays a pivotal role in the pathogenesis of acne. In recent years, extensive research on acne has revealed an increasing number of natural remedies exhibiting therapeutic efficacy through the modulation of macrophage polarization. This review investigates the role of cutaneous macrophages, elucidates their potential significance in the pathogenesis of acne, a prevalent chronic inflammatory skin disorder, and explores the therapeutic mechanisms of natural plant products targeting macrophages. Despite these insights, the precise role of macrophages in the pathogenesis of acne remains poorly elucidated. Subsequent investigations in this domain will further illuminate the pathogenesis of acne and potentially offer guidance for identifying novel therapeutic targets for this condition.

KEYWORDS

macrophages, acne vulgaris, inflammatory response, sebum metabolism, natural plant products

1 Introduction

Acne is a prevalent chronic inflammatory skin disease affecting the hair follicles and sebaceous glands, with skin lesions primarily appearing on the face and chest back. The clinical manifestations encompass a diverse range of acneiform lesions, including comedones, papules, pustules, nodules, and cysts. These are often accompanied by excessive sebum secretion (1–3). Acne, affecting 9.4% of the global population, ranks as the eighth most prevalent disease worldwide. Despite its clinical commonality, post-acne erythema and scarring contribute significantly to psychological disorders among young individuals, thereby elevating the risk of mood disorders and psychiatric comorbidity (4–7). Consequently, acne has emerged as a significant societal concern. Currently, the internationally recommended pharmacological treatments for acne encompass topical retinoids, benzoyl peroxide, antibiotic ointments, as well as oral antibiotics and anti-androgen medications (8–10). Despite their efficacy, these existing therapeutic strategies often give rise to adverse effects such as cutaneous irritation, dryness, and disturbances in the skin's microecology due to topical agents. Additionally, concerns regarding the emergence of antibiotic-resistant bacteria have also been raised (1). The management of acne is increasingly challenging, thus necessitating an urgent exploration of novel targets and mechanisms in acne research.

The pathogenesis of acne involves inflammatory responses, hypersecretion of sebum, abnormal keratinization of the sebaceous glands in hair follicles, colonization by *Cutibacterium acnes*(*C. acnes*), and dysregulated androgen secretion (11–15). The inflammatory response is observed throughout the entire course of acne (16). Increasing evidence suggests that the inflammatory reaction in acne is associated with abnormal sebum metabolism, colonization of *C. acnes*, and abnormal androgen levels. Macrophages are essential components of the inflammatory response and, as integral members of the immune effector cells, also contribute significantly to maintaining skin homeostasis. Hence, it is imperative to investigate the role of macrophages in the pathogenesis of acne. In this review, we initially introduced the pivotal role of macrophages in skin physiology, elucidated their intricate associations with sebum metabolism, androgen regulation abnormalities, and *C. acnes* colonization, followed by a comprehensive summary of natural compounds that modulate the phenotypic alterations of acne-associated macrophages. This review further elucidates the correlation between macrophages and acne pathogenesis, as well as contributes to the development of potential therapeutic agents.

2 Role of macrophages in the skin

Macrophages are derived from hematopoietic stem cell-derived monocytes in the bone marrow (17), or originate from all tissues during embryonic development through the yolk sac and fetal liver, subsequently establishing themselves as resident cells within the tissues (18, 19). Macrophage populations exhibit significant heterogeneity across various tissues and perform important physiological functions specific to the tissues in which they reside. In general, resident macrophages maintain tissue homeostasis, while monocyte-derived macrophages primarily contribute to host defense and pathological signaling (20, 21). Additionally, macrophages exhibit significant plasticity and undergo polarization in response to environmental changes within different tissues, giving rise to distinct subtypes of macrophages (22).

Traditionally, macrophages can be polarized into two distinct phenotypes, namely classically activated M1 macrophages and alternatively activated M2 macrophages (23). M1 macrophages are stimulated by lipopolysaccharide (LPS) and interferon-γ (IFN-γ) (24, 25) to elicit a pro-inflammatory response and secrete various pro-inflammatory factors, including interleukin (IL)-1β, IL-6, IL-12, IL-23, inducible nitric oxide synthase (iNOS), monocyte chemotactic protein-1 (MCP-1), and tumor necrosis factor-alpha (TNF-α) (18, 26). Activated M1 macrophages promote Th1 cell-mediated immune responses, thereby safeguarding the host (27, 28). Additionally, they generate reactive oxygen species (ROS) and active nitrogen intermediates (29), which effectively eliminate pathogens. However, these mechanisms can also lead to collateral tissue damage and excessive inflammation, consequently impeding tissue regeneration and wound healing processes (30, 31). During the process of skin pathology, M1 macrophages play a crucial role in eliminating pathogenic microorganisms. However, sustained polarization toward the M1 phenotype can perpetuate a highly inflammatory state within the lesions, impeding optimal wound tissue healing (32–34).

M2 activation occurs in response to stimulation by IL-4, IL-10, and IL-13 (35, 36). As reparative macrophages, M2 macrophages play a crucial role in suppressing inflammatory responses and facilitating tissue repair and wound healing (37, 38). They are characterized by their ability to promote TH2 responses and exhibit overexpression of cytokines such as IL-10, transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and arginase 1(Arg1) (35). M2 macrophages can be further classified into four subtypes: M2a, M2b, M2c, and M2d, each exhibiting distinct functionalities (39). Among these subtypes, IL-4 or IL-13 induces the polarization of M2a macrophages which predominantly express IL-12, interleukin-1 receptor antagonist (IL-1RA), IL-8, and IL-10. This subtype plays a crucial role in anti-inflammatory responses and tissue repair (40–42); Immune complex and LPS/IL-1β stimulation triggers the activation of M2b macrophages leading to increased secretion of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. These cells significantly contribute to immune regulation while also promoting infection and tumor progression (43, 44); Activation of M2c macrophages by either IL-10 or glucocorticoids results in the release of numerous anti-inflammatory cytokines (IL-10, TGF-β, IL-1RA). Primarily involved in tissue remodeling and immunosuppression (45, 46), this subtype is often referred to as "inactivated" macrophages; Lastly, the M2d phenotype arises from synergistic induction by both IL-6 and adenosine A2a receptor agonists; it primarily expresses IL-10 and VEGF, thereby facilitating angiogenesis and tumor growth (42, 47). M2 macrophages are involved in tissue repair and angiogenesis in skin lesions, but M2

hyperpolarization may lead to excessive collagen production and scar formation (48). Therefore, maintaining the balance of M1/M2 macrophages is crucial for restoring the normal skin immune environment, as disrupting this balance can lead to pathological conditions (49, 50). Figure 1 provides an overview of the phenotype and function of macrophages stimulated by various factors.

As crucial components of the skin's immune response, macrophages are present in both the dermis and epidermis. Langerhans cells (LCs) in the epidermis develop similarly to macrophages, originating from yolk sac-derived progenitor cells and fetal liver monocytes. They are recruited into the epidermis prenatally, and under homeostatic conditions, LCs undergo self-renewal; only during inflammation do blood monocytes replenish the population of epidermal LCs. LCs serve as the primary barrier of the skin's immune system, contributing to maintaining skin barrier integrity, immune homeostasis, and limiting viral infections (51–53). Dermal macrophages are also derived from the yolk sac and/or fetal liver. Recent studies have found that CD163 perivascular macrophages and CD64 perinerve macrophages exist in the human dermis. When an injury occurs, dermal macrophages can be rapidly activated to exert antigenic phagocytosis effect (54, 55). Macrophages play a pivotal role in various cutaneous disorders, particularly inflammatory skin conditions (32). Foamy macrophages have been observed abundantly in acne lesions (56), and these cells have been found to express TREM2 (57). Tran et al. utilized single-cell transcriptome analysis to demonstrate the

enhanced specificity and abundance of TREM2-expressing macrophages at the site of skin lesions in acne patients (58). Further investigation into the macrophage phenotype in acne revealed a persistent presence of M1-type macrophages within the skin lesions, potentially contributing to chronic inflammation in affected individuals (59).

3 Evidence of macrophages involvement in acne

3.1 Macrophages and sebum metabolism

Recently, several authors have emphasized the association between acne and metabolic diseases, positing that acne is essentially a metabolic disorder (60, 61). Disruption of sebum metabolism represents the primary characteristic of acne and is also deemed a necessary condition for its onset (62, 63). Sebum consists of triglycerides, free fatty acids, cholesterol, squalene, and other constituents (64). The increase in sebum secretion from related sebaceous glands leads to abnormal keratinization of the follicular sebaceous glands, microbial proliferation, inflammation induction as well as initiation of potential immune mechanisms and inflammatory cascade reactions resulting in skin lesion formation (65).
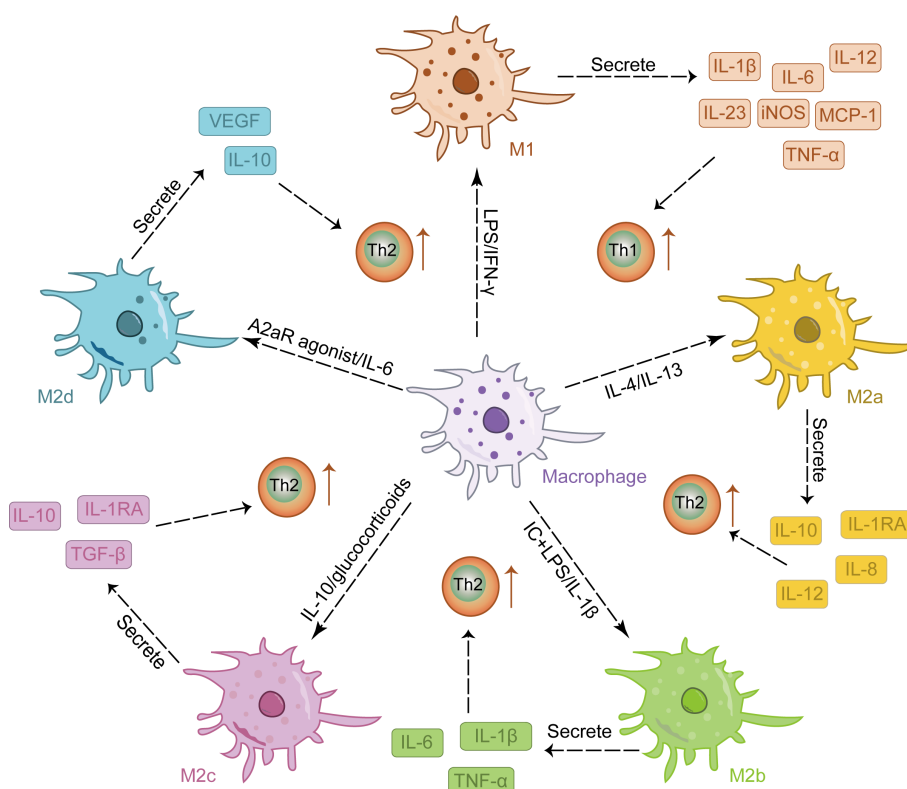

FIGURE 1
The stimulation of various factors induced the differentiation of macrophages into distinct M1 and M2 phenotypes, each exhibiting a unique cytokine secretion profile to facilitate immune response.

The squalene content in the skin sebum of acne patients increases to varying degrees (66). Squalene induces macrophages to express TREM2, promoting lipid uptake and catabolic metabolism, thereby enhancing the metabolic activity of macrophages and their phagocytic ability toward lipids and *C. acnes* (56, 67). Knockout of TREM2 in macrophages can inhibit downstream signaling pathways and negatively regulate the recruitment of macrophages, leading to insulin resistance (IR), adipose cell hypertrophy, and lipid accumulation (68). However, it has been observed that squalene epoxide can be generated from squalene by TREM2-expressing macrophages. This conversion results in the formation of a polyunsaturated lipid known as squalene epoxide which possesses ROS-clearing properties. Consequently, this process blocks the antibacterial effect of macrophages directly triggering inflammation and exacerbating acne (69, 70). Concurrently, squalene stimulates TREM2 macrophages to induce the secretion of pro-inflammatory cytokines (IL-18, IL-1β), suppress the production of anti-inflammatory cytokine IL-10, and exacerbate inflammation. These pro-inflammatory factors also contribute to IR and worsen sebum metabolism disorders (15, 71). These findings unveil a distinctive interaction pattern between TREM2 macrophages and sebum metabolism in patients with acne. In summary, disruption of sebum metabolism in acne leads to excessive squalene production, which enhances the phagocytosis of lipids and *C. acnes* by TREM2 macrophages. However, the converted squalene epoxides effectively eliminate ROS, thereby impeding the antimicrobial response of macrophages. Consequently, these TREM2 macrophages fail to reduce bacterial load but instead secrete IL-18 and upregulate chemokine expression, resulting in a disease-specific inflammatory response that further exacerbates sebum metabolism disorder.

Epidemiological evidence suggests a higher prevalence of acne among individuals with obesity compared to those with normal weight, and a positive correlation has been observed between body mass index (BMI) and the severity of acne (72). The presence of excessive peripheral androgens and IR often accompanies obesity, which may contribute to the increased susceptibility of obese patients to acne. In this context, adipose tissue macrophages play a pivotal role in regulating inflammation (73, 74). Studies have demonstrated a significant increase in pro-inflammatory M1 macrophage infiltration in the adipose tissue of obese mice compared to normal-weight mice (75, 76). Obesity can impair the innate immune function of adipose tissue, promoting macrophage polarization toward a pro-inflammatory phenotype and resulting in excessive secretion of TGF-β by mature adipocytes (77), which subsequently induces Th17 cell production (78). Th17 cells are capable of secreting IFN-γ and IL-17, contributing to the formation of acne lesions (79).

The Sterol Regulatory Element-Binding Protein(SREBP), Peroxisome Proliferator-Activated Receptor (PPAR), and Liver X Receptor(LXR) pathways play crucial roles in regulating metabolism and are closely associated with obesity. Increasing evidence has highlighted their involvement in the pathogenesis of acne (80–82). Active LXR can inhibit sebum cell proliferation, stimulate lipid synthesis required for epidermal barrier formation (83), and induce increased sebum production (84). Additionally, LXR activation has been shown to upregulate the expression of inflammatory factors such as IFN-γ and promote M1 macrophage polarization (85).

The SREBP serves as a direct target gene of LXR (86), promoting cholesterol biosynthesis and playing a crucial role in macrophage lipid metabolism (87, 88). In macrophages, SREBP hinders cholesterol efflux through the ATP-binding cassette transporter A1 (87, 89), potentially contributing to foam cell formation in acne. Intriguingly, activation of SREBP induces alterations in cholesterol metabolism that impede affection while inducing pro-inflammatory M1 polarization in macrophages (90). The regulation of sebaceous lipids involves the coordinated action of PPAR and LXR, which play a synergistic role in controlling epidermal growth, differentiation, and lipid metabolism (91, 92). Treatment with PPARγ ligands has been shown to reduce sebum production in human sebaceous glands (93); however, it has also been observed that PPARγ can enhance lipid accumulation in these cells and promote sebum secretion when patients are treated with PPARγ agonists (91, 94). Additionally, activation of PPARγ inhibits immune activation markers such as TNF-α, IL-6, and IL-1β in mouse macrophages (95).

Acne patients frequently experience complications such as IR, obesity, and disturbances in glucose and lipid metabolism, which collectively contribute to heightened levels of M1 macrophages in sebum, thereby exacerbating tissue inflammation and metabolic disorders that further promote acne development (Figure 2).

3.2 Macrophages and abnormal androgen regulation

Abnormal regulation of androgens plays a pivotal role in the pathogenesis of acne. Women with acne generally exhibit higher levels of serum testosterone and dihydrotestosterone compared to non-acne patients, albeit within the normal range (96, 97). A questionnaire survey involving 400 women revealed that over 50% of acne patients reported experiencing premenstrual episodes (98), suggesting that fluctuations in androgen production rather than solely excessive androgen production are likely to be the triggering factor for acne. The sebaceous gland serves as a pivotal target organ for androgens. Sebum secretion and the development of sebaceous glands are directly regulated by androgens, particularly testosterone (T), which directly controls sebaceous glands. T is enzymatically converted into dihydrotestosterone (DHT) by type I 5α-reductase (99). DHT promotes the proliferation of sebaceous cells, augments sebum secretion, and induces the release of pro-inflammatory factors. However, when there is an improper excretion of increased sebum production, it accumulates within hair follicles forming lipid thrombi that combine with *C. acnes* invasion to trigger acne formation (100–102). The regulation of androgens on sebaceous glands is closely related to the affinity between androgens and androgen receptors (AR). Moreover, AR can independently regulate the development of sebaceous glands, stimulate excessive secretion, up-regulate certain inflammatory factors, promote inflammatory response, and contribute to acne pathogenesis (103, 104).

The binding of active androgens to AR can stimulate macrophages to secrete pro-inflammatory factors IL-1, IL-6, and TNF-α (105), which is consistent with the inflammatory response observed at acne lesion sites. Androgen precursors can inhibit the secretion of
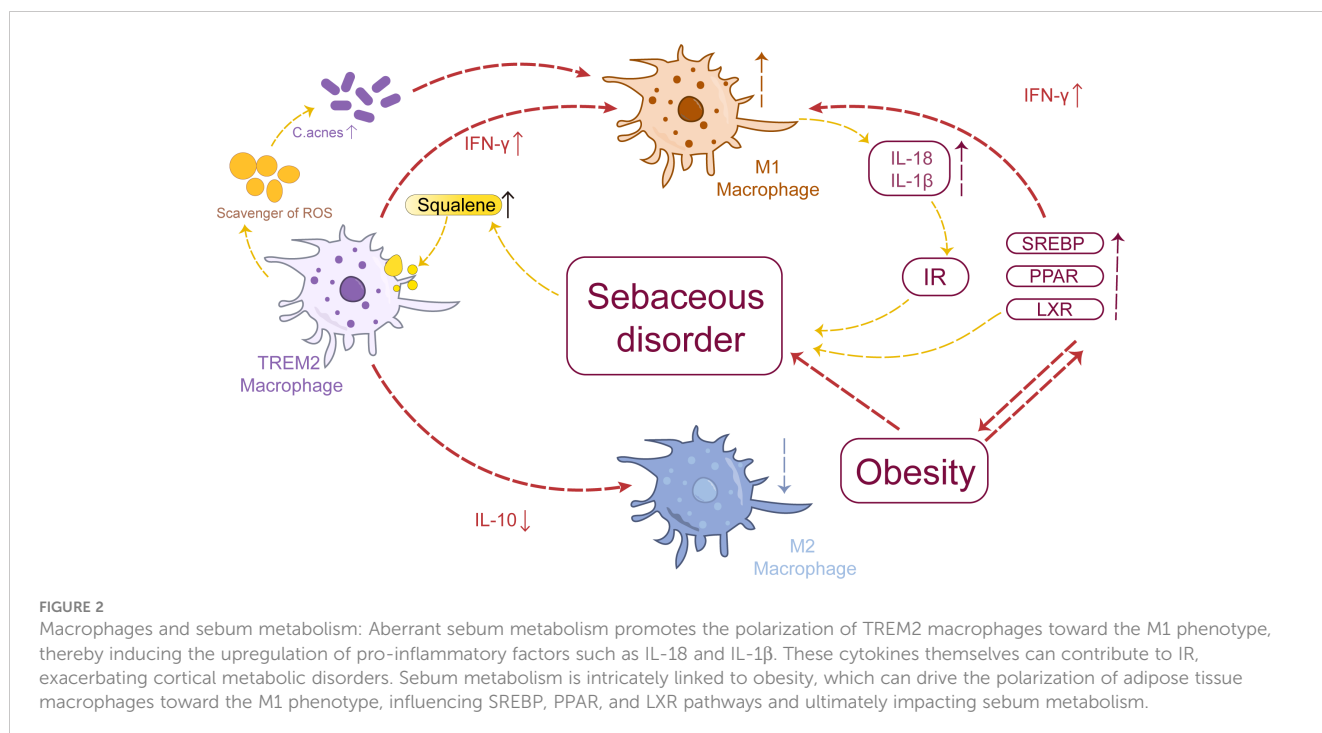
FIGURE 2
Macrophages and sebum metabolism: Aberrant sebum metabolism promotes the polarization of TREM2 macrophages toward the M1 phenotype, thereby inducing the upregulation of pro-inflammatory factors such as IL-18 and IL-1β. These cytokines themselves can contribute to IR, exacerbating cortical metabolic disorders. Sebum metabolism is intricately linked to obesity, which can drive the polarization of adipose tissue macrophages toward the M1 phenotype, influencing SREBP, PPAR, and LXR pathways and ultimately impacting sebum metabolism.

corticotropin-releasing hormone and adrenocorticotropin through feedback regulation, reducing the level of α-melanocyte stimulating hormone that possesses anti-inflammatory effects, thereby indirectly promoting the release of pro-inflammatory factors (102). It has been demonstrated that IL-6 and TNF-α can stimulate androgen synthesis and secretion (106). Therefore, it can be inferred that dysregulated androgen regulation leads to macrophage-mediated secretion of pro-inflammatory factors in acne lesions, inducing M1 macrophage polarization, local inflammatory responses, further exacerbating abnormal androgen levels, forming a vicious cycle contributing to the onset and progression of acne symptoms.

Recent studies have revealed a close association between acne and IR as well as hyperinsulinemia, with the severity of acne exhibiting a consistent correlation (107). Hyperinsulinemia stimulates the IGF-1 receptor, leading to increased expression of IGF-1, augments adrenal sensitivity to adrenocorticotropic hormone, facilitates adrenal androgen production, enhances AR activity, and subsequently manifests clinical characteristics indicative of aberrant androgen regulation (108). The occurrence of IR is intricately linked to inflammation (73). Macrophages, as the primary source of inflammatory mediators, can secrete pro-inflammatory factors such as TNF-α to facilitate IR formation by augmenting serine phosphorylation of insulin receptor substrate-1 (109). Under conditions characterized by IR or inflammation, macrophage-mediated insulin signaling phosphorylates forkhead box O1 (FOXO1) and promotes nuclear exclusion. The heightened activity of FOXO1 further stimulates excessive IL-1β production in macrophages (110), which potentially exacerbates IR and contributes to abnormal androgen regulation. Inhibiting FOXO1 in macrophages can induce polarization toward an M2-like phenotype in lipopolysaccharide-stimulated macrophages, thereby reducing inflammatory response, alleviating IR, and diminishing androgen

secretion along with AR activity (111, 112). In acne pathogenesis, IR may promote the upregulation of FOXO1 expression in macrophages leading to their polarization toward an M1 phenotype instead of an M2 phenotype. This phenomenon subsequently aggravates IR and disrupts normal androgen regulation.

In summary, dysregulated androgen signaling promotes the polarization of cutaneous macrophages toward the M1 phenotype, subsequently inducing the upregulation of pro-inflammatory cytokines such as IL-6 and TNF-α, thereby triggering a local inflammatory response. This cascade further enhances androgen synthesis and secretion, ultimately leading to acne development.

3.3 Macrophages and *C. acnes*

The bacterium *C. acnes* is widely distributed on the skin and constitutes the predominant microbe in the sebaceous glands of hair follicles, accounting for approximately 89% (113). *C. acnes* has the ability to produce endogenous porphyrins that oxidize squalene, thereby promoting acne vulgaris formation in keratinocytes (114). On the other hand, *C. acnes* can hydrolyze sebum into glycerol and free fatty acids, stimulating hair follicles and exacerbating acne (115). Mice exposed to an excess of *C. acnes* exhibit symptoms resembling human acne, including redness and erythema. Microscopic examination reveals a significant increase in infiltrating inflammatory cells such as macrophages (116). Consequently, exposure to excessive amounts of *C. acnes* is commonly employed to establish animal models mimicking acne-like conditions (117).

According to extensive *in vivo* and *in vitro* investigations, it has been observed that *C. acnes* infiltration into sebaceous glands leads to the secretion of a diverse range of bioactive enzymes, including lipase. This enzyme is capable of hydrolyzing triglycerides present in sebum,

resulting in the generation of free fatty acids and low molecular weight polypeptides. The activation of toll-like receptors (TLRs) on keratinocytes and sebum cells by these low molecular weight peptides subsequently upregulates the expression levels of TLR2 and TLR4. Additionally, this process triggers macrophages to adopt an M1 phenotype and release pro-inflammatory cytokines (such as IL-1 and TNF-α), which play pivotal roles in acne-associated inflammatory responses (118–120). IL-1β plays a pivotal role in the initiation of acne inflammation (121). Simultaneously, pro-inflammatory cytokines like IL-1β and TNF-α can also induce excessive production of proteolytic enzymes (e.g., matrix metalloproteinases), leading to collagen fiber degradation, impaired recombination, and subsequent alterations in local skin tissue structure during the reparative phase of post-acne erythema, ultimately resulting in scar formation (122, 123).

In summary, *C. acnes* in the skin can induce macrophages to polarize into M1 type and secrete pro-inflammatory factors, thereby driving the inflammatory response associated with acne. On the other hand, these pro-inflammatory factors contribute to collagen fiber degradation and recombination, ultimately leading to the development of acne erythema.

4 Natural plant products modulate the influence of macrophages in acne

4.1 Quercetin

Quercetin is a natural flavonoid of significant medicinal value, characterized by its yellow needle-like crystal monomer (124). It is widely distributed in Chinese herbal medicine as well as various vegetables and fruits. This compound exhibits diverse biological and pharmacological effects, encompassing anti-inflammatory, antioxidant, antibacterial, and cardiovascular protective properties (125). The anti-inflammatory and antibacterial effects of quercetin have shown promising potential in the treatment of acne (126, 127). Studies have demonstrated that quercetin effectively inhibits the upregulation of pro-inflammatory cytokines including IL-1β, IL-8, IL-6, and TNF-α in *C. acnes*-stimulated macrophages. Furthermore, quercetin significantly mitigated skin erythema induced by *C. acnes*. The study also revealed that quercetin exerts an inhibitory effect on TLR-2, a key innate immune receptor, thereby influencing the functioning of the innate immune system. Although the specific phenotype of macrophages stimulated by quercetin was not specified in this study, considering TLR-2's high expression on macrophage surfaces and its impact on macrophage polarization, it is plausible to suggest that quercetin promotes the polarization of macrophages toward the M2 phenotype while reducing their M1 phenotype. Consequently, we propose that quercetin can effectively suppress pro-inflammatory factor secretion by M1 macrophages in acne (128).

4.2 Baicalin

Baicalin is a lipophilic flavonoid glycoside isolated from Scutellaria baicalensis (129). It has anti-inflammatory, antioxidant, cardioprotective, anticancer, and antiviral effects

(130, 131). It was found that baicalin significantly decreased the expression of M1 macrophage-related cytokines such as IL-1β, IL-6, TNF-α and NLRP3 in acne models, and inhibited the M1 polarization of macrophages by inhibiting the nuclear translocation of NF-κB p65. Consequently, it is anticipated to emerge as a viable therapeutic option for the management of acne (132).

4.3 Schisandrin

Schisandrin (SCH) is a lignan-like compound that is the main bioactive component isolated from Schisandra chinensis (133). It has been reported to have a variety of biological activities, such as anti-inflammatory, hepatoprotective, anti-tumor, and antioxidant, and affects the respiratory, cardiovascular, and central nervous systems (134). In addition, SCH has been found to prevent lipopolysaccharide-induced inflammation (135). Therefore, some scholars have studied the mechanism of SCH to improve acne. Firstly, it was observed that SCH significantly suppressed caspase-1 activation and downregulated the expression of the inflammatory cytokine IL-1β. Moreover, SCH exhibited the ability to attenuate NLRP3 levels by inhibiting mitochondrial ROS production, ATP release, and K efflux, thereby impeding NLRP3 inflammasome activation. In conclusion, we propose that SCH exerts its acne-inhibitory effects by restraining the phenotypic transformation of M1 macrophages and mitigating inflammatory infiltration (136).

Acne comorbidities suggest that diabetes mellitus is closely related to acne, and it has been found that SCH C can attenuate diabetic nephropathy by regulating macrophage M1 to M2 polarisation via Swiprosin-1/IFN-γ-Rβ, which could also potentially serve as a future target for SCH in the treatment of acne (137).

4.4 Licochalcone A

The compound licochalcone A (LicA), derived from glycyrrhizin (138), is a flavonoid with diverse pharmacological effects including anti-inflammatory, antimicrobial, and antioxidant properties in the skin (139). Cai et al. (140) found that LicA significantly inhibited the binding of LPS and TLR4 and blocked the activation of signaling pathways downstream of TLR4, including MAPK and NF-κB, thereby suppressing macrophage inflammation. Ludger et al. (141) found similar anti-inflammatory effects of LicA in a model of skin irritation, and the researchers further demonstrated that moisturizers containing LicA can ameliorate disease severity in patients with mild to moderate acne (142). Subsequent investigations have further elucidated the mechanism of action of LicA on acne, revealing its potential for alleviating ear inflammation and swelling symptoms in mice with acne models. *In vitro*, experiments utilizing bone marrow-derived macrophage (BMDM) cells have indicated that LicA hampers NLRP3 inflammasome activation in *C. acnes*-induced macrophages by impeding mitochondrial ROS production. LicA inhibits the production of ROS in macrophages, which are secreted

by M1-type macrophages and can further drive M1 polarisation, so we hypothesized that LicA could inhibit M1-type macrophage polarisation by inhibiting ROS production (143).

4.5 Phenolic compounds from Quercus acutissima Carruth. leaves

The perennial tree Quercus acutissima Carruth., belonging to the Fagaceae family, exhibits anti-allergic, anti-inflammatory, and anti-edema properties, making it an effective treatment for conditions such as eczema, boils, diarrhea, and tonsillitis (144). The researchers conducted a comparative analysis of the effects of phenolic compounds derived from Quercus acutissima Carruth. leaves, namely hyperoside, astragalin, kaempferol 3-O-(6''-galloyl)-β-D-glucopyranoside, quercetin 3-O-(6''-O-galloyl)-β-D-glucopyranoside, pedunculagin, and casuarinin on acne. Among these compounds, casuarinin exhibited superior efficacy. *In vitro* assays using RAW264.7 cells demonstrated that the extracts effectively suppressed the production of NLRP3, IL-1β, and 5α reductase in macrophages. This effect can be attributed to the inhibitory action of phenolic compounds present in Quercus acutissima Carruth. leaves on M1 macrophage polarization and subsequent reduction in inflammatory response (145).

4.6 Cembrene diterpenoids from the cultured soft coral sinularia flexibilis

Diterpenoids, the most abundant class of metabolites in soft corals, exhibit diverse biological activities including anti-tumor, anti-inflammatory, and antibacterial effects (146). The diterpenoid compound derived from Taiwan soft coral has been discovered to possess inhibitory effects on the expression of pro-inflammatory proteins, including iNOS and cyclohexane-2 (COX-2), in LPS-stimulated macrophages (147). Six cembrene diterpenoids were isolated from cultured soft coral sinularia flexibilis by researchers, who observed their significant reduction of ear edema induced by *C. acnes* in rats. Moreover, these compounds demonstrated a decrease in the expression of inducible NO synthase in RAW264.7 cells. We propose that cembrene diterpenoids inhibit M1 macrophage polarization, thereby reducing NO production during this process. Additionally, cembrene diterpenoids were found to significantly inhibit the phosphorylation of related proteins within the MAPK pathway in skin lesions. Therefore, the therapeutic potential of cultured soft coral Sinularia flexibilis-derived cembrene diterpenoids for acne treatment is supported and they play an active role as an alternative therapy for acne patients (148).

4.7 Meconopsis quintuplinervia Regel

The Meconopsis quintuplinervia Regel (MQ), a plant belonging to the genus Meconopsis Vig in the Papaveraceae family, predominantly thrives in the Tibet Autonomous Region. Initial investigations have revealed that its active extract primarily comprises flavonoids and polyphenols. According to Tibetan Medicine Annals, it is documented that MQ possesses properties such as heat-clearing and detoxification, antioxidation, anti-inflammatory, and analgesic effects. It is commonly employed for treating ailments including headaches, hepatitis, pneumonia, and edema, among others (149). In a murine model of acne, it has been observed that MQ mitigates erythema and inflammatory infiltration in ear acne. Furthermore, the expression of M1-related cytokines (IL-6, IL-1β, and TNF-α) was reduced in an inflammatory macrophage cell model, while phosphorylation of proteins associated with the MAPKs pathway such as ERK and JNK was significantly inhibited in RAW264.7 cells. Additionally, nuclear translocation of NF-κB p65 was suppressed. Hence, MQ exhibits therapeutic potential by modulating macrophage infiltration and polarization within acne lesions (150).

4.8 Kaempferia parviflora extracts

The herbaceous plant Kaempferia parviflora (KP), a member of the ginger family (151), exhibits anti-inflammatory, anti-allergic, and anti-obesity effects (152). It is rich in various flavonoids such as 5,7-dimethoxy-flavonoids, 5-hydroxy-3,7,4'- trimethoxyflavone, and 5-hydroxy-3,7- dimethoxyflavone (153), which have been implicated in metabolic diseases, cognitive disorders, and cancer research (154). The extracts of Kaempferia parviflora (KP) were observed to attenuate the expression of inflammatory cytokines, specifically TNF-α, in lipopolysaccharide-stimulated macrophages. Additionally, it exhibited inhibitory effects on NO production and downregulated the expression of iNOS and COX-2. Furthermore, it suppressed the phosphorylation of IκBα and NF-κB as well as the enhanced nuclear translocation of NF-κB p65. Lastly, KP extracts demonstrated an inhibitory effect on sebum cell-mediated lipid synthesis. In conclusion, KP extracts possess potential anti-acne properties by modulating M1 macrophage polarization and reducing inflammatory infiltration (155).

4.9 Jumihaidokuto

Jumihaidokuto (JHT) is a traditional Japanese-Chinese herbal medicine formulated with platycodon root, dandelion, bamboo leaves, bupleurum root, snake seed root, tuckahoe, oak bark, licorice, Schisandra spicule and ginger (156). The herb possesses heat-clearing and detoxifying properties, commonly employed in the treatment of suppurative dermatosis, urticaria, eczema, and athlete's foot among other ailments (156, 157). JHT has demonstrated efficacy in inhibiting acne breakouts (157). Experimental findings indicate that JHT significantly enhances the expression of M2-associated CD206 cells as well as M1-associated CD86 and CD192 markers, suggesting a non-selective activation of macrophages rather than targeting specific subtypes. Considering its observed inhibition of rat ear acne model rashes at 24 hours and beyond, it is hypothesized that macrophage activation may contribute to the reduction or acceleration of dermatitis regression; however, further investigation is required to elucidate the underlying mechanism (158).

5 Conclusion

The pathological features of acne include inflammation, disturbance of sebum metabolism, abnormal androgen regulation, colonization of *C. acnes*, and abnormal keratosis of hair follicles and sebaceous glands (159–163). These characteristics are not independent but rather intertwined and mutually causal (164). With the continuous advancement of research on macrophages in various fields, including inflammation and metabolism, our understanding of macrophages is expanding. As summarized in this paper, the close association between macrophages and acne suggests a reciprocal relationship between these two fields. In the context of acne pathogenesis, macrophages polarize into pro-inflammatory M1 type and secrete pro-inflammatory cytokines, thereby connecting these underlying mechanisms. Although there have been sufficient studies on the role of macrophages in sebum metabolism disorder, abnormal androgen regulation, and colonization of *C. acnes* as independent pathogenic factors (165, 166), their specific involvement in acne remains limited, and further studies are needed to understand the specific mechanisms of macrophage regulation in acne. In recent years, the occurrence and mechanisms of macrophages in the context of inflammatory skin disease have been a focal point of research in the field of dermatology. Further investigation into the mechanism of macrophages in acne will not only advance our knowledge of acne but also shed light on the prevention and treatment of other inflammatory skin disease, such as rosacea (167, 168).

Studies conducted in the past have indicated that natural plant products possess therapeutic properties that can be beneficial in treating acne. However, fewer studies have been conducted on the therapeutic effects of natural plant products on acne through macrophage modulation, focusing mainly on flavonoids, phenols, lignans, and other compound classes. Most of these studies indirectly indicate that they can treat acne through macrophage targeting by investigating the inhibition of M1 macrophage-associated cytokine expression by natural compounds. Moreover, most of these studies are based on animal experiments and lack validation in large-scale, long-term clinical studies. These limitations highlight the need for further research to bridge the gap between basic experiments and clinical translation. We encourage researchers to further explore and elucidate the signaling pathways associated with macrophages, to study the mechanisms linking macrophages to the pathological process of acne, and to further investigate the key targets of natural plant compounds that regulate macrophages, so as to provide value for the development of new drugs and to further provide new ideas and effective strategies for the treatment of acne and even inflammatory skin diseases in the future.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

DZ: Data curation, Conceptualization, Investigation, Writing – original draft. YW: Data curation, Investigation, Writing – review & editing. SW: Data curation, Writing – review & editing. XJ: Data curation, Writing – review & editing. KG: Data curation, Writing – review & editing. HZ: Data curation, Writing – review & editing. MZ: Funding acquisition, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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