

Mechanisms and Recent Advances of Small-Molecule Therapeutics in Rosacea Treatment

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Abstract: Rosacea is a common dermatological disease, and the complexity of its etiology and pathogenesis makes conventional treatment of rosacea difficult. Small-molecule drugs are a new option for the treatment of rosacea. Based on its good efficacy, convenience of use, affordable price and other advantages, more and more small-molecule drugs are used in the treatment and management of rosacea, involving a variety of molecular pathways, including JAK/STAT signaling pathway, TRPV, TLR2-KLK5-LL37 and mTOR pathways, Th1/Th17-IL17, PED-4, AhR and MRGPRX2. However, the specific treatment mechanism and research progress have not been systematically elucidated. This review summarizes the latest advances in small molecules targeting key inflammatory pathways in rosacea, provides new ideas for the treatment of rosacea and new directions for the clinical management of rosacea. In addition, we need to pay attention to individual differences in patients, the side effects of drugs and formulations. Therefore, further research on small-molecule drugs for the treatment of rosacea is very necessary.

Keywords: rosacea, small-molecule drugs, mechanism of action

Introduction

Rosacea is a chronic inflammatory dermatological condition that impacts the facial blood vessels and sebaceous glands of hair follicles, predominantly affecting individuals aged 30 to 50, with a higher incidence among young to middle-aged women. Its clinical presentation encompasses transient or persistent redness (erythema), papules, pustules, and the appearance of telangiectasias on the mid-face,¹ with or without burning, itching and discomfort in the middle of the face,² and some patients can also have dark red plaques or even rhinophyma when the course of the disease is long. The incidence of rosacea in adults worldwide is about 5.46%.³

The origins of rosacea remain unidentified. The onset and recurrence of this disease are related to microecological disorders (such as a large number of Demodex mites,⁴ Propionibacterium acnes⁵), poor skincare habits (such as excessive cleansing,⁶ wrong moisturizing, sun protection and long-term makeup⁷), skin barrier destruction,⁸ ultraviolet rays,⁹ diet,¹⁰ alcohol consumption¹¹ and other factors, and the lesions involve blood vessels, nerves, and hair follicle sebaceous glands.

The underlying etiology of rosacea is multifaceted. The intricate interactions among genetic factors,^{12,13} immune factors (including innate immunity and adaptive immunity imbalance)^{14,15} and neurovascular function factors^{16,17} are involved in the pathogenesis of rosacea.

Rosacea affects the appearance of patients. It frequently induces negative psychological effects, including embarrassment and diminished self-worth,¹⁸ severely impairs the quality of life,¹⁹ and even leads to anxiety and depression.^{20,21} At present, rosacea Western medicine mainly uses antibiotics,²² isotretinoin, hydroxychloroquine,²³ photoelectric therapy^{24–26} and other treatment methods. Western medicine has a certain effect in the treatment of rosacea, but there are many adverse reactions in the treatment,²⁷ and the possibility of recurrence is greater.

Some patients do not respond well to conventional treatment or are unable to tolerate adverse effects. Therefore, there is a need for effective new therapies.



Currently, small molecule inhibitors are at the vanguard of medical research endeavors.²⁸ In recent times, with the ongoing and profound exploration of inflammatory mediators and signaling cascades implicated in the pathophysiology of rosacea, more and more targeted therapies have emerged, including biologics and small-molecule drugs.^{29,30} Compared with biologics, small-molecule drugs with a molecular weight <1 kDa have unique properties: they can act by targeting intracellular targets that biologics cannot act on through cell membranes; Reduce the loss of response caused by immunogenicity of macromolecular proteins; The adjustment of its chemical structure and dosage is conducive to achieving the balance of clinical pharmacokinetics and pharmacodynamics. Convenient oral or topical administration and relatively low cost are more acceptable to patients.^{31,32} For patients with rosacea who are tolerated or even unable to respond to conventional treatment regimens, small-molecule drugs are a new alternative to treatment. This paper provides an overview of the mechanisms of action and advancements in clinical research concerning small-molecule drugs utilized for rosacea treatment in recent years.

JAK/STAT Pathway and JAK Inhibitors

JAK is a class of intracellular, non-transmembrane tyrosine kinases with four isoforms: JAK1, JAK2, JAK3, and Tyk2 (tyrosine kinase 2). Each JAK member binds to a specific cytokine receptor, and its function is related to upstream cytokines: JAK1 is involved in mediating the downstream inflammatory response of cytokines such as IL-6 and IL-13; JAK2 plays a role in being involved in hematopoiesis, especially erythropoiesis; JAK3 is confined to hematopoietic cells and specifically binds to IL-2, IL-4. JAK is activated when membrane receptors specifically bind to cytokines and undergo conformational dimerization, thereby recruiting and phosphorylating signal transduction and transcription factors (signal transducers and activators of transcription, STAT).³³ The JAK-STAT signaling cascade plays a role in the transduction of signals from various cytokines implicated in rosacea pathogenesis.

Research has demonstrated that STAT1³⁴ facilitates communication between keratinocytes and immune cells within the skin, which is associated with both skin barrier function and immune cells and plays a significant role in the pathogenesis of rosacea. The activation of STAT1 can subsequently induce inflammatory cytokines such as IFN- α , IFN- γ , and IL-6.³⁵

Expression of STAT1/3 induces ROS production and release, and ROS-activated pro-inflammatory signaling plays a pivotal role in the immunomodulation of rosacea by mediating inflammatory responses via TLR2 receptors and inducing vasodilation through neurogenic mechanisms.³⁶⁻³⁸

Transcription factor 3 (STAT3) signal transduction and activator overexpression are thought to be associated with skin barrier dysfunction in rosacea.³⁹ In patients with papulopustular rosacea, the researchers found that in addition to the classic inflammatory molecules, the expression of the JAK3 pathway was also abnormally elevated.⁴⁰ One study confirmed that STAT3 is a central gene associated with rosacea and SBD (skin barrier dysfunction) by WGCNA (Weighted Correlation Network Analysis) and suggests that STAT3 may partially promote the progression of rosacea by activating cytokine/chemokine signaling to modulate the immune response.³⁹ In vitro experiments show that tape stripping-induced SBD significantly induces STAT3 expression and increases CD4 T cell infiltration in mouse LL37-induced rosacea skin lesions.³⁹

Elevated levels of JAK2 and STAT3 in ll37-treated HaCaT cells suggest a strong link between JAK/STAT signaling and rosacea inflammatory response. JAK2/STAT3 activation interacts with TLR2 signaling.⁴¹

Upon specific recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), TLR2 initiates a cascade of signaling events, culminating in the secretion of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-8, chemokines, and antimicrobial peptides (AMPs).⁴² TLR2 promotes NLRP3 inflammasome activation, which mediates the release of IL-1 β , and TLR-2 upregulation of KLK-5 expression (KLK-5) to bioactive LL-37, causing erythema, telangiectasia, pustules, and inflammation.^{43,44}

Jak inhibitors block intracellular transcription of JakStat through target genes and have anti-inflammatory, immunomodulatory, or immunopriming effects.^{45,46}

Clinical trials have been conducted on a variety of JAK inhibitors to observe their efficacy and safety in treating rosacea, including tofacitinib, upadacitinib and abrocitinib.

Tofacitinib

Sun YH⁴⁷ et al retrospectively analyzed 21 rosacea patients who underwent treatment with oral tofacitinib. The results of the analysis showed that 71.4% of patients with rosacea had significant resolution of facial erythema. Not only that, topical tofacitinib is also effective in the treatment of rosacea. A study shows that the topical application of tofacitinib led to a significant improvement in rosacea-associated phenotypes, decreased infiltration of CD4+ T cells and mast cells, and suppressed dermal angiogenesis.⁴⁸ Two case reports⁴⁹ highlighted the outcomes of 24 patients with refractory rosacea who underwent treatment with tofacitinib, either as monotherapy or as an adjunctive therapy. Additionally, one instance of steroid-induced rosacea was effectively managed with the JAK inhibitor tofacitinib, without any reported adverse effects.⁵⁰ In conclusion, these reports demonstrate that tofacitinib is effective in treating rosacea and alleviating its symptoms.

Upadacitinib

A case report⁵¹ of 2 patients receiving the JAK1 inhibitor upadacitinib and 4 patients receiving the JAK1 inhibitor abrocitinib for refractory rosacea implied that upadacitinib and abrocitinib, both JAK1 inhibitors, may present as promising therapeutic alternatives for patients suffering from refractory rosacea.

Abrocitinib

A 53-year-old female patient diagnosed with granulomatous rosacea (GR) underwent a 20-week treatment regimen with the JAK-1 inhibitor abrocitinib, which led to a notable enhancement in her rash and alleviated the accompanying burning sensation. Subsequent follow-up evaluations confirmed the absence of any adverse effects or recurrence of symptoms.⁵² Four Chinese women who received oral abrocitinib for steroid-induced rosacea showed significant improvement in skin condition, and no adverse effects were observed.⁵³ Based on this, abrocitinib emerges as a promising candidate for the treatment of steroid-induced rosacea.

AhR Agonists and Applications

The aryl hydrocarbon receptor (AhR), serving as a transcription factor that modulates the immune response in keratinocytes (KCs), holds promise as a therapeutic target for inflammatory skin disorders.⁵⁴ As a cellular component of the innate immune system, KCs is the main constituent cell of the epidermis and plays an important role in the immune barrier by identifying pathogenic microorganisms through pattern recognition receptors (PRRs) and inducing itself and other innate immune cells to produce cytokines, chemokines, and antimicrobial peptides to participate in the immune response. Toll-like receptor (TLR) 2 and some chemokines have been found to be overexpressed in patients with rosacea.^{43,55}

Aryl hydrocarbon receptor (AhR) activation suppresses the inflammatory response induced by TLR activation,⁵⁶ suggesting that AhR agonists may be a potentially effective treatment for rosacea. A study conducted on mice administered with the AhR agonist Benvitimod revealed that activation of AhR decreased the upregulated expression of TLR2 and chemokines, including CCL5, CXCL9, CXCL10, and CXCL11, following treatment with LL-37. In a mouse model of LL-37-induced rosacea, AhR activation proved beneficial for therapeutic purposes. Furthermore, in a HaCaT cell model mimicking rosacea, it was observed that AhR activation involved the inhibition of the TLR signaling pathway.⁵⁷

TRPV Antagonists and Their Applications

Recently, numerous studies have indicated that transient receptor potential (TRP) channel proteins are related to the occurrence and development of rosacea.⁵⁸

Transient receptor potential cation channel subfamily V (TRPV) is a nociceptive cation channel expressed on sensory nerve endings that senses and transduces nociceptive signals. Physical stimuli such as temperature changes and chemical stimuli such as fragrances can activate the release of neuropeptides from sensory nerve endings through transient receptor potential (TRP) family cation channels that play a role in cutaneous neurogenic pain. The TRPV subfamily consists of four non-selective cation channels (TRPV1, TRPV2, TRPV3, and TRPV4) and two high-Ca²⁺-selective channels (TRPV5 and TRPV6).^{59,60}

TRPV1

TRPV1 (transient receptor potential vanillic acid isoform 1) is a cation channel that reacts to high temperatures (>43°C) and capsaicin.⁶¹ Activation of TRPV1 in endothelial cells is involved in NOS and IKCa/SKCa-mediated vasodilation,⁶² suggesting that TRPV1 channels may be involved in the development of transient erythema in the early stages of rosacea.

The researchers performed an in vitro study employing Capsazepine as a TRPV1 antagonist⁶³ to assess the impact of TRPV1 on keratinocytes. Their findings revealed that the application of capsazepine in the treatment of rosacea led to decreased expression levels of TRPV1, tropomyosin receptor kinase A (TrkA), and nerve growth factor (NGF) in keratinocytes. In an in vitro experiment,⁶⁴ the TRPV1 antagonist 4-t-butylcyclohexanol (BCH) alone inhibited the expression of IL-8 and the chemokines CXCL1 and CXCL6 in keratinocytes exposed to rosacea and reduced calcium influx, thereby reducing the inflammatory state of rosacea.

TRPV2

TRPV2 is expressed by various skin and immune cells and may be involved in vascular regulation and immunomodulation.⁶⁵ In rosacea, upregulated TRPV2 can be activated by triggers (eg, harmful heat)⁶⁶ and thus may play a role in the pathophysiology of rosacea.

TRPV3

TRPV3 channels are particularly highly expressed in keratinocytes, where their initial activation requires high temperatures (>50°C) and can be sustainably activated by temperatures in the range of 31~39°C.⁶⁶ It plays a role in the regulation of inflammation, cell differentiation, vasodilation, heat signaling, and nociception.

TRPV4

TRPV4 channel is a multimodally activated multireceptor channel, which is widely distributed in tissues and organs, especially in non-neuronal cells of the epidermis (such as keratinocytes, mast cells, macrophages) and skin neuronal cells and can be activated by a wide range of stimuli such as temperature in the range of 24~33°C, mechanical stimulation, pH, ultraviolet irradiation, and endogenous inflammatory mediators, and can be activated by regulating the osmotic pressure of a variety of cations in edema, vasodilation, angiogenesis caused by shear stress, and inflammation to play a role.⁶⁷⁻⁶⁹

Activated TRPV4 channels promote endothelial eNOS activity and NO release, inducing vasodilation⁷⁰ and leading to sudden facial flushing and persistent erythema. TRPV4 is also involved in the mechanism of rosacea pruritus.⁷¹

In summary, the TRPV pathway plays an important role in the occurrence and development of rosacea. Existing studies have proposed the effectiveness of (TRPV)1 antagonist, including capsazepine and 4-t-butylcyclohexanol, in the treatment of rosacea, so pinpointing this pathway as a potential therapeutic target could signify a pivotal advancement in rosacea research, with the potential to lead to more effective and targeted rosacea treatments.

The TLR2-KLK5-LL37 Axis and mTOR-Related Pathways and Their Therapeutic Drugs

Rosacea is a chronic inflammatory skin disease prone to the central facial region. Its pathogenesis involves a variety of complex biological pathways, among which TLR2 (Toll-like receptor 2) -KLK5 (kallikrein 5) - LL37 (antimicrobial peptide) and mTOR (mammalian target of rapamycin) pathways play key roles^{72,73}

In the pathogenesis of rosacea, external stimuli such as ultraviolet (UV) radiation, Demodex colonization, and microbial infection can directly or indirectly lead to the enhancement of KLK5 activity through the TLR2 pathway. KLK5, as a cutaneous stratum corneum trypsin, catalyzes the antimicrobial peptide precursor into the activated form of LL37. LL37 plays a crucial role in innate immunity, exhibiting both antibacterial and inflammatory-inducing properties. Not only does it directly kill microorganisms, but it also triggers a cascade of inflammatory responses by activating multiple cell types, such as macrophages, neutrophils, T cells, mast cells, and plasmacytoid dendritic cells (pDCs). Notably, the binding of LL37 to TLR2 can further activate the mTOR signaling pathway. The activation of mTOR, in turn, promotes the generation of LL37, forming a positive feedback loop.³ The abundant LL37 production of this circuit

further stimulates NF- κ B signaling activation and the production of related cytokines and chemokines, thereby amplifying the inflammatory response and promoting the development and progression of rosacea. In addition, studies have shown that the mTORC1 (complex 1 of mTOR) signaling pathway is highly enriched in lesions in rosacea patients and mouse models.⁷⁴

In LL37-induced rosacea-like mouse models, either epidermal-specific knockout or drug inhibition of mTORC1 significantly ameliorates the rosacea-like phenotype. The enhanced amplified regulatory loop formed by mTORC1-LL37 may be one of the reasons why rosacea is difficult to cure. Therefore, treatment strategies targeting this pathway may provide a new direction for the treatment of rosacea.

Therapeutics targeting this signaling pathway include retinoids, azelaic acid, doxycycline, carvedilol, and ivermectin, and multiple studies have confirmed their effectiveness against rosacea.

Retinoic Acids and Azelaic Acid

Tretinoin and azelaic acid exhibit significant anti-inflammatory effects in the treatment of rosacea, which can significantly reduce the mRNA levels of TLR2 and KLK5, thereby reducing the production of LL37. Its anti-inflammatory effect may indirectly affect the activity of the mTOR pathway. A meta-analysis of 20 studies of rosacea⁷⁵ showed significant improvements in erythema severity and inflammatory lesion count after treatment of rosacea with azelaic acid.

Doxycycline

Doxycycline may indirectly affect the expression of KLK5 and LL37 by reducing the bacterial load by reducing TLR2 activation.⁷⁶ However, it is crucial to acknowledge that prolonged antibiotic use may result in the development of resistance and disrupt gut microbiota balance. Therefore, we need to use them sparingly.

Carvedilol

Carvedilol is a β receptor blocker, and carvedilol is able to inhibit sympathetic-mediated flushing and inflammation, which may help reduce the symptoms of rosacea.⁷⁷ Retrospective analysis suggests that carvedilol can be an effective and safe treatment option for patients with rosacea with facial flushing and erythema.⁷⁸

Ivermectin

Ivermectin is a broad-spectrum antiparasitic agent that also has some anti-inflammatory effects. In rosacea, ivermectin may inhibit the activation of the endoplasmic reticulum stress kinase p38 through ivermectin, thereby inhibiting the activation of the pro-inflammatory transcription factor NF- κ B.⁷⁹ This mechanism of action helps to reduce LL37 production and inflammatory responses.

There may be some crossover and mutual influence of the drugs mentioned above on the mechanism of action of TLR2-KLK5-LL37 and the mTOR pathway.

In conclusion, the pathways involving TLR2-KLK5-LL37 and mTOR are pivotal in the development of rosacea. The treatment strategies targeting this pathway may bring breakthroughs in the treatment of rosacea.

NLRP3 Inflammasome and Related Small-Molecule Drugs

Tranilast (TR)

TR is an anti-allergic clinical drug, a direct NLRP3 inhibitor, and a derivative of tryptophan. It has been studied for its role in various fibrosis, such as for COVID-19,⁸⁰ hypertensive heart disease,⁸¹ and so on. NLRP3 plays an important role in the development of rosacea, inducing the release of multiple inflammatory factors, including IL-1 β and IL-18, leading to inflammatory responses in the skin. A recent animal experiment⁸² on Tranilast showed that TR can effectively reduce the expression levels of inflammatory cytokines TNF- α , IL-1 β , IL-6 and IL-18 associated with rosacea, and inhibit the activation of NLRP3 inflammasomes, reducing skin inflammation and fibrosis in rosacea-like mice.

Supramolecular Salicylic Acid (SSA)

SSA is an intermolecular water-soluble supramolecular salicylic acid aggregate formed by molecular recognition and self-assembly of non-water-soluble salicylic acid molecules through modern supramolecular chemistry technology. It has keratolytic, antibacterial, and anti-inflammatory properties. Supramolecular salicylic acid effectively inhibits the production of multiple biomarkers associated with rosacea, including Toll-like receptor 2, matrix metalloproteinase 9, kallikrein 5, and LL-37. At the same time, it also blocks the activation process of inflammasomes mediated by LL-37-induced NLRP3,⁸³ which plays an important role in the treatment of papulopustular rosacea (PPR).⁸⁴

MCC950

MCC950 is a selective small molecule inhibitor specifically designed to target NLRP3 inflammasome activation. Recently, research on MCC950 has been broadening, and its mechanisms of action have become increasingly elucidated.⁸⁵ The NLRP3-specific inhibitor MCC950 protects the treatment of NLRP3-mediated inflammatory diseases, such as rosacea, which is effective in alleviating the LL37-triggered rosacea-like phenotype and attenuating the inflammatory response.⁸⁶

Th1/Th17-IL17 in Rosacea and Therapeutic Drugs

Studies conducted recently have highlighted the significant role of the Th1/Th17-IL-17 pathway in the pathogenesis of rosacea.⁸⁷ In the onset of rosacea, an imbalance in the immune system plays a key role. In particular, Th1 and Th17 subsets in T helper cells (Th cells) regulate the immune response by secreting specific cytokines. Th1 cells mainly secrete cytokines such as interferon- γ (IFN- γ) and participate in cellular immune responses. Th17 cells, on the other hand, mainly secrete cytokines such as interleukin-17 (IL-17), which are involved in inflammatory response and tissue damage. The signaling pathway involving IL-17 is crucial in rosacea, impacting angiogenesis and the production of inflammatory cytokines.⁷³ IL-17 can act on a variety of cell types, such as keratinocytes, endothelial cells, monocytes, and fibroblasts, inducing them to secrete more pro-inflammatory factors such as IL-6, IL-1 β , and tumor necrosis factor (TNF). These cytokines further activate immune cells, forming a positive feedback loop that exacerbates the inflammatory response.⁸⁸

Hence, the Th1/Th17-driven IL-17 pathway holds a significant role in the underlying mechanisms of rosacea. Therapeutic strategies targeting this pathway – inhibiting the differentiation of Th17 cells and blocking IL-17 signaling – may provide new directions and hope for the treatment of rosacea.

Aspirin

One study⁸⁹ using RNA sequencing analysis showed that aspirin relieves inflammation of rosacea primarily by modulating the immune response. Aspirin decreased the levels of chemokines and cytokines implicated in rosacea and inhibited the Th1 and Th17 polarized immune responses in LL37-induced rosacea-like mice.

Thalidomide

The study found⁹⁰ that thalidomide reduced LL37-induced cytokine and chemokine production in mouse skin and HaCaT keratinocytes, while also reducing CD4+ T helper cell infiltration and downregulating Th1 and Th17 polarization genes.

In addition, both aspirin and thalidomide can reduce vascular endothelial growth factor (VEGF) expression in rosacea.^{89,90}

Small-Molecule Drugs That Inhibit Phosphodiesterase-4 to Regulate Inflammatory Balance (PDE4)

Phosphodiesterases (PDEs) are a large multigene family of 11 isoforms (PDE1-PDE11), which can degrade cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).⁹¹ PDE4 is found in immune cells such as keratinocytes, dendritic cells, T cells, and eosinophils in the skin.⁹² PDE4 plays a key regulatory role in the production of pro-inflammatory cytokines by specifically hydrolyzing cAMP, which regulates the cascade of inflammatory signaling, such as the nuclear factors that activate T lymphocytes, and then control the expression of cytokines such as IL-2, IL-4, IL-10, and IL-13.⁹³

Research indicates that the activity of PDE4 is linked to prostaglandin E2 (PGE2), which promotes the upregulation of IL-10 levels and inhibits the expression of tumor necrosis factor (TNF)- α , resulting in Th1/Th2 imbalance.⁹⁴

Phosphodiesterase inhibitor 4 has undergone testing for the management of various inflammatory skin disorders⁹⁵ but has been less studied for the treatment of rosacea. In a pilot study⁹⁶ of moderate to severe inflammatory rosacea treated with the oral phosphodiesterase-4 inhibitor apremilast, the results showed improvement in erythema, but the primary endpoint of papule and pustule counts was not met statistically significant. Therefore, the PDE4 inhibitor apremilast may be a new alternative therapy for rosacea.

MRGPRX2 Antagonists

Ogasawara et al identified two MRGPRX2 antagonists that have the potential to prevent IGE-independent allergic reactions by specifically blocking MRGPRX2-mediated activation of human mast cells.⁹⁷ Cutaneous mast cells (MCs) express the Mas-associated G protein-coupled receptor-X2, the inappropriate activation of which may lead to the production of rosacea.

MRGPRX2 has now been identified as a target receptor for LL37, which causes MCs degranulation, the release of inflammatory mediators (IL-8, IL-13, IL-17, IL-31) and chemotaxis,⁹⁸ leading to the development of associated symptoms such as rosacea flushing, erythema, and papules. MCs expressing MRGRPX2 on skin biopsy has been reported to be positively associated with symptoms in patients with rosacea.¹⁵ MRGPRX2 is emerging as a new drug target, and MRGPRX2-specific antibodies and inhibitors are a new way to treat rosacea.

Challenges

Most of the existing data on the safety of small-molecule drugs come from small-scale clinical trials, animal trials, retrospective studies or case reports, and the level of evidence is limited, and large-scale clinical trials are urgently needed for further validation. Emerging targeted agents, such as JAK inhibitors, have shown potential, but the risk of infection associated with immunosuppression⁹⁹ needs to be further evaluated. Doxycycline, a therapeutic drug associated with the TLR2-KLK5-LL37 pathway, is widely used in papulopustular rosacea¹⁰⁰ and has a generally good safety profile, but long-term use may cause gastrointestinal upset, photosensitivity, and the risk of microbial resistance. Isotretinoin is effective in recalcitrant rosacea, but its adverse effects such as teratogenicity, dyslipidemia and dry skin limit its clinical application, especially in women of childbearing age. Thalidomide plays a role in the treatment of rosacea through the Th1/Th17-IL17 pathway, but its use should be closely monitored due to its potential adverse effects, especially teratogenicity.¹⁰¹

Limitations of the available studies included insufficient sample size and follow-up time, with most studies having small sample sizes and short follow-up periods, making it difficult to assess rare or long-term adverse effects. Analysis of population heterogeneity was insufficient, and the existing trials were mostly population-specific, lacking subgroup analysis of patients with comorbidities. Real-world data in existing studies are relatively lacking, and post-marketing monitoring data are sparse, especially the long-term safety of novel small-molecule drugs has not yet been determined.

Conclusions

In recent years, with further research on rosacea, more and more signaling pathways and their molecule receptors have been found to be involved in the pathogenesis of rosacea (Figure 1 and Table 1), including jak/stat signaling pathway, TRP channel, TLR2-KLK5-LL37 and mTOR-associated pathways, Th1/Th17-IL17, PED-4, AhR, transient receptor potential ankyrin (TRPA)1, MRGPRX2. Small molecule inhibitors targets or molecular receptors may be a potential treatment option for the clinical treatment of rosacea in the future, but more clinical research data are still needed.

Small molecule inhibitors represent a promising treatment for inflammatory skin diseases due to their ease of administration, high bioavailability, and good safety profile, and recent studies on small-molecule drugs related to rosacea treatment have shown that small-molecule drugs are a new alternative option for the treatment of rosacea. At present, the long-term safety and durability of small-molecule drugs in the treatment of rosacea are still unclear. The existing clinical data are rather limited. Therefore, larger, randomized clinical trials are necessary to assess the efficacy and safety of these medications comprehensively. At the same time, more in-depth clinical and molecular phenotyping studies on rosacea are needed at the mechanism level. In the future, how to improve the selectivity of small-molecule drug targets and discover new targeted

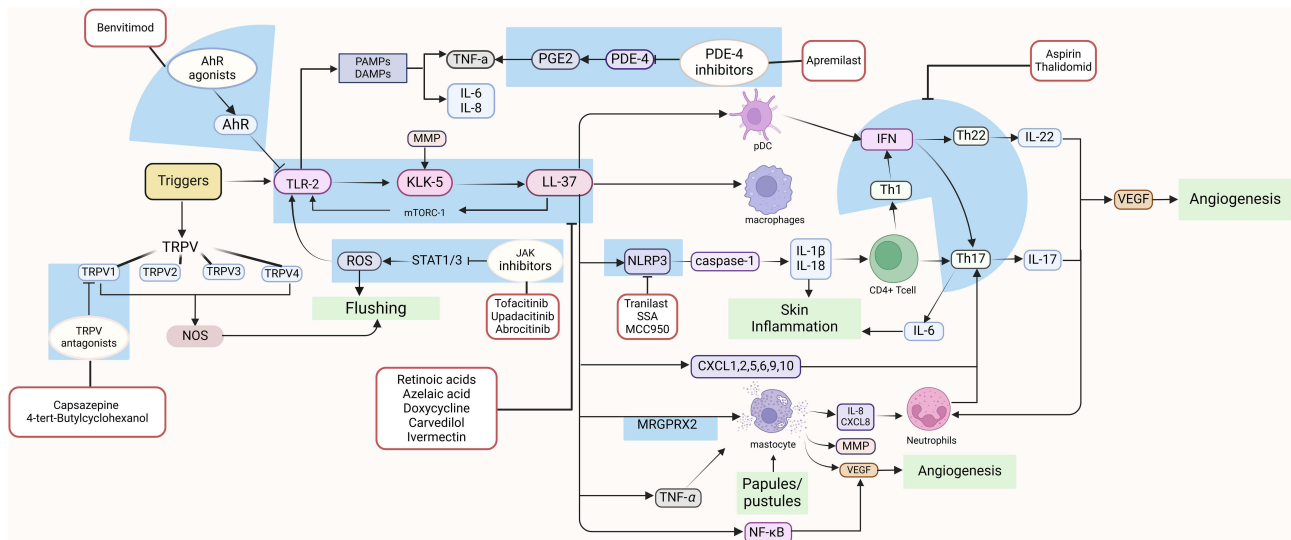


Figure 1 Pathogenesis of rosacea and the key points of action of small-molecule drugs. Triggers include microbiome disorders (eg, lots of Demodex mites, Propionibacterium acnes), ultraviolet rays, temperature changes, mental stress, poor skincare habits (eg, over-cleansing, wrong moisturizing, sun protection and long-term makeup), diet, alcohol consumption, etc. The blue area represents the target and mode of action of the small molecule drug. The green area represents clinical signs associated with rosacea. The red boxes indicate small-molecule drugs that have a therapeutic effect on related targets and pathways. (Created in BioRender. Ye, m. (2025) <https://BioRender.com/e44x077>).

molecules is also one of the focuses of basic research in the exploration of small-molecule drugs for the treatment of rosacea. Overall, small-molecule therapeutics offer a promising new approach in rosacea management by targeting critical inflammatory pathways, yet robust clinical trials are imperative to validate their efficacy and safety.

Table 1 Summary of Key Signaling Pathways and Small-Molecule Therapeutics in Rosacea Treatment

Pathway	Targeted Molecule(s)	Small Molecule Drug(s)	References
JAK/STAT	STAT1, STAT3, JAK1, JAK2	Tofacitinib, Upadacitinib, Abrocitinib,	Sun YH, 2022 ⁴⁷ Sun R, 2024 ⁴⁸ Zhang T, 2024 ⁵¹
AhR	TLR2	Benvitimod	Ren M, 2023 ⁵² Kado, 2017 ⁵⁶ Sun Y, 2022 ⁵⁷
TRPV	TRPV1, TRPV2, TRPV3, TRPV4	Capsazepine, 4-t-butylcyclohexanol	Lee SG, 2023 ⁶³ Hernandez-Pigeon H, 2018 ⁶⁴ Marziano C, 2017 ⁷⁰
TLR2-KLK5-LL37 and mTOR	TLR2, KLK5, LL37, mTOR1	Retinoids, Azelaic Acid, Doxycycline, Carvedilol, Ivermectin	King S, 2023 ⁷⁵ Seo BH, 2020 ⁷⁸ Lee JJ, 2024 ⁷⁹
NLRP3	IL-1β, IL-18	TR, SSA, MCC950	Jin H, 2024 ⁸² Xu L, 2022 ⁸⁴ Yoon SH, 2021 ⁸⁶
Th1/Th17-IL17	Th1, Th17, Th22, IL-6, IL-17, IL-22, IFN	Aspirin, Thalidomid	Yang F, 2024 ⁷³ Amir Ali A, 2019 ⁸⁸ Deng Z, 2021 ⁸⁹ Chen M, 2019 ⁹⁰

(Continued)

Table 1 (Continued).

Pathway	Targeted Molecule(s)	Small Molecule Drug(s)	References
PDE4	PGE2, TNF- α	Apremilast	FERTIG B A, 2018 ⁹³ Thompson BJ, 2013 ⁹⁶
MRGPRX2	LL37, IL-8, MMP	Rocuronium, ZINC3573, C48/80	Roy S, 2021 ⁹⁷ Alkanfari I, 2022 ⁹⁸

Abbreviations: JAK/STAT, Janus kinase/signal transducer and activator of transcription; AhR, Aryl Hydrocarbon Receptor; TRPV, Transient receptor potential cation channel subfamily V; TLR2, Toll-like receptor 2; KLK5, kallikrein 5; LL37, Antimicrobial Peptide; mTOR, mammalian target of rapamycin; NLRP3, Nucleotide binding oligomerization domain-like receptor protein3; PDE4, Phosphodiesterase 4; MRGPRX2, Mas-related G protein-coupled receptor-X2; TR, Tranilast; SSA, Supramolecular Salicylic Acid; PGE2, prostaglandin E2; MMP, Matrix Metalloproteinase; IFN, Interferon; TNF- α , Tumor necrosis factor- α ; IL, Interleukin.

Data Sharing Statement

The datasets generated during the current study are available.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

- Li Y, Wang R. Efficacy comparison of pulsed dye laser vs. microsecond 1064-nm neodymium: yttrium-aluminum-garnet laser in the treatment of rosacea: a meta-analysis. *Front Med.* 2022;8:798294. doi:10.3389/fmed.2021.798294
- Gether L, Overgaard LK, Egeberg A, Thyssen JP. Incidence and prevalence of rosacea: a systematic review and meta-analysis. *Br J Dermatol.* 2018;179(2):282–289. doi:10.1111/bjd.16481
- Deng Z, Chen M, Liu Y, et al. A positive feedback loop between mTORC1 and cathelicidin promotes skin inflammation in rosacea. *EMBO Mol Med.* 2021;13:e13560. doi:10.15252/emmm.202013560
- Forton F, De Maertelaer V. Erythematotelangiectatic rosacea may be associated with a subclinical stage of demodicosis: a case-control study. *Br J Dermatol.* 2019;181(4):818–825.
- Kim HS. Microbiota in rosacea. *Am J Clin Dermatol.* 2020;21(1):25–35. doi:10.1007/s40257-020-00546-8
- Li G, Wang B, Zhao Z, et al. Excessive cleansing: an underestimating risk factor of rosacea in Chinese population. *Archives of Dermatological Res.* 2021;313(4):225–234. doi:10.1007/s00403-020-02095-w
- Huang Y, Li J, Zhao Z, et al. Effects of skin care habits on the development of rosacea: a multi-center retrospective case-control survey in Chinese population. *PLoS One.* 2020;15(4):e0231078. doi:10.1371/journal.pone.0231078
- Medgyesi B, Dajnoki Z, Béke G, et al. Rosacea is characterized by a profoundly diminished skin barrier. *J Invest Dermatol.* 2020;140(10):1938–1950.e5. doi:10.1016/j.jid.2020.02.025

9. McCoy IV WH. "Shedding light" on how ultraviolet radiation triggers rosacea. *J Invest Dermatol.* 2020;140(3):521–523. doi:10.1016/j.jid.2019.09.008
10. Yuan X, Huang X, Wang B, et al. Relationship between rosacea and dietary factors: a multicenter retrospective case–control survey. *J Dermatol.* 2019;46(3):219–225. doi:10.1111/1346-8138.14771
11. Li S, Cho E, Drucker AM, et al. Alcohol intake and risk of rosacea in US women. *J Am Acad Dermatol.* 2017;76(6):1061–1067.e2. doi:10.1016/j.jaad.2017.02.040
12. Aldrich N, Fu P, Fu P, et al. Genetic vs environmental factors that correlate with rosacea: a cohort-based survey of twins. *JAMA Dermatol.* 2015;151(11):1213–1219. doi:10.1001/jamadermatol.2015.2230
13. Yazici AC, Tamer L, Ikizoglu G, et al. GSTM1 and GSTT1 null genotypes as possible heritable factors of rosacea. *Photodermatol Photoimmunol Photomed.* 2006;22(4):208–210. doi:10.1111/j.1600-0781.2006.00220.x
14. Teraki Y, Hitomi K, Sato Y, et al. Tacrolimus-induced rosacea-like dermatitis: a clinical analysis of 16 cases associated with tacrolimus ointment application. *Dermatology.* 2012;224:309–314. doi:10.1159/000338693
15. Muto Y, Wang Z, Vanderberghe M, et al. Mast cells are key mediators of cathelicidin-initiated skin inflammation in rosacea. *J Invest Dermatol.* 2014;134:2728–2736. doi:10.1038/jid.2014.222
16. Kulkarni NN, Takahashi T, Sanford JA, et al. Innate immune dysfunction in rosacea promotes photosensitivity and vascular adhesion molecule expression. *J Invest Dermatol.* 2020;140(3):645–655. doi:10.1016/j.jid.2019.08.436
17. Egeberg A, Hansen PR, Gislason GH, et al. Exploring the association between rosacea and Parkinson disease: a Danish nationwide cohort study. *JAMA Neurol.* 2016;73(5):529–534. doi:10.1001/jamaneurol.2016.0022
18. van Zuuren EJ. Rosacea. *N Engl J Med.* 2017;377(18):1754–1764. doi:10.1056/NEJMcpl506630.
19. Huang Y, Yan S, Xie H, et al. Health related quality of life of rosacea patients in china assessed by dermatology life quality index and willingness to pay. *Patient Preference Adherence.* 2022;16:659. doi:10.2147/PPA.S345258
20. Chen M, Deng Z, Huang Y, et al. Prevalence and risk factors of anxiety and depression in rosacea patients: a cross-sectional study in China. *Frontiers in Psychiatry.* 2021;12:912.
21. Chang HC, Huang YC, Lien YJ, et al. Association of rosacea with depression and anxiety: a systematic review and meta-analysis. *J Affective Disorders.* 2021;299:239–245. doi:10.1016/j.jad.2021.12.008
22. Di Nardo A, Holmes AD, Muto Y, et al. Improved clinical outcome and biomarkers in adults with papulopustular rosacea treated with doxycycline modified-release capsules in a randomized trial. *J Am Acad Dermatol.* 2016;74(6):1086–1092. doi:10.1016/j.jaad.2016.01.023
23. Wang B, Yuan X, Huang X, et al. Efficacy and safety of hydroxychloroquine for treatment of patients with rosacea: a multicenter, randomized, double-blind, double-dummy, pilot study. *J Am Acad Dermatol.* 2021;84(2):543–545. doi:10.1016/j.jaad.2020.05.050
24. Fan L, Yin R, Lan T, et al. Photodynamic therapy for rosacea in Chinese patients. *Photodiagn Photodyn Ther.* 2018;24:82–87. doi:10.1016/j.pdpdt.2018.08.005
25. Luo Y, Luan XL, Zhang JH, et al. Improved telangiectasia and reduced recurrence rate of rosacea after treatment with 540 nm-wavelength intense pulsed light: a prospective randomized controlled trial with a 2-year follow-up. *Exp Ther Med.* 2020;19(6):3543–3550.
26. Zhang Y, Jiang S, Lu Y, et al. A decade retrospective study of light/laser devices in treating nasal rosacea. *J Dermatological Treat.* 2020;31(1):84–90. doi:10.1080/09546634.2019.1580669
27. Zhang H, Tang K, Wang Y, Fang R, Sun Q. Rosacea treatment: review and update. *Dermatol Ther.* 2021;11(1):13–24. doi:10.1007/s13555-020-00461-0
28. Chen C, Wang P, Zhang L, et al. Exploring the pathogenesis and mechanism-targeted treatments of rosacea: previous understanding and updates. *Biomedicines.* 2023;11(8):2153. doi:10.3390/biomedicines11082153
29. Meng X, Zhong Y, Kuang X, et al. Targeting the STAT3/IL-36G signaling pathway can be a promising approach to treat rosacea. *J Adv Res.* 2024. doi:10.1016/j.jare.2024.06.013
30. Kalhan V, Sadick N. The latest drugs and small molecule inhibitors for skin and hair. *J Drugs Dermatol.* 2017;16(12):1224–1228.
31. Torres T, Filipe P. Small molecules in the treatment of psoriasis. *Drug Dev Res.* 2015;76(5):215–227.
32. Adams JL, Smothers J, Srinivasan R, et al. Big opportunities for small molecules in immuno-oncology. *Nat Rev Drug Discov.* 2015;14(9):603–622.
33. Szilveszter KP, Németh TM, Mócsai A. Tyrosine kinases in autoimmune and inflammatory skin diseases. *Front Immunol.* 2019;10:1862.
34. Deng Z, Liu F, Chen M, et al. Keratinocyte-immune cell crosstalk in a STAT1-mediated pathway: novel insights into Rosacea pathogenesis. *Front Immunol.* 2021;12:674871. doi:10.3389/fimmu.2021.674871
35. Olbrich P, Freeman AF. STAT1 and STAT3 mutations: important lessons for clinical immunologists. *Expert Rev Clin Immunol.* 2018;14(12):1029–1041.
36. Wang Y, Yu X, Song H, et al. The STAT-ROS cycle extends IFN-induced cancer cell apoptosis. *Int J Oncol.* 2018;52(1):305–313. doi:10.3892/ijo.2017.4196
37. Zhang Y, Li Y, Zhou L, et al. Nav1.8 in keratinocytes contributes to ROS-mediated inflammation in inflammatory skin diseases. *Redox Biol.* 2022;55:102427. doi:10.1016/j.redox.2022.102427
38. Graepel R, Fernandes ES, Aubdool AA, Andersson DA, Bevan S, Brain SD. 4-oxo-2-nonenal (4-ONE): evidence of transient receptor potential ankyrin 1-dependent and -independent nociceptive and vasoactive responses in vivo. *J Pharmacol Exp Ther.* 2011;337(1):117–124. doi:10.1124/jpet.110.172403
39. Wang Y, Wang B, Huang Y, et al. Multi-transcriptomic analysis and experimental validation implicate a central role of STAT3 in skin barrier dysfunction induced aggravation of rosacea. *J Inflamm Res.* 2022;15:2141–2156. doi:10.2147/JIR.S356551
40. Shih YH, Xu J, Kumar A, et al. Alterations of immune and keratinization gene expression in papulopustular rosacea by whole transcriptome analysis. *J Invest Dermatol.* 2020;140(5):1100–1103. doi:10.1016/j.jid.2019.09.021
41. Liu YD, Yu L, Ying L, et al. Toll-like receptor 2 regulates metabolic reprogramming in gastric cancer via superoxide dismutase 2. *Int J Cancer.* 2019;144:3056–3069. doi:10.1002/ijc.32060
42. Margalit A, Kowalczyk MJ, Zaba R, et al. The role of altered cutaneous immune responses in the induction and persistence of rosacea. *J Dermatol Sci.* 2016;82(1):3–8. doi:10.1016/j.jdermsci.2015.12.006

43. Woo YR, Lim JH, Cho DH, et al. Rosacea: molecular mechanisms and management of a chronic cutaneous inflammatory condition. *Int J Mol Sci.* 2016;17:1562.
44. Casas C, Paul C, Lahfa M, et al. Quantification of demodex folliculorum by PCR in rosacea and its relationship to skin innate immune activation. *Exp Dermatol.* 2012;21:906–910. doi:10.1111/exd.12030
45. Xin P, Xu X, Deng C, et al. The role of JAK/STAT signaling pathway and its inhibitors in diseases. *Int Immunopharmacol.* 2020;80:106210. doi:10.1016/j.intimp.2020.106210
46. Xue C, Yao Q, Gu X, et al. Evolving cognition of the JAK-STAT signaling pathway: autoimmune disorders and cancer. *Signal Transduct Target Ther.* 2023;8(1):204. doi:10.1038/s41392-023-01468-7
47. Sun YH, Man XY, Xuan XY, Huang CZ, Shen Y, Lao LM. Tofacitinib for the treatment of erythematotelangiectatic and papulopustular rosacea: a retrospective case series. *Dermatol Ther.* 2022;35(11):e15848. doi:10.1111/dth.15848
48. Sun R, Fan H, Liu J, et al. The treatment of Tofacitinib for rosacea through the inhibition of the JAK/STAT signaling pathway. *Arch Dermatol Res.* 2024;316(8):566. doi:10.1007/s00403-024-03314-4
49. Yaqi Cao LA, Han C, Jianwen Han: evaluation of the efficacy of tofacitinib in the treatment of 3 cases of refractory rosacea. *Dermatol Venereol.* 2023;66–69. doi:10.3969/j.issn.1002-1310.2023.01.016
50. Li T, Wang H, Wang C, Hao P. Tofacitinib for the treatment of steroid-induced rosacea. *Clin Cosmet Invest Dermatol.* 2022;15:2519–2521. doi:10.2147/CCID.S392280
51. Zhang T, Liu X, Zhang L, Jiang X. Treatment of rosacea with upadacitinib and abrocitinib: case report and review of evidence for Janus kinase inhibition in rosacea. *Front Immunol.* 2024;15:1416004. doi:10.3389/fimmu.2024.1416004
52. Ren M, Yang X, Teng Y, Lu W, Ding Y, Tao X. Successful treatment of granulomatous rosacea by jak inhibitor abrocitinib: a case report. *Clin Cosmet Invest Dermatol.* 2023;16:3369–3374. doi:10.2147/CCID.S440138
53. Xu B, Xu Z, Ye S, et al. JAK1 inhibitor abrocitinib for the treatment of steroid-induced rosacea: case series. *Front Med.* 2023;10:1239869. doi:10.3389/fmed.2023.1239869
54. Wang L, Cheng B, Ju Q, Sun BK. AhR regulates peptidoglycan-induced inflammatory gene expression in human keratinocytes. *J Innate Immun.* 2022;14(2):124–134. doi:10.1159/000517627
55. Yamasaki K, Kanada K, Macleod DT, et al. TLR2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes. *J Invest Dermatol.* 2011;131(3):688–697. doi:10.1038/jid.2010.351
56. Kado S, Chang WLW, Chi AN, Wolny M, Shepherd DM, Vogel CFA. Aryl hydrocarbon receptor signaling modifies toll-like receptor-regulated responses in human dendritic cells. *Archives of Toxicology.* 2017;91:2209–2221. doi:10.1007/s00204-016-1880-y
57. Sun Y, Chen L, Wang H, et al. Activation of aryl hydrocarbon receptor ameliorates rosacea-like eruptions in mice and suppresses the TLR signaling pathway in LL-37-induced HaCaT cells. *Toxicol Appl Pharmacol.* 2022;451:116189. doi:10.1016/j.taap.2022.116189
58. Rainer BM, Kang S, Chien AL. Rosacea: epidemiology, pathogenesis, and treatment. *Dermatoendocrinol.* 2017;9:e1361574. doi:10.1080/19381980.2017.1361574
59. Nilius B, Owsianik G, Voets T, et al. Transient receptor potential cation channels in disease. *Physiol Rev.* 2007;87:165–217. doi:10.1152/physrev.00021.2006
60. Baylie RL, Brayden JE. TRPV channels and vascular function. *Acta Physiol.* 2011;203:99–116. doi:10.1111/j.1748-1716.2010.02217.x
61. Boillat A, Alijevic O, Kellenberger S. Calcium entry via TRPV1 but not ASICs induces neuropeptide release from sensory neurons. *Mol Cell Neurosci.* 2014;61:13–22.
62. Poblete IM, Orliac ML, Briones R, et al. Anandamide elicits an acute release of nitric oxide through endothelial TRPV1 receptor activation in the rat arterial mesenteric bed. *J Physiol.* 2005;568:539–551. doi:10.1113/jphysiol.2005.094292
63. Lee SG, Kim J, Lee YI, et al. Cutaneous neurogenic inflammation mediated by TRPV1-NGF-TRKA pathway activation in rosacea is exacerbated by the presence of Demodex mites. *J Eur Acad Dermatol Venereol.* 2023;37(12):2589–2600. doi:10.1111/jdv.19449
64. Hernandez-Pigeon H, Garidou L, Galliano MF, et al. Effects of dextran sulfate, 4-t-butylcyclohexanol, pongamia oil and hesperidin methyl chalcone on inflammatory and vascular responses implicated in rosacea. *Clin Cosmet Inv Derm.* 2018;11:421–429.
65. Link TM, Park U, Vonakis BM, et al. TRPV2 has a pivotal role in macrophage particle binding and phagocytosis. *Nat Immunol.* 2010;11:232–239. doi:10.1038/ni.1842
66. Sulk M, Seeliger S, Aubert J, et al. Distribution and expression of non-neuronal transient receptor potential (TRPV) ion channels in rosacea. *J Invest Dermatol.* 2012;132(4):1253–1262. doi:10.1038/jid.2011.424
67. Dutta B, Arya RK, Goswami R, et al. Role of macrophage TRPV4 in inflammation. *Lab Invest.* 2020;100:178–185. doi:10.1038/s41374-019-0334-6
68. Sonkusare SK, Laubach VE. Endothelial TRPV4 channels in lung edema and injury. *Curr Top Membr.* 2022;89:43–62.
69. Chen YL, Sonkusare SK. Endothelial TRPV4 channels and vasodilator reactivity. *Curr Top Membr.* 2020;85:89–117.
70. Marziano C, Hong K, Cope EL, et al. Nitric oxide-dependent feedback loop regulates transient receptor potential vanilloid 4 (TRPV4) channel cooperativity and endothelial function in small pulmonary arteries. *J Am Heart Assoc.* 2017;6:e007157.
71. Zhou X, Su Y, Wu S, Wang H, Jiang R, Jiang X. The temperature-sensitive receptors TRPV4 and TRPM8 have important roles in the pruritus of rosacea. *J Dermatol Sci.* 2022;108(2):68–76. doi:10.1016/j.jdermsci.2022.11.004
72. Lee JB, Bae SH, Moon KR, Na EY, Yun SJ, Lee SC. Light-emitting diodes downregulate cathelicidin, kallikrein and toll-like receptor 2 expressions in keratinocytes and rosacea-like mouse skin. *Exp Dermatol.* 2016;25(12):956–961. doi:10.1111/exd.13133
73. Yang F, Wang L, Song D, et al. Signaling pathways and targeted therapy for rosacea. *Front Immunol.* 2024;15:1367994. doi:10.3389/fimmu.2024.1367994
74. Peng Q, Sha K, Liu Y, et al. mTORC1-mediated angiogenesis is required for the development of rosacea. *Front Cell Dev Biol.* 2021;9:751785. doi:10.3389/fcell.2021.751785
75. King S, Campbell J, Rowe R, Daly ML, Moncrieff G, Maybury C. A systematic review to evaluate the efficacy of azelaic acid in the management of acne, rosacea, melasma and skin aging. *J Cosmet Dermatol.* 2023;22(10):2650–2662. doi:10.1111/jocd.15923
76. Kanada KN, Nakatsuji T, Gallo RL. Doxycycline indirectly inhibits proteolytic activation of tryptic kallikrein-related peptidases and activation of cathelicidin. *J Invest Dermatol.* 2012;132:1435–1442. doi:10.1038/jid.2012.14

77. Li J, Tang JY, Fu J, et al. Carvedilol ameliorates persistent erythema of erythematotelangiectatic rosacea by regulating the status of anxiety/depression. *J Dermatol.* 2022;49(11):1139–1147. doi:10.1111/1346-8138.16525
78. Seo BH, Kim DH, Suh HS, Choi YS. Facial flushing and erythema of rosacea improved by carvedilol. *Dermatol Ther.* 2020;33(6):e14520. doi:10.1111/dth.14520
79. Lee JJ, Chien AL. Rosacea in older adults and pharmacologic treatments. *Drugs Aging.* 2024;41(5):407–421. doi:10.1007/s40266-024-01115-y
80. Saeedi-Boroujeni A, Mahmoudian-Sani MR, Nashibi R, Houshmandfar S, Tahmaseby Gandomkari S, Khodadadi A. Tranilast: a potential anti-inflammatory and NLRP3 inflammasome inhibitor drug for COVID-19. *Immunopharmacol Immunotoxicol.* 2021;43(3):247–258. doi:10.1080/08923973.2021.1925293
81. Pfab T, Hocher B. Tranilast and hypertensive heart disease: further insights into mechanisms of an anti-inflammatory and anti-fibrotic drug. *J Hypertens.* 2004;22(5):883–886. doi:10.1097/00004872-200405000-00006
82. Jin H, Wu Y, Zhang C, et al. Tranilast alleviates skin inflammation and fibrosis in rosacea-like mice induced by long-term exposure to LL-37. *Biochem Biophys Res Commun.* 2024;737:150523. doi:10.1016/j.bbrc.2024.150523
83. Wang J, Sun Y, Chen L, et al. Supramolecular salicylic acid ameliorates rosacea-like eruptions by suppressing NLRP3-mediated inflammasome activation in mice [published correction appears in *Int Immunopharmacol.* 2023Jun;119:110233. doi:10.1016/j.intimp.2023.110233]. *IntImmunopharmacol.* 2023;118:110057. doi:10.1016/j.intimp.2023.110057
84. Xu L, Yao B, Xu T, Huang H. Assessment of the efficacy and safety of 30% supramolecular salicylic acid peeling for papulopustular rosacea treatment. *Indian J Dermatol.* 2022;67(5):625. doi:10.4103/ijd.ijd_353_21
85. Li H, Guan Y, Liang B, et al. Therapeutic potential of MCC950, a specific inhibitor of NLRP3 inflammasome. *Eur J Pharmacol.* 2022;928:175091. doi:10.1016/j.ejphar.2022.175091
86. Yoon SH, Hwang I, Lee E, et al. Antimicrobial peptide LL-37 drives rosacea-like skin inflammation in an NLRP3-dependent manner. *J Invest Dermatol.* 2021;141(12):2885–2894.e5. doi:10.1016/j.jid.2021.02.745
87. Long J, Deng Z, Chen M, Liu T. Impaired angiogenesis and Th1/Th17 polarization: a possible explanation for the decreased incidence of rosacea in the aged. *Immun Inflamm Dis.* 2024;12(12):e70108. doi:10.1002/iid3.70108
88. Amir Ali A, Vender R, Vender R. The role of IL-17 in papulopustular rosacea and future directions. *J Cutan Med Surg.* 2019;23(6):635–641. doi:10.1177/1203475419867611
89. Deng Z, Xu S, Peng Q, et al. Aspirin alleviates skin inflammation and angiogenesis in rosacea. *Int Immunopharmacol.* 2021;95:107558. doi:10.1016/j.intimp.2021.107558
90. Chen M, Xie H, Chen Z, et al. Thalidomide ameliorates rosacea-like skin inflammation and suppresses NF- κ B activation in keratinocytes. *Biomed Pharmacother.* 2019;116:109011. doi:10.1016/j.biopha.2019.109011
91. Wu Y, Li Z, Huang YY, et al. Novel phosphodiesterase inhibitors for cognitive improvement in Alzheimer's disease. *J Med Chem.* 2018;61(13):5467–5483. doi:10.1021/acs.jmedchem.7b01370
92. Chiricozzi A, Caposiena D, Garofalo V, Cannizzaro MV, Chimenti S, Saraceno R. A new therapeutic for the treatment of moderate-to-severe plaque psoriasis: apremilast. *Expert Rev Clin Immunol.* 2016;12(3):237–249. doi:10.1586/1744666X.2016.1134319
93. Fertig BA, Baillie GS. PDE4-mediated cAMP signalling. *J Cardiovasc Dev Dis.* 2018;5(1):8. doi:10.3390/jcdd5010008
94. Guttman-Yassky E, Hanifin JM, Boguniewicz M, et al. The role of phosphodiesterase 4 in the pathophysiology of atopic dermatitis and the perspective for its inhibition. *Exp Dermatol.* 2019;28(1):3–10. doi:10.1111/exd.13808
95. Samrao A, Berry TM, Goreski R, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. *Arch Dermatol.* 2012;148(8):890–897. doi:10.1001/archdermatol.2012.812
96. Thompson BJ, Furniss M, Zhao W, Chakraborty B, Mackay-Wiggan J. An oral phosphodiesterase inhibitor (apremilast) for inflammatory rosacea in adults: a pilot study. *JAMA Dermatol.* 2014;150(9):1013–1014. doi:10.1001/jamadermatol.2013.10526
97. Roy S, Chompunud Na Ayudhya C, Thapaliya M, Deepak V, Ali H. Multifaceted MRGPRX2: new insight into the role of mast cells in health and disease. *J Allergy Clin Immunol.* 2021;148(2):293–308. doi:10.1016/j.jaci.2021.03.049
98. Roy S, Alkanfari I, Chaki S, Ali H. Role of MrgprB2 in rosacea-like inflammation in mice: modulation by β -Arrestin 2. *J Invest Dermatol.* 2022;142(11):2988–2997.e3.
99. Mansilla-Polo M, Morgado-Carrasco D. Biologics versus JAK inhibitors. part II: risk of infections. a narrative review. *Dermatol Ther (Heidelb).* 2024;14(8):1983–2038. doi:10.1007/s13555-024-01203-2
100. Husein-ElAhmed H, Steinhoff M. Evaluation of the efficacy of subantimicrobial dose doxycycline in rosacea: a systematic review of clinical trials and meta-analysis. *J Dtsch Dermatol Ges.* 2021;19(1):7–17. doi:10.1111/ddg.14247
101. Hussain K, Patel P, Roberts N. The role of thalidomide in dermatology. *Clin Exp Dermatol.* 2022;47(4):667–674. doi:10.1111/ced.15019

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