Open Access Library Journal
2025, Volume 12, e14570
ISSN Online: 2333-9721
ISSN Print: 2333-9705

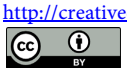
Interaction between *Malassezia* and Novel Therapeutic Agents in Chronic Inflammatory Cutaneous Conditions

Edosa Derartu Shumet, Yi Sun*

Department of Dermatology, Hubei Provincial Clinical Research Center for Diagnosis and Therapeutics of Pathogenic Fungal Infection, Jingzhou Hospital Affiliated to Yangtze University, Jingzhou, China
Email: *jzzxyysy@163.com

How to cite this paper: Shumet, E.D. and Sun, Y. (2025) Interaction between *Malassezia* and Novel Therapeutic Agents in Chronic Inflammatory Cutaneous Conditions. *Open Access Library Journal*, **12**: e14570.
https://doi.org/10.4236/oalib.1114570

Received: November 7, 2025
Accepted: November 24, 2025
Published: November 27, 2025



Abstract

Chronic inflammatory cutaneous diseases, such as atopic dermatitis (AD) and psoriasis, are complex disorders influenced by immune dysregulation, various genetic factors, and more recently identified alterations within the skin microbiome. Among the skin's commensal organisms, *Malassezia* species play a significant role in modulating both skin inflammation and barrier function. These fungi are normally harmless; becoming pathogenic under specific immune or environmental conditions is one of the proposed mechanisms of disease exacerbation. Recent advances in treatment, with biologic agents and smaller molecule therapies, have revolutionized disease management by precisely targeting certain immune pathways (IL-4, IL-13, IL-17, IL-23, and JAK-STAT cascade) being the primary focus of these interventions. The subsequent effects that such targeted therapies have on the skin microbiome itself, *Malassezia* included, are yet to be fully understood. Emerging evidence points towards biologics and/or novel treatments altering the local immune environment and to some degree skin barrier integrity, which in turn affects microbial composition and activity. This review details the current knowledge of *Malassezia* distribution and behavior in AD and psoriasis patients, their immune interactions, and potential impact of the novel therapies on *malassezia*. Personalized, microbiome conscious, therapeutic approaches are the end goal, improving treatment outcome and long term skin health in patients with chronic inflammatory skin disease.

Subject Areas

Dermatology

Keywords

Malassezia, Skin Microbiome, Atopic Dermatitis, Psoriasis, Biologic Therapies

1. Introduction

Inflammatory skin diseases encompass a broad range of skin disorders. Atopic dermaitis (AD) and psoriasis are considered the two most prevalent chronic cutaneous skin conditions [1]. Chronic inflammatory skin diseases are multifactorial disorders influenced by genetic, environmental, and immunological factors. These diseases impact quality of life and are associated with other comorbidities including cardiovascular and coronary artery diseases [2]-[7].

There has been an increasing interest in the involvement of the skin microbiome in the development of chronic inflammatory skin diseases over the past few years. The skin is colonized by a diverse variety of microorganisms that coexist in close contact with the immune system and the skin barrier. Disturbances in this balance may lead to inflammation and exacerbation of the disease. Among the organisms typically found in these conditions, the *Malassezia* species have been recognized to play a key role in the pathogenesis [8].

Malassezia represents lipid-dependent yeasts, which are normal inhabitants of healthy skin, particularly sebaceous gland-rich areas. Though they are part of the normal flora, in an appropriate setting, they can become opportunistic and contribute to inflammation and exacerbation of skin disease. By producing enzymes and metabolic products that interact with keratinocytes and immune cells, they influence skin homeostasis. In AD and psoriasis, *Malassezia* may induce immune pathways that lead to pro-inflammatory responses. These are mediated through pattern recognition receptors on host cells and result in cytokine expression that leads to chronic inflammation [9].

Recent advances in research have translated into the development of new therapeutic agents that target specific immune pathways involved in AD and psoriasis. In AD, small molecule inhibitors, including Janus kinase (JAK) inhibitors and phosphodiesterase-4 (PDE-4) inhibitors, reduce inflammation by inhibiting intracellular signaling pathways that drive cytokine production [10]. Biologic therapies, including dupilumab and tralokinumab, target the interleukin-4 (IL-4) and IL-13 signaling pathways that mediate T helper 2 (Th2)-driven inflammation and barrier dysfunction. In psoriasis, biologic agents inhibiting IL-17 or IL-23, including secukinumab, ixekizumab, guselkumab, and risankizumab, have shown extraordinary clinical efficacy in controlling disease activity via suppression of the Th17/IL-23 axis. Oral treatment with small molecules such as tyrosine kinase (TYK) 2 inhibitors adds to the options in moderate to severe disease [11]. Improved clinical outcomes associated with these targeted therapies provide novel opportunities to understand the way immune modulation both relieves skin in-

flammation and remodels the surrounding microbial environment.

Gaining insight into how these new treatments interact with *Malassezia* will be important to understand their overall impact on the disease. Biologic or small molecule-driven alterations in immune signaling have the potential to affect the composition and function of the skin microbiome, including *Malassezia* spp. Conversely, persistent colonization by *Malassezia* spp. could influence the response to these therapies. Understanding these relationships will provide further insight into novel therapeutic approaches targeting both microbial and immune elements.

This review presents current knowledge on the interaction between *Malassezia* and new therapeutic agents in AD and psoriasis. Attention is given to how *Malassezia* contributes to disease mechanisms, how new treatments alter its activity, and what this means in terms of long-term disease management. A better understanding of these interactions may support more comprehensive treatment approaches that address both immune dysfunction and microbial imbalance in chronic inflammatory skin diseases.

2. Atopic Dermatitis and Psoriasis

2.1. Atopic Dermatitis

AD is a chronic, relapsing inflammatory skin disorder clinically identified by the presence of itchy and dry as well as inflamed skin. It has been increasingly observed during the past few decades, especially in developed countries. It poses a significant global health challenge due to its impact on quality of life and high healthcare costs. It affects 10% - 30% of children and 2% - 10% of adults [12].

AD pathophysiology involves a dynamic interplay between the dysfunction of immune system and the structural integrity of the skin barrier. From an immunological viewpoint, AD is typically dominated by an exaggerated Th2-mediated immune response during the acute phases of the disease, characterized by the overproduction of cytokines such as IL-4, IL-5, and IL-13, promoting inflammation, pruritus, and barrier dysfunction. As such, there is a gradual shift towards a mixed immune profile during chronic phases, with Th1 cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), taking on more important roles. This shift from Th2 to Th1 dominance reflects the changing nature of the inflammatory response in AD and thus contributes to both the acute eczematous lesions and chronic lichenified plaques seen in long-standing disease [13].

The relation between immune dysregulation and impairment of the barrier is mediated through cytokine pathways, especially those induced through IL-4 and IL-13, signature cytokines of the Th2 response. These cytokines activate intracellular cascades through the interleukin-4 receptor alpha (IL-4Rα) in keratinocytes, engaging signal transducer and activator of transcription (STAT) 6 and STAT3. The activation of such transcription factors causes changes in the expression of genes within the epidermal cells, thereby suppressing the synthesis of FLG, LOR,

and IVL. This cytokine-induced inhibition disturbs epidermal differentiation and impairs barrier formation, initiating a vicious circle in which immune activation perpetuates weakness in the barrier and barrier weakness, in turn, sustains immune activation [14].

2.2. Psoriasis

Psoriasis is a chronic, immune-mediated inflammatory skin disease affecting 2% of the world's population and is thus one of the most common dermatological conditions. It may occur at any age, though research finds two peaks of onset between 30 and 39 years of age and between 60 and 69 years of age. Prevalence varies across ethnic populations and geographical areas due to differences in genetic and environmental influences. Psoriasis remains a chronic and often lifelong condition that seriously impacts the physical and psychosocial well-being of affected individuals [15].

Plaque psoriasis is the most common clinical type and makes up 85% - 90% of all cases of the condition. It is typically presented as **raised**, **well-demarcated**, **erythematous plaques** covered with **silvery-white scales** which most commonly appear on extensor surfaces such as the elbows, knees, scalp, and lower back. The affected skin is often dry, thickened, and prone to cracking or bleeding. Itching, burning, or pain in the affected areas may be reported by the patient. The disease exhibits a chronic and relapsing nature, with periods of flare-ups and remission, reflecting the underpinning complexity of the immune driving mechanisms of its pathogenesis [16].

Psoriasis basically involves a disturbed interplay between innate and adaptive immunity. It is well accepted that adaptive immunity, particularly Th1 and Th17 subsets, plays a leading role in the pathology, but emerging data indicate that innate immune cells are also pivotal players in the development of plaque formation. The process begins with the cellular stress or damage of keratinocytes. Thus, the damaged cells release various antimicrobial peptides (AMPs), including but not limited to LL-37 (cathelicidin), β-defensins, and S100 proteins, which act as early signs that initiate the activation of immune responses [17].

Of these peptides, LL-37 has a critical role in the pathogenesis of psoriasis. At first, the generation of AMP can be a common reaction to injury or infection. However, in psoriasis, LL-37 acquires an abnormal, pathogenic role. It associates with self-DNA or self-RNA derived from damaged cells to generate LL-37–nucleic acid complexes, which are aberrantly sensed as foreign by plasmacytoid dendritic cells (pDCs). This activation depends on the stimulation of Toll-like receptors (TLRs), particularly TLR9 (that recognises DNA) and TLR7 (that recognises RNA). Activation of these receptors on pDCs induces the production of type I interferons (IFNs) (mainly IFN-α), potent cytokines that then activate myeloid dendritic cells (mDC).

Activated mDCs subsequently produce important pro-inflammatory cytokines, such as TNF-α, IL-12 and IL-23. These cytokines are an essential factor in T-

helper cell differentiation and activation, especially Th1 and Th17 cells. Th1 cells generate IFN-γ and TNF-α, whereas Th17 cells release IL-17 and IL-22, which act directly on keratinocytes to drive their excessive proliferation while impeding the epidermis' normal differentiation. This is what causes the thickened plaques of scaly skin in psoriasis. In addition, when keratinocytes become activated, they generate other cytokines and chemokines, keeping the inflammation cycle going by recruiting further immune cells to the skin [18].

This inflammatory loop is the reason why psoriasis continues to plague even without an outside cause. The interaction of genetic predisposition and environmental factors like infectious agents, stress, trauma, and drugs also modulates the expression of disease. Moreover, the systemic nature of inflammation can place patients at increased risk for psoriatic arthritis, cardiovascular disease, and metabolic disorders.

Great advances in therapy have resulted from our understanding of the molecular and immunological basis of psoriasis. Topical corticosteroids, vitamin D analogs, and phototherapy remain useful for treating mild-to-moderate disease. But recently, treatments that block specific parts of the immune response, such as TNF-α inhibitors, IL-17 inhibitors, and IL-23 inhibitors, have transformed care for patients with moderate to severe psoriasis. These drugs disrupt the inflammatory response, resulting in successful long-term disease control and improved quality of life [19] [20].

3. Pathophysiology of *Malassezia*

Malassezia is a genus of fungi consisting of 18 known species that inhabit the skin of various warm-blooded animals, including humans, and deep-sea sponges. Among these, ten species such as, *M. restricta*, *M. globosa*, *M. sympodialis*, *M. furfur*, *M. dermatis*, *M. slooffiae*, *M. obtusa*, *M. arunalokei*, *M. japonica*, and M. yamatoensis are commonly found on human skin [21].

Recognition of *Malassezia* by the immune system is done through pattern recognition receptors (PRRs) on immune cells like dendritic cells and macrophages. These receptors identify molecular components of fungal cell walls, including pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP). One important immune complex in such recognition is the inflammasome, which consists of Nod-like receptors, adaptor proteins ASC, and the effector protease caspase-1. Activation of the inflammasome by *Malassezia* triggers the release of pro-inflammatory cytokines such as IL-1β and IL-18, initiating an inflammatory response that helps clear the infection but can also cause inflammatory cell death (pyroptosis) [22].

In addition to immune activation, *Malassezia* produces proteases, toxic metabolites, and reactive oxygen species (ROS), which contribute to skin barrier damage and intensify inflammation. ROS are involved in a multifaceted manner in the interaction between *Malassezia* and the host. Both the fungus and host immune cells produce ROS within the frame of their metabolic activity and defense mech-

anisms. At high concentrations, however, ROS accumulation causes oxidative stress, resulting in cellular damage, impairment of the barrier function, and intensification of inflammatory signaling. This oxidative imbalance and subsequent inflammatory cascade constitute a critical point in the pathogenesis of *Malassezia*-associated skin diseases [23].

In the context of inflammatory skin diseases, these mechanisms manifest differently in atopic dermatitis and psoriasis. Atopic dermatitis is characterized by enhanced *Malassezia*-driven inflammasome activation and ROS production because of the already compromised skin barrier and Th2-skewed immunity, thereby amplifying IL-1β release, inducing pruritus, and disrupting the barrier. Conversely, in psoriasis, the response is dominated by a Th17/IL-23 axis, with *Malassezia*-induced inflammasome signaling contributing more to sustained keratinocyte activation, rather than barrier fragility, promoting plaque formation. Including these differences will help illustrate how *Malassezia*'s pathogenic mechanisms interact uniquely with the immunologic environment of each disease [23].

4. *Malassezia* in Chronic Inflammatory Cutaneous Diseases

Malassezia is a commensal yeast that plays a versatile role in the pathogenesis of chronic inflammatory skin diseases, especially AD and psoriasis. Under certain conditions of immune dysregulation and barrier disruption, *Malassezia* becomes pathogenic. The interaction of this fungus with the host immune system promotes prolonged inflammation, exacerbation of lesions, and enhancement of disease chronicity. The ability of *Malassezia* species to change from a harmless commensal into an inflammatory trigger is highly relevant for their involvement in these complex dermatoses [8].

In **AD**, *Malassezia* species, most notably *M. sympodialis* and *M. globosa*, are implicated in worsening inflammation, particularly in head and neck variants of the disease. The compromised epidermal barrier in AD provides a favorable environment for *Malassezia* colonization [24]. Once present, the yeast releases allergens, cell wall components, and metabolites that penetrate the disrupted barrier and activate cutaneous immune cells. Sensitization to antigens of *Malassezia* may lead to specific IgE responses, promoting a type I hypersensitivity reaction characterized by accentuated pruritus and inflammation. Further, this IgE-mediated immune activation, along with Th2-dominant cytokine signals-which involve increased expression of IL-4, IL-5, and IL-13-promotes the development of epidermal barrier dysfunction. Furthermore, *Malassezia* components may stimulate PRRs, including TLR2 and Dectin-2, expressed on keratinocytes and dendritic cells. The stimulation of these PRRs initiates NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways, leading to the production and release of pro-inflammatory cytokines and antimicrobial peptides. These molecular interactions highlight the dual impact of *Malassezia* in AD: direct inflammation via innate immune activation and indirect exacerbation through allergic sensitization [25] [26].

The relationship between *Malassezia* and psoriasis is complex but increasingly thought of as clinically relevant. *Malassezia* species, especially *M. restricta* and *M. globosa*, can act as environmental triggers that exacerbate psoriatic inflammation in genetically susceptible individuals. The yeast produces lipases and phospholipases that degrade sebum and cell membrane lipids, producing free fatty acids and bioactive metabolites that are capable of disrupting the homeostasis of keratinocytes. These metabolic products stimulate dendritic cells and keratinocytes through TLR2 and Dectin-2, with subsequent activation of the IL-23/Th17 axis, a key immunologic pathway driving psoriatic inflammation. Downstream effects involve increased production of IL-17, IL-22, and TNF-α, leading to keratinocyte hyperproliferation, scaling, and erythema. New studies also have shown that *Malassezia* biofilms enhance its persistence and resistance to treatment, thus allowing low-grade chronic inflammation to persist even during clinical remission. The chronic microbial-immune interaction might thus explain flare-ups occurring notwithstanding systemic immunosuppressive therapy [27].

Malassezia have been implicated in exacerbating skin barrier impairment, particularly in inflammatory skin diseases. This happens through downregulation of the molecules related to the barrier (ceramides), increased inflammation, and secretion of enzymes (lipases, proteases) that break down skin components resulting in an impaired integrity of the barrier with worsening of disease severity.

Its lipid-dependent metabolism also shown to modify the skin lipid profile important for barrier function. Therefore, *Malassezia* overactivity has been shown to disrupt lipid homeostasis leading to barrier disruption [28]. *Malassezia* drives Th2 and Th17 immune responses leading to inflammation and addition barrier impairment in an already compromised epidermis, especially seen in individuals with pre-existing barrier defects [29].

5. Novel Therapies for Atopic Dermatitis and Psoriasis

Over the past decade, the therapeutic landscape for chronic inflammatory skin diseases, most prominently AD and psoriasis, has dramatically changed. Conventional treatments have traditionally included topical corticosteroids, phototherapy, and conventional systemic immunosuppressants such as methotrexate or cyclosporine. Such therapies may temporarily improve symptoms but often with significant adverse effects and generally only limited long-term efficacy [30].

Recent advances in targeted immunotherapy have transformed the management away from broad immune suppression toward precise modulation of particular inflammatory pathways. Newly developed biologics and small-molecule inhibitors provide treatment that is safer, more efficient, and longer-lasting. In addition to the overall quality of life improvement, these novel therapies offer symptom and improved skin integrity.

5.1. Biological Agents

Biotherapeutic agents are produced from living cells via recombinant DNA tech-

niques or hybridoma production techniques and are usually composed of intricately designed protein molecules. The major biologics used for the treatment of various dermatoses are monoclonal antibodies, fusion proteins, and receptors designed to block specific proteins engaged in the immune process. Unlike other conventional therapies such as methotrexate and cyclosporine, biologics are designed to specifically interrupt the action of certain cytokines and immune cells engaged in the chronic inflammatory processes [31].

Biologic therapies selectively modulate the immune response pathway for the development of the inflammatory response in the skin. In chronic inflammatory conditions such as AD and psoriasis, the immune response pathway in the body gets dysregulated, resulting in the overactivation of certain subsets of T-cytokines, such as helper T-cytokines, such as Th1, Th2, Th17, and Th22 variants. These variants produce certain inflammatory cytokines such as TNF-α, IL-4, IL-13, IL-17, and IL-23, which are major participants in the development of inflammatory responses within the body [32].

Biological therapies directly affect the biology of certain proteins such as TNF-α, interleukins, and other cytokines perpetuating the inflammatory process (**Table 1**). Biologics focusing on the IL-17 and IL-23 pathway offer great results in the treatment of psoriasis, whereas biologics focusing on the pathway of both IL-4 and IL-13 are useful in the management of AD. In fact, biologics can inhibit the immune cell migration by inhibiting the resultant pathway in the skin, thus significantly reducing the inflammatory process and symptoms such as erythema, scaling, and pruritus [33]-[35].

Table 1. Novel therapies for AD and psoriasis.

Category	Type/Target Pathway	Mechanism of Action	Key Drugs/Examples	Main Clinical Effects
Traditional Therapies	Broad immunosuppressive & anti-inflammatory	Suppress global immune activity and inflammation	Corticosteroids, Phototherapy, Methotrexate, Cyclosporine	Temporary symptom relief, reduced inflammation
Biologic Therapies	**TNF-α Inhibitors**	Block TNF-α → reduce keratinocyte hyperproliferation and IL-23/IL-17 activation	Infliximab, Adalimumab, Etanercept, Certolizumab, Golimumab	↓ Inflammation, reduced erythema, scaling, pruritus
	IL-12/IL-23 inhibitors	Bind IL-12/IL-23, suppress Th17 activation → ↓ IL-17	Ustekinumab (IL-12/23), Guselkumab, Risankizumab, Tildrakizumab (IL-23 selective)	Effective in psoriasis, long-term remission
	IL-17 pathway inhibitors	Block IL-17A or IL-17 receptor → inhibit keratinocyte activation	Secukinumab, Ixekizumab, Brodalumab	Rapid improvement in psoriatic plaques, scaling
	IL-4/IL-13 inhibitors (AD-specific)	Suppress Th2-driven inflammation via IL-4Rα or IL-13 blockade	Dupilumab (IL-4Rα), Tralokinumab (IL-13 selective)	Improved barrier function, ↓ itching & inflammation

Continued

Small-Molecule Therapies	**JAK/STAT pathway inhibitors**	Inhibit intracellular Janus kinases → block cytokine signaling (IL-6, IFN-γ, etc.)	Tofacitinib, Baricitinib, Upadacitinib, Abrocitinib	Oral/topical forms; ↓ cytokine-mediated inflammation
	NF-κB pathway inhibitors	Suppress transcription of inflammatory cytokine genes (e.g. TNF-α, IL-1β)	Experimental agents	↓ Keratinocyte proliferation & inflammation
	Phosphodiesterase-4 (PDE4) inhibitors	↑ cAMP → ↓ cytokine production (IL-17, TNF-α)	Apremilast (oral), Crisaborole (topical)	Anti-inflammatory, enhances barrier repair
	Retinoids (nuclear receptor modulators)	Regulate keratinocyte differentiation & epidermal renewal	Acitretin, Alitretinoin, Tazarotene	Normalizes scaling, restores barrier
	Aryl Hydrocarbon Receptor (AhR) modulators	Modulate immune-epidermal crosstalk, reduce oxidative stress	Tapinarof (topical)	Restores skin homeostasis; ↓ inflammation
	Tyrosine kinase inhibitors	Inhibit intracellular kinases involved in cytokine signaling	Experimental	Highly specific targeting; reduced systemic toxicity

Besides diminishing visible symptoms of inflammation, biologics are able to restore the integrity of the skin's surface layer. Improved skin hydration and increased resistance to secondary infections are consequences of the skin surface layer restoration. Consistent, visible recuperation of the skin is often followed by significant improvement in the overall quality of life. Nevertheless, given their great efficiency, biologics require careful monitoring throughout the treatment, since they may increase the risk of the patient developing an infection [36] [37].

TNF-α inhibitors infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab block TNF-α, a cytokine responsible for promoting various forms of inflammation and subsequent immune cell recruitment. Within psoriasis the IL-23/Th17 axis plays a major role; several biologics have been created to at least partially target this pathway [38]. Ustekinumab inhibits both IL-12 and IL-23 through binding to their common p40 subunit, more recent agents go further and selectively block the p19 subunit of IL-23, preventing all downstream activation of these Th17 cells, reducing overall IL-17 production [39]. Direct targeting of the IL-17 pathway is achieved by biologics such as secukinumab, ixekizumab and brodalumab. Inhibition can be of IL-17A or the receptor itself, keratinocyte activation and the associated lesions are subsequently lessened [40].

The IL-4/IL-13 pathway is the key driver of AD. Current first-line biologic treatments targeting this pathway include dupilumab and tralokinumab. Among these, tralokinumab acts more selectively by inhibiting IL-13, while dupilumab blocks the shared IL-4Rα receptor, thereby disrupting signaling from both IL-4 and IL-13, leading to broader suppression of the inflammatory response. Selective interruption of these cytokine pathways leads to all round reduced inflammation,

partial or complete restoration of the skin barrier, and in many patients long term control of the disease [41].

5.2. Small Molecules

Small molecules are low in molecular weight drugs that can penetrate cells easily, which will allow them to target intracellular signal pathways which makes them very effective for modulating inflammation at its source. These drugs are designed to modulate key molecular processes that contributes to disease progression whether the drugs are administered orally or topically. Because of their cell-permeable nature, they act precisely within immune or skin cells, hence offering more adaptable and targeted therapeutic approach than the traditional systemic immunosuppressants. In addition, ongoing research continues to identify new molecules with improved efficacy, enhanced specificity, and fewer side effect which offers renewed hope for people affected by chronic skin inflammation [42].

One of the most widely acknowledged small molecule therapies identified relates to the JAK inhibitors. These drugs, including tofacitinib, baricitinib, and upadacitinib, directly interfere with the JAK/STAT pathway, an essential pathway of cytokine signaling essential for the activation of the immune cell and the inflammatory response. Cytokines, such as IL-6, and interferon-gamma (IFN-γ), among others, are able to utilize the activity of the Janus kinase enzymes for the inception of the inflammatory response through their specific signaling pathways to facilitate their effects. By inhibiting the activity of these enzymes, the JAK inhibitors effectively inhibit the production of a variety of inflammatory cytokines, therefore having a marked anti-inflammatory response that has proved to be successful in the treatment of AD, psoriasis, and other immune-related dermatitis conditions [43].

Another pathway targeted by small molecule drugs are the pathway involving the nuclear factor kappa B (NF-κB). NF-κB is a transcription factor, which regulates the gene responsible for the immune response and the production of cytokines. In conditions such as psoriasis, the overexpression of NF-κB leads to the production of excess levels of keratinocytes and an inflammatory response in the lesions. Small molecule drugs for the prevention of the overproduction of cytokines such as TNF-α, IL-1β, among others, are used [44].

Besides regulating the inflammatory response, small molecules are also useful for the restoration and repair of the skin barrier. Some of these compounds regulate lipid biology, keratinocyte differentiation, and the process of renewal of the epidermis. For example, retinoids act via the retinoic receptors found in the nucleus and regulate the turnover of keratinocytes, scaling, and the quality of the skin. Other small molecules are the PDE-4 inhibitors, including apremilast and crisaborole, which result in the elevated levels of cyclic adenosine monophosphate (cAMP) in immune cells leading to reduced production of inflammatory cytokines and result in an enhanced barrier function [45] [46].

The specificity of small molecules also makes it possible to inhibit intracellular

enzymes/kinases involved in inflammatory pathways. Tyrosine kinase inhibitors, for example, are presently under investigation for their capability to inhibit major kinases mediating the activation of the immune response and the production of cytokines. Highly specific kinase inhibitors are proposed to be useful for their capability to reduce systemic side effects without impairing the therapeutic performance of the drugs. Precision medicine makes it possible to administer treatment based on the characteristics of the disease [47].

In spite of their numerous benefits, challenges still lie ahead in their administration in the clinical setting. The problem of resistance, off-target effects, and lack of long-term data on their cytotoxic effects are still under research for small molecule drugs. Moreover, the fact that small molecules are quickly metabolized by the liver makes their administration rather intricate for optimal effects. Despite this, enhanced technologies in the development of drugs, their delivery, and targets are continually optimizing the safety and efficacy of small molecule drugs.

Tapinarof, a new, first-in-class, small-molecule topical therapeutic aryl hydrocarbon receptor (AhR) modulator, has presented an encouraging response for the treatment of psoriasis and is under investigation for the treatment of AD [48].

6. Interaction between *Malassezia* and Novel Therapies

Recent evidence has underlined that the relationship between *Malassezia* species and new biologic targeting therapies is one of the most important factors able to influence the composition of skin microbiota in the context of chronic inflammatory dermatosis, including psoriasis and AD. Skin microbiota analyses in relation to modifications in treatment involving biologics have revealed differences in levels of both bacterial and fungal microorganisms, in which *Malassezia* is often involved [23].

In psoriasis, several investigations have focused on the mycobiome and microbiome dynamics under biologic therapy. Treatment with ustekinumab, an anti–IL-12/23 monoclonal antibody, led to notable shifts in the skin microbiota, with microbial communities diverging between lesional and nonlesional sites as treatment progressed. This differential body site effect emerged more overtly with greater microbial diversity, indicating that new lesions differed in recolonization ability. Though alterations in bacterial diversity increased, no treatment effects occurred in the psoriasis-associated mycobiome, consisting of primarily *Malassezia* species, in either anti-TNFα- or anti-IL-17 biotherapy. A similar article conducted a TNF-α and IL-17 inhibitor treatment in one group of patients, concluding that *M. restricta* and *M. globosa* remained dominant in the fungal flora of post-auricular skin in treated individuals, as stated in one article, asserting that biologics reduce but do not abolish the native fungal flora of sebum-producing skin sites [49].

Nevertheless, biologic therapies against IL-23 seem to have a different effect on fungal populations. Treatment with anti-IL-23 significantly reduced the alpha diversity of the mycobiome in the antecubital region; a marked decrease in *Malas-*

sezia was observed, from approximately 29% down to 8% after 16 weeks of treatment. Similar observations were made with ustekinumab, with decrease in several forms of fungal diversity, particularly in skin fold areas. *Malassezia* levels were specifically reduced, while there were additional bacterial changes involving *Pseudomonas* and *Agrobacterium*. These findings suggest that inhibition of the IL-23 signaling pathway may cause a localized mycobiome imbalance, with antimicrobial effects or certain immune-mediated signals being the most likely mechanisms of change. One proposed explanation is that IL-23 blockade suppresses Th17-driven antifungal pathways, altering cytokines such as IL-17 that normally support epithelial defense against fungi. This reduction in Th17 activity may shift the skin environment in a way that discourages *Malassezia* survival while promoting broader microbial restructuring [50].

In contrast, the relationship between *Malassezia* and IL-4R*α* blockade with dupilumab in AD has been more complex. Several clinical reports describe the emergence of dupilumab-associated head and neck dermatitis (DAHND); erythematous, poorly scaling lesions specifically affecting sebaceous regions being the primary characteristic. Multiple case series detail new or worsening head and neck dermatitis during dupilumab therapy; topical corticosteroids often failing to improve these conditions, while some form of antifungal intervention leads to at least partial resolution. A direct link to *Malassezia* proliferation or sensitization is strongly implied by these observations [51] [52]. A large-scale cohort analysis illustrated that high pre-existing IgE antibody levels to *Malassezia* is a powerful positive predictor of DAHND, suggesting that individuals with this condition faced a risk of increased values of up to 26 times in developing the condition over those not having any prior exposure to this antigen. It has been proposed that IL-4R*α* blockade may shift the local immune balance from a suppressed Th2 response toward an unopposed Th1/Th17-dominant state. This shift could impair normal control of *Malassezia* colonization, allowing increased microbial proliferation in sebaceous areas. Such altered immune dynamics may therefore contribute to the development or worsening of head and neck dermatitis in susceptible individuals [53].

More recent mechanistic findings also underpin the pathogenic role of *Malassezia* in conjunction with biologic treatment in AD. In 2024 invitro model of human epidermis, M. restricta altered the barrier in a way that increased Th2 and Th17 inflammation via JAK/STAT pathways. However, the presence of dupilumab or ruxolitinib only partly inhibited this process, suggesting that overgrowth of *M. restricta* could decrease treatment response of targeted biologics to these pathways of inflammation [23]. Conversely, dupilumab treatment in AD has been found to alter bacterial as well as fungal microbiotas, where *M. restricta* and *M. globosa* remained dominant, however reduced in number, with new strains of non-*Malassezia* yeasts overgrowing, thereby increasing diversity. This decrease in fungal components in turn correlated with a reduction in *S. aureus* colonization, suggesting that dupilumab treatment could alter bacterial as well as fungal balance according to prior fungal colonization [54].

Finally, findings from studies of antifungal susceptibility support the pathophysiological importance of *Malassezia* persistence during conditions of chronic inflammation and immunomodulation. Isolates obtained from patients having psoriasis had higher minimum inhibitory concentrations (MIC) values of popular antifungals such as ketoconazole and terbinafine than those obtained from normal individuals, indicating that resistant forms of *Malassezia* can develop in a condition of long-term inflammation [55].

Taken together, these results emphasize that not only do new treatments targeting cytokine pathways like IL-23, IL-12/23, and IL-4Rα suppress inflammation, but they also alter the skin microbiota in a way that is primarily moderated by the genus *Malassezia*. As important agents of both treatment response and toxicity, the balance between host immunity, *Malassezia* colonization, and biologic therapy suggests a need for a holistic approach in treating various inflammatory conditions that target both the host immunity as well as the microbiota.

7. Clinical Implications and Therapeutic Considerations

The understanding of the complex relationship between *Malassezia* species and chronic inflammatory skin diseases has profound clinical implications in both diagnosis and treatment. These skin commensal yeasts, particularly *M. globosa*, *M. restricta*, and *M. furfur*, have been found to be important in the etiopathogenesis of seborrheic dermatitis, psoriasis, and AD [56].

Small molecule drugs and biologics exhibit improvements in the specificities of treatment targets. Small molecule drugs, such as oxymatrine (OMT), PDE-4 inhibitors, and JAK inhibitors, have been found to exhibit dual antifungal and anti-inflammatory activities in the inhibition of *Malassezia*-induced cytokine production, besides inhibiting fungal replication, in addition to biofilm formation [57]. On the other hand, biologics have been found to target major immune mechanisms, namely the interleukin (IL-17), IL-23, and IL-4/IL-13 axes specifically, in an approach to specifically reduce the overall levels of inflammation generated by the immune response induced by *Malassezia*. Considering both, the treatment approach becomes more synergistic, such that antifungal drugs specifically target microbial replication, whereas biologics and small molecule drugs, specifically modulate the aberrant immune response contributing to the overall level of inflammation [40].

However, some therapeutic factors must be considered during the application of such targeted drugs. Antifungal resistance is becoming an important emerging threat, especially in chronic or subtherapeutic antifungal agent treatment, such as azoles and topical antifungal agents. Repeated application of such drugs might cause mutations in the *Malassezia* genome, ultimately leading to reduced susceptibility [58] [59]. Moreover, systemic biologics and targeted antifungal small molecules, although highly potent, might pose certain threats to the immune homeostasis and, consequently, the skin microbiome. This, in turn, might ultimately cause the overgrowth of pathogenic fungi. Thus, antifungal small molecules tar-

geting innovative mechanisms such as nitrogen metabolism and cell membrane formation might serve as promising approaches in *Malassezia*-mediated cutaneous disorders [60].

Safety and tolerability are critical considerations in selecting any form of therapy; chronic conditions, in particular, require prolonged management. Biologics are generally well tolerated, though their systemic immunosuppressive effects increase susceptibility to various infections. Small molecules present several advantages, oral or topical administration being prime examples, along with a near rapid onset of action. But hepatotoxicity, numerous drug-drug interactions, and to a certain extent off target effects are all significant risks [61].

Looking forward, the integration of precision medicine into the management of *Malassezia*-related skin diseases holds substantial promise. Advances in metagenomic sequencing, immune profiling, and various forms of bioinformatics are enabling a more detailed understanding of the host-microbe-drug interface. Personalized treatment strategies can be supported by this type of knowledge; tailoring therapy to a patient's specific microbiome composition, immune signature, and to some extent genetic predisposition, is the end goal of such an approach. In future clinical practice, this may include routine microbiome profiling to predict which patients will respond best to antifungal agents, biologics, or small-molecule therapies, allowing clinicians to select the most effective treatment before symptoms worsen.

8. Conclusion

The interaction between *Malassezia* and novel therapies in the context of chronic inflammatory skin diseases, such as atopic dermatitis and psoriasis, is very important in regard to improved long-term management of the disease. While *Malassezia* species represent a part of the healthy skin microbiome, under conditions of altered immunity they can assume the role of opportunistic pathogens that promote inflammation, barrier dysfunction, and exacerbations. With the introduction of targeted therapies, including biologics and small-molecule drugs, many of these diseases have undergone a paradigm shift in treatment strategies by selectively targeting key immune pathways in disease pathogenesis such as IL-4, IL-13, IL-17, IL-23, and JAK-STAT signaling. Besides direct mechanisms of action, new treatments may influence skin microbiota balance indirectly. In particular, these treatments alter the cutaneous environment by modulating immune responses and diminishing skin inflammation and could thus impact *Malassezia* colonization, virulence, and diversity. Several studies have demonstrated that biologics may restore a healthier microbiome composition, while other reports suggest possible changes in microbial composition, which may influence treatment response or risk of relapse. Further studies of the interaction between *Malassezia* and these novel therapies are needed to understand their combined effect on skin immunity and microbial ecology. Such knowledge could inform integrated therapeutic approaches targeting not only inflammation but also microbial balance for

more sustainable control of chronic inflammatory skin diseases. Future research may also explore the development of combination therapies that simultaneously modulate immune pathways and address microbial dysbiosis to achieve more durable and comprehensive disease control.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Song, A., Lee, S.E. and Kim, J.H. (2022) Immunopathology and Immunotherapy of Inflammatory Skin Diseases. *Immune Network*, **22**, e7. https://doi.org/10.4110/in.2022.22.e7

[2] Yamanaka, K. and Mizutani, H. (2015) "Inflammatory Skin March": Il-1-Mediated Skin Inflammation, Atopic Dermatitis, and Psoriasis to Cardiovascular Events. *Journal of Allergy and Clinical Immunology*, **136**, 823-824. https://doi.org/10.1016/j.jaci.2015.06.009

[3] Abuabara, K., Azfar, R.S., Shin, D.B., Neimann, A.L., Troxel, A.B. and Gelfand, J.M. (2010) Cause-Specific Mortality in Patients with Severe Psoriasis: A Population-Based Cohort Study in the U.K. *British Journal of Dermatology*, **163**, 586-592. https://doi.org/10.1111/j.1365-2133.2010.09941.x

[4] Silverberg, J.I. (2015) Association between Adult Atopic Dermatitis, Cardiovascular Disease, and Increased Heart Attacks in Three Population-Based Studies. *Allergy*, **70**, 1300-1308. https://doi.org/10.1111/all.12685

[5] Andersen, Y.M.F., Egeberg, A., Gislason, G.H., Hansen, P.R., Skov, L. and Thyssen, J.P. (2016) Risk of Myocardial Infarction, Ischemic Stroke, and Cardiovascular Death in Patients with Atopic Dermatitis. *Journal of Allergy and Clinical Immunology*, **138**, 310-312.e3. https://doi.org/10.1016/j.jaci.2016.01.015

[6] Hu, S. and Lan, C.E. (2017) Psoriasis and Cardiovascular Comorbidities: Focusing on Severe Vascular Events, Cardiovascular Risk Factors and Implications for Treatment. *International Journal of Molecular Sciences*, **18**, Article 2211. https://doi.org/10.3390/ijms18102211

[7] Gelfand, J.M., Dommasch, E.D., Shin, D.B., Azfar, R.S., Kurd, S.K., Wang, X., *et al.* (2009) The Risk of Stroke in Patients with Psoriasis. *Journal of Investigative Dermatology*, **129**, 2411-2418. https://doi.org/10.1038/jid.2009.112

[8] Ruchti, F. (2024) Immunity to the Skin Commensal Yeast *Malassezia* in Healthy and Atopic Skin. Dissertation, University of Zurich.

[9] Vijaya Chandra, S.H., Srinivas, R., Dawson, T.L. and Common, J.E. (2021) Cutaneous *Malassezia*: Commensal, Pathogen, or Protector? *Frontiers in Cellular and Infection Microbiology*, **10**, Article 614446. https://doi.org/10.3389/fcimb.2020.614446

[10] Pinto, L.M., Chiricozzi, A., Calabrese, L., Mannino, M. and Peris, K. (2022) Novel Therapeutic Strategies in the Topical Treatment of Atopic Dermatitis. *Pharmaceutics*, **14**, Article 2767. https://doi.org/10.3390/pharmaceutics14122767

[11] Kim, H. (2022) Targeting Cytokines and Signaling Molecules Related to Immune Pathways in Atopic Dermatitis: Therapeutic Implications and Challenges. *Archives of Pharmacal Research*, **45**, 894-908. https://doi.org/10.1007/s12272-022-01421-2

[12] Kolb, L. and Ferrer-Bruker, S.J. (2024) Atopic Dermatitis. StatPearls.

[13] Malajian, D. and Guttman-Yassky, E. (2015) New Pathogenic and Therapeutic Paradigms in Atopic Dermatitis. *Cytokine*, **73**, 311-318. https://doi.org/10.1016/j.cyto.2014.11.023

[14] Fujii, M. (2020) Current Understanding of Pathophysiological Mechanisms of Atopic Dermatitis: Interactions among Skin Barrier Dysfunction, Immune Abnormalities and Pruritus. *Biological and Pharmaceutical Bulletin*, **43**, 12-19. https://doi.org/10.1248/bpb.b19-00088

[15] Iskandar, I.Y.K., Parisi, R., Griffiths, C.E.M. and Ashcroft, D.M. (2020) Systematic Review Examining Changes over Time and Variation in the Incidence and Prevalence of Psoriasis by Age and Gender. *British Journal of Dermatology*, **184**, 243-258. https://doi.org/10.1111/bjd.19169

[16] Sterry W. (2014) Plaque Psoriasis. In: Sterry, W., Sabat, R. and Philipp, S., eds., *Psoriasis*: *Diagnosis and Management*, John Wiley & Sons, 55-75.

[17] Harden, J.L., Krueger, J.G. and Bowcock, A.M. (2015) The Immunogenetics of Psoriasis: A Comprehensive Review. *Journal of Autoimmunity*, **64**, 66-73. https://doi.org/10.1016/j.jaut.2015.07.008

[18] Boniface, K., Blom, B., Liu, Y. and De Waal Malefyt, R. (2008) From Interleukin-23 to T-Helper 17 Cells: Human T-Helper Cell Differentiation Revisited. *Immunological Reviews*, **226**, 132-146. https://doi.org/10.1111/j.1600-065x.2008.00714.x

[19] Morizane, S. and Gallo, R.L. (2012) Antimicrobial Peptides in the Pathogenesis of Psoriasis. *The Journal of Dermatology*, **39**, 225-230. https://doi.org/10.1111/j.1346-8138.2011.01483.x

[20] Hänsel, A., Günther, C., Ingwersen, J., Starke, J., Schmitz, M., Bachmann, M., *et al.* (2011) Human Slan (6-Sulfo LacNAc) Dendritic Cells Are Inflammatory Dermal Dendritic Cells in Psoriasis and Drive Strong T_H17/T_H1 T-Cell Responses. *Journal of Allergy and Clinical Immunology*, **127**, 787-794.e9. https://doi.org/10.1016/j.jaci.2010.12.009

[21] Boekhout, T., *et al.* (2010) *Malassezia* and the Skin: Science and Clinical Practice. Springer, 1-319.

[22] Park, H.R., Oh, J.H., Lee, Y.J., Park, S.H., Lee, Y.W., Lee, S., *et al.* (2020) Inflammasome-Mediated Inflammation by *Malassezia* in Human Keratinocytes: A Comparative Analysis with Different Strains. *Mycoses*, **64**, 292-299. https://doi.org/10.1111/myc.13214

[23] Lee, Y., Yassa, C., Park, S., Song, S.W., Jung, W.H., Lee, Y.W., *et al.* (2023) Interactions between *Malassezia* and New Therapeutic Agents in Atopic Dermatitis Affecting Skin Barrier and Inflammation in Recombinant Human Epidermis Model. *International Journal of Molecular Sciences*, **24**, Article 6171. https://doi.org/10.3390/ijms24076171

[24] Nowicka, D. and Nawrot, U. (2019) Contribution of *Malassezia* spp. to the Development of Atopic Dermatitis. *Mycoses*, **62**, 588-596. https://doi.org/10.1111/myc.12913

[25] Deng, R., Wang, X. and Li, R. (2023) Dermatophyte Infection: From Fungal Pathogenicity to Host Immune Responses. *Frontiers in Immunology*, **14**, Article 1285887. https://doi.org/10.3389/fimmu.2023.1285887

[26] Sparber, F. and LeibundGut-Landmann, S. (2017) Host Responses to *Malassezia* spp. in the Mammalian Skin. *Frontiers in Immunology*, **8**, Article 1614. https://doi.org/10.3389/fimmu.2017.01614

[27] Angiolella, L., Leone, C., Rojas, F., Mussin, J., de los Angeles Sosa, M. and Giusiano, G. (2017) Biofilm, Adherence, and Hydrophobicity as Virulence Factors in *Malassezia* Furfur. *Medical Mycology*, **56**, 110-116. https://doi.org/10.1093/mmy/myx014

[28] Cheng, Y., Cong, J., Xu, J., Tang, L., Zhou, Z., Yang, X., *et al.* (2025) Research Progress on the Exacerbation of Lipid Metabolism by *Malassezia* and Its Impact on the Skin Barrier Function. *Cosmetics*, **12**, Article 67. https://doi.org/10.3390/cosmetics12020067

[29] Ruchti, F. and Leibund Gut-Landmann, S. (2022) New Insights into Immunity to Skin Fungi Shape Our Understanding of Health and Disease. *Parasite Immunology*, **45**, e12948. https://doi.org/10.1111/pim.12948

[30] Kanatoula, D.D., Bodner, E., Ghoreschi, K., Meier, K. and Solimani, F. (2024) Non-biologic Immunosuppressive Drugs for Inflammatory and Autoimmune Skin Diseases. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*, **22**, 400-421. https://doi.org/10.1111/ddg.15270

[31] Baldo, B.A. and Pham, N.H. (2020) Biologics: Monoclonal Antibodies for Non-Cancer Therapy, Cytokines, Fusion Proteins, Enzymes, and Hormones. In: Baldo, B.A. and Pham, N.H., Eds., *Drug Allergy*, Springer, 533-593. https://doi.org/10.1007/978-3-030-51740-3_13

[32] Akhter, S., Tasnim, F.M., Islam, M.N., Rauf, A., Mitra, S., Emran, T.B., *et al.* (2023) Role of Th17 and IL-17 Cytokines on Inflammatory and Auto-Immune Diseases. *Current Pharmaceutical Design*, **29**, 2078-2090. https://doi.org/10.2174/1381612829666230904150808

[33] Ghoreschi, K., Balato, A., Enerbäck, C. and Sabat, R. (2021) Therapeutics Targeting the IL-23 and IL-17 Pathway in Psoriasis. *The Lancet*, **397**, 754-766. https://doi.org/10.1016/s0140-6736(21)00184-7

[34] Mohd Noor, A.A., Azlan, M. and Mohd Redzwan, N. (2022) Orchestrated Cytokines Mediated by Biologics in Psoriasis and Its Mechanisms of Action. *Biomedicines*, **10**, Article 498. https://doi.org/10.3390/biomedicines10020498

[35] Numerof, R.P. and Asadullah, K. (2006) Cytokine and Anti-Cytokine Therapies for Psoriasis and Atopic Dermatitis. *BioDrugs*, **20**, 93-103. https://doi.org/10.2165/00063030-200620020-00004

[36] Sander, N., Stölzl, D., Fonfara, M., Hartmann, J., Harder, I., Suhrkamp, I., *et al.* (2024) Blockade of Interleukin-13 Signalling Improves Skin Barrier Function and Biology in Patients with Moderate-To-Severe Atopic Dermatitis. *British Journal of Dermatology*, **191**, 344-350. https://doi.org/10.1093/bjd/ljae138

[37] Boyman, O., Comte, D. and Spertini, F. (2014) Adverse Reactions to Biologic Agents and Their Medical Management. *Nature Reviews Rheumatology*, **10**, 612-627. https://doi.org/10.1038/nrrheum.2014.123

[38] Balato, A., Scala, E., Balato, N., Caiazzo, G., Di Caprio, R., Monfrecola, G., *et al.* (2017) Biologics That Inhibit the Th17 Pathway and Related Cytokines to Treat Inflammatory Disorders. *Expert Opinion on Biological Therapy*, **17**, 1-12. https://doi.org/10.1080/14712598.2017.1363884

[39] Benson, J.M., Peritt, D., Scallon, B.J., Heavner, G.A., Shealy, D.J., Giles-Komar, J.M., *et al.* (2011) Discovery and Mechanism of Ustekinumab: A Human Monoclonal Antibody Targeting Interleukin-12 and Interleukin-23 for Treatment of Immune-Mediated Disorders. *mAbs*, **3**, 535-545. https://doi.org/10.4161/mabs.3.6.17815

[40] Liu, T., Li, S., Ying, S., Tang, S., Ding, Y., Li, Y., *et al.* (2020) The IL-23/IL-17 Pathway in Inflammatory Skin Diseases: From Bench to Bedside. *Frontiers in Immunology*, **11**, Article 594735. https://doi.org/10.3389/fimmu.2020.594735

[41] Pescitelli, L., Rosi, E., Ricceri, F., Pimpinelli, N. and Prignano, F. (2020) Novel Therapeutic Approaches and Targets for the Treatment of Atopic Dermatitis. *Current Pharmaceutical Biotechnology*, **22**, 73-84. https://doi.org/10.2174/1389201021666200611112755

[42] Gosia, M., Doshi, G., Bagwe Parab, S. and Godad, A. (2025) Innovative Approaches to Psoriasis: Small Molecules Targeting Key Signaling Pathways. *Immunological Investigations*, **54**, 457-493. https://doi.org/10.1080/08820139.2025.2449960

[43] Ryguła, I., Pikiewicz, W. and Kaminiów, K. (2023) Novel Janus Kinase Inhibitors in the Treatment of Dermatologic Conditions. *Molecules*, **28**, Article 8064. https://doi.org/10.3390/molecules28248064

[44] Goldminz, A.M., Au, S.C., Kim, N., Gottlieb, A.B. and Lizzul, P.F. (2013) NF-*κ*B: An Essential Transcription Factor in Psoriasis. *Journal of Dermatological Science*, **69**, 89-94. https://doi.org/10.1016/j.jdermsci.2012.11.002

[45] Szymański, Ł., Skopek, R., Palusińska, M., Schenk, T., Stengel, S., Lewicki, S., *et al.* (2020) Retinoic Acid and Its Derivatives in Skin. *Cells*, **9**, Article 2660. https://doi.org/10.3390/cells9122660

[46] Li, H., Zuo, J. and Tang, W. (2018) Phosphodiesterase-4 Inhibitors for the Treatment of Inflammatory Diseases. *Frontiers in Pharmacology*, **9**, Article 1048. https://doi.org/10.3389/fphar.2018.01048

[47] Yang, Y., Li, S., Wang, Y., Zhao, Y. and Li, Q. (2022) Protein Tyrosine Kinase Inhibitor Resistance in Malignant Tumors: Molecular Mechanisms and Future Perspective. *Signal Transduction and Targeted Therapy*, **7**, Article No. 329. https://doi.org/10.1038/s41392-022-01168-8

[48] Bissonnette, R., Saint-Cyr Proulx, E., Jack, C. and Maari, C. (2023) Tapinarof for Psoriasis and Atopic Dermatitis: 15 Years of Clinical Research. *Journal of the European Academy of Dermatology and Venereology*, **37**, 1168-1174. https://doi.org/10.1111/jdv.18925

[49] Jiraskova Zakostelska, Z., Reiss, Z., Tlaskalova-Hogenova, H. and Rob, F. (2023) Paradoxical Reactions to Anti-TNF*α* and Anti-IL-17 Treatment in Psoriasis Patients: Are Skin and/or Gut Microbiota Involved? *Dermatology and Therapy*, **13**, 911-933. https://doi.org/10.1007/s13555-023-00904-4

[50] Koike, Y., Kuwatsuka, S., Motooka, D. and Murota, H. (2025) Dysbiosis of the Human Skin Mycobiome in Patients Receiving Systemic IL-23 Inhibitors. *Allergology International*, **74**, 72-77. https://doi.org/10.1016/j.alit.2024.06.003

[51] Wijs, L.E.M., Nguyen, N.T., Kunkeler, A.C.M., Nijsten, T., Damman, J. and Hijnen, D.J. (2019) Clinical and Histopathological Characterization of Paradoxical Head and Neck Erythema in Patients with Atopic Dermatitis Treated with Dupilumab: A Case Series. *British Journal of Dermatology*, **183**, 745-749. https://doi.org/10.1111/bjd.18730

[52] Soria, A., Du-Thanh, A., Seneschal, J., Jachiet, M., Staumont-Sallé, D. and Barbarot, S. (2019) Development or Exacerbation of Head and Neck Dermatitis in Patients Treated for Atopic Dermatitis with Dupilumab. *JAMA Dermatology*, **155**, 1312-1315. https://doi.org/10.1001/jamadermatol.2019.2613

[53] Kozera, E., Flora, A., Stewart, T., Gill, K., Xu, J., De La Vega, M.A., *et al.* (2023) Dupilumab-Associated Head and Neck Dermatitis Resolves Temporarily with Itraconazole Therapy and Rapidly with Transition to Upadacitinib, with *Malassezia*-Specific Immunoglobulin E Levels Mirroring Clinical Response. *Journal of the American Academy of Dermatology*, **88**, 255-257. https://doi.org/10.1016/j.jaad.2022.05.021

[54] Umemoto, N., Kakurai, M., Matsumoto, T., Mizuno, K., Cho, O., Sugita, T., *et al.* (2024) Dupilumab Alters Both the Bacterial and Fungal Skin Microbiomes of Patients with Atopic Dermatitis. *Microorganisms*, **12**, Article 224. https://doi.org/10.3390/microorganisms12010224

[55] de Aguiar Cordeiro, R., Reis, A.T., Lima, X.T.V., de Andrade, A.R.C., Aguiar, A.L.R., Portela, F.V.M., *et al.* (2022) *Malassezia* spp. and *Candida* spp. from Patients with Psoriasis Exhibit Reduced Susceptibility to Antifungals. *Brazilian Journal of Microbiology*, **54**, 169-177. https://doi.org/10.1007/s42770-022-00883-2

[56] Park, M., Park, S. and Jung, W.H. (2021) Skin Commensal Fungus *Malassezia* and Its Lipases. *Journal of Microbiology and Biotechnology*, **31**, 637-644. https://doi.org/10.4014/jmb.2012.12048

[57] Han, X., Ma, T., Wang, Q., Jin, C., Han, Y., Liu, G., *et al.* (2023) The Mechanism of Oxymatrine on Atopic Dermatitis in Mice Based on SOCS1/JAK-STAT3 Pathway. *Frontiers in Pharmacology*, **13**, Article 1091090. https://doi.org/10.3389/fphar.2022.1091090

[58] Leong, C., Chan, J.W.K., Lee, S.M., Lam, Y.I., Goh, J.P.Z., Ianiri, G., *et al.* (2021) Azole Resistance Mechanisms in Pathogenic *Malassezia furfur*. *Antimicrobial Agents and Chemotherapy*, **65**, e01975-20. https://doi.org/10.1128/aac.01975-20

[59] Leong, C., Chua, W., Chong, C., Lee, S.M., Maurer-Stroh, S., Jung, W.H., *et al.* (2025) Non-Synonymous ERG11 Mutations in *M. restricta* and *M. arunalokei*: Impact on Azole Susceptibility. *Microbiology Spectrum*, **13**, e00007-25. https://doi.org/10.1128/spectrum.00007-25

[60] Siemieniuk, M., Czyzewska, U., Strumilo, S. and Tylicki, A. (2015) Thiamine Antivitamins—An Opportunity of Therapy of Fungal Infections Caused by *Malassezia pachydermatis* and *Candida albicans*. *Mycoses*, **59**, 108-116. https://doi.org/10.1111/myc.12441

[61] Veerman, G.D.M., Hussaarts, K.G.A.M., Jansman, F.G.A., Koolen, S.W.L., van Leeuwen, R.W.F. and Mathijssen, R.H.J. (2020) Clinical Implications of Food-Drug Interactions with Small-Molecule Kinase Inhibitors. *The Lancet Oncology*, **21**, e265-e279. https://doi.org/10.1016/s1470-2045(20)30069-3