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Evidence for the Clinical Association between *Demodex* and Rosacea: A Review

Fen Wei[a, b] Li Li[c] Yi Kong[d] Xiaofeng Yan[e] Kevin J. Varghese[f]
Song Zhang[d] Jian Jiang[d] Bao Chai[a, b] Hongxiang Chen[a, d]

[a]Department of Dermatology, Huazhong University of Science and Technology Union Shenzhen Hospital, Shenzhen, China; [b]Department of Dermatology, The 6th Affiliated Hospital of Shenzhen University Health Science Center, Shenzhen, China; [c]Department of Dermatology, School of Medicine, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [d]Department of Dermatology, Tongji Medical College, Huazhong University of Science and Technology, Union Hospital, Wuhan, China; [e]Department of Psychiatry, University of Missouri - Kansas City, Kansas City, MO, USA; [f]University of Missouri - Kansas City School of Medicine, Kansas City, MO, USA

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Keywords
Rosacea · *Demodex* · Reflectance confocal microscopy · Fluorescence-advanced videodermatoscopy · Pathogenesis · Treatment

Abstract
Background: Rosacea is a chronic inflammatory dermatological condition in humans, and its pathogenesis remains unclear. However, the development of rosacea is suspected to be related to *Demodex*, a microscopic commensal organism that resides in or near hair follicles and sebaceous glands. Although *Demodex* is known to be a host-specific, obligate commensal organism, it is currently difficult to be cultured in vitro to parasitize and infect other animal hosts. Therefore, direct evidence for a pathogenic role of *Demodex* in rosacea is currently lacking. ***Summary:*** As circumstantial evidence, non-invasive skin-detecting techniques have shown abnormally elevated numbers of *Demodex* in rosacea patients. Increased cytokine levels such as IL-10, IL-8, and IL-12p70 have been observed in human sebocytes following the *Demodex* challenge, and acaricides have been found to be effective in rosacea therapy, all point to a close relationship between *Demodex* and rosacea. Based on these findings, we conducted a comprehensive literature review to summarize the current state of knowledge, research insights, and clinical treatment recommendations for *Demodex*-associated rosacea, with the ultimate goal of improving patient outcomes.

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Introduction

Rosacea is a chronic inflammatory condition that manifests primarily on the skin of the central face and is characterized by persistent facial erythema, papules, pustules, telangiectasia, and flushing [1, 2]. Rosacea affects 5.5% of the global population, and its prevalence in the white population is up to 10% or higher [2]. Unfortunately, current therapies are not curative, and the pathogenesis remains uncertain.

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Correspondence to:
Bao Chai, chaibao@email.szu.edu.cn
Hongxiang Chen, hongxiangchen@hotmail.com

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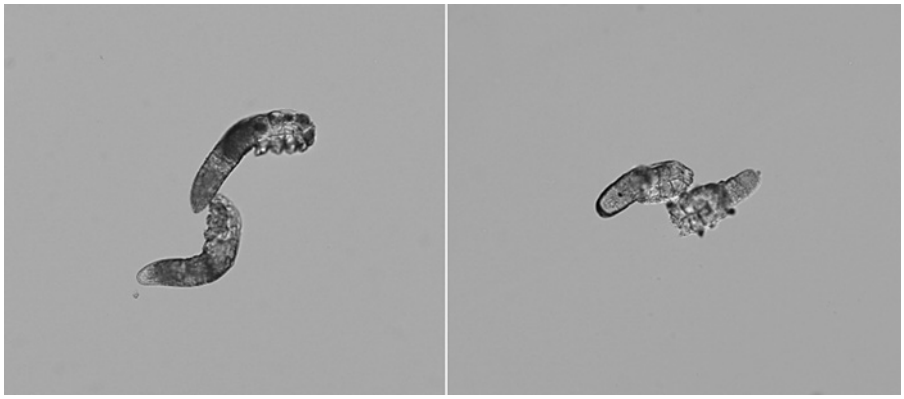

Fig. 1. The microscopic images of *Demodex folliculorum* (left) and *Demodex brevis* (right). The former has greater length, while the latter appears shorter.

The *Demodex* mites are some of the most widespread but often overlooked human commensals. There are more than 100 species of *Demodex* mite, many of which are commensal organisms of the pilosebaceous unit of mammals, including cats, dogs, sheep, cattle, pigs, etc. Currently, two species of *Demodex* mites are identified as being present on human skin: *Demodex folliculorum* and *Demodex brevis*. The former is longer and primarily parasitic in hair follicles, while the latter is shorter and tends to reside in sebaceous glands [3] (shown in Fig. 1). *Demodex* is observed in normal skin with a prevalence of 100% and a density of ≤5 D/cm^2 in the adult population [4]. Most humans are carriers of *Demodex* and do not develop clinical symptoms. The pathogenicity of *Demodex* remains questioned by clinicians due to the high infection but low morbidity and an incomplete correlation between mite loads and the severity of clinical symptoms.

Demodicosis and rosacea are common skin disorders encountered in dermatology practice. While demodicosis is the result of infestation by the *Demodex* mites, the etiology of rosacea remains unclear [5]. Although papulopustular rosacea (PPR) and rosacea-like demodicosis have numerous similarities, they are generally considered two distinct entities [6]. On the other hand, rosacea appears to have a close relationship with *Demodex*. A systematic review and meta-analysis of twenty-three case-control studies concluded that patients with rosacea had significantly higher prevalence and degrees of *Demodex* mite infestation compared with control patients [7]. Forton et al. [4] analyzed the direction of the causal relationship at several levels (molecular, histologic, clinic) and concluded that PPR is caused by the *Demodex* mite and not the inverse. In addition, she suggested that erythematotelangiectatic rosacea (ETR) may be related to a subclinical stage of demodicosis and that rosacea which manifests with papulopustules should be considered a demodicosis [8, 9].

All of these indicate that *Demodex* mites may be involved in the development of rosacea. However, more direct proof is needed to confirm the pathogenic role of *Demodex* in rosacea. This evidence has not been established and might not be easily available in the near future because *Demodex* is a host-specific, obligate commensal that is currently difficult to be cultured in vitro to parasitize other animal hosts [10]. However, there are promising case reports currently available: *Demodex canis* infestation has been found in a ferret [11], canine *Demodex* mites were cultured on SCID mice [12, 13], and the first ex vivo cultivation study of *Demodex* was conducted by Clanner-Engelshofen et al. [14]. Still, there is a lack of direct evidence for the relationship between *Demodex* and rosacea. Therefore, we explored the relationship between *Demodex* and rosacea through a review of the existing literature in order to orient future research and suggest clinical treatments.

Skin Measurement Methods

Methods for detecting the density of *Demodex* mite infestation in skin are categorized as non-invasive and invasive. In recent years, non-invasive detection methods have been widely used due to their advantages of non-invasiveness and simplicity, which make them more easily accepted by patients. Invasive methods, while valuable, are less utilized. Although direct evidence for the pathogenic role of *Demodex* mites in rosacea is not available, indirect evidence provided by skin testing techniques shows significantly higher *Demodex* density (Dd) in rosacea patients than in controls.

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Non-Invasive Skin Measurement Methods

Standardized superficial skin biopsies and reflection confocal microscopy are currently the most widely utilized non-invasive skin detection methods for *Demodex* infection.

Standardized Superficial Skin Biopsy

The standardized superficial skin biopsy is a common non-invasive method to determine Dd which was developed by Forton et al. [15] in 1993 to detect Dd on a facial surface of 1 cm^2, with a normal value being <5 D/cm^2. Briefly, the method requires three steps. First, a drop of cyanoacrylate glue is placed in the center of a 1 cm^2 grid on a glass slide. Second, the slide is adhered to a designated area of the patient's forehead for 1 min. Third, the slide is gently removed from the skin, extracting the follicular contents [16]. During a clinical trial among 39 patients with mild-to-severe bilateral PPR, 35 patients were determined to carry ≥5 D/cm^2 on both sides of their faces by standardized superficial skin biopsy [17], which is higher than the normal value of <5 D/cm^2. A case-control study demonstrated via two consecutive standardized skin surface biopsies that Dd was higher in both ETR patients and PPR patients when compared to healthy controls and patients with other skin conditions [8]. The aberrant increase in Dd in rosacea patients indicates an association of *Demodex* with rosacea.

Reflectance Confocal Microscopy

Reflectance confocal microscopy (RCM; also called confocal laser scanning microscopy) is an imaging technique that has emerged in recent years which demonstrates utility in diagnosing and monitoring rosacea [18–25]. Under RCM, *Demodex* appears as small, round bodies with a hyperreflective contour in the horizontal section [26]. RCM also identifies adult mites with a worm-like appearance and four pairs of short legs within the hair follicle in the longitudinal section [23]. Substantial evidence provided via RCM indicates that rosacea patients have significantly higher Dd on the face than healthy controls [19, 25, 27]. According to a study that used RCM to investigate 30 PPR patients, 30 ETR patients, and 40 healthy controls, Dd was significantly higher in ETR and PPR patients compared to healthy controls and higher in PPR patients than in ETR patients [28]. RCM was used to examine 25 patients with facial rosacea before and after treatment in a prospective study. *Demodex* mites were significantly reduced after treatment with metronidazole 2% cream or gel in combination with systemic tetracyclines (doxycycline or minocycline) [19]. Another study found that residual mites detected by RCM were altered in number and appearance after topical ivermectin treatment in rosacea patients [21]. The appearance of *Demodex* mites decreased in brightness and the definition of their bright contours disappeared. Because these structural changes of the *Demodex* mites coincided with a significant clinical improvement in the affected patients, *Demodex* infection may have a role in the progression of rosacea.

Others

Other methods for measuring *Demodex* include Tape method, Fluorescence Advanced Video Dermatoscopy (FAV), PCR for *D. folliculorum*, and so on. In 79 rosacea patients and 87 healthy controls detected by the tape method, the numbers of *Demodex* infections were 64 (81%) and 11 (13%), respectively [29]. FAV is a novel non-invasive method for in vivo detection of *Demodex* mites. Like RCM, FAV also detected an abnormally high density of *Demodex* mites in rosacea patients [24, 30]. Quantitative PCR was used to assess *Demodex* infestation in 50 people with facial rosacea and 48 healthy participants. *Demodex* was found to be present more frequently in rosacea patients than in healthy controls. The density of *Demodex* in rosacea patients was 5.7 times higher than in healthy participants [31]. All of these methods demonstrate abnormally elevated Dd in rosacea patients.

Invasive Skin Measurement Methods

The invasive method for Dd detection generally refers to skin biopsy. One study compared the prevalence of *Demodex* mites on the faces of 80 patients with rosacea and 80 patients with other skin diseases via skin biopsy, and the results showed that the prevalence of mites in the rosacea group was significantly higher than that in the control group [32]. According to the results of another study, the facial biopsies of 75 patients with rosacea, 75 patients with discoid lupus erythematosus, and 75 patients with actinic lichen planus demonstrated that the prevalence of *Demodex* mites was significantly higher in patients with rosacea than in the other two skin disease patients [33]. Biopsies from several other studies have shown abnormally high densities of *Demodex* mites in patients with rosacea [34–36].

Pathogenesis

The etiology and pathogenesis of rosacea remain uncertain. However, the possible role of *Demodex* mites in the pathogenesis of rosacea has been previously reported. Researchers co-cultured live *Demodex* mites with

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human sebocytes and found that Toll-like receptor 2 (TLR2) immune responses were down-regulated when mite numbers were low, but pro-inflammatory responses were activated when mite numbers increased [16]. It is speculated that in normal skin, low numbers of *Demodex* mites may downregulate the host immune TLR signaling pathway to favor their survival, whereas a large mite burden may trigger a host immune reaction via the TLR2 pathway, leading to the inflammatory skin changes typical of rosacea.

Furthermore, low doses of *Demodex* limited cytokine production, whereas high doses of *Demodex* promoted the release of inflammatory cytokines such as IL-10, IL-8, and IL-12p70 [16]. Elevated levels of the inhibitory inflammatory factor IL-10 can protect *Demodex* mites from excessive inflammatory responses, which may be another survival strategy. IL-8 can chemotacticize neutrophils and lead to a septic inflammatory response. Only the highest number of mite challenges (30) induced a significant increase in pro-inflammatory factor, IL-8 [16], consistent with papular pustules only occurring in severe cases of rosacea. IL-12p70 can induce a marked infiltration of $CD4^+$ T helper cells, Langerhans cells, and macrophages, which also characterizes the histological findings in rosacea [37]. Furthermore, IL-17, a cytokine released by $CD4^+$ T helper cells, is increased in *Demodex* blepharitis patients. IL-17 can induce the production of vascular endothelial growth factor-A (VEGF-A), promote angiogenesis, and cause rosacea-like lesions with telangiectasias [38]. These findings suggest that *Demodex* plays an important role in the pathogenesis of rosacea.

Treatment

The treatment of rosacea also provides some evidence for the pathogenic role of *Demodex* in rosacea. The first-line treatments recommended by N Engl J Med in 2017 for PPR were topical ivermectin 1% cream, metronidazole 0.75% or 1% cream or gel for mildly affected patients, and oral tetracycline or doxycycline for moderately affected patients [39]. Established rosacea treatments primarily utilize direct acaricidal effects (such as permethrin) or anti-inflammatory properties (antibiotics such as metronidazole) or both (ivermectin). Twenty patients with mild-to-severe bilateral PPR were found to carry ≥5 *Demodex* mites per cm^2 on both sides of their faces before therapy. After treatment with permethrin 5% topical gel, Dd and the severity of clinical manifestations were greatly reduced compared to placebo [17].

Although *Demodex* mites were significantly reduced after treatment with metronidazole 2% cream or gel in combination with systemic tetracyclines (doxycycline or minocycline), the post-treatment mite levels were still higher than the average number of mites in healthy controls. Papules and pustular lesions resolved in most patients, but erythema was only partially reduced and telangiectasias persisted [19, 40]. Besides the anti-inflammatory effects of the antibiotics, such therapies for treating rosacea might also act on the mites' endobacteria, as Clanner-Engelshofen et al. showed [41]. Forton et al. [42] found that metronidazole showed no acaricidal effect on *Demodex*, while benzyl benzoate induced complete elimination of *Demodex*. Topical administration of benzyl benzoate was effective in lowering Dd and improving clinical symptoms, both in demodicosis and PPR [43]. Due to the lack of anti-inflammatory effect, the therapeutic effect of benzyl benzoate is solely attributed to its acaricidal effect.

Ivermectin acts on rosacea in a dual anti-inflammatory and anti-parasitic manner, reducing *Demodex* burden and significantly improving clinical signs and symptoms [25]. In a monocentric pilot study, twenty Caucasian patients with moderate to severe rosacea were treated with topical ivermectin 1% cream once daily for 12 weeks. At weeks 6 and 12, the mean mite density was significantly decreased ($p < 0.001$), and IL-8, LL-37, HBD3, TLR4, and TNF-α gene expression were all down-regulated at both time periods [44]. In addition, Ebbelaar et al. conducted a systematic review of both medical literature and clinical guideline recommendations, including three randomized trials, three extension studies, and two meta-analyses. Their results demonstrated that topical ivermectin was more effective than topical metronidazole in the treatment of moderate to severe PPR [45], suggesting that eliminating *Demodex* mites is beneficial for treating rosacea.

Discussion

The debate regarding the pathogenic role of *Demodex* in rosacea is ongoing. Forton et al. analyzed the causal relationship direction between *Demodex* and rosacea at different levels (molecular, histologic, clinic), and concluded that PPR is caused by *Demodex* and not the inverse. Furthermore, another paper suggested that pityriasis folliculorum (PF) is the link between *Demodex* and PPR [4]. Finally, another study proposed that ETR is a subclinical stage of demodicosis that should be treated with acaricidal creams [5]. Hypothyroidism,

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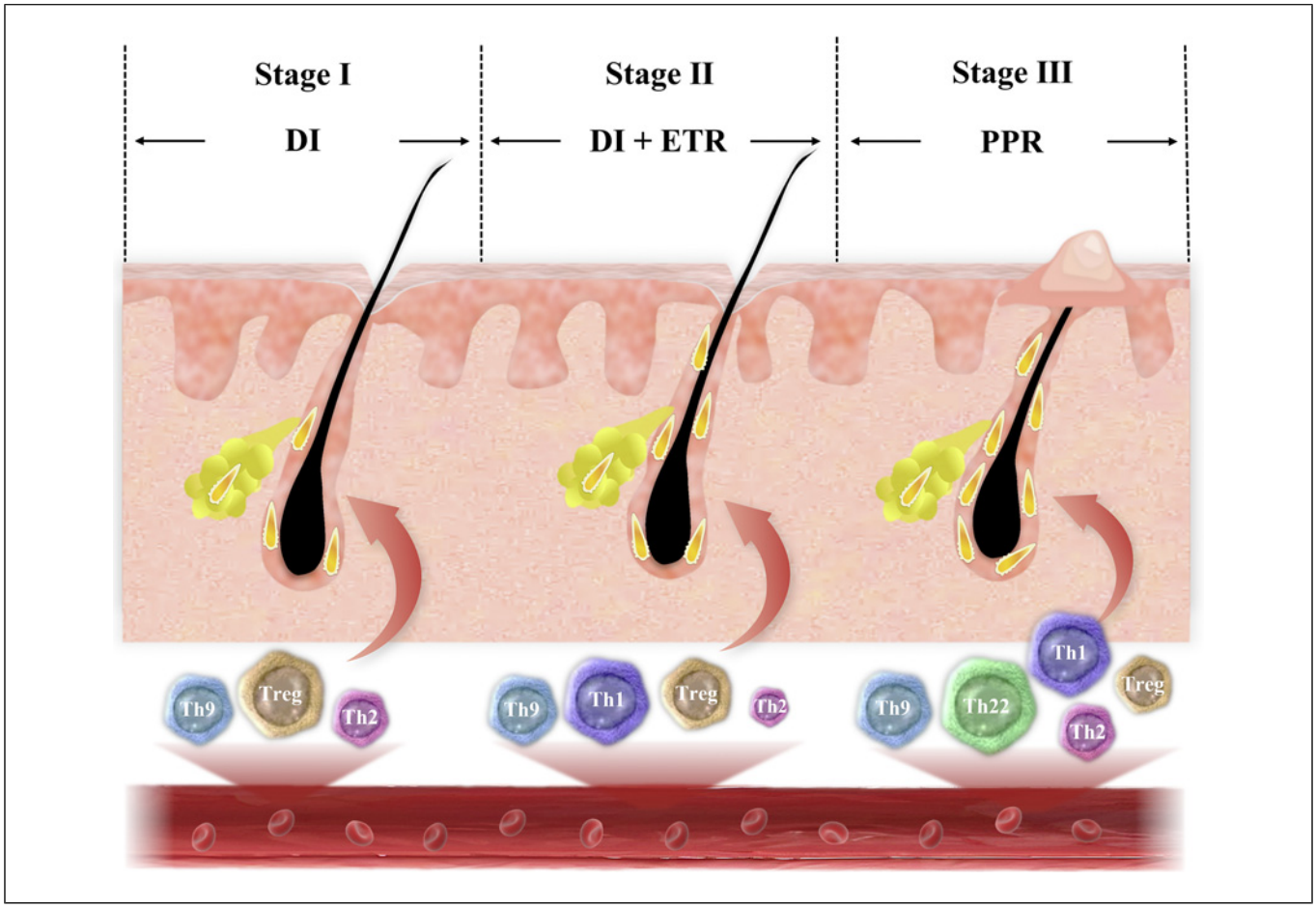

Fig. 2. Usually, *Demodex* mites can proliferate under the protection of local Treg cells, and their proliferation only presents as PF. If the patient is also affected by rosacea, Th1 immunity is triggered and Th2 immunity is inhibited, disrupting the immune balance between Th2 and Treg. Without the suppression of Th2 immunity, *Demodex* mites take advantage of the opportunity to proliferate rapidly during the ETR phase. Overproliferative *Demodex* mites trigger an increase in Th2 cells and restore them to their previous levels. Due to the decrease in Treg cells and the increase in Th22 cells, large numbers of *Demodex* mites cause severe inflammatory responses that manifest clinically as papular pustules. DI, *Demodex* infestation; ETR, erythematotelangiectatic rosacea; PPR, papulopustular rosacea.

pregnancy, corticosteroid administration, *Staphylococcus epidermidis*, contagiousness, and genetic background were proposed to influence *Demodex* proliferation via another study [46].

However, some phenomena remain unanswered: (i) ETR patients have been shown to have a milder inflammatory response and lower Dd than PPR patients [8, 28]. Furthermore, it is proposed that the more intense the inflammatory reaction, the lower the Dd. For this reason, the Dd in patients with PF was significantly higher than in patients with PPR [4]. However, if this theory is valid, then how is it that the Dd of ETR – which results in a lesser inflammatory response – is lower than that of PPR patients? (ii) What is the relationship between PF and ETR? It has been shown that PF is potentially misdiagnosed as ETR, as the two often coincide [5]. However, the Dd in ETR patients was lower than that in PPR patients, while the Dd in PF patients was significantly higher than that in PPR patients [4].

Gazi et al. collected human whole blood samples and analyzed skin-homing $CD4^+$ T-cell subsets. They found that, compared with controls, non-rosacea patients with *Demodex* infection (*Demodex* group) had higher levels of Treg and Th9 cells, while PPR patients without *Demodex* infection (Rosacea group) showed increased

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levels of Th1 cells. PPR patients with *Demodex* infestation exhibited lower Treg but higher Th1 and Th22 cell levels than the *Demodex* group and higher Th2 cell levels than the rosacea group [47]. It appears that the rosacea disease process reduced the number of Treg cells and increased the number of Th1 cells in patients with *Demodex* infection. Similarly, *Demodex* infection increased the number of Th2 cells in patients with rosacea. Th2 immunity is activated in response to both allergens and parasitic infections [48]. In recent years, cases of rosacea-like lesions have been reported in patients following the use of dupilumab [49, 50]. Live *Demodex* mites' colonization of the face was discovered after further study by direct scraping of pustules [50]. Th2 immune responses are essential in the control of extracellular parasitic infections [47]. Dupilumab is a Th2 pathway inhibitor, which may boost *Demodex* proliferation [50]. The elevated Th1 skin-homing cells in rosacea [47] can also inhibit the proliferation of Th2 cells [51]. These may explain the massive proliferation of *Demodex* in rosacea. A low number of *Demodex* can proliferate under the protection of Treg cells [47] and IL-10 [16] without triggering an inflammatory response. A high load of *Demodex* can trigger an immune response. The factors affecting the proliferation of *Demodex* mites are complex [46], which is why most patients with *Demodex* infections are asymptomatic while some patients show a robust inflammatory response.

Therefore, a hypothesis is proposed based on all of the above. Usually, *Demodex* mites can proliferate under the protection of local Treg cells, and proliferation of *Demodex* presents as PF. If a patient develops rosacea and a *Demodex* infection, Th1 immunity is triggered and Th2 immunity is inhibited [47]. The immune balance between Th2 and Treg is disrupted. Without the suppression of Th2 immunity, *Demodex* takes advantage of the opportunity to proliferate rapidly during the ETR phase. This is consistent with Forton et al.'s [8] assertion that ETR is a subclinical stage of demodicosis. Overproliferative *Demodex* mites trigger an increase in Th2 cells and restore them to their previous levels [47]. Due to the decrease in Treg cells and the increase in Th22 cells, large numbers of *Demodex* mites cause severe inflammatory responses that manifest clinically as papular pustules. This is in agreement with Forton et al. that PPR is indeed caused by *Demodex* [4]. Therefore, both rosacea treatment and acaricidal treatment are necessary. A combination of topical Th1 inhibitor and ivermectin is recommended for the treatment of rosacea patients with *Demodex* infection. Downregulation of Th1 immunity can not only inhibit the progression of rosacea but also promote the upregulation of Th2 immunity, thereby inhibiting the overgrowth of *Demodex*. The administration of ivermectin may alleviate symptoms caused by the excessive proliferation of *Demodex* mites (shown in Fig. 2).

Rosacea favors the proliferation of *Demodex*, and the over-proliferation of *Demodex* aggravates the symptoms of rosacea, thus forming a vicious circle. This cycle is interrupted when pharmacological interventions are used. However, if favorable factors persist, the vicious cycle tends to repeat again. This is likely why the use of the acaricides such as ivermectin, benzyl benzoate, and metronidazole, which has only anti-inflammatory effects, can reduce the number of *Demodex* mites and improve the patient's symptoms but cannot eliminate telangiectasia. This is also likely why acaricidal and anti-inflammatory treatments are prone to relapse [19, 25, 43]. Therefore, early use of ivermectin, which has acaricidal and anti-inflammatory properties, in combination with topical Th1 inhibitors to block the progression of the inflammatory response which facilitates *Demodex* survival, can break this vicious cycle and stop disease progression.

Conclusion

Rosacea favors the growth of *Demodex*, and overgrowth of *Demodex* exacerbates the symptoms of rosacea, creating a vicious cycle. The changes in immune interactions when PF encounters ETR and throughout the course of the disease need further exploration. The early use of topical ivermectin in combination with topical Th1 inhibitors early should be considered for the treatment of patients with rosacea and *Demodex* infection.

Key Messages

Rosacea appears to have a close bond with *Demodex*. Recent studies have implicated that *Demodex* mites are involved in the development of rosacea. Based on a comprehensive review of the current literature, we have cited substantial evidence supporting this relationship, proposed a possible vicious cycle between *Demodex* and rosacea, and illustrated the changes in immune responses during this process. In addition, we recommend that patients with both rosacea and *Demodex* infection be treated early with a combination of topical ivermectin and topical Th1 inhibitors to improve treatment outcomes.

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Conflict of Interest Statement

All authors have no conflict of interest to declare.

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Author Contributions

Fen Wei conceived the idea for this review, performed the literature search, and wrote the first draft of the manuscript. Li Li drafted the visualization. Yi Kong, Song Zhang, and Jian Jiang provided critical feedback. Xiaofeng Yan and Kevin Varghese participated in manuscript writing and editing. Bao Chai and Hongxiang Chen supervised the work. All authors commented on previous versions of the manuscript and critically revised the draft. All authors have read and approved the final version of the manuscript.

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