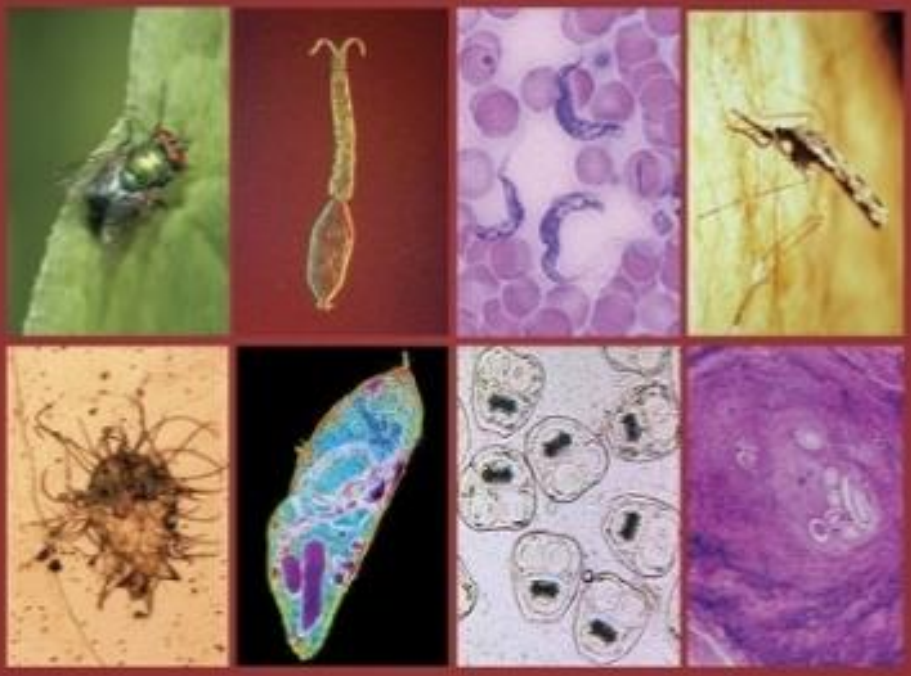
EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES

E

MEDICAL ENTOMOLOGY & PARASITOLOGY



ISSN
2090-0783

WWW.EAJBS.EG.NET

Vol. 14 No. 1 (2022)

Citation: *Egypt. Acad. J. Biolog. Sci. (E-Medical Entom. & Parasitology Vol.14(1) pp **51-61**(2022)*
DOI: 10.21608/EAJBSE.2022.227953

Egypt. Acad. J. Biology. Sci., 14 (1):51–61 (2022)

Egyptian Academic Journal of Biological Sciences
E. Medical Entomology. & Parasitology

ISSN: 2090–0783
www.eajbse.journals.ekb.eg

Re-Evaluating The Role of Demodex Mite in Skin Bio-Balance and Disease

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REVIEW INFO
Review History
Received:25/2/2022
Accepted:26/3/2022
Available:29/3/2022

Keywords:
Demodex, pilosebaceous units, microbiome, rosacea, immunological imbalance

ABSTRACT

Demodex mites are obligate human ectoparasites that live in or near pilosebaceous units. *D. folliculorum* ingests skin cells and sebum, whereas *D. brevis* burrows deeper into the sebaceous glands and ducts, feeding on gland cells. They may even provide a mutualistic host advantage by feeding on bacteria or other organisms in the follicular canal to keep the dermal bio-balance in check. Demodicosis is the umbrella term for all skin disorders related to Demodex mites. It is still unclear whether Demodex is the underlying cause or the result of pre-existing conditions such as rosacea and other dermatological diseases. Given that, Demodex is not the only cutaneous microbiota involved in these conditions. This review aims to re-evaluate the pathogenicity of the Demodex mite, with a focus on systematic internal causes that may drive pathogenicity, such as immunological imbalance, microbiome alterations, or concomitant infections. Clinical suspicion of the underlying causes of Demodex pathogenicity in various dermatoses can thus aid in early diagnosis and appropriate, timely, and cost-effective treatment.

INTRODUCTION

Demodex is a genus of parasitic mites that reside in or near the hair follicles of mammals. The human species *D. folliculorum* was identified in 1841-42, while *D. brevis* was later identified in 1963 (Aylesworth and Vance,1982).

The morphology of the adult *D. folliculorum* mite is 0.3-0.4 mm in length and that of *D. brevis* is slightly shorter by 0.15-0.2 mm in length; hair, brows, and sebaceous glands on the nose are all common locations to transmit the mites from one human host to another (Rufli and Mumcuoglu,1981).

Demodex mites are believed to be symbionts or commensals, living on the sebum of their hosts. They may even provide a mutualistic host advantage by eating bacteria or other organisms in the follicular canal to keep the dermal bio-balance in check (Forton *et al.*,1993). Demodex mites were mostly recovered in people between the ages of 20 and 30 when sebum secretion is at its maximum (Zomorodian *et al.*,2004). Mites are also more common in the elderly (Zomorodian *et al.*,2004), but uncommon in children under the age of five (Delfos *et al*., 2004). Demodex is thought to be transmitted to neonates by close physical contact after birth, although due to minimal sebum production, infants and children do not have considerable Demodex colonization. Men are more likely than females to be infested by both species, with males colonizing more than females (23 percent vs 13 percent) and holding more *D. brevis* species (23 percent vs 9 percent) (Basta *et al.*,2002).

Nevertheless, Demodex prevalence in skin samples reached 100% using modern, sensitive assays; Such cutaneous dominance suggests that the mere presence of Demodex does not indicate disease. It's postulated that the density of mites or their extra-follicular position, rather, is more important in identifying Demodex pathology (Crawford *et al*.,2004). Demodex mites naturally inhabit the skin with no clinical symptoms, thus the majority of people are considered carriers of this mite. However, Demodex is clinically classified as asymptomatic, symptomatic, or may present as an aggravation of a concomitant dermatological problem. Demodicosis is the umbrella term for all cutaneous disorders related to Demodex mites. Although higher levels of Demodex are present in these situations, no research has established a conclusive link (Cases *et al.*,2012).

The immune status of the host, which orchestrates cellular interactions, inflammatory state, and whole-body homeostasis down to its smallest parts (here concerning the pilosebaceous unit, the specified Demodex habitat) is crucial for this variation in the clinical spectrum of demodicosis. (Zhong *et al.*,2019). The disturbance of this well-balanced systemic internal milieu may disrupt or accelerate Demodex mite proliferation, and so contribute to the etiology of skin problems (Aquilina *et al.*,2002). As a result, human demodicosis can be viewed as a multifactorial disease impacted by both the exterior environment of the particular host as well as internal systemic factors that keep the mite's micro-environment in a condition of critical equilibrium (Gothe,1989).

This review offers a holistic overview, exploring Demodex microecology to systematic drivers of pathogenicity and the implications of changing the role of Demodex from commensal to pathogenic in the ecological theatre of different microbial communities of the skin.

Demodex Microecology:

Demodex is a saprophytic mite that comprises about 65 species and belongs to the family Demodicidae, class Arachnida, and order Acarina (Burns,1992). It is an obligate human ectoparasite that inhabits the pilosebaceous units (Rufli and Mumcuoglu, 1981). Both species, *D. folliculorum* and *D. brevis*, are collectively known as Demodex, and appear in 10% of skin biopsies and 12% of hair follicles (Basta *et al.*,2002).

Demodex folliculorum feeds on skin cells and sebum and is thus frequently found in the upper canal of the pilosebaceous unit at a density of 5/Square cm. A single follicle is frequently occupied by many mites with heads that aim at the fundus (Bonnar *et al*.,1993). In comparison, *D. brevis* burrows further into the sebaceous glands and ducts, feeding on gland cells (Basta *et al.*,2002).

With aging, the number of Demodex mites on the skin rises (Forton,1986). The face is more commonly affected by *D. folliculorum*, whereas the neck and chest are more commonly affected by *D. brevis*. Although *D. brevis* has a larger body distribution, *D. folliculorum* infestations are more common (Forton,1986). The nasolabial folds, peri-orbital areas, nose, chin, forehead, temples, eyelashes, brows, the balding scalp, neck, and ears, are all affected by Demodex as well as all external genital organs and ectopic sebaceous glands in the buccal mucosa (Rufli and Mumcuoglu, 1981).

The structure of the invisible mite can be seen under light microscopy as a semi-transparent, elongated body with two joined segments and eight legs. During the night, the mite moves at a rate of 8-16 mm/h, while intense light induces the mite to recede within its follicle. It has scales on its body to help it anchor itself in the hair follicle, and pin-like mouthparts to devour skin cells, hormones, and oils (sebum) that build up in the hair follicles (Basta *et al*.,2002). Demodex females are smaller and more rounded than Demodex males. Eggs

are placed inside hair follicles or sebaceous glands in the follicular opening after fertilization. The larvae hatch and mature into adults after 3-4 days, and the entire life cycle takes 14 days (Rufli and Mumcuoglu,1981). A Demodex mite can live for several weeks in its habitat, where dead mites decompose inside hair follicles or sebaceous glands (Zomorodian *et al*.,2004).

Demodex identification is difficult in histological preparations. Demodex density can thus be measured using cyanoacrylic adhesion and skin surface biopsy (SSB), given the limitation of collecting the whole *D. folliculorum* biotope, yet this standard method can still collect the surface portion of the horny layer as well as the contents of the pilosebaceous follicle (Forton *et al*.,1993).

Other sampling approaches used to determine the existence of Demodex by microscopy include adhesive bands, skin scrapings, skin impressions, expressed follicular contents, comedone extraction, hair epilation, and punch biopsies. The number of mite counts varies greatly depending on the method used (Crawford *et al*.,2004).

Demodex Drivers of Pathogenicity:

Demodex mites, like other cutaneous microflora, have the potential to change their status from commensal to pathogenic if the host cutaneous environment favours their proliferation, causing Demodicosis (Akilov and Mumcuoglu, 2004).

a) Immune System Status:

The host's innate immune system appears to tolerate the presence of these mites, presumably by downregulating the immunological response, with a culling or inhibitory effect on mite multiplication, keeping the number of mites in the canal under control without inducing an inflammatory reaction (Forton *et al*.,1993).

Physical follicle distension and keratinocyte disruption will occur if mite numbers reach a critical level. As a result, the release of cytokines and chemokines is stimulated, triggering a humoral immune-inflammatory response with clinically visible skin changes. A granulomatous 'foreign-body' reaction occurs when the follicle is damaged to the point of rupture (Bonnar *et al*.,1993).

One of the contributing factors in the progression from clinically undetectable mite infestation to dermatosis is the development of primary or secondary immunodepression (Liu *et al*.,2010). Primary immunological suppression in people with intact B cell immunity is most likely due to a hereditary T- cell deficiency, which is subsequently exacerbated by metabolites produced by mites and bacteria (Lacey *et a*l.,2007). The proliferation of mites has also been linked to specific forms of HLA more than others (Akilov and Mumcuoglu, 2003).

Patients with secondary immune suppression, such as those on corticosteroids or cytostatic medicine, as well as those with cancer and HIV infection, are more likely to develop demodicosis (Benessahraoui *et al*.,2003). It is debatable if *D. folliculorum* is involved in the pathophysiology of rosacea produced by topical corticosteroids, it is debatable. Demodex mites were reported to be more prevalent in these patients (Ljubojeviae *et al*.,2002).

The pathophysiology of demodicosis and the immune response to mite invasion are both poorly understood. A dermal infiltrate of lymphocytes, eosinophils, and distinctive granulomas predominantly composed of CD4+ T-helper cells, commonly distributed around a Demodex body, indicate hypersensitivity to the mite itself (Akilov and Mumcuoglu, 2004).

In Demodex mite-infested areas, there is an increase in lymphocyte apoptosis and a high proportion of NK cells with Fc receptors (Akilov and Mumcuoglu, 2004). This explains why patients suffering from severe demodicosis exhibit a remarkable drop in the absolute numbers of lymphocytes and T-cell subsets, as well as a considerable

increase in IgM levels (El-Bassiouni *et al.*,2005).

b) *Relation with the Microbiome:*

Microbial communities exist on the skin, in the gut, and in the blood (Cao *et al.*,2017). They are made up of 100 trillion microorganisms from many domains, such as viruses, bacteria, archaea, fungi, and protozoans, and are believed to coexist in the human host; the term "*microbiome*" was coined to characterize them all (Song *et al*.,2018).

Accordingly, each individual's topography for the three major skin microenvironments - dry, wet, and sebaceous - is unique (Grice,2014). In these three skin microenvironments, *Firmicutes*, *Actinobacteria*, and *Proteobacteria* make up around 90% of all resident taxa. The alpha diversity of bacterial species is highest in dry skin, while it is lowest in sebaceous skin (Musthaq *et al*.,2018). In healthy persons, the genera *Staphylococcus* and *Corynebacterium* prefer high humidity and colonize moist areas more frequently, whereas lipophilic *Propionibacterium* colonizes sebaceous areas more frequently (Grice,2009).

Skin disorders may be influenced by the microbiome, which is connected to numerous microenvironments. In sebaceous areas, acne and rosacea symptoms emerge, whereas, in moist areas, body odour and atopic dermatitis symptoms appear. Psoriasis symptoms are more noticeable in dry skin (Grice,2014).

According to cutaneous microbiome studies, *Proteobacteria* was the most prevalent phylum in acne patients, while *Actinobacteria* was the most abundant phylum in rosacea patients (Grice, 2014 and Musthaq *et al*., 2018).

Furthermore, the blood microbiome of rosacea patients exhibited a relative abundance of the *Chromatiaceae* and *Fusobacteriaceae* groups (Thompson *et al*.,2021), whereas the faecal microbiome was abundant in *Rhabdochlamydia*, *Bifidobacterium*, *Sarcina*, and *Ruminococcus* in another study (Cheng *et al.*,2015). The ability of Demodex to ingest and transport a range of microorganisms found in its cutaneous habitat may function as a vector for bacteria transmission from one place of the body to another or between persons (Rainer *et al.*,2020). Mites also produce lipase enzymes, carry bacteria on their surfaces, and harbour endobacteria (Pena *et al.*,2000).

Demodex As A Disease Agent:

Demodicosis is the umbrella term for all cutaneous disorders related to Demodex mites. It is unclear if Demodex is the root of these problems or whether it aggravates pre-existing conditions. Demodex mites per se can elicit inflammation or allergy by blocking the hair follicle, or they can introduce bacteria locally and facilitate their pathogenesis. These conditions are briefly described below.

1-Rosacea and Demodex Rosacea:

Rosacea is a chronic inflammation of the facial skin that may present with facial flushing, chronic facial erythema, telangiectasia, and inflammatory papules and pustules (Wilkin *et al.*,2002). The pathophysiology of rosacea is unknown. Suggested mechanisms include aberrant neurovascular activation, dysregulated production and release of inflammatory mediators, and an overgrowth of organisms that naturally inhabit the skin (Two *et al.*,2015).

Demodex folliculorum, which inhabits the sebaceous glands, is often a pathogen involved in rosacea, as it has been detected in excess on the skin of affected patients in multiple investigations (Chang and Huang *et al.*,2017). Furthermore, skin biopsies with higher Demodex counts have larger inflammatory cell populations near hair follicles and increased expression of genes that code for inflammatory peptides and cellular growth factors (Cases *et al.*,2012). The mite exoskeleton was postulated to induce these proinflammatory mediators (Fig. 1) (Koller *et al.*,2011). Furthermore, the increased number of Demodex mites on the skin has long been

recognized in erythematotelangiectatic rosacea and papulopustular rosacea. Other nutritional sources for this mite include cellular debris or bacteria found in the pilosebaceous unit, such as *Cutibacterium acnes* (Grice,2014). Demodex mites and the *Bacillus oleronius* bacterium together can stimulate inflammatory pathways in patients with rosacea (O'Reilly *et al.*,2012a).

Although rosacea treatment with topical anti-Demodex cream (permethrin 5%) reduced Demodex levels, it was not superior to topical antibiotics (metronidazole 0.75%) in the treatment of rosacea, implying that bacterial pathogens can be involved (Kocak *et al.*,2002). *Bacillus oleronius* is a proinflammatory gram-negative bacterium that is sensitive to many drugs widely used to treat rosacea, including doxycycline (O'Reilly *et al.*,2012b). It is believed to be carried by Demodex mites as an endobacterium that expresses many antigenic proteins, which then can enhance neutrophil migration, degranulation, and cytokine production in patients with papulopustular rosacea (Watson *et al.*,2018).

Staphylococcus epidermidis was also isolated from a biopsy of follicullar samples of rosacea patients using standard aerobe culture methods. Because *S. epidermidis* is one of the most abundant bacteria in normal skin flora, its significance in rosacea is unclear. Cultivation of *S. epidermidis* at high temperatures results in the expression of a variety of proteins. It is suggested that these proteins may be included in the pathogenesis of rosacea, as the skin of patients with rosacea was observed to be warmer than that of normal people (Lacey *et al.*,2007).

Infection with *Helicobacter pylori*, the gut bacterium has been investigated as an etiological factor in the pathogenicity of rosacea (Muto *et al.*,2014). The colonization rate of *H. pylori* was considerably higher in rosacea patients than in the control group when the C urea- breath test was used as a diagnostic method. Several studies have reported the seropositivity of *H. pylori* in rosacea patients, although this claim is not universally recognized (Jorgensen *et al.*,2017). ROS (reactive oxygen species) are produced by *H. pylori*, including NO (nitric oxide), together with cag-A cytotoxin, TNFα, and IL-8 upregulation with a cascade of inflammatory reactions, which may cause the flushing, erythema, and inflammation accompanying rosacea (Song *et al.*,2018).

Moreover, population-based research has shown a relationship between rosacea and gastrointestinal illnesses like gastroesophageal reflux, irritable bowel syndrome, and small bowel bacterial overgrowth (SIBO). Studies showing an improvement in rosacea in combination with SIBO antibiotic therapy support the link (Holmes *et al.*,2018 and Rainer *et al.*,2020).

2- Blepharitis:

For many years, the relevance of the Demodex mite as an etiologic cause of chronic blepharitis has been disputed (Kheirkhah *et al.*, 2007 and Zhong *et al.*,2019). Both *D. folliculorum* and *D. brevis*, are linked to blepharitis, meibomian gland dysfunction, and dry eye illnesses. Demodex was assumed to primarily serve as mechanical carriers of harmful bacteria such as *Staphylococcus* and *Streptococcus* (Fig. 1) (Liu *et al.*,2010).

The global incidence of mite infection in blepharitis cases was found at a rate of 13–70% (Elston *et al.*,2011). Furthermore, Demodex has been found in the eyelashes of 18% of healthy people aged 21 to 35 years. Demodex blepharitis is a chronic inflammatory illness affecting the lid border and ocular surface and can cause major eye difficulties (Cheng *et al.*,2015 and Biernat *et al.*,2018). Itching, burning, dryness, irritation, watering, impaired vision, and the sense of heavy eyelids are all common symptoms (Amescua *et al.*,2019).

Loss of eyelashes can occur when *D. folliculorum* colonizes in the

pilosebaceous components of the eyelids. Demodex mite promotes follicular inflammation, which leads to oedema and easier eyelash epilation. It also causes cilia constriction, resulting in brittle and falling lashes (Rabensteiner *et al*.,2019).

Investigating the influence of mites on ocular surface bacteria can help elucidate the pathogenic process of Demodex blepharitis and improve treatment techniques. *Streptophyta*, *Corynebacterium*, and *Enhydrobacter* were found in higher abundance in the tear samples and eyelashes of blepharitis patients (Naik *et al.*,2012). Patients with Demodex blepharitis, have shown significant changes in the tear film and tear cytokine levels (Rabensteiner *et al*.,2019). The relationship between Demodex and the ocular microbial ecology, on the other hand, is still in its infancy (Lee *et al.*,2012). *Propionibacterium acnes* colonies were dramatically abundant in the eyelashes of patients with Demodex blepharitis (*D. folliculorum*), laying the foundations for the potential synergistic role of the bacterium and the mite in the pathogenesis of blepharitis for further investigation (Zhu *et al.*,2018).

Even if the Demodex dies, the pathogenic bacteria they carry can still induce inflammatory reactions, therefore anti-inflammatory treatment is just as vital as mite removal. For many years, scientists have been studying the efficacy of various therapies for Demodex blepharitis. Topical administration of topical tea tree oil (TTO) and metronidazole ointment are two therapeutic techniques for Demodex that focus on diminishing or eradicating parasites (Navel *et al.*,2019).

3- Non-Specific Facial Dermatitis:

Demodex dermatitis is distinct from rosacea and seborrheic dermatitis, and the presence of facial erythema, dryness, scaling, and roughness with or without papules/pustules could be caused by the over-growth of *D. folliculorum* (Fig. 1) (Bikowski *et al.*,2009). Patients with nonspecific facial symptoms such as facial pruritus with or without erythema, seborrheic dermatitis-like eruptions, perioral dermatitis-like lesions and papulopustular, and/or acneiform lesions without telangiectasia, flushing, or comedones had significantly higher median mite density (Vollemer, 1996).

4-Androgenetic Alopecia (AGA):

Demodex has been linked to the development of AGA. Either directly or indirectly (Zari *et al.*,2008). Demodex mites have an immune-active lipase, which causes inflammation (Fig. 1). It has been claimed that the inflammatory reaction in AGA is limited to the area around the sebaceous glands and infundibulum and that follicular infiltration with activated T-cells cause increased collagen synthesis by dermal sheath fibroblasts, leading to hair follicle replacement by fibrosis (Mahi *et al.*,1998).

The inflammatory response alters local hormone metabolism. Under the influence of dihydrotestosterone, the sebaceous glands of alopecia-affected hair follicles are larger and more active, generating oils at a faster pace and thus providing a better environment for Demodex. Demodex infection is thought to be a result of AGA rather than the cause. Long-term parasite invasion causes hair bulb exhaustion and a shift in the hair cycle from anagen to telogen (Zari *et al.*,2008).

5-Miscellaneous Conditions:

Perioral dermatitis, acarica, blepharo-conjunctivitis, Grover's disease, eosinophilic folliculitis, papulovesicular facial, papulopustular scalp eruptions, pityriasis folliculorum, pustular folliculitis, Demodex abscess, and demodicosis gravis have all been described as granulomatous rosacea similar to demodicosis (Pena *et al.*,2000). Dissecting folliculitis of the scalp is considered an inflammatory reaction to microorganisms in the hair follicle, including bacteria (especially *Propionibacterium acnes* and *Staphylococcus aureus*), yeasts (*Micrococcus mutans*), and fungi (*Candida albicans*), in addition to the Demodex mite

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(Tchernev,2011). Several authors claim that Lupus Miliaris Disseminatus Faciei (LMDF) is a reaction to *D. folliculorum*, however, this has yet to be proven (Mehta *et al.*,2007).

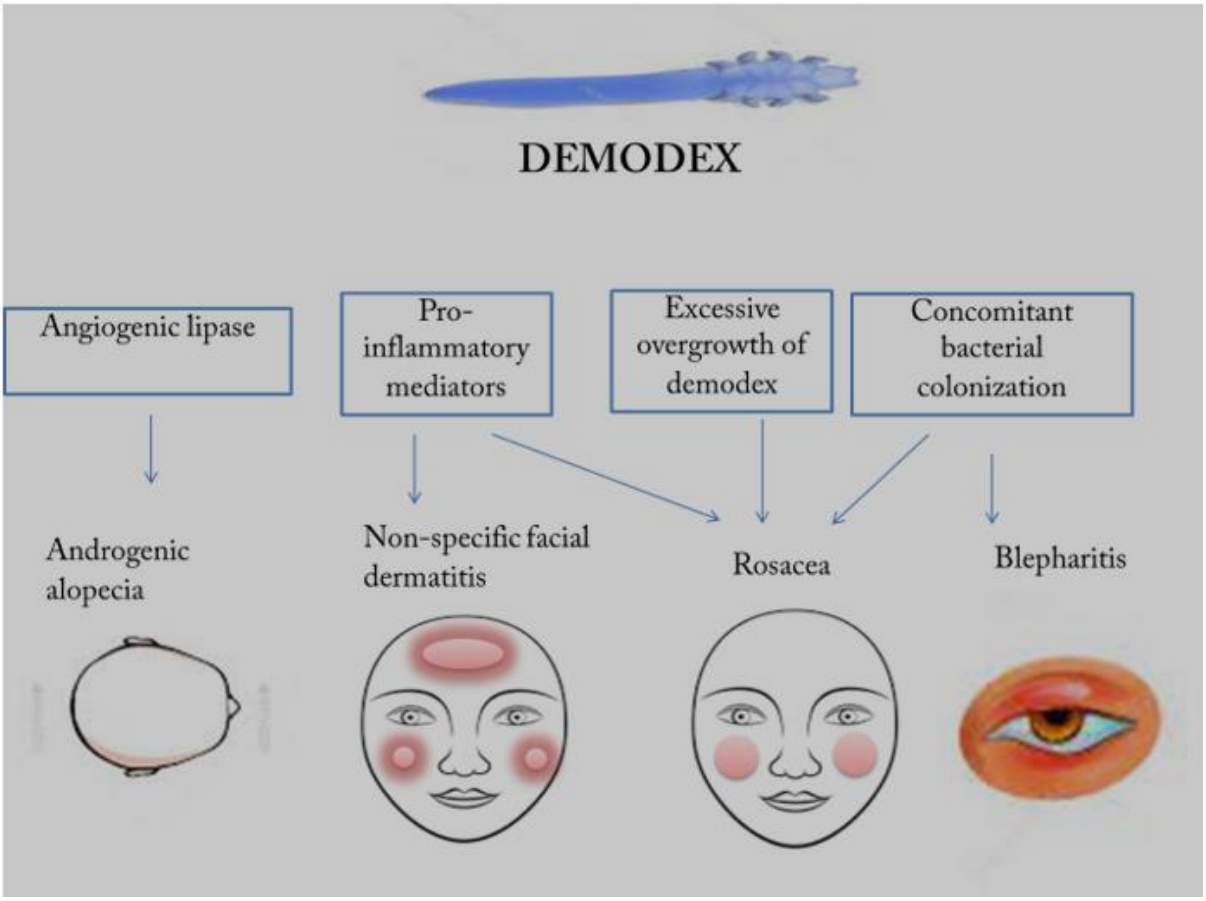

Fig.1: Summary of the most important skin disorders associated with Demodex mites and the possible underlying mechanisms

CONCLUSION

Demodex mites, like several other cutaneous microorganisms, are vulnerable to the host immune status, transitioning from commensals (or even mutualistic organisms) to pathogens if the host's defences are altered. The emergence of microbiome science may favour a paradigm shift to our understanding of Demodex mites, their role in healthy skin, involvement as a disease agent, or as carriers of other bacteria that may have a synergistic role in the pathogenicity of skin diseases. More research is needed to identify the opportunistic pathogens associated with Demodex skin disorders, as well as to compare the microbial communities in patients with and without Demodex infestation for effective treatment of dermatological conditions that may be attributed to root systemic causes rather than just demodicosis.

Acknowledgment:

The authors of this article would like to acknowledge Dr.Madga S.A. Abdeltawab for her critical reading and enhancement of the manuscript.

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