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Review

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Comparison of the efficacy of tea tree (*Melaleuca alternifolia*) oil with other current pharmacological management in human demodicosis: A Systematic Review

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Abstract

Various treatments are found to be moderately effective in managing *Demodex*-related diseases except tea tree oil (TTO) and terpinen-4-ol (T4O), which showed superior miticidal and anti-inflammatory effects in numerous clinical studies. Their possible effects include lowering mite counts, relieving *Demodex*-related symptoms, and modulating the immune system. This review summarizes the current clinical topical and oral treatments in human demodicosis, their possible mechanisms of action, side-effects and resistance in treating this condition. TTO (especially T4O) is found to be the most effective followed by metronidazole, ivermectin and permethrin in managing the disease. This is because TTO has anti-parasitic, anti-bacterial, anti-fungal, anti-inflammatory and wound-healing effects. Furthermore, nanoTTO can even release its contents into fungus and *Pseudomonas* biofilms. Combinations of different treatments are occasionally needed for refractory cases, especially for individuals with underlying genetic predisposal or are immuno-compromised. Although the current treatments show efficacy in controlling the *Demodex* mite population and the related symptoms, further research needs to be focused on the efficacy and drug delivery technology in order to develop alternative treatments with better side-effects profiles, less toxicity, lower risk of resistance and are more cost-effective.

Introduction

Human demodicosis is a transmittable parasitic dermatosis caused by the acarine mite *Demodex*, which are found in human pilosebaceous follicles. There are two species of *Demodex* in humans: *Demodex folliculorum* which is approximately 0.3–0.4 mm long and has a longer opisthosoma and usually resides in the hair follicles, and *Demodex brevis*, which is approximately 0.2–0.3 mm long, and has a shorter opisthosoma and usually resides in sebaceous and Meibomian glands (Cheng *et al.*, 2015). *Demodex* is most commonly found in the hair follicles of the nasolabial folds, the nose and eyelids, but other regions such as genital regions have also been reported in humans (Aylesworth and Vance, 1982; Ugras *et al.*, 2009). They can migrate from one follicle to another during the night as bright light can deter them from coming out of the follicles in day time (Norn, 1971; Rather and Hassan, 2014). The life cycle of the *Demodex* mite is approximately 14–18 days from the egg to the larval stage and eventually reaches its adult stage that lasts for 5 days. The female mite may live an additional 5 days after oviposition (Rufli and Mumcuoglu, 1981). The mating of the parasite takes place in the follicle opening and eggs are laid inside the hair follicles or sebaceous glands (Maraghi *et al.*, 2013). The mites can survive longer at lower temperatures (68 h at 20°C *vs* 23 h at 37°C *in vitro*) and they have better motility at 16–20°C (Zhao *et al.*, 2009).

Epidemiology study of human demodicosis

Several research studies reported that the two *Demodex* species which can infest humans are found in all ethnic groups without any gender preference, but it may be occupation dependent (Norn, 1971; Rufli and Mumcuoglu, 1981; Lacey *et al.*, 2009; Ozer *et al.*, 2012; Biernat *et al.*, 2018). Transmission occurs by human-to-human transfer of mites through close contact (Ozer *et al.*, 2012). The *Demodex* rate of infestation in healthy individuals is about 80–90% (Enginyurt *et al.*, 2015) and the number of *Demodex* is positively correlated with age. Human *Demodex* mites are present in all age groups except in newborn infants (Akcinar *et al.*, 2018; Zhong *et al.*, 2019) and the prevalence is as high as 100% in elderly people

(Basta-Juzbasic *et al.*, 2002; Vargas-Arzola *et al.*, 2012). Since *Demodex* passes to newborns through close physical contact from their parents after birth, it is postulated that due to low sebum production in their skins, infants and children have a much lower incidence of *Demodex* colonization compared to adults (Basta-Juzbasic *et al.*, 2002).

Diseases associated with human demodicosis

Demodex infection has been reported to be associated with ocular and auricular conditions such as chalaza (Liang *et al.*, 2014), blepharo-conjunctivitis (Liang *et al.*, 2010), blepharitis (Liu *et al.*, 2010; Salem *et al.*, 2013), otitis externa and myringitis (Klemm *et al.*, 2009). *Demodex* infestation is also associated with dermatological conditions such as acne vulgaris (Karincaoglu *et al.*, 2004), pityriasis folliculorum (Patrizi *et al.*, 1997; Hsu *et al.*, 2009), rosacea (Ozturkcan *et al.*, 2004), perioral dermatitis (Karincaoglu *et al.*, 2004), neutrophilic sebaceous adenitis (Liaqat *et al.*, 2015), sebaceous adenoma (Dhingra *et al.*, 2009), seborrheic dermatitis (Bikowski and Del Rosso, 2009), papulo-pustular eruption (Aydogan *et al.*, 2006), alopecia (Helou *et al.*, 2016), androgenic alopecia (Zari *et al.*, 2008), scalp folliculitis (Fernandez-Flores and Alija, 2009; Helou *et al.*, 2016) and nipple infection (Yokoyama *et al.*, 2014; Hoda and Cheng, 2019). There are also associations with systemic conditions such as oily skin complexion (Porta Guardia, 2015), ageing (Baima and Sticherling, 2002), type II and gestational diabetes (Gokce *et al.*, 2013; Keskin Kurt *et al.*, 2014), malignancy (Erbagci *et al.*, 2003; Inci *et al.*, 2012; Sonmez *et al.*, 2013), polycystic ovarian syndrome (Benk Silfeler *et al.*, 2015), obesity (Dokuyucu *et al.*, 2016), sickle cell anaemia (Kaya *et al.*, 2019), immunosuppression (Cotliar and Frankfurt, 2013; Yamaoka *et al.*, 2014; Chovatiya and Colegio, 2016; Hitraya-Low *et al.*, 2016; Hachfi *et al.*, 2019), malnutrition and low socioeconomic status (Kaya *et al.*, 2013). Other factors such as alcohol dependency (Kokaçya *et al.*, 2016*b*) and contact lens use (Jalbert and Rejab, 2015; Tarkowski *et al.*, 2015) also play a part in the pathogenesis in demodicosis infection. Interestingly, *Demodex* infections have also been associated with psychiatric conditions such as depression (Kokacya *et al.*, 2015) and schizophrenia (Kokaçya *et al.*, 2016*a*). This may be due to the weakening of the immune system and frequently impaired social behaviours such as a lack of hygienic self-care.

Pathogenesis of human demodicosis

The pathogenesis of demodicosis involves the direct blockage of the meibomian glands (Gao *et al.*, 2007) and skin barrier impairment of the follicles caused by the *Demodex* mite's mouthpiece and claws. Digestive enzymes such as protease and lipase secreted by the *Demodex* mites may provoke host protease-activated receptors, and may promote the expression of the anti-microbial peptide and upregulate pro-inflammatory cytokines (Bevins and Liu, 2007). The chitin exoskeleton of the mites, crystalline biological waste products and contaminant bacterium inside the mites such as *Streptococci*, *Staphylococci*, *Bacillus cereus* and *Bacillus oleronius* may trigger the inflammatory cascade by the toll-like receptor (TLR2) innate immunity pathway (Liu *et al.*, 2010) and may help the induction of T_H9 cells *via* IL-4 secretion (Gazi *et al.*, 2019). *Bacillus oleronius* may increase the release of the 83 and 62 kDa proteins that activate the inflammatory responses in the host (Lacey *et al.*, 2009). *Bacillus cereus* is strongly associated with tissue-destructive or reactive exoenzyme productions such as different kinds of haemolysins, phospholipases and enterotoxins (Tatu *et al.*, 2016). An adaptive immune response such as CD4 helper T cells can infiltrate the site with other immune responding cells including macrophages and Langerhans cells (Georgala *et al.*, 2001).

Genetic predisposition is an important risk factor for human demodicosis. Patients with human leukocyte antigen phenotype HLA-Cw2 and HLA-Cw4 are more susceptible to *Demodex* overproliferation due to reduction in Nk2 cells and T1 cells adaptive immunity response where those with the HLA-A2 phenotype were less susceptible (Akilov and Mumcuoglu, 2003). Other haplotypes such as HLA A3-Cw4, A3-Cw2, A3-B17, A3-B35 and B35-Cw4 also showed a positive correlation with human demodicosis (Akilov and Mumcuoglu, 2003). The carbohydrate-like Tn antigen expressed by *Demodex* and modulation of the secretion of pro-inflammatory mediators such as interleukin (IL)-8 and tumour necrosis factor (TNF)-α from the pilosebaceous unit may play a role in interfering with the innate immune response of the host to facilitate the invasion and population expansion of *Demodex* (Moran *et al.*, 2017). Moreover, infestation of mites can elevate tear cytokine levels, especially IL-1β and IL-17, which can cause inflammation of the lid margin and ocular surface in some individuals (Kim *et al.*, 2011*a*; Kim *et al.*, 2011*c*).

Methodology of this systematic review

This review will address the following objectives:

1. To examine the strengths and limitations of the current research concerning the use of tea tree oil (TTO), terpinen-4-ol (T4O), metronidazole, ivermectin, permethrin, crotamiton, lindane and miscellaneous treatments in treating human demodicosis.
2. To explore and determine the most effective treatments studied in this article for human demodicosis.

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.*, 2009). Strategies to identify eligible studies included a systematic search of four electronic databases including Embase, PubMed, Medline and Cochrane. The search strategy covered the time period from 1970 to 2020 June 6th; therefore, this review will examine randomized control trials completed during this period in which TTO, T4O, metronidazole, ivermectin, permethrin, crotamiton, lindane, pilocarpine and miscellaneous treatments were significant in treating human demodicosis. The following search terms were used: demodicosis, *Demodex*, *D. folliculorum*, *D. brevis*, TTO, T4O, metronidazole, ivermectin, permethrin, crotamiton, lindane, pilocarpine, hexachlorocyclohexane (full search strategy available upon request). This search was performed with library staff to ensure inclusion of all relevant articles and Boolean operators were used with care. All references were initially reviewed by title, abstract and screened according to the following inclusion and exclusion criteria.

Inclusion criteria

Studies met inclusion criteria if they were original research; English language; prospective and retrospective data; drugs including TTO, T4O, metronidazole, ivermectin, permethrin, crotamiton, lindane, pilocarpine and miscellaneous treatments which had pharmacological significance in treating demodicosis were included; only human studies were included.

Exclusion criteria

Exclusion criteria comprised the following: review articles, theoretical discussions, conference articles, abstract articles, comment or reply articles, erratum or corrigendum. Data regarding the use of TTO, T4O, metronidazole, ivermectin, permethrin, crotamiton, lindane, pilocarpine and miscellaneous treatments not

used for human demodicosis were excluded. Demodicosis not related to humans but in animals such as canine were excluded.

There was a total of 769 articles identified from all databases. After removal of duplicates, 535 articles remained. In all, 417 articles were excluded based on title and review of abstract. When there was uncertainty regarding the inclusion of an article, this was screened by two reviewers. A total of 118 full-text articles were selected. Twenty-three articles did not meet inclusion criteria and were removed, leaving a total of 95 articles for critical review (see Fig. 1). The best available National Health and Medical Research Council (NHMRC) level of evidence (LOE) available was II (randomized control trial). The studies were rated according to NHMRC (National Health and Medical Research Council, 2009) referred in Table 1.

Throughout this review, recommendations for specific treatments are made based on the category of LOE provided by the National Health and Medical Research Council in Australia described in Table 1 and on the highest evidence available at the time of writing. In general, recommendations of a lower Roman numeral number should be considered as having a greater LOE supporting the specific treatment.

For most of the recommendations in this article, the evidence was derived from results of a recent systematic review or meta-analysis (LOE I), randomized control clinical trials (RCTs) (LOE II), and other types of clinical trials other than RCTs (LOE III 1-3) and case series or case studies (LOE IV). There are a few randomized controlled studies and open-label trial studies published evaluating therapeutic options for human demodicosis. Recommendations for a specific treatment did not take into consideration whether the products are available in a specific country and whether it is approved for the treatment of human demodicosis by the local health governing body. Pharmaceutical products and treatment protocols in the respective countries need to be verified by the treating clinicians.

Current pharmacological management of human demodicosis

A recent systematic review and meta-analysis by Navel *et al.* focusing on *Demodex* pharmacological managements identified several systemic and topical treatments and they proposed topical TTO (5–50%) or T4O (0.1–38%) with usual lid hygiene once or twice daily for the first 3 months should be the first-line treatment (LOE I) in *Demodex*-related infections especially if blepharitis is present. As the adverse effects such as eyelid erythema, cutaneous eczema, itching or burning sensations in orbital and surrounding area with topical uses of TTO (5–50%) (Gao *et al.*, 2005; Gao *et al.*, 2007; Kheirkhah *et al.*, 2007; Liang *et al.*, 2010; Kim *et al.*, 2011*a*; Galea *et al.*, 2014; Yam *et al.*, 2014; Hirsch-Hoffmann *et al.*, 2015; Nicholls *et al.*, 2016; Karakurt and Zeytun, 2018; Ergun *et al.*, 2019) or T4O (0.1–38%) (Tighe *et al.*, 2013; Murphy *et al.*, 2018; Evren Kemer *et al.*, 2020) were very rare and benign, and systemic reactions were never reported in those trials. In second-line or in severe cases, systemic treatments such as ivermectin or metronidazole could be added (LOE I), which may also decrease recurrence in complicated cases (Navel *et al.*, 2019). Another systematic review by Jacob *et al.* about *Demodex*-associated inflammatory skin conditions recommended metronidazole taken orally has shown efficacy in reducing *Demodex* density (LOE I) but the long-term outcomes of this treatment are unknown. Additionally, topical application of permethrin daily or twice daily was shown to be efficacious across multiple human dermatological studies (LOE I) but it was associated with adverse skin irritation. Crotamiton and benzyl benzoate were recommended in the same review as moderate effective treatments in reducing mite counts (LOE I) but their effects on clinical improvement are unknown. Surprisingly, TTO or T4O treatment were not investigated or mentioned in that systematic review (Jacob *et al.*, 2019). One of the systematic reviews by Ebbelaar *et al.* on topical ivermectin in the treatment of papulopustular rosacea suggested that topical ivermectin 1.0% cream daily is a new and effective treatment in papulopustular rosacea because of its anti-inflammatory and acaricidal activity against *Demodex* mites (LOE I). Topical ivermectin demonstrated a significant reduction in inflammatory lesions compared to topical metronidazole (LOE I). Although topical ivermectin seems to be more efficacious than topical metronidazole to manage dermatological human demodicosis, with both treatment options, about 60% of patients relapsed within 36 weeks after discontinuation of treatment (Ebbelaar *et al.*, 2018). By evaluating the results according to the systematic reviews mentioned above, TTO or T4O appear to have superior clinical outcomes compared with other treatments commercially available in terms of their efficacy and adverse effects profile.

In this review, we discuss several classes of treatment in human demodicosis available in the clinical setting. TTO or T4O demonstrated complete eradication of mites and reduction of *Demodex*-related symptoms across many studies without any major adverse effects being reported (Gao *et al.*, 2007; Kim *et al.*, 2011*a*; Gao *et al.*, 2012; Koo *et al.*, 2012; Tighe *et al.*, 2013; Galea *et al.*, 2014; Hirsch-Hoffmann *et al.*, 2015; Karakurt and Zeytun, 2018). Some of the treatments other than TTO or T4O may have patient compliance issues due to the side-effects or the dosing regimens (Hirsch-Hoffmann *et al.*, 2015). So far, other than TTO and T4O, metronidazole, ivermectin, doxycycline, permethrin, crotamiton, lindane, benzyl benzoate and pilocarpine have been trialled and showed some anti-*Demodex* effects. The structures of the treatment molecules included in this publication are shown in Fig. 2.

Tea tree oil and terpinen-4-ol

TTO is an essential oil, extracted and distillated from the leaves and terminal branches of an Australian native plant called *Melaleuca alternifolia* (Huynh *et al.*, 2012). There are 15 major monoterpenes in TTO. They are T4O, γ-terpinene, α-terpinene, 1,8-cineole, *p*-cymene, terpinolene, α-terpineol, α-pinene, sabinene, aromadendrene, ledene, δ-cadinene, limonene, globulol and viridiflorol of the ISO 4730 T4O type TTO (ISO, 2017). Because of its acaricidal, anti-bacterial, anti-viral, anti-inflammatory, wound healing and immunomodulatory effects, TTO shows favourable results in managing human demodicosis (Lam *et al.*, 2018). T4O is the major TTO component that may competitively block the neurotransmitter terminating enzyme acetylcholinesterase (AchE) in parasites that may mediate to the arthropodicidal effect (Mills *et al.*, 2004); it is also a potent inhibitor of lipopolysaccharide (LPS)-induced cytokines, such as IL-1β, IL-6 and IL-10, produced by mononuclear phagocytic macrophages upon activation of TLR4 and TLR2/4; this inhibition is mediated by interfering with the NF-κB, p38 or ERK mitogen-activated protein kinase (MAPK) metabolic pathways (Nogueira *et al.*, 2014) and thereby reducing inflammation.

The anti-demodicosis effect of TTO is still not fully understood. TTO could disrupt various membranes structures of different pathogens by its lipophilic properties (Low *et al.*, 2017). In one of the *in vitro* trials, when TTO was added to suspensions containing *Staphylococcus aureus* cells, quick responses such as leakage of potassium ions and inhibition of cellular respiration were observed, caused by disruption of the cytoplasmic and mitochondrial membranes (Cox *et al.*, 2000). Moreover, in *S. aureus*, autolysin activity of TTO was demonstrated due to the release of membrane-bound cell wall autolytic enzymes that resulted in

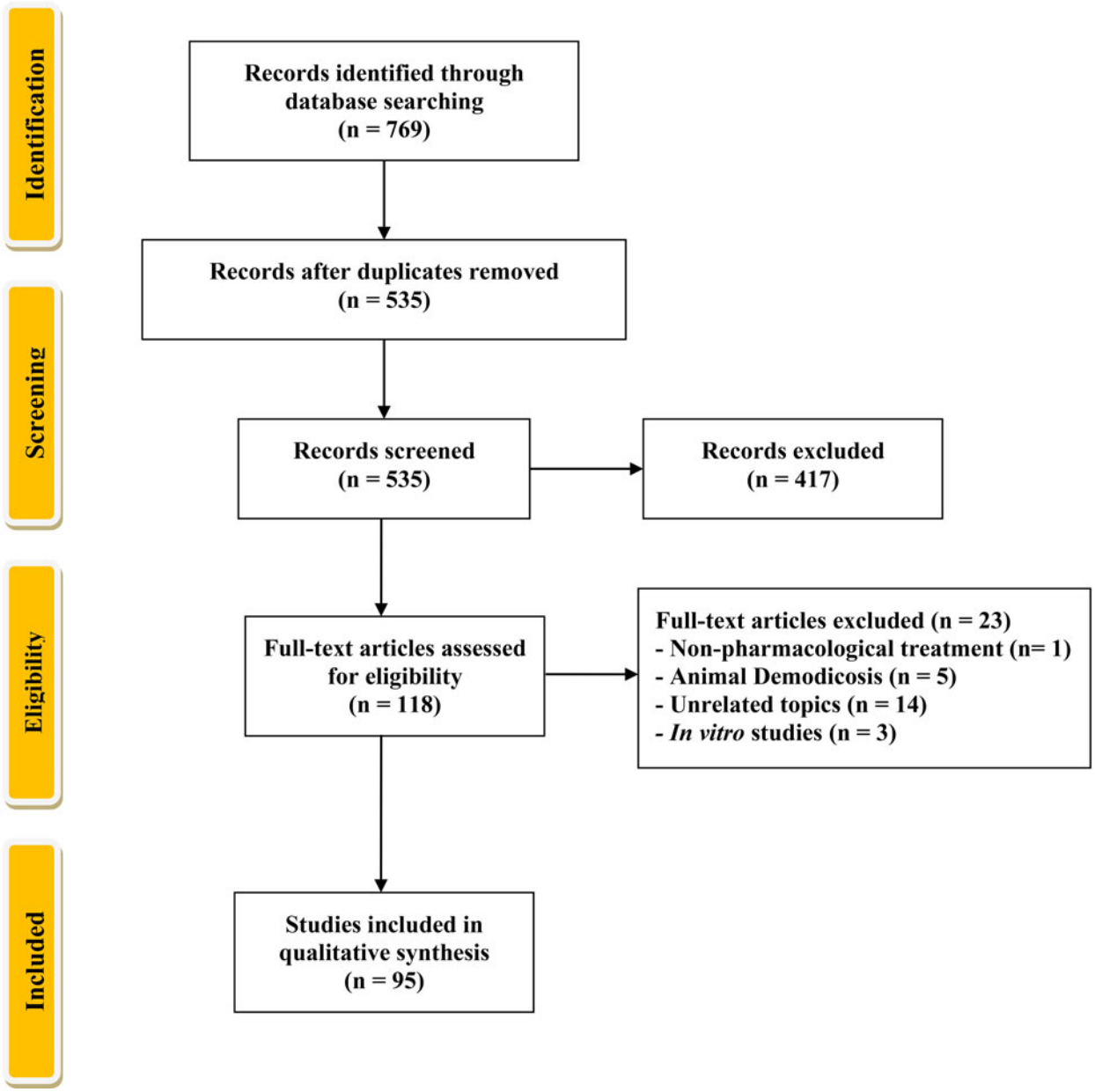

Fig. 1. PRISMA flow diagram of this systematic review.

cell death (Carson *et al.*, 2002). TTO nanoparticles can enter various cells more efficiently through the extracellular matrix, by releasing the TTO into fungus (Souza *et al.*, 2017) and *Pseudomonas* biofilms (Comin *et al.*, 2016) resulting in the enhancement of antimicrobial effect (Rai *et al.*, 2017), as some of the *Demodex* species are associated with opportunistic *Pseudomonas* and fungal infections (Abu-Samra and Shuaib, 2014; Vanam *et al.*, 2018).

In a *Demodex* blepharitis randomized control trial by Koo *et al.*, 50% TTO lid scrub followed by 10% TTO daily lid scrub for 4 weeks decreased mean *Demodex* count from 4 to 3.2 per 8 epilated lashes and the ocular surface discomfort index (OSDI) score was reduced from 34.5 to 24.1 (LOE II). Complete eradication of *Demodex* was demonstrated in 23.6% of patients post-treatment in the TTO intervention group. There were no major side-effects of TTO treatment reported when the patients were doing the correct scrubbing method (Koo *et al.*, 2012).

One of the randomized controlled interventional treatment studies by Murphy *et al.* using TTO facewash contains 38% T4O in treating *D. folliculorum* blepharitis. Patients were given step-by-step instructions provided to subjects for nightly lid scrubs at home. OSDI decreased from 27.4 to 16.2 and the average count of *D. folliculorum* reduced from 4.9 to 1.9 per each eyelash (LOE II). No adverse effect was reported in this study (Murphy *et al.*, 2018).

In another randomized single-blinded control trial by Karakurt and Zeytun in patients with demodectic blepharitis, twice a day 7.5% TTO eyelash shampoo was recommended to the patients. Complete eradication was attained in 4 weeks in 36% of the patients who used eyelash shampoo with TTO with the average *Demodex* count of 6.33 per eyelash ($P < 0.001$) (LOE II). Ocular symptoms and average scores also reduced significantly within the 4 weeks treatment period ($P < 0.001$). The results demonstrated that eyelash shampoo with TTO is three times more effective at achieving full *Demodex* eradication compared with the TTO-free eyelash shampoo control, significantly reducing the *Demodex* count, and relieving ocular symptoms in patients where full reduction cannot be attained, without adverse side-effects being reported (Karakurt and Zeytun, 2018).

Table 1. Hierarchy of evidence provided by the National Health and Medical Research Council in Australia

Level of evidence (LOE)	Design
I	A systematic review of level II studies
II	A randomized control trial
III-1	A pseudo-randomized control trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomized experimental trial • Cohort study • Case–control study • Interrupted time series with a control group
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single-arm studies • Interrupted time series without a parallel control group
IV	Case series/study with either post-test or pre-test/post-test outcomes

One of the randomized double-blind clinical studies by Ergun *et al.* compared the efficacy and safety of two topical TTO-based cleansing gel formulations in the chronic blepharitis study. Patients were instructed to use the formulation twice daily for 4 weeks: cleansing gel formulation containing 3% (w/w) TTO plus calendula oil, borage oil, vitamin E, vitamin B5 <5% (w/w) in the treatment group and cleansing gel formulation containing 3% TTO only as a control group. The mean OSDI scores and the average *Demodex* population per eyelash decreased and fluorescein tear breakup time increased significantly in both treatment groups suggesting that basic washing gel containing only 3% TTO is also as effective as the other formula in reducing the related symptoms and complaints of patients (LOE II). No adverse effects of either formulation were reported (Ergun *et al.*, 2019).

In an open-label trial by Gao *et al.*, topical 5% TTO ointment was used to treat ocular pruritis associated with ocular demodicosis. Twice daily lid massage with 5% TTO ointment for 5 min was recommended to patients for 4 weeks. *Demodex* counts decreased from 5.5 to 0.7 per 8 epilated lashes and 16 out of 24 patients were totally free of pruritis and the remaining eight patients had different degrees of relief (LOE III-2). Lid massage with 5% TTO ointment for a period of 5 min twice per day was able to stimulate mites to emigrate from the lash follicle in the same manner as 50% TTO solution performed weekly but without the side-effects such as inflammation and irritation as mentioned in this study (Gao *et al.*, 2012).

Another open-label controlled trial compared treatment options for *Demodex* blepharitis by Hirsch-Hoffmann *et al.*, daily topical 5% TTO ointment or 0.02% TTO foam, topical or systemic metronidazole or systemic ivermectin with daily lid hygiene only as a control group for 8 weeks. The complete eradication rate and the improvement of symptoms were 6 and 40.5% in the 0.02% TTO foam group compared to 0 and 20% in topical 5% TTO ointment, respectively (LOE III-3). No adverse effects of topical TTO formulations were reported in this study (Hirsch-Hoffmann *et al.*, 2015).

In a case series study, 5% TTO solution lid toileting followed by 5% TTO ointment at night for 12 weeks in patients with *Demodex*-related chronic primary conjunctivitis and dry eye disease resulted in 100 and 95% improvement of symptoms, respectively (LOE IV) (Nicholls *et al.*, 2016). In an open-label retrospective clinical study, 50% TTO weekly lid scrub and 0.5 mL TTO shampoo lid scrub twice daily for 3 weeks had a 96.8% success rate of preventing recurrence of chalazion associated with demodicosis (LOE IV) (Yam *et al.*, 2014). Another clinical study demonstrated that 50% TTO weekly lid scrub by clinicians and 0.5 mL TTO shampoo lid scrub twice daily for 1 month and then once daily thereafter is effective in eradicating ocular demodicosis (LOE IV) (Gao *et al.*, 2005). In addition, an open-label trial and a case study about *Demodex* blepharitis showed that eyelid cleanser containing T4O eyelid rub twice daily alone resulted in significant improvement of ocular symptoms and complete eradication of mites, respectively (LOE IV) (Tighe *et al.*, 2013; Evren Kemer *et al.*, 2020).

Topical TTO, typically in diluted form, is usually well-tolerated. Local adverse effects are mostly skin and ocular allergic or irritant reactions to the oil, in which irritant reactions were usually concentration dependent (Hammer *et al.*, 2006). Contact sensitization and allergic contact dermatitis reactions have been reported for TTO at 5–10%; however, latest prevalence rates in the USA suggested that only 1.4% of patients referred for patch testing had a positive reaction to TTO (Larson and Jacob, 2012). Clinical resistance of *Demodex* to TTO or its monoterpenes constituents has not been reported (Lam *et al.*, 2018). The TTO and T4O dosage, direction and administration form showing effectiveness against the human demodicosis are summarized in Table 2.

Metronidazole

Metronidazole is a synthetic nitroimidazole derivative, which is active against parasitic and anaerobic bacterial infections by inhibiting nucleic acid synthesis thereby disrupting the DNA of microbial cells. Since *Demodex* infection is one of the important factors in rosacea (Holmes, 2013), metronidazole's mechanism of action in rosacea is related both to the agent's anti-inflammatory and antioxidant effects (Schaller *et al.*, 2016). Metronidazole interferes with granulocytic neutrophil release of reactive oxygen species (ROS) production and inactivating existing ROS, which decreases the release of further pro-inflammatory cytokines (Narayanan *et al.*, 2007). Topical metronidazole has demonstrated variable efficacy in various clinical studies (Kocak *et al.*, 2002; Hsu *et al.*, 2009). A randomized double-blind placebo-controlled study for *Demodex*-related papulopustular rosacea showed that topical metronidazole 0.75% twice a day for 8 weeks could significantly improve erythema, the number of papules and pustules, and lowered the *Demodex* count compared to placebo (Kocak *et al.*, 2002) (LOE II). In one case series on dermatological demodicosis, it was demonstrated that topical metronidazole 2% twice daily for 45 days appeared to be effective in controlling *Demodex* infection in terms of the *Demodex* count but long-term benefits and risks are unknown (Forton *et al.*, 1998) (LOE III-3). An open trial study on *Demodex* acne rosacea demonstrated that topical metronidazole 0.75% gel twice daily for 8 weeks resulted in marked clinical symptoms improvement and complete remission and eradication of *Demodex* (LOE III-3) (Ozturkcan *et al.*, 2004). Moreover, in some report series studies of *Demodex*-related dermatological conditions, oral metronidazole may be effective eradicating mites and relieve the overall dermatological signs and symptoms but relapse happened post-treatment in some cases (LOE IV) (Hsu *et al.*, 2009; Helou *et al.*, 2016). Adverse effects include the gastrointestinal side-effects such as metallic taste in the mouth, nausea, vomiting, a disulfiram-like reaction with ingestion of alcohol (Swygard *et al.*, 2004) and neurological side-effects such as seizure, encephalopathy and ataxia (Sunderkotter *et al.*, 2006). Metronidazole is safe in pregnancy, breastfeeding and young infants (Hall *et al.*, 1983; Passmore *et al.*, 1988; Einarson *et al.*, 2000), although it has carcinogenic potential (Sunderkotter *et al.*, 2006). The metronidazole dosage, direction and

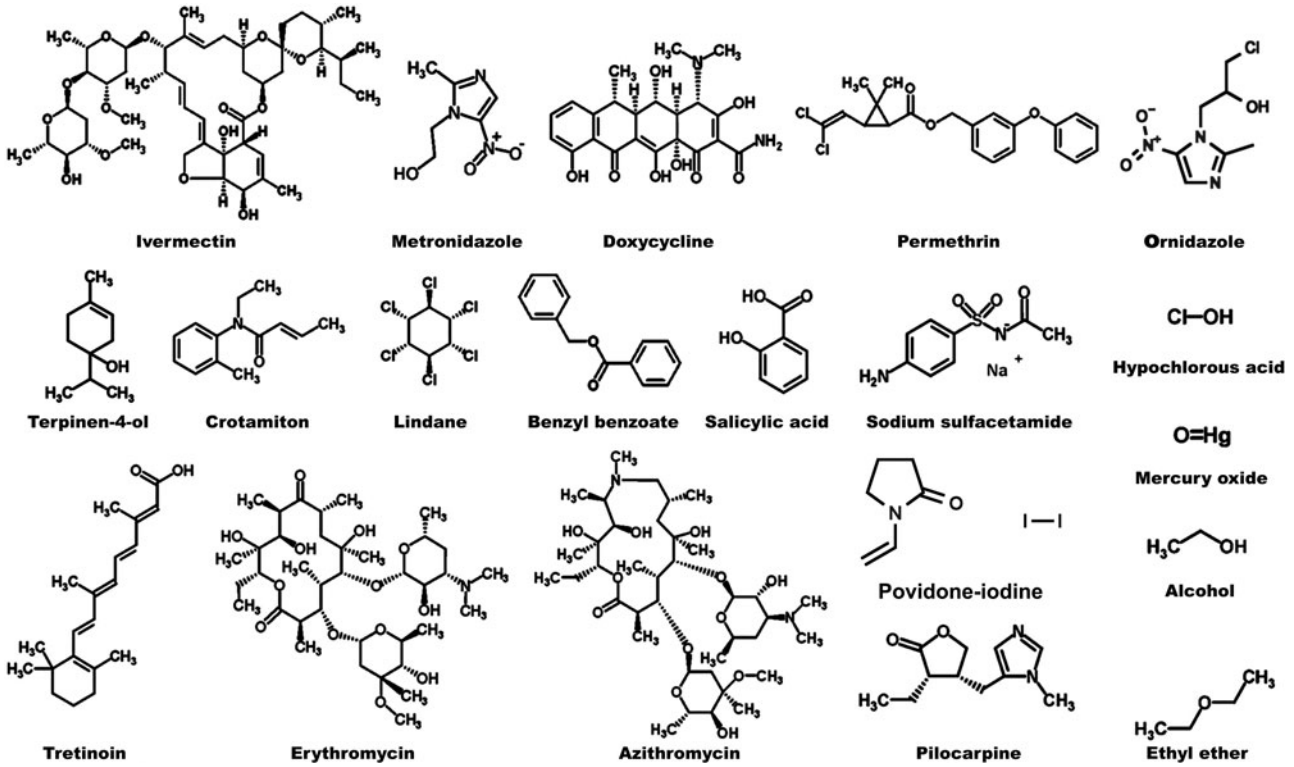

Fig. 2. The chemical structures of terpinen-4-ol, ivermectin, metronidazole, permethrin, doxycycline, crotamiton, lindane, benzyl benzoate, erythromycin, alcohol, azithromycin, ethyl ether, hypochlorous acid, mercury oxide, pilocarpine, tretinoin, salicylic acid, povidone-iodine and sodium sulfacetamide.

administration form showing effectiveness against the human demodicosis are summarized in Table 3.

Ivermectin

Ivermectin is a macrocyclic lactone derived from the soil bacterium *Streptomyces avermectinius*. Except for its well-known anti-onchocerca and anti-filarial effects in the world public health campaigns, ivermectin also demonstrates anti-parasitic activities against many other parasitic infections, such as human demodicosis. The anti-parasitic activity of ivermectin is possibly due to its selectively binding to glutamate or γ-aminobutyric acid (GABA) in the peripheral motor synapses of neurons, resulting in the permanent opening of chloride ion channels. The chloride ion influx might inhibit the neuronal and muscular activities in the parasite and subsequently cause paralysis and death of the parasite (Dourmishev *et al.*, 2005; Kobylinski *et al.*, 2012). The anti-inflammatory properties of ivermectin are likely due to the inhibition of phosphorylation of the MAPKs, JNK and p38 pathways as well as blocking the translocation of the transcription factor NF-κB that results in decreasing LPS-induced inflammation (Zhang *et al.*, 2008; Zhang *et al.*, 2009). The reduction of LPS-induced inflammation may decrease neutrophil phagocytosis and chemotaxis, inhibit pro-inflammatory cytokines such as IL-1β, IL-8 and TNF-α, and upregulate the anti-inflammatory cytokine IL-10 (Stein *et al.*, 2014; Abokwidir and Fleischer, 2015). Compared with metronidazole, ivermectin is superior in reducing inflammatory lesions, with a faster onset of action for papulopustular rosacea (Taieb *et al.*, 2016). The benefit of ivermectin in *Demodex*-related dermatological conditions is probably due to its anti-parasitic, anti-inflammatory and immunomodulatory properties. A single-blind, randomized controlled trial in patients with anterior blepharitis or skin lesions caused by *Demodex* evaluated the efficacy of ivermectin compared to ivermectin plus metronidazole. Two doses of ivermectin 200 μg kg^{-1} orally given 1 week apart or metronidazole 250 mg orally three times daily for 2 weeks in addition to the two doses of ivermectin. At week 4, there was a significant decrease in *Demodex* count, 71.6% showed complete remission on combined therapy, 26.7% showed marked clinical improvement and <2% of patients showed no clinical improvement, and compared favourably to those patients on ivermectin therapy alone (LOE III-1). No adverse events were reported (Salem *et al.*, 2013). An open-label trial about treatment options in *Demodex* blepharitis, oral ivermectin 6 mg single dose and repeated after 2 weeks improved symptoms in 35% and eradicated *Demodex* in 6% at 8 weeks follow-up without any adverse effects reported (LOE III-3) (Hirsch-Hoffmann *et al.*, 2015). Ivermectin can reduce the mite count (LOE IV) (Holzchuh *et al.*, 2011; Ruini *et al.*, 2017), and relieve the *Demodex*-related signs and symptoms in both ocular and dermatological demodicosis (LOE IV) (Filho *et al.*, 2011; Friedman *et al.*, 2017; Kaser *et al.*, 2017). However, there has been one human *Demodex* ivermectin-resistant case reported recently (LOE IV) (Hervás Ontiveros *et al.*, 2014). Adverse effects of topical ivermectin are mostly mild. They include dermatological side-effects such as skin irritation, allergic dermatitis, exacerbation of rosacea, erythema, pruritus and general flushing (Taieb *et al.*, 2015). Systemic ivermectin treatment may result in transient and mild systemic adverse reactions including anorexia, asthenia, headache, arthralgia, myalgia, fever, eosinophilia, and maculopapular rashes (Hengge *et al.*, 2006). Ivermectin should be avoided in pregnancy, breastfeeding and children weighing <15 kg (Hay *et al.*, 2012). The ivermectin dosage, direction, administration form showing effectiveness against the human demodicosis are summarized in Table 4.

Permethrin

Permethrin is a synthetic pyrethroid agent derived from *Chrysanthemum cinerariifolium* (Casida, 1980). It is insecticidal

Table 2. TTO dosage and direction in treating human demodicosis

NHMRC	Diseases	Age (years); gender	Sample size (n)	Dosage form	Administration (dose, route and time)	Effect	Reference
II	Blepharitis	Average age: 53.7 ± 10.3; male 34%, female 66%	106	Topical	50% TTO lid scrub weekly followed by 10% TTO lid scrub daily for 1 month	Decrease in average *Demodex* count and OSDI score from 4.0 ± 2.5 to 3.2 ± 2.3 per 8 cilia and 34.5 ± 10.7 to 24.1 ± 11.9 respectively, and complete eradication of *Demodex* in 23.6% of patients post-treatment	(Koo *et al*., 2012)
II	Blepharitis	49.6 ± 17.1; gender not specified	28	Topical	Dr Organic Tea Tree Face Wash™ (38% terpinen-4-ol) lid scrub nightly for 4 weeks	Decrease in mean *Demodex* count from 4.9 to 1.9 post-treatment	(Murphy *et al*., 2018)
II	Blepharitis	Mean age: 57.52 ± 14.22; male 46.7%, female 53.3%	75	Topical	7.5% TTO eyelash shampoo twice daily for 4 weeks	Decrease in average *Demodex* count from 6.33 to 0 and 12.46 to 4.15 per eyelash in 36% and 64% patients respectively, and reduction in itching, burning, foreign body sensation, redness and cylindrical dandruff of eye post-treatment	(Karakurt and Zeytun, 2018)
II	Blepharitis	Mean age: 53.16 ± 9.59; male 37.5%, female 62.5%	24	Topical	Blefar-ex® Plus cleansing gel formulation containing 3% (w/w) TTO plus calendula oil, borage oil, vitamin E, vitamin B5 less than 5% (w/w) twice daily for 1 month	*Demodex* presence decreased from 54.2 to 20.6%, mean OSDI score decreased, TNF-α, IL-1β and IL-6 tear cytokines decreased	(Ergun *et al*., 2019)
II	Blepharitis	Mean age: 48.80 ± 13.22; male 52%, female 48%	25	Topical	Basic washing gel formulation containing 3% (w/w) TTO twice daily for 1 month	*Demodex* presence decreased from 42 to 27.8%, mean OSDI score decreased, TNF-α tear cytokines decreased	(Ergun *et al*., 2019)
III-2	Ocular demodicosis	37.2 ± 15.6; male 42%, female 58%	24	Topical	5% TTO ointment lid massage twice per day for 4 weeks	Decrease in mean *Demodex* count from 5.5 ± 1.6 to 0.7 ± 0.8 per 8 epilated lashes with complete eradication of *Demodex* in 11 patients post-treatment	(Gao *et al*., 2012)
III-3	Blepharitis	Not specified	7 and 45 for ointment and foam regimen respectively	Topical	5% TTO ointment to lid margins and lashes nightly for 2 months or 0.02% diluted TTO foam to clean eyelids, eyebrow and face skin daily for 2 months	Complete eradication of *Demodex* in 0% patients and 20% with improvement of symptoms for 5% TTO regimen post-treatment; complete eradication of *Demodex* in 6% patients and 40.5% with improvement of symptoms for 0.02% diluted TTO regimen after 2 months	(Hirsch-Hoffmann *et al*., 2015)
IV	Blepharitis	Mean age: 52.8 ± 15.8; male 53.6%, female 46.7%	30	Topical	0.1% Terpinen-4-ol soaked wipes to eyelids twice daily for 2 weeks, followed by 7–10 day break followed by the same treatment again; patients were examined after the first and second cycle of treatment and after 1 year	Significant improvement in Schirmer test, ocular surface disease index, lid margin score, meibomian gland expressibility scores, and Oxford grade after the first cycle of treatment; the improvement in symptoms and tear function tests of patients after the second cycle was significantly better than in pre-treatment levels	(Evren Kemer *et al*., 2020)
IV	Blepharitis	Average age: 48.3 ± 18.9;	10	Topical	50% TTO weekly lid scrub and 10% TTO shampoo lid scrub twice daily for 1 month	Decrease in mean *Demodex* count from 3.8 ± 2.2 to 0.2 ± 0.4 per eye, significant decrease in mean tear concentrations of cytokines for	(Kim *et al*., 2011*a*)

(*Continued*)

Table 2. (*Continued.*)

NHMRC	Diseases	Age (years); gender	Sample size (n)	Dosage form	Administration (dose, route and time)	Effect	Reference
		male 40%, female 60%				IL-1β and IL-17 from 1141.5 ± 440.3 to 561.7 ± 261.0 and 1,907.8 ± 861.0 to 1124.2 ± 545.1 pg mL^{-1} respectively, and complete eradication of *Demodex* in 10 of 13 eyes post-treatment	
IV	Blepharitis	Average age: 49.3 ± 17; male 66.7%, female 33.3%	6	Topical	50% TTO lid scrub weekly and tea tree shampoo lid scrub daily for 6 weeks	Decrease in mean *Demodex* count from 6.8 ± 2.8 to 1 ± 0.9 per 8 lashes, all patients showed subjective improvement of ocular surface irritation and pain with complete disappearance of conjunctival redness and regression of corneal superficial vascularization at mean follow-up of 7.9 ± 7.7 months	(Kheirkhah *et al.*, 2007)
IV	External ocular diseases	Average age: 62; male 25%, female 75%	333	Topical	Eyelid toileting followed by 5% tea tree ointment nightly for 3 months	91% of patients with improvement of symptoms post-treatment	(Nicholls *et al.*, 2016)
IV	Ocular demodicosis	60.2 ± 11.6; male 54.5%, female 45.5%	11	Topical	50% TTO office lid scrub weekly and 0.5 mL tea tree shampoo lid scrub twice daily for 4 weeks	Complete eradication of *Demodex* in 8 patients in <4 weeks with 9 patients experiencing 50–100% improvement in symptoms	(Gao *et al.*, 2007)
IV	Ocular demodicosis	59.86 ± 8.7; gender not specified	9	Topical	50% TTO office lid scrub weekly and 0.5 mL tea tree shampoo lid scrub twice daily for 4 weeks	Complete eradication of *Demodex* in 5 and 2 patients in 3 and 4 weeks respectively	(Gao *et al.*, 2005)
IV	Blepharoconjunctivitis	Age range: 2.5–11; male 41.7%, female 58.3%	12	Topical	50% TTO eyelid scrubs 3 times weekly for 4–6 weeks or 5% TTO ointment eyelid massage twice daily for 4–6 weeks	Decrease in *Demodex* count with resolution of ocular irritation and inflammation in all patients after 1 week, all corneal signs resolved in 2 weeks	(Liang *et al.*, 2010)
III-3	Recurrent chalazion	39.1 ± 10.2; male 46.7%, female 53.3%	30	Topical	50% TTO lid scrub weekly and 0.5 mL tea tree shampoo lid scrub twice daily for 3 weeks	96.8% success rate of preventing recurrent chalazion associated with demodicosis at mean follow-up of 10.0 ± 3.0 months	(Yam *et al.*, 2014)
IV	Blepharitis	60; male	1	Topical	5% TTO and 50% tea tree lid scrub for 3 months	Improvement of blepharitis with reversal of ectropion, light microscopy of multiple eyelash confirmed eradication of *Demodex* post-treatment	(Galea *et al.*, 2014)
IV	Blepharitis	61; female	1	Topical	Cliradex™ (lid cleanser containing water and T4O) eyelid rub twice daily for 8 weeks	Marked resolution of symptoms and repeated examination showed clearer lashes and no *Demodex* post-treatment	(Tighe *et al.*, 2013)

Table 3. Metronidazole dosage and direction in treating human demodicosis

NHMRC	Diseases	Age (years); gender	Sample size (*n*)	Dosage form	Administration (dose, route and time)	Effect	Reference
II	Papulopustular rosacea	Mean age: 51; male 23.8%, female 76.2%	20	Topical	0.75% gel twice daily for 2 months	Decrease in mean *Demodex* count, erythema score, papules and pustules from 2.60 ± 0.74 to 2.00 ± 0.56, 2.85 ± 0.36 to 1.40 ± 0.68, 8.00 ± 6.70 to 2.90 ± 2.80 and 4.90 ± 4.78 to 2.40 ± 3.10 respectively post-treatment	(Kocak *et al*., 2002)
III-3	Acne rosacea	Mean age: 46.96 ± 1.74; male 27.6%, female 72.4%	29	Topical	0.75% gel twice daily for 2 months	73.3, 26.7 and 17.2% patients showed marked clinical improvement, complete remission and complete eradication of *Demodex* respectively post-treatment	(Ozturkcan *et al*., 2004)
III-3	Blepharitis	Not specified	5 for topical or oral regimen	Topical or oral	2% ointment nightly for 2 months or 500 mg twice daily for 10 days	Complete eradication of *Demodex* in 0% patients and 20% with improvement of symptoms for topical or oral regimen after 2 months	(Hirsch-Hoffmann *et al*., 2015)
III-3	Demodicosis	Not specified	6	Topical	2% twice daily for 45 days	Normalization of *Demodex* count in 2 patients and reduced *Demodex* count in 4 patients post-treatment	(Forton *et al*., 1998)
IV	Acne rosacea	64; male	1	Oral	500 mg twice daily for 4 weeks	Complete resolution at 3rd week follow-up	(Hsu *et al*., 2009)
IV	*Demodex* abscess	53; male	1	Oral	250 mg three times daily for 2 weeks	Complete recovery after 2 weeks and at 9 months follow-up respectively, repeated scrapings remained negative for *Demodex*	(Schaller *et al*., 2003)
IV	*Demodex* folliculitis	38; female	1	Oral	250 mg three times daily for 1 week	Complete resolution at 15th month follow-up	(Hsu *et al*., 2009)
IV	*Demodex* folliculitis	27; female	1	Oral and topical	Oral 250 mg three times daily for 3 weeks and topical 0.75% gel twice daily for 3 weeks	Complete resolution at 82nd month follow-up with two relapses at 40th and 47th month	(Hsu *et al*., 2009)
IV	*Demodex* folliculitis	40; male	1	Oral	1 g daily for 3 weeks	Papulopustular eruption resolved without *Demodex* mites on previously affected areas post-treatment	(Aydogan *et al*., 2006)
IV	*Demodex* folliculitis	27 and 50; male	2	Oral	500 mg twice daily for 2 weeks or 2 months	Complete cessation of hair loss, erythema and pustules post-treatment	(Helou *et al*., 2016)
IV	*Demodex* folliculitis	7; male	1	Topical	Cream twice daily for 9 months	Improvement within 1 month without resolution of rash after 9 months	(Herron *et al*., 2005)
IV	Demodicosis	53; male	1	Oral and topical	Oral 250 mg three times daily for 3 weeks and topical 0.75% gel twice daily for 3 weeks	Complete resolution at 2nd week follow-up	(Hsu *et al*., 2009)
IV	Demodicosis	18; female	1	Oral and topical	Oral 250 mg three times daily for 3 weeks and topical 0.75% gel twice daily for 3 weeks	Complete resolution at 2nd week follow-up	(Hsu *et al*., 2009)
IV	Demodicosis	52; male	1	Oral	250 mg three times daily for 1 week	Complete resolution without follow-up	(Hsu *et al*., 2009)
IV	Eosinophilic folliculitis	42; female	1	Topical	0.75% gel twice daily for 2 weeks	Complete resolution without follow-up	(Hsu *et al*., 2009)

(*Continued*)

Table 3. (*Continued.*)

NHMRC	Diseases	Age (years); gender	Sample size (*n*)	Dosage form	Administration (dose, route and time)	Effect	Reference
IV	Neutrophilic sebaceous adenitis	61; male	1	Topical	Gel for 3 days	Disappearance of plaque after 3 days	(Liaqat *et al.*, 2015)
IV	Plaque forming demodicosis	88; female	1	Topical	0.75% gel twice daily for 3 months	Improvement after 1 month and complete resolution post-treatment	(Fichtel *et al.*, 2005)
IV	Rosacea	60; female	1	Topical	0.75% gel twice daily for 1 week	Complete resolution without follow-up	(Hsu *et al.*, 2009)
IV	Rosacea-like demodicosis	Age range: 10 months–5 years; male 50%, female 50%	8	Topical	1% gel twice daily for 3–4 weeks	Complete eradication of *Demodex* in 50% patients post-treatment and complete recovery in all patients at 12–38th month follow-up	(Patrizi *et al.*, 1997)

and scabicidal with selectively low mammalian toxicity properties (Casida, 1980). Permethrin may slow the rate of the voltage-gated sodium channel closure of arthropods, resulting in prolonged depolarization of nerve-cell membranes that could disrupt neurotransmission, causing nerve depolarization and hyper-excitation result in muscle paralysis and death of the parasite (Zlotkin, 1999). The neurotoxic effect of permethrin on vertebrates is relatively mild compared to invertebrates due to structural differences in voltage-gated sodium channels between vertebrates and invertebrates (Zlotkin, 1999). Moreover, it may also interfere with the GABA receptor chloride ionophore complexes and neurotransmitters (Imamura *et al.*, 2000; Wang *et al.*, 2016). The anti-demodicosis mechanism is unknown, but topical 5% permethrin twice daily for 8–12 weeks can decrease the *Demodex* mite count (LOE II) (Raoufinejad *et al.*, 2016), and improve the erythema score (LOE II) (Kocak *et al.*, 2002) and dermatological signs and symptoms (LOE IV) (Morras *et al.*, 2003). One of the randomized, double-blind, placebo-controlled studies evaluated the effect of permethrin 5% cream or placebo twice daily in the management of *Demodex* papulopustular rosacea. From baseline to day 60, the extent of erythema, the number of papules and *Demodex* count showed a significant reduction in the permethrin group (LOE II). Side-effects were evaluated and no complications were reported during the study (Kocak *et al.*, 2002). However, it is important to mention that while permethrin did cause some skin irritation and erythema, it did not result in discontinuation of therapy in some *Demodex* clinical studies (Forton *et al.*, 1998; Jansen *et al.*, 2001; Morras *et al.*, 2003) (LOE III-3 to LOE IV). Permethrin is poorly absorbed through the skin and the small percentage absorbed is then metabolized rapidly and excreted in the urine in the form of inactive metabolites (Tomalik-Scharte *et al.*, 2005). Adverse effects including dermatological effects such as pruritus, numbness, erythema, paresthesia; systematic effects such as headache, dizziness, muscle spasms, convulsions and dystonic action of the neck have been reported (Coleman *et al.*, 2005; Raoufinejad *et al.*, 2016). Topical use of permethrin is safe for pregnancy, breastfeeding and infants more than 2 months old (Hay *et al.*, 2012). The strength, direction and administration form showing effectiveness against the human demodicosis are summarized in Table 5.

Crotamiton

Crotamiton is a pale yellow oil with a faint amine-like odour used as an anti-scabies, anti-bacterial and anti-pruritic for many dermatological conditions (Hausen and Kresken, 1988). It is a common scabies treatment recommended for newborn babies and infants (Hengge *et al.*, 2006). The anti-pruritic effect is believed due to crotamiton's moderate inhibition of histamine, serotonin and PAR-2 agonist that is TRPV-1 independent and produces the counter-irritation and cooling effect (Sekine *et al.*, 2012). Crotamiton can reduce the *Demodex* mite count (LOE IV) (Purcell *et al.*, 1986) and improve the *Demodex*-related dermatological signs and symptoms (LOE IV) (Bikowski and Del Rosso, 2009; Hsu *et al.*, 2009). An open-label, randomized study with patients suffering from a variety of *Demodex* skin conditions showed that 10% crotamiton was applied daily for 45 days, achieved normalization of *Demodex* count which was observed after the treatment period in one patient only and reduction of *Demodex* count occurred in other participants (LOE III-3) (Forton *et al.*, 1998). Adverse effect included dermatological side-effects such as flushing, irritation, conjunctivitis and contact dermatitis (Hengge *et al.*, 2006). It is safe for pregnancy, breastfeeding and young infants (Hay *et al.*, 2012). The strength, direction, administration form showing effectiveness against the human demodicosis are summarized in Table 6.

Table 4. Ivermectin dosage and direction in treating human demodicosis

NHMRC	Diseases	Age (years); gender	Sample size (n)	Dosage form	Administration (dose, route and time)	Effect	Reference
III-1	Acne vulgaris, blepharitis, peri-oral dermatitis or rosacea	Mean age: 36.71 ± 12.4; male 48.4%, female 51.6%	60	Oral	200 $\mu g\,kg^{-1}$ 2 doses 1 week apart	Decrease in mean *Demodex* density from 12.3 ± 3.2 to 2.3 ± 2.7, 12.8 ± 6.8 to 5.3 ± 5.4, 21.3 ± 7.5 to 1.7 ± 1.7 and 51.7 ± 20.8 to 31.4 ± 18.9 mites per cm^2 for acne vulgaris, blepharitis, peri-oral dermatitis and rosacea respectively at 4^{th} week follow-up	(Salem *et al.*, 2013)
III-3	Blepharitis	Not specified	32	Oral	6 mg single dose and repeated after 2 weeks	Complete eradication of *Demodex* in 6% patients and 35% with improvement of symptoms after 2 months	(Hirsch-Hoffmann *et al.*, 2015)
IV	Blepharitis	Mean age: 50.4 ± 21.0; male 25%, female 75%	12	Oral	200 $\mu g\,kg^{-1}$ 2 doses 1 week apart	Decrease in average number of mites from 4.79 to 0.54 in superior and inferior lashes with improvement in tear break-up time, and Schirmer I test results 28 days post-treatment	(Holzchuh *et al.*, 2011)
IV	Blepharitis	Mean age: 65.75; male 69.02%, female 31.58%	19	Oral	6 mg twice for daily and repeated after 2 weeks	Symptoms improved in 84.3% patients with complete eradication of *Demodex* 3 months post-treatment	(Filho *et al.*, 2011)
IV	*Demodex* folliculitis	46; female	1	Oral	12 mg single dose	Complete resolution of skin lesions within 24 h	(Cotliar and Frankfurt, 2013)
IV	Demodicosis	25; female	1	Oral and topical	Oral 200 $\mu g\,kg^{-1}$ single dose followed by topical ivermectin (10% dilution in propylene glycol) locally for 1 month 1 month later	Clinical improvement with decrease in papulopustules and only dead parasites on lesion scrapings after oral treatment, papulopustular lesions reappeared 1 month later which was resolved by topical treatment	(Clyti *et al.*, 2006)
IV	Demodicosis	38; female	1	Oral	200 $\mu g\,kg^{-1}$ single dose	Eradication of demodicosis	(Clyti *et al.*, 2006)
IV	Demodicosis	Age not specified; female	1	Oral	200 $\mu g\,kg^{-1}$ single dose	Dead or only slightly mobile *Demodex* in scrapings 1 week post-treatment and eradication of demodicosis at day 15	(Clyti *et al.*, 2006)
IV	Demodicosis	34; male	1	Topical	1% nightly for 2 weeks	Significant improvement after 2 weeks	(Friedman *et al.*, 2017)
IV	Papulopustular rosacea	63; male	1	Topical	1% cream for 4 weeks	Clinical improvement with reduction of *Demodex* density and inflammatory components within 4 weeks	(Kaser *et al.*, 2017)
IV	Papulopustular rosacea	Mean age: 56; male 25%, female 75%	50	Topical	1% nightly over 16 weeks	Complete eradication of *Demodex* and decreased inflammatory lesions post-treatment	(Trave *et al.*, 2019)
IV	Papulopustular rosacea	Average age: 52.3; 40% male, 60% female	20	Topical	1% cream daily over 12 weeks	Decrease in mean *Demodex* count from 99.9 to 3.8 per cm^2 after 6 weeks and to 0.8 cm^2 after 12 weeks of treatment with 80% of patients reaching therapeutic success	(Schaller *et al.*, 2017)
IV	Papulopustular rosacea	Mean age: 58; male 50%, female 50%	10	Topical	Soolantra™ 10 mg g^{-1} Crème daily for 4 weeks	Reduction in erythematic papulopustules and subjective symptoms, > 50% reduction of number of mites in 50% of patients, and 10% of patients had complete recovery with disappearance of mites after 4 weeks	(Ruini *et al.*, 2017)
IV	Papulopustular rosacea or peri-oral dermatitis	Mean age: 9.8 ± 2.2; male 40%, female 60%	15	Oral or topical	Oral 200–250 $\mu g\,kg^{-1}$ single dose or topical 1% cream daily for 3 months	93% of patients achieved complete or almost complete clearance of lesions at mean follow-up of 11.9 ± 7.1 months	(Noguera-Morel *et al.*, 2017)
IV	Rosacea	12; female	1	Oral	12 mg single dose	Improvement of lesions and progressive resolution of ocular symptoms at 1 month follow-up	(Brown *et al.*, 2014)

Table 5. Permethrin dosage and direction in treating demodicosis

NHMRC	Diseases	Age (years); gender	Sample size (n)	Dosage form	Administration (dose, route and time)	Effect	Reference
II	Papulopustular rosacea	Mean age: 51; male 23.8%, female 76.2%	23	Topical	5% cream twice daily for 2 months	Decrease in mean *Demodex* count, erythema score, papules and pustules from 2.20 ± 1.04 to 0.65 ± 0.71, 2.60 ± 0.48 to 1.34 ± 0.7, 6.04 ± 7.60 to 1.73 ± 2.20 and 2.30 ± 3.73 to 0.56 ± 1.27 respectively post-treatment	(Kocak *et al.*, 2002)
II	Papulopustular rosacea	Mean age: 42.2 ± 7.8; male 15%, female 85%	20	Topical	5% twice daily for 12 weeks	Decrease in median *Demodex* density from 274.1 to 8.1 with reductions of papules, pustules and telangiectasia post-treatment	(Raoufinejad *et al.*, 2016)
III-2	Demodicosis	Mean age: 35.7 ± 11.40; male 12.5%, female 87.5%	26	Topical	5% cream twice daily for 15 days	Complete eradication of median *Demodex* in patients who had erythema, facial itching and pityriasiform squame lesions respectively post-treatment	(Karincaoglu *et al.*, 2004)
III-3	Demodicosis	Not specified	6	Topical	1% once every 2 days for 45 days	Average *Demodex* decreased by 20.3% with normalization of *Demodex* count in 0 patients and reduced *Demodex* count in 4 patients post-treatment	(Forton *et al.*, 1998)
IV	Blepharitis	Mean age: 57.2 ± 16.8; male 38%, female 62%	21	Topical	5% cream daily for 6 months	Decrease in mean *Demodex* count from 1.36 ± 1.233 to 0.48 ± 0.6 per eyelash with improvement in blepharitic symptoms and clinical findings at 4–6th month follow-up	(Hecht *et al.*, 2019)
IV	*Demodex* folliculitis	21 months; male	1	Topical	5% cream for three consecutive nights weekly for 3 weeks	Incomplete resolution post-treatment	(Herron *et al.*, 2005)
IV	Demodicosis	2; female	1	Topical	5% cream for 1 night	Eruption cleared after overnight treatment	(Sahn and Sheridan, 1992)
IV	Rosacea-like demodicosis	4; male	1	Topical	1.5% nightly for 1 week	Complete disappearance of lesions in 1 month and 1 year follow-up	(Morras *et al.*, 2003)
IV	Rosacea-like demodicosis	35; male	1	Topical	5% cream twice daily for 4 weeks	Complete resolution of skin lesions and pruritus with few *Demodex* post-treatment	(Jansen *et al.*, 2001)

Table 6. Crotamiton therapy dosage and direction in treating human demodicosis

NHMRC	Diseases	Age (years); gender	Dosage form	Administration (dose, route and time)	Effect	Reference
IV	Atopic dermatitis	14 months; male	Topical	Cream daily for 3 nights	Lesions cleared post-treatment	(Won *et al.*, 1993)
IV	*Demodex* dermatitis	Mean age: 50.4; male 44.4%, female 55.6%	Topical	10% twice daily	50% reduction in erythema, dryness, scaling, roughness, papules and/or pustules in 56 of 62 patients at average follow-up of 18.6 days	(Bikowski and Del Rosso, 2009)
IV	*Demodex* folliculitis	49; male	Topical	Cream twice daily for 17 days	Decreased number of *Demodex* to 8 in affected area and pruritic eruption resolved in 72 h	(Purcell *et al.*, 1986)
IV	Acne-rosacea like demodicosis	1; female	Topical	10% daily for 1 week	Complete resolution without follow-up	(Hsu *et al.*, 2009)
IV	Demodicosis	24; female	Topical	Cream daily	Disappearance of lesions 5 days post-treatment and dermatitis lasted for about 1 month	(Banuls *et al.*, 1991)
III-3	Demodicosis	Not specified	Topical	10% daily for 45 days	Average *Demodex* decreased by 64.4% with normalization of *Demodex* count in 1 of 6 patients and reduced *Demodex* count in 6 of 6 patients post-treatment	(Forton *et al.*, 1998)
IV	External genitalia demodicosis	43; male	Topical	Cream for 3 nights	Clearing of multiple, match-head-sized, skin-coloured papulous lesions on penile shaft and scrotum	(Hwang *et al.*, 1998)

Lindane

Lindane, also known as γ hexachlorocyclohexane or benzene hexachloride, is an organochloride of the cyclohexane family. It acts on the GABA-gated chloride channels as a neurotoxin in arthropods, leading to paralysis and death of the parasite (Turberg, 2015). One of the open-label, randomized trials with patients suffering from a variety of dermatological *Demodex* conditions demonstrated that topical lindane 1% every second day for 15 days could reduce *Demodex* mite count but failed to achieve normalization of mites (LOE III-3). Longer treatment is not recommended due to its potential risks of intoxication (Forton *et al.*, 1998). A case series study about dermatological demodicosis showed that lindane topical 1% daily for 2 weeks resulted in complete resolution of any clinical signs of pityriasis folliculorum demodicosis even at the 3 months follow-up (LOE IV) (Hsu *et al.*, 2009). The adverse effects of lindane include dermatological side-effects such as irritation and allergic contact dermatitis; as well as neurological side-effects such as insomnia, irritability, vertigo, convulsions, restlessness and collapse (Hengge *et al.*, 2006). Lindane needs to be avoided in pregnancy, breastfeeding and infant (Hay *et al.*, 2012). The strength, direction, administration form showing effectiveness against the human demodicosis are summarized in Table 7.

Miscellaneous treatments

Doxycycline

Doxycycline is a board-spectrum bacteriostatic antibiotic that inhibits the bacterial ribosomal protein synthesis unit to prevent bacteria from reproducing through the inhibition of protein synthesis. Doxycycline inhibits the production and activity of matrix metalloproteinases (MMPs, especially MMP-9) directly and kallikrein (KLK) indirectly (Kim *et al.*, 2005; Di Nardo *et al.*, 2016). *In vitro* study shows corneal epithelial cells from human telomerase immortalized corneal epithelial cell line (hTCEpi) exposed to *Demodex* endogenous bacterial *B. oleronius* proteins can upregulate the expression of many pro-inflammatory mediators including IL-1β, IL-6, IL-8, TNF-α, cathelicidin, MMP-3 and MMP-9 (O'Reilly *et al.*, 2012; McMahon *et al.*, 2016). The chitin from the exoskeleton of *Demodex* may activate TLR2 receptors in keratinocyte, resulting in increased IL-8, TNF-α, cyclooxygenase-2 and the inflammasome, which subsequently increased KLK-5, LL-37, cathelicidin and MMP-9 (Casas *et al.*, 2012; Woo *et al.*, 2016). Increased MMP-9 levels have been observed in patients with ocular rosacea, and with some of these patients displaying recurrent corneal erosion, therapeutic treatment often includes the use of the doxycycline (Dursun *et al.*, 2001). In addition, the inhibition of the nitric oxide (NO) synthase activity by doxycycline might explain the anti-inflammatory action in rosacea-associated vasodilation (Woo *et al.*, 2016). Doxycycline has been demonstrated to inhibit neutrophil activity and several pro-inflammatory reactions including those associated with phospholipase A2, endogenous NO, TNF-α, IL-6, IL-8 and IL-10 (Bikowski, 2003; Baldwin, 2006; Jantzie and Todd, 2010). However, oral doxycycline is never used as a monotherapy in treating *Demodex*-related conditions. It is always combined with other therapeutic agents such as metronidazole or prednisolone to control the disease (LOE IV) (Hsu *et al.*, 2009; Sattler *et al.*, 2015; Douglas and Zaenglein, 2019). A case study of *D. folliculorum*-associated oculocutaneous rosacea showed that patients using oral doxycycline 100 mg daily and topical tacrolimus for 8 weeks achieved temporary improvement in the *Demodex* skin lesions but the ocular symptoms persisted. However, the patient had a flare 4 weeks after discontinuing doxycycline and restarting the doxycycline did not result in improvement (LOE IV) (Brown *et al.*, 2014).

Table 7. Lindane therapy dosage and direction in treating human demodicosis

NHMRC	Diseases	Age; gender	Dosage form	Administration (dose, route and time)	Effect	Reference
IV	*Demodex* folliculitis	45; male	Topical	1% lotion for 1 night	Complete resolution at 2nd week follow-up	(Ashack *et al.*, 1989)
IV	Demodicosis	Not specified	Topical	1% once every 2 days for 15 days	Normalization of *Demodex* in 0 patients and reduction of *Demodex* in 4 of 6 patients after 15 days	(Forton *et al.*, 1998)
IV	Otitis externa and myringitis	84; female	Topical	Daily for 10 days	Complete eradication of mites, remission of all symptoms and normal clinical presentation of ear at 1 year follow-up	(Klemm *et al.*, 2009)
IV	Papulonodular demodicosis	49; male	Topical	1% lotion for 3 consecutive nights	Clearance of lesions overnight with normalization of *Demodex* post-treatment	(Dominey *et al.*, 1989*a*)
IV	Rosacea	28; female	Topical	1% daily for 2 weeks	Complete resolution at 3rd month follow-up	(Hsu *et al.*, 2009)

Sub-anti-microbial dosing of doxycycline, e.g. 20 mg twice a day or 40 mg daily, was likely as effective or more effective than anti-microbial doses (⩾50 mg per day), in decreasing the release of pro-inflammatory cytokines and downregulating the production of ROS (Wise, 2007), but with much fewer adverse effects such as nausea, diarrhoea and lower the risk of developing bacteria resistance (van Zuuren *et al.*, 2015; Asai *et al.*, 2016). The adverse effects of doxycycline include oesophageal erosion, gastrointestinal discomfort and photosensitivity (Smith and Leyden, 2005). Doxycycline is not recommended in pregnancy, breastfeeding and infant (Aupee *et al.*, 2009).

Benzyl benzoate

Benzyl benzoate is an organic ester that can be rapidly hydrolysed to benzoic acid and benzyl alcohol which are neurotoxic to the mites and active against their ova (Buffet and Dupin, 2003). One of the open-label, randomized studies with patients suffering from a variety of *Demodex* skin diseases showed that benzyl benzoate 10% applied to the affected area twice daily can reduce *Demodex* mite count by 98.2% and improve dermatological signs and symptoms with only moderate irritation (LOE III-3) (Forton *et al.*, 1998). Adverse effects including transient skin irritation, burning sensation and post-treatment eczematous reaction happened in high strength preparations of ≥25% (Brooks and Grace, 2002). Topical use of benzyl benzoate is safe during second or third trimester pregnancy (Mytton *et al.*, 2007), breastfeeding (Hengge *et al.*, 2006) and in children that are more than 1 year old (Sunderkotter *et al.*, 2007).

Pilocarpine

Pilocarpine is a well-known treatment for glaucoma in humans. It is a cholinergic parasympathomimetic agent acting primarily as a non-selective muscarinic agonist that may cause paralysis of mites' respiration and mobility (Celorio *et al.*, 1989; Fulk *et al.*, 1996). A case series on ocular demodicosis demonstrated that 4% pilocarpine gel spread once in the evening on the base of eyelashes, and removed in the morning for 2 weeks, could reduce the number of mites and alleviate the related symptoms (LOE IV) (Fulk *et al.*, 1996). No side-effects were observed secondary to pilocarpine when applied to the lid margins only (Fulk *et al.*, 1996). Another study also confirms its efficacy for the miticidal effect (LOE IV) (Celorio *et al.*, 1989). Pilocarpine is not recommended during pregnancy, and the use of pilocarpine in breastfeeding mothers and young children should be done cautiously (Coppens *et al.*, 2010).

Other treatments

Several topical treatments have been found useful to relieve or control human *Demodex* conditions (LOE II to IV), such as sulphur (Robinson, 1965; Nakagawa *et al.*, 1996; Forton *et al.*, 1998; Sarro *et al.*, 1998; Gao *et al.*, 2005; Herron *et al.*, 2005), 0.01–0.02% hypochlorous acid (Bachir and Bitton, 2015; Roan, 2016), 0.25% povidone-iodine gel (Pelletier *et al.*, 2017), 99.9% ethyl-ether solution (Hervás Ontiveros *et al.*, 2014), 2% mercury oxide ointment (Rodríguez *et al.*, 2005; Anane *et al.*, 2011), 100% alcohol (Gao *et al.*, 2005), camphorated oil (Czepita *et al.*, 2007; Liu *et al.*, 2010), salicylic acid cream (Hoekzema *et al.*, 1995; Karincaoglu *et al.*, 2004), azithromycin (Kim *et al.*, 2011*b*), erythromycin (Sanchez-Viera *et al.*, 1992), sodium sulfacetamide (Herron *et al.*, 2005) and tretinoin (Dominey *et al.*, 1989*b*). Many of these treatments alone are often insufficiently effective in managing the condition (Salem *et al.*, 2013). Further investigations are needed to understand their mechanisms of action and toxicities to determine the optimum dosage and length of treatment in demodicosis. The dosage, direction and

Table 8. Miscellaneous treatment dosage and direction in treating human demodicosis

NHMRC	Diseases	Age (years); gender	Sample size (*n*)	Drug	Dosage form	Administration (dose, route and time)	Effect	Reference
II	Rosacea	Mean age: 46.9; male 78.2%, female 21.8%	23	Precipitated sulphur	Topical	3% precipitated sulphur twice daily for 28 days	Rosacea responded clinically	(Robinson, 1965)
III-1	Blepharitis	49.6 ± 16.9; gender not specified	30	OcuSoft™ Lids Scrub Plus (0.5% 1, 2-Octanediol)	Topical	OcuSoft™ Lids Scrub Plus wipes nightly for 4 weeks	Decrease in mean *Demodex* count from 3.8 to 1.9 post-treatment	(Murphy *et al*., 2018)
III-3	Acne rosacea	Mean age: 49.5 ± 2.33; male 33%, female 66.7%	27	Benzoyl peroxide erythromycin (5% benzoyl peroxide and 3% erythromycin)	Topical	Benzoyl peroxide-erythromycin gel twice daily for 2 months	91.7, 8.3 and 40.7% patients showed marked clinical improvement, complete remission and complete eradication of *Demodex* respectively post-treatment	(Ozturkcan *et al*., 2004)
III-3	Demodicosis	Median age: 63.5; male 30%, female 70%	20	Blephadex™ (Glycerin, Aloe Barbadensis Leaf Juice, Cocamidopropyl Betaine, Cocos Nucifera oil, Lauryl Glucoside, *Melaleuca alternifolia* Leaf oil, Sodium Laureth Sulfate)	Topical	Blephadex™ eyelid wipes daily for 30 days	50% reduction in *Demodex* burden post-treatment and overall comfort improved over time in treated eyes	(Wong *et al*., 2019)
III-3	Demodicosis	Not specified	5	Benzyl benzoate	Topical	10% twice daily for 45 days	Average *Demodex* decreased by 98.5% with normalization of *Demodex* count in 5 patients and reduced *Demodex* count in 5 patients post-treatment	(Forton *et al*., 1998)
III-3	Demodicosis	Not specified	5	Sublimed sulphur	Topical	10% sublimed sulphur once every 2 days for 45 days	Average *Demodex* decreased by 6.4% with normalization of *Demodex* count in 2 patients and reduced *Demodex* count in 3 patients post-treatment	(Forton *et al*., 1998)
III-3	Demodicosis or rosacea	Mean age: 44.8 ± 12.7; male 12.5%, female 87.5%	72	Sulphur-sodium sulfacetamide or crotamiton or permethrin	Topical	5% sulphur-sodium sulfacetamide or 10% crotamiton lotion or 5% permethrin cream twice daily for 8 weeks	Decrease in median *Demodex* count from 10 to 3, 17 to 6, and 14.5 to 6 per cm^2 for sulphur-sodium sulfacetamide, crotamiton and permethrin treatment respectively post-treatment	(Sarac, 2019)
IV	Blepharitis	95; female	1	0.25% PVP-I in a dimethylsulfoxide vehicle	Topical	PVP-I gel to the lash surface from the skin side	Remarkable improvements in signs and symptoms 1 week post treatment; changes to the anterior eyelid was preserved, the corneal punctate erosions were no longer present, and the posterior eyelid meibum was less viscous at 1 month	(Pelletier *et al*., 2017)
IV	Blepharitis	53; male	1	Ethyl ether (99.9% ethyl ether, 0.02% water, density 0.713 g mL^{-1})	Topical	Ether lid massage daily for 2 weeks	Improvement of symptoms and disappearance of palpebral crusty lesions post-treatment	(Hervás Ontiveros *et al*., 2014)

(*Continued*)

Table 8. (*Continued.*)

NHMRC	Diseases	Age (years); gender	Sample size (*n*)	Drug	Dosage form	Administration (dose, route and time)	Effect	Reference
IV	*Demodex* folliculitis	43; male	1	Sulphur	Topical	6% sulphur lotion twice daily for 2 weeks	Complete eradication of *Demodex* and resolution of pustular lesion post-treatment	(Nakagawa *et al*., 1996)
IV	Demodicosis	39; male	1	Aquaphor™ (3% sulphur in hydrophilic petrolatum)	Topical	Aquaphor™ for 2 weeks	Lesion cleared and no mites present post-treatment	(Sarro *et al*., 1998)
IV	Demodicosis	Not specified	Not specified	Camphor oil	Topical	100, 75, 50 or 25–20% camphor oil	100% cure at concentrations of 100, 75, and 50% with decreased *Demodex* density at concentrations of 25-20% post-treatment	(Morsy *et al*., 2002)
IV	Ocular demodicosis	Age range: 68–83; male 20%, female 80%	10	Pilocarpine	Topical	4% pilocarpine gel nightly for 2 weeks	Decrease in average number of mites from 2.4 to 0.7 post-treatment	(Fulk *et al*., 1996)
IV	Rosacea	4; female	1	Erythromycin	Oral	250 mg erythromycin daily	Sustained improvement	(Sanchez-Viera *et al*., 1992)
IV	Rosacea	52; female	1	Azythromycin	Oral	500 mg daily for 2 weeks	Facial erythema and swelling reduced after 2 weeks followed by reduction in papular lesions, most lesions disappeared after 10 weeks	(Kim *et al*., 2011*b*)

Table 9. Combination therapy dosage and direction in treating human demodicosis

NHMRC	Diseases	Age (years); gender	Sample size (n)	Dosage form	Administration (dose, route and time)	Effect	Reference
II	Papulopustular rosacea	Age range: 18–60; male 25.4%, female 71.4%	35	Topical	2.5% permethrin with tea tree oil gel formulation twice daily for 12 weeks	Reduction of mites, non-transient erythema, papule, pustules, dry appearance, burning and stinging post-treatment	(Ebneyamin *et al*., 2020)
II	Dry eye disease	Mean age: 66.37 ± 8.83; male 21%, female 79%	33	Topical	Artificial tears, topical steroid drops and eyesol shampoos with tea tree oil for 1 month	Significant decrease in *Demodex* count, tear break-up time, osmolarity and ocular surface disease index scores were significantly better than control at 1 month follow-up	(Mohammadpour *et al*., 2019)
III-1	Acne vulgaris, blepharitis, peri-oral dermatitis or rosacea	Mean age: 36.71 ± 12.4; male 45%, female 55%	60	Oral	250 mg metronidazole three times daily for 2 weeks and 200 $\mu g\,kg^{-1}$ ivermectin 2 doses 1 week apart	Decrease in mean *Demodex* density from 12.9 ± 6.1 to 0.5 ± 1.2, 15 ± 5.7 to 0.2 ± 0.4, 21.9 ± 6.8 to 0.2 ± 0.4 and 51.5 ± 26.3 to 5.5 ± 19.5 mites per cm^2 for acne vulgaris, blepharitis, peri-oral dermatitis and rosacea respectively at 4^{th} week follow-up	(Salem *et al*., 2013)
III-1	Blepharitis	Mean age: 34; male 33%, female 67%	45	Topical	Palpebral hygiene with neutral shampoo three times daily or palpebral hygiene with neutral shampoo and topical 0.75% metronidazole gel twice daily or palpebral hygiene with neutral shampoo and antibiotic cream comprised (3.5% neomycin and 10% polymixin with 0.5% dexamethasone) three times daily	Significant improvement of signs and symptoms with all regimen	(Arrua *et al*., 2015)
III-1	Blepharitis	Mean age: 71 ± 5.8; male 46.1%, female 53.9%	26	Topical	Monthly in-office microblepharoexfoliation, followed by Cliradex™ (terpinen-4-ol) lid scrub twice daily for 2 months	Reduction in *Demodex* infestation from 4.7 to 3.6 per 4 lashes after first month and 2.6 per 4 lashes after second month	(Epstein *et al*., 2020)
III-1	Blepharitis	Mean age: 49.86 ± 19.7; gender not specified	28	Topical	BlephEx™ (microblepharoexfoliation) with OcuSoft™ Lid Scrub Plus foam (0.5% 1, 2-octanediol) nightly for 4 weeks	Decrease in mean *Demodex* count and from 6.5 to 2.7 after 4 weeks	(Murphy *et al*., 2018)
III-1	*Demodex* folliculitis	Age range: 20–45; male 21%, female 79%	100	Oral, injection and topical	Oral 500 mg ornidazole three times daily for 2 weeks, 1 mL compound betamethasone injection intramuscularly or oral 10 mg ebastine daily for 3 weeks, topical 1 g recombinant bovine basic fibroblast growth factor gel three times daily on lesion for 2 weeks beginning on day 7 post-ornidazole, oral anti-histamine for 4 weeks for patients who used ebastine	Overall effective rate of 94% and only 6 patients with *Demodex* mite relapse after 2 weeks	(Luo *et al*., 2016)
III-1	*Demodex* folliculitis	Age range: 20–45; male 28%, female 72%	100	Oral, injection, and topical	Oral 200 mg metronidazole four times daily for 2 weeks, 1 mL compound betamethasone injection intramuscularly or 10 mg ebastine daily for 3 weeks, topical 1 g recombinant bovine basic fibroblast growth factor gel three times daily on lesion for 2 weeks beginning on day 7 post-metronidazole, oral anti-histamine for 4 weeks for patients who used ebastine	Overall effective rate of 78% and only 26 patients with *Demodex* mite relapse after 2 weeks	(Luo *et al*., 2016)

(*Continued*)

Table 9. (*Continued.*)

NHMRC	Diseases	Age (years); gender	Sample size (n)	Dosage form	Administration (dose, route and time)	Effect	Reference
III-1	Blepharitis	Mean age: 55.4 ± 19.1; gender not specified	30	Topical	Ivermectin 0.1% Metronidazole 1% gel on days 0, 15 and 30	Complete eradication of *Demodex* in 96.6% of patients, significant reduction of inflammation signs found in all patients	(Avila *et al.*, 2020)
III-2	Demodicosis	Mean age: 35.7 ± 11.40; male 12.5%, female 87.5%	6	Topical	5% permethrin cream twice daily and 2% salicylic acid for 1 month	Complete eradication of median *Demodex* in 2 of 3 patients who had acneiform lesions and complete eradication of median *Demodex* in all patients with granulomatous rosacea like lesion and pustular folliculitis post-treatment	(Karincaoglu *et al.*, 2004)
III-2	Anterior blepharitis	Mean age: 52 ± 16.2; male 62.5%, female 37.5%	24	Topical	Blepha*Demodex*® (preservative-free cleansing lotion containing 2.5%T4O and 0.2% hyaluronic acid) once daily in the evening 29 days	Overall ocular discomfort significantly reduced, ocular symptom associated with *Demodex* blepharitis was improved, eyelid margin hyperaemia significantly reduced at day 8 and day 29, total disappearance of cylindrical dandruff in 30.4% of patients; follow-up on day 8 and 29	(Messaoud *et al.*, 2019)
III-2	Anterior blepharitis	Mean age: 56.5 ± 15.1; male 50%, female 50%	24	Topical	Blepha*Demodex*® (preservative-free cleansing lotion containing 2.5%T4O and 0.2% hyaluronic acid) twice daily in morning and evening for 29 days	Overall ocular discomfort was significantly reduced, ocular symptom associated with *Demodex* blepharitis was improved, eyelid margin hyperaemia significantly reduced at day 8 and day 29, total disappearance of cylindrical dandruff in 43.5% of patients; follow-up on day 8 and 29	(Messaoud *et al.*, 2019)
III-3	Rosacea	Age range: 34–77; male 36%, female 64%	25	Oral and topical	Topical 2% metronidazole cream or gel twice daily combined with oral 50 mg doxycycline or minocycline daily	Decrease in mean *Demodex* from 115 to 96.2 and 86.2 to 58.5 for 8 × 8 and 5 × 5 mm^2 mosaic respectively at mean follow-up of 53.5 days	(Sattler *et al.*, 2015)
III-3	Rosacea or demodicosis	Mean age: 48.1 ± 1.0; male 23%, female 77%	195	Topical	10% crotamiton cream daily and 12% benzyl benzoate with 10% crotamiton cream nightly for 2 months	Decrease in mean *Demodex* count from 88 ± 8 to 28 ± 3 per cm^2 with 20% patients without symptoms at mean follow-up of 2.7 ± 0.2 months	(Forton and De Maertelaer, 2020)
III-3	Rosacea or demodicosis	Mean age: 47.1 ± 1.2; male 34%, female 66%	171	Topical	12% benzyl benzoate and 10% in cetomacrogol cream twice daily for 2 months	Decrease in mean *Demodex* count from 103 ± 9to 23 ± 4 per cm^2 with 40% patients without symptoms at mean follow-up of 2.7 ± 0.2 months	(Forton and De Maertelaer, 2020)
III-3	Rosacea or demodicosis	Mean age: 45.1 ± 3.1; male 46%, female 54%	28	Topical	Moisturizing cream daily and 20–24% benzyl benzoate with 10% crotamiton in cetomacrogol cream nightly for 2 months	Decrease in mean *Demodex* count from 78 ± 19 to 22 ± 6 per cm^2 with 54% patients without symptoms at mean follow-up of 2.7 ± 0.2 months	(Forton and De Maertelaer, 2020)
IV	Pityriasis folliculorum	Mean age: 38; female 100%	3	Topical	0.01% tretinoin gel nightly for 4 weeks and 1% lindane lotion weekly for 4 weeks	Responded to treatment regimen	(Dominey *et al.*, 1989*b*)

IV	Acute lymphoblastic leukaemia-associated *Demodex*	6; male	1	Oral and topical	Oral ivermectin 200 $\mu g\,kg^{-1}$; topical steroid for 2 days and 5% permethrin cream for 2 nights for 2 weeks	The eruption gradually cleared 5 weeks after additional treatments of oral ivermectin and topical permethrin at 6^{th} and 7^{th} week post-treatment	(Damian and Rogers, 2003)
IV	Blepharitis	22, male	1	Oral	12 mg ivermectin two doses 10 days apart followed by 400 mg metronidazole three times daily for 7 days	Subjective and objective improvement post-treatment	(Nath *et al*., 2012)
IV	Blepharitis	59; female	1	Topical	Theralid™ and Cliradex™ (tea tree oil-based eyelid cleansers) for 6 weeks followed by hypochlorous acid cleanser for 2 weeks	Improved symptoms and reduction in the cylindrical dandruff post-treatment	(Bachir and Bitton, 2015)
IV	Blepharitis	30; female	1	Topical	Pulse dosing with Cliradex™, followed by hypochlorous acid cleanser for 2 weeks	Improved symptoms and reduction in the cylindrical dandruff post-treatment	(Bachir and Bitton, 2015)
IV	Blepharoconjunctivitis	30; female	1	Oral and topical	Oral 2% metronidazole and topical lid scrubs	50% reduction in number of *Demodex* post-treatment	(Junk *et al*., 1998)
IV	Crusted demodicosis	7; female	1	Oral and topical	Oral 200 $\mu g\,kg^{-1}$ ivermectin once weekly for 10 weeks, topical 5% permethrin lotion for 3 nights followed by oral 30 mg kg^{-1} erythromycin and topical metronidazole cream	Lesions improved greatly within following 3 months	(Guerrero-Gonzalez *et al*., 2014)
IV	Demodicosis	2; female	1	Topical	5% Permethrin cream nightly for 3 nights followed by metronidazole 0.75% cream twice daily	Symptoms improved after 2 weeks without recurrence at 6 month follow-up	(Douglas and Zaenglein, 2019)
IV	Demodicosis	13; male	1	Topical and oral	5% Permethrin cream weekly overnight for 4 weeks with 100 mg doxycycline oral daily for 8 weeks	Improvement of mild erythema of the forehead and cheeks with a few pustules, and limited *Demodex* was found at 3 month follow-up	(Douglas and Zaenglein, 2019)
IV	Demodicosis	19 months; male	1	Topical	5% Permethrin cream once weekly for 2 weeks and 0.75% metronidazole cream daily for maintenance	Improvement of symptoms	(Douglas and Zaenglein, 2019)
IV	Demodicosis	5; female	1	Topical	0.75% Metronidazole cream twice daily, resulting in some improvement followed by 5% permethrin cream topically once a week for 2 weeks after 1 month	Improvement of symptoms	(Douglas and Zaenglein, 2019)
IV	Demodicosis	11; female	1	Topical and oral	5% permethrin cream weekly for a month and 20 mg doxycycline orally twice daily, as well as 0.75% metronidazole cream daily to the affected area	Improvement within 2 weeks; 2-month follow-up, examination showed a few small papules; no signs of demodicosis were found at 9-month follow-up	(Douglas and Zaenglein, 2019)
IV	*Demodex* folliculitis	10; male	1	Topical	10% sodium sulfacetamide and 5% sulphur lotion	Eruption resolved completely	(Herron *et al*., 2005)
IV	*Demodex* folliculitis	3; female	1	Topical	5% permethrin cream for 5 consecutive nights for 4 weeks, followed by metronidazole cream twice daily and 0.05% desonide cream daily	Improvement of facial eruption post-treatment	(Herron *et al*., 2005)
IV	*Demodex* folliculitis	5; male	1	Topical	5% permethrin cream for 3 consecutive nights for 7 weeks followed by metronidazole cream twice daily for 2 months	Symptoms resolved and rash improved after permethrin but did not clear after 7 weeks or metronidazole regimen	(Herron *et al*., 2005)
IV	*Demodex* folliculitis	68; female	1	Topical	Daily lid scrub with polyhexamethylene biguanide, 1,2 hexanediol and 1,2-octanediol and erythromycin ointment twice daily	Complete resolution of symptoms after 4 weeks	(Yun *et al*., 2013)

(*Continued*)

Table 9. (*Continued.*)

NHMRC	Diseases	Age (years); gender	Sample size (n)	Dosage form	Administration (dose, route and time)	Effect	Reference
IV	*Demodex* folliculitis	24; female	1	Oral and topical	Oral 500 mg metronidazole three times daily for 2 weeks and topical 1% lindane for 2 weeks	Complete resolution at 3rd month follow-up	(Hsu *et al.*, 2009)
IV	*Demodex* scalp folliculitis	73; female	1	Oral and topical	Topical metronidazole gel along with fusidic acid cream and oral betamethasone-17-valerate for several weeks	Complete cessation of hair loss and signs of inflammation post-treatment	(Helou *et al.*, 2016)
IV	*Demodex* scalp folliculitis	16; male	1	Oral and topical	Oral 250 mg metronidazole three times daily and topical 5% minoxidil solution	Complete cessation of hair loss, erythema and pustules post-treatment	(Helou *et al.*, 2016)
IV	*Demodex* scalp folliculitis	75; male	1	Oral and topical	Topical permethrin plus oral metronidazole	Good response to treatment within few days, with clearance of lesions; regression of disease after 7 months	(Fernandez-Flores and Alija, 2009)
IV	*Demodex* scalp folliculitis	57; male	1	Topical	10% sulfacetamide and 5% sulphur cream twice daily in addition to a 2 weeks course of 2.5% selenium sulphide shampoo daily	Scalp cleared of erythematous plaque with hyper keratosis and pustules at 3rd month follow-up	(Sanfilippo and English, 2005)
IV	Demodicosis	34; male	1	Oral and topical	Oral 250 mg doxycycline daily for 3 weeks and oral prednisolone 10 mg twice daily tapered in 3 weeks; topical lindane for 2 weeks	Complete resolution at 10th month follow-up with relapse in 1st and 2nd month	(Hsu *et al.*, 2009)
IV	Demodicosis	44; female	1	Oral and topical	Oral 250 mg metronidazole three times daily for 3 weeks, 10 mg prednisolone twice daily tapered in 3 weeks; topical 0.75% metronidazole gel twice daily for 3 weeks	Complete resolution at 6th week follow-up	(Hsu *et al.*, 2009)
IV	Demodicosis	3; female	1	Topical and oral	0.75% metronidazole cream twice daily for 2 weeks followed by 1% lindane cream nightly for 2 weeks and oral 250 mg erythromycin daily for 1 week	Lesions gradually cleared after metronidazole followed by complete resolution of skin eruption after lindane regimen	(Castanet *et al.*, 1997)
IV	Demodicosis	56; male	1	Oral and topical	Oral ivermectin 200 $\mu g\,kg^{-1}$ single dose followed by topical 5% permethrin cream weekly	Dramatic response obtained within 2 weeks and no recurrence after a year	(Aquilina *et al.*, 2002)
IV	Demodicosis	75; male	1	Oral and topical	Oral 500 mg metronidazole twice daily, scales were removed with topical 5% salicylic acid in white petrolatum twice daily for 2 days followed by 1% metronidazole cream twice daily	Excellent response to treatment with oral therapy was ceased on day 15, dermatosis gradually cleared within the next month with topical metronidazole, resolution of residual erythema on cheeks 9 months later	(Hoekzema *et al.*, 1995)
IV	Demodicosis	76; male	1	Oral and topical	Oral 200 $\mu g\,kg^{-1}$ ivermectin single dose followed by topical 5% permethrin for 4 weeks	Visible improvement starting after 2 weeks, complete resolution after 5 weeks	(Eismann *et al.*, 2010)
IV	Demodicosis	56; male	1	Topical	Metronidazole and lindane twice daily for 3 months	Treatment was successful after 3 months	(Kim *et al.*, 2014)
IV	Demodicosis	32; male	1	Oral and topical	Oral 200 $\mu g\,kg^{-1}$ ivermectin single dose followed by bland oil-in-water preparation after 1 month	Reduction of pruritus within 2 weeks, no *Demodex* mites in skin scrapings with reduction in size and intensity of inflammation within 4 weeks	(Forstinger *et al.*, 1999)
IV	Demodicosis	37; female	1	Oral and topical	Oral metronidazole for 2 months and topical yellow mercury ointment for 15 days	Disappearance of facial mites and complete remission post-treatment	(Anane *et al.*, 2011)

IV	Demodicosis	43; female	1	Oral and topical	250 mg metronidazole three times daily and topical crotamiton ointment daily	Marked improvement of lesion with mild erythema after 6 weeks of treatment	(Park *et al*., 2011)
IV	Demodicosis	38; female	1	Oral and topical	Oral 750 mg metronidazole daily and 100 mg daily prednisolone for 3 weeks followed by topical 0.15% lindane emulsion and 2% metronidazole cream	Treatment led to gradual regression of pustules after 3 weeks	(Grossmann *et al*., 1999)
IV	Granulomatous rosacea	48; female	1	Oral and topical	Oral 500 mg metronidazole three times daily tapered in 3 weeks, 5 mg prednisolone three times daily tapered in 3 weeks; topical 0.75% metronidazole gel twice daily for 8 weeks	Complete resolution at 7th week follow-up	(Hsu *et al*., 2009)
IV	Papulonodular demodicosis	51; male	1	Topical	1% lindane lotion and 1% permethrin cream rinse daily	Expressed follicular contents revealed few *Demodex* and lesions cleared after 1 week of treatment	(Dominey *et al*., 1989*a*)
IV	Papulopustular rosacea	68; male	1	Oral and topical	Oral ivermectin and topical 5% permethrin cream	Resolution of folliculitis	(Allen *et al*., 2007)
IV	Peri-oral dermatitis	47; female	1	Oral	250 mg metronidazole three times daily for 3 weeks, 0.03% tacrolimus twice daily for 5 weeks and then changed to 1% pimecrolimus for another 11 weeks	Complete resolution at 7th week follow-up	(Hsu *et al*., 2009)
IV	Phymatous rosacea	57; male	1	Oral and injection	Oral 100 mg minocycline twice daily and intralesional triamcinolone injections every 3 months	Ear partially diminished in size and external auditory canal was wider after 8 months	(Carlson *et al*., 2008)
IV	Pityriasis folliculorum	37; female	1	Topical	0.01% tretinoin gel nightly for 2 weeks and 1% lindane lotion weekly for 2 weeks	Responded to treatment regimen	(Dominey *et al*., 1989*b*)
IV	Pityriasis folliculorum	34; female	1	Topical	0.05% tretinoin cream alternate nights for 10 days and 1% lindane lotion alternate nights for 10 days	Responded to treatment regimen	(Dominey *et al*., 1989*b*)
IV	Pityriasis folliculorum	31; female	1	Oral and topical	Oral isotretinoin 0.5 mg kg^{-1} daily for 14 weeks and topical 1% permethrin cream rinse daily for 2 weeks	Responded to treatment regimen	(Dominey *et al*., 1989*b*)
IV	Rosacea	Age not specified; female	15	Oral and topical	Oral 500 mg metronidazole and topical 1/3 diluted camphor oil with glycerol daily for 15 days	Treatment successful	(El-Shazly *et al*., 2004)
IV	Rosacea-like demodicosis	2; male	1	Oral and topical	Oral erythromycin 250 mg daily and topical metronidazole daily	Remarkable improvement after 2 months	(Barrio *et al*., 1996)

administration form of miscellaneous treatments showing effectiveness against the human demodicosis are summarized in Table 8.

Combination therapy

Many combination regimens have been trialled for human demodicosis, especially TTO or T4O with other topical treatments. In a double-blind, randomized controlled clinical trial of *Demodex*-related rosacea by Ebneyamin *et al.*, twice daily topical 2.5% permethrin with 100% TTO gel for 12 weeks is used to treat *Demodex*-related rosacea. *Demodex* density on the intervention side of the face was significantly reduced at week 12 (P value = 0.001) (LOE II). Clinical presentations, symptoms and global assessments showed papules, pustules, non-transient erythema, burning and stinging sensations had improvement in the treatment group after 12 weeks (P values < 0.05) (LOE II). Patients in the intervention group only experienced mild-to-moderate adverse effects that did not result in discontinuation of the treatment (Ebneyamin *et al.*, 2020). In a triple-blinded randomized controlled clinical trial on dry eye after phacoemulsification cataract surgery by Mohammadpour *et al.*, treatment combinations including daily artificial tears, topical steroid drops and eyesol shampoos with TTO daily for 4 weeks were used in the intervention group and the control group had the same treatment combinations without the TTO. Results demonstrated that a greater significant improvement in tear break-up time test, corrected distance visual acuity, osmolarity and ocular surface disease index score and a dramatic reduction in the number of *Demodex*, respectively, in the treatment group (LOE II) (Mohammadpour *et al.*, 2019). A randomized prospective double-masked trial in *Demodex* blepharitis by Epstein *et al.* by using T4O lid scrubs with microblepharoexfoliation (MBE) twice daily for 8 weeks as a treatment showed in-office MBE with T4O lid scrubs has no significant improvement over sham scrubs. The results between the intervention and the control group were not statistically meaningful, possibly because of the low sample size of the study. Overall, patients in the treatment group with T4O tolerated the medicated eyelid scrubs well; with only a low incident of transient burning (LOE III-1) (Epstein *et al.*, 2020). In a multicentre, open, randomized, two-parallel group comparative study by Messaoud *et al.*, a cleaning wipe that contains both T4O 2.5% and hyaluronic acid 0.2% was used to treat *Demodex* anterior blepharitis daily or twice a day for 29 days. Overall ocular discomfort hyperaemia was significantly reduced from baseline ($P < 0.0001$) in both groups at day 8 (-3.6 ± 0.3 in daily and -4.0 ± 0.4 in twice daily treatment groups) and day 29 (-5.7 ± 0.4 daily and -6.8 ± 0.7 twice daily treatment groups), respectively (LOE III-2). Eyelid margin hyperaemia improved progressively at day 8 and day 29 as well for both groups (LOE III-2). Total disappearance of cylindrical dandruff was reported in 30.4% of patients in daily and 43.5% in twice daily treatment groups, respectively (LOE III-2). The T4O-based product was well tolerated and patients were willing to continue that for long-term use (Messaoud *et al.*, 2019).

Other combination treatments such as metronidazole, ivermectin and permethrin also were trialled. A single-blind, randomized controlled trial in patients with ocular or dermatological demodicosis, oral metronidazole and ivermectin combined therapy showed a significant reduction in mite count in acne, perioral dermatitis, anterior blepharitis and rosacea group compared with the oral ivermectin treatment alone (LOE III-1) (Salem *et al.*, 2013). This regimen was significantly better at reducing the mite count to the normal level in the rosacea and anterior blepharitis groups (Salem *et al.*, 2013). In one of the single-blind, randomized clinical trials, the efficacy of metronidazole was compared with ornidazole when paired with the administration of anti-inflammatory agents betamethasone and ebastine of mites folliculitis. Ornidazole had a significantly higher effective rate compared to metronidazole in controlling the disease. Up to 12 weeks after finishing the treatment course, metronidazole-treated patients had significantly higher rates of mite relapse and new lesion occurrence. (LOE III-1) (Luo *et al.*, 2016). The fulminant rosacea-like eruption with multiple *D. folliculorum* mites show excellent response to oral and topical metronidazole combination treatments, and dermatosis gradually cleared within 1 month, and the residual erythema on the patients' cheeks was resolved 9 months later (LOE IV) (Hoekzema *et al.*, 1995). The oral metronidazole and ivermectin combination therapy also showed subjective and objective improvement in blepharitis (LOE IV) (Nath *et al.*, 2012). A trial of combined oral metronidazole and prednisolone for 3 weeks in conjunction with topical metronidazole and lindane emulsion showed a gradual reduction in pustules in tuberous-pustular demodicosis (LOE IV) (Grossmann *et al.*, 1999). Facial mites disappeared with complete remission without recurrence in rosacea-like demodicosis by using topical and oral metronidazole for 2 months and yellow mercury ointment for 15 days (LOE IV) (Anane *et al.*, 2011). Topical camphor oil and oral metronidazole were given for 15 days, and satisfactory results were achieved without observable side-effects (LOE IV) (El-Shazly *et al.*, 2004). Oral ivermectin and topical permethrin were used to treat acute lymphoblastic leukaemia-associated demodicosis (LOE IV). No apparent adverse effects were experienced and eruption resolved 5 weeks later (Damian and Rogers, 2003). The oral ivermectin and topical permethrin combination regimen were also used for resolution of the rosacea-like folliculitis (LOE IV) (Allen *et al.*, 2007). The combination treatment of dosage, direction and administration form showing effectiveness against the human demodicosis are summarized in Table 9.

Conclusion

There are a large number of reports of human demodicosis indicating sustained interest and needs for efficacious treatments. However, only limited double-blinded randomized controlled trials were done and many treatments have not been compared with each other. Five treatments have emerged but further work is required to vigorously evaluate their efficacy. TTO and T4O, metronidazole, ivermectin and permethrin have shown promising results in reducing mite counts and dermatological symptoms in *Demodex* infection. TTO or T4O topical treatment should be considered as the first-line therapy because of its satisfactory clinical results with minimal side-effects. Systemic treatments such as oral ivermectin or oral metronidazole could be added, which may also decrease recurrence in complicated cases. As a second-line treatment or in severe cases, topical permethrin is another alternative to be considered as an option based on consistent data showing moderate to satisfactory clinical improvement in *Demodex*-associated skin condition. However, side-effects such as skin irritation of permethrin should be carefully monitored. Treatment with benzyl benzoate or crotamiton may also be considered as they did demonstrate moderate anti-demodicosis properties. Although these treatments are effective, their repeated use may result in the development of resistance. These problems have highlighted the need for the development of new alternatives. Moreover, the goal of treatment should be to reduce the mite count below a certain threshold and restore the ocular and dermatological ecology to a balanced state. This should control the symptoms and achieve remissions. In refractory cases, such as immunocompromised and systemic disease patients, combination therapies such as TTO or T4O with other topical or systemic treatments may be needed to relieve the symptoms and prevent

recurrence. Therefore, further research should focus on the efficacy, formulations and toxicity to improve the miticidal potency and pharmacological stability for human demodicosis.

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