TITLE

ANTIMICROBIAL COMPOSITIONS COMPRISING DGLA, 15-OHEPA AND/OR 15-HETRE AND METHODS OF USE THEREOF

FIELD

[0001] The disclosure generally relates to compositions comprising fatty acids including, for example, DGLA, 15-OHEPA and/or 15-HETrE, alone or in combination with one or more antibiotic or anti-fungal agents for the treatment of disease and/or disorders such as a skin or gingival infection.

BACKGROUND

[0002] Scores of different microbial species colonize the skin and oral cavity as normal flora. However, when the skin's normal continuity or the oral microenvironment becomes disrupted, the resulting contusions, wounds, lesions, incisions, pockets, lacerations, and/or other disruptions can become infected by a wide variety of microbial species, some of which have become or are rapidly becoming resistant to existing therapies. Accordingly, there exists a need for compositions that are more effective in the treatment of skin and oral infections.

SUMMARY

[0003] The present disclosure provides compositions comprising one or more fatty acids agents including, for example, DGLA, 15-OHEPA and/or 15-HETrE, used alone or in combination with antibiotic agents for the treatment of disease and/or disorders of the skin and gingiva.

[0004] The present disclosure also provides methods for treating or preventing skin and gingival infections in a subject in need thereof comprising administering to the subject an antimicrobial composition (*e.g.*, a composition having antimicrobial properties or a antimicrobial composition) comprising a therapeutically effective amount of DGLA, 15-OHEPA, or 15-HETrE or combinations thereof alone or in combination with one or more antibiotic agents. Described herein is the use of a pharmaceutical composition comprising 15-HETrE in the manufacture of a medicament for treating or preventing a microbial infection. Also described herein is the use of a pharmaceutical composition comprising 15-HETrE in the manufacture of a medicament for minimizing or preventing scarring, the use comprising the pharmaceutical composition to be administered to a wound of a subject. In some ~~embodiments~~examples, the

antimicrobial composition comprises about 0.1 wt.% to about 20 wt.% of DGLA, 15-OHEPA, or 15-HETrE.

[0005] In some ~~embodiments~~examples, the antimicrobial composition comprises a sub-therapeutic amount of one or more of DGLA, 15-OHEPA, or 15-HETrE along with a therapeutic amount of one or more antibiotic agents. In some examples~~embodiments~~, the antimicrobial composition comprises a therapeutic amount of one or more of DGLA, 15-OHEPA, or 15-HETrE along with a sub-therapeutic amount of one or more antibiotic agents. In some examples~~embodiments~~, the antimicrobial composition comprises a sub-therapeutic amount of one or more of DGLA, 15-OHEPA, or 15-HETrE along with a sub-therapeutic amount of one or more antibiotic agents.

[0006] In some examples~~embodiments~~, the antimicrobial composition comprises one or more pharmaceutically acceptable excipients.

[0007] In some examples~~embodiments~~, the one or more antibiotic agents are selected from the group consisting of: neomycin sulfate, polymyxin B, bacitracin zinc, β-lactams (*e.g.,* ampicillin, amoxicillin, imipenem, meropenem), carbapenems, cephalosporins (*e.g.,* cephalexin, cephalothin, cefalozin, cefuroxime, cefotaxime, ceftazidime), fluoroquinolones, oxazolidinones, lincosamides, metronidazole, macrolide antibiotics (*e.g.,* clindamycin, erythromycin), quinolone anibiotics (*e.g.,* levofloxacin, ciprofloxacin), penicillins, glycopeptides (*e.g.,* vancomycin), aminoglycosides (*e.g.,* neomycin, gentamicin, tobramycin), trimethoprim/sulfamethoxazole (also known as co-trimoxazole or TMP/SMX), doxycycline, triclosan, metronidazole, monocycline and tetracycline.

[0008] In some examples~~embodiments~~, the one or more antibiotic agents are selected from the group consisting of: neomycin salts (*e.g.,* neomycin sulfate), polymixin B, and/or bacitracin salts (*e.g.,* bacitracin zinc). In some ~~embodiments~~examples, the one or more antibiotic agents are neomycin sulfate, polymyxin B and bacitracin zinc.

[0009] In some examples~~embodiments~~, the step of administering comprises topically applying the composition to an area of the skin or gingival afflicted with lesions. As used herein, the term "lesion" refers broadly to any disruption in the normal continuity and function of the skin or gingiva and includes, for example, contusions, wounds, burns, sores, ulcers, scrapes, incisions, lacerations, skin infection, gingivitis and periodontal disease. In some examples~~embodiments~~, the area of the skin afflicted with lesions is washed prior to application of the antimicrobial composition. In some examples~~embodiments~~, the lesions are inflammatory type and/or non-inflammatory type lesions.

[0010] In some examples~~embodiments~~, applying the composition results in about a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more reduction in the lesion.

[0011] In some examples~~embodiments~~, the lesion is associated with a microbe such as gram positive bacteria, gram negative bacteria or fungi.

[0012] In some examples~~embodiments~~, the lesion is associated with one or more of: *Staphylococcus spp.*, *Propionibacterium spp.*, *Streptococcus spp*, *Corynebacterium spp.*, *Porphyromonas spp.*, *Micrococcus spp.*, *Pseudomonas aeruginosa*, *Pasteurella multocida*, *Capnocytophaga canimorsus*, *Bartonella spp.*, *Klebsiella rhinoscleromatis*, *Helicobacter spp.*, *Aspergillus niger*, *Aureobasiduim pullulans*, *Chaetomium globosum*, *Gliocladium virens*, *Penicillum funiculosum*, *Candida albicans*, *Saccharomyces cerevisiae* and *Vibrio vulnificus*.

[0013] In some examples~~embodiments~~, the antimicrobial composition is administered to the subject once a day, twice a day, or three times a day.

[0014] In some examples~~embodiments~~, the antimicrobial composition is a cream, lotion, gel or emulsion.

[0015] In some examples~~embodiments~~, the subject previously exhibited lesions.

[0016] The present disclosure also provides methods of treating or preventing a microbial infection (e.g. a skin or gingival infection) in a subject in need thereof comprising administering to the subject an antimicrobial composition comprising a therapeutically effective amount of DGLA. In some examples~~embodiments~~, the antimicrobial composition comprises about 0.1% to about 20 wt.% of DGLA.

[0017] In some examples~~embodiments~~, the step of administering comprises topically applying the composition to an area of the skin or gingiva afflicted with lesions. In some examples~~embodiments~~, the area of the skin afflicted with lesions is first washed prior to application of the antimicrobial composition.

[0018] In some examples~~embodiments~~, the lesions are inflammatory type and/or non-inflammatory type lesions.

[0019] In some examples~~embodiments~~, the composition reduces about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the lesion.

[0020] In some examples~~embodiments~~, the lesion is associated with one or more of: *Staphylococcus spp.*, *Propionibacterium spp.*, *Streptococcus spp*, *Corynebacterium spp.*, *Porphyromonas spp. Micrococcus spp.*, *Pseudomonas aeruginosa*, *Pasteurella multocida*, *Capnocytophaga canimorsus*, *Bartonella spp.*, *Klebsiella rhinoscleromatis*, *Helicobacter spp.*, *Aspergillus niger*, *Aureobasiduim pullulans*, *Chaetomium globosum*, *Gliocladium virens*, *Penicillum funiculosum*, *Candida albicans*, *Saccharomyces cerevisiae and Vibrio vulnificus.*

[0021] In some examples~~embodiments~~, the antimicrobial composition is administered to the subject once a day, twice a day, or three times a day.

[0022] In some examples~~embodiments~~, the antimicrobial composition is a cream, lotion, gel, rinse, paste or emulsion.

[0023] In some examples~~embodiments~~, the subject previously exhibited a lesion.

[0024] The present disclosure also provides compositions for use in treating a skin or oral infection (e.g a microbial, bacterial or fungal infection) comprising a therapeutically effective amount of DGLA, 15-OHEPA, or 15-HETrE. In some examples~~embodiments~~, the composition comprises about 0.1% to about 20 wt.% of DGLA, 15-OHEPA, or 15-HETrE. In some examples~~embodiments~~, the therapeutically effective amount is an amount sufficient to kill or eradicate the microbe in one to a plurality of administrations.

[0025] The present disclosure also provides methods for treating or preventing microbial (e.g. bacterial or fungal) infection on the skin or gingiva comprising applying to the lesion one or more of DGLA, 15-OHEPA, or 15-HETrE. In some examples~~embodiments~~, the composition comprises about 0.1% to about 20 wt.% of DGLA, 15-OHEPA, or 15-HETrE.

[0026] The present disclosure also provides methods for improving the antimicrobial activity of an agent used in the treatment or prevention of skin or gingival infections comprising adding a composition comprising one or more of DGLA, 15-OHEPA, or 15-HETrE to the agent. In some examples~~embodiments~~, the agent used in the treatment or prevention of skin or gingival infections is an antibiotic or antifungal agent. In some examples~~embodiments~~, the composition comprises about 0.1% to about 20 wt.% of DGLA, 15-OHEPA, or 15-HETrE.

[0027] The present disclosure also provides methods of inhibiting one or more skin or gingival pathogens including, for example, its reproduction, growth or recolonization,

comprising contacting the one or more skin or oral pathogens with a composition comprising DGLA, 15-OHEPA, or 15-HETrE. In some examplesembodiments, the composition comprises about 0.1% to about 20 wt.% of DGLA, 15-OHEPA, or 15-HETrE.

[0028] In some examplesembodiments, the methods may further comprise administering to the subject a steroid. In some examplesembodiments, the steroid is a corticosteroid such as hydrocortisone, prednicarbate, fluticasone and derivatives thereof, or mometasone and derivatives thereof.

[0029] In some examplesembodiments, the subject is administered the therapeutically effective amount of DGLA, 15-OHEPA, or 15-HETrE, the one or more antibiotic agents, and the steroid concomitantly.

[0030] In some examplesembodiments, the antimicrobial composition comprises about 0.1 wt.% to about 20 wt.% of DGLA, 15-OHEPA, or 15-HETrE.

[0031] In some examplesembodiments, the step of administering comprises topically applying the composition to an area afflicted with contusions, wounds, burns, sores, ulcers, scrapes, incisions, lacerations, skin infection, gingivitis or periodontal disease. ~~.~~

[0032] In some examplesembodiments, the area afflicted with contusions, wounds, burns, sores, ulcers, scrapes, incisions, lacerations, skin infection, gingivitis or periodontal disease. is first washed prior to application of the antimicrobial composition.

[0033] In some examplesembodiments, the antimicrobial composition is administered to the subject once a day, twice a day, or three times a day.

[0034] In some examplesembodiments, the antimicrobial compositions described herein are in the form of a cream, lotion, paste, gel, etc.

[0035] The present disclosure also provides methods for improving the efficacy of an agent used in the treatment of contusions, wounds, burns, sores, ulcers, scrapes, incisions, lacerations, skin infection, gingivitis or periodontal disease comprising adding a therapeutically effective amount of DGLA, 15-OHEPA, or 15-HETrE to the agent. In some examplesembodiments, the agent is one or more antibiotic agents.

[0036] In some examplesembodiments, about 0.1% to about 20 wt.% of DGLA, 15-OHEPA, or 15-HETrE is added to the agent.

[0037] The present disclosure also provides methods for reducing the efficacious dose of an agent used in the treatment of contusions, wounds, burns, sores, ulcers, scrapes, incisions, lacerations, skin infection, gingivitis or periodontal disease comprising adding a therapeutically effective amount of DGLA, 15-OHEPA, or 15-HETrE to the agent.

[0038] In some examples~~embodiments~~, about 0.1% to about 20 wt.% of DGLA, 15-OHEPA, or 15-HETrE is added to the agent.

[0039] These and other examples ~~embodiments of the invention~~ are described in further detail below.

BRIEF DESCRIPTION OF THE FIGURE

[0040] FIG. 1 depicts measurements obtained to determine the CZOI values for in vitro inhibition of bacterial growth according to one embodiment of the present disclosure.

DETAILED DESCRIPTION

[0041] The present disclosure provides compositions (*e.g.*, antimicrobial compositions) and formulations that comprise fatty acid agents including, for example, DGLA, 15-OHEPA and/or 15-HETrE alone; or with one or more antibiotic agents, for example, neomycin sulfate, polymyxin B, and/or bacitracin zinc. Such agents have been found to reduce including, inhibit, the growth of bacteria associated with skin and gingival infections such as Staphylococcus spp. (including, for example, *S. aureus*, *S. lugdunensis*, *S. schleiferi* and other coagulase-negative Staphylococcus spp.), Streptococcus spp. (including, for example, β-haemolytic Streptococci, Viridans group Streptococci, non-haemolytic Streptococci, and Streptococcus milleri group), Corynebacterium spp., Bacillus spp. (including, for example, *B. anthracis* and *B. cereus*), Acinetobacter spp., Moraxella spp., Peptostreptococcus spp., Propionibacterium spp.,(including, for example, *P. Acnes*), Candida spp., Pseudomonas spp. and other non-fermentative bacilli (including, for example, *P. aeruginosa*), Dermatophytes, Enterobacteriaceae, *Pasturella multocida*, Mycobacterium spp., Haemophilus spp., Nocardia spp., *Erysipelothrix rhusiopathiae*, Vibrio spp., Enterococcus spp., *Eikenella corrodens*, anaerobes, Corynebacterium spp., Actinomyces spp., and fungal pathogens. Furthermore, the inventors have found that, in many cases, the use of these fatty acid agents in combination with existing antibacterial agents (*e.g.*, nicotinamide, benzoyl peroxide, adapalene, metronidazole, neomycin sulfate, polymyxin B, bacitracin zinc, β-lactams (*e.g.*, ampicillin, amoxicillin, imipenem, meropenem), carbapenems, cephalosporins (*e.g.*, cephalexin,

CLAIMS

The invention is claimed as follows:

1. ~~A method of~~ Use of a pharmaceutical composition comprising 15-HETrE in the manufacture of a medicament for treating or preventing a microbial infection~~comprising administering to a subject in need thereof a pharmaceutical composition comprising 15-HETrE~~.

2. The ~~method~~ use of claim 1, wherein the pharmaceutical composition is topically applied to the subject.

3. The ~~method~~ use of claim 2, wherein the pharmaceutical composition is topically applied to a wound of the subject.

4. The ~~method~~ use of any of the preceding claims wherein the microbial infection is a bacterial infection.

5. The ~~method~~ use of any of the preceding claims wherein the microbial infection is a fungal infection.

6. The ~~method~~ use of any of the preceding claims wherein the pharmaceutical composition is to be administered in an amount effective to treat or prevent the microbial infection.

7. The ~~method~~ use of any of the preceding claims, wherein the pharmaceutical composition comprises about 0.1 wt.% to about 20 wt.% of 15-HETrE and one or more excipients.

8. The ~~method~~ use of any of the preceding claims, wherein the 15-HETrE is in free acid form.

9. The ~~method~~ use of any of the preceding claims, wherein the 15-HETrE is a pharmaceutically acceptable ester, derivative, conjugate, or salt of 15-HETrE.

10. The ~~method~~ use of any of the preceding claims, wherein the 15-HETrE is an alkyl ester of 15-HETrE.

11. The ~~method~~ use of any of the preceding claims, wherein the pharmaceutical composition further comprises an additional active agent selected from neomycin sulfate, polymyxin B, bacitracin zinc, ampicillin, amoxicillin, imipenem, meropenem, carbapenems, cephalexin, cephalothin, cefalozin, cefuroxime, cefotaxime, ceftazidime, fluoroquinolones, oxazolidinones, lincosamides, metronidazole, clindamycin, erythromycin, quinolone anibiotics, levofloxacin, ciprofloxacin, penicillins, glycopeptides, vancomycin, aminoglycosides, neomycin, gentamicin, tobramycin, trimethoprim/sulfamethoxazole, doxycycline, triclosan, metronidazole, monocycline and tetracycline and combinations thereof.

12. The ~~method~~ use of any of the preceding claims, wherein the additional active agent is present in an amount that is less than a generally recognized therapeutic amount for said additional active agent.

13. The ~~method~~ use of any of the preceding claims, wherein the 15-HETrE has been deodorized.

14. The ~~method~~ use of any of the preceding claims, wherein the composition inhibits growth of *P. aeroginosa*, *E. coli*, *K. pneumoniae*, *S. aureus*, *E. faecalis*, *S. epidermidis*, *C. striatum*, *A. brasiliensis*, *C. albicans*, or any combination thereof.

15. Use of a pharmaceutical composition comprising 15-HETrE in the manufacture of a medicament for ~~A method of~~ minimizing or preventing scarring of a wound. ~~comprising administering to a wound of a subject a pharmaceutical composition comprising 15-HETrE.~~

16. A pharmaceutical composition comprising 15-HETrE for use in treatment or prevention a microbial infection.

17. A pharmaceutical composition comprising 15-HETrE for use in minimizing or preventing scarring.