**[0010]** **Figure 4** includes two bar graphs, illustrating the effect of CBD, CBG and CBC on biofilms of *E. faecium* strain 33D3.

## SUMMARY

**[0011]** One general example of the innovations disclosed herein includes formulations that include at least two antibiotically active ingredients, for example selected from: a cannabinoid that is one or more of cannabichromene (CBC), cannabidiol (CBD) and/or cannabigerol (CBG). The formulations may also include a sesquiterpene that is one or both of α-humulene and/or β-caryophyllene. The formulations can also include a lipopeptide antibiotic that is daptomycin or an analogue thereof. The formulations may include the antibiotically active ingredients in synergistically effective relative amounts, for example where an effective amount of the formulation is synergistically effective in an assay to inhibit growth and/or reproduction of an *Enterococcus faecium* or *an Enterococcus faecalis*.

**[0011a]** In one aspect, the present disclosure refers to an antibiotic formulation, comprising at least two active ingredients selected from: a cannabinoid that is one or both of cannabichromene (CBC) and/or cannabigerol (CBG); a sesquiterpene that is one or both of α-humulene and/or β-caryophyllene; and, a lipopeptide antibiotic that is daptomycin or an analogue thereof.

**[0012]** Implementations may include one or more of the following features. The formulation where there are two antibiotically active ingredients, and the two antibiotically active ingredients are the cannabinoid and the sesquiterpene. The formulation where there are two antibiotically active ingredients, and the two antibiotically active ingredients are the cannabinoid and the lipopeptide antibiotic. The formulation including the cannabinoid, the sesquiterpene and the lipopeptide antibiotic. The formulation where there are two antibiotically active ingredients, and the two antibiotically active ingredients are the sesquiterpene and the lipopeptide antibiotic. The formulation of any one where the cannabinoid is one of CBC, CBD or CBG. The formulation of any one where the cannabinoid is two of CBC, CBD and CBG. The formulation of any one where the cannabinoid includes CBC, CBD and CBG. The formulation of any one where the sesquiterpene, if present, is one of α-humulene or β-caryophyllene. The formulation of any one where the sesquiterpene, if present, includes α-humulene and β-caryophyllene. The formulation of any one where the lipopeptide antibiotic, if present, is daptomycin. The formulation of any one where the sesquiterpene, when present, is present in a relative amount that provides at least a 2 to 128 fold decrease in the minimum inhibitory concentration (MIC) of the cannabinoid in the assay. The formulation of any one where the cannabinoid, when present, is present in a relative amount that provides at least a 2 to 128 fold decrease

*faecium* or an *Enterococcus faecalis* infection. The formulation where the enterococcal infection is an oral infection. The formulation where the oral infection is a marginal periodontitis, a root canal infection, a primary endodontic infection, a persistent or secondary infection, dental caries, peri-implantitis, periradicular abscess or an oral mucosal lesion. The formulation of any one where the enterococcal infection is an antibiotic resistant enterococcal infection. The formulation where the antibiotic resistant enterococcal infection is a vancomycin and/or daptomycin resistant enterococcal infection. The formulation of any one where the formulation is for use in an amount of that delivers an effective dose of the cannabinoid, when present, of from 1 to 5,000 mg per day, and/or an effective dose of the sesquiterpene, when present, of from 1 to 10,000 mg per day.

**[0013]** Alternative examples of the disclosed innovations include methods of treating an enterococcal infection in a subject in need thereof, including administering to the subject an effective amount of the formulations disclosed herein. Implementations may include one or more of the following features. The method including two antibiotically active ingredients, where the two antibiotically active ingredients are the cannabinoid and the sesquiterpene, further including treating the subject with an effective amount of one or more antibiotics, optionally where the antibiotic is daptomycin. The method including administering the cannabinoid in an effective amount of 1-5,000 mg/day. The method of any one including administering the sesquiterpene in an effective amount of 1-10,000 mg/day. The method of any one where the subject is a mammal. The method where the mammal is a human.

**[0014]** Alternative examples of the present innovations include methods of treating a microbial infection in a subject in need thereof, including administering to the subject, sequentially or in combination, an effective amount of at least two antibiotically active compounds selected from: a cannabinoid that is one or more of cannabichromene (CBC), cannabidiol (CBD) and/or cannabigerol (CBG). The method of treating also includes a sesquiterpene that is one or both of α-humulene and/or β-caryophyllene; and. The method of treating also includes a lipopeptide antibiotic that is daptomycin or an analogue thereof. The method of treating also includes where the antibiotically active compounds are administered in synergistically effective relative amounts effective to treat the microbial infection.

**[0014a]** In another aspect, the present disclosure refers to use of at least two active compounds in the manufacture of a medicament for treating a microbial infection in a subject in need thereof, wherein the active compounds are selected from:

a cannabinoid that is one or both of cannabichromene (CBC) and/or cannabigerol (CBG);

a sesquiterpene that is one or both of α-humulene and/or β-caryophyllene; and,

a lipopeptide antibiotic that is daptomycin or an analogue thereof;

wherein the active compounds are to be administered sequentially or in combination.

dental caries, peri-implantitis, periradicular abscess or an oral mucosal lesion. The method of any one where the microbial infection is an antibiotic resistant infection. The method where the antibiotic resistant infection is a vancomycin and/or daptomycin resistant microbial infection.

**[0016]** In an alternative example, methods are provided for treating a bacterial infection in a subject in need thereof, comprising administering to the subject an effective amount of: a cannabinoid that is one or more of cannabichromene (CBC), cannabidiol (CBD) and/or cannabigerol (CBG); and, a lipopeptide antibiotic that is daptomycin or an analogue thereof; wherein the cannabinoid and the lipopeptide antibiotic are administered in an antibiotically effective weight ratio of from 16:1 to 1:16; and, wherein: if the cannabinoid is CBD, then the lipopeptide antibiotic is administered in an effective amount that is less than 4 mg/kg; and/or, if the cannabinoid is CBD, then the bacterial infection comprises infection by an infectious organism having a daptomycin MIC of 4 μg/mL or greater; and/or, if the cannabinoid is CBD, then the bacterial infection comprises infection by an infectious organism for which results from an assay of bacterial growth indicate that daptomycin produces an inhibitory and/or bactericidal effect at concentrations of less than 4 μg/mL when administered with CBD in an amount that is less than the MIC of CBD. The infection may for example include an infection by an *Enterococcus faecium* or an *Enterococcus faecalis.* These treatments may further include administering to the subject an effective amount of a sesquiterpene that is one or both of α-humulene and/or β-caryophyllene.

**[0016a]** In another aspect, the present disclosure refers to use of a cannabinoid that is one or both of cannabichromene (CBC) and/or cannabigerol (CBG), in the manufacture of a medicament for treating a bacterial infection in a subject in need thereof, wherein the subject is one that is undergoing or will undergo treatment with a lipopeptide antibiotic that is daptomycin or an analogue thereof.

**[0017]** In an alternative example, antibiotic formulations are provided that include: a cannabinoid that is one or more of cannabichromene (CBC) and/or cannabigerol (CBG); and, a lipopeptide antibiotic that is daptomycin or an analogue thereof; wherein the cannabinoid and the lipopeptide antibiotic are present in an antibiotically effective weight ratio of from 16:1 to 1:16. The cannabinoid may for example be present in an amount that reduces the minimum inhibitory concentration (MIC) of the lipopeptide antibiotic in an antibiotic assay, such as an Enterococcal assay that assesses the inhibition of growth and/or reproduction of an *Enterococcus faecium* or an *Enterococcus faecalis*. In select examples, the cannabinoid reduces the MIC of the lipopeptide antibiotic in the assay when the cannabinoid is present in an amount that is less than the MIC of the cannabinoid.

**CLAIMS**

1. Use of a cannabinoid that is one or both of cannabichromene (CBC) and/or cannabigerol (CBG), in the manufacture of a medicament for treating a bacterial infection in a subject in need thereof, wherein the subject is one that is undergoing or will undergo treatment with a lipopeptide antibiotic that is daptomycin or an analogue thereof.

2. The use of claim 1, wherein the cannabinoid is to be administered in an antibiotically effective weight ratio of from 16:1 to 1:16 to the lipopeptide antibiotic.

3. The use of claim 1, wherein the bacterial infection comprises infection by an *Enterococcus faecium* or an *Enterococcus faecalis.*

4. The use of claim 1, wherein a sesquiterpene that is one or both of α-humulene and/or β-caryophyllene is to be further administered to the subject.

5. An antibiotic formulation, comprising at least two active ingredients selected from:

a cannabinoid that is one or both of cannabichromene (CBC) and/or cannabigerol (CBG);

a sesquiterpene that is one or both of α-humulene and/or β-caryophyllene; and,

a lipopeptide antibiotic that is daptomycin or an analogue thereof.

6. The formulation of claim 5, wherein there are two active ingredients, and the two active ingredients are the cannabinoid and the sesquiterpene.

7. The formulation of claim 5, wherein there are two active ingredients, and the two active ingredients are the cannabinoid and the lipopeptide antibiotic.

8. The formulation of claim 5, comprising the cannabinoid, the sesquiterpene and

the lipopeptide antibiotic.

9. The formulation of claim 5, wherein the cannabinoid is one of CBC or CBG.

10. The formulation of claim 5, wherein the cannabinoid comprises both of CBC and CBG.

11. The formulation of claim 5, wherein the sesquiterpene is one of α-humulene or β-caryophyllene.

12. The formulation of claim 5, wherein the sesquiterpene comprises both α-humulene and β-caryophyllene.

13. The formulation of claim 5, wherein the lipopeptide antibiotic comprises daptomycin.

14. The formulation of claim 5, wherein the sesquiterpene and the cannabinoid are present in a molar ratio that is ≥50.

15. Use of at least two active compounds in the manufacture of a medicament for treating a microbial infection in a subject in need thereof, wherein the active compounds are selected from:

a cannabinoid that is one or both of cannabichromene (CBC) and/or cannabigerol (CBG);

a sesquiterpene that is one or both of α-humulene and/or β-caryophyllene; and,

a lipopeptide antibiotic that is daptomycin or an analogue thereof;

wherein the active compounds are to be administered sequentially or in combination.

16. The use of claim 15, wherein the active compounds are to be administered in synergistically effective relative amounts effective to treat the microbial infection and the synergistically effective relative amounts are synergistically effective to inhibit

growth and/or reproduction of an *Enterococcus faecium* or an *Enterococcus faecalis* in an assay.

17. The use of any one of claim 1, wherein the bacterial infection comprises a gram positive bacterial infection or an enterococcal infection.

18. The use of claim 17, wherein the enterococcal infection is an oral infection and the subject is a human patient.

19. The use of claim 1, wherein the bacterial infection is an antibiotic resistant infection.

20. The use of claim 19, wherein the antibiotic resistant infection is a vancomycin and/or daptomycin resistant bacterial infection.

21. The use of claim 1, wherein the cannabinoid is to be administered in an amount that is synergistically effective with the lipopeptide antibiotic to treat the bacterial infection.

22. The use of claim 1, wherein the cannabinoid is one of CBC or CBG.

23. The use of claim 1, wherein the cannabinoid is both of CBC and CBG.

24. The use of claim 1, wherein the lipopeptide antibiotic is daptomycin.