~~ANTIMICROBIAL AGENTS AND METHODS OF USE~~

ANTIMICROBIAL AGENT COMPRISING PEROXIDE, ALCOHOL AND CHELATING AGENT

TECHNICAL FIELD

[0001] The present application relates to novel antimicrobial compositions and methods of using said antimicrobial compositions for inhibiting and treating microbial growth, microbial infections, inflammatory diseases, viral diseases, cardiovascular diseases, diabetes and/or conditions that may be regulated or associated with microbial infections, such as cancer.

BACKGROUND

[0002] The formation of biofilms on the surface of medical devices is a serious and increasing problem for the medical community. Biofilms form on many types of surfaces, composed of a wide variety of materials, including catheters and ports, metal surfaces such as implanted prosthetic devices, live tissue such as deep wound trauma areas, and oral tissues such as teeth, gum tissue and bone. A number of types of organisms can originate biofilms including bacteria and fungi. Further, while some biofilms can be occupied by a single species, more commonly biofilms consist of an entire community of a variety of organisms. In some cases, even viruses can participate in the pathology generated by the biofilm community by way of bacteriophages. Both gram-negative and gram-positive bacterial organisms as well as fungi can produce biofilms.

[0003] While occupying a biofilm, many organisms, especially pathogens, exhibit a changed profile of sensitivities or resistances to antibiotics. This, coupled with the physico-chemical protections provided by the biofilm, make treating patients with biofilm infections very difficult. The problem is increasingly difficult as more

CLAIMS

1. An antimicrobial solution comprising:

(a) water;

(b) from about 20% to about 60% by volume of ethanol;

(c) from about 0.5% to about 7.5% by volume of hydrogen peroxide; and

(d) from about 5 mg/mL to about 40 mg/mL of ethylenediamine tetraacetic acid (EDTA), acids of EDTA, salts of EDTA or any combination thereof.

2. The solution of claim 1, wherein the concentration of ethanol is about 50% by volume.

3. The solution of claim 1, wherein the ethylenediamine tetraacetic acid (EDTA), acids of EDTA, salts of EDTA or any combination thereof is present at a concentration of about 10 mg/mL.

4. The solution of claim 1, wherein the hydrogen peroxide is present at a concentration of about 1.5% by volume.

5. The solution of claim 1, further comprising a viscosity-increasing agent.

6. The solution of claim 5, wherein the viscosity-increasing agent comprises hydroxypropyl methylcellulose (HPMC).

WHAT IS CLAIMED:

1. An antimicrobial agent comprising a synergistically effective combination of:
   (a) water;
   (b) a low molecular weight alcohol;
   (c) a peroxide or peroxide-generating agent; and
   (d) a chelating agent,
   wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

2. The agent of claim 1, wherein the alcohol comprises ethanol.

3. The agent of claim 1, wherein the alcohol is present in the agent at a concentration of from about 1% to about 95% by volume.

4. The agent of claim 3, wherein the concentration of alcohol is from about 20% to about 60% by volume.

5. The agent of claim 4, wherein the concentration of alcohol is about 50% by volume.

6. The agent of claim 1, wherein the chelating agent comprises ethylenediamine tetraacetic acid (EDTA) and its acids and salts thereof.

7. The agent of claim 6, wherein the EDTA is present at a concentration of from about 5 mg/mL to about 50 mg/mL.

8. The agent of claim 7, wherein the EDTA is present at a concentration of about 10 mg/mL.

9. The agent of claim 1, wherein the peroxide or peroxide-generating agent comprises hydrogen peroxide (H_2O_2).

10. The agent of claim 9, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 40% by volume.

11. The agent of claim 10, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 10% by volume.

12. The agent of claim 11, wherein the H_2O_2 is present at a concentration of about 1.5% by volume.

13. The agent of any one of claims 1-12, further comprising a viscosity-increasing agent.

14. The agent of claim 13, wherein the viscosity-increasing agent comprises hydroxypropyl methylcellulose (HPMC).

15. The agent of any one of claims 1-14, wherein the agent is useful in reducing or inhibiting microbial growth, microbial infections, inflammatory diseases, viral diseases or conditions resulting from or associated with microbial growth or infection.

16. The agent of any one of claims 1-14, wherein the agent is useful in treating microbial growth, microbial infections, inflammatory diseases, viral diseases or conditions resulting from or associated with microbial growth or infection.

17. A method of inhibiting or reducing microbial growth, comprising administering to a subject a therapeutically effective amount of an antimicrobial agent comprising a synergistically effective combination of:

(a) water;

(b) a low molecular weight alcohol;

(c) a peroxide or peroxide-generating agent; and

(d) a chelating agent,

wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

18. A method of treating microbial growth, comprising administering to a subject a therapeutically effective amount of an antimicrobial agent comprising a synergistically effective combination of:
(a) water;
(b) a low molecular weight alcohol;
(c) a peroxide or peroxide-generating agent; and
(d) a chelating agent,
wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

19. A method of inhibiting or reducing a microbial infection, comprising administering to a subject a therapeutically effective amount of an antimicrobial agent comprising a synergistically effective combination of:
(a) water;
(b) a low molecular weight alcohol;
(c) a peroxide or peroxide-generating agent; and
(d) a chelating agent,
wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

20. A method of treating a microbial infection, comprising administering to a subject a therapeutically effective amount of an antimicrobial agent comprising a synergistically effective combination of:
(a) water;
(b) a low molecular weight alcohol;
(c) a peroxide or peroxide-generating agent; and
(d) a chelating agent,
wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

21. The method of any one of claims 17-20, wherein the subject is human.

22. The method of any one of claims 17-21, wherein the microbial growth or microbial infection is due to a microorganism selected from the group consisting of a bacterium, a fungus, a protozoa and a virus.

23. The method of any one of claims 17-22, wherein the agent is administered by topical application, intravenous injection, intraperitoneal injection or implantation, intramuscular injection or implantation, intralesional injection, subcutaneous injection or implantation, intradermal injection, suppositories, pessaries, enteric application, or nasal route.

24. The method of claim 23, wherein the agent is administered by topical application.

25. The method of any one of claims 17-24, wherein the agent is administered to a site selected from the group consisting of a wound site, a catheter site, a surgical site, an injection site, a catheter, a catheter lumen, a thermal burn site, a chemical burn site, a radiation burn site, a skin lesion, oral sites, bony sites, anal sites, vaginal sites, cervical sites, vulvar sites, penile sites, ulcerated skin sites, acne sites, actinic keratosis sites, inflamed sites, irritated sites, gastric sites, gastrointestinal sites, esophageal sites, esophagogastrointestinal sites, intestinal sites, cardiac sites, vascular sites, nasal sites, nasopharyngeal sites, and aural sites.

26. The method of any one of claims 17-25, wherein the method is for treating microbial growth or microbial infection associated with a medical device.

27. The method of any one of claims 17-26, wherein the alcohol comprises ethanol.

28. The method of any one of claims 17-26, wherein the alcohol is present in the agent at a concentration of from about 1% to about 95% by volume.

29. The method of claim 28, wherein the concentration of alcohol is from about 20% to about 60% by volume.

30. The method of claim 29, wherein the concentration of alcohol is about 50% by volume.

31. The method of any one of claims 17-30, wherein the chelating agent comprises ethylenediamine tetraacetic acid (EDTA) and its acids and salts thereof.

32. The method of claim 31, wherein the EDTA is present at a concentration of from about 5 mg/mL to about 50 mg/mL.

33. The method of claim 32, wherein the EDTA is present at a concentration of about 10 mg/mL.

34. The method of any one of claims 17-33, wherein the peroxide or peroxide-generating agent comprises hydrogen peroxide (H_2O_2).

35. The method of claim 34, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 40% by volume.

36. The method of claim 35, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 10% by volume.

37. The method of claim 36, wherein the H_2O_2 is present at a concentration of about 1.5% by volume.

38. The method any one of claims 17-37, further comprising a viscosity-increasing agent.

39. The method of claim 38, wherein the viscosity-increasing agent comprises hydroxypropyl methylcellulose (HPMC).

40. A method of inhibiting or reducing an inflammatory condition or disease comprising administering to a subject a therapeutically effective amount of an antimicrobial agent comprising a synergistically effective combination of:
(a) water;
(b) a low molecular weight alcohol;

(c) a peroxide or peroxide-generating agent; and

(d) a chelating agent,

wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

41. A method of treating an inflammatory condition or disease comprising administering to a subject a therapeutically effective amount of an antimicrobial agent comprising a synergistically effective combination of:

(a) water;

(b) a low molecular weight alcohol;

(c) a peroxide or peroxide-generating agent; and

(d) a chelating agent,

wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

42. A method of inhibiting or reducing a viral condition or disease comprising administering to a subject a therapeutically effective amount of an antimicrobial agent comprising a synergistically effective combination of:

(a) water;

(b) a low molecular weight alcohol;

(c) a peroxide or peroxide-generating agent; and

(d) a chelating agent,

wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

43. A method of treating a viral condition or disease comprising administering to a subject a therapeutically effective amount of an antimicrobial agent comprising a synergistically effective combination of:

(a) water;

(b) a low molecular weight alcohol;

(c) a peroxide or peroxide-generating agent; and

(d) a chelating agent,

wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

44. The method of any one of claims 40-43, wherein the subject is human.

45. The method of any one of claims 40-44, wherein the agent is administered by topical application, intravenous injection, intraperitoneal injection or implantation, intramuscular injection or implantation, intralesional injection, subcutaneous injection or implantation, intradermal injection, suppositories, pessaries, enteric application, or nasal route.

46. The method of claim 45, wherein the agent is administered by topical application.

47. The method of any one of claims 40-46, wherein the agent is administered to a site selected from the group consisting of a wound site, a catheter site, a surgical site, an injection site, a catheter, a catheter lumen, a thermal burn site, a chemical burn site, a radiation burn site, a skin lesion, oral sites, bony sites, anal sites, vaginal sites, cervical sites, vulvar sites, penile sites, ulcerated skin sites, acne sites, actinic keratosis sites, inflamed sites, irritated sites, gastric sites, gastrointestinal sites, esophageal sites, esophagogastrointestinal sites, intestinal sites, cardiac sites, vascular sites, nasal sites, nasopharyngeal sites, and aural sites.

48. The method of any one of claims 40-47, wherein the method is for treating inflammatory or viral conditions or diseases associated with microbial growth or microbial infection.

49. The method of claim 48, wherein the microbial growth or microbial infection is associated with a medical device.

50. The method of any one of claims 40-49, wherein the alcohol comprises ethanol.

51. The method of any one of claims 40-49, wherein the alcohol is present in the agent at a concentration of from about 1% to about 95% by volume.

52. The method of claim 51, wherein the concentration of alcohol is from about 20% to about 60% by volume.

53. The method of claim 52, wherein the concentration of alcohol is about 50% by volume.

54. The method of any one of claims 40-53, wherein the chelating agent comprises ethylenediamine tetraacetic acid (EDTA) and its acids and salts thereof.

55. The method of claim 54, wherein the EDTA is present at a concentration of from about 5 mg/mL to about 50 mg/mL.

56. The method of claim 55, wherein the EDTA is present at a concentration of about 10 mg/mL.

57. The method of any one of claims 40-56, wherein the peroxide or peroxide-generating agent comprises hydrogen peroxide (H_2O_2).

58. The method of claim 57, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 40% by volume.

59. The method of claim 58, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 10% by volume.

60. The method of claim 59, wherein the H_2O_2 is present at a concentration of about 1.5% by volume.

61. The method any one of claims 40-60, further comprising a viscosity-increasing agent.

62. The method of claim 61, wherein the viscosity-increasing agent comprises hydroxypropyl methylcellulose (HPMC).

63. A method of inhibiting or reducing a condition or disease resulting from or associated with microbial growth or infection comprising administering to a subject a therapeutically effective amount of an antimicrobial agent comprising a

synergistically effective combination of:

(a) water;

(b) a low molecular weight alcohol;

(c) a peroxide or peroxide-generating agent; and

(d) a chelating agent,

wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

64. A method of treating a condition or disease resulting from or associated with microbial growth or infection comprising administering to a subject a therapeutically effective amount of an antimicrobial agent comprising a synergistically effective combination of:

(a) water;

(b) a low molecular weight alcohol;

(c) a peroxide or peroxide-generating agent; and

(d) a chelating agent,

wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

65. The method of any one of claims 63-64, wherein the subject is human.

66. The method of any one of claims 63-65, wherein the microbial growth or microbial infection is due to a microorganism selected from the group consisting of a bacterium, a fungus, a protozoa and a virus.

67. The method of any one of claims 63-64, wherein the condition or disease is selected from the group consisting of cancer, pre-cancerous conditions, inflammatory disease and viral disease.

68. The method of claim 67, wherein the condition is cancer or pre-cancerous conditions,.

69. The method of any one of claims 63-68, wherein the agent is administered by topical application, intravenous injection, intraperitoneal injection or implantation,

intramuscular injection or implantation, intralesional injection, subcutaneous injection or implantation, intradermal injection, suppositories, pessaries, enteric application, or nasal route.

70. The method of claim 69, wherein the agent is administered by topical application.

71. The method of any one of claims 63-70, wherein the agent is administered to a site selected from the group consisting of a wound site, a catheter site, a surgical site, an injection site, a catheter, a catheter lumen, a thermal burn site, a chemical burn site, a radiation burn site, a skin lesion, oral sites, bony sites, anal sites, vaginal sites, cervical sites, vulvar sites, penile sites, ulcerated skin sites, acne sites, actinic keratosis sites, inflamed sites, irritated sites, gastric sites, gastrointestinal sites, esophageal sites, esophagogastrointestinal sites, intestinal sites, cardiac sites, vascular sites, nasal sites, nasopharyngeal sites, and aural sites.

72. The method of any one of claims 63-71, wherein the alcohol comprises ethanol.

73. The method of any one of claims 63-71, wherein the alcohol is present in the agent at a concentration of from about 1% to about 95% by volume.

74. The method of claim 73, wherein the concentration of alcohol is from about 20% to about 60% by volume.

75. The method of claim 74, wherein the concentration of alcohol is about 50% by volume.

76. The method of any one of claims 63-75, wherein the chelating agent comprises ethylenediamine tetraacetic acid (EDTA) and its acids and salts thereof.

77. The method of claim 76, wherein the EDTA is present at a concentration of from about 5 mg/mL to about 50 mg/mL.

78. The method of claim 77, wherein the EDTA is present at a concentration of about 10 mg/mL.

79. The method of any one of claims 63-78, wherein the peroxide or peroxide-generating agent comprises hydrogen peroxide (H_2O_2).

80. The method of claim 79, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 40% by volume.

81. The method of claim 80, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 10% by volume.

82. The method of claim 81, wherein the H_2O_2 is present at a concentration of about 1.5% by volume.

83. The method any one of claims 63-82, further comprising a viscosity-increasing agent.

84. The method of claim 83, wherein the viscosity-increasing agent comprises hydroxypropyl methylcellulose (HPMC).

85. A method of inhibiting or reducing an immune response comprising administering to a subject a therapeutically effective amount of an antimicrobial agent comprising a synergistically effective combination of:
(a) water;
(b) a low molecular weight alcohol;
(c) a peroxide or peroxide-generating agent; and
(d) a chelating agent,
wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

86. The method of claim 85, wherein the amount is effective in inhibiting local or systemic toxicity.

87. The method of claim 85, wherein the amount is effective in inhibiting cytokine or chemokine levels or activity and/or cytokine or chemokine receptor levels or activity.

88. The method of claim 87, wherein the inhibition of cytokine or chemokine levels or activity is the result of chemical inhibition or modification of the cytokine or chemokine and/or its receptor.

89. The method of any one of claims 85-88, wherein the subject is human.

90. The method of any one of claims 85-89, wherein the immune response is associated with cancer, pre-cancerous conditions, inflammatory disease, viral disease, microbial infection, cardiovascular disease or diabetes.

91. The method of claim 90, wherein the immune response is associated with cancer or pre-cancerous conditions.

92. The method of claim 90, wherein the microbial infection is due to a microorganism selected from the group consisting of a bacterium, a fungus, a protozoa and a virus.

93. The method of any one of claims 85-92, wherein the agent is administered by topical application, intravenous injection, intraperitoneal injection or implantation, intramuscular injection or implantation, intralesional injection, subcutaneous injection or implantation, intradermal injection, suppositories, pessaries, enteric application, or nasal route.

94. The method of claim 93, wherein the agent is administered by topical application.

95. The method of any one of claims 85-94, wherein the agent is administered to a site selected from the group consisting of a wound site, a catheter site, a surgical site, an injection site, a catheter, a catheter lumen, a thermal burn site, a chemical burn site, a radiation burn site, a skin lesion, oral sites, bony sites, anal sites, vaginal sites, cervical sites, vulvar sites, penile sites, ulcerated skin sites, acne sites, actinic keratosis sites, inflamed sites, irritated sites, gastric sites, gastrointestinal sites, esophageal sites, esophagogastrointestinal sites, intestinal sites, cardiac sites, vascular sites, nasal sites, nasopharyngeal sites, and aural sites.

96. The method of any one of claims 85-95, wherein the alcohol comprises ethanol.

97. The method of any one of claims 85-95, wherein the alcohol is present in the agent at a concentration of from about 1% to about 95% by volume.

98. The method of claim 97, wherein the concentration of alcohol is from about 20% to about 60% by volume.

99. The method of claim 98, wherein the concentration of alcohol is about 50% by volume.

100. The method of any one of claims 85-95, wherein the chelating agent comprises ethylenediamine tetraacetic acid (EDTA) and its acids and salts thereof.

101. The method of claim 100, wherein the EDTA is present at a concentration of from about 5 mg/mL to about 50 mg/mL.

102. The method of claim 101, wherein the EDTA is present at a concentration of about 10 mg/mL.

103. The method of any one of claims 85-95, wherein the peroxide or peroxide-generating agent comprises hydrogen peroxide (H_2O_2).

104. The method of claim 103, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 40% by volume.

105. The method of claim 104, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 10% by volume.

106. The method of claim 105, wherein the H_2O_2 is present at a concentration of about 1.5% by volume.

107. The method any one of claims 85-105, further comprising a viscosity-increasing agent.

108. The method of claim 107, wherein the viscosity-increasing agent comprises hydroxypropyl methylcellulose (HPMC).

109. A method of inhibiting or reducing biofilm formation, comprising:
identifying a site; and
applying an antimicrobial agent to the site, the antimicrobial agent comprising a synergistically effective combination of:
(a) water;
(b) a low molecular weight alcohol;
(c) a peroxide or peroxide-generating agent; and
(d) a chelating agent,
wherein said combination synergistically enhances the stability and activity of said antimicrobial agent.

110. The method of claim 109, wherein the biofilm formation is the result of microbial growth or microbial infection.

111. The method of claim 110, wherein the microbial growth or microbial infection is due to a microorganism selected from the group consisting of a bacterium, a fungus, a protozoa and a virus.

112. The method of any one of claims 109-111, wherein the agent is administered by topical application, intravenous injection, intraperitoneal injection or implantation, intramuscular injection or implantation, intralesional injection, subcutaneous injection or implantation, intradermal injection, suppositories, pessaries, enteric application, or nasal route.

113. The method of claim 112, wherein the agent is administered by topical application.

114. The method of any one of claims 109-113, wherein the site is selected from the group consisting of a wound site, a catheter site, a surgical site, an injection site, a catheter, a catheter lumen, a thermal burn site, a chemical burn site, a radiation burn site, a skin lesion, oral sites, bony sites, anal sites, vaginal sites, cervical

sites, vulvar sites, penile sites, ulcerated skin sites, acne sites and actinic keratosis sites.

115. The method of any one of claims 109-114, wherein the alcohol comprises ethanol.

116. The method of any one of claims 109-114, wherein the alcohol is present in the agent at a concentration of from about 1% to about 95% by volume.

117. The method of claim 116, wherein the concentration of alcohol is from about 20% to about 60% by volume.

118. The method of claim 117, wherein the concentration of alcohol is about 50% by volume.

119. The method of any one of claims 109-114, wherein the chelating agent comprises ethylenediamine tetraacetic acid (EDTA) and its acids and salts thereof.

120. The method of claim 119, wherein the EDTA is present at a concentration of from about 5 mg/mL to about 50 mg/mL.

121. The method of claim 120, wherein the EDTA is present at a concentration of about 10 mg/mL.

122. The method of any one of claims 109-114, wherein the peroxide or peroxide-generating agent comprises hydrogen peroxide (H_2O_2).

123. The method of claim 122, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 40% by volume.

124. The method of claim 123, wherein the H_2O_2 is present at a concentration of from about 0.05% to about 10% by volume.

125. The method of claim 124, wherein the H_2O_2 is present at a concentration of about 1.5% by volume.

126. The method any one of claims 109-125, further comprising a viscosity-increasing agent.

127. The method of claim 126, wherein the viscosity-increasing agent comprises hydroxypropyl methylcellulose (HPMC).