AMMONIA OXIDIZING MICROORGANISMS FOR USE AND DELIVERY TO THE INTRANASAL SYSTEM

Cross-Reference to Related Applications

This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Serial No. 62/397,642 as filed on September 21, 2016, the entire disclosure of which is hereby incorporated herein by reference in its entirety for all purposes.

Field of the Technology

Aspects relates generally to the microbiome and, more specifically, to the restoration of ammonia oxidizing microorganisms in relation to the microbiome.

Background

Bacteria and other microorganisms are ubiquitous in the environment. The discovery of pathogenic bacteria and the germ theory of disease have had a tremendous effect on health and disease states. Microorganisms are a normal part of the environment of all living things and may be beneficial. In the nasal passages, inhaled air passes over specialized nasal structures. Microorganisms, ambient molecules, and particles elicit responses in the nasal passages and become trapped in a layer of high viscosity mucus. The internal nasal surface is characterized by groups of ciliated cells which act to transport the layer of high viscosity mucus for local or systemic delivery.

Summary

In one aspect, there is provided a method of introducing ammonia oxidizing microorganisms (AOM) to a subject, comprising: intranasally administering a preparation comprising AOM to the subject. A method of introducing ammonia oxidizing microorganisms (AOM) to a subject is disclosed. The method may comprise intranasally administering a preparation comprising AOM to the subject.

In some embodiments, intranasal administration may comprise topical application, inhalation, instillation, or olfactory transfer administration.

In another aspect, there is provided a method of delivering AOM to a nasal cavity of a subject, comprising: administering an effective amount of a preparation comprising AOM to the nasal cavity of the subject, wherein the AOM colonize a target tissue of the nasal cavity. A method of delivering AOM to a nasal cavity of a subject is disclosed. The method may comprise administering an effective amount of a

preparation comprising AOM to the nasal cavity of the subject, wherein the AOM colonize a target tissue of the nasal cavity.

In another aspect, there is provided the use of AOM in the manufacture of a preparation for treating neurogenic inflammation, e.g., oxidative stress, in a subject, wherein an effective amount of the preparation is to be administered to the subject. A method of treating a neurogenic inflammation in a subject is disclosed. The neurogenic inflammation may comprise, for example, oxidative stress. The method may comprise administering to the subject an effective amount of a preparation comprising AOM, thereby treating the neurogenic inflammation in the subject.

In another aspect, there is provided the use of AOM in the manufacture of a preparation for treating a neurological disorder in a subject, wherein an effective amount of the preparation is to be administered to the subject. A method of treating a neurological disorder in a subject is disclosed. The method may comprise administering to the subject an effective amount of a preparation comprising AOM, thereby treating the neurological disorder in the subject.

In another aspect, there is provided the use of AOM in the manufacture of a preparation for treating a nasal or sinus disorder in a subject, wherein an effective amount of the preparation is to be administered to the subject. A method of treating a nasal or sinus disorder in a subject is disclosed. The method may comprise administering to the subject an effective amount of a preparation comprising AOM, thereby treating the nasal or sinus disorder in the subject.

In another aspect, there is provided the use of AOM in the manufacture of a preparation for treating a systemic inflammatory condition in a subject, wherein an effective amount of the preparation is to be intranasally administered to the subject. A method of treating a systemic inflammatory condition in a subject is disclosed. The method may comprise intranasally administering to the subject an effective amount of a preparation comprising AOM, thereby treating the systemic inflammatory condition in the subject. In some embodiments, the systemic inflammatory condition is associated with one or more of: headaches (e.g., migraines), cardiovascular diseases (e.g., hypertension), inflammation, immune responses, autoimmune disorders, liver diseases, infections, neurological diseases, psychiatric disorders,

nitric oxide disorders, urea cycle disorders, congestion, vasodilation disorders, skin diseases, wound healing, reactions to insect bites, ophthalmic disorders, connective tissue disorders, and certain viral, bacterial, or fungal infections.

In another aspect, there is provided the use of AOM in the manufacture of a preparation for treating a headache or migraine headache in a subject, wherein an effective amount of the preparation is to be intranasally administered to the subject. A method of treating a headache or a migraine headache in a subject is disclosed. The method may comprise intranasally administering to the subject an effective amount of a preparation comprising AOM, thereby treating the headache or migraine headache in the subject.

In some embodiments, an amount and/or a frequency of administration is sufficient to increase mucus thickness in at least a portion of the nasal cavity of the subject. Administering the preparation may result in anti-triggering of ischemic pre-conditioning or modulation of an ATP

level in the subject. An amount and/or a frequency of administration may be sufficient to induce ischemic anti-triggering in the subject.

In at least some embodiments, the preparation comprising AOM is administered intranasally to a nasal cavity of a subject. The subject may have a substantially cleared nasal cavity when the preparation is administered. The preparation may be administered subsequent to administration of an antibiotic or a nasal cavity cleansing preparation. In some embodiments, a target percentage of administered AOM are transferred to a central nervous system (CNS) of the subject. The method may further comprise administering water or a buffer solution, e.g., an aqueous buffer solution to the subject subsequent to administering the preparation.

In some embodiments, administering the preparation results in decongestion, decreased sinus pressure, or modulation of an inflammatory response. In at least some embodiments, the neurological disorder is an inflammatory condition. The inflammatory condition may be a nasal or sinus disorder. The nasal or sinus disorder may be allergic rhinitis.

The inflammatory condition may be neurogenic inflammation, e.g., associated with headache, neuropathy (e.g., diabetic neuropathy, peripheral neuropathy, Lewy body neuropathy), epilepsy, systemic sclerosis, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's Disease, Parkinson's Disease, white matter hyperintensities, diabetic retinopathy, anxiety, post-traumatic stress disorder, chronic fatigue syndrome, fibromyalgia, depression, insomnia, arthritis, rheumatoid arthritis, allergic rhinitis, dilative cardiomyopathy, atherosclerosis, cardioprotection, heart failure, hypertension (e.g., pulmonary hypertension, gestational hypertension, portal hypertension), eclampsia, pre-eclampsia, capillary rarefaction, peripheral vasculopathy, gestational diabetes, type 2 diabetes, obesity, metabolic syndrome, kidney failure, liver failure, pancreatitis, or hepatitis.

In some embodiments, the nasal or sinus disorder may relate to an allergen, a bacterial infection, or a viral infection, e.g., the coronavirus, rhinovirus, meningitis, or influenza. The inflammatory condition may be associated with an injury, cancer, or an infection.

In some embodiments, administration may precede or follow a medical procedure, e.g., a catheterization, endoscopy, intubation, e.g., nasogastric intubation, administration of a nasal cannula, or a dental procedure. The inflammatory condition may be associated with or follow an injury, e.g., spinal cord injury, head trauma, or brain injury.

In some embodiments, the nasal or sinus disorder may be characterized by congestion or sinus pressure. In some embodiments, the neurological disorder may be a degenerative disorder or a genetic disorder. The neurological disorder may comprise a psychological disorder.

In some embodiments, administration may be to a deposit tissue or directly to a target tissue. A deposit tissue, target tissue, or both may be a mucous membrane of the subject. The deposit tissue, target tissue, or both may be associated with a nasal cavity of the subject. The deposit tissue, target tissue, or both may be a nasal cavity, septal wall, nasal valve, nostril, nasopharanyx, vestibular area, turbinate (e.g., inferior, middle, superior), meatus (e.g., inferior, middle, superior), concha (e.g., inferior, middle, superior), maxillary sinus, sphenoidal sinus, sphenoethmoidal recess, ethmoidal bulla, semi-lunar hiatus, nasolacrimal duct, frontonasal duct, or olfactory region of the subject.

In some embodiments, the target tissue may be associated with a desired local effect. The target tissue may be associated with a desired systemic effect. For example, a desired systemic effect may involve treatment of one or more of: headaches, cardiovascular diseases, inflammation, immune responses, autoimmune disorders, liver diseases, infections, neurological diseases, psychiatric disorders, nitric oxide disorders, urea cycle disorders, congestion, vasodilation disorders, skin diseases, wound healing, reactions to insect bites, ophthalmic disorders, connective tissue disorders, and certain viral, bacterial, or fungal infections.

In some embodiments, administering an effective amount of the preparation may promote endothelial function. Administering an effective amount of the preparation may change or alter a level of nitrite or NO at a target tissue or in circulation. Administering an effective amount of the preparation may modulate a microbiome associated with the intranasal system of the subject. Administering an effective amount of the preparation may modulate a microbiome associated with the CNS of the subject. Administering an effective amount of the preparation may modulate a systemic microbiome associated with a remote system, e.g., gastrointestinal system, circulatory system, respiratory system, endocrine system, or immune system, of the subject.

In some embodiments, administration may be device-assisted. The preparation may be administered prior to onset, during incidence, or subsequent to the subsiding of a gastrointestinal condition. The preparation may be administered in response to an inflammatory symptom, trigger or warning sign, e.g. discomfort, a change in sinus pressure, or a stress state. A method

may involve determining if the subject is in need of treatment for a neurological disorder. A method may involve determining if the subject is in need of treatment for a nasal or sinus disorder.

In some embodiments, the preparation may be administered as a solution, suspension, emulsion, ointment, bougie, powder, gel, hydrogel, or liquid, e.g. drop, spray, aerosol, or mist. The preparation may be formulated as a drop, spray, aerosol, or mist. The preparation may include microspheres or microcapsules. The preparation may be formulated to be compatible with the mucous membrane of the nasal cavity of the subject. The preparation may be formulated for immediate release or extended release. The preparation may be formulated to deliver nitrite or NO to a target tissue, locally or systemically. The preparation may be formulated for transmucosal delivery and/or circulation, *e.g.* locally or systemically.

In some embodiments, administration may reduce inflammation, congestion, sinusitis, asthma, sneezing, sinus pressure, or discomfort in the subject.

In some embodiments, a treatment method may further comprise administering a second amount of the preparation to the subject. In at least some embodiments, the preparation may be administered as part of a combination therapy. The method may further comprise administering a second treatment in combination with the preparation. The preparation may be administered for a period of time prior to initiating the second treatment, concurrently with the second treatment, or for a period of time subsequent to ceasing the second treatment. The second treatment may be administered via an alternate mode of administration, e.g. via inhalation or enteral technique. The subject may have a therapeutic level of a second treatment. The preparation may be administered in conjunction with an anti-inflammatory agent. The preparation may be administered in conjunction with a medical approach that treats, e.g., is approved to treat or is commonly used to treat, the relevant disease or disorder, or a symptom of the relevant disease or disorder. The preparation may be administered before or after a surgical or diagnostic procedure. The second treatment may comprise a surgical procedure. The preparation may be administered in conjunction with decongestant, probiotic, therapeutic, exercise, or stress management.

In at least some embodiments, the preparation may be administered in combination with a therapeutic treatment for headache, neuropathy (e.g., diabetic neuropathy, peripheral neuropathy,

Lewy body neuropathy), epilepsy, systemic sclerosis, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's Disease, Parkinson's Disease, white matter hyperintensities, diabetic retinopathy, anxiety, post-traumatic stress disorder, chronic fatigue syndrome, fibromyalgia, depression, insomnia, arthritis, rheumatoid arthritis, allergic rhinitis, dilative cardiomyopathy, atherosclerosis, cardioprotection, heart failure, hypertension (e.g., pulmonary hypertension, gestational hypertension, portal hypertension), eclampsia, pre-eclampsia, capillary rarefaction, peripheral vasculopathy, gestational diabetes, type 2 diabetes, obesity, metabolic syndrome, kidney failure, liver failure, pancreatitis, or hepatitis. The preparation may be administered in conjunction with nitrite, nitrate, and/or NO.

In some embodiments, the effective amount is a therapeutically effective dose of AOM. The therapeutically effective dose of AOM is about or greater than about 1 x 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, or 10^{14} CFU. The preparation may be administered as an analgesic and/or as a prophylactic. The preparation may be self-administered. The preparation may be administered about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 times per day. The preparation may be administered for about 1-3, 3-5, 5-7, 7-9, 5-10, 10-14, 12-18, 12-21, 21-28, 28-35, 35-42, 42-49, 49-56, 46-63, 63-70, 70-77, 77-84, or 84-91 days. The preparation may be administered within 30, 60, 90, 120, 150, or 180 minutes of the subject waking from sleep. The preparation may be administered within 30, 60, 90, 120, 150, or 180 minutes prior to the subject sleeping. The preparation may be administered within 30, 60, 90, 120, 150, or 180 minutes of the subject eating. The preparation may be administered 30, 60, 90, 120, 150, or 180 minutes before the subject cleanses or showers.

In some embodiments, the subject may be female. In other embodiments, the subject may be male. The subject may be characterized as one of the following ethnicity/race: Asian, black or African American, Hispanic or Latino, white, or multi-racial. The subject may have a disrupted microbiome. The subject may be of an age less than 1, or between 1-5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, or over 60 years.

In some embodiments, the preparation may comprise AOM in a buffer solution, e.g., an aqueous buffer solution. The buffer solution, e.g., aqueous buffer solution, comprises disodium phosphate and magnesium chloride, for example, 50 mM Na_2HPO_4 and 2 mM $MgCl_2$ in water. The buffer solution e.g., aqueous buffer solution, consisting essentially of disodium phosphate

and magnesium chloride, for example, 50 mM Na_2HPO_4 and 2 mM $MgCl_2$ in water. The buffer solution, e.g., aqueous buffer solution, consists of disodium phosphate and magnesium chloride, for example, 50 mM Na_2HPO_4 and 2 mM $MgCl_2$ in water. The preparation may be characterized by a physiological pH level. The preparation may further comprise or be administered concurrently with a compound that promotes growth or metabolism of the AOM, NO production, and/or urease activity. In at least some embodiments, the preparation may comprise at least one of ammonia, ammonium salts, and urea. The preparation may comprise a controlled release material, e.g., slow release material. The preparation may further comprise an excipient, e.g., a pharmaceutically acceptable excipient. The excipient may comprise an absorption or penetration enhancer, preservative, antioxidant, buffer, chelating agent, ion exchange agent, solubilizing agent, suspending agent, thickener, surfactant, wetting agent, tonicity-adjusting agent, enzyme inhibitor, or vehicle for proper drug delivery. In at least some embodiments, the preparation may comprise a mucoadhesive agent, disintegrant, chelator, coating agent, modified-release product, or filler. The preparation may be substantially free of other organisms.

In some embodiments, the preparation may comprise between about 1×10^3 CFU/mL to about 1×10^{14} CFU/mL AOM. The preparation may comprise between about 1×10^9 CFU/mL to about 10×10^9 CFU/mL AOM. The AOM may comprise ammonia oxidizing bacteria (AOB). In some embodiments, the AOM may consist essentially of AOB. In at least some embodiments, the AOM may consist of AOB. The AOM may comprise *Nitrosomonas*, *Nitrosococcus*, *Nitrosospira*, *Nitrosocystis*, *Nitrosolobus*, *Nitrosovibrio*, and combinations thereof. The AOM may be *Nitrosomonas eutropha* (*N. eutropha*). The AOM may be *N. eutropha* D23, having ATCC accession number PTA-121157. In at least some embodiments, the AOM may comprise ammonia oxidizing archaea (AOA). The AOM may be capable of converting ammonia or ammonium to nitrite at a rate of at least about 1 pmol/min/mg protein. The AOM may be capable of converting ammonia or ammonium to nitrite at a rate of at least about 0.1 nmol/min/mg protein.

In some embodiments, the preparation may be administered, e.g., intranasally to a first tissue, e.g. a deposit tissue. The first tissue may be the target tissue. In at least some embodiments, the first tissue is other than the target tissue, e.g., the preparation may be applied to a first tissue and the preparation, or a product of the preparation, e.g., NO, may be transported, e.g., by diffusion, to a second tissue, e.g. the target tissue.

In some embodiments, the treatment may comprise a surgical procedure. The excipient may comprise an anti-adherent, binder, coat, disintegrant, filler, flavor, color, lubricant, glidant, sorbent preservative, or sweetener.

In some embodiments, a biome-friendly product may be used in connection with the administered preparation comprising AOM.

In another aspect, there is provided a preparation comprising AOM as disclosed herein for intranasal administration to a subject.

In some embodiments, the preparation may be a nasal drop, spray, aerosol, or mist.

In some embodiments, a preparation may comprise AOM. The preparation may be for treatment of a neurological disorder in a subject. The preparation may be for treatment of a nasal or sinus disorder in a subject. In another aspect, there is provided a preparation comprising AOM as disclosed herein for use in the treatment of a neurological disorder in a subject. In another aspect, there is provided a preparation comprising AOM as disclosed herein for use in the treatment of a nasal or sinus disorder in a subject.

In some embodiments, the preparation may be packaged for single use. In some embodiments, the preparation may be packaged for multiple use.

In some embodiments, the preparation may further comprise other organisms, e.g., a community of organisms.

In another aspect, there is provided a device configured to administer a preparation comprising AOM as disclosed herein to a target tissue of a nasal cavity of a subject.

In another aspect, there is provided a kit comprising a preparation comprising AOM as disclosed herein. In embodiments, a kit may comprise a preparation comprising AOM, e.g., for delivery to an intranasal system of a subject or for treatment of a neurological disorder or nasal or sinus disorder in a subject.

The disclosure contemplates all combinations of any one or more of the foregoing aspects and/or embodiments, as well as combinations with any one or more of the embodiments set forth in the detailed description and any examples.

Detailed Description

In accordance with one or more embodiments, the present disclosure provides for various methods or modes of introducing ammonia oxidizing microorganisms to a subject. These methods or modes comprise administering to a subject ammonia oxidizing microorganisms, for example, a preparation, composition, formulation, or product comprising ammonia oxidizing microorganisms. In at least some embodiments, ammonia oxidizing microorganisms may

CLAIMS

1. A method of introducing ammonia oxidizing microorganisms (AOM) to a subject, comprising:

intranasally administering a preparation comprising AOM to the subject.

2. The method of any of the preceding claims, wherein intranasal administration comprises topical application, inhalation, instillation, or olfactory transfer administration.

3. A method of delivering AOM to a nasal cavity of a subject, comprising:

administering an effective amount of a preparation comprising AOM to the nasal cavity of the subject,

wherein the AOM colonize a target tissue of the nasal cavity.

4. Use of AOM in the manufacture of a preparation for treating neurogenic inflammation, e.g., oxidative stress, in a subject, wherein an effective amount of the preparation is to be administered to the subject.

5. Use of AOM in the manufacture of a preparation for treating a neurological disorder in a subject, wherein an effective amount of the preparation is to be administered to the subject.

6. Use of AOM in the manufacture of a preparation for treating a nasal or sinus disorder in a subject, wherein an effective amount of the preparation is to be administered to the subject.

7. Use of AOM in the manufacture of a preparation for treating a systemic inflammatory condition in a subject, wherein an effective amount of the preparation is to be intranasally administered to the subject.

8. The use of claim 7, wherein the systemic inflammatory condition is associated with one or more of: headaches (e.g., migraines), cardiovascular diseases (e.g., hypertension), inflammation, immune responses, autoimmune disorders, liver diseases, infections, neurological diseases, psychiatric disorders, nitric oxide disorders, urea cycle disorders, congestion, vasodilation disorders, skin diseases, wound healing, reactions to insect bites, ophthalmic disorders, connective tissue disorders, and certain viral, bacterial, or fungal infections.

9. Use of AOM in the manufacture of a preparation for treating a headache or migraine headache in a subject, wherein an effective amount of the preparation is to be intranasally administered to the subject.

10. The use of any of claims 4-9, wherein the preparation is to be administered in an amount and/or at a frequency sufficient to increase mucus thickness in at least a portion of the nasal cavity of the subject.

11. The use of any of claims 4-10, wherein the preparation anti-triggers ischemic pre-conditioning or modulates an ATP level in the subject.

12. The use of any of claims 4-11, wherein the preparation is to be administered in an amount and/or at a frequency sufficient to induce ischemic anti-triggering in the subject.

13. The use of any of claims 4-12, wherein the preparation is to be administered intranasally to a nasal cavity of the subject.

14. The use of any of claims 4-13, wherein the nasal cavity of the subject is substantially cleared when the preparation is administered.

15. The use of any of claims 4-14, wherein the preparation is to be administered subsequent to an antibiotic or a nasal cavity cleansing preparation.

16. The use of any of claims 4-15, wherein a target percentage of AOM is to be transferred to a central nervous system (CNS) of the subject.

17. The use of any of claims 4-16, wherein water or a buffer solution, e.g., an aqueous buffer solution, is to be further administered to the subject subsequent to the preparation.

18. The use of any of claims 4-17, wherein the preparation results in decongestion, decreased sinus pressure, or modulation of an inflammatory response.

19. The use of any of claims 4-18, wherein the neurological disorder is an inflammatory condition.

20. The use of any of claims 4-19, wherein the inflammatory condition is a nasal or sinus disorder.

21. The use of any of claims 4-20, wherein the nasal or sinus disorder is allergic rhinitis.

22. The use of any of claims 4-21, wherein the inflammatory condition is neurogenic inflammation, e.g., associated with headache, neuropathy (e.g., diabetic neuropathy, peripheral neuropathy, Lewy body neuropathy), epilepsy, systemic sclerosis, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's Disease, Parkinson's Disease, white matter hyperintensities, diabetic retinopathy, anxiety, post-traumatic stress disorder, chronic fatigue syndrome, fibromyalgia, depression, insomnia, arthritis, rheumatoid arthritis, allergic rhinitis, dilative cardiomyopathy, atherosclerosis, cardioprotection, heart failure, hypertension (e.g.,

pulmonary hypertension, gestational hypertension, portal hypertension), eclampsia, pre-eclampsia, capillary rarefaction, peripheral vasculopathy, gestational diabetes, type 2 diabetes, obesity, metabolic syndrome, kidney failure, liver failure, pancreatitis, or hepatitis.

23. The use of any of claims 4-22, wherein the nasal or sinus disorder relates to an allergen, a bacterial infection, or a viral infection, e.g., the coronavirus, rhinovirus, meningitis, or influenza.

24. The use of any of claims 4-23, wherein the inflammatory condition is associated with an injury, cancer, or an infection.

25. The use of any of claims 4-24, wherein the preparation is to be administered preceding or following a medical procedure, e.g., a catheterization, endoscopy, intubation, e.g., nasogastric intubation, administration of a nasal cannula, or a dental procedure.

26. The use of any of claims 4-25, wherein the inflammatory condition follows an injury, e.g., spinal cord injury, head trauma, or brain injury.

27. The use of any of claims 4-26, wherein the nasal or sinus disorder is characterized by congestion or sinus pressure.

28. The use of any of claims 4-27, wherein the neurological disorder is a degenerative disorder or a genetic disorder.

29. The use of any of claims 4-28, wherein the neurological disorder comprises a psychological disorder.

30. The use of any of claims 4-29, wherein a deposit tissue, target tissue, or both is a mucous membrane of the subject.

31. The use of any of claims 4-30, wherein a deposit tissue, target tissue, or both is associated with a nasal cavity of the subject.

32. The use of any of claims 4-31, wherein a deposit tissue, target tissue, or both is a nasal cavity, septal wall, nasal valve, nostril, nasopharanyx, vestibular area, turbinate (e.g., inferior, middle, superior), meatus (e.g., inferior, middle, superior), concha (e.g., inferior, middle, superior), maxillary sinus, sphenoidal sinus, sphenoethmoidal recess, ethmoidal bulla, semi-lunar hiatus, nasolacrimal duct, frontonasal duct, or olfactory region of the subject.

33. The use of any of claims 4-32, wherein the target tissue is associated with a desired local effect.

34. The use of any of claims 4-33, wherein the target tissue is associated with a desired systemic effect.

35. The use of any of claims 4-34, wherein the desired systemic effect involves treatment of one or more of: headaches, cardiovascular diseases, inflammation, immune responses, autoimmune disorders, liver diseases, infections, neurological diseases, psychiatric disorders, nitric oxide disorders, urea cycle disorders, congestion, vasodilation disorders, skin diseases, wound healing, reactions to insect bites, ophthalmic disorders, connective tissue disorders, and certain viral, bacterial, or fungal infections.

36. The use of any of claims 4-35, wherein an effective amount of the preparation is to be administered to promote endothelial function.

37. The use of any of claims 4-36, wherein an effective amount of the preparation is to be administered to change or alter a level of nitrite or NO at a target tissue or in circulation.

38. The use of any of claims 4-37, wherein an effective amount of the preparation is to be administered to modulate a microbiome associated with the intranasal system of the subject.

39. The use of any of claims 4-38, wherein an effective amount of the preparation is to be administered to modulate a microbiome associated with the CNS of the subject.

40. The use of any of claims 4-39, wherein an effective amount of the preparation is to be administered to modulate a systemic microbiome associated with a remote system, e.g., gastrointestinal system, circulatory system, respiratory system, endocrine system, or immune system, of the subject.

41. The use of any of claims 4-40, wherein the preparation is to be administered device-assisted.

42. The use of any of claims 4-41, wherein the preparation is to be administered prior to onset of an inflammatory condition.

43. The use of any of claims 4-42, wherein the preparation is to be administered during incidence of an inflammatory condition.

44. The use of any of claims 4-43, wherein the preparation is to be administered subsequent to the subsiding of an inflammatory condition.

45. The use of any of claims 4-44, wherein the preparation is to be administered in response to an inflammatory symptom, trigger or warning sign, e.g. discomfort, a change in sinus pressure, or a stress state.

46. The use of any of claims 4-45, wherein it is determined whether the subject is in need of treatment for a neurological disorder.

47. The use of any of claims 4-46, wherein it is determined whether the subject is in need of treatment for a nasal or sinus disorder.

48. The use of any of claims 4-47, wherein the preparation is to be administered as a solution, suspension, emulsion, ointment, bougie, powder, gel, hydrogel, or liquid, e.g. drop, spray, aerosol, or mist.

49. The use of any of claims 4-48, wherein the preparation is formulated as a drop, spray, aerosol, or mist.

50. The use of any of claims 4-49, wherein the preparation includes microspheres or microcapsules.

51. The use of any of claims 4-50, wherein the preparation is formulated to be compatible with the mucous membrane of the nasal cavity of the subject.

52. The use of any of claims 4-51, wherein the preparation is to be administered to reduce inflammation, congestion, sinusitis, asthma, sneezing, sinus pressure, or discomfort in the subject.

53. The use of any of claims 4-52, wherein the preparation is formulated for immediate release or extended release.

54. The use of any of claims 4-53, wherein the preparation is formulated to deliver nitrite or NO to a target tissue, locally or systemically.

55. The use of any of claims 4-54, wherein the preparation is formulated for transmucosal delivery and/or circulation, *e.g.* locally or systemically.

56. The use of any of claims 4-55, wherein a second amount of the preparation is to be administered to the subject.

57. The use of any of claims 4-56, wherein the preparation is to be administered as part of a combination therapy.

58. The use of any of claims 4-57, wherein a second treatment is to be administered in combination with the preparation.

59. The use of any of claims 4-58, wherein the preparation is to be administered for a period of time prior to initiating the second treatment.

60. The use of any of claims 4-59, wherein the preparation is to be administered concurrently with the second treatment.

61. The use of any of claims 4-60, wherein the preparation is to be administered for a period of time subsequent to ceasing the second treatment.

62. The use of any of claims 4-61, wherein the second treatment is to be administered via an alternate mode of administration, e.g. via inhalation or enteral technique.

63. The use of any of claims 4-62, wherein the subject has a therapeutic level of a second treatment.

64. The use of any of claims 4-63, wherein the preparation is to be administered in conjunction with an anti-inflammatory agent.

65. The use of any of claims 4-64, wherein the preparation is to be administered in conjunction with a medical approach that treats, e.g., is approved to treat or is commonly used to treat, the relevant disease or disorder, or a symptom of the relevant disease or disorder.

66. The use of any of claims 4-65, wherein the preparation is to be administered before or after a surgical or diagnostic procedure.

67. The use of any of claims 4-66, wherein the preparation is to be administered in conjunction with a decongestant, probiotic, therapeutic, exercise, or stress management.

68. The use of any of claims 4-67, wherein the preparation is to be administered in combination with a therapeutic treatment for headache, neuropathy (e.g., diabetic neuropathy, peripheral neuropathy, Lewy body neuropathy), epilepsy, systemic sclerosis, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's Disease, Parkinson's Disease, white matter hyperintensities, diabetic retinopathy, anxiety, post-traumatic stress disorder, chronic fatigue syndrome, fibromyalgia, depression, insomnia, arthritis, rheumatoid arthritis, allergic rhinitis, dilative cardiomyopathy, atherosclerosis, cardioprotection, heart failure, hypertension (e.g., pulmonary hypertension, gestational hypertension, portal hypertension), eclampsia, pre-eclampsia, capillary rarefaction, peripheral vasculopathy, gestational diabetes, type 2 diabetes, obesity, metabolic syndrome, kidney failure, liver failure, pancreatitis, or hepatitis.

69. The use of any of claims 4-68, wherein the preparation is to be administered in conjunction with nitrite, nitrate, and/or NO.

70. The use of any of claims 4-69, wherein the effective amount is a therapeutically effective dose of AOM.

71. The use of any of claims 4-70, wherein the therapeutically effective dose of AOM is about or greater than about 1 x 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, or 10^{14} CFU.

72. The use of any of claims 4-71, wherein the preparation is to be administered as an analgesic.

73. The use of any of claims 4-72, wherein the preparation is to be administered as a prophylactic.

74. The use of any of claims 4-73, wherein the preparation is to be self-administered.

75. The use of any of claims 4-74, wherein the preparation is to be administered about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 times per day.

76. The use of any of claims 4-75, wherein the preparation is to be administered for about 1-3, 3-5, 5-7, 7-9, 5-10, 10-14, 12-18, 12-21, 21-28, 28-35, 35-42, 42-49, 49-56, 46-63, 63-70, 70-77, 77-84, or 84-91 days.

77. The use of any of claims 4-76, wherein the preparation is to be administered within 30, 60, 90, 120, 150, or 180 minutes of the subject waking from sleep.

78. The use of any of claims 4-77, wherein the preparation is to be administered within 30, 60, 90, 120, 150, or 180 minutes prior to the subject sleeping.

79. The use of any of claims 4-78, wherein the preparation is to be administered within 30, 60, 90, 120, 150, or 180 minutes of the subject eating.

80. The use of any of claims 4-79, wherein the preparation is to be administered 30, 60, 90, 120, 150, or 180 minutes before the subject cleanses or showers.

81. The use of any of claims 4-80, wherein the subject is female.

82. The use of any of claims 4-81, wherein the subject is male.

83. The use of any of claims 4-82, wherein the subject is characterized as one of the following ethnicity/race: Asian, black or African American, Hispanic or Latino, white, or multi-racial.

84. The use of any of claims 4-83, wherein the subject has a disrupted microbiome.

85. The use of any of claims 4-84, wherein the subject is of an age less than 1, or between 1-5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, or over 60 years.

86. The use of any of claims 4-85, wherein the preparation comprises AOM in a buffer solution, e.g., an aqueous buffer solution.

87. The use of any of claims 4-86, wherein the buffer solution, e.g., aqueous buffer solution, comprises disodium phosphate and magnesium chloride, for example, 50 mM Na_2HPO_4 and 2 mM $MgCl_2$ in water.

88. The use of any of claims 4-87, wherein the buffer solution e.g., aqueous buffer solution, consisting essentially of disodium phosphate and magnesium chloride, for example, 50 mM Na_2HPO_4 and 2 mM $MgCl_2$ in water.

89. The use of any of claims 4-88, wherein the buffer solution, e.g., aqueous buffer solution, consists of disodium phosphate and magnesium chloride, for example, 50 mM Na_2HPO_4 and 2 mM $MgCl_2$ in water.

90. The use of any of claims 4-89, wherein the preparation is characterized by a physiological pH level.

91. The use of any of claims 4-90, wherein the preparation further comprises or is to be administered concurrently with a compound that promotes growth or metabolism of the AOM, NO production, and/or urease activity.

92. The use of any of claims 4-91, wherein the preparation comprises at least one of ammonia, ammonium salts, and urea.

93. The use of any of claims 4-92, wherein the preparation comprises a controlled release material, e.g., slow release material.

94. The use of any of claims 4-93, wherein the preparation further comprises an excipient, e.g., a pharmaceutically acceptable excipient.

95. The use of any of claims 4-94, wherein the excipient comprises an absorption or penetration enhancer, preservative, antioxidant, buffer, chelating agent, ion exchange agent, solubilizing agent, suspending agent, thickener, surfactant, wetting agent, tonicity-adjusting agent, enzyme inhibitor, or vehicle for proper drug delivery.

96. The use of any of claims 4-95, wherein the preparation comprises a mucoadhesive agent.

97. The use of any of claims 4-96, wherein the preparation includes a disintegrant, chelator, coating agent, modified-release product, or filler.

98. The use of any of claims 4-97, wherein the preparation is substantially free of other organisms.

99. The use of any of claims 4-98, wherein the preparation comprises between about 1×10^3 CFU/mL to about 1×10^{14} CFU/mL AOM.

100. The use of any of claims 4-99, wherein the preparation comprises between about 1×10^9 CFU/mL to about 10×10^9 CFU/mL AOM.

101. The use of any of claims 4-100, wherein the AOM comprise ammonia oxidizing bacteria (AOB).

102. The use of any of claims 4-101, wherein the AOM consist essentially of AOB.

103. The use of any of claims 4-102, wherein the AOM consist of AOB.

104. The use of any of claims 4-103, wherein the AOM comprise *Nitrosomonas*, *Nitrosococcus*, *Nitrosospira*, *Nitrosocystis*, *Nitrosolobus*, *Nitrosovibrio*, and combinations thereof.

105. The use of any of claims 4-104, wherein the AOM is *Nitrosomonas eutropha* (*N. eutropha*).

106. The use of any of claims 4-105, wherein the AOM is *N. eutropha* D23, having ATCC accession number PTA-121157.

107. The use of any of claims 4-106, wherein the AOM comprise ammonia oxidizing archaea (AOA).

108. The use of any of claims 4-107, wherein the AOM are capable of converting ammonia or ammonium to nitrite at a rate of at least about 1 pmol/min/mg protein, e.g., at least about 0.1 nmol/min/mg protein.

109. The use of any of claims 4-108, wherein the preparation is to be administered, e.g., intranasally to a first tissue, e.g. a deposit tissue.

110. The use of any of claims 4-109, wherein the first tissue is the target tissue.

111. The use of any of claims 4-110, wherein the first tissue is other than the target tissue, e.g., the preparation is to be applied to a first tissue and the preparation, or a product of the preparation, e.g., NO, is to be transported, e.g., by diffusion, to a second tissue, e.g. the target tissue.

112. The use of any of claims 4-111, wherein the second treatment comprises a surgical procedure.

113. The use of any of claims 4-112, wherein the excipient comprises an anti-adherent, binder, coat, disintegrant, filler, flavor, color, lubricant, glidant, sorbent preservative, or sweetener.

114. The use of any of claims 4-113, wherein a biome-friendly product is used in connection with the preparation comprising AOM.

115. A preparation comprising AOM, as recited in any of the preceding claims, for intranasal administration to a subject.

116. The preparation of any of the preceding claims, wherein the preparation is a nasal drop, spray, aerosol, or mist.

117. A preparation comprising AOM, as recited in any of the preceding claims, for use in the treatment of a neurological disorder in a subject.

118. A preparation comprising AOM, as recited in any of the preceding claims, for use in the treatment of a nasal or sinus disorder in a subject.

119. The preparation of any of the preceding claims, wherein the preparation is packaged for single use.

120. The preparation of any of the preceding claims, wherein the preparation is packaged for multiple use.

121. The preparation of any of the preceding claims, comprising AOM and other organisms, e.g., a community of organisms.