BRIEF SUMMARY

[0004] The present inventors discovered in their studies the certain gut microbial species and their metabolites can enhance the benefits of vaccines against infectious pathogens (*e.g.*, viral or bacterial pathogens such as SARS-CoV-2) including improving the efficacy and safety of the vaccines, thus provide important utility in the prevention and eradication of such diseases. The microorganisms and metabolites so identified now serve to provide new methods and compositions for enhancing or improving an individuals' immunity from vaccination against infectious diseases such as COVID-19.

[0005] In a first example, the present disclosure provides a composition that is useful for improving vaccine efficacy and safety, for reducing inflammation, and for increasing antibody response induced by the vaccine, thereby enhancing the overall effectiveness of a vaccine in a subject. The composition is typically administered to a subject at approximately the same time of vaccination. The composition comprises (1) an effective amount of *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum* or their metabolites; and (2) a physiologically acceptable excipient. In some examples, the composition further comprises an effective amount of xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber). In some examples, the composition consists of or consists essentially of (1) an effective amount of *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum*; and (2) one or more physiologically acceptable excipients. In some examples, the composition consists of or consists essentially of (1) an effective amount of *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum*, xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber); and (2) one or more physiologically acceptable excipients. In some examples, included in the composition is the medium in which *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum* have been cultured and therefore contains an effective amount of their metabolites.

[0006] In some examples, *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum* are present in the composition in the weight ratio of about (0.57-3.56): about 1: about (0.21-2.36). In some examples, *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum* are present in the composition in the weight ratio of about (0.75-1): about 1: about (0.75-1) for an adult subject, or about (0.57-3.09):about 1: about

(0.21-1.7) for a child subject. In some examples, xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber) are present in the composition in the weight ratio of about (0.25-0.5): about (2-4): about (0.5-0.75). In some examples, the composition is formulated for oral ingestion. In some examples, the composition is formulated in a daily dosage comprising *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum* in a combined range of about 10^6 to about 10^{12} colony-forming unit (CFU). In some examples, the composition is formulated in a daily dosage comprising xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber) in a combined range of about 0.01 to about 12 grams, for example, about 0.5 to about 6 grams, about 1 to about 3 grams, or about 1.2 to about 1.5 grams, with higher levels more suitable for use in combination with food especially when mixed in a food item. In some examples, the composition is formulated in the form of a food or beverage item, for example, in a daily dosage comprising xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber) in the amount of about 0.1 to about 12 grams. In some examples, the composition may further includes one or more agents known to effectively suppress SARS-CoV-2 and facilitate patient recovery from COVID-19 (*e.g.*, ivermectin, hydroxychloroquine, fluvoxamine/fluoxetine, Zinc, vitamin C, vitamin D, quercetin, melatonin, azithromycin, doxycycline, or any combination thereof).

[0007] In the second example, the present disclosure provides a method for improving vaccine efficacy and safety, for reducing inflammation, and for increasing antibody response induced by the vaccine, thereby enhancing the overall effectiveness of a vaccine in a subject. The method includes the step of administering to an individual an effective amount of a composition described above or herein, typically administered at approximately the same time of vaccination. In some examples, the composition is orally administered to the subject. In some examples, the subject is administered one single composition comprising an effective amount of *bifidobacteria adolescentis*, *bifidobacteria bifidum*, *bifidobacteria longum*, xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber). In some examples, the subject is administered two or more compositions each comprising one or more of *bifidobacteria adolescentis*, *bifidobacteria bifidum*, *bifidobacteria longum*, xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber), together providing a combined effective amount of these

individual components. In some examples, the subject is not diagnosed with COVID-19 but may have had exposure to SARS-CoV-2 virus and therefore may be at risk of becoming infected. In some examples, the subject has received a vaccine for COVID-19 within the past 24 or 48 hours. In some examples, the subject is to receive a vaccine for COVID-19 within the next 24 or 48 hours. Thus, in some cases the method may further include a step of vaccinating the subject just prior or after administering to the subject the composition of this disclosure, *e.g.*, within 1 or 2 days, preferably on the same day. In some examples, especially when the subject is seeking prophylaxis for COVID-19, the method further includes administering to the subject one or more agents known to effectively suppress SARS-CoV2 and facilitate patient recovery from COVID-19 (*e.g.*, ivermectin, hydroxychloroquine, fluvoxamine or fluoxetine, Zinc, vitamin C, vitamin D, quercetin, melatonin, azithromycin, doxycycline, or any combination thereof), which may be in the same composition or in one or more separate compositions. In some examples, the vaccine is comprises a whole virus (*e.g.*, heat-inactivated or otherwise attenuated), a viral protein, a viral vector, or a nucleic acid (DNA or RNA) encoding a viral protein. For example, the vaccine is a Sinovac or Sinopharm vaccine, a Pfizer vaccine, a Moderna vaccine, a Janssen vaccine, or an AstraZeneca vaccine produced in March 2021 or later.

[0008] In a related example, the present disclosure provides a novel use of a composition for improving vaccine efficacy and safety, for reducing inflammation, and for increasing antibody response induced by the vaccine, thereby enhancing the overall effectiveness of a vaccine in a subject. The composition is typically administered to a subject at approximately the same time of vaccination. The composition, as described above or herein, includes an effective amount of *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum*, optionally further including an effective amount of xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber), and is intended for administration to a subject, *e.g.*, by oral ingestion. In some examples, the subject is not diagnosed with COVID-19 but may have had an exposure to SARS-CoV-2 virus and is therefore at risk of becoming infected. In some examples, the subject has received a vaccine for COVID-19 within the past 24 or 48 hours. In some examples, the subject is to receive a vaccine for COVID-19 within the next 24 or 48 hours. In some examples, especially when the subject is seeking prophylaxis for COVID-19, the method further

includes administering to the subject one or more agents known to effectively suppress SARS-CoV2 and facilitate patient recovery from COVID-19 (*e.g.*, ivermectin, Zinc, hydroxychloroquine, fluvoxamine/fluoxetine, vitamin C, vitamin D, quercetin, melatonin, azithromycin, doxycycline, or any combination thereof), which may be in the same composition or in one or more separate compositions. In some examples, the vaccine is comprises a whole virus (*e.g.*, heat-inactivated or otherwise attenuated), a viral protein, a viral vector, or a nucleic acid (DNA or RNA) encoding a viral protein. For example, the vaccine is a Sinovac or Sinopharm vaccine, a Pfizer vaccine, a Moderna vaccine, an AstraZeneca vaccine, or a Janssen vaccine produced in March 2021 or later.

[0009] In a third example, the present disclosure provides a kit for improving vaccine efficacy and safety, for reducing inflammation, and for increasing antibody response induced by the vaccine, thereby enhancing the overall effectiveness of a vaccine in a subject. The kit includes at least two, possibly more, containers, each containing a composition comprising an effective amount of one or more active ingredients, which may be *bifidobacteria adolescentis*, *bifidobacteria bifidum*, *bifidobacteria longum*, xylooligosaccharides, galactooligosaccharides. resistant dextrin (soluble corn fiber), or any combination thereof. For example, a first and second containers containing two different compositions, one comprising three of the above-named bifidobacterium species and the other comprising the three above-named metabolites. Typically, the compositions are in the form of a powder, liquid, paste, cream, tablet, or capsule. The kit may further include an additional container containing one or more agents known to effectively suppress SARS-CoV-2 and facilitate patient recovery from COVID-19 (*e.g.*, ivermectin, fluvoxamine/fluoxetine, vitamin C, vitamin D, quercetin, melatonin, Zinc, azithromycin, doxycycline, hydroxychloroquine, or any combination thereof). Moreover, a user instruction manual may be included in the kit for the proper use of the kit, providing information such as suitable subjects for treatment and time, dosing *etc*.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **Figure 1**. Comparison of sCD40L, IL-1β, TNF-α, IL-17A level between synbiotic and no synbiotic group after COVID-19 vaccination. 4 subjects had taken the synbiotic composition (synbiotic group) and 5 subjects had not taken the synbiotic composition prior to COVID-19 vaccination (no synbiotic group). Blood samples were collected after these

WHAT IS CLAIMED IS:

1. Use of an effective amount of (1) *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum* or their metabolites; and (2) a physiologically acceptable excipient in the manufacture of a medicament for enhancing vaccine efficacy and safety in a subject.

2. The use of claim 1, further comprising an effective amount of xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber).

3. The use of claim 1 or 2, wherein *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum* are present in the composition in the weight ratio of about (0.57-3.56):1:(0.21-2.36).

4. The use of claim 3, wherein *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum* are present in the composition in the weight ratio of about (0.75-1):1:(0.75-1) for an adult subject.

5. The use of claim 3, wherein *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum* are present in the composition in the weight ratio of about (0.57-3.09):1:(0.21-1.7) for a child subject.

6. The use of claim 2, wherein xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber) are present in the composition in the weight ratio of about (0.25-0.5):(2-4):(0.5-0.75).

7. The use of claim 1, which is formulated for oral ingestion.

8. The use of claim 1, which is formulated in a daily dosage comprising *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum* in a combined range of about 10^6 to about 10^{12} colony-forming unit (CFU).

9. The use of claim 2, which is formulated in a daily dosage comprising xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber) in a combined range of about 0.01 to about 6 grams, preferably about 1.2 to about 1.5 grams.

10. The use of claim 1, which is in the form of a food or beverage item.

11. The use of claim 10, which is formulated in a daily dosage comprising xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber) in the amount of about 0.1 to about 12 grams.

12. Use of an effective amount of the composition of any one of claims 1-11 in the manufacture of a medicament for enhancing vaccine efficacy and safety in a subject.

13. The use of claim 12, wherein the use comprises oral ingestion of the composition.

14. The use of claim 12, wherein the use comprises one composition comprising *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum*, plus xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber) which is to be administered to the subject.

15. The use of claim 12, wherein the use comprises a first composition comprising *bifidobacteria adolescentis*, *bifidobacteria bifidum*, and *bifidobacteria longum* which is to be administered to the subject, and a second composition comprising xylooligosaccharides, galactooligosaccharides, and resistant dextrin (soluble corn fiber) which is to be administered to the subject.

16. The use of claim 12, wherein the subject is not diagnosed with COVID-19.

17. The use of claim 12, wherein the subject has received a vaccine for COVID-19 within the past 24-48 hours.

18. The use of claim 12, wherein the subject is to receive a vaccine for COVID-19 within the next 24-48 hours.

19. The use of claim 12, wherein the vaccine comprises a whole virus, a viral protein, a viral vector, or a nucleic acid encoding a viral protein.

20. A kit for enhancing vaccine efficacy and safety in a subject comprising a plurality of compositions each comprising an effective amount of one or more of the

following: *bifidobacteria adolescentis*, *bifidobacteria bifidum*, *bifidobacteria longum*, xylooligosaccharides, galactooligosaccharides. and resistant dextrin (soluble corn fiber).