[0008] In another study with healthy participants, researchers inquired as to the effect of a similar dietary antioxidant supplement on certain oxidative stress markers (OSM). Boris V. Nemzer, et. al., (2014): *Food Science & Nutrition*, DOI: 10.1002/fsn3.178. By observing OSM the researchers were measuring ex-vivo intra- and extracellular formation of ROS, respiratory activity of blood cells, mitochondrial-dependent ROS formation, and respiratory activity. This study also followed healthy participants' ability to modulate ex vivo cellular inflammatory responses induced by stimulation with exogenous TNF-α, nitrosative stress, and changes in NOHb concentrations. Although interesting, the administration of the antioxidant supplement resulted in inhibition of mitochondrial and cellular ROS generation by only 17%, 3.5 times inhibition of extracellular NOX2-dependent ROS generation, but nearly complete inhibition of extracellular H_2O_2, and a significant increase in circulating levels of NO.

[0009] Alternatively, in obese individuals, upon administration of a propriety polyphenol-rich blend, participants exhibited a 33-53% increase in NOHb and a 54-75% decrease in mitochondrial ROS. Boris V. Nemzer, et. al., (2021): *A … Study on the Effects of a Plant-Based Dietary Supplement*, DOI: 10.5539/jfr.v10n2p21. Although impressive, this study failed to consider any effect of the polyphenol-rich blend on additional ROS pathways beyond the mitochondrial ROS pathway.

[0010] Thus, even though various systems and methods of modulating immune responses are known in the art, all or almost all of them suffer from several drawbacks especially when it comes to combined targeting of three specific ROS pathways - mitochondrial, iNOS dependent, and NOX2 - in individuals with post-viral syndrome. Therefore, there remains a need for improved compositions and methods of alleviating signs or symptoms after viral infection, and especially after SARS-CoV2 infection.

Summary

[0011] The inventive subject matter is directed to various compositions and methods of alleviating signs or symptoms of post-viral syndrome, and particularly post-COVID syndrome, in which oral administration of a polyphenol-rich composition that preferably contains at least 50 wt% total catechins and at least 20 wt% total chlorogenic acids modulates multiple and distinct pathways that generate reactive oxygen species, leading to a reduction in inflammation, mitochondrial dysfunction, and/or oxidative nitrosative stress.

[0012] The inventors contemplate a method of alleviating a sign or symptom of a post-viral syndrome (and especially post-COVID syndrome or post-viral fatigue syndrome) that includes a step of orally administering a polyphenol-rich composition that predominantly comprises a plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids. Most typically, administration of the polyphenol-rich composition acutely modifies multiple and distinct pathways that generate reactive oxygen species, thereby alleviating the sign or symptom of the post-viral syndrome.

[0012a] In an aspect, there is provided use of a polyphenol-rich composition in the manufacture of a medicament for alleviating a sign or symptom of a post-viral syndrome, wherein: the polyphenol-rich composition predominantly comprises a plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids; and wherein the polyphenol-rich composition is to be orally administered and administration of the polyphenol-rich composition is to acutely modify multiple and distinct pathways that generate reactive oxygen species, thereby alleviating the sign or symptom of the post-viral syndrome.

[0013] Preferably, alleviation of the sign or symptom of the post-viral syndrome is associated with partial or complete amelioration of physical and/or mental function as compared to a subject not having been administered the composition.

[0014] In some examples, the plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids are found in one or more of a green coffee bean extract, a green tea extract, a turmeric extract, tart cherry or extract thereof, and a cruciferous plant or extract thereof For example, the polyphenol-rich composition may be prepared from at least one of a green coffee bean extract, a green tea extract, a turmeric extract, a tart cherry or extract thereof, a broccoli or extract thereof, and a kale or extract thereof. Alternatively, or additionally, the polyphenol-rich composition may be prepared from at least two of a green coffee bean extract, a green tea extract, a turmeric extract, a tart cherry or extract thereof, a broccoli or extract thereof, and a kale or extract thereof. Therefore, and viewed from a different perspective, the polyphenol-rich composition will preferably include at least 50 wt% total catechins and at least 20 wt% total chlorogenic acids. In other examples, the polyphenol-rich composition may further comprise up to 30 wt% total supplemental antioxidants. For example, at least one of the supplemental antioxidants may be selected from the group consisting of a stilbenoid, curcumin, vitamin E, manganese, and coenzyme Q10. It is further generally contemplated that 10-150 mg of the polyphenol-rich composition are

administered in a single dose (e.g., as a solid composition in a capsule) for a period of between 1 and 60 days, and is administered for at least 7 days after a negative viral test

[0015] After administration, alleviation of the sign or symptom of the post-viral syndrome will most typically occur within 30 minutes and 3 hours. As will be readily appreciated, the polyphenol-rich composition may be formulated in a capsule, a tablet, a gummy, a chewable, a dissolvable film, a powder or as a ready-to-drink beverage, a juice beverage, a carbonated beverage, or a liquid concentrate.

[0016] Preferably, the post-viral syndrome is post-COVID syndrome or post-viral fatigue syndrome.

[0017] In further examples of the inventive subject matter, the sign or symptom is fatigue, mitochondrial dysfunction, endothelial dysfunction, immune dysfunction, oxidative stress, chronic subacute inflammation, neurological dysfunction, and/or cognitive dysfunction. For example, contemplated pathways include mitochondrial reactive oxygen species generation, NOX2 dependent reactive oxygen species generation, and iNOS dependent reactive oxygen species generation. Additionally, administration of the polyphenol-rich composition may also acutely increase bioavailable NO, and/or acutely decrease proinflammatory cytokines (*e.g.*, circulating IL1-beta, IL8, IL10, and/or TNF-alpha). In some examples, mitochondrial reactive oxygen species levels are reduced by at least 50%, iNOS activity was reduced by at least 55%, NOX2-dependent reactive oxygen species (ROS) generation was reduced by at least 40%, and/or circulating nitric oxide as measured by HbNO was increased by at least 30%.

[0018] Consequently, the inventors contemplate a polyphenol-rich composition for treatment of a sign or symptom of a post-viral syndrome, wherein the composition predominantly comprises a plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids, and wherein the composition, upon oral administration at a dosage of between 10-150 mg, acutely modifies multiple and distinct pathways that generate reactive oxygen species, thereby alleviating the sign or symptom of the post-viral syndrome.

[0018a] In another aspect, there is provided use of a polyphenol-rich composition in the manufacture of a medicament for treatment of a sign or symptom of a post-viral syndrome, wherein the composition predominantly comprises a plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids, and wherein the composition, upon oral administration at a dosage of between 10-150 mg, is to acutely modify multiple and distinct pathways that generate reactive oxygen species, thereby alleviating the sign or symptom of the post-viral syndrome.

[0019] For example, the polyphenol-rich composition may include at least 50 wt% total catechins, at least 20 wt% total chlorogenic acids and optionally up to 30 wt% total supplemental antioxidants. Where desired, the polyphenol-rich composition may be prepared from at least one of a green coffee bean extract, a green tea extract, a turmeric extract, a tart

cherry or extract thereof, a broccoli or extract thereof, and a kale or extract thereof. Among other suitable dosage forms, 10-150 mg of the polyphenol-rich composition may be prepared in a solid form and formulated into a capsule or tablet that is administered in a single dose daily for a period of between 1 and 60 days. Upon administration, the sign or symptom of post-viral syndrome may be alleviated within 30 minutes and 3 hours. In other examples, the polyphenol-rich composition may be formulated in a capsule, a tablet, a gummy, a chewable, a dissolvable film, or a powder. Among other formulations, the polyphenol-rich composition may also be formulated as aready-to-drink beverage, a juice beverage, a carbonated beverage, or a liquid concentrate.

[0020] As noted above, contemplated post-viral syndromes include post-COVID syndrome and post-viral fatigue syndrome. For example, aches, pains, fever, upper and/or lower respiratory discomforts, shortness of breath, dyspnea, sore throat, fatigue, headache, abnormal chest imaging, and/or general malaise. Contemplated signs or symptoms may further include mitochondrial dysfunction, endothelial dysfunction, immune dysfunction, oxidative stress, chronic subacute inflammation, neurological dysfunction, and/or cognitive dysfunction. As such, observable markers for modification of these ROS pathways may be associated with inflammation (*e.g.*, an interleukin or pro-inflammatory cytokine), may be associated with mitochondrial function (*e.g.*, mitochondrial reactive oxygen species (ROS)), and/or may be associated with oxidative nitrosative stress (*e.g.*, due to iNOS activity, NOX2-dependent ROS generation, etc.).

[0021] Viewed from another perspective, the inventors contemplate the use of a polyphenol-rich composition for the manufacture of a medicament for treatment of a sign or symptom of a post-viral syndrome, wherein the composition predominantly comprises a plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids, and wherein the composition is formulated for administration at a dosage of between 10-150 mg.

[0022] In other words, the inventors contemplate a polyphenol-rich composition for use as a medicament in the treatment of post-viral syndrome, wherein the composition predominantly comprises a plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids, and wherein the composition is formulated for administration at a dosage of between 10-150 mg.

[0022a] In another aspect, there is provided use of a polyphenol-rich composition in the manufacture of a medicament for treatment of a sign or symptom of a post-viral syndrome, wherein the composition predominantly comprises a plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids, and wherein the composition is formulated for administration at a dosage of between 10-150 mg.

[0023] Most typically, the polyphenol-rich composition acutely modifies multiple and distinct pathways that generate reactive oxygen species. Consequently, acute modification of the multiple and distinct pathways may alleviate aches, pains, fever, upper and/or lower respiratory discomforts, sore throat, fatigue, and/or general malaise typically associated with post-viral syndrome. The sign or symptom of a post-viral syndrome may further include mitochondrial

dysfunction, endothelial dysfunction, immune dysfunction, oxidative stress, chronic subacute inflammation, neurological dysfunction, and/or cognitive dysfunction.

[0024] In some examples, the pathways include mitochondrial reactive oxygen species generation, NOX2 dependent reactive oxygen species generation, and/or iNOS dependent reactive oxygen species generation.

[0025] Preferably, the polyphenol-rich composition is provided in the form of plant materials and/or extracts thereof. For example, the plant materials may be selected from the group consisting of a green coffee bean extract, a green tea extract, a turmeric extract, a tart cherry or extract thereof, a broccoli or extract thereof, and a kale or extract thereof. In some examples, the polyphenol-rich composition may include at least 50 wt% total catechins, at least 20 wt% total chlorogenic acids, and optionally up to 30 wt% total supplemental antioxidants.

[0026] Consequently, administration of the polyphenol-rich composition may acutely increase bioavailable NO, and/or acutely decrease proinflammatory cytokines and/or chemokines, and/or acutely reduce circulating IL1-beta, IL8, IL10, and/or TNF-alpha. Such that mitochondrial reactive oxygen species levels are reduced by at least 50%, iNOS activity is reduced by at least 55%, wherein the NOX2-dependent ROS generation is reduced by at least 40%, and/or wherein the circulating nitric oxide as measured by NOHb is increased by at least 30%.

[0027] Various objects, features, aspects and advantages of the inventive subject matter will become more apparent from the following detailed description of preferred embodiments, along with the accompanying drawing figures in which like numerals represent like components.

Brief Description of The Drawing

[0028] FIG.1 is a graph depicting exemplary results for changes to cellular metabolic activity after administration of vitamin C and an exemplary polyphenol rich blend according to the inventive subject matter.

[0029] FIG.2 is a graph depicting exemplary results for changes to iNOS dependent cellular metabolic activity after administration of vitamin C and an exemplary polyphenol rich blend according to the inventive subject matter.

[0030] FIG.3 is a graph depicting exemplary results for changes to NOX2 dependent cellular metabolic activity after administration of vitamin C and an exemplary polyphenol rich blend according to the inventive subject matter.

CLAIMS

What is claimed is:

1. Use of a polyphenol-rich composition in the manufacture of a medicament for alleviating a sign or symptom of a post-viral syndrome, wherein:
   the polyphenol-rich composition predominantly comprises a plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids; and
   wherein the polyphenol-rich composition is to be orally administered and administration of the polyphenol-rich composition is to acutely modify multiple and distinct pathways that generate reactive oxygen species, thereby alleviating the sign or symptom of the post-viral syndrome.

2. The use of claim 1, wherein alleviating the sign or symptom of the post-viral syndrome is associated with partial or complete amelioration of physical and/or mental function as compared to a subject not having been administered the composition.

3. The use of claim 1, wherein the plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids are present in one or more of a green coffee bean extract, a green tea extract, a turmeric extract, tart cherry or extract thereof, and a cruciferous plant or extract thereof.

4. The use of claim 1, wherein the polyphenol-rich composition is prepared from at least one of a green coffee bean extract, a green tea extract, a turmeric extract, a tart cherry or extract thereof, a broccoli or extract thereof, and a kale or extract thereof.

5. The use of claim 1, wherein the polyphenol-rich composition is prepared from at least two of a green coffee bean extract, a green tea extract, a turmeric extract, a tart cherry or extract thereof, a broccoli or extract thereof, and a kale or extract thereof.

6. The use of claim 1, wherein the polyphenol-rich composition comprises at least 50 wt% total catechins and at least 20 wt% total chlorogenic acids.

7. The use of claim 1, wherein the polyphenol-rich composition further comprises up to 30 wt% total supplemental antioxidants.

8. The use of claim 7, wherein at least one of the supplemental antioxidants is selected from the group consisting of a stilbenoid, curcumin, vitamin E, manganese, and coenzyme Q10.

9. The use of claim 1, wherein 10-150 mg of the polyphenol-rich composition are to be administered in a single dose daily for a period of between 1 and 60 days.

10. The use of claim 1, wherein alleviation of the sign or symptom of post-viral syndrome is to occur within 30 minutes and 3 hours upon administration.

11. The use of claim 1, wherein the polyphenol-rich composition is formulated in a capsule, a tablet, a gummy, a chewable, a dissolvable film, or a powder.

12. The use of claim 1, wherein the polyphenol-rich composition is formulated as a ready-to-drink beverage, a juice beverage, a carbonated beverage, or a liquid concentrate.

13. The use of claim 1, wherein the post-viral syndrome is post-COVID syndrome or post-viral fatigue syndrome.

14. The use of claim 1, wherein the polyphenol-rich composition is to be administered for at least 7 days after negative viral test.

15. The use of claim 1, wherein the sign or symptom is fatigue, mitochondrial dysfunction, endothelial dysfunction, immune dysfunction, oxidative stress, chronic subacute inflammation, neurological dysfunction, and/or cognitive dysfunction.

16. The use of claim 1, wherein one of the pathways is mitochondrial reactive oxygen species generation.

17. The use of claim 1, wherein one of the pathways is NOX2 dependent reactive oxygen species generation.

18. The use of claim 1, wherein one of the pathways is iNOS dependent reactive oxygen species generation.

19. The use of claim 1, wherein administration of the polyphenol-rich composition is to acutely increase bioavailable NO, and/or wherein administration of the polyphenol-rich composition is to acutely decrease proinflammatory cytokines.

20. The use of claim 1, wherein administration of the polyphenol-rich composition is to acutely reduce circulating IL1-beta, IL8, IL10, and/or TNF-alpha.

21. The use as in any one of the preceding claims, wherein mitochondrial reactive oxygen species levels are to be reduced by at least 50%, iNOS activity is to be reduced by at least 55%, wherein the NOX2-dependent ROS generation is to be reduced by at least 40%, and/or wherein the circulating nitric oxide as measured by NOHb is to be increased by at least 30%.

22. Use of a polyphenol-rich composition in the manufacture of a medicament for treatment of a sign or symptom of a post-viral syndrome, wherein the composition predominantly comprises a plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids, and wherein the composition, upon oral administration at a dosage of between 10-150 mg, is to acutely modify multiple and distinct pathways that generate reactive oxygen species, thereby alleviating the sign or symptom of the post-viral syndrome.

23. The use of claim 22, wherein the polyphenol-rich composition comprises at least 50 wt% total catechins, at least 20 wt% total chlorogenic acids, and optionally up to 30 wt% total supplemental antioxidants.

24. The use of claim 22, wherein the polyphenol-rich composition is prepared from at least one of a green coffee bean extract, a green tea extract, a turmeric extract, a tart cherry or extract thereof, a broccoli or extract thereof, and a kale or extract thereof.

25. The use of claim 22, wherein 10-150 mg of the polyphenol-rich composition are to be administered in a single dose daily for a period of between 1 and 60 days.

26. The use of claim 22, wherein alleviation of the sign or symptom of post-viral syndrome is to occur within 30 minutes and 3 hours upon administration.

27. The use of claim 22, wherein the polyphenol-rich composition is formulated in a capsule, a tablet, a gummy, a chewable, a dissolvable film, or a powder.

28. The use of claim 22, wherein the polyphenol-rich composition is formulated as a ready-to-drink beverage, a juice beverage, a carbonated beverage, or a liquid concentrate.

29. The use of claim 22, wherein the post-viral syndrome is post-COVID syndrome or post-viral fatigue syndrome.

30. The use of claim 29, wherein the sign or symptom is aches, pains, fever, upper and/or lower respiratory discomforts, shortness of breath, dyspnea, sore throat, fatigue, headache, abnormal chest imaging, and/or general malaise.

31. The use of claim 22, wherein the sign or symptom is mitochondrial dysfunction, endothelial dysfunction, immune dysfunction, oxidative stress, chronic subacute inflammation, neurological dysfunction, and/or cognitive dysfunction.

32. The use of claim 22, wherein one of the pathways is mitochondrial reactive oxygen species generation, wherein one of the pathways is NOX2 dependent reactive oxygen species generation, and/or wherein one of the pathways is iNOS dependent reactive oxygen species generation.

33. The use of claim 22, wherein administration of the polyphenol-rich composition is to acutely increase bioavailable NO, and/or wherein administration of the polyphenol-rich composition is to acutely decrease proinflammatory cytokines.

34. The use of any one of claims 22-33, wherein mitochondrial reactive oxygen species levels are to be reduced by at least 50%, iNOS activity is to be reduced by at least 55%, wherein the NOX2-dependent ROS generation is to be reduced by at least 40%, and/or wherein the circulating nitric oxide as measured by NOHb is to be increased by at least 30%.

35. Use of a polyphenol-rich composition in the manufacture of a medicament for treatment of a sign or symptom of a post-viral syndrome, wherein the composition predominantly comprises a plurality of chemically distinct catechins and plurality of chemically distinct chlorogenic acids, and wherein the composition is formulated for administration at a dosage of between 10-150 mg.

36. The use of claim 35, wherein the polyphenol-rich composition is to acutely modify multiple and distinct pathways that generate reactive oxygen species.

37. The use of claim 36, wherein acute modification of the multiple and distinct pathways is to alleviate aches, pains, fever, upper and/or lower respiratory discomforts, sore throat, fatigue, and/or general malaise typically associated with post-viral syndrome.

38. The use of claim 35, wherein the sign or symptom of a post-viral syndrome further includes mitochondrial dysfunction, endothelial dysfunction, immune dysfunction, oxidative stress, chronic subacute inflammation, neurological dysfunction, and/or cognitive dysfunction.

39. The use of claim 35, wherein the polyphenol-rich composition is provided in the form of plant materials and/or extracts thereof.

40. The use of claim 39, wherein the plant materials are selected from the group consisting of a green coffee bean extract, a green tea extract, a turmeric extract, a tart cherry or extract thereof, a broccoli or extract thereof, and a kale or extract thereof.

41. The use of claim 35, wherein the polyphenol-rich composition comprises at least 50 wt% total catechins, at least 20 wt% total chlorogenic acids, and optionally up to 30 wt% total supplemental antioxidants.

42. The use of claim 35, wherein one of the pathways is mitochondrial reactive oxygen species generation.

43. The use of claim 35, wherein one of the pathways is NOX2 dependent reactive oxygen species generation.

44. The use of claim 35, wherein one of the pathways is iNOS dependent reactive oxygen species generation.

45. The use of claim 35, wherein administration of the polyphenol-rich composition is to acutely increase bioavailable NO, and/or is to acutely decrease proinflammatory cytokines and/or chemokines, and/or is to acutely reduce circulating IL1-beta, IL8, IL10, and/or TNF-alpha.

46. The use of claim 35, wherein mitochondrial reactive oxygen species levels are to be reduced by at least 50%, iNOS activity is to be reduced by at least 55%, wherein the NOX2-dependent ROS generation is to be reduced by at least 40%, and/or wherein the circulating nitric oxide as measured by NOHb is to be increased by at least 30%.