The Role of Nutraceuticals in the Prevention and/or Treatment of COVID-19: An Umbrella Review

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ABSTRACT

Background: To identify the results of published review literature regarding nutraceuticals, including probiotics, melatonin, poly-unsaturated fatty acids (PUFAs), quercetin, N-acetyl cysteine (NAC), and propolis as they relate to the prevention and/or treatment of COVID-19 (CV) and/or long COVID (long CV) and to outline key areas to consider for clinical application and for further research.

Methods: This paper is part of a six-part umbrella review which progresses from a living review. This review incorporates systematic reviews and narrative reviews as they relate to nutraceuticals. A live literature search occurred monthly in PubMed and Google Scholar from May 2022 to May 2023. Assessing the Methodological Quality of Systematic Reviews Version 2 (AMSTAR-2) scoring assessed systematic review quality, while the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines evaluated narrative reviews. Only those studies that were relevant to the nutraceuticals outlined above and that addressed COVID-19 prevention and/or treatment of CV and/or long CV were extracted from each review.

Results: Fifteen narrative reviews and 16 systematic reviews were included in this umbrella review. Studies indicate that nutraceuticals may be beneficial in improving the rate of recovery from various COVID-19 symptoms, rate of conversion parameters such as rate or duration of hospital stay and risk of intensive care unit (ICU) admission, and an improvement in various laboratory tests.

Conclusion/Summary: The broad antioxidant, anti-inflammatory, antiviral, and immune modulatory characteristics make the nutraceuticals included in this review reasonable choices for further research. Of the nutraceuticals discussed above, probiotics, melatonin, NAC, and quercetin indicate the greatest potential for benefit in the prevention and treatment of COVID-19 and long CV.

Key Words Anti-viral, anti-oxidant, anti-inflammatory, complementary therapies, immune system, naturopathic medicine, nutritional medicine, respiratory syndrome, SARS-CoV-2 vitamins, minerals

INTRODUCTION

The first cases of atypical pneumonia were reported in December of 2019 and quickly spread to all areas of the globe. Within 1 year of those first cases, COVID-19 was declared a pandemic by the World Health Organization (WHO; see Appendix 1 for a glossary of terms and acronyms used in this manuscript).[1] The development of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, was a prominent focus during the pandemic,[2] with the aim of reducing the death rate and the number and severity of new cases of COVID-19.[2] Yet 3 years later, there remains a serious public health concern and the need for treatment and prevention is as great as ever, as even fully vaccinated individuals are not completely immune to infection.[3] Early on in the pandemic,

many varied conventional and natural therapies were suggested as potential agents to reduce the risk of infection and improve the prognosis of the disease.[4] In this umbrella review, a team of naturopathic researchers supported by the World Naturopathic Federation (WNF) examine the available literature of common natural health products used by patients that are available over the counter or prescribed by naturopathic practitioners and other traditional, complementary and integrative healthcare (TCIH) practitioners for the prevention and/or treatment of COVID-19 and long COVID (long CV). Nutraceuticals included in this review are melatonin, poly-unsaturated fatty acids (PUFAs), probiotics, quercetin, N-acetyl cysteine (NAC), and propolis.

The nutraceuticals are worth considering for respiratory infections based on their historic use. The understanding of their biochemical properties—defined as nutritionally-based natural

health products that are not commonly classified as vitamins or minerals—justify the need to consider their value in the prevention and treatment of viral infections. For instance, NAC is established as a mucolytic nutrient with antioxidant properties and has been found to improve outcomes for acute respiratory distress syndrome and acute lung injury patients.[5] Quercetin, a flavonoid found in fruits such as grapes, apples, strawberries, cloudberries, and raspberries and in vegetables such as onions, tomatoes, lettuce, and green beans,[6-7] has demonstrated *in vitro* effects of increasing neutrophil chemotaxis, natural killer (NK) cell lytic activity, and inhibition of influenza A.[8] *In vitro, in vivo*, and clinical studies have highlighted the broad spectrum of antiviral properties of propolis.[9] Some common actions of these nutraceuticals include anti-inflammatory, antioxidative, immune-modulating, and antiviral mechanisms.[5-10] Melatonin is regarded as a positive regulator of immune responses and a negative regulator of inflammation.[11] Lower melatonin levels are common in the elderly and, as there is a correlation between age and severity of COVID-19, there is value in considering the role of melatonin in COVID-19 prevention and treatment.[12] PUFAs have demonstrated effectiveness in preventing respiratory tract infections,[13] and broad evidence indicates that intestinal immune cells interact with consumed probiotics, and this interaction improves host immune homeostasis and immune function. Furthermore, the meta-analyses investigating probiotic clinical interventions on respiratory tract infections (RTIs) indicates that probiotic use is associated with a lower incidence and duration of mild RTIs, in both children and adults.[14]

The aim of this paper is to review the available literature on probiotics, melatonin, PUFAs, quercetin, NAC, and propolis with the goal of describing the published peer review literature and identifying key areas to consider for research and clinical application in the treatment of COVID-19.

METHODS

Design

This umbrella review began as a high-level live review monitoring of all narrative and systematic reviews on nutraceuticals and natural treatments for the prevention and symptomatic management of COVID-19 and its sequellae.[15] The umbrella review is part of a six-part review in which this paper focuses on a group of nutraceuticals that are likely of value for the treatment of COVID-19 but do not fit neatly into other categories, such as herbal medicines, vitamins, or minerals. While narrative reviews are not typically included in an umbrella review, this paper included those that met specific criteria in order to provide context to the rationale for considering nutraceuticals in the prevention and/or treatment of COVID-19 and long CV.

Search Strategy

Over the course of 1 year (May 2022–May 2023), monthly literature searches were performed to collect the current and emerging data on natural prevention or treatment of COVID-19. Searches followed Cochrane Guidelines for a live systematic review.[16] PubMed and Google Scholar were searched using the following terms:

"natur*," "herb*," "nutraceutical," "botanical," "medicinal plant," "fish oil," "quercetin," "melatonin," "vitamin," "mineral," combined with "prevention," "prophylaxis," "deficiency," "treatment," "management," and "*COVID*," "Coronavirus," "SARS-CoV-2." Individual names of nutraceuticals, compounds, vitamins, minerals and other health protocols were also searched. These papers were then classified as systematic reviews, narrative reviews, meta-analyses, or other based on their description in the abstract.

Inclusion/Exclusion Analysis

Narrative reviews and systematic reviews from the live review were eligible for inclusion in this paper if they were related to the use of the nutraceuticals for the prevention or treatment of COVID-19. Both review types were appraised by at least two blinded reviewers, systematic reviews based on the Assessing the Methodological Quality of Systematic Reviews Version 2 (AMSTAR-2) guidelines[17] and narrative reviews according to the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines.[18] Systematic reviews were included if the review authors, at least partially, accounted for risk of bias (RoB) in individual studies and used a satisfactory technique for assessing the RoB. Narrative reviews were included if the scientific reasoning score was 1 or 2 and the overall total sum >5. Nutraceuticals that appeared in more than three systemic reviews after AMSTAR-2 assessment were included.

PICO eligibility criteria requirements for study inclusion were as follows:

Population: Clinical/observational (humans of any age/gender, any setting), *in vivo* (including animals), *in vitro*, or *in silico* studies.

Intervention: probiotics, melatonin, PUFAs, quercetin, N-acetyl cysteine (NAC), and propolis.

Comparison: No comparator limitation.

Outcome: Symptoms, biological markers, diagnostic criteria, or viral traits related to severe acute respiratory syndrome, viral respiratory tract infections, or COVID-19.

Excluded were secondary analyses, literature reviews, editorial discussions, best practice guidelines, and book chapters. To ensure that results were not overstated, researchers utilized a citation overlap analysis to track the duplication of papers. Due to the diverse topics covered in this umbrella review, a sub-analysis of overlap was also conducted focusing on each of the nutraceuticals covered. The overlap was categorised as "slight" (0%–5%), "moderate" (6%–10%), "high" (11%–15%), or "very high" (>15%) (see Table S1 in the supplemental material for full details of the overlap analysis).

Data Extraction

Data extraction for the systematic and narrative reviews was completed using separate shared, online spreadsheets. Some reviews covered topics that spanned multiple categories of the umbrella review, but only outcomes related to nutraceuticals were extracted for this paper.

Narrative reviews were included to highlight the therapeutic considerations and known mechanism of action of each criterion. The data extracted from the narrative reviews included study number, study identification, citation in American Medical Association (AMA) style, author(s), date, journal, country/world region, review objective, details of any search conducted, area of focus (prevention, treatment, long CV), and therapeutic considerations, including properties (anti-inflammatory, antiviral, etc.), based on the therapeutic properties outlined on https://www.ndhealthfacts.org/wiki/Action_of_Herbs and associations to other vitamins, minerals, or pathways.

The data extracted from the systematic reviews included study number, study identification, citation in AMA style, author(s), date, journal, country/world region, area of focus (prevention, treatment, long CV), review objective, review type (narrative, systematic, or meta-analysis), search date, search databases, study designs included, countries included in the studies, publication date range, tools for assessment of risk of bias and methods of synthesis/analysis. The study results data extracted included the intervention or exposure assessed, the outcomes measured, the number of studies included in the synthesis, the number of participants included in the studies, the age of the participants, the sex of the participants, the results or findings and results of heterogeneity analysis (if applicable). An overview of the umbrella review process is presented in Figure 1.

RESULTS

Narrative Reviews

Given that the role of nutraceuticals in the prevention and treatment of COVID-19 is relatively new, narrative reviews were included as they provide an overview of the biochemical properties, and potential therapeutic considerations and they complement the details of the systematic reviews. Of the 93 narrative reviews included in the live review, 16 were originally identified for the nutraceuticals section and 15 were included (see Table 1).[19-33] Of those, 6 were from the region of the Americas (Brazil,[19,20] Argentina,[21] Canada,[22] Mexico,[23] USA[24]), 5 from the European region (Italy,[25,26] Denmark,[27] Romania,[28] Russia[29]), 2 from the South-East Asia region (India,[30] Korea[31]), and one each from the Western Pacific region (Australia[32]) and Eastern Mediterranean region (Iran[33]). The individual nutraceuticals covered by these reviews included melatonin,[20,21,25,26,28,29,31,33] quercetin,[23,26,27,30,31] PUFAs,[22,24,27,32] probiotics,[19,24,32] and NAC.[28]

Systematic Reviews

The live review included 308 systematic reviews, of which 43 were initially identified as containing reporting about nutraceuticals; 15 were included (see Table 2).[34-48] The included systematic reviews were conducted in the Western Pacific region (WPR),[34-39] European region (EUR),[40,41,42] region of the Americas (AMR),[42-45] South-East
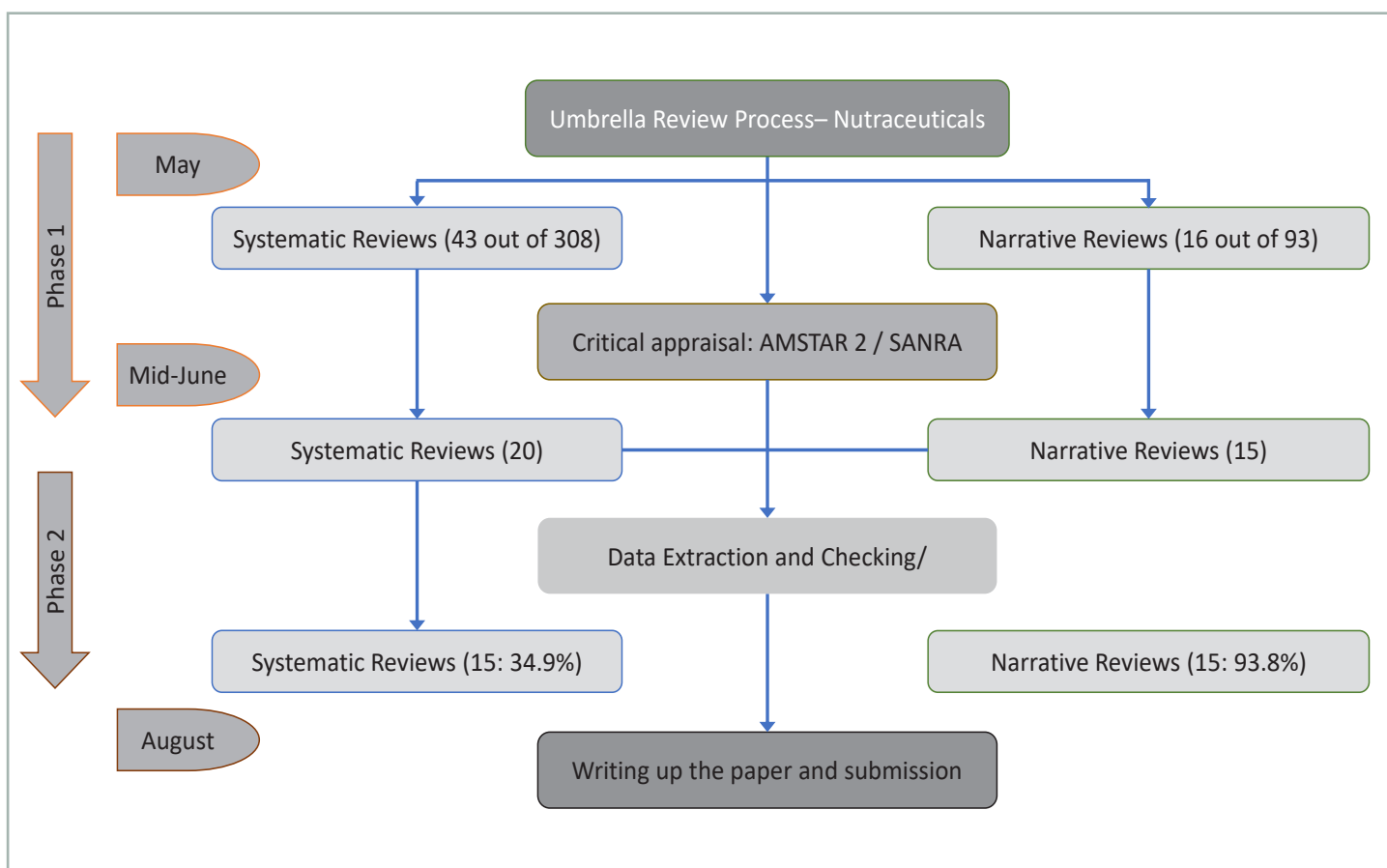

FIGURE 1 Umbrella review process — nutraceuticals

TABLE 1 (Part 1 of 2) Narrative Reviews – Nutraceuticals

First Author, Publication year (study #)	Area of Focus	WHO Region / Country	SANRA Score / Search details (Y or N)	Therapies Investigated	Properties / Association (if listed in paper)	Therapeutic Considerations
Bader-Larsen KS et al., 2021[27] (125)	Treatment	EUR / Denmark	11 / N	PUFAs (P)	P: anti-inflammatory, immune modulating	P: may play a role in decreasing the severity of CV infection by inhibiting cellular viral entry, suppressing the production of pro-inflammatory cytokines, and increasing the phagocytic capacity of the innate immune system.
Choe K et al., 2022[31] (22)	Treatment	SEA / Korea	7 / Y	Melatonin (M)	M: Anti-inflammatory, neuroprotective, immunoregulation / regulating effects against neurodegenerative diseases associated with oxidative stress, neuroinflammation, and mitochondrial dysfunction.	M: may reduce CV–associated complications, as has been suggested to block the nuclear translocation of NF-κB, expression of c-Fos, and suppression of matrix metalloproteinases-3 (MMP-3), which are responsible for pro-fibrotic and pro-inflammatory cytokine production. Has shown promising regulating effects against neurodegenerative diseases associated with oxidative stress, neuroinflammation, and mitochondrial dysfunction.
Cardinali DP et al., 2022[21] (279)	Long CV	AMR / Argentina	9.5 / Y	Melatonin (M)	M: antioxidant, anti-inflammatory, immunomodulatory	M: may reduce delirium and restore circadian imbalance seen in ICU CV patients; aids in the prevention of comorbidities, including diabetes, metabolic syndrome, and ischemic and non-ischemic CVD; neuroprotective and may help to control cognitive deterioration.
Gareau MG et al., 2023[24] (353)	Long CV	AMR / USA	7 / N	Probiotics (Pr) PUFAs (P)	Pr / P: anti-inflammatory, supportive role in gut microbiome / microbiota–gut–brain axis (MGB), gut–lung axis	Pr / P: improved MGB which may decrease long CV symptoms and decrease brain fog and neurological impairments, decrease in chronic dysbiosis, improved gut–lung axis.
Hosseini A et al., 2022[33] (299)	Prevention, Treatment	EMR / Iran	11.5 / Y	Melatonin (M)	M: antioxidant, anti-inflammatory; increases antioxidant enzymes (e.g., superoxide dismutase), decreasing preoxidative enzymes (e.g., nitric oxide synthase) and as a free radical scavenger	M: adjuvant and a potential alternative for the better management of SARS-CoV-2 infection in high-risk populations.
Inchingolo AD et al., 2021[25] (347)	Long CV	EUR / Italy	7 / N	Melatonin (M)	M: anti-inflammatory, antioxidant	M: may assist long haulers affected by chronic symptoms (chest and heart pain, intestinal disorders, headache, difficulty concentrating, memory loss, and tachycardia)
Notarbartolo V et al., 2022[26] (260)	Prevention, Treatment	EUR / Italy	12 / Y	Melatonin (M) Quercetin (Q)	M: immune modulating, anti-inflammatory. Q: antiviral, viricidal; inhibits activation of NF-κB, modulation of the acid sphingomyelinase / ceramide system, increase in neutrophil chemotaxis, NK-cells' activity and macrophages' phagocytosis. Increase in lymphocyte proliferation and regulation of IFN-γ secretion; inhibit SARS-CoV-2 proteins 3CL and PLpro.	M: Inhibits viral replication so theoretically it may inhibit SARS-CoV-2. Significant improvement in respiratory symptoms (cough, dyspnea) and fatigue, as well as a significant reduction in CRP serum levels and an improvement in the chest X-ray. Inhibits the expression of inflammasome genes, the inflammasome activation and the translocation and expression of NF-κB. Q: expected to reduce viral replication and support adaptive immunity for faster clearance of the virus.
Paudel KR et al., 2022[32] (331)	Prevention, Treatment	WPR / Australia	7 / Y	Probiotics (Pr) PUFAs (P)	Pr / P: immune-modulating, anti-inflammatory	Pr / P: modulate local immunity (by maintaining the well-being of the gut microbiome and boosting gut health) and systemic immunity (by stimulating specific/non-specific immune response).

TABLE 1 (Part 2 of 2) Narrative Reviews – Nutraceuticals

First Author, Publication year (study #)	Area of Focus	WHO Region / Country	SANRA Score / Search details (Y or N)	Therapies Investigated	Properties / Association (if listed in paper)	Therapeutic Considerations
Pisoschi AM et al., 2022[28] (262)	Prevention, Treatment	EUR / Romania	6 / N	NAC (N), Melatonin (M)	**N:** mucolytic, antioxidant, anti-inflammatory, immunomodulatory, **M:** antioxidant, anti-inflammatory, immunomodulatory, antiviral	**N:** Oral and intravenous glutathione, as well as precursors like NAC and alpha lipoic acid, constitute therapeutic alternatives to block NF-κB, hamper cytokine storm, and alleviate respiratory symptoms in CV pneumonia
Quintal Martínez JP et al., 2022[23] (325)	Treatment	AMR / Mexico	11.5 / Y	Quercetin (Q)	**Q:** antiplatelet, anticoagulant, fibrinolytic, and nitric oxide regulating effects	**Q:** may assist in regulating platelet aggregation, blood coagulation, fibrinolysis, and NO production due to their action on multiple receptors and enzymes
Savant S et al., 2021[30] (108)	Treatment	SEA / India	8 / N	Quercetin (Q), Probiotics (Pr), PUFA (P)	**Q:** antiviral, antioxidant, hypolipidemic / inhibitor of SARS-CoV-2 3CL, affects ACE2 expression, inhibits NF-κB pathway, reduces expression of pro-inflammatory cytokines (IL-6), **Pr:** anti-inflammatory / gut-brain axis, gut-lung axis, **P:** anti-inflammatory / hypolipidemic, regulates fat oxidation by enhancing β-oxidation, improves insulin sensitivity, anti-hyperglycemic function	**Q:** broad antiviral properties which may be beneficial in the treatment of CV. **Pr:** may decrease the spread of infection and decrease duration. **P:** may be beneficial in the management of CV.
Shchetinin E et al., 2022[29] (78)	Treatment	EUR / Russia	7.5 / N	Melatonin (M)	**M:** antioxidant, anti-inflammatory, antifibrotic, psychotropic, antiviral / decreases the levels of IL-2, IL-4, and IFN-γ. Improves sleep.	**M:** ROC: may decrease mortality, may improve survival of intubated patients and may reduce the risk of delirium in ICU patients. Reduces the risk of thrombosis and sepsis. Labs: may result in a decrease in positive PCR-test for SARS-CoV-2, decrease in CRP levels, and improved CT lung scan.
Trivedi P et al, 2022[22] (237)	Treatment	AMR / Canada	7 / N	PUFAs (P)	**P:** Anti-inflammatory	**P:** likely to be beneficial in reducing systemic inflammation in CV patients.
Xavier-Santos D et al., 2022[19] (715)	Treatment	AMR / Brazil	7 / Y	Probiotics (Pr)	**Pr:** antiviral, immunomodulatory, inhibition of microbial adherence, enhancement of the gut barrier function	**Pr:** may contribute to reducing the duration of the disease and the severity of symptoms such as fatigue, olfactory dysfunction and breathlessness, nausea and vomiting and other gastrointestinal symptoms. **Caution:** Not recommended for immunocompromised patients on corticosteroid therapy
Xerfan E et al., 2022[20] (297)	Prevention / Treatment	AMR / Brazil	8 / Y	Melatonin (M)	**M:** anti-inflammatory, antioxidant / Role in circadian rhythmic balance, participates in immunomodulatory, metabolic and endocrinological processes	**M:** Possible direct role of SARS-CoV-2 in the pineal gland/hypothalamus-pituitary axis, and in melatonin receptors in the olfactory bulb. Circadian rhythm dysregulation leads to sleep disturbance which impacts immune function. Melatonin helps regulate circadian rhythms.

3CL=3C-like proteinase protein; ACE2=angiotensin-converting enzyme 2; AMR=region of the Americas; CRP=C-reactive protein; CT=computed tomography; CV=COVID-19; CVD=cardio-vascular disease; EMR=Eastern Mediterranean region; EUR=European region; ICU=intensive care unit; IFN=interferon; IL=interleukin; long CV=long COVID; M=melatonin; MGB=microbiota–gut–brain axis; MMP-3=matrix metalloproteinase-3; N=no; NAC= N-acetyl cysteine; NF=nuclear factor; NK=natural killer; NO=nitric oxide; P=PUFAs; PCR=polymerase chain reaction; PLpro=papain-like protease; Pr=probiotics; PUFA=poly-unsaturated fatty acids; Q=quercetin; ROC=rate of conversion; SANRA=Scale for the Assessment of Narrative Review Articles; SARS-CoV-2=severe acute respiratory syndrome caused by Coronavirus 2; SEA=Southeast Asian region; USA=United States of America; WHO=World Health Organization; Y=yes.

TABLE 2 (Part 1 of 4) Systematic Reviews – Nutraceuticals

First Author, Publication Date (study #)	Area of Focus / WHO Region / Countries in Study	Number of Studies / Design Method / Search Date / Search Databases / Risk of Bias	Intervention	Participants: Number / Age / Sex	Review Objectives and Measurements	Findings
Aldhafiri FK et al., 2022[46] (714)	Treatment / SEA / Saudi Arabia	8 / RCTs, prospective cohorts, varied / 2019–2022 / PubMed, Embase, Cochrane library, CNKI / PRISMA	PUFAs (P) various dosages Probiotics (Pr) P and Pr compared to CWM and placebo.	P 2013, Pr 1111 / NS / NS	Efficacy **ROC:** duration **ROR:** gastrointestinal **Labs/Imaging:** inflammation, renal, respiratory **QoE:** CI and RR determined for each intervention.	**Improved ROC:** P and Pr may shorten duration of COVID-19. **Improved ROR:** Pr direct effect on GI symptoms, P decreased inflammation, P improved levels of several respiratory and renal functions in critically ill COVID-19 patients.
Arentz S et al., 2021[34] (675)	Treatment / WPR / Brazil	1 / RCT / 29 April – 15 August 2020 / PubMed, Embase, Central, AMED, Alt Health Watch, medRxiv, bioRxiv, clinicaltrials.gov, ISRCTN, WHO ICTRP / Cochrane RoB-2	Propolis (B) 400 mg to 800 mg QD compared with CWM.	124 / adults mean 50 (±12.8) / all genders	**ROC:** duration, severity, ROR, ICU admissions, oxygen dependency, AR **QoE:** low due to small number of studies and differences in study designs.	**Impr ROC:** decreased duration of hospital admissions; reduced risk of shock, respiratory failure and kidney injury. **No ROC impr:** duration of oxygen therapy, risks of ICU admission
Cheema HA et al., 2023[47] (761)	Treatment / SEA / Pakistan	6 / RCT, MA / database inception until 5 October 2022 / PubMed, Cochrane Library, Embase	Quercetin (Q) 260 to 1000 mg QD compared with CWM.	951 / all ages / all genders	**ROC:** risk of ICU admission, incidence of hospitalization, mortality **QoE:** low risk of bias, yet some concerns with randomisation	**Improved ROC:** decreased the risk of ICU admission (OR=0.31, 95% CI: 0.10–0.99, I^2=0%) and the incidence of hospitalisation (OR=0.25, CI: 0.10–0.62, I^2=0%). **No ROC improvement:** no decrease in risk of all-cause mortality.
Chen CH et al., 2023[35] (763)	Treatment / WPR / Taiwan	4 / RCTs (3) and observational study / inception to 14 May 2022 / Cochrane Library, PubMed, Embase, Web of Science, and SCOPUS / Cochrane RoB-2	NAC (N) compared to CWM and control	355 / 58.4 ± 4.9 / NS /	**ROC:** intubation rate, duration of hospital and ICU, mortality **QoE:** very low due to small number of patients included in the RCTs.	**Non-sig ROC:** RCTs negative for all primary and secondary outcomes; non-randomized studies were mixed with high degrees of heterogeneity regarding in-hospital mortality; respiratory outcome, duration of ICU stay, and hospital stay.
Dilokthornsakul W et al., 2022[36] (673)	Treatment / WPR / Brazil, Turkey, Egypt, Pakistan, Iran	15 / RCT, case reports / series / database inception to April 2021 / PubMed, Scopus, ScienceDirect, Cochrane Library / Cochrane RoB	Propolis (B) (various dosages and strains) lab changes, 3 RCT compared with CWM.	569 / 18–65, avg female 52, avg male 38 / all genders	**ROR:** clinical symptoms **Binding affinity:** SARS-CoV-2 ACE2, protease enzyme, RNA polymerase as the target enzyme, spike protein subunit. **QoE:** ranged from low to high	**Improved ROR:** fever, dry cough, shortness of breath, sore throat, chest pain, headache, muscular pain, diarrhea, runny nose, sore larynx, fatigue, nausea, vomiting, dizziness. May help with prevention. **High binding affinity:** to SARS-CoV-2 ACE2, to main protease enzyme, to spike protein subunit 1.

TABLE 2 (Part 2 of 4) Systematic Reviews – Nutraceuticals

First Author, Publication Date (study #)	Area of Focus / WHO Region / Countries in Study	Number of Studies / Design Method / Search Date / Search Databases / Risk of Bias	Intervention	Participants: Number / Age / Sex	Review Objectives and Measurements	Findings
Faridzadeh A et al., 2022[48] (733)	Treatment / EMR / Iran	10 / RCTs (5), CTs (3), ORC (2) / Oct 2021 – Jan 2022 / Web of Science, PubMed /MEDLINE, Cochrane Library, SCOPUS / Cochrane RoB tool	Melatonin (M) adjunctive tx	665 / 18 ± 72 / 93 females, 130 males	**ROR:** platelet aggregation **ROC:** recovery time, mortality, incubation **Labs:** inflammatory markers **QoE:** low due to small number of studies and differences in study designs.	**Improved ROR:** thrombosis and sepsis in severe cases **Improved ROC:** recovery time, mortality rate, incubation outcomes **Improved labs:** decreased inflammatory markers, inflammatory cytokines, and the expression of some genes, including the STAT4, STAT6, T-bet, GATA binding protein 3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and caspase-1 (CASP1).
Lan SH et al., 2022[37] (678)	Treatment / WPR / China	3 / RCTs, MA / April – Aug 2020 / Pubmed, Web of Science, Cochrane Library, Ovid MEDLINE, clinicaltrials. gov / Cochrane RoB	Melatonin (M) – 3 to 6 mg dosage, 7- to 14-day duration compared with CWM and control	86 / NS / NS	**ROC:** ROR, risk of ICU admission, mortality. **QoE:** low due to small number of studies and differences in study designs.	**Improved ROC:** clinical recovery rates were higher (OR 3.67; 95% CI: 1.21–11.12; I^2=0%, p=0.02). Risk of ICU admission (8.3% vs. 17.6%, OR 0.45; 95% CI: 0.16–1.25; I^2=0%, p=0.13). Risk of mortality lower (1.4% [1/72] vs. 4.4% [3/68], OR 0.32; 95% CI: 0.03–3.18; I^2=0%, p=0.33).
Neris AVS et al., 2022[42] (737)	Treatment / AMR / Turkey, Italy, Mexico, China, Russia	9 / clinical trials, cohort studies / inception through 16 March 2022 / PubMed, Embase, Scopus, Web of Science, ICTRP, BioXiv / Cochrane RoB 2 and ROBINS	Probiotics (Pr) (various strains) along with CWM	1410 / 18–77 / 6 studies both genders, 3 only males	**ROR:** overall symptoms, cough, headaches, diarrhea **ROC:** hospital stay, blood oxygenation, ICU admissions, invasive mechanical ventilation **Labs:** inflammatory markers, CBC, albumin, IgM, IgG **QoE:** low due to lack of homogeneity between studies and strains of probiotics.	**Sig. Improved ROR:** symptoms 51% reduction (RR 0.49, 95% CI 0.40–0.61), cough (RR 0.56, 95% CI 0.37–0.83), headaches (RR 0.17, 95% CI 0.05–0.65), and diarrhea (RR 0.33, 95% CI 0.12–0.96). **Improved ROC:** decreased hospital stay, decreased secondary infection, decreased ICU admissions and invasive mechanical ventilation, increased blood oxygenation. **Improved labs:** CRP, IgM, IgG, ESR, albumin, LYM, PLT, LEU, NK, IL-6

TABLE 2 (Part 3 of 4) Systematic Reviews – Nutraceuticals

First Author, Publication Date (study #)	Area of Focus / WHO Region / Countries in Study	Number of Studies / Design Method / Search Date / Search Databases / Risk of Bias	Intervention	Participants: Number / Age / Sex	Review Objectives and Measurements	Findings
Paraskevas T et al., 2023[40] (755)	Treatment / EUR / Italy and others not specified	8 / RCT, retrospective observational study, pros cohort, MA / database inception to Sept 2022 / PubMed, Medline, Embase / Cochrane RoB	NAC (N) along with CWM	21141 / >18 years / any sex / Italy plus others not stated	**ROR:** dyspnea, walking distance **ROC:** necessity for mechanical and non-invasive ventilation, rate of endotracheal intubation, ICU admissions, mortality, supplemental oxygen, rate of respiratory failure **Labs:** liver function **Imaging:** chest computed tomography scan **QoE:** low due to small number of studies and differences in study designs.	**Non-sig ROC:** RCTs negative for all primary and secondary outcomes; non-randomized studies were mixed with high degrees of heterogeneity regarding in-hospital mortality. **Improved ROC:** Observational studies suggest favorable results yet have a high degree of heterogeneity.
Pechlivanidou E et al., 2022[41] (610)	Treatment / EUR / Mexico	1 / CT / PubMed, CINAHL, Cochrane, database inception to April 2021 / NS	NAC (N) and melatonin (M) along with other NHPs – treatment every 12 h for 5 days	110 / avg 58 / all	**ROC:** survival rates **Labs:** inflammation markers, PCT **QoE:** low due to small number of studies and differences in study designs.	**Improved ROC:** survival scores **Labs:** IL-6 decreased (N), CRP decreased (N and M), in NAC and melatonin; PCT decreased (N)
Sobrinho RCS et al., 2022[43] (692)	Treatment / AMR / Turkey, Canada, Egypt, Indonesia, India, Brazil, Iran	13 / RCT and others / December 2021 to April 2021 / Central, PubMed, Scielo, Scholar Goggle, SCOPUS, Web of Science / Cochrane RoB	Propolis (various strains) compared with CWM	105 / NS / all genders	**ROC:** efficacy, length of hospitalization, clinical outcome **Binding affinity:** SARS-CoV-2 ACE2, protease enzyme, RNA polymerase as the target enzyme, spike protein subunit. **QoE:** low due to small number of studies and differences in study designs.	**Potentially improved ROC:** varied results, but some studies indicated decreased hospitalization and improved clinical outcomes. **Varied results re: binding affinity:** interaction with main protease less than remdesivir, but greater than hydroxychloroquine. B has potential to inhibit binding of virus to ACE2.
Wang XC et al., 2022[38] (736)	Treatment / WPR / Iran	6 / RCT / Dec 2019 – June 2022 / PubMed, Embase, Web of Science, Cochrane library, clinicaltrials.gov / NS	Melatonin in combination with CWM + control group.	338 / 18-65 / all / Iran	**ROR:** clinical recovery rate **Labs:** CRP, Sa02, WBC **QoE:** low due to small number of studies and differences in study designs.	**Improved ROR:** improvement in symptoms, improves quality of life when combined with CWM. **Improved ROR:** clinical recovery rate (OR 3.05, 95% CI: 1.47–6.31; p=.003). No sig difference in labs. Reduced adverse reactions
Xavier-Santos D et al., 2022[44] (690)	Treatment / AMR / Austria, Romania, Japan + 34 other countries	84 / clinical studies, other studies / Scopus	Probiotics (Pr) (various strains) compared with CWM + Pr	4423 / 1–99 / NS	**ROR:** gastrointestinal and microbiota, general symptoms **ROC:** efficacy, prevention **Labs:** viral entry **QoE:** low due to small number of studies and differences in study designs.	May decrease risk of infection. **Improved ROR:** decrease symptoms due to inflammation, decrease diarrhea, **Improved ROC:** decrease cytokine storm, improved intestinal microbiota, improved immune response, decrease secondary infection, improved gut–brain and gut–lung barriers. **Improved labs:** NK cells, block viral entry by binding with RdRp, RBD and ACE2, decreased IL-6, increased IL-10

TABLE 2 (Part 4 of 4) Systematic Reviews – Nutraceuticals

First Author, Publication Date (study #)	Area of Focus / WHO Region / Countries in Study	Number of Studies / Design Method / Search Date / Search Databases / Risk of Bias	Intervention	Participants: Number / Age / Sex	Review Objectives and Measurements	Findings
Yao J et al., 2022[39] (677)	Treatment / WPR / NS	5 / RCTs, MA / database inception until 16 September 2021 / PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, clinicaltrials.gov / Cochrane RoB	Propolis (P) and quercetin (Q) compared with CWM + flavonoids (B and Q), compared with controls	1060 / no restriction / all genders	**ROR:** symptoms **ROC:** necessity for oxygen, hospitalization duration, rate requiring mechanical ventilation, ICU rates, mortality **Labs:** IL-6, IL-8, TNF-alpha, RT-PCR clearance **QoE:** low due to small number of studies and differences in study designs.	**Sign improved ROR** : decreased time for alleviation of symptoms (WMD=−4.92, 95% CI: −7.46 to −2.37, p<.001) **Sig improved ROC:** decreased number patients needing oxygen, hospitalization and mechanical ventilation, decreased ICU days and mortality. **Improved labs:** decreased time for RT-PCR clearance vs control (WMD: −4.11, 95% CI: −4.54 to −3.68, p<0.001) No adverse effects reported
Zhu J et al., 2023[45] (767)	Treatment / AMR / USA, Italy, Russia, Mexico, Spain, India	8 / RCTs, MA / database inception until 31 July 2022 / PubMed, Cochrane Library, Embase, CINAHL, clinicaltrials.gov, Cochrane Central Register of Controlled Trials, PROSPERO / Cochrane RoB	Probiotics (various strains) compared to CWM + Pr	1027 / any age / 49.2% male, 50.8% female	**ROR:** cough, dyspnea, diarrhea, gastrointestinal symptoms, respiratory symptoms **ROC:** mortality, rate of recovery **Labs:** CRP **QoE:** heterogeneity assessed	**Improved ROR:** improved cough and dyspnea (RR 0.37 [0.19 to 0.73]), diarrhea (RR 0.61 [0.43 to 0.87]) **Improved ROC:** larger effect in hospitalized patients (RR 0.13 [95% CI 0.05 to 0.39]) **Uncertain change in labs:** CRP Reduced adverse events

ACE2= angiotensin-converting enzyme 2; AMED=Allied and Complementary Medicine Database; AMR=region of the Americas; AR=adverse reactions; B=propolis; CBC=complete blood count; CI=confidence interval; CINAHL=Cumulated Index to Nursing and Allied Health Literature; CNKI=China National Knowledge Infrastructure; CRP=C-reactive protein; CT=clinical trials; CWM=conventional western medicine; EMR=Eastern Mediterranean region; EUR=European region; GI=gastrointestinal; ICU=intensive care unit; IgG=immunoglobulin G; IgM=immunoglobulin M; IL6=interleukin-6; ISRCTN=International Standard Randomised Controlled Trial Number; M=melatonin; MA=meta-analysis; NAC=N-acetyl cysteine; NK=natural killer; NS=not stated; OR=odds ratio; ORC=observational retrospective cohorts; PCT=procalcitonin; Pr=probiotics; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO=International Prospective Register of Systematic Reviews; PUFA=polyunsaturated fatty acid; Q=quercetin; QD=every day; QoE=quality of evidence; RBD=receptor binding domain; RCT=randomized controlled trial; RdRp=RNA-dependent RNA polymerase; ROC=rate of conversion; ROR=rate of response; RR=relative risk; RT-PCR=reverse transcriptase polymerase chain reaction; SaO2=arterial oxygen saturation; SARS-CoV-2= severe acute respiratory syndrome caused by Coronavirus 2; SEA=South-East Asian region; Sig=significant; TNF=tumour necrosis factor; WBC=white blood cell; WHO ICTRP=World Health Organization International Clinical Trials Registry Platform; WHO=World Health Organization; WMD=weighted mean difference; WPR=Western Pacific region.

Asia region (SEA)[46,47] and Eastern Mediterranean region (EMR)[48] and covered the following nutraceuticals: melatonin,[37,38,41,48] probiotics,[42,44-46] NAC,[35,40,41] propolis,[34,36,39,43] quercetin[39,47] and PUFAs.[46] The overlap analysis of the included systematic reviews found 2.6% overlap, which is classified as a "slight" overlap. Sub-analyses by nutraceutical category found "very high" for the reviews covering flavonoids (20%), PUFAs (24.2%), propolis (25%), and NAC (25%). "Slight" overlap was found for probiotics (1.3%). Melatonin was only covered in one systematic review and as such the overlap was nil.

Five papers included multiple nutraceuticals and although specific nutraceuticals were listed as being included in the review, those that did not provide adequate details were excluded. Reviews were excluded if they did not refer to COVID-19. Only individual nutraceuticals that had at least three reviews were included.

Melatonin

Eight narrative reviews addressed the clinical and biochemical properties of melatonin as it relates to COVID-19 treatment and/or prevention. The anti-oxidant ($n = 3$), anti-inflammatory ($n = 6$), and immune modulating ($n = 4$) properties were the main focus of the narrative reviews on melatonin.[20,21,26,28,29,30,33] Several of the reviews suggested that the actions of melatonin may be valuable for reducing complications from COVID-19 via suppression of the cytokine storm as well as improving long-term outcomes via neuroprotective effects,[26,29,31] and sleep regulation.[20,21,29] The benefits of melatonin in high-risk, aging populations and in those with long CV was also covered.[25,29,33]

Four systematic reviews included melatonin as an intervention. These focused mainly on antioxidant and immunomodulatory properties of melatonin clinical outcomes, including changes in laboratory biomarkers indicating a decrease in inflammation,[41,48] and three reported on improved rates of recovery.[37,38,48] Lan et al. (2022)[37] included a meta-analysis of three small studies, only one of which was double-blinded, which showed a statistically significant improvement in clinical recovery rate (odds ratio [OR]: 3.67; 95% confidence interval [CI]: 1.21–11.12; $I^2 = 0\%$, $p = .02$) for patients with COVID-19 treated with melatonin compared with those treated with placebo, but no significant difference in the risk of intensive care unit (ICU) admission (OR: 0.45; 95% CI: 0.16–1.25; $I^2 = 0\%$, $p = .13$), mortality (OR: 0.32; 95% CI: 0.03–3.18; $I^2 = 0\%$, $p = .33$), the rate of CRP (C-reactive Protein; an inflammatory marker) normalization (OR: 1.14; 95% CI: 0.34–3.89; $I^2 = 0\%$, $p = .83$), or values of follow-up CRP (mean difference [MD], −1.03; 95% CI: −3.47 to 1.42; $I^2 = 0\%$, $p = .41$). Wang et al. (2022)[38] reported better total effective rate among patients with COVID-19, 18 years of age and older, who were treated with melatonin plus conventional treatments compared with conventional treatments alone (OR = 3.05, 95% CI: 1.47–6.31; $p = .003$) in a meta-analysis of six small studies. Again, no significant difference was found for the biomarkers CRP (weighted mean difference [WMD] = −0.36, 95% CI: −3.65 to 2.92, $p = .83$), arterial saturated oxygen (SaO_2) (WMD = 1, 95% CI: −1.21 to 3.22, $p = .37$), or white blood cell (WBC) count (WMD = −1.07, 95% CI: −2.44 to 0.30, $p = .13$).

Probiotics

The four narrative reviews discussing probiotics focused on their potential for prevention through the beneficial manipulation of the gut microbiome.[19,24,30,32] Probiotics were ascribed actions such as antiviral[19,30] and anti-inflammatory,[19,30,32] mostly in the context of maintaining a functional gut lining and attenuating local and systemic immunity[32] and limiting downstream gut–lung mucosal immune responses.[24] Through the microbiome–gut–brain axis and the gut–lung axis, probiotics were argued to have the potential to reduce the risk of COVID-19 incidence as well as long CV symptoms.[24]

The four systematic reviews that included studies investigating probiotics all suggested to some degree that the immune modulatory effects of probiotics, likely due to improvement of mucosal barriers of the gut and lung and associated immune monitoring, may be protective against SARS-CoV-2 infection.[40,42,44,46] Three of the studies emphasized the benefits of probiotics for gastrointestinal symptoms due to COVID-19.[40,42,44] Neris et al. (2022) indicated that probiotics were associated with a significant 51% reduction in symptoms reported by COVID-19 patients (relative risk [RR] 0.49, 95% CI: 0.40–0.61). There was a significant improvement in cough (RR 0.56, 95% CI: 0.37–0.83), headaches (RR 0.17, 95% CI: 0.05–0.65), and diarrhea (RR 0.33, 95% CI: 0.12–0.96) of patients on probiotic therapy. These findings suggest that probiotic supplementation is effective in improving symptoms of COVID-19.[42]

N-Acetyl Cysteine

The one narrative review exploring the value of NAC highlighted its antioxidant, mucolytic, anti-inflammatory, and immune modulating properties and indicated that NAC can alleviate oxidative stress and dampen the cytokine storm, thus having a protective effect on organ damage.[28] It described the NAC as able to reduce inflammation by blocking the nuclear factor kappa B (NF-kappa B) pathway, as a precursor to glutathione, and as a free radical scavenger.[28]

Three systematic reviews included NAC, of which two reported on studies focused on NAC alone[35,40] and one synthesized study involving NAC alongside other nutraceuticals.[41] While one systematic review did find that NAC can reduce inflammatory markers interleukin-6 (IL-6), CRP, and procalcitonin (PCT),[41] none of the systematic reviews found a relation between NAC treatment and reduced hospital stays, ICU admissions, or mortality.[35,40]

Quercetin

Two of the three narrative reviews describing research related to quercetin emphasized its antiviral, antioxidant, and hyperlipidemic properties.[26,30] Savant et al. (2021) stated quercetin has broad antiviral properties and is specifically an inhibitor of SARS-CoV-2,[30] while Quintal Martinez et al. (2022) highlighted quercetin's antiplatelet, anticoagulant, fibrinolytic, and nitric oxide (NO) regulating effects.[23] The reviews suggest that, due to its antiviral activity and other targets of action, quercetin could play a role in prevention and to help reduce recovery time from COVID-19.

The two systematic reviews on quercetin focused on the treatment benefits of supplementation, and both reported similar

findings.[39,47] The two reviews were in general agreement and their conclusions were summarized nicely by Cheema et al. (2023), who concluded that "quercetin decreased the risk of intensive care unit admission (OR = 0.31; 95% CI: 0.10–0.99) and the incidence of hospitalisation (OR = 0.25; 95% CI 0.10–0.62) but did not decrease the risk of all-cause mortality and the rate of no recovery and that quercetin may be of benefit in COVID-19 patients but large-scale RCTs [randomized controlled trials] are needed to confirm these findings."[47]

Propolis

No narrative reviews on propolis met the inclusion criteria. However, four systematic reviews were included. Three of the reviews looked mostly at clinical outcomes of COVID-19, including symptom severity, duration of illness, duration of hospitalization, and duration of respiratory support.[34,36,39] The rate of recovery results reported by Sobrinho et al. (2022) were not as positive as the other three papers, but the focus of this paper was more on the biochemical actions of propolis, which were stated to be anti-inflammatory, immunoregulatory, and anti-COVID19 effects, including protein kinase-1 (PAK-1) inhibition and binding to angiotensin-converting enzyme 2 (ACE2), one of the main routes of infection for SARS-CoV-2.[43] All systematic reviews were in agreement that propolis may be useful but further research into the efficacy for the treatment of COVID-19 is needed to confirm.

Polyunsaturated Fatty Acids (PUFAs)

The five narrative reviews that included PUFAs highlight their anti-inflammatory,[22,24,27,30,32] antioxidant,[30] and immune modulating properties.[27,32] Paudel et al. (2022)[32] and Gareau et al. (2023)[24] focused on the ability of PUFAs to modulate immune system functions through alterations in the gut microbiome. Although each of these reviews provides some analysis of PUFAs and their effect on COVID-19, they are relatively inconsistent with regard to the form of PUFA assessed and the outcomes measured. For instance, Bader-Larsen et al. (2021) cautioned against the supplementation of omega-3 fatty acids in cancer patients (despite also suggesting it may be beneficial for COVID-19 symptoms) and barely mentions PUFAs other than to mention that short chain fatty acids (SCFAs) may be helpful for relieving gastrointestinal symptoms associated with SARS-CoV-2 pathology.[27]

The systematic review by Aldhafiri et al. (2022) was the only review focused on PUFAs included. It indicated that PUFAs together with probiotics may shorten the duration of COVID-19 and may have a direct effect on decreasing inflammation and gastrointestinal symptoms.[46.]

DISCUSSION

COVID-19 is a highly communicable disease caused by SARS-CoV-2 infection leading to a wide range of clinical manifestations, from mild forms, such as fever, cough, and myalgia, to moderate forms requiring hospitalization (pneumonia and localized inflammation), to severe/critical forms with fatal outcomes.[49] As vaccine efficacy can be jeopardised by the rapid emergence and spread of SARS-CoV-2 variants,[50] there remains a need for therapies to reduce the severity and duration of COVID-19 as well as long COVID.[51] Three key areas where nutraceuticals may provide benefit relate to prevention, immune modulation, and anti-inflammatory support and supporting aging and high-risk populations.

Prevention

A focus on prevention reduces the likelihood of contracting COVID-19 and reduces the risk of long CV. Of the nutraceuticals discussed, probiotics may have a unique role to play in reducing the risk of contracting COVID-19 as well as the risk or severity of long CV symptoms. The interaction of the gut microbiome with the immune system and the subsequent effects on inflammation, mental health, and a host of other health outcomes is no longer a novel concept.[52] While tailoring the microbiome to precise parameters is not yet (and may never be) a possibility, we are aware of measures that may be taken to alter the gut microbiome to a state of eubiosis or a composition that is beneficial for human hosts.[53] It is generally believed that certain beneficial bacteria generate certain SCFAs, such as butyrate, propionate, and acetate, that appear to be key mediators of the beneficial effects elicited by the gut microbiome. Microbial SCFA production is essential for gut integrity by regulating the luminal pH and mucus production, providing fuel for epithelial cells, and procuring beneficial effects on mucosal immune function. SCFAs also directly modulate host metabolic health through a range of tissue-specific mechanisms related to appetite regulation, energy expenditure, glucose homeostasis and immunomodulation, leading the immune system to better recognize infectious agents and to suppress the unnecessary activation of the innate inflammatory response. Therefore, increased microbial SCFA production can be considered a health benefit.[54] Given this potential, further studies of probiotics (as well as synbiotics, prebiotics, and postbiotics) are warranted to determine how much benefit they can provide, the expected time frame to show effects, dosing, and the most effective species to prevent and treat COVID-19.

Immune Modulating and Anti-Inflammatory Support

Many of the nutraceuticals in this paper are anti-inflammatory or immune modulating. NAC, for instance, is a precursor molecule to glutathione,[55] the most important low-molecular-weight antioxidant synthesized in cells.[56] COVID-19 leads to an immune response resulting in what is known as a cytokine storm.[57] Long CV may develop via mechanisms involving neuroinflammation owing to unique signaling pathways and blood–brain barrier dysfunction, persistent inflammation related to an altered homeostatic milieu and organs, persistence of proinflammatory cells, altered cytokine production, and altered immune metabolic pathways in the lingering inflammatory response of the SARS-CoV-2 infection COVID-19.[58] Anti-inflammatory and immune modulation would seemingly be the ideal properties needed to combat these effects of SARS-CoV-2. Although the nutraceuticals breadth of research in this field is limited, of the nutraceuticals covered in this review, NAC and quercetin seem to have the potential for the

greatest benefit, NAC given its particular role as a precursor to one of the most important antioxidants in the body, and quercetin as it seems to be a potent inhibitor of the interaction between spike glycoproteins of SARS-CoV-2 and the ACE2 receptor.[59] In addition, active compounds in propolis and honey have anti-inflammatory properties. Galangin, an active compound in propolis, has been shown to inhibit tumor necrosis factor-α and interleukin-8, leading to a decrease in tissue inflammation and clinical symptoms. PUFAs' primary role is anti-inflammatory, reducing systemic inflammation and infections.

Aging and High-Risk Populations

Older adults and those with comorbidities are at greater risk for developing COVID-19 and have worse outcomes. Many of the nutraceuticals studied in this paper may be beneficial indirectly as they are associated with decreasing the risk of comorbidities such as diabetes, cardiovascular disease, gastrointestinal diseases, and others.[21,23,31] Melatonin warrants further consideration and research as it is well known that melatonin levels are often significantly lower in the elderly and are associated with decreased immune function.[11,12] Melatonin protects against cellular damage induced by reactive oxidative species due to its anti-inflammatory and antioxidant effects, and promotes an adaptive immune activity.

Limitations

Although the results of many nutraceuticals are promising, there are not nearly enough quality studies available to truly understand the significance of any of the above-mentioned nutraceuticals in their therapeutic role for COVID-19 or long CV treatment and prevention. Further studies are warranted to understand optimal effectiveness, dosing, and delivery methods for any of the nutraceuticals considered above. When interpreting the results, it is important to note that there was great heterogeneity between studies within most of the reviews and much more so between systematic reviews. Many of the studies included in the reviews also had small sample sizes, which limits the statistical power and generalizability of the findings. It is also important to note that there was very high overlap across systematic reviews for some of the nutraceuticals studied. This has implications for this umbrella review as it is important not to overemphasise findings arising from different systematic reviews if the reviews themselves draw upon the same original research articles. However, the high level of overlap is also an important finding for the wider research community investigating natural health products as it suggests significant duplication in research efforts have occurred during the COVID-19 pandemic, and that greater coordination is needed to avoid such duplication in the future.

CONCLUSION

The need for COVID-19 treatments remains significant, even after the development of effective vaccines. The antioxidant, anti-inflammatory, antiviral and immune modulatory characteristics make the nutraceuticals included in this review reasonable choices for further research. Additional high-quality randomized controlled trials with large sample sizes are required to fully determine their efficacy, with the inclusion of recommendations on dosing and administration. Of the nutraceuticals discussed above, probiotics, melatonin, NAC, and quercetin appear to have the greatest potential for benefit in the prevention and treatment of COVID-19 and long COVID.

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SUPPLEMENTAL MATERIAL

Supplemental material linked to the online version of the paper at https://doi.org/10.54434/candj.165:
- Table S1: Citation overlap: Umbrella review other NHPs

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APPENDIX 1: GLOSSARY OF TERMS

ACE2 = angiotensin-converting enzyme 2

AMA = American Medical Association

AMR = region of the Americas

AMSTAR-2 = Assessing the Methodological Quality of Systematic Reviews Version 2

CI = confidence interval

CV = COVID-19

EMR = Eastern Mediterranean region

EUR = European region

ICU = intensive care unit

IL-6 = interleukin-6

long CV = long COVID

NAC = N-acetyl cysteine

NF = nuclear factor

NK = natural killer

NO = nitric oxide

OR = odds ratio

PAK1 = protein kinase-1

PCT = procalcitonin

PUFA = polyunsaturated fatty acid

RCT = randomized controlled trial

RoB = risk of bias

RR = relative risk

RTI = respiratory tract infection

SANRA = Scale for the Assessment of Narrative Review Articles

SARS-CoV-2 = severe acute respiratory syndrome caused by Coronavirus 2

SCFA = short chain fatty acid

SEA = Southeast Asian region

TCIH = traditional, complementary and integrative healthcare

WBC = white blood cell

WHO = World Health Organization

WMD = weighted mean difference

WNF = World Naturopathic Federation

WPR = Western Pacific region