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REVIEW

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Dietary foods containing nitric oxide donors can be early curators of SARS-CoV-2 infection: A possible role in the immune system

S Swathi Krishna[1] | Arumugam Thennavan[2] | S K Kanthlal[1]

[1]Department of Pharmacology, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Science Campus, Kochi, Kerala 682041, India

[2]Central Lab Animal Facility, Amrita Vishwa Vidyapeetham, AIMS Health Science Campus, Kochi, Kerala 682041, India

Correspondence
S K Kanthlal, Department of Pharmacology, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS, Kochi, Kerala, India 682041.
Email: skkanthlal@aims.amrita.edu and kanthsklal@rediffmail.com

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is a lethal virus that causes COVID-19 (Coronavirus disease 2019), the respiratory illness that has caused the COVID-19 pandemic. Even though multiple pharmacological trials are ongoing, there is no proof that any treatment will effectively cure or prevent COVID-19. Currently, COVID-19-infected patients are being managed with non-specific medications to suppress the symptoms and other associated co-morbidities. Nitric oxide is a bio-signaling molecule that has been shown to be effective for treating several viral infections in humans. Household Natural foods rich in nitrites and nitrates (NO donors) have been scientifically proven to have therapeutic benefits against immune-related respiratory tract infections. It was understood that NO could inhibit the early stage of SARS CoV-2 invasion into the human cell. Fruits and vegetables containing nitrites and nitrates have been revised and are now thought to be potential anti-CoV agents for effective control of other associated systemic disorders. The purpose of this review is to highlight some key facts about the treatment and prevention of COVID-19 infection with foods rich in nitric oxide and its donors.

Practical applications

Improving the body's immune system is the early step to be considered as a preventive measure to stop the spreading of COVID-19 infection. Emerging research continues to mount that dietary nitrates/nitrites from plant foods are being healthy as well as keep us away from infectious diseases. They are now incorporated into low-risk adjuvant therapy for various infections and systemic disorders. This concept portrays the regular consuming foods such as fruits and vegetables that are rich in nitric oxide which have the potential to promote health, improve general well-being, and reduce the risk associated with the highly contagious diseases. Hence, we recommend adding nitrates and nitrites-containing food to the regular diet to improve the self-immunity as well as to fight against COVID-19 disease.

KEYWORDS

COVID-19, Dietary nitric oxide, Fruits and vegetables, Immune function

1 | INTRODUCTION

SARS-CoV-2, a rapidly spreading pandemic virus, has affected 216 countries or territories, or areas so far (WHO). Apart from its severity in causing the acute respiratory syndrome, recent reports have revealed evidence of multiple organ effects, suggesting the virulence potential of this novel virus (Baby et al., 2020). To restrict the spread of the disease, epidemiological measures such as isolation, quarantine, social distancing, lockdown, and curfew are being followed (Kumar et al., 2021). The lack of efficacious drugs or vaccines making the circumstances unpredictable for having a normal life (Coppola & Mondola, 2020). Although the worldwide vaccination drive is ongoing, WHO reports that vaccination rates remain inconsistent between nations, ranging from less than 1% of the population in some to more than 60% in others. The FDA also granted permission for medications approved for other diseases to be used to treat and manage COVID-19 people (Wu et al., 2020). Antiviral drugs, like Remdesivir and Favilavir, antimalarial drug chloroquine and hydroxychloroquine, monoclonal antibodies like Gimsilumab, TZLS-501, REGN3048-3051, and systemic corticosteroids, etc., were a few drugs in the pipeline for COVID-19 treatment (Duddu, 2020). Broad-spectrum antiviral agents, antibiotics, hydroxychloroquine, and convalescent plasma transfusion, etc., used currently are to prevent the exacerbations of pneumonia, suppress lung inflammations, virus-negative conversion, boost the immune system for the body's antiviral defense mechanisms, and shortening the disease course.

Scientific shreds of evidence have revealed fascinating facts about biological nitric oxide (NO) and its anti-retroviral activity. NO is a signaling molecule produced by mammalian cells that are involved in a variety of functions. NO was commonly released by inducible nitric oxide synthase (iNOS) activation after viral infection, which might either inhibit or encourage viral replication (Akerström et al., 2009). Common to all known, for cell fusion activity (the initial step after entry into the human body), a specialized viral glycoprotein (S protein) binds to the host cell angiotensin-converting enzyme 2 (ACE2) receptors present in the epithelial cell surface of the respiratory system. To achieve its functionality, it undergoes post-translational modifications such as glycosylation and S-palmitoylation. A study found that NO donor leads to the nitration of the S protein of SARS-CoV and reduces its fusion activity by inhibiting palmitoylation and inactivating the cysteine protease (identical to the S2 subunit of spike proteins of SARS-CoV as mentioned earlier). S-nitroso-N-acetyl-penicillamine (SNAP), an exogenous NO donor, has been shown to suppress viral replication in its early stages (Akerström et al., 2009). NO can also inhibit the replication cycle of SARS CoV by inhibiting viral protease (nitrosylation of cysteine residues) and RNA synthesis (Akerstrom et al., 2005).

NO stimulates cyclic guanosine monophosphate (cGMP), which elevates the cytoplasmic p53 tumor suppressor gene and nitrosylates the host and virus molecules, contributing to innate resistance mediated by the Th1-Th2 immune response (Uehara et al., 2015). It also promotes T-cell response, downregulates dendritic cell maturation and activation, suppresses adaptor proteins by modulating interleukin-6, and activation of interferon-alpha (Deakin et al., 1995). Other effects, such as improved alveolar blood supply, decreased mucosal production, improved lung repair, enhanced phagocytosis, bronchodilation by neural activation, and reduced lung infiltrate density, are predictors of symptom relief that favor comfort and well-being of the SARS-CoV infected patient. Despite the lack of clinical evidence for NO as a potential anti-SARS-CoV-2 molecule, preliminary study suggests that NO could play a constructive role in the early prevention and management of the infection.

The global economy is on the verge of collapse, and a lasting solution to the pandemic is urgently needed. This condition has prompted extensive studies in conventional medical systems. Ayurveda, India's traditional medical system, has a strong understanding of the causes and treatments of pandemics (Adithya et al., 2020; Al-Sehemi et al., 2020). Most of the fruits and vegetables that we consume daily in edible form, as well as constituents from beetroots, leafy vegetables, citrus fruits, apple, berries, grapefruits, and other fruits and vegetables that are high in dietary nitrates and nitrates (converted to NO in the body), have been scientifically proven to have possible benefits against acute immune-mediated respiratory tract infections including pulmonary fibrosis, diffuse alveolar damage, pneumonia, and acute respiratory distress syndrome (Garcia-Larsen et al., 2017; Hosseini et al., 2017; Kroll et al., ,2009, 2018; Lv et al., 2015; OM et al., 2021; Ritz et al., 2019). Because many of these symptoms are also associated with COVID-19 infection, consuming these fruits and vegetables may help people stay healthy at this time.

In this study, we aimed to highlight the importance of nitric oxide donors containing fruits and vegetables, as well as their putative involvement in the immunomodulatory pathway, to improve the prevention of COVID-19 infection, mortality, and risk rate.

2 | METHODS

We performed an open-ended, English-restricted search of databases such as Scopus, Web of Science, and Pubmed for all available literature, using terms related to dietary nitric oxide, fruits, vegetables, respiratory and lung infection/immunity, and coronavirus. Various studies reported on clinical, animal, and in-vitro models were considered for shortlisting the outcome effects. We particularly focused on respiratory and lung-related diseases, and we have limited the reported studies related to the effect on immune and inflammatory-related activities of selected dietary sources.

2.1 | Apple

Consumption of apple has been inversely correlated with asthma and has also been positively linked to general pulmonary health. Apple (rich in bioactive flavonoids and NO) has anti-inflammatory effects in human lung and tracheal epithelial cells by alleviating pro-inflammatory cytokines and chemokine signaling. Apple fruit, juice as well as apple peel can decrease Th 2 cell proliferation and

suppress allergic responsive IgE and mast cells (Boyer & Liu, 2004; Romieu et al., 2006). Accumulating of alternatively activated (M2) macrophages facilitates tissue repair by directly inhibiting pro-inflammatory pathways and shortening the pro-inflammatory phase by increasing the expression of the Arg1 gene in lungs proven that apple has wider lung health benefits beyond allergic asthma disease. Adding Boysenberry along with apple can reduce lung inflammation via increased macrophage activity by increased granulocyte apoptosis mediated by IL-17A and F (Shaw et al., 2016).

2.2 | Grapes

Along with nitrate contents, the fruit, as well as seed and skin, also contains other medicinally beneficial compounds such as resveratrol, quercetin, and anthocyanin (Gao et al., 2001). In the respiratory system, whole fruit and its components are reported to have protective activities against lung injury by inhibiting interleukin (IL)-8, granulocyte-macrophage colony-stimulating factor, TNF-α, eosinophils and neutrophil recruitment, modulation of Th1 and Th2 cells, etc., in various respiratory cell lines(Percival, 2009). The grape pomace and grape seeds extract also relieved some pathological complications of viral infection in the respiratory tract by inhibiting viral replication, reducing the expression of mucins and pro-inflammatory interleukins, including IL-1β, -6, and -88 (Kim et al., 2019).

2.3 | Berries

Strawberry and blackberry are rich sources of dietary nitrates. The strawberry extract reduced the level of Ig-G, Ig-M, and total immunoglobulin in hepatic rats. Strawberries may increase the immunological response of the immunity cells, T lymphocytes and monocytes, in obese people who are at greater risk for developing infections (Zunino et al., 2013). These red berries help support cell survival, growth, and antioxidant defense and can protect cells by repairing DNA damage (Giampieri et al., 2017). Blackberry extract also reported having immune-modulating activity by slowing down the expression of intercellular adhesion molecule-1 which is the indicator of arresting the infiltration of neutrophils (Wang & Lin, 2000). Blackberries can be your warm-weather fix immune booster.

2.4 | Citrus fruits

Citrus fruits are loaded with potent bioactive compounds antioxidants which can protect against immune-mediated inflammatory reactions by modulating cytokine-regulated pathways (Arya et al., 2020). These fruits are rich in vitamin C, which increases the bioavailability of nitric oxide from other sources, and can inhibit NF-KB activation by IL 1, TNF alpha, and block the production of IL 8. They ameliorate several aspects of immunity and enhancing epithelial barrier function, white blood cell migration to sites of infection, phagocytosis and microbial killing, and antibody production (Douglas et al., 1998). With 0.8 and 0.02 mg nitrates and nitrites per gram, orange is the best source of NO donor among the other citrus fruits (Hord et al., 2009). Citrus fruits also soothe the bronchioles, liquefies the sputum which prevents respiratory infections (Padhani et al., 2020). It can also inhibit cytokine-stimulated inflammation in human primary airway epithelial cells by inhibiting ERK1/2 phosphorylation (Yildiz et al., 2015).

2.5 | Carrots and radish

Carrot is one of the highest natural sources of beta carotene (an anti-oxidant) as well as it contains essential various amino acids for the human body. One such amino acid is L-arginine which acts as a precursor for the biosynthesis of NO (Madu & Bello, 2018). Carrots have been shown to protect cells from oxidative stress and increase the activity of glutathione transferase for cytoprotective effect (Sies, 1993). Carrots have also been shown to reduce inflammation induced by Toll-like receptor 4 agonists in macrophage cells. It also exhibited a cytoprotective effect when tested in alveolar epithelial cells suggesting that carrot can help in preventing the alveolar damage induced by the COVID-induced immune response (Alves-Silva et al., 2016). Carotenoids in carrots aid to regulate immunological function by boosting lymphocyte proliferation and cytotoxic T-cell activity.

Another popular vegetable, radish, contains beneficial antioxidants as well as a chemical known as nitric oxide, which is thought to lower blood pressure and hence reduce the risk of stroke or heart attack. Radish has been shown to inhibit the secretion of IL 6 and so reduce the concentration of neutrophils in the lungs. Additionally, bioactive components found in the hydro-alcoholic extract of radish were found to significantly reduce TGF-1 levels, preventing pulmonary fibrosis from worsening (Asghari et al., 2015). Water extract of radish showed a prophylactic effect against A/PR 8/34 influenza virus-induced experimental infection in mice. The modification of isoenzymatic structures, especially phosphatases, and the decrease in hemagglutinating titers (of lung extract) produced by radish extract has been reported to have the potential effect of decreasing the mortality rate and increasing the mean survival time of the influenza-infected mice (Prahoveanu & Eşanu, 1990).

Both the carrots and radish protect the cell by modulating immune function by enhancing lymphocyte proliferation and cytotoxic T-cell activity and through TLR4-MAPK/NF-KB signaling pathway in macrophages. They also help in forming healthy tissues in the lungs and increase resistance against respiratory infections by the production of interleukin-10 (Romieu et al., 2006). All the results published show evidence of their potential role in preventing or modulating the physiological effects of lung disorders as complementary medicine.

2.6 | Beetroot

Beets are rich in natural chemicals called nitrates, and through a chain reaction, the body converts nitrates into nitric oxide, which helps in improving blood flow and blood pressure. Beetroot juice reduced symptoms of cold and sickness, and those with asthma showed the greatest benefit. Owing to the high levels of nitrates present in beetroot, drinking its juice can increase blood oxygenation levels which can indirectly boost the immune system against many pathogens. Preliminary evidence demonstrates its special asthma benefits by decreasing asthmatic attack exacerbations due to respiratory infections (Ritz et al., 2019). In a randomized controlled crossover trial study, physical performance in COPD patients was assessed after supplementation with dietary beetroot juice. After 7 days of interventional study, there was an increased plasma nitrite concentration concerning reduced blood pressure level and optimizes the oxygen uptake indicates that beetroot juice could able to alleviate the cardiovascular complication in lung/respiratory disorders especially COVID infections (Friis et al., 2017). Ingestion beetroot juice increases F_ENO_{50} (fraction of exhaled NO at a flow rate of 50 ml per second) robustly which is likely to persist for over 3 hr in healthy individuals. F_ENO_{50} is a clinically used marker of allergic airway inflammation as part of the innate immune system's defense against pathogens, and it has been related to a reduction in protection against bronchoconstriction. Beetroot, a good source of NO, may provide potential long-term benefits on airway health (Kroll et al., 2018). All the observed evidence delivers the information that, beetroot can improve metabolism and immune functions in the respiratory system which may help to keep the lungs safe during corona invasion.

2.7 | Mushroom

Bioactive compounds particularly present in mushroom shows anti-inflammatory, anti-viral, anti-allergic as well as immunomodulatory effects (Elsayed et al., 2014). It can activate the host immune response by enhancing the immune-system-dependent responses of natural NK cells, T cells, B cells, and macrophages. It also causes a cascade of cytokine activations, including tumor necrosis factor (TNF)-alpha and a variety of interleukin variants, to be released, as well as opsonic and non-opsonic phagocytosis (Sliva, 2012). The activation of NK cells, macrophages, and cytokine secretion in T cells in preclinical and clinical trials showed that mushroom extract enhances the host's native immunity by activating the dendritic cell. Whole edible mushrooms and their extract enhance innate and adaptive immune by stimulating cell surface receptor activity of neutrophils and macrophages, modulate antigen-presenting cell functions, and promote antigen presentation by Th1/Th2 cells in viral infection (Borchers et al., 2008; Johnson et al., 2009). Natural cordyceps help to treat asthma, cough, colds, and tuberculosis, as well as reducing inflammation and slowing the aging of bronchial cells (Panda & Swain, 2011). Mushroom maintains the respiratory epithelial integrity by preventing excessive development of mucus as well as and mucolytic capacity (Sliva, 2012). Mushrooms affect the un-coating and binding of viral proteins to the host cellular receptor by acting on the virus particle directly. Lowering the levels of unique immunoglobulin (Ig)E and IgG1 by medicinal mushrooms will also benefit in preventing the severity of lung infections by its anti-allergic action (Hetland et al., 2020).

2.8 | Leafy vegetables

Spinach, a popular green leafy vegetable, has the ability to remove mucus and aid in the treatment of pulmonary illnesses. The highest concentrations of nitrates and nitrites were found in spinach (926 and 0.27 mg/serving of raw spinach, respectively) (Merino et al., 2017). In the ancient times, asthma, bronchitis, TB lung inflammation, cough, sneezing, and other respiratory disorders were treated with an expectorant tonic made with an infusion of fresh spinach leaves prepared with two tablespoons of fenugreek seeds combined with honey. (Bakhru, 2005). Aqueous extract of spinach shows anti-allergic activity by regulating the signaling pathways (suppressing Ca_2^+ mobilization) involved in mast cell degranulation induced by the antigen–antibody interaction in RBL-2H3 cells (Ishida et al., 2013). The immunomodulatory action of spinach is explained by the fact that it reduces the number of CD4 cells and the lung levels of IL-4 and IL-13 in ovalbumin-challenged mice. It can also activate macrophages through TLRs and enhances the phagocytosis of foreign pathogens (Ishida et al., 2016). Another commonly used leafy vegetable found in the Indian kitchen is the green lettuce rich in nitrate has been reported for its immune-enhancing activity by its ability to produce NO, which brings its beneficial role as a possible immune-enhancing agent (Seo & Jeong, 2020). It can stimulate TLR4, p38, JNK, and NF-βB which continually increases the development of immune defense, which is thought to improve the human body's immune function by activating macrophages (Reddy et al., 2015). Broccoli, another nitrate-rich leafy vegetable (25 and 0.09 mg/half cup) that contains sulforaphane and other phytochemicals, helps to protect against asthma-causing respiratory inflammation.

2.9 | Constituents other than NO found in fruits and vegetables with anti-COVID effect

Most scientists have begun to investigate the effects of various naturally occurring organic compounds for the treatment of COVID infections. Many phytoconstituents were investigated and reported for their ability to bind with the proteins involved in the entry and replication of the virus by computational and in-vitro studies.

In terms of their pharmacophore structure, Mehany and colleagues reviewed and conceptualized the possible mechanisms of polyphenols such as triterpenoids, anthraquinones, flavonoids, and tannins. They proposed that natural polyphenols could be a better anti-COVID-19 designs for drug development (Mehany et al., 2021).

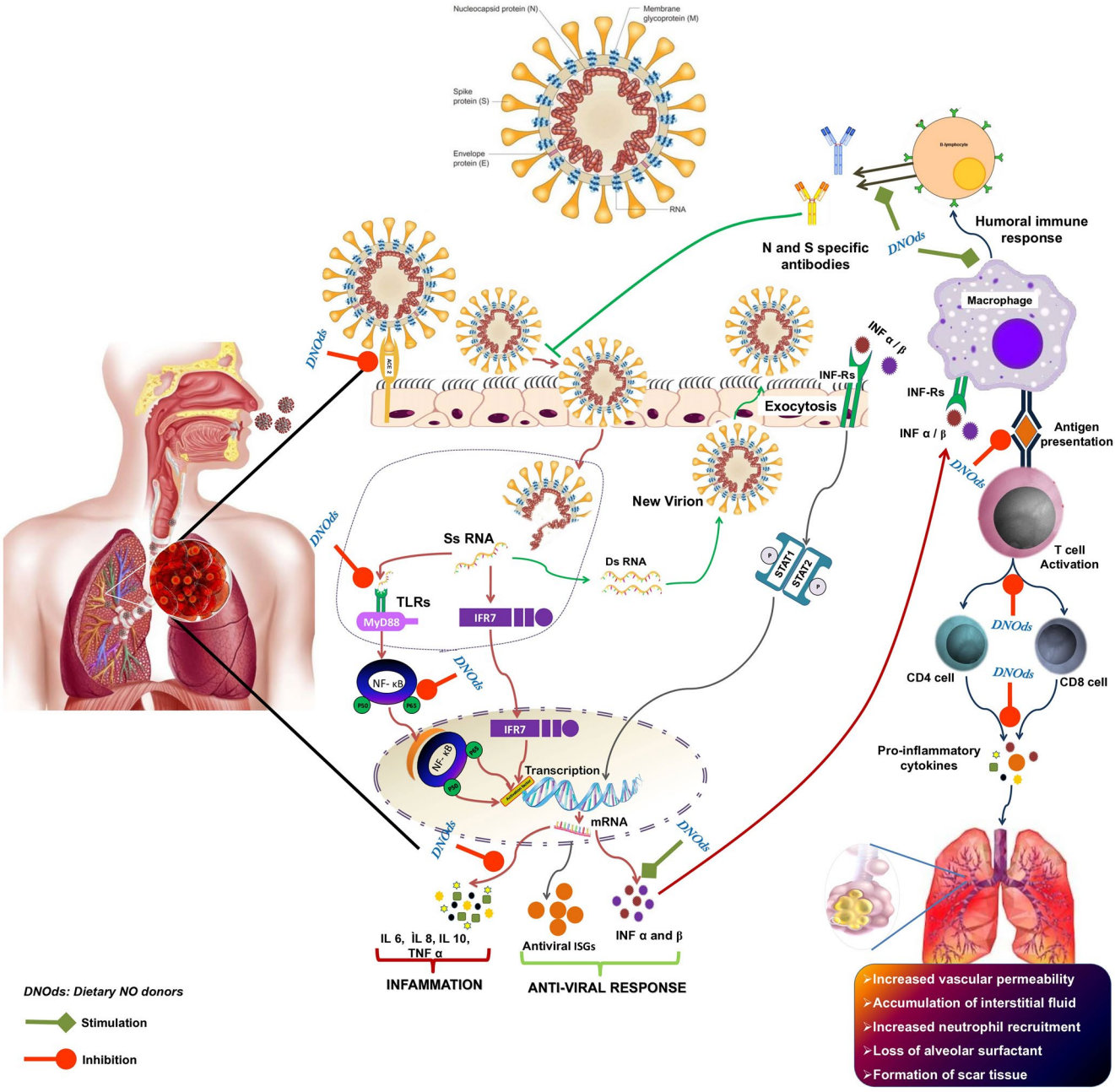

FIGURE 1 The involvement of immune and inflammatory signaling cascade after the invasion of the virus in bronchial epithelial cells and possible sites of action of donors of nitric oxide. Toll-like receptors recognize the virus and activates NFκB via MyD88 which activates the expression of pro-inflammatory cytokines. This modulates the adaptive immune response by recruiting and activating macrophages, B and T lymphocytes in order to orchestrate the elimination of the virus. The expression of interferon stimulated genes inhibits viral activity. An imbalanced immune response can lead to further hyper inflammation and lung injury causing the severity symptoms in COVID-19 infected patients

Flavanoids such as apigenin, fiestin, chrysin, hesperitin, luteolin, naringenin, quercetin, and rutin found in common fruits and vegetables such as oranges, grapes, apples, berries, carrots, spinach, and tomatoes are thought to be effective against Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) as they have a higher binding affinity with proteases (3Cl pro and PL pro), spike protein, RNA-dependent RNA polymerase (RdRp), and angiotensin-converting enzyme II receptor. They hypothesized that flavonoids may reduce the entrance ability, human transmission capability, and inflammatory response (Jain et al., 2021; Mouffouk et al., 2021).

Flavanoids can also act as an immune modulator by regulating mediators such as toll-like receptors (TLRs) and bromodomain-containing protein 4 (BRD4), as well as the activation of the nuclear factor erythroid-derived 2-related factor 2 (Nrf2), which could be effective in regulating the cytokine storm during SARS-CoV-2 infection (Liskova et al., 2021). Hydrolyzable tannins like pedunculagin,

tercatain, and castalin showed strong interactions with binding sites such as Cys145 and His41 of the SARS-CoV-2–3 CLpro protein. This led to the conclusion that these three hits could be used as possible anti-SARS-CoV-2 lead compounds to combat COVID-19 (Khalifa et al., 2020). In addition, plant flavan-3-ols and dimeric proanthocyanidins found in grapes had a greater affinity with the major protease (Mpro) enzyme of SARS-Cov-2, and an in-vitro assay demonstrated the inhibitory effect.

All of these evidences suggest that consuming NO-containing fruits and vegetables with these compounds could also result in synergistic health benefits, such as anti-inflammation, immunomodulatory, and antiviral properties, which should be taken into account and heavily incorporated in future development steps.

3 | CONCLUSION

Good nutrition is crucial for health, particularly in times when the immune system might need to fight back. Hence, it was understood that nitrate and nitrite-rich natural diet supplementation can halt instantly the progression of the infection by acting via multiple pathways (Figure 1) and also can mitigate many of the co-morbidities associated with COVID-19. Nonetheless, even with these limited ingredients, one can continue eating a healthful diet that supports good health so that such home-based inexpensive remedies can be easily implemented to break the chain of this highly pandemic spreading of the disease.

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CONFLICT OF INTEREST

We wish to confirm that there are no known conflicts of interest associated with this publication.

AUTHOR CONTRIBUTIONS

Conceptualization; Data curation; Methodology; Writing-original draft: S. Swathi Krishna *Formal analysis*: Arumugam Thennavan *Conceptualization; Formal analysis; Supervision*: S K. Kanthlal

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

S K Kanthlal https://orcid.org/0000-0003-2655-846X

REFERENCES

Adithya, J., Nair, B., Aishwarya, S., & Nath, L. R. (2020). The plausible role of Indian traditional medicine in combating corona virus (SARS-CoV 2): A mini-review. *Current Pharmaceutical Biotechnology*, *22*(7), 906–919. https://doi.org/10.2174/1389201021666200807111359

Akerstrom, S., Gunalan, V., Keng, C. T., Tan, Y. J., & Mirazimi, A. (2009). Dual effect of nitric oxide on SARS-CoV replication: Viral RNA production and palmitoylation of the S protein are affected. *Virology*, *395*(1), 1–9. https://doi.org/10.1016/j.virol.2009.09.007

Akerstrom, S., Mousavi-Jazi, M., Klingstrom, J., Leijon, M., Lundkvist, A., & Mirazimi, A. (2005). Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus. *Journal of Virology*, *79*(3), 1966–1969. https://doi.org/10.1128/JVI.79.3.1966-1969.2005

Al-Sehemi, A. G., Olotu, F. A., Dev, S., Pannipara, M., Soliman, M. E., Carradori, S., & Mathew, B. (2020). Natural products database screening for the discovery of naturally occurring SARS-Cov-2 spike glycoprotein blockers. *ChemistrySelect*, *5*(42), 13309–13317. https://doi.org/10.1002/slct.202003349

Alves-Silva, J. M., Zuzarte, M., Gonçalves, M. J., Cavaleiro, C., Cruz, M. T., Cardoso, S. M., & Salgueiro, L. (2016). New claims for wild carrot (Daucus carota subsp. carota) essential oil. *Evidence-Based Complementary and Alternative Medicine*, *2016*, 1–10. https://doi.org/10.1155/2016/9045196

Arya, V. S., Kanthlal, S. K., & Linda, G. (2020). The role of dietary polyphenols in inflammatory bowel disease: A possible clue on the molecular mechanisms involved in the prevention of immune and inflammatory reactions. *Journal of Food Biochemistry*, *44*(11), e13369. https://doi.org/10.1111/jfbc.13369

Asghari, M. H., Hobbenaghi, R., Nazarizadeh, A., & Mikaili, P. (2015). Hydro-alcoholic extract of *Raphanus sativus* L. var niger attenuates bleomycin-induced pulmonary fibrosis via decreasing transforming growth factor β1 level. *Research in pharmaceutical sciences*, *10*(5), 429–435. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4691963/.

Baby, B., Devan, A. R., Nair, B., & Nath, L. R. (2020). The impetus of COVID -19 in multiple organ affliction apart from res-piratory infection: Pathogenesis, diagnostic measures and current treatment strategy. *Infectious Disorders Drug Targets*. https://doi.org/10.2174/1871526520999200905115050

Bakhru, H. K. (2005). *Food that heal the natural way to good health* (17th ed.). Orient Paperbacks.

Borchers, A. T., Krishnamurthy, A., Keen, C. L., Meyers, F. J., & Gershwin, M. E. (2008). The immunobiology of mushrooms. *Experimental Biology and Medicine (Maywood, N.J.)*, *233*(3), 259–276. https://doi.org/10.3181/0708-MR-227

Boyer, J., & Liu, R. H. (2004). Apple phytochemicals and their health benefits. *Nutrition journal*, *3*, 5. https://doi.org/10.1186/1475-2891-3-5

Coppola, M., & Mondola, R. (2020). Potential unconventional medicines for the treatment of SARS-CoV-2. *Drug Research*, *70*(6), 286–286. https://doi.org/10.1055/a-1170-4624

Deakin, A. M., Payne, A. N., Whittle, B. J., & Moncada, S. (1995). The modulation of IL-6 and TNF-alpha release by nitric oxide following stimulation of J774 cells with LPS and IFN-gamma. *Cytokine*, *7*(5), 408–416. https://doi.org/10.1006/cyto.1995.0056

Douglas, R. M., Chalker, E. B., & Treacy, B. (1998). Vitamin C for preventing and treating the common cold. *The Cochrane Database of Systematic Reviews*, (2), CD000980. https://doi.org/10.1002/14651858.CD000980

Duddu, P. (2020). Coronavirus treatment: Vaccines/drugs in the pipeline for COVID-19. https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/

Elsayed, E. A., El Enshasy, H., Wadaan, M. A. M., & Aziz, R. (2014). Mushrooms: A potential natural source of anti-inflammatory compounds for medical applications. *Mediators of inflammation*, *2014*. https://doi.org/10.1155/2014/805841

Friis, A. L., Steenholt, C. B., Løkke, A., & Hansen, M. (2017). Dietary beetroot juice – Effects on physical performance in COPD patients: A randomized controlled crossover trial. *International journal of*

chronic obstructive pulmonary disease, *12*, 1765–1773. https://doi.org/10.2147/COPD.S135752

Gao, X., Xu, Y. X., Janakiraman, N., Chapman, R. A., & Gautam, S. C. (2001). Immunomodulatory activity of resveratrol: Suppression of lymphocyte proliferation, development of cell-mediated cytotoxicity, and cytokine production. *Biochemical Pharmacology*, *62*(9), 1299–1308. https://doi.org/10.1016/s0006-2952(01)00775-4

Garcia-Larsen, V., Potts, J. F., Omenaas, E., Heinrich, J., Svanes, C., Garcia-Aymerich, J., Burney, P. G., & Jarvis, D. L. (2017). Dietary antioxidants and 10-year lung function decline in adults from the ECRHS survey. *European Respiratory Journal*, *50*(6), 1602286. https://doi.org/10.1183/13993003.02286-2016

Giampieri, F., Forbes-Hernandez, T. Y., Gasparrini, M., Afrin, S., Cianciosi, D., Reboredo-Rodriguez, P., Varela-Lopez, A., Quiles, J. L., Mezzetti, B., & Battino, M. (2017). The healthy effects of strawberry bioactive compounds on molecular pathways related to chronic diseases. *In Annals of the New York Academy of Sciences*, *1398*(1), 62–71. https://doi.org/10.1111/nyas.13373

Hetland, G., Tangen, J. M., Mahmood, F., Mirlashari, M. R., Nissen-Meyer, L. S. H., Nentwich, I., Therkelsen, S. P., Tjønnfjord, G. E., & Johnson, E. (2020). Antitumor, Anti-Inflammatory and Antiallergic Effects of Agaricus blazei Mushroom Extract and the Related Medicinal Basidiomycetes Mushrooms, Hericium erinaceus and Grifolafrondosa: A Review of Preclinical and Clinical Studies. *Nutrients*, *12*(5), 1339. https://doi.org/10.3390/nu12051339

Hord, N. G., Tang, Y., & Bryan, N. S. (2009). Food sources of nitrates and nitrites: The physiologic context for potential health benefits. *American journal of clinical nutrition*, *90*(1), 1–10. https://doi.org/10.3945/ajcn.2008.27131

Hosseini, B., Berthon, B. S., Wark, P., & Wood, L. G. (2017). Effects of Fruit and Vegetable Consumption on Risk of Asthma, Wheezing and Immune Responses: A Systematic Review and Meta-Analysis. *Nutrients*, *9*(4), 341. https://doi.org/10.3390/nu9040341

Ishida, M., Nishi, K., Watanabe, H., & Sugahara, T. (2013). Inhibitory effect of aqueous spinach extract on degranulation of RBL-2H3 cells. *Food Chemistry*, *136*(2), 322–327. https://doi.org/10.1016/j.foodchem.2012.08.079

Ishida, M., Ose, S., Nishi, K., & Sugahara, T. (2016). Immunostimulatory effect of spinach aqueous extract on mouse macrophage-like J774.1 cells and mouse primary peritoneal macrophages. *Bioscience, Biotechnology, and Biochemistry*, *80*(7), 1393–1402. https://doi.org/10.1080/09168451.2016.1146068

Jain, A. S., Sushma, P., Dharmashekar, C., Beelagi, M. S., Prasad, S. K., Shivamallu, C., Prasad, A., Syed, A., Marraiki, N., & Prasad, K. S. (2021). In silico evaluation of flavonoids as effective antiviral agents on the spike glycoprotein of SARS-CoV-2. *Saudi Journal of Biological Sciences*, *28*(1), 1040–1051. https://doi.org/10.1016/j.sjbs.2020.11.049

Johnson, E., Førland, D. T., Sætre, L., Bernardshaw, S. V., Lyberg, T., & Hetland, G. (2009). Effect of an extract based on the medicinal mushroom Agaricus blazei murill on release of cytokines, chemokines and leukocyte growth factors in human blood ex vivo and in vivo. *Scandinavian Journal of Immunology*, *69*(3), 242–250. https://doi.org/10.1111/j.1365-3083.2008.02218.x

Khalifa, I., Zhu, W., Mohammed, H. H. H., Dutta, K., & Li, C. (2020). Tannins inhibit SARS-CoV-2 through binding with catalytic dyad residues of 3CLpro: An in silico approach with 19 structural different hydrolysable tannins. *Journal of Food Biochemistry*, *44*(10), e13432. https://doi.org/10.1111/JFBC.13432

Kim, S. J., Lee, J. W., Eun, Y. G., Lee, K. H., Yeo, S. G., & Kim, S. W. (2019). Pretreatment with a grape seed proanthocyanidin extract downregulates proinflammatory cytokine expression in airway epithelial cells infected with respiratory syncytial virus. *Molecular Medicine Reports*, *19*(4), 3330–3336. https://doi.org/10.3892/mmr.2019.9967

Kroll, J. L., Werchan, C. A., Rosenfield, D., & Ritz, T. (2018). Acute ingestion of beetroot juice increases exhaled nitric oxide in healthy individuals. *PLoS One*, *13*(1), e0191030. https://doi.org/10.1371/journal.pone.0191030

Percival S, S (2009). Grape consumption supports immunity in animals and humans. *Nutrients*, *139*(9), 1801S–1805S. https://doi.org/10.3945/jn.109.108324

Kumar, R., Harilal, S., Al-Sehemi, A. G., Mathew, G. E., Carradori, S., & Mathew, B. (2021). The Chronicle of COVID-19 and Possible Strategies to Curb the Pandemic. *Current Medicinal Chemistry*, *28*(15), 2852–2886. https://doi.org/10.2174/0929867327666200702151018

Liskova, A., Samec, M., Koklesova, L., Samuel, S. M., Zhai, K., Al-Ishaq, R. K., Abotaleb, M., Nosal, V., Kajo, K., Ashrafizadeh, M., Zarrabi, A., Brockmueller, A., Shakibaei, M., Sabaka, P., Mozos, I., Ullrich, D., Prosecky, R., La Rocca, G., Caprnda, M., Kubatka, P. (2021). Flavonoids against the SARS-CoV-2 induced inflammatory storm. In *Biomedicine and pharmacotherapy*, *138*, 111430. https://doi.org/10.1016/j.biopha.2021.111430

Lv, X., Zhao, S., Ning, Z., Zeng, H., Shu, Y., Tao, O., Xiao, C., Lu, C., & Liu, Y. (2015). Citrus fruits as a treasure trove of active natural metabolites that potentially provide benefits for human health. *Chemistry Central Journal*, *9*(68). https://doi.org/10.1186/S13065-015-0145-9

Madu, A. N., & Bello, S. E. (2018). Quantitative determination of some amino acids and nutritional components of selected tropical fruits. *International Journal of Scientific Research in Chemistry*, *3*(2), 8–10. https://ijsrch.com/IJSRCH18322.

Mehany, T., Khalifa, I., Barakat, H., Althwab, S. A., Alharbi, Y. M., & El-Sohaimy, S. (2021). Polyphenols as promising biologically active substances for preventing SARS-CoV-2: A review with research evidence and underlying mechanisms. *Food Bioscience*, *40*. https://doi.org/10.1016/J.FBIO.2021.100891

Merino, L., Örnemark, U., & Toldrá, F. (2017). Chapter Three - Analysis of Nitrite and Nitrate in Foods: Overview of Chemical, Regulatory and Analytical Aspects. In T. Fidel (Ed.), *Advances in Food and Nutrition Research* (Vol. *81*. pp. 65–107). Academic Press. https://doi.org/10.1016/bs.afnr.2016.11.004

Mouffouk, C., Mouffouk, S., Mouffouk, S., Hambaba, L., & Haba, H. (2021). Flavonols as potential antiviral drugs targeting SARS-CoV-2 proteases (3CL(pro) and PL(pro)), spike protein, RNA-dependent RNA polymerase (RdRp) and angiotensin-converting enzyme II receptor (ACE2). *European journal of pharmacology*, *891*, 173759. https://doi.org/10.1016/j.ejphar.2020.173759

Padhani, Z. A., Moazzam, Z., Ashraf, A., Bilal, H., Salam, R. A., Das, J. K., & Bhutta, Z. A. (2020). Vitamin C supplementation for prevention and treatment of pneumonia. *The Cochrane database of systematic reviews*, *4*(4), CD013134. https://doi.org/10.1002/14651858.CD013134.pub2

Panda, A. K., & Swain, K. C. (2011). Traditional uses and medicinal potential of Cordyceps sinensis of Sikkim. *Journal of Ayurveda and integrative medicine*, *2*(1), 9–13. https://doi.org/10.4103/0975-9476.78183

Percival, S. S. (2009). Grape consumption supports immunity in animals and humans. *The Journal of Nutrition*, *139*(9), 1801S–1805S. https://doi.org/10.3945/jn.109.108324

Prahoveanu, E., & Eşanu, V. (1990). The effects of aqueous extracts of Raphanus niger on an experimental influenza infection in mice and on the enzyme polymorphism in lung tissue extracts. *Revue roumaine de virologie (Bucharest, Romania : 1990)*, *41*(2), 113–117.

Reddy, S. A., Shelar, S. B., Dang, T. M., Lee, B. N. C., Yang, H., Ong, S. M., Ng, H. L., Chui, W. K., Wong, S. C., & Chew, E. H. (2015). Sulforaphane and its methylcarbonyl analogs inhibit the LPS-stimulated inflammatory response in human monocytes through modulating cytokine production, suppressing chemotactic migration and phagocytosis in a NF-κB- and MAPK-dependent manner. *International immunopharmacology*, *24*(2), 440–450. https://doi.org/10.1016/j.intimp.2014.12.037

Ritz, T., Werchan, C. A., Kroll, J. L., & Rosenfield, D. (2019). Beetroot juice supplementation for the prevention of cold symptoms associated

with stress: A proof-of-concept study. *Physiology & behavior*, *202*, 45–51. https://doi.org/10.1016/j.physbeh.2019.01.015

Romieu, I., Varraso, R., Avenel, V., Leynaert, B., Kauffmann, F., & Clavel-Chapelon, F. (2006). Fruit and vegetable intakes and asthma in the E3N study. *Thorax*, *61*(3), 209–215. https://doi.org/10.1136/thx.2004.039123

Seo, H.-J., & Jeong, B. (2020). Immune-Enhancing Effects of Green Lettuce (Lactuca sativa L.) Extracts through the TLR4-MAPK/NF-κB Signaling Pathways in RAW264.7 Macrophage Cells. *Korean Journal of Plant Reources*, *33*(3), 183–193. https://doi.org/10.7732/kjpr.2020.33.3.183

Shaw, O. M., Hurst, R. D., Cooney, J., Sawyer, G. M., Dinnan, H., & Martell, S. (2021). Boysenberry and apple juice concentrate reduced acute lung inflammation and increased M2 macrophage-associated cytokines in an acute mouse model of allergic airways disease. *Food Science & Nutrition*, *9*(3), 1491–1503. https://doi.org/10.1002/FSN3.2119

Shaw, O. M., Hurst, R. D., & Harper, J. L. (2016). Boysenberry ingestion supports fibrolytic macrophages with the capacity to ameliorate chronic lung remodeling. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, *311*(3), L628–L638. https://doi.org/10.1152/ajplung.00309.2015

Sies, H. (1993). Strategies of antioxidant defense. *European journal of biochemistry*, *215*(2), 213–219. https://doi.org/10.1111/j.1432-1033.1993.tb18025.x

Sliva, D. (2012). Cellular and physiological effects of Ganoderma lucidum (Reishi). *Mini reviews in medicinal chemistry*, *4*(8), 873–879. https://doi.org/10.2174/1389557043403323

Uehara, E. U., Shida, B. de S., & de Brito, C. A. (2015). Role of nitric oxide in immune responses against viruses: beyond microbicidal activity. *Inflammation Research*, *64*(11), 845–852. https://doi.org/10.1007/s00011-015-0857-2

Wang, S. Y., & Lin, H. S. (2000). Antioxidant activity in fruits and leaves of blackberry, raspberry, and strawberry varies with cultivar and developmental stage. *Journal of Agricultural and Food Chemistry*, *48*(2), 140–146. https://doi.org/10.1021/jf9908345

Wu, R., Wang, L., Kuo, H. C. D., Shannar, A., Peter, R., Chou, P. J., Li, S., Hudlikar, R., Liu, X., Liu, Z., Poiani, G. J., Amorosa, L., Brunetti, L., & Kong, A. N. (2020). An update on current therapeutic drugs treating COVID-19. *Current pharmacology reports*, *11*, 1–15. https://doi.org/10.1007/s40495-020-00216-7

Yildiz, G., Yildiz, Y., Ulutas, P., Yaylali, A., & Ural, M. (2015). Resveratrol pretreatment ameliorates TNBS colitis in rats. *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery*, *9*(2), 134–140. https://doi.org/10.2174/1872214809666150806105737

Zunino, S. J., Storms, D. H., Freytag, T. L., Mackey, B. E., Zhao, L., Gouffon, J. S., & Hwang, D. H. (2013). Dietary strawberries increase the proliferative response of CD3/CD28-activated CD8+ T cells and the production of TNF-α in lipopolysaccharide-stimulated monocytes from obese human subjects. *The British journal of nutrition*, *110*(11), 2011–2019. https://doi.org/10.1017/S0007114513000937

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