Nutrition and Dietary Supplements

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REVIEW

Potential Nutraceuticals for COVID-19

This article was published in the following Dove Press journal:
Nutrition and Dietary Supplements

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Abstract: SARS-CoV-2 infection has caused, and is continuing to cause, considerable human suffering. Studies on the viral pathogenesis has resulted in convergent findings from several lines of evidence on the entry and spread of the virus in the host. These studies have also revealed a strong association between innocuous inflammation, ageing and metabolic disorders, with SARS-CoV-2 infection and its prognosis. Diet helps modulate inflammation, and nutraceuticals can inhibit viral entry. Hence, we have collated literature on antiviral nutraceuticals effective against other similar coronaviruses. The objective of this study is to comprehensively review available information on the antiviral activity of nutraceuticals and to discuss the implications of these findings in designing a diet that would boost the innate immunity and act as preventive care against COVID-19. This review highlights the fundamental impact of nutraceuticals and diet on inhibition of viral entry and provides a new perspective on the prevention and treatment of COVID-19.

Keywords: SARS-CoV-2, diet, plant protease inhibitors, polyphenols, bioactive peptides

Introduction

SARS-CoV-2 has disrupted global health and economic wellbeing since the beginning of 2020. The regional office of World Health Organization (WHO) in China was first alerted to the virus infection in Wuhan on December 31, 2019 and termed the infection as an epidemic on March 11, 2020. Since then, laboratories across the globe have been collaborating to develop vaccines and therapeutic agents for this novel coronavirus.

The SARS-CoV-2 belongs to a group of viruses called the coronaviruses. These are single-stranded, positive sense, RNA viruses, enveloped in a helical capsid with spike shaped trans-membrane proteins. They can further be classified into four subtypes: alpha, beta, delta, and gamma.[1] The coronaviruses are capable of infecting both humans and animals and have the ability to jump the species barrier thereby accelerating the spread of the disease into an epidemic or a pandemic. The severe acute respiratory syndrome coronaviruses (SARS-CoV and SARS-CoV-2) and Middle East respiratory syndrome coronavirus (MERS-CoV) are the three highly pathogenic coronaviruses. The remaining four (HCoV-NL63, HCoV-229E. HCoV-OC43, and HCOV-HKU1) human coronaviruses are less virulent.[2]

What makes the SARS-CoV-2 threatening is not just the viral infection but the accompanying cytokine storm and other associated comorbidities. Analysis of clinical data from 326 confirmed COVID-19 patients in Shanghai revealed IL-6 and IL-8 to show the most significant changes and the levels of these two interleukins inversely co-related with the lymphocyte count.[3] A reduced $CD4^+/CD8^+$ ratio is also a manifestation of the disease. A detailed explanation of the host immune response and the viral evasion methods follows in the later part of this paper.

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http://doi.org/10.2147/NDS.S294231

Initial genomic phylogeny testing revealed that the SARS-CoV-2 virus shared about 79% and 50% gene similarity with SARS-CoV and MERS-CoV, respectively.[2] Therefore, the initial treatment has included therapeutics known to be effective against SARS-CoV and MERS-CoV for SARS-CoV-2.

In this article we give an overview of the present understanding of the viral lifecycle and host immune responses, which would form the basis for selecting nutraceuticals and natural products that can be potentially explored both as therapeutic and preventive interventions for the SARS-CoV-2 infection.

Virus Replication Cycle and Potential Therapeutic Targets

Understanding the cellular basis of SARS-CoV-2 infection could reveal treatments that prevent the development to a severe disease, and thus reduce mortality. Figure 1 represents a simplified illustration of the infection cycle of SARS-CoV-2.

The spike glycoprotein (S) is a 180–200 kDa transmembrane homotrimer which recognizes and binds to the host angiotensin-converting enzyme 2 (ACE2) receptors.[4] The S protein can further be subdivided into S1 (the homotrimer head) and the S2 protein (the tail part). Figure 2 gives an enlarged view of the spike protein of the virus. ACE2 is a human receptor largely found in the respiratory and intestinal epithelial cells but it is also present in the kidney, heart, brain, etc. ACE2 has a short C-terminal intracellular domain and a long N-terminal extracellular domain, to which the S2 head of the virus binds.[5] The spike protein mediates two essential events: binding to ACE2 by the amino-terminal region and fusion of viral and cellular membranes through the carboxyl terminal region.

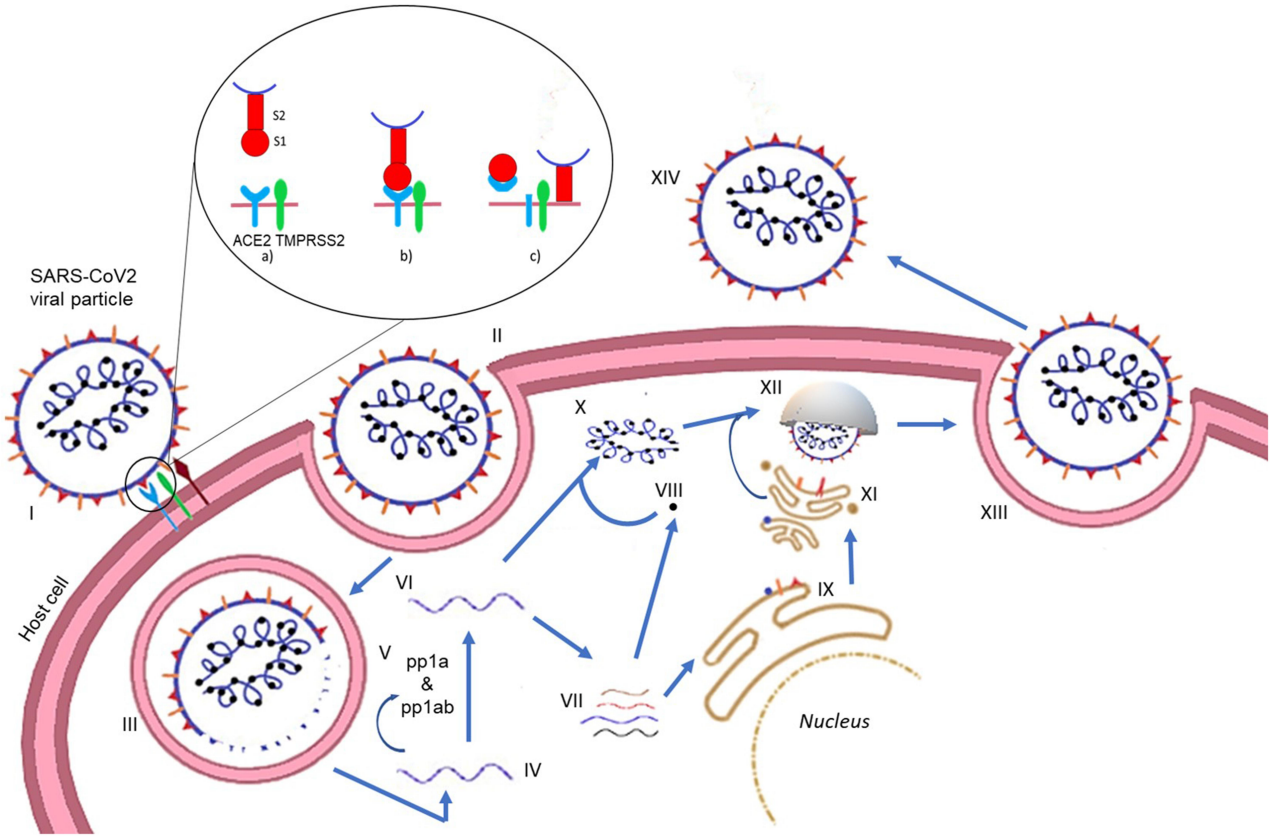

Figure 1 SARS-CoV-2 replication cycle. (I) The spike protein (S) on SARS-CoV-2 facilitates attachment to the host cell through the ACE2, TMPRSS2. The S protein has two subunits, S1 and S2 (a). The S1 subunit attaches to ACE2 (b) following which TMPRSS2 cleaves ACE2 (c). The S2 subunit facilitates fusion of the viral particle with the host cell membrane thereby leading to viral entry (c). (II and III) Alternatively, the viral entry can also occur via endocytosis. (IV) Release of the viral genome (+ strand) after entry. (V) Translation of the strand leads to the formation of polyproteins (pp1a and pp1ab) which are cleaved by the main protease (MPro) and papain-like protease (PLPro) into the nonstructural proteins (nsps). (VI) The genome is replicated by RdRp. (VII) The transcription of the genome gives the subgenomic transcripts which encode the structural proteins. (VIII) The nucleocapsid is translated in the cytoplasm. (IX) The other structural proteins are translated in the endoplasmic reticulum (ER). (X) The nucleocapsid and the genomic strand form the genomic RNA. (XI) The structural proteins are glycosylated in the golgi bodies. (XII) A budding vesicle forms with the virion particles assembling. (XIII) Exocytosis of the assembled viral particle occurs. (XIV) The newly released viral particles can now infect other host cells.

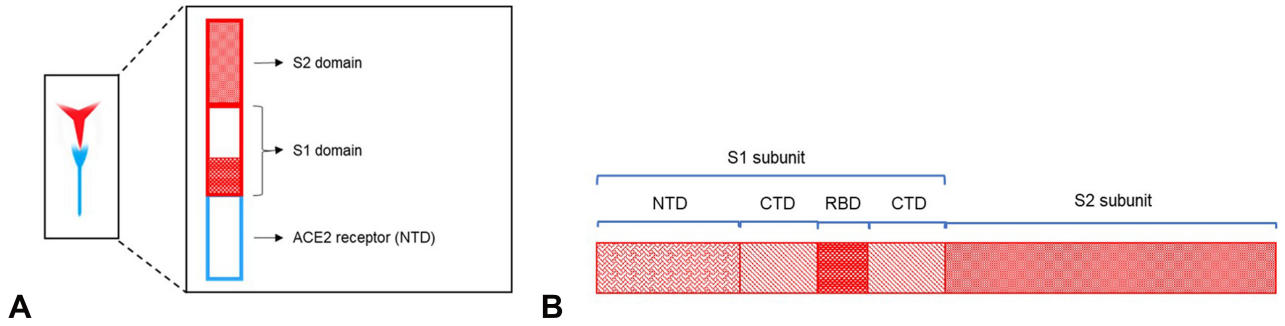

Figure 2 Enlarged view of spike protein. (**A**) The binding of the S protein to the *ACE2* receptor occurs at the receptor binding domain (RBD site) of the S1 domain, binding to the N-terminal domain of the host receptor, (**B**) the amino- or N-terminal domain (NTD), carboxy- or C-terminal domain (CTD) and the receptor binding domain (RBD) of the S1 subunit and the S2 subunit that constitute the spike protein (S).

The spike protein bound to ACE2 can be cleaved by two enzymes, the transmembrane serine protease 2 (TMPRSS2) at the S2 site and by furin at the S1/S2 connection site.[6] TMPRSS2 acts at monobasic cleavage sites, ie it cleaves at a single arginine or lysine residue. Furin, however, cleaves at a polybasic site.[6] Infection of lung cells requires host proteolytic activation of spike at a polybasic furin cleavage site. Cleavage by the furin protease, therefore, can expand SARS-CoV-2 cell tropism and may have facilitated transmission from bats to humans.[2] SARS-CoV-2 tropism is, therefore, dependent on expression of cellular proteases, as well as ACE2.

However, TMPRSS2 is not expressed in all the cells expressing ACE2 suggesting the existence of alternative pathways for viral entry such as through use of cathepsin L and cathepsin B.[7] However, this is a matter of debate since studies have also found that cathepsins are not required for SARS-CoV-2 infection.[6] Post-cleavage, the virus can enter the host cells either through membrane fusion or through endocytosis.[5]

Two-thirds of the viral genome produces two polypeptides, pp1a and pp1ab which are processed by the viral proteases chymotrypsin like cysteine protease (3CLPro) or main protease (MPro) and one or two papain-like proteases into 16 nonstructural proteins (nsps) that play diverse roles in the subsequent viral replication and infection.[8] The remaining one-third of the genome encodes for the main viral proteins namely, the spike protein, the nucleocapsid protein, the membrane protein, and the envelope protein. Replication occurs within double membrane vesicles (DMVs) which comprise RNA-dependent RNA polymerase (RdRp) and the nsps. The sub-genomic particles manufactured here then move towards the endoplasmic reticulum golgi complex compartment where they undergo maturation. The virulent particles present in vesicles are further released through the process of exocytosis.[1] Thus, the life cycle of the virus with the host consists of five steps: attachment, penetration, biosynthesis, maturation, and release.

Therapeutics, therefore, can target either the viral proteins or the host proteases. Since the host proteases play multiple roles within the human body, targeting the host proteases may also interfere with other physiological activities in the host body and so caution must be exerted in this approach. Hence, viral proteins seem more attractive and safe targets.

In case of the SARS-CoV-2 virus, the following have been identified as the potential therapeutic targets: the spike glycoprotein (S), the envelope glycoprotein (E), the nucleocapsid protein (NP), the membrane protein (M), the papain like protease (PLPro) or the chymotrypsin like cysteine protease (CLPro), (also known as the main protease MPro) and the RNA dependent RNA polymerase (RdRp). In addition to this, certain nsps could also be targeted. The nsp13 helicase is an important component for replication of the virus which is target for many virus inhibitors.[9] Nsp10 plays a major role in viral transcription wherein nsp14 3′-5′ exoribonuclease and nsp16 2′-O methyltransferase are stimulated by playing a lead role in viral mRNAs cap methylation.[10]

The following sections give an overview of the different plant-derived ingredients and more specifically nutraceuticals, that can potentially be developed into therapeutic molecules targeting one or more multiple targets discussed above.

Nutraceuticals and Coronavirus Infection

Nutraceuticals is a portmanteau of "nutrition" and "pharmaceuticals". The structure of the word itself directs us towards

the dual use of these molecules: for preventive health care (source of nutrients that will prevent the occurrence of disease) and as therapeutic molecules (like pharmaceuticals taken to cure a disorder or disease). Table 1 mentions the details of a few nutraceuticals that have been tested against the earlier coronaviruses SARS-CoV and MERS-CoV.

Yi et al[11] performed in vitro and animal testing on multiple small molecules and found luteolin to be effective in blocking the S2 protein of the SARS-CoV virus. The SARS-CoV and SARS-CoV-2 S proteins share about 76% amino acid similarity.[7] Since both the viruses bind to the same host receptor, there is an increased likelihood that molecules that block or interact with SARS-CoV S protein will most likely be effective against SARS-CoV-2 S protein. The authors also tested the effect of quercetin using a pseudotype virus assay, the rationale being that quercetin shared structural similarity to luteolin. Quercetin is an ingredient of antioxidant and antiallergy medicines that had been approved by the US Food and Drug Administration (FDA; the national drug code numbers of the medicines are 65448–3085, 65448–3005).

Table 1 Experimentally Tested Nutraceuticals Against Different Coronavirus and Host Proteins

S. No.	Molecule	Target	Type of Study/ Techniques Used	Results	Study, Year, Reference
1	Luteolin	SARS-CoV S2 protein	• Frontal-affinity chromatography-mass spectrometry • HIV-luc/SARS pseudotype virus assay • MTT assay with wild-type SARS-CoV	• Luteolin-inhibited SARS-CoV infection in a dose-dependent manner. • EC_{50} was 10.6 μM. CC_{50} was 0.155 mM. LD_{50} in mice was 232.2 mg/kg	Yi et al, 2004[11]
2	Quercetin	SARS-CoV S2 protein	HIV-luc/SARS pseudotype virus assay	EC_{50} of 83.4 μM and CC_{50} of 3.32 mM	Yi et al, 2004[11]
3	GCG (gallocatechin gallate)	SARS-CoV 3CLPro	• Expression of recombinant 3CLPro in *Pichia pastoris* and its inhibition. • Molecular docking	• 91% inhibition by 200 μM. • IC_{50} of 47 μM. • Binding energy of −14 kcal/mol	Nguyen et al, 2012[14]
4	Quercetin	SARS-CoV 3CLPro	• Expression of recombinant 3CLPro in *Pichia pastoris* and its inhibition. • Molecular docking	• 80% inhibition at 200 μM. • IC_{50} of 23.8 μM • Binding energy −10.2 kcal/mol	Nguyen et al, 2012[14]
5	EGCG	SARS-CoV 3CLPro	• Expression of recombinant 3CLPro in *Pichia pastoris* and its inhibition. • Molecular docking	• 85% inhibition at 200 μM. • IC_{50} of 73 μM • Binding energy −11.7 kcal/mol	Nguyen et al, 2012[14]
6	Resveratrol	MERS-CoV NP	• MTT assay using vero-E6 cell line • Nucleocapsid protein staining	• Found to be effective in the 125–250 μM range on viral titre as well as viral RNA amount. • Inhibits caspase 3 cleavage.	Lin et al, 2017[12]
7	Hesperetin	SARS-CoV 3CLPro	Cell free and cell-based cleavage assays	IC_{50} of 60 μM in cell free assay, IC_{50} of 8.3 μM in cell-based assay and a CC_{50} of 2718 μM	Lin et al, 2005[15]
8	Quercetin	*ACE2* and *FURIN*	• Gene silencing • Expression studies • Transgenic mouse models	• Quercetin affected *ACE2* expression. • In addition, it was found to alter the expression of 98 of 332 (30%) genes encoding human proteins that serve as target for the SARS-CoV-2.	Glinsky, 2020[16]

This strategy by Yi et al[11] can be extended to current search by identifying structures similar to the ones that are showing promise in silico and in vitro, but already have a generally recognized as safe (GRAS) status owing to their documented food or medicinal use. This can drastically reduce the time required for regulatory approvals and give more confidence for clinical trials. In fact, a similar strategy was earlier used by Lin et al[12] when they decided to test the efficacy of resveratrol, a stilbene derivative, based on earlier studies that showed antiviral activities on SARS-CoV.

The coronavirus main protease (MPro or 3CLPro) structural backbone and active site conformation are conserved despite sequence variations.[13] Hence, nutraceuticals such as epigallocatechin gallate (EGCG), gallocatechin gallate (GCG), hesperetin, quercetin, which were previously shown to be effective against SARS-CoV 3CLPro can be tested for their efficacy in SARS-CoV-2 infection. Nguyen et al[14] found that a galloyl moiety present at the 3′OH position of a potential inhibitor, belonging to the flavonoid class, is crucial for inhibition of 3CLPro in SARS-CoV. Enzyme kinetics suggested that GCG competitively inhibited 3CLPro with an inhibition constant of 25 μM.

As seen in Table 1, quercetin seems to have multiple targets of action and may prove to be a better candidate molecule for therapeutic development. Administration of quercetin (1000 mg) showed a decrease in the incidence and extent of upper respiratory tract infections (URTIs). Abian et al[17] identified quercetin as a reasonably potent inhibitor of SARS-CoV-2 3CLpro protease, with the inhibition constant being $-K_i \sim 7$ μM. Quercetin also modulates the cellular unfolded protein response (UPR). As coronaviruses can utilize the UPR to complete different stages of the viral life cycle during infection, this is an important finding.[18] Early clinical data suggests that quercetin has broad antiviral property and acts at various steps of viral life cycle. As an FDA-approved drug ingredient, with potent antiviral action, quercetin offers great promise as a potential drug candidate in the clinical treatment of SARS.

In silico Studies Reveal Potential Therapeutic Nutraceuticals

Given the importance of rapid generation of lead compounds, many authors have used in silico docking and modelling studies to generate a library of potential therapeutic lead molecules targeting different stages of the viral infection life cycle, some of which have been collated in Table 2. It is interesting to observe the structural similarities among these molecules—having a catechol/

Table 2 Potential Nutraceutical Therapeutic Targets as Revealed by in silico Studies

S. No.	Molecule	Target	Binding Energy ΔG; Inhibition Constant K_i	Study, Year, Reference
1	EGCG	MPro	ΔG: −9.30 kcal/mol; K_i: 0.152 μM	Khan et al, 2020[19]
2	Myricetin	S	ΔG: −6.14 kcal/mol; K_i: 31.32 μM	Khan et al, 2020[19]
3	Quercetin	S	ΔG: −6.14 kcal/mol; K_i: 31.32 μM	Khan et al, 2020[19]
4	Curcumin	MPro	ΔG: −6.07 kcal/mol; K_i: 37.57 μM	Khan et al, 2020[19]
5	Curcumin	NP	ΔG: −8.75 kcal/mol; K_i:0.39 μM	Suravajhala et al, 2020[10]
6	Curcumin	Nsp10	ΔG: −7.85 kcal/mol; K_i:1.77 μM	Suravajhala et al, 2020[10]
7	δ- viniferin	MPro	ΔG: −8.4 kcal/mol	Joshi et al, 2020[13]
8	δ- viniferin	RdRp	ΔG: −8.3 kcal/mol	Joshi et al, 2020[13]
9	δ- viniferin	Human ACE2 receptor	ΔG: −8.4 kcal/mol	Joshi et al, 2020[13]
10	Myricitrin	MPro	ΔG: −8.9 kcal/mol	Joshi et al, 2020[13]
	Myricitrin	RdRp	ΔG: −7.9 kcal/mol	Joshi et al, 2020[13]
	Myricitrin	Human ACE2 receptor	ΔG: −7.5 kcal/mol	Joshi et al, 2020[13]
11	Carnosol	MPro	ΔG: −8.2 kcal/mol; K_i: 0.97 μM	Umesh et al, 2020[20]
12	Rosmanol	MPro	ΔG: −7.99 kcal/mol; K_i: 1.38 μM	Umesh et al, 2020[20]
13	Silibinin	RdRp	NA	Bosch-Barrera et al, 2020[21]
14	Rutin	MPro	ΔG −8.67kcal/mol	Hu et al, 2020[22]
15	Mangiferin	S	ΔG: −7.5 kcal/mol; K_i: 3.16 μM	Kar et al, 2020[23]
16	Mangiferin	MPro	ΔG: −7.8 kcal/mol; K_i: 1.90 μM	Kar et al, 2020[23]
17	Eugenol	S	ΔG: −7.3 kcal/mol; K_i: 4.42 μM	Kar et al, 2020[23]
18	Eugenol	MPro	ΔG: −7.6 kcal/mol; K_i: 2.67 μM	Kar et al, 2020[23]
19	Stigmasterol	S	ΔG: −7.2 kcal/mol;	Kar et al, 2020[24]
20	Stigmasterol	MPro	ΔG: −7.7 kcal/mol;	Kar et al, 2020[24]
21	Stigmasterol	RdRp	ΔG: −7.0 kcal/mol;	Kar et al, 2020[24]

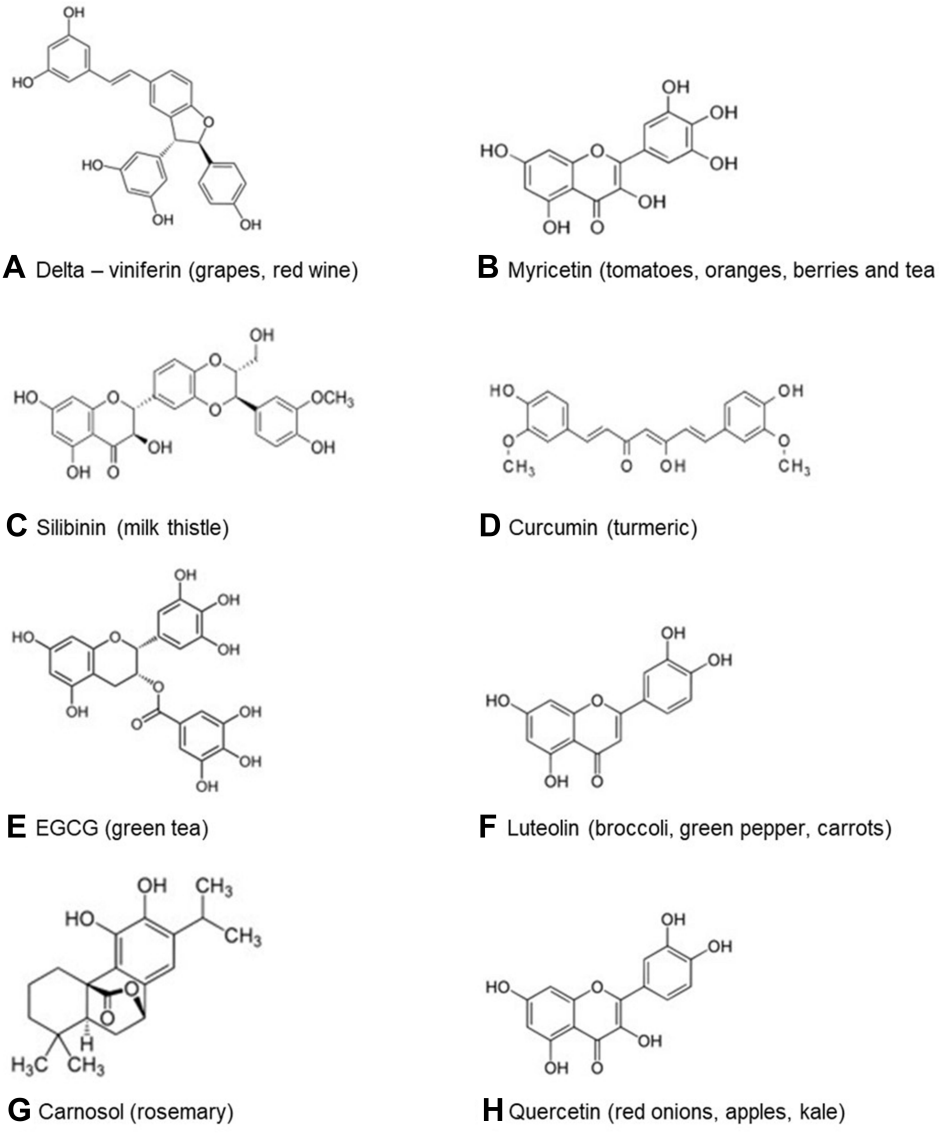

Figure 3 Nutraceuticals shown to be binding to target sites of SARS-CoV-2 are as follows: (**A**) δ-viniferin binds to RdRP, MPro and human ACE2 receptor, (**B**) myricetin binds to S protein, (**C**) silibinin binds to RdRp, (**D**) curcumin binds to MPro, NP, nsp 10, (**E**) EGCG binds to MPro, (**F**) luteolin binds to S protein, (**G**) carnosol binds to MPro, (**H**) quercetin binds to S protein.

resorcinol moiety—seems to be a common feature in these nutraceuticals (Figure 3).

Khan et al[19] docked 18 known natural antiviral compounds against seven SARS-CoV-2 proteins and compared them with remdesivir and chloroquine. Their modelling studies showed EGCG and curcumin to affect multiple targets of SARS-CoV-2. EGCG showed binding affinity towards main protease, spike protein, post fusion S2 protein, and nsp15 endoribonuclease. Curcumin, however, showed increased binding affinity towards the main protease and nsp15 endoribonuclease. Curcumin binding to NP and nsp10 was observed by Suravajhala et al.[10]

Joshi et al[13] screened a custom-made library of more than 7000 natural molecules such as flavonoids, glucosinolates, terpenoids, alkaloids, and others against the MPro. MPro does not have a sequence homologous structure in humans and hence targeting this protease would be specific for the virus. Since coughing is a major symptom of COVID-19, Joshi et al also screened traditionally known antitussive medicines against various structural proteins of SARS-CoV-2. They followed this up by screening the hits against RdRp and ACE2 in order to find multi-target inhibitors. Multi-target inhibitors have the added advantage that they could be effective in all stages of the virus

life cycle. EGCG is shown to reduce TMPRSS2 secretion. *Clerodendrum* species have been used as an age-old remedy for respiratory ailments. Hence, phytochemicals from 12 different species were assessed for their potential to bind to the coronavirus proteins, wherein stigmasterol was found to be a promising candidate.[24]

Silibinin not only acts as a direct inhibitor of viral proteins, but is also found to play a role in modifying the inflammatory response. Similarly, EGCG, has additional fat burning action (increasing fat oxidation), which prevents disease progression.

Hu et al,[22] observed that flavonoids in general, showed higher affinity towards MPro compared to alkaloids, terpenes and saponins. They suggest that this may be owing to the phenolic hydroxyl group of the flavonoids which can interact more easily with the heteroatoms of the amino acids of MPro. They found rutin to be especially effective in binding to MPro. Buckwheat, apple and tea contain considerable amount of rutin and can be consumed in higher quantities to protect oneself from the infection. The screening study conducted by Fischer et al,[25] revealed rhamnetin, found in *Moringa oleifera* plant, to show greater affinity for MPro. Rhamnetin is already commercially available. Rhamnetin is also structurally similar to quercetin. Myricitrin is a glycosylated analog of myricetin and is found in black grapes. Glycosylated flavonoids have an increased bioavailability compared to the aglycone forms.[25] Myricitrin, myricetin, resveratrol, and δ-viniferin, have been found to be potential anti-COVID-19 therapeutics.

Kar et al,[23] evaluated multiple phytochemicals and nutraceuticals for their potential to bind to either S, MPro or RdRp proteins. Post evaluation of in silico binding, these authors have also assessed the adherence of the selected ligands to the Lipinsky's rule of five. While eugenol was found to adhere to the Lipinsky's rule of five, mangiferin showed slight deviation. However, these deviations can be corrected through formulation innovations.

Octacosanol, cinametic acid, lauric acid, ascorbyl palmitate, and palmidrol are few of the nutraceuticals found to bind to the envelope protein. These can potentially disrupt the viroporin activity, and can provide relief from edema and inflammation, commonly observed in acute respiratory distress syndrome (ARDS).[26]

Sulforaphane is an isothiocyanate formed upon hydrolysis of glucosinolates found in cruciferous vegetables like broccoli and cabbage and can modulate levels of TMPRSS2.[27] It is also shown to upregulate Nrf2 thus enhancing the anti-inflammatory response of the body. Hence, consumption of cruciferous vegetables may be helpful as a preventive strategy against SARS-CoV-2.

Given that these molecules target different viral proteins at different stages of viral replication, and a majority of them are common ingredients of the food chain (eg curcumin from turmeric, carnosol from rosemary, quercetin in apples, etc), it can be assumed that consumption of such foods may positively impact protection against SARS-CoV-2 infection. However, supraphysiological dosing of nutraceuticals is a double-edged sword, with evidence on both sides—of effectiveness and toxicity. For example, the supraphysiological dosing of vitamins and nutrients (mainly flavonoids and omega-3 fatty acids) for treatment of brain injury is now well established with strong evidence backing their use.[28] However, high doses of chlorogenic acid are known to increase plasma homocysteine levels.[29] This kind of unexpected spinoff is more pronounced in the case of antioxidants, as they function as antioxidants at physiological dose, while occasionally at higher amounts a pro-oxidant activity is observed. Antioxidants by their very nature are "redox" agents, hence they have both antioxidant and pro-oxidant activities inherent in their structure. It is important to note that the physiological concentration of these nutraceuticals determines their function.

Plant Protease Inhibitors as Potential Therapeutic Molecules Against SARS-CoV-2

Viruses make use of proteases (generally host proteases) to gain entry into the host. Synthetic protease inhibitors have been widely used as treatment tools for a variety of viral diseases such as those caused by HIV, HCV, picornaviruses, SARS, rotavirus and others.[30] They are also being investigated as potential treatment options for diabetes, cancer and inflammation. Viral protease inhibitors against HIV, HCV, picornaviruses, SARS have also been studied from bacterial and fungal origins.[31]

TMPRSS2 and furin are host serine proteases that facilitate the entry of SARS-CoV-2 into the host cell. TMPRSS2 is a trypsin like serine protease while furin is a subtilisin type serine protease.[32] In addition, PLPro and the MPro which is a chymotrypsin-like cysteine protease, play important roles in viral replication. The epithelial cells of the respiratory tract themselves release proteases/protease inhibitors that help maintain homeostasis required for healthy lung functioning.[27] The protease/protease inhibitors balance determines the extent of respiratory viral pathogenesis. A

Table 3 Examples of Plant Protease Inhibitors (PPIs) as Potential Antiviral Agents

S. No.	Plant Source—Scientific Name	Name of PPI	Type of Inhibitor	Enzyme Inhibited
1	*Vigna unguiculata* (seeds)	BTCi	Bowman–Birk inhibitor	Trypsin, chymotrypsin
2	*Hordeum vulgare*	HorvuZx (BSZx)	Serpin	Trypsin, chymotrypsin
		CI-I	Potato type I	Trypsin, chymotrypsin, subtilisin
3	*Cicer arietenum*	CPTI	Kunitz	Trypsin
4	*Glycine max*	SKTI-3	Kunitz	Trypsin, chymotrypsin
		BBI	Bowman–Birk inhibitor	Trypsin
5	*Tamarindus indica*	Tamarind kunitz I	Kunitz	Trypsin
6	*Ananus comosus*	BI-I	Bowman–Birk inhibitor	Trypsin, chymotrypsin, papain
7	*Cucurbita maxima*	CMTI-V	Potato type I	Trypsin
8	*Solanum lycopersicum*	TI-II	Potato type II	Trypsin, chymotrypsin, subtilisin
9	*Brassica oleracea*	Cabbage TI	Mustard type PI	Trypsin
10	*Fagopyrum esculentum* (seeds)	BWI-1	Potato type I	Trypsin, chymotrypsin, subtilisin
11	*Moringa oleifera* (leaf extract)	Moringa protease I	Kunitz	Trypsin, chymotrypsin, papain

shift towards more proteases can increase viral pathogenesis while the reverse may help protect against it.

Animal studies by Deng et al[33] have shown that coronaviruses can gain quick resistance to 3CLPro inhibitors but this resistance comes at the fitness cost of the virus not being able to replicate fast enough thereby reducing infectivity. TMPRSS2 is a host secreted type 2 transmembrane serine protease and is shown to be sensitive to antiproteases in the midst of an infection.[22] Therefore, protease inhibitors or antiproteases against these protease enzymes can be explored as potential therapeutic molecules.

The reviews by Hellinger and Gruber[34] as well as Srikanth and Chen[35] describe a number of plant protease inhibitors, some of which have been collated in Table 3. This could be a good starting point to start assessing these molecules for their effectiveness against the SARS-CoV-2 virus 3CLPro and papain-like proteases.

Although the main function of antiproteases is inhibiting or deactivating proteases, newer research is identifying more roles for them in controlling excessive inflammation and microbial infection.[27] Hence identifying multifunctional plant protease inhibitors can allow multistep protection in coronavirus infection.

Immunomodulatory Effects and Inflammatory Responses Brought About by the SARS-CoV-2 Virus

The Immune System—Natural Defense Mechanism

During viral infection, the host cells recognize an invading virus through the pathogen-associated molecular patterns (PAMPs). This recognition further activates a series of cell signaling pathways through the pattern recognition receptors (PRRs). The toll-like receptors (TLRs), particularly TLR3 and TLR7 (endosomal receptors) and TLR8, recognize single-stranded RNA while other TLRs recognize the different viral components and set off the cellular signaling pathways. This leads to the production of pro-inflammatory cytokines (IL-6, TNF-α, type-I interferons (IFNs) etc) (Figure 4) and certain chemokines which further triggers the immune responses by the various immune cells (such as the antigen presenting cells, APCs). The release of the cytokines and chemokines is the starting point for the downstream effects such as inflammatory responses, apoptosis or pyroptosis, and the activation of the adaptive immune response. Type-I IFN pathway plays a central role in mediating innate immune responses to viral infections.

The type-I IFNs activate the JAK-STAT pathway and the phosphorylation of the STAT1and STAT2 causes the transcription of IFN-stimulated genes (ISGs) to further reduce viral replication and thereby reduce the viral load in the system.[1] The release of NF-κB transcription factors occurs downstream of TLRs activation and causes the release of pro-inflammatory cytokines.

The mitogen-activated protein kinases (MAPKs) pathway also gets activated during SARS-CoV infection. SARS-CoV also distinctly enhances the *NLRP3* inflammasome pathway leading to a profound expression of pro-inflammatory cytokines and ROS.

The adaptive immune system is activated by the phagocytes that present the antigen to the $CD4^+$ T-helper cells which fight against the virus by developing into Th1 cells. The APCs can also activate $CD8^+$T cells which further exhibit their cytotoxic effects along with natural killer

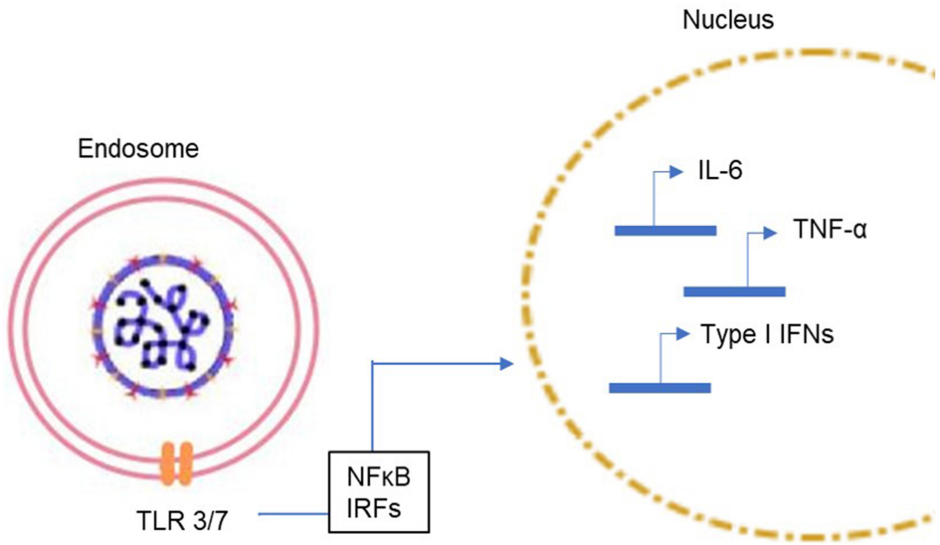

Figure 4 Signal cascade following the virus entry into the host cell. Viral entry results in the activation of the toll-like receptors (TLRs) present in the endosome and subsequent activation of the innate immune system through the NFκB transcription factor and interferon-regulatory factors (IRFs) which enter the nucleus and upregulate the expression of cytokines (IL-6, TNFα and type I interferons, etc).

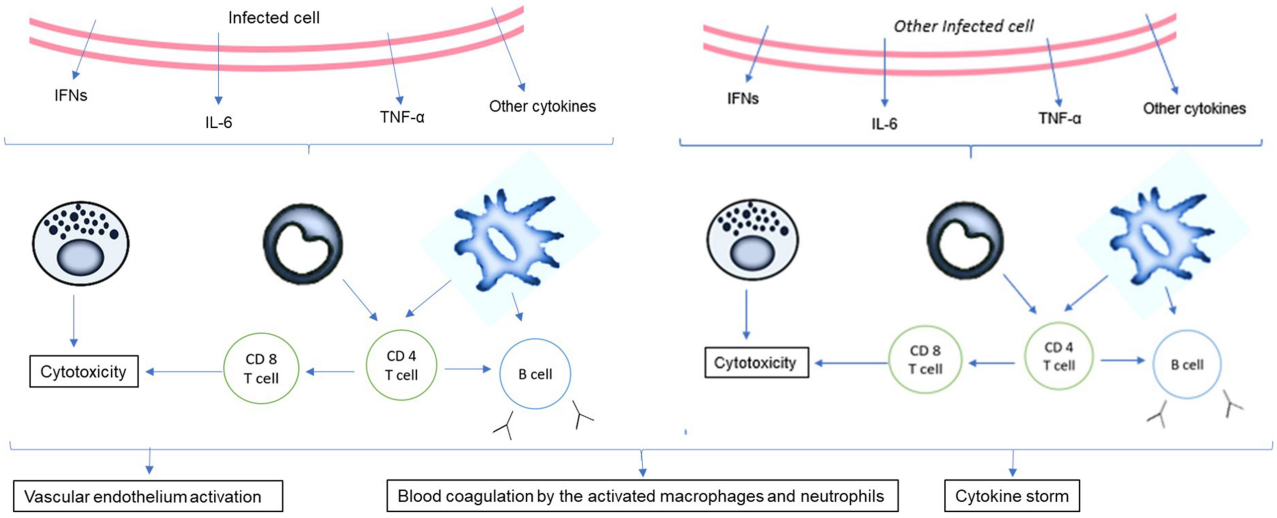

Figure 5 Activation of cytokines post infection. The release of the virions and the subsequent spread of the infection to other cells leads to the production of several cytokines that activate the adaptive immune system. High viral titer leads to activation of the vascular endothelium and blood coagulation, especially in those suffering from comorbidities.

(NK) cells. The $CD4^+$ cells also stimulate the $CD8^+$ cells through co-stimulatory signals. The T cells further activate the B cells leading to antibody production (specifically IgM and IgG) (Figure 5).

Immunomodulatory and Inflammatory Responses Triggered by SARS-CoV-2

At the onset of the infection cytokines play an important role in recruiting other phagocytes at the site of infection and eliciting immune response. Increase in viral load and evasion of the innate immune system by the virus causes a cytokine storm viz a marked increase in the levels of pro-inflammatory cytokines through various cellular pathways triggering inflammation, which contributes to morbidity and mortality. It has been reported that the cytokine storm aggravates the disease resulting in ARDS, a characteristic condition exhibited by critically ill patients.

The virus has developed several strategies to evade the human defense system. It avoids the immune system by forming double vesicles that escape detection through PRRs. Furthermore, the viral particles are able to inhibit the STAT family transcription factors and suppress the expression of type-I IFNs.[36] The nsps function to alter the structure of the virus to mimic the host cell components and thereby evade detection by the host immune system.[1]

Lymphopenia has also been cited as a cause for exacerbation of adverse effects of the disease.[37] The low count of T cells results are not only due to the viral load, but also due to the cytokine storm. Previously, it was observed in SARS-CoV infected individuals that there was an imbalance in the $CD4^+$ and $CD8^+$ ratio with a significant decrease in the $CD4^+$ count compared to $CD8^+$ cell count.[38,39] Ageing, by itself results in similar disruption of $CD4^+/CD8^+$ ratios, which in turn may be responsible for the increased susceptibility of the aged to SARS- CoV-2 infection. The cytokine storm and the immune dysregulation renders an individual with other comorbidities more susceptible to the disease. Hence, it is essential to build or enhance immunity not only to prevent infection, but also to prevent the acute stage of the disease once infected.

Interventions to Regulate Immune Response in COVID-19 Patients

Several nutraceuticals and natural compounds are known to have antiviral and immunomodulatory properties. Some of these compounds exhibit their functions by counteracting inflammation and ameliorating the ROS. Some of the strategies used in the past to counteract SARS-CoV infection were downregulation of MAPK pathway, reduction of *NLRP3* inflammasome effects and inhibition of NF-κB while targeting a decrease in the pro-inflammatory cytokines, especially IL-6.[40,41]

Over expression of IL-6 causes enhanced expression of *STAT3*. Studies suggest that the use of inhibitors of the JAK-STAT pathway can be potential therapeutic strategy. Recent studies have discovered the positive effect of silibinin, a flavolignan obtained from milk thistle and apigenin obtained from dried parsley in inhibiting cytokine storm by preventing *STAT3* activation and its nuclear translocation.[21] Some of the nutraceuticals that can downregulate these different pathways are mentioned in Table 4. Immunity boosters that restore the adaptive immunity are also potential targets. Jacalin (a lectin from jackfruits) was shown to increase the levels of $CD4^+$cells and thus restore the $CD4^+$ and $CD8^+$ cell ratio in an immunocompromised individual. Thus, it could be used to address the issue of lymphopenia and further enhance immunity.[42]

COVID-19 and Metabolic Diseases

A large number of people suffering from various metabolic diseases, such as hypertension, obesity, cardiovascular diseases, type 2 diabetes, etc are more susceptible to infection from the SARS-CoV-2 virus.[60] The immunomodulatory effects due to the infection not only contribute to the severity of the metabolic diseases, but also exacerbate the adverse effects of infection.

An understanding of the onset and subsequent severity of the viral infection along with other comorbidities will help in identifying suitable nutraceuticals that can act on relevant pathways to ameliorate the conditions. Figure 6 succinctly delineates the cross-talk between the immune and metabolic pathways.

Noncommunicable Diseases

Two major noncommunicable diseases, obesity and type-2 diabetes, are characterized by the dysregulation of PPARγ and IRS-1 expression occurring through the influence of IL-1 and TNF- α.[61–63] Downregulation of ppargc1a further leads to pulmonary damage of the alveolar macrophages and epithelial cells, a characteristic symptom in the critically-ill COVID-19 patients. Furthermore, in addition to the alveolar epithelial cells, adipose and pancreatic tissues too express ACE2 and are thus prone to SARS-CoV-2 attack.[64] Diabetic patients are often treated with ACE inhibitors, which results in higher expression of ACE2.[65] Impaired glucose metabolism in diabetic patients results in dysregulated T cell activation and causes oxidative stress, further compromising the immune system of the infected individual.[66]

Dyslipidemia

A disruption in lipid homeostasis leads to dyslipidemia, characterized by elevated total cholesterol, triglycerides and low-density lipoprotein (LDL) with low levels of high-density lipoprotein (HDL).[67] IL-6 leads to vascular cell damage by enhancing the permeability of oxidized LDL, resulting in lung injury. During the SARS-CoV-2 infection, the cytokine storm increases LDL oxidation

Table 4 List of Nutraceuticals Exhibiting Immunomodulatory and Anti-inflammatory Effects

S. No.	Nutraceutical	Common Sources	Action	Study, Year, Reference
1	Curcumin	Turmeric	• Inhibits NF-kB pathway • Inhibits p38 MAPK pathway • Downregulates *STAT3* of the JAK/STAT pathway	Al Mijan and Lim, 2018[43]
2	Epicatechins	Tea leaves, apples, cocoa, grapes	Downregulates *STAT3* of the JAK/STAT pathway	Yang et al, 2015[44]
3	Quercetin and dihydroquercetin	Onions, apples, citrus fruits, honey	• Downregulates *STAT3* of the JAK/STAT pathway • Inhibits NF-κB pathway • Reduces expression of pro-inflammatory cytokines (IL-6)	Khan et al, 2016[45]
4	Hesperetin	Lemons, oranges	Downregulates *STAT3* of the JAK/STAT pathway	Choi et al, 2008[46]
5	Kaempferol	Apples, grapes, tomato, green tea, onions, cucumbers	• Downregulates JAK/STAT pathway • Inhibits NF-κB pathway • Inhibits MAPK pathway • Reduces expression of pro-inflammatory cytokines (IL-6)	Hämäläinen et al, 2007[47]
6	Emodin	Rhubarb	• Downregulates *STAT3* of the JAK/STAT pathway • Inhibits NF-κB pathway • Inhibits MAPK pathway • Reduces expression of pro-inflammatory cytokines (IL-6)	Hsu and Chung, 2012[48]
7	Ursolic acid	Apples, basil, oregano, thyme, prunes	• Downregulates *STAT3* of the JAK/STAT pathway • Inhibits NF-κB pathway • Reduces expression of pro-inflammatory cytokines (IL-6)	Kashyap et al, 2016[49]
8	Vitamin E	Nuts (like almonds and peanuts), seeds (sunflower seeds), vegetable oil and green leafy vegetables	• Inhibits NF-κB pathway • Reduces expression of pro-inflammatory cytokines (IL-6)	Huang et al, 2004[50]
9	Vitamin C	Guava, citrus fruits, tomatoes	Inhibits NF-κB pathway	Huang et al, 2004[50]
10	Vitamin B6	Whole grain cereals, eggs, soybeans, fish and meat products	• Inhibits NF-κB pathway • Inhibits activation of *NLRP3* inflammasome)	Yanaka et al, 2005[51]
11	Resveratrol	Grapes, peanuts	Inhibits NF-kB pathway	Huang et al, 2004[50]
12	Theaflavins	Tea leaves	• Inhibits NF-κB pathway • Reduces expression of pro-inflammatory cytokines (IL-6)	Huang et al, 2004[50]
13	Genistein	Soybeans	• Inhibits NF-kB pathway • Reduces expression of pro-inflammatory cytokines (IL-6)	Huang et al, 2004[50]

(*Continued*)

Table 4 (Continued).

S. No.	Nutraceutical	Common Sources	Action	Study, Year, Reference
14	Chlorogenic acid	Coffee, tea, apples, carrots	• Inhibits NF-κB pathway • Reduces expression of pro-inflammatory cytokines (IL-6) • Inhibits activation of *NLRP3* inflammasome	Zhang et al, 2018[52]
15	Zingerone and 12-dehydrogingerdione	Ginger	• Inhibits NF-κB pathway • Reduces expression of pro-inflammatory cytokines (IL-6)	Dos Tramontins et al, 2020[53]
16	Sesamol	Sesame	• Inhibits NF-κB pathway • Inhibits MAPK pathway • Reduces expression of pro-inflammatory cytokines	Majdalawieh and Mansour, 2019[54]
17	Alliin	Garlic	• Inhibits MAPK pathway • Reduces expression of pro-inflammatory cytokines (IL-6)	Sánchez-sánchez et al, 2020[55]
18	Apigenin	Grapefruit, onion, oranges, chamomile, parsley	• Inhibits NF-κB pathway and STAT3 • Reduces expression of pro-inflammatory cytokines (IL-6)	Nicholas et al, 2007[56]
19	Luteolin	Broccoli, carrot, thyme, chamomile	• Inhibits NF-κB pathway • Inhibits MAPK pathway	Nicholas et al, 2007[56]
20	L-carnitine	Dairy products (whey portion), meat and fish	• Inhibits NF-κB pathway • Reduces expression of CRP and pro-inflammatory cytokines (IL-6)	Haghighatdoost et al, 2019[57]
21	Berberine	Turmeric	• Inhibits NF-κB pathway • Inhibits MAPK pathway • Reduces expression of pro-inflammatory cytokines	Marín-Aguilar et al, 2017[58]
22	Taxifolin	Milk thistle, onion	• Downregulates *STAT3* of the JAK/STAT pathway • Inhibits NF-κB pathway	Sunil and Xu, 2019[59]

and reduces the levels of HDL-c and *PON1*, leading to dyslipidemia and exacerbation of other metabolic diseases.[68]

In accordance with these observations, the lipid profile of the epithelial cells in patients suffering from SARS-CoV showed high concentrations of fatty acids and phospholipids and this condition has been considered to be conducive for viral replication.[64] Furthermore, SARS-CoV-2 entry results in higher levels of angiotensin II which can lead to upregulation of IL-6, CAMs and several other cytokines and chemokines via the NF-κB pathway causing vascular diseases.[69]

Suitable Interventions to Address the Metabolic Diseases

In order to reduce this influence of the metabolic diseases and COVID-19 on one another, the target nodes in focus could be, (a) AMPK pathway (the upregulation of AMPK pathway downregulates inflammation and exhibits hypolipidemic effects), (b) specialized pro-resolving mediators, SPMs (agonists of PPARγ as their activation would target lipid metabolism as well as work as potential SPMs to restore homeostasis in a COVID-19 patient), (c) lipid oxidation (fatty acid oxidation ensures minimization of lipotoxicity as well as reduces damages caused to cells by dyslipidemia).

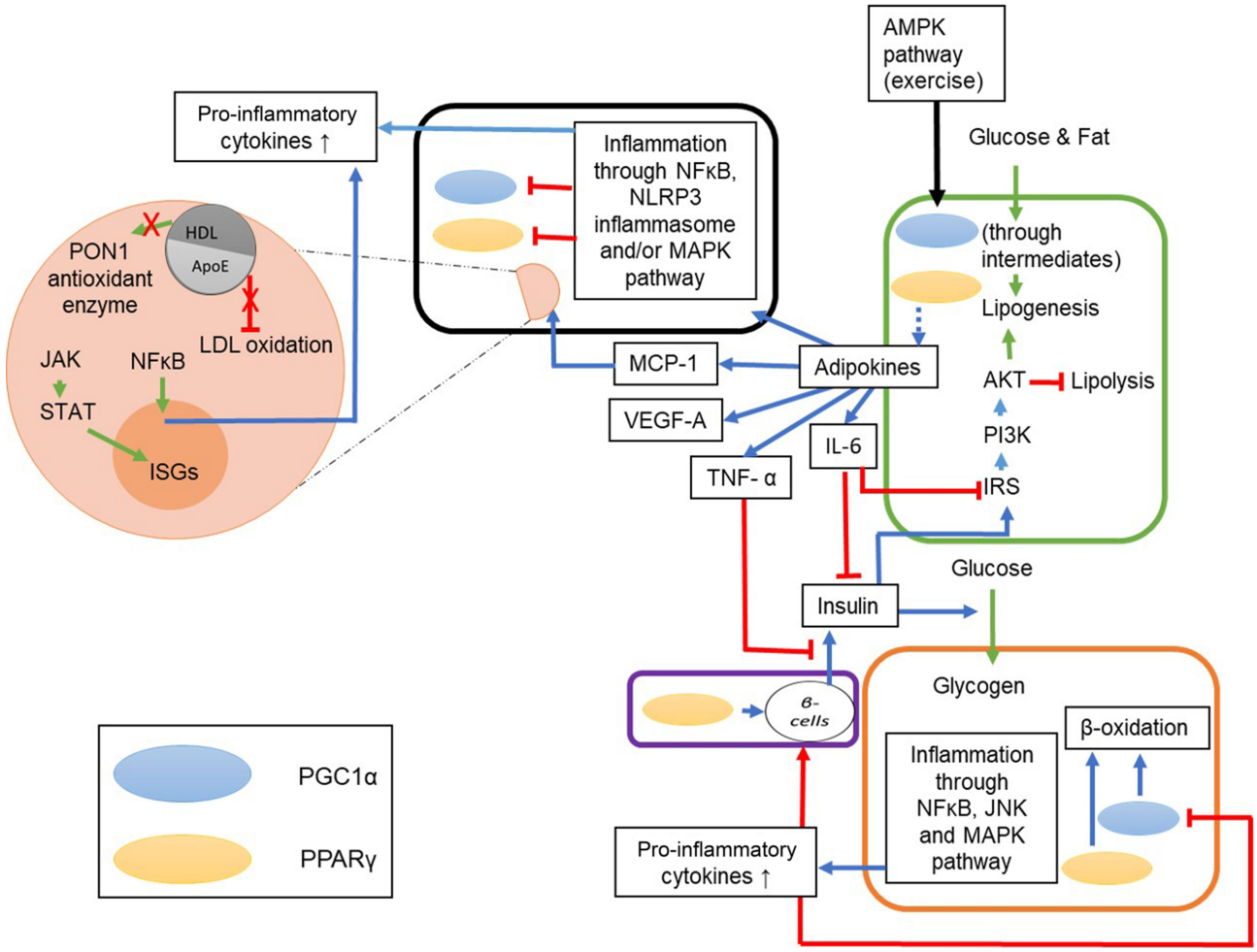

Figure 6 The interlinked immune signaling pathways and metabolism. The green box represents adipocytes, orange box represents hepatocytes, and purple box represents pancreatic cells. The green arrows represent the metabolic process and the cellular machinery process, the blue arrows represent the immune response elicited by molecules or factors and the red lines represent inhibition. The PPARs and PGC1α present in the cells influence adipokines and β-oxidation; the blue dotted line represent regulation (either up- or downregulation). The immune signaling involved during the metabolism process includes release of pro-inflammatory cytokines by the adipocytes (IL-6, TNFα, MCP-1, VEGF-A, etc), inhibition of lipolysis via activation of PI3K/Akt pathway, inhibition of insulin function by the adipokines (IL-6 and TNF-α) and activation of AMPK pathway, which upregulates PGC1α further enhancing β-oxidation. Dyslipidemia results in inflammation in the hepatocytes through the JNK and MAPK pathways which release pro-inflammatory cytokines that can inhibit β-oxidation and expression of β-cells in the pancreas. The black box represents a SARS-CoV-2 infected cell where the MCP-1 causes macrophage infiltration (orange circle) at the site of infection resulting in a decrease in HDL levels, loss of PON1 enzyme activity and increase in oxidization of LDL. It also results in activation of inflammatory pathways (JAK/STAT and NF-κB) and hence the cytokine storm.

Nutraceuticals used in the management of metabolic disorders are suitable interventions to alleviate the comorbidities in a COVID-19 patient. These are listed in Tables 5 and 6.

Probiotics and Prebiotics

Probiotics or the gut microbiota play an important role in curbing inflammatory response and the associated metabolic diseases. Strains of *Bifidobacterium* and *Lactobacillus* species are the common probiotics found naturally as well as available commercially. The brain–gut axis facilitates the expression of anti-inflammatory cytokines through inhibition of TLRs.[113] The intestine has a high expression of ACE2 and is thus susceptible to SARS-CoV attack, evident from the GI symptoms exhibited in a few patients.[114] Therefore, supplementing a patient with probiotics is a therapeutic approach to control the spread of the infection and can also act as a prophylactic treatment. The presence of microorganisms in the lungs has also been reported, with *Bacteroidetes, Firmicutes*, and *Proteobacteria* being the three main phyla characterized.[114] Similar to the brain–gut axis, there exists the gut–lung axis—a link between the gut microbiota and the lungs acting through blood vessels, whereby the metabolites from the gut has an influence on the functioning of the lungs, acting via Nod-2 and GM-

Table 5 Natural Food Sources Exhibiting Anti-obesity, Antidiabetic and Hypolipidemic Effects

S. No.	Source	Bioactive Molecules	Effects	Studies Undertaken	Study, Year, Reference
1	Bitter gourd *(Momordica charantia)*	Charantin Vicine Cucurbitane Momordicin II Kuguaglycoside G α-eleostearic acid	Hypolipidemic function: • Increases HDL-c levels. • Enhances expression of PGC1α • Enhances PPARα and PPARγ via AMPK pathway Anti-hyperglycemic function: Improves insulin sensitivity	Mice were administered bitter gourd extract (250, 500 and 1000 mg/kg of body weight) and the mRNA expression of PPARs and their target genes were studied.	Chao et al, 2011[70]
				Rats fed high fat diet extract for 10 weeks were supplemented with bitter gourd for two weeks.	Sridhar et al, 2008[71]
2	Ginger (*Zingiber officinale*)	Zingerone Zingiberene Gingerols 6-shogaol Gingerenone A	Hypolipidemic function: • Enhances β-oxidation • Upregulates PGC1α • Increases HDL-c levels • Activates PPARs Anti-hyperglycemic function: improves insulin sensitivity	In vivo and in vitro studies were carried out on obese mice to observe the effects of ginger extracts on obesity and its mechanism of action	Misawa et al, 2015[72]
				A meta-analysis was performed to study the effects of ginger on lipid profile in obesity.	Maharlouei et al, 2019[73]
3	Turmeric (*Curcuma longa*)	Curcumin Curcuminoids	Hypolipidemic function: • Upregulates PGC1α • Increases HDL-c levels. Restoring homeostasis: Activates AMPK/PPAR pathway	Mice were fed high fat diet along with curcumin (4 g/kg body weight).	Shao et al, 2012[74]
				Subjects with T2D were supplemented with curcuminoids (1000 mg/day) with piperine (10 mg/day) for 12 weeks.	Panahi et al, 2017[75]
				In vitro studies were carried out to evaluate the effects of curcumin on adipocytes	Lone et al, 2016[76]
4	Green tea	Epigallocatechin-3-gallate (EGCG)	Hypolipidemic function: • Enhances β-oxidation. • Activates AMPK/PPAR pathway. • Restores PON1 activity. • Reduces levels of LDL, cholesterol and triglycerides. • Increase in HDL levels Anti-hyperglycemic function: Improves insulin sensitivity	Male SD rats were studied under normal, hyperglycemic and hypercholesterolemic conditions and were fed diet with green tea powder (functional food) and green tea extracts (nutraceutical)	Yousaf et al, 2014[77]
				Subjects were given catechin supplementation in the form of decaffeinated green tea extracts (equivalent to four cups of green tea)	Hsu et al, 2007[78]
5	Capsicum	Capsaicin Dihydrocapsaicin Homocapsaicin Nordihydrocapsaicin	Hypolipidemic function: upregulates PPARα	In vitro studies of the effect of capsaicin on adipocytes were carried out.	Kang et al, 2007[79]

(*Continued*)

Table 5 (Continued).

S. No.	Source	Bioactive Molecules	Effects	Studies Undertaken	Study, Year, Reference
6	Drumstick (*Moringa oleifera*)	β-sitosterol Quercetin Chlorogenic acid Benzylamine	Hypolipidemic function: decreases total cholesterol, LDL-c levels and increases the HDL-c/non-HDL-c levels.	Rats were fed various doses of *Moringa oleifera* extracts (150, 300 and 600 mg/kg) along with high fat diet.	Jain et al, 2010[80]
				Type 2 diabetic patients received a treatment of Moringa leaves powder (8 g) for 40 days.	Kumari 2010[81]
7	Soybean	β-sitosterol Quercetin Chlorogenic acid Benzylamine Genistein Daidzein Glycitein	Hypolipidemic function: • Decreases the LDL-c levels. • Reduces the LDL-c to HDL-c ratio.	• A double-blind randomized study on adults with type 2 diabetes where the study group were fed soy protein isolates (80 mg/d of aglycone isoflavones). • Isoflavone composition was 65% genistein, 31% daidzein, and 4% glycitein.	Pipe et al, 2009[82]
8	Rosemary	Rosmarinic acid Carnosic acid	Hypolipidemic function: • Increases HDL-c levels • Reduces total cholesterol and LDL-c levels. Antidiabetic function: Stimulates insulin secretion	Adults were fed 10 g of rosemary leaves powder each day for four weeks.	Labban et al, 2014[83]
9	Pomegranate	Ellagic acid Gallic acid Quercetin	Hypolipidemic function: Reduces TC, TG, LDL-c levels, LDL-c to HDL-c ratio. Antioxidant effect: increase the stability and association of *PON1* with HDL	Diabetic patients were supplemented with concentrated pomegranate juice for eight weeks.	Esmaillzadeh et al, 2006[84]
				Patients with type 2 diabetes were administered pomegranate fruit juice or pomegranate polyphenol extracts.	Rock et al, 2008[85]
10	Strawberry	Ellagic acid Catechins Kaempferol Anthocyanins	Hypolipidemic function: • Reduces LDL-c levels, LDL-c to HDL-c ratio. • Reduces Ox-LDL levels Antioxidant effect: increase the stability and association of *PON1* with HDL	Hyperlipidemic adults were supplemented with a strawberry beverage containing approximately 338 mg total phenolic compounds over a six-week period.	Burton-Freeman et al, 2010[86]

CSF signaling, and in turn a respiratory ailment could lead to dysbiosis.[113]

Several studies reported alleviation of symptoms of the common cold and a reduction in its duration by supplementation with *Lactobacillus plantarum* HEAL9 (DSM 15312) and *Lactobacillus paracasei* 8700:2 (DSM 13434) at a concentration of 1×10^9cfu/day[115] and *Lactobacillus gasseri* PA 16/8, *Bifidobacterium longum* SP 07/3, *Bifidobacterium bifidum* MF 20/5 at a concentration of 5×10^7cfu/day.[116] When these probiotics were administered along with the influenza vaccine, an increase in the antibody titer was observed.[117] An ongoing clinical trial is noteworthy in this regard.[118,119]

Prebiotics too have a beneficial role in conferring anti-inflammatory activity by inducing the production of IL-10 and IL-17.[120] The short chain fatty acids (SCFA) like acetate and butyrate activate FFA receptors, leading to a downregulation of NFκB and MAPK

Table 6 Natural Products and Their Bioactive Molecules Exhibiting Anti-obesity, Antidiabetic and Hypolipidemic Effects

Natural Products	Bioactive Molecules	Sources	Clinical Trials	Observed Results	Study, Year, Reference
PUFA	Docosahexaenoic acid (DHA) Eicosapentaenoic acid (EPA) Conjugated linolenic acid (CLA) Arachidonic acid (ALA)	Fish oil Flaxseed	Male mice were fed high-fat and high-glucose diet with 1% EPA supplementation for four weeks	Hypolipidemic function: Regulate fat oxidation by enhancing β-oxidation Improves insulin sensitivity	Liu et al, 2013[87]
			PPARα null mice were fed high fat diet with 8% fish oil for two weeks	Anti-hyperglycemic function: hepatic insulin resistance, induced through high fat diet is prevented via PARR pathway	Neschen et al, 2007[88]
			Male mice were fed high-fat diet with 6% EPA and 51% DHA	Anti-obesity function: upregulation of *PPARGC1A*	Flachs et al, 2005[89]
			A three-week study was carried out where male mice were fed a diet of 4.5% fat and 0.26% omega-3 fatty acids and from second week it was subjected to a four-day treatment of protectin followed by induced infection.	Restoring homeostasis: Protectins from DHA resolve inflammation in the lungs and function as SPMs	Levy et al, 2010[90]
			In vitro studies were carried out in alveolar cells obtained from asthmatic patients	Restoring homeostasis: EPA and DHA inhibit inflammatory responses in asthmatic alveolar macrophages with EPA being more potent than DHA	Mickleborough et al, 2009[91]
Flavonoids					
Anthocyanins	Cyanidin Cyanidin-3-glucoside	Red berries Legumes	Male apoE$^{-/-}$ mice were fed a diet with 1.25% (w/w) black elderberry extract for six weeks	Antioxidant effect: Increases the activity of *PON1*	Farrell et al, 2015[92]
			A randomized, double-blind trial was conducted on 29 diabetic patients supplemented with 160 mg of anthocyanins (from bilberry and blackcurrant) twice a day for 24 weeks.	Preventing dyslipidemia: anthocyanin supplementation reduced the serum triglycerides level Anti-hyperglycemic function: supplementation increased adiponectin levels in diabetic patients leading to lower blood glucose concentration	Li et al, 2015[93]
Flavanols	Catechins (epicatechins, epigallocatechins, etc)	Green tea	Male mice were fed diet supplemented with EGCG (0.25–1% w/w) for five weeks.	Preventing dyslipidemia: increases fatty acid oxidation Anti-hyperglycemic function: Increases stimulation of insulin secretion	Wolframet al, 2006[94]
			Male C57BL/6J mice were fed high fat diet and a supplement of epicatechin (20 mg EC/kg body weight)	Anti-hyperglycemic function: improves insulin sensitivity	Cremonini et al, 2016[95]

(*Continued*)

Table 6 (Continued).

Natural Products	Bioactive Molecules	Sources	Clinical Trials	Observed Results	Study, Year, Reference
Flavonols	Quercetin	Onion Apples	In vitro studies were performed to observe the effect of quercetin (onion peel extract) on 3T3-L1 pre-adipocyte cells. Male rats fed high fat diet were treated with quercetin (onion peel extract).	Preventing dyslipidemia and regulating obesity: in vitro studies showed a reduction in the triglycerides levels as well as lipid accumulation. In vivo studies showed that the mRNA expressions of several genes involved in lipid oxidation were regulated and hence also exhibit anti-obesity effects.	Moonet al, 2013[96]
			In vitro studies were performed to observe the effect of quercetin (onion peel extract) on 3T3-L1 pre-adipocyte cells.	Preventing dyslipidemia and regulating obesity: onion peel extract upregulated the PGC1α expression and quercetin of 100 μM increased protein levels of PGC1α.	Lee et al, 2017[97]
			Male rats were fed a liquid diet containing quercetin (10mg/L) for four weeks and compared to control (diet without quercetin)	Antioxidant effect: quercetin-fed rats showed an increase in hepatic *PON1* expression and its activity.	Gong et al, 2009[98]
			Obese rats were fed diet supplemented with quercetin (2 mg/kg of body weight or 10 mg/kg of body weight)	Preventing dyslipidemia: both doses reduced hyperlipidemia Antidiabetic function: Both doses reduced insulin resistance. Anti-inflammatory effects: higher dosage of 10 mg/kg of body weight caused a decrease in the levels of pro-inflammatory cytokines (TNF-α in adipose tissues and plasma NOx). Anti-obesity function: higher dosage also resulted in weight loss	Rivera et al, 2008[99]
	Kaempferol	Pomegranate	Diabetic rats were treated with kaempferol (50 or 150 mg/kg)	Increases insulin sensitivity by inhibiting the NFκB pathway and restoring IRS-1 function.	Luo et al, 2015[100]
			In vitro studies were carried out on INS-1E beta-cells and human islets treated with 10 μM of kaempferol.	Antidiabetic function: Increases translational activation of insulin	Zhang and Liu, 2011[101]

(*Continued*)

Table 6 (Continued).

Natural Products	Bioactive Molecules	Sources	Clinical Trials	Observed Results	Study, Year, Reference
	Tiliroside	Strawberry Raspberry	Obese-diabetic mice were administered tiliroside (100 mg/kg body weight/day) for three weeks.	Hypolipidemic function: enhanced adiponectin signalling leading to FA oxidation. Reduced TG levels. Restoring homeostasis: activated PPARα pathway in the liver and the AMPK pathway in the liver as well as skeletal muscles.	Gotoet al, 2012[102]
Flavanones	Naringenin (aglycone) Naringin (glycone)	Citrus fruits (oranges, lemon) Grapefruit Tomatoes Cocoa	Male diabetic rats were treated with naringenin (25 mg/kg body weight) for 45 days.	Hypolipidemic function: naringenin treatment resulted in lowering of triglycerides, free fatty acids, LDL levels and increase in HDL levels. Prevented lipid oxidation. Antidiabetic function: Naringenin treatment upregulated GLUT-4 and downregulated TNF-α expressions.	Priscillaet al, 2015[103]
			Type 2 diabetic rats fed high fat diet were supplemented with naringin (50 mg/kg body weight) for 30 days.	Hypolipidemic function: decrease in serum levels of free fatty acids (FFA). Increases HDL-c levels. Increases serum adiponectin levels. Anti-hyperglycemic function: Improves insulin sensitivity	Ahmed et al, 2012[104]
	Hesperidin	Citrus fruits (oranges, lemon) Grapefruit	Mice were fed high fat diet supplemented with hesperidin.	Anti-obesity function: reduced body fat accumulation Hypolipidemic function: Reduced LDL levels.	Liu et al, 2020[105]
			Type 2 diabetic rats fed high fat diet were supplemented with hesperidin (50 mg/kg body weight) for 30 days.	Hypolipidemic function: increased HDL-c levels.	Ahmed et al, 2012[104]
Flavones	Luteolin Apigenin Chrysin Tangeritin	Celery Thyme Chamomile tea Honey Oranges Onions Grapefruit	Diabetes induced male rats with induced diabetes received a treatment of either chrysin (0.25% w/w) or luteolin (1% w/w)	Hypolipidemic function: luteolin and chrysin reduced the levels of triglycerides and total cholesterol.	El-Bassossy et al, 2013[106]

(*Continued*)

Table 6 (Continued).

Natural Products	Bioactive Molecules	Sources	Clinical Trials	Observed Results	Study, Year, Reference
			Male rats with fructose-induced hyperinsulinemia received a treatment of either chrysin (0.25% w/w) or luteolin (1% w/w)	Hypolipidemic function: luteolin and chrysin reduced the levels of LDL-c Anti-hyperglycemic function: reduced insulin resistance Restoring homeostasis: luteolin and chrysin stimulated PPARγ activity	El-Bassossy et al, 2014[107]
			Male C57BL/6 mice were fed high fat diet supplemented with 0.01% luteolin for 20 weeks.	Hypolipidemic function: activated AMPKα1 in macrophages present in the adipose tissues.	Zhang et al, 2016[108]
Isoflavones	Genistein	Soy	In vitro analysis of effects of genistein (5 μM) on INS-1E cells for 48 h exposure was carried out.	Antidiabetic function: increased insulin secretion by the pancreatic β-cells.	Fu and Liu, 2009[109]
	Rutin	Apricots Cherries Grapes Plums	Obese rats were fed rutin (100 mg/kg) for eight weeks.	Anti-obesity function: decreased body fat accumulation	Hsu et al, 2009[110]
Phenolic acids	Coumaric acid	Peanuts Tomatoes Basil Garlic Spinach	Obese rats were fed o-coumaric acid (100 mg/kg) for eight weeks.	Hypolipidemic function: decreased LDL-c levels	Hsu et al, 2009[110]
			Type 2 diabetic rats were fed p-coumaric acid of 40 mg/kg of body mass for six weeks.	Antihyperglycemic function: Increased HDL-c levels in serum. Decreased LDL-c, TG, TC levels. Antihyperglycemic function: Improves β-cell function. Restoring homeostasis: Increased the expression of PPARγ.	Abdel-Moneim et al, 2018[111]
	Gallic acid	Tea leaves Dates Cloves Chicory	Rats were fed high-fructose diet and were supplemented with gallic acid (40 mg/kg body weight) for four weeks.	Hypolipidemic function: reduced TC, TG, LDL-c levels. Increased HDL-c levels. Increases levels of adiponectin. Anti-hyperglycemic function: reduces plasma insulin levels.	Ibitoye and Ajiboye, 2018[112]
			Type 2 diabetic rats were fed gallic acid of 20 mg/kg of body mass for six weeks.	Anti-hyperglycemic function: increased HDL-c levels in serum. Restored adiponectin levels Anti-hyperglycemic function: restored β-cell function. Reduced insulin resistance. Restoring homeostasis: increased the expression of PPARγ.	Abdel-Moneim et al, 2018[111]

(*Continued*)

Table 6 (Continued).

Natural Products	Bioactive Molecules	Sources	Clinical Trials	Observed Results	Study, Year, Reference
	Caffeic acid	Coffee Apples Pears	Rats were fed high-fructose diet and were supplemented with caffeic acid (40 mg/kg body weight) for four weeks.	Hypolipidemic function: reduced TC, TG, LDL-c levels. Increased HDL-c levels. Increases levels of adiponectin. Anti-hyperglycemic function: reduces plasma insulin levels.	Ibitoye and Ajiboye, 2018[112]
	Ferulic acid	Oats Pineapple Rice Wheat Peanuts	Rats were fed high-fructose diet and were supplemented with gallic acid (40 mg/kg body weight) for four weeks.	Hypolipidemic function: reduced TC, TG, LDL-c levels. Increased HDL-c levels. Increases levels of adiponectin. Anti-hyperglycemic function: reduces plasma insulin levels.	Ibitoye and Ajiboye, 2018[112]
	Protocatechuic acid	Plums Grapes Almonds	Rats were fed high-fructose diet and were supplemented with gallic acid (40 mg/kg body weight) for four weeks.	Hypolipidemic function: reduced TC, TG, LDL-c levels. Increased HDL-c levels. Increases levels of adiponectin. Anti-hyperglycemic function: reduces plasma insulin levels.	Ibitoye and Ajiboye, 2018[112]

pathways.[121] The levels of certain LPS-induced pro-inflammatory cytokines and chemokines, like TNF-α, *CXCL8*, *CCL20* show downregulation during butyrate administration to the system.[120] SCFAs also exhibit immunomodulatory functions by regulating the function of T cells.[120] Oat bran and psyllium husk fiber act as natural prebiotic by undergoing fermentation by the gut microbiota to yield SCFA. These can also bind to PPARs and facilitate homeostasis.[122]

Bioactive Peptides and Other Natural Molecules and Their Immunomodulatory Actions

Some of the bioactive peptides that have shown beneficial effects in reducing inflammation and functioning as anti-oxidants are summarized in Table 7.

Vitamin C

Vitamin C (ascorbic acid) possesses antioxidant and immune-modulatory property. It helps in mitigating the injury caused by oxidative stress during viral infections.[135] Patients suffering from ARDS show reduced levels of vitamin C (Vit C) and external administration of Vit C reduced the extent of pulmonary inflammation in ARDS.[136] With inflammation being a major cause of severity of COVID-19, supplementation with Vit C is hypothesized to aid in counteracting the actions of pro-inflammatory cytokines, especially IL-6. Treatment with Vit C (500 mg twice a day)[137] and its intravenous administration (doses of 6 to 12 g/day and 24 g/day for seven days) (NCT04264533) reduces the levels of IL-6 and other inflammatory cytokines (ferritin and D-dimer).[138] Vit C as an adjunct treatment could help in reducing the pneumonia-like symptoms and significantly reduce the mortality rates.[139]

Clinical trials are being carried out with a combinatorial treatment of Vit C along with other substances such as quercetin, vitamin D and zinc in different formats (IV or oral dosages) to treat COVID-19.[137] Co-administering quercetin with Vit C and vitamin Vit B3 in mice with stress-induced H1N1 infection showed a delay in the time-to-death and reduced the mortality, as opposed to administration of single vitamins.[140] A similar co-administration of Vit C along with quercetin, vitamins D and B3 could help to ameliorate the symptoms of severe COVID-19 cases. Vit C is known to increase the efficacy of quercetin[139] and a combinatorial therapy of quercetin (500 mg)—Vit C (500 mg)—bromelain (50 mg) as a prophylactic treatment on health-care workers was found to be effective over a three-month study.[141]

Table 7 Bioactive Peptides and Their Functional Properties in Ameliorating Metabolic Diseases

Bioactive Peptides	Activity	Study, Year, Reference
Casein hydrolysates (eg VPP, IPP, QEPV, glycomacropeptide (GMP) etc)	Inhibit c-Jun N-terminal kinase (JNK) pathway, exhibit hypolipidemic effects, increase levels of IL-10	Chakrabarti and Wu, 2015; Ortega-González et al, 2014; Nakamura et al, 2013,[123–125]
Whey protein hydrolysates	Reduce IL-8 levels in pathogen infected respiratory cells	Iskandar et al, 2013,[126]
Egg tripeptides (eg IRW, IQW)	Inhibit NFκB pathway, regulate RAAS pathway	Majumder et al, 2013,[127]
Soybean hydrolysates (eglunasin, VPY, FLV)	Inhibit NFκB pathway, reduce COX-2 levels, reduce cytokine storm (TNF-α, IL-6 and MCP-1) in airway inflammation, reduction of oxidative stress	de Mejia and Dia, 2009; Kovacs-Nolan et al 2012[128,129]
Fish protein hydrolysates (eg PAY)	Reduce obesity-induced inflammation, reduce levels of TNF-α, IL-6 and IL-1β	Bjørndal et al, 2013[130]
Chicken collagen hydrolysate	Reduces levels of pro-inflammatory cytokines, regulate lipid profiles	Zhang et al, 2010[131]
Wheat gluten hydrolysate (eg pEL)	Reduce levels of TNF-α and IL-6, inhibit NFκB and MAPK pathway	Suzuki et al, 2011 Hirai et al, 2014,[132,133]
Rye secalin-derived hydrolysates (QCA, CQV, QVC, QCV)	Inhibit ADAM metallopeptidase domain 17 (*ADAM17*)	Udechukwu et al, 2017,[134]

Vitamin D

Studies have indicated the role of vitamin D (Vit D) in immune modulation. The review by Grant et al,[142] mentions the different mechanisms by which Vit D may exert its antiviral effectiveness. It has been observed that Vit D downregulates the ACE2 receptors by negatively regulating the renin-angiotensin system (RAS).[143] A recent study observed an association between COVID-19 severity and the high latitude countries which receive less sunlight leading to Vit D deficiency in people. However, this observation needs to be taken with the understanding that every population would show a mix of people suffering/not suffering from Vit D deficiency and hence generalizations as such may be difficult.[144]

Ghavideldarestani et al[145] suggested the role of Vit D in preventing local lung inflammation in COVID-19 patients. Angiotensin II through binding to the receptor AT1 can increase vasoconstriction, oxidative stress and inflammation. This angiotensin II can be cleaved by ACE2 into angiotensin1-7 which counteracts the harmful effects of angiotensin II. However, in patients with COVID-19, the ACE2 is hijacked by the virus for its entry and hence less of it is available for this regular physiological role. Vit D deficiency is shown to increase renin production thereby increasing ACE and angiotensin II production. This can lead to inflammation in the lungs that is observed in severe cases of COVID-19.

Glinsky[16] took a gene-first approach to investigate potential therapeutic targets for COVID-19. They first identified the human genes responsible for the expression and function of *ACE2* and *FURIN*, the attachment molecules of the virus. Next, they studied the expression profile of these genes when infected by the coronavirus. This was followed by searching the literature for molecules that may downregulate the concerned gene expression which led to the discovery of three potential therapeutic molecules—Vit D, quercetin, and estradiol. Vit D was found to alter the expression of 84 of 332 (25%) genes encoding human proteins that serve as target for the SARS-CoV-2. The author suggested a two-ingredient (quercetin-Vit D) or a three-ingredient (quercetin-Vit D-estradiol) formulation as an adjunct therapy for coronavirus patients. In fact, two clinical studies involving Vit D are already registered.

Given the potent antiviral effects of quercetin, especially in the crucial stages of viral entry and its replication, and the ability of ascorbic acid and Vit D to efficiently reduce the oxidative stress induced by inflammation and activate the RAS pathway, respectively, adjunct therapy with these molecules is an approach that warrants further research for its potential benefits.

Lactoferrin

Lactoferrin, experimentally, has been found to inhibit viral entry in murine coronavirus, and human coronaviruses hCOV-NL63 and pseudotype SARS-CoV. Besides preventing viral entry, lactoferrin can also suppress virus replication after the viral entry. Lactoferrin was shown to

chelate ferritin thereby downregulating IL-6 and TNF-alpha. There is a clinical trial currently underway to study the effect of lactoferrin as an adjunct therapy for COVID-19.[146]

Conclusion

Studies have hitherto revealed many details about the SARS-COV-2 virus infection. Although we have gained insights into the SARS-CoV-2 viral pathogenesis, a definitive treatment course is still distant. In such times, the intelligent way is to maintain the best possible health by taking suitable adjuvants to avoid falling ill.

It is evident that there are many ingredients that can be included in daily diet to possibly gain immunity or protection against coronavirus. Polyphenols, leguminous seeds containing plant protease inhibitors, as well as proteins, such as whey protein or jackfruit seed protein, could be incorporated in the daily diet. Other bioactive polyphenols, such as EGCG, GCG are common constituents of green tea, quercetin is found abundantly in apples while hesperetin is present in citric foods. These foods can also become components of daily diet. Spices such as turmeric, thyme, rosemary, garlic have anti-inflammatory properties and can be used in daily cuisine. In conclusion, the current review highlights the potential benefits of a range of nutraceuticals in the management of COVID-19. Further work aimed at clarifying the mechanisms of actions and potential therapeutic utility requires further investigation.

Abbreviations

WHO, World Health Organization; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; ACE2, angiotensin converting enzyme 2; TMPRSS2, transmembrane serine protease 2; 3CLPro, chymotrypsin like cysteine protease; MPro, main protease; nsps, nonstructural proteins; DMVs, double membrane vesicles; RdRp, RNA dependent RNA polymerase; PLPro, papain-like protease; FDA, Food and Drug Administration; GRAS, generally regarded as safe; EGCG, epigallocatechin gallate; GCG, gallocatechin gallate; URTIs, upper respiratory tract infections; UPR, unfolded protein response; ARDS, acute respiratory distress syndrome; PAMPs, pathogen-associated molecular pattern; PRRs, pattern recognition receptors; TLRs, toll-like receptors; IFNs, interferons; APCs, antigen presenting cells; MAPKs, mitogen-activated protein kinases; JNK, c-Janus kinase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SPMs, specialized proresolving mediators; SCFA, short chain fatty acids; RAS, renin-angiotensin system; ADAM17, ADAM metallopeptidase domain 17; ER, endoplasmic reticulum; RBD, receptor binding domain; CTD, C-terminal domain; NTD, N-terminal domain.

Acknowledgments

The authors are thankful to AIPL Director Mr Cyrus P Mistry for his unstinting support and motivation.

Disclosure

The authors are employees of Arna Immuno Ingredients Private Limited and report no other potential conflicts of interest in this work. This article/research received no external funding.

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