Dietary Supplements for COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is a highly contagious infectious disease that can rapidly escalate to respiratory failure and death. It has infected millions of people worldwide. The trajectory of this disease continues to progress in some areas of the United States and worldwide. The Institute for Health Metrics now predicts a resurgence of infections in the fall of 2020. The pathogenesis of COVID-19 includes an inflammatory phase with either resolution or the potential to accelerate to a cytokine storm, characterized by high interleukin (IL)-6 and other inflammatory markers. COVID-19 is a condition without a gold-standard treatment. The US Federal Drug Administration (FDA) issued an emergency use authorization for remdesivir in severe cases of COVID-19, which shortened the recovery time in hospitalized patients with lower respiratory tract infection in one study. Although several vaccine trials are underway, no vaccines are available for primary prevention of COVID-19 at this time. Dietary supplement sales have dramatically risen during the COVID-19 pandemic despite depressed economic conditions. Commonly used immune-modulating dietary supplements, including vitamin D, ascorbic acid, zinc, and melatonin, are reviewed in this manuscript highlighting biological plausibility for salutary benefit against COVID-19. Ongoing clinical trials recruiting subjects at the time of this writing are provided for each dietary supplement.

Keywords

COVID-19 · Cytokine storm · Inflammasome · Melatonin · SARS-CoV-2 · Vitamin D · Vitamin C · Zinc

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29.1 Introduction

29.1.1 COVID-19: Epidemiology and Pathogenesis

Coronavirus disease 2019 (COVID-19) is responsible for the third major coronavirus (CoV) pandemic in recent history (Mahase 2020). There is no definitive treatment for COVID-19, which remains a highly contagious infectious disease that can escalate rapidly to respiratory failure and death (Mahase 2020). The pandemic of COVID-19 has infected over nine million people worldwide, including over two million people in the United States ((JHU); Jin et al. 2015; Urwyler et al. 2019). The trajectory of disease continues to progress in some areas of the United States and worldwide, and the University of Washington Institute for Health Metrics and Evaluation (IHME) now predicts a resurgence of infections in the fall of 2020 ((IHME) 2020). Overall, 81% of adults infected by COVID-19 self-resolve while 19% progress, and many require hospitalization ((JHU)). Older people aged 65 or over and those with comorbidities (immunocompromised, cardiopulmonary disease, cancer, diabetes, obesity, and kidney failure) are most at risk to experience rapid disease progression, respiratory deterioration requiring intensive care unit (ICU) admission, and mortality (Park et al. 2020; Zhou et al. 2020). COVID-19 is classified according to four levels of severity based on symptoms: mild, moderate, severe, and critical (Siddiqi and Mehra 2020). Critical disease has a 49% case fatality rate related to acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), septic shock, and multiorgan failure) (Wang et al. 2020c).

The pathogenesis of COVID-19 illness proceeds variably according to distinct phases of the disease:

- Incubation with asymptomatic viral replication.
- Symptomatic with constitutional, respiratory, and other systemic symptoms (i.e., gastrointestinal) of variable duration and severity.
- An inflammatory phase with either resolution or acceleration to a cytokine storm, whereby severe illness is associated with increased plasma concentrations of pro-inflammatory cytokines, including interleukin (IL)-6, IL-10, granulocyte colony-stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP)-1α, and tumor necrosis factor (TNF)-α (Huang et al. 2020; Alunno et al. 2020). Most severe conditions, such as multiorgan failure, occur in those with high IL-6 levels (Han et al. 2020).

The coronavirus responsible for COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also attaches to toll-like receptors (TLRs) in pulmonary macrophages, causing IL-1-beta production and inflammasome activation. Once inflammasomes are activated, and injurious pro-inflammatory cytokines are produced, an extensive injury with loss of lung tissue and subsequent fibrosis with permanent respiratory dysfunction may result (Conti et al. 2020). Respiratory decompensation is frequent and can include the development of ARDS requiring mechanical ventilation. Angiotensin-converting enzyme 2 (ACE2) converts angiotensin I to angiotensin (1–7), which regulates blood pressure, systemic vascular resistance, and fluid-electrolyte balance. COVID-19 infects human cells as spike (S) protein enters cells via ACE2 receptors. Once inside the cell, furin facilitates the cleavage of COVID-19 spike protein by transmembrane protease serine 2. The glycoprotein cleavage byproduct of S protein facilitates the entry of viral genetic material into the cell. This step appears to be required for infection of lung tissues and occurs in other aggressive viral infections such as dengue, avian influenza, and anthrax (Shang et al. 2020; Walls et al. 2020). However, furin protease activation has not been seen with prior coronavirus infections or its ancestor viruses (i.e., SARS-CoV-1). Conditions associated with elevated furin, including diabetes, obesity, and hypertension, overlap significantly with vulnerability to the

severe form of COVID-19. ACE2 is constitutively expressed in respiratory and oral epithelium, lung parenchyma, and other tissues, including gut epithelium. Increased ACE2 activity under physiologic conditions appears to protect against COVID-19 (Brojakowska et al. 2020). However, higher expression of ACE2 on the surface of cells in COVID-19 is linked to heightened disease severity (Brojakowska et al. 2020). Furthermore, it seems that furin is implicated in the pathogenesis of SARS-CoV-2 infection and potentially in the increased rates of human-to-human transmission. ACE2 expression appears to be associated with COVID-19 severity.

NOD-, LRR-, and pyrin domain-containing protein 3 (*NLRP3*) is an intracellular sensor that detects a broad range of microbial motifs. Inflammasomes are formed by different substances, including lipopolysaccharide (LPS) from bacterial cell walls, pathogen-associated molecular patterns (PAMPs) from viruses, bacteria, and fungi. Inflammasomes can be activated by damage-associated molecular patterns (DAMPs) and pro-inflammatory cytokines (IL-1β, TNFα) (Korakas et al. 2020). Activation of the NLRP3 inflammasome appears to be another critical event in the acceleration of the inflammatory phase of the disease to cytokine storm (Fig. 29.1). Inflammasomes activate caspase-1 leading to pyroptosis, a pathway of cell death is uniquely dependent on caspase-1 (Fink and Cookson 2005), and stimulate maturation and secretion of the pro-inflammatory cytokines, interleukin-1beta (IL-1β) (Parisi and Leosco 2020) and interleukin-18 (IL-18) through nuclear factor kappa-B (NF-κB) signaling. A cytokine storm may occur in COVID-19 patients characterized by a failure of the immune system to counter regulate NLRP3 inflammasome activity

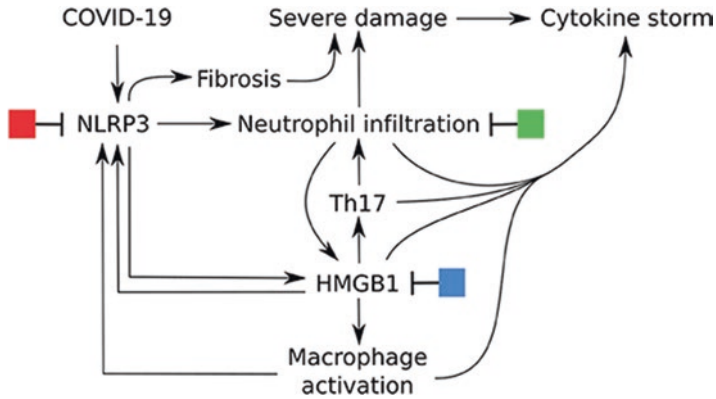

Fig. 29.1 Central role of NLRP3 inflammasome activation in the severe symptomatic phase of COVID-19 and potential options for treatment. The DAMPs released after NLRP3 inflammasome activation have a dual function. In a normal immune reaction, they induce the necessary co-stimulatory activation of the APC, but they also play a role in resolution and tissue regeneration. Only in case of a hyperactivation of the NLRP3 inflammasome DAMPs are released in high concentrations and result in pyroptosis, high-mobility group box 1 (HMGB1) release, activation of macrophages, neutrophil infiltration and reduced apoptosis, excessive cytokine production (IL-1β, IL-2, IL-6, IL-17, TNF-α, GM-CSF, IFN-γ, CXCL10, CCL2, and CCL3, cytokine storm), and fibrosis *DAMPs* damage-associated molecular patterns, *NLRP3* NOD-, LRR- and pyrin domain-containing protein 3, *PAMPs* pathogen-associated molecular patterns, *IL-1β* interleukin-1 beta, *IL-2* interleukin-2, *IL-6* interleukin-6, *IL-7* interleukin-7, *TNF-a* tumor necrosis factor-alpha, *CXCL10* interferon gamma-induced protein 10 or chemokine 10, *GM CSF* granulocyte colony-stimulating factor, *CCL2* C-C motif chemokine ligand 2, *CCL3* C-C motif chemokine ligand 3, *NF-κB* nuclear factor kappa-B, *Th17* T-helper 17 cells, *HMGB1* high-mobility group box 1 Adapted with permission (van den Berg and te Velde 2020)

(Paramo 2020). Modulation of ACE2 expression and furin proteases and prevention of the induction NLRP3 are targets of therapy in COVID-19.

29.1.2 COVID-19: Current Treatment Paradigm

Investigational therapies against COVID-19 that are being tested include antiviral agents, immune modulators, cellular therapies, vaccines, convalescent plasma, traditional Chinese medicines, combination agents, or other medications (Bhagavathula et al. 2020; Guo et al. 2020). Hospitalization for COVID-19-related complications is primarily for supportive care, as therapies to prevent the progression of the respiratory disease remain investigational.

The treatment with the most testing thus far has been the antiviral remdesivir. A double-blind, randomized placebo-controlled trial (RCT) of 1063 patients with COVID-19 and lower respiratory tract involvement compared to remdesivir (200 mg loading on day one, 100 mg daily days 2–10) to placebo and showed benefit in shortening recovery time from 15 to 11 days (rate ratio for recovery, 1.32; 95% CI, 1.12–1.55; $P < 0.001$) (Beigel et al. 2020). The benefit was seen mainly in those with a severity score of 5 (required oxygen), which represents more severe disease. Remdesivir may facilitate quicker recovery for patients who are hospitalized with COVID-19 and require supplemental oxygen therapy.

Wang et al. reported a double-blind RCT of 237 hospitalized patients with COVID-19 lower respiratory tract infections and severe disease, comparing intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) to placebo infusions for 10 days (Wang et al. 2020d). The primary endpoint was clinical improvement up to day 28, defined as the time from randomization to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1 = discharged to 6 = death) or discharged alive from the hospital, whichever came first. The study was terminated before reaching the anticipated sample size as stringent public health measures in Wuhan created difficulties with enrollment. The intention to treat populations did not show a difference in time to clinical improvement. However, those who had symptom onset in less than 10 days before treatment appeared to trend toward benefit with remdesivir over placebo.

Goldman et al. conducted a randomized non-placebo-controlled clinical trial of remdesivir in 397 patients who underwent 1:1 randomization with intravenous remdesivir for either 5 days or 10 days. A total of 200 subjects were treated for 5 days, and 197 were treated for 10 days. Remdesivir was administered intravenously to subjects at 200 mg on day 1 and then 100 mg once daily after that. The primary endpoint was the clinical status of subjects on day 14, assessed on a 7-point ordinal scale. There was no difference between a 5-day course and a 10-day course of remdesivir in non-ventilated subjects with severe COVID-19. Both groups showed an improvement by reduction of 2 more points in the 7-point ordinal scale [64% (5 days) vs. 54% (10 days), $p = 0.14$] (Goldman et al. 2020). However, a placebo was not utilized, limiting the conclusions drawn from the study.

Treatment to prevent the progression of COVID-19 to severe disease is lacking, and the public is using a variety of nutraceutical agents as a preventative measure to prevent or mitigate the progression of COVID-19 (Table 29.1) (Hemila and Chalker 2013). The nutraceutical agents with biological plausibility (Iddir et al. 2020) with the potential to address in part the pathophysiology of COVID-19 are being explored in clinical trials (clinicaltrials.gov, WHO database) and are reviewed below.

29.2 Dietary Supplements Being Studied for COVID-19

29.2.1 Ascorbic Acid

Ascorbic acid contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune systems (Holmannova et al. 2012). Ascorbic acid accu-

Table 29.1 Summary of dietary supplements being studied in clinical trials

Dietary supplements used by the public and in clinical trials	Dose	Mechanism(s) of action				
	Oral = PO Intravenous = IV	Innate and/or adaptive immunity	Antiviral	NLRP3	Cytokines	Adverse events
Ascorbic acid	1–3 g PO daily Intravenous doses (12–24 g daily) used in the critical care setting	xx	xx			Risk of loose stools at high doses >5 ms daily. History of oxalate kidney stones a contraindication
Curcumin	500–1000 mg PO twice daily	xx	xx	xx	xx	GI intolerance in formulations that use black pepper to enhance absorption
Green tea (epigallocatechin gallate; EGCG).	4 cups of tea or 225 mg of EGCG PO daily.	xx	xx	xx	xx	Palpitations from excessive caffeine. Extracts can cause liver injury
Melatonin	5–20 mg PO daily	xx	xx	xx	xxx	Drowsiness.
Quercetin	1000 mg PO twice daily	xx	xx	xx	xx	Generally regarded as safe (GRAS)
Resveratrol	100–150 mg PO daily	xx	xx	xx	xx	NA
Vitamin D	5000–10,000 IU D3 formulation PO daily, emulsified formulation	xx	xx		xx	Risk of hypercalcemia with excessive serum levels [(25(OH) D>100 ng/ml]
Zinc	30–60 mg PO daily, in divided dose	xx	xx			Depletes serum copper. Consider copper supplement

Adapted with permission (Evans et al. 2020)

mulates in phagocytic cells, such as neutrophils, and can enhance chemotaxis, phagocytosis, generation of reactive oxygen species, and ultimately microbial killing (Carr and Maggini 2017). Ascorbic acid has a long history of use for viral respiratory infections, and there is in vitro evidence of its activity against coronavirus in chick embryo ciliated tracheal organ cultures (Atherton et al. 1978). Intravenous ascorbic acid has been shown to reduce the length of stay and ventilator requirements in the critical care unit setting. *Vitamin C* has been shown to shorten the duration of mechanical *ventilation* by about 20% in patients who required mechanical *ventilation* for over a 24 h period (95% CI 7.7% to 27%; p = 0.001) (Hemila and Chalker 2019). In combination with thiamine (Amrein et al. 2011), ascorbic acid and hydrocortisone may improve outcomes among patients with a critical illness such as sepsis and ARDS (Hager et al. 2019, 2020; Fowler 3rd et al. 2019, 2020; Kim et al. 2018, 2019; Hwang et al. 2019; Shin et al. 2019). The putative mechanisms include improvement of pulmonary capillary integrity, correction of sepsis-induced coagulopathy, attenuation of oxidative endothelial injury, and lowering of serum TNF-alpha (Chen et al. 2014).

Vitamin C supplementation could help the prevention and treatment of respiratory and systemic infections (Turski et al. 2020; Carr and Maggini 2017). High doses of ascorbic acid reduce the severity and duration of common cold symptoms caused by rhinovirus, a coronavirus with a typical mild self-limited course if untreated (Hemila and Chalker 2013). The treatment of critically ill patients with ascorbic acid has shown

mixed results on mortality, length of intensive care unit stay, and duration of mechanical ventilation (Carr 2019a, b; Hager et al. 2020). There are some clinical trials involving ascorbic acid for COVID-19 underway (Carr 2020). A clinical trial to investigate vitamin C infusion for the treatment of severe 2019-nCoV-infected pneumonia will treat 140 patients with intravenous vitamin C at a dose of 24 g/day versus matching placebo for 7 days. Study endpoints include the need for mechanical ventilation, vasopressor drug requirements, sequential organ failure assessment scores, intensive care unit length of stay, and 28-day mortality (Identifier: NCT04264533na). Other clinical trials involving ascorbic acid for COVID-19 are registered in clinical trials.gov, and the World Health Organization Trial Registry Network (WHO ICTRP database).

29.2.2 Phytochemicals

Phytonutrients are plant-derived biochemicals, some of which impart disease-fighting health-benefits when ingested. Some phytonutrients are powerful anti-inflammatory agents modulating NLRP3 inflammasome activation, thereby mitigating degenerative diseases (Table 29.2 and Fig. 29.2) (Jahan et al. 2017b). The following

Table 29.2 Phytochemicals shown to inhibit NLRP3 inflammasome activation in disease model systems being studies in COVID-19

Phytochemical	Model system	Inflammasome activator	Signaling pathway	Human disease
Catechins (Green tea)	AGS cells, BALB/c mice	*Helicobacter pylori*	Inhibited NLRP3 and IL-1β activation and caspase-1 signaling	*Helicobacter pylori* infection
Curcumin (*Curcuma longa*)	C57BL/6 mice, murine macrophage cells line J774A.1	LPS, cells infected with Salmonella	Modulated TLR4-NF-κB pathway, inhibits NLRP3 including IL-1β- HMGB-1- ROS	Septic shock
Epigallocatehin-3 gallate (*Camellia sinensis*)	Human metastatic melanoma cell lines; 1205Lu & HS294T, female athymic nu/nu mice, New Zealand lupus mice	Melanoma cells, lupus prone mice	Inhibited NLRP3-ROS-NF-κB activation, impairs caspase-1 and IL-1β expression, enhances autophagy, Nrf2 antioxidant signaling pathway and increases Treg cell activity systemically	Melanoma (skin cancer), systemic lupus erythematous, lupus nephritis
Quercetin (*Quercus tinctoria*)	STZ-induced and fructose fed rat models of diabetic complications in rats	STZ, fructose	Inhibited NLRP3 activation, caspase-1, ASC, IL-1β, -6 and TNF-α, mediates JAK2-STAT3- PPAR-γ & IR-IRS1-Akt-ERK1/2 signaling pathways	Diabetic nephropathy, hyperuricemia dyslipidemia
Sulforaphane (broccoli and other cruciferous vegetables	Murine hepatic cells	High-fat diet	Inhibited NLRP3 expression, ASC and caspase-1, activates AMPK and reduced ROS and mitochondrial dysfunction	Non-alcoholic fatty liver disease

STZ streptozocin, *ROS* reactive oxygen species, *TNF* tumor necrosis factor, *PPARs peroxisome proliferator-activated receptors*, *JAK-2* Janus kinase-2, *ASC* apoptosis-associated speck-like protein containing a CARD, *AMPK* AMP-activated protein kinase, *STAT-3* signal transducer and activator of transcription 3, *IL-1β* interleukin-1beta, *IL-6* interleukin-6, *ERK1/2* extracellular signal-regulated protein kinase 1/2, *IRS1* insulin receptor substrate 1, *Treg* T-regulatory cells, *Nrf2* nuclear factor erythroid *2*-related factor 2, *TLR4* toll-like receptor 4, *NF-kβ* nuclear factor kappa B, *HMGB1* high-mobility group box 1
Adapted with permission (Jahan et al. 2017a)

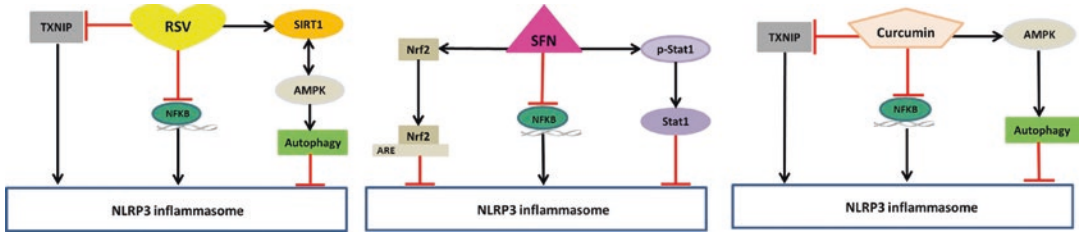

Fig. 29.2 Schematic model illustrating the underlying anti-inflammatory mechanisms of curcumin through regulation of NLRP3 inflammasome activity. Curcumin could suppress the activity of NLRP3 inflammasome through different pathways, including deterrence of K+ efflux, inhibition of ER stress and decreased levels of ROS and TXINP through AMPK activation, prevention of NLRP3 components assembly via blocking the binding of ASC to NLRP3, and suppression of NF-κB signaling pathway, which leads to the prevention of NLRP3 and pro-IL-1β expression
PAMPS pathogen-associated molecular patterns, *DAMPS* damage-associated molecular patterns, *TLR* toll-like receptor, *TNFR* tumor necrosis factor receptor, *NF-κB* nuclear factor kappa-B, *NLRP3* NOD-like receptor pyrin domain-containing 3, *IL-1β* interleukin-1β, *IL-18* interleukin 18, *AMPK* 5′ adenosine monophosphate-activated protein kinase, *ER* endoplasmic reticulum, *ROS* reactive oxygen species, *TXNIP* thioredoxin-interacting protein, *ATP* adenosine triphosphate, *P2 × 7R* purinergic 2 × 7 receptor, *MSU* monosodium urate crystal, *K+* potassium, *Ca+* calcium, *ASC* apoptosis-associated speck-like protein containing a caspase recruitment domain
Adapted with permission (Hassanzadeh et al. 2020)

phytonutrients described here are essential to consider for COVID-19, due to their actions on NLRP3 activation, viral replication, and immunity. Curcumin can exert its anti-inflammatory role mainly by preventing the activation of NLRP3 inflammasomes (Hasanzadeh et al. 2020; Olcum et al. 2020). Curcumin downregulates NF-kappa B (NF-κB) signaling, interrupts IL-1β maturation, and reduces the secretion and release of interleukins. Collectively, these actions are the most prominent mechanisms of curcumin in modulating inflammasomes (Figs. 29.3 and 29.4) (Hasanzadeh et al. 2020). A recent review of phytochemicals and their influence on intracellular signaling mechanisms of action on NLRP3 inflammasome activation focused on sulforaphane (SFN), curcumin, and resveratrol (RSV) (Olcum et al. 2020). SFN, which is present in cruciferous vegetables, was identified as a potent inhibitor of NLRP3 inflammasome activation. SFN is also known as a strong promoter of the Nrf2 transcription factor, which is the primary regulator of numerous cytoprotective, antioxidant, and anti-inflammatory genes in various tissues and cell types, and it has a role in maintaining cellular redox balance (Fig. 29.4). RSV can suppress NLRP3 inflammasome by different mechanisms and pathways, including NAD-dependent deacetylase sirtuin-1 (SIRT1) and autophagy activation. RSV appears to be a potent SIRT1 activator, which alters and inhibits the acetylation of inflammatory proteins (Sui et al. 2016). In most of the studies, RSV inhibits NLRP3 inflammasome via enhancing autophagy by activating SIRT1 (Qi et al. 2019). RSV may also upregulate ACE2 expression and may benefit the host against COVID-19 infection (Horne and Vohl 2020).

Other NLRP3 activation inhibitors include green tea phytochemicals (Zhang et al. 2019; Wang et al. 2020a). Phytochemicals can also prevent and or mitigate COVID-19 by serving as virus main protease (Mpro) inhibitors to replication. A study using molecular docking technology revealed that *Phaseolus vulgaris* phytochemicals had maximum binding with Mpro and ACE2, while quercetin 3-glucuronide-7-glucoside and quercetin 3-vicianoside gave even

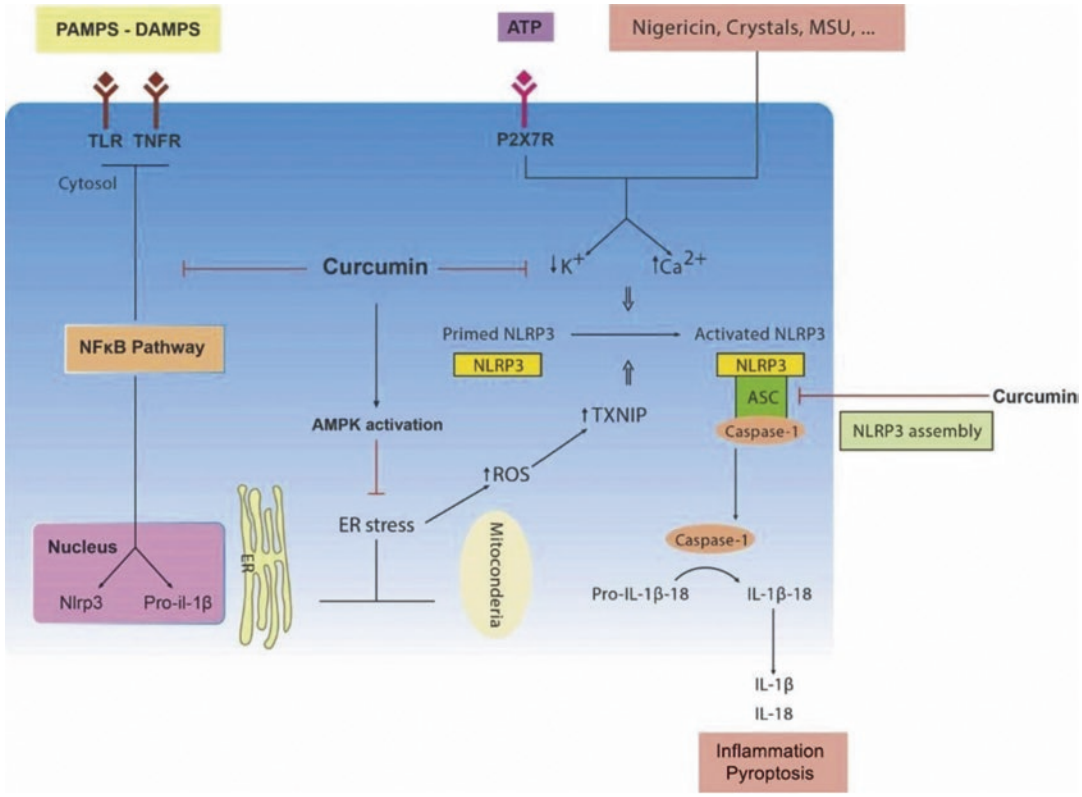

Fig. 29.3 NLRP3 inflammasome suppression mechanisms of sulforaphane (SFN), curcumin, and resveratrol (RSV). All three phytochemicals use NF-kB inhibition to suppress inflammasome activation. Other than this mechanism, SFN leads to inflammasome suppression via Nrf2 activation, STAT-1 activation. RSV and curcumin lead to inflammasome suppression via TXNIP inhibition or leading to AMPK-induced autophagy Adapted with permission (Olcum et al. 2020)

better binding energy with both the targets (Joshi et al. 2020). Quercetin has been shown to inhibit hepatitis C viral replication (Khan et al. 2013) and modulate NLRP3 inflammasome activation, is antifibrotic by stabilizing mast cell function, and promotes resolvins, which stabilize collateral damage to host tissues. A subsequent study also using molecular docking technology showed that robust one exhibited excellent binding affinity properties against Mpro of SARS-CoV-2 (Rasool et al. 2020). This phytonutrient antioxidant flavonoid compound has also been shown to be an inhibitor against the protease of the dengue virus (Mishra et al. 2016). RSV has also been shown to have in vitro activity against coronaviruses such as MERS-CoV and is effective clinically against rhinovirus (Baldassarre et al. 2020; Lin et al. 2017).

29.2.3 Melatonin

Melatonin is receiving increasing attention in the press as a natural product with a multitude of biological effects that may be relevant to COVID-19 (Reiter et al. 2020). Melatonin attenuates several actions that protect the host against COVID-19, including pro-inflammatory cytokine production, inducible nitric oxide synthases, neuronal nitric oxide synthase, cyclooxygenase-2, high-mobility group box 1 signaling, TLR4 activation, inflammasome NLRP3 activation, and NF-κB activation (El-Missiry et al. 2020). Melatonin induces anti-inflammatory cytokines while having a high antioxidant capacity, which buffers the injurious inflammatory injury during the resolution phase of COVID-19 (El-Missiry et al. 2020). In COVID-19, melatonin may increase resistance to

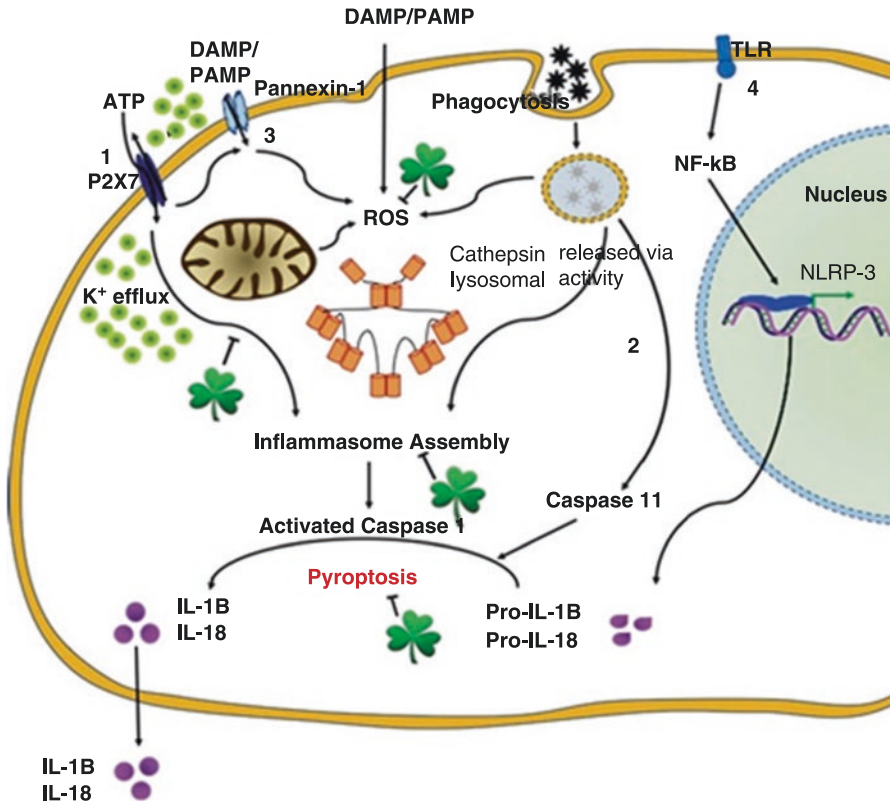

Fig. 29.4 Inflammasome activation pathways concerning disease development and phytonutrients: i, some inflammasome agonists as ATP, triggers P2X7-dependent pore formation by the pannexin-1 hemichannel, allowing extracellular agonists to enter the cytosol and directly trigger inflammasome assembly; ii, crystalline or particulate inflammasome agonists that are engulfed by the cells have characteristic physical properties which lead to lysosomal rupture. The inflammasome senses lysosomal content released in the cytoplasm, for example, via cathepsin B-dependent processing of a direct NLRP3 ligand; iii, all danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), stressed mitochondria including ATP and particulate/crystalline activators, cause the generation of reactive oxygen species (ROS). A ROS-mediated pathway triggers inflammasome complex formation; and iv, toll-like receptor (TLR) senses lipopolysaccharides and prime the NF-κB, a transcription factor which triggers pro-IL-1 and pro-IL-18 expressions which sequentially get converted into IL-1beta and IL-18. Caspase-1 clustering induces autoactivation and caspase-1-dependent maturation and secretion of pro-inflammatory cytokines, such as interleukin-1beta (IL-1b) and IL-18. Against all possible pathways, phytochemicals (shown by green leaf) are used for the therapeutic activity to inhibit inflammasome induced diseases
Adapted with permission (Jahan et al. 2017a)

infection by upregulating ACE2 expression while inhibiting NLRP3 inflammasome activation (Zhang et al. 2019). Multiple actions of melatonin as an anti-inflammatory, antioxidant, and antiviral (against other viruses) make it a reasonable choice for use (Reiter et al. 2020). Mitochondrial intracellular heme oxygenase (HO-1) is low in the elderly, hypertensives, and diabetics, which may relate to COVID-19 susceptibility, and melatonin raises HO-1 (Hooper 2020). Two active COVID-19 clinical trials include melatonin. One clinical trial (NCT04409522) is evaluating the therapeutic effects of high-dose melatonin (9 mg) vs. usual care for 7–10 days in 55 patients with COVID-19 while measuring inflammatory cytokines and pathways to include NLRP3 inflammasome activation. The other study (NCT04353128) involves

450 Spanish healthcare workers who will be randomized to either melatonin 2 mg or placebo before bed for 12 weeks as primary prevention of COVID-19. The World Health Organization (WHO) database lists two melatonin intervention COVID-19 studies: evaluation of the efficacy of melatonin tablets as auxiliary medication in accelerating the improvement of the COVID-19 symptoms and clinical findings (IRCT20200408046988N1) and the effect of melatonin on the quality of sleep in COVID-19 patients (IRCT20200411047030N1).

29.2.4 Vitamin D

Vitamin D, once converted to the active 1,25hydroxyvitamin D (1,25VitD) form, has endocrine and paracrine properties. The paracrine action of 1,25VitD may be most important for immunity. Activated vitamin D augments innate cellular immunity against microbes, protects against bacterial and viral acute respiratory tract infections (including influenza), and regulates adaptive immune responses such as those seen in the COVID-19-associated cytokine storm (Zdrenghea et al. 2017; Martineau et al. 2017). Vitamin D influences T-helper cell (Th) cell differentiation by its effect on antigen-presenting cells (APCs). Vitamin D is involved in APC activity that modulates T-cell differentiation into an effector cell with pro-inflammatory (Th1) or anti-inflammatory (Th2) properties; thus, modulation of APCs is crucial in initiating and maintaining adaptive immune response and self-tolerance. Vitamin D modulates adaptive immunity by suppressing Th1 and Th17 responses that are overactivated in a COVID-19 cytokine storm (Wu and Yang 2020; Miraglia Del Giudice et al. 2018). Vitamin D induces Th2 cytokines such as IL-10, which counterbalance Th1 pro-inflammatory cytokines while increasing T-regulatory cells (Tregs) and their activity (Fawaz et al. 2016). By inducing Tregs and increasing their numbers, vitamin D harmonizes inflammatory responses. In COVID-19, there are reports that Th1/Th17 cytokines are high, Th2 cytokines such as IL-10 are low, and Tregs are low in number and dysfunctional in the setting of a cytokine storm (Wang et al. 2020b; Chen et al. 2020).

Vitamin D enhances innate cellular immunity to prevent and mitigate viral respiratory infections. There are two main mechanisms by which vitamin D has been shown to prevent viral respiratory tract infections. One is the promotion of respiratory epithelial and alveolar barrier function junctions to prevent the infiltration of immune cells in the lungs and other respiratory tissues. The other is an increased immune-enhanced viral killing while avoiding injurious inflammatory response (Grant et al. 2020). Vitamin D enhances the production of β-defensin-2 and LL-37 cathelicidin. Pulmonary epithelial cells have a high expression of 1α-hydroxylase, which produces calcitriol, the active form of vitamin D. Calcitriol inhibits bronchial smooth muscle cell proliferation and elaboration of pro-inflammatory cytokines, chemokines, and matrix metalloproteinases, preventing lung injury (Sandhu and Casale 2010). Vitamin D upregulates cAMP, not only by monocytes and macrophages but also in cells participating in the innate immune system, including the respiratory tract, by increasing their antimicrobial activity and epithelial barrier function (Dhawan et al. 2015).

Vitamin D is well-known to participate in the defense against some respiratory pathogens, including intracellular pathogens and bacterial and viral pathogens (Anderson et al. 2020). Lower-serum vitamin D levels are associated with adult new-onset severe sepsis, including septic shock, and high doses of enteral vitamin D3 (400,000 IU) have been shown to increase circulating cAMP and reduce inflammatory cytokines IL-6 and IL-1 when compared to placebo (Quraishi et al. 2015). In viral respiratory infections, vitamin D metabolites modulate several chemokines and pro-inflammatory cytokines (CXCL8, CXCL10, TNF-α, and IL-6) (Greiller and Martineau 2015). Observational and interventional studies demonstrate that Vitamin D can impart primary and secondary protection against viral respiratory tract illness (Teymoori-

Rad et al. 2019; Beard et al. 2011). A meta-analysis of 25 eligible randomized controlled trials (total 11, 321 participants) concluded that Vitamin D supplementation was safe and protected against acute respiratory tract infection (adjusted odds ratio 0.88, 95% confidence interval 0.81–0.96) (Martineau et al. 2017). Patients who were very vitamin D-deficient as defined by baseline 25-hydroxyvitamin D levels <25 nmol/L (adjusted odds ratio 0.30, 0.17–0.53) derived more protection against respiratory tract infection compared to patients who were not so identified with baseline 25-hydroxyvitamin D levels ≥25 nmol/L (adjusted odds ratio 0.75, 0.60–0.95). Those not receiving bolus doses experienced the most benefit (adjusted odds ratio 0.81, 0.72–0.91).

There is growing speculation that vitamin D deficiency may render hosts vulnerable to COVID-19 infection and that vitamin D may serve a primary and secondary preventative role (Weir et al. 2020; Grant et al. 2020; Wei and Christakos 2015; Dhawan et al. 2015). Countries related to high mortality rates early in the COVID-19 pandemic (Italy, Spain, and the United Kingdom) are more likely to suffer from lower vitamin D levels than countries that were not as severely affected (Grant et al. 2020). An analysis of a world database by investigators at Northwestern University examined severe SARS-CoV-2 illness and vitamin D deficiency prevalence; data revealed that the risk of severe SARS-CoV-2 cases among patients with severe vitamin D deficiency was 17.3%, compared with a risk of 14.6% for patients with normal vitamin D levels (a relative reduction of 15.6%) (Daneshkhah et al. 2020). The authors suggested that the correction of vitamin D deficiency may reduce SARS-CoV-2 severity by suppressing the cytokine storm. The WHO database lists one study that is actively recruiting; IRCT2020040146909N1 9 (https://en.irct.ir/trial/46875), an RCT to evaluate the efficacy of 1000 IU of vitamin D3 or placebo daily for 8 weeks. The duration of COVID-19 infection is the primary endpoint and the WHO severity scale as the secondary endpoint.

29.2.5 Zinc

Zinc is a micronutrient with an established role in robust and effective immune responses, including antiviral immunity and adaptive immune responses, including antibody formation (Gammoh and Rink 2017). Older adults (65 years and older) are at increased risk of zinc insufficiency or deficiency. Further, because of the high incidence of diarrhea with SARS-CoV2 infection (seen in approximately 20% of patients), it was possible to assume these patients were zinc insufficient (Lee et al. 2020). Zinc is particularly attractive to consider in SARS-CoV2 infection. In vitro studies show zinc to inhibit coronavirus RNA replication (Fig. 29.5) (te Velthuis et al. 2010; Read et al. 2019). Zinc lozenges at symptom onset reduce the duration of symptoms from illness attributed to more innocuous coronavirus infections (i.e., the common cold) (Mossad et al. 1996; Hemila 2017; Hemila et al. 2020). Also, hydroxychloroquine (HCQ) mobilizes zinc into lysosomes suggesting there may be synergy between HCQ and zinc to amplify efficacy (in vitro data support this synergy in cell culture assays of HCQ-induced cytotoxicity and HCQ-induced inhibition of autophagic flux) (Xue et al. 2014). The WHO database lists one study using zinc sulfate (IRCT20180425039414N2; https://en.irct.ir/trial/47516). It investigates the effect of 220 mg of zinc sulfate on the clinical course of 80 inpatients with COVID-19. Forty patients will receive a combination of zinc sulfate 220 mg with hydroxychloroquine 200 mg twice daily and then once for 5 days, and the other 40 patients will receive only hydroxychloroquine in the same manner in a parallel clinical trial at the Esfahan University of Medical Sciences in Iran (https://en.irct.ir/trial/47516).

29.3 Conclusion

There is a dearth of surveys to precisely indicate the usage of dietary supplements by the public for COVID-19. However, the dietary supplement industry has reported a global boost in sales during the COVID-19 pandemic as people sought

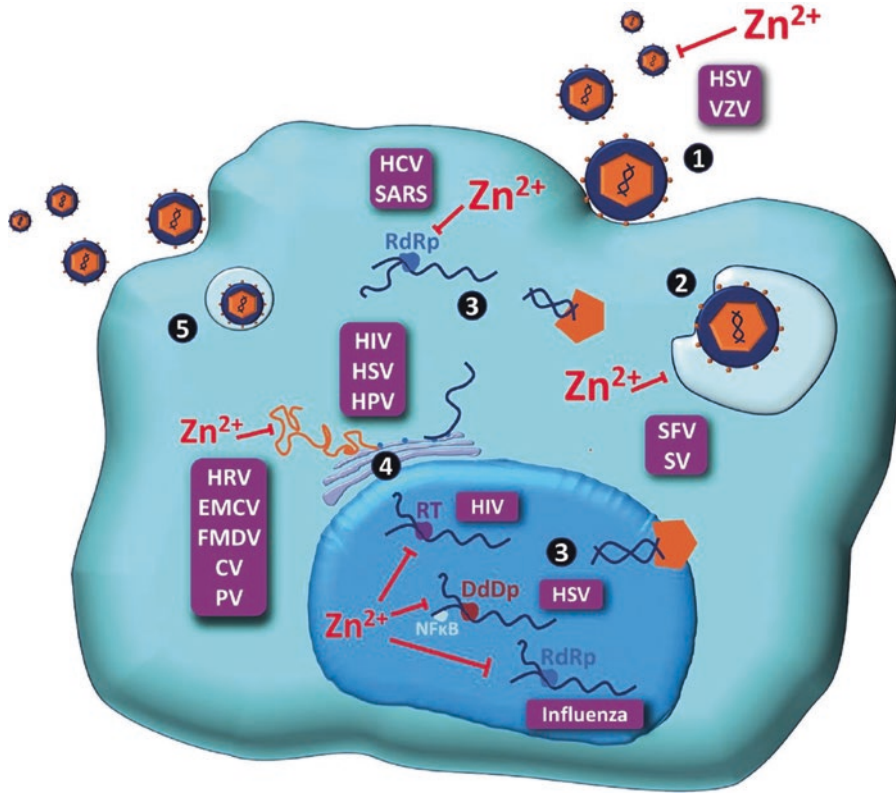

Fig. 29.5 The diverse stages of viral replication cycles that are inhibited by zinc. In vitro studies have demonstrated some mechanisms by which zinc interferes with the viral replication cycle. These include free virus inactivation: i, inhibition of viral uncoating; ii, viral genome transcription; iii and iv, viral protein translation and polyprotein processing. No studies to date, however, have demonstrated zinc-mediated inhibition of virus assembly and/or particle release

CV coronavirus, *DdDp* DNA-dependent DNA polymerase, *EMCV* encephalomyocarditis virus, *FMDV* foot and mouth disease virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *HPV* human papilloma virus, *HRV* human rhinovirus, *HSV* herpes simplex virus, *PV* polio virus, *RdRp* RNA-dependent RNA polymerase, *RT* reverse transcriptase, *SARS* severe acute respiratory syndrome coronavirus, *SFV* Semliki Forest virus, *SV* sindbis virus, *VZV* varicella-zoster virus, *Zn* zinc

Adapted with permission (Read et al. 2019)

the aid of natural medicines in an attempt to prevent or mitigate COVID-19. There is some evidence to indicate that immune-modulating dietary supplements may play a role in benefiting the public from COVID-19. However, dietary supplements are not without cost or potential harm, albeit low risk in the majority of cases. Any benefit of dietary supplements against COVID-19 depends on biological plausibility, the peer-reviewed literature, not direct studies in humans, preferably RCT. The approach was heuristic and served its place at a time when morbidity and mortality spread across the world in an uncontrolled manner. Ultimately, the many clinical trials underway now that will soon illuminate whether the millions of dollars spent by the public and their actions during the COVID-19 pandemic had any merit. Only time will tell.

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