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Inflammopharmacology

REVIEW

Lycopene: a therapeutic strategy against coronavirus disease 19 (COVID- 19)

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Abstract

Lycopene is a group of phytochemicals found in nature, primarily in fruits and vegetables. Lycopene is thought to protect against a variety of diseases attributed to its antioxidant capabilities. Lycopene has anti-inflammatory, anti-cancer, and immunity-boosting qualities, among other biological and pharmacological benefits. COVID-19 (coronavirus disease 19) is an infectious disease caused by the SARS-CoV-2 virus, which has recently emerged as one of the world's leading causes of death. Patients may be asymptomatic or show signs of respiratory, cytokine release syndrome, gastrointestinal, or even multiple organ failure, all of which can lead to death. In COVID-19, inflammation, and cytokine storm are the key pathogenic mechanisms, according to SARS-CoV-2 infection symptoms. ARDS develops in some vulnerable hosts, which is accompanied by an inflammatory "cytokine syndrome" that causes lung damage. Immunological and inflammatory markers were linked to disease severity in mild and severe COVID-19 cases, implying that inflammatory markers, including IL-6, CRP, ESR, and PCT were significantly linked with COVID-19 severity. Patients with severe illness have reduced levels of several immune subsets, including CD4 + T, NK, and CD8 + cells. As a result, lycopene can be commended for bolstering physiological defenses against COVID-19 infections

Keywords COVID-19 · Lycopene · Pro-inflammatory cytokine · Immune response · Oxidative stress

Introduction

Wackenroder discovered an orange pigment in carrots (Daucus Carota) in 1831 and named it "Carotene" after the Latin term Carota (Pfander 1992). Carotenoids are antioxidants that may have an impact on the immune system (Mihailovic et al. 2021), exhibiting a wide range of biological effects in addition to acting as an immunomodulator, influencing T and B cell activity, inducing differentiation, and inhibiting cell proliferation in some cells, and influencing humoral and cellular immunity (Zhao et al. 2017). Lycopene is a dietary component that can be derived from a variety of plant sources. They are potential antioxidants and have been found to possess free radical scavenging activities and antioxidative (George et al. 2004; Shami and Moreira 2004). Color is the first thing a customer notices about a product, and it sets expectations for quality and flavor (Di Mascio et al. 1989; Magne et al. 2022). Lycopene and other hydrocarbon carotenoids are made completely of hydrogen and carbon. Lycopene has two non-conjugated double bonds and eleven conjugated double bonds. It's lipophilic, meaning it dissolves better in fat. Cis–trans isomerization happens due to their double bonds (see Fig. 1) (Rao and Rao 2007). Lycopene is also high in vitamins K, A, C, fiber, and carbohydrates, as well as a little amount of iron, potassium, phosphorus, and sulfur. Furthermore, it has a minimal sodium, fat, and calorie content. Tomatoes are a good source of lycopene, while other popular sources include watermelon, grapefruit, and guava (Fig. 2).

COVID-19 was discovered in Wuhan, China in December 2019 from a cluster of pneumonia patients linked to a

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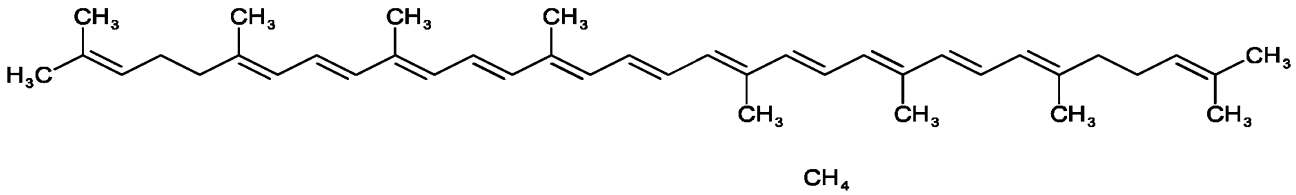

Fig. 1 Chemical structure of lycopene (C40H56, Mw: 536.873 g/mL)

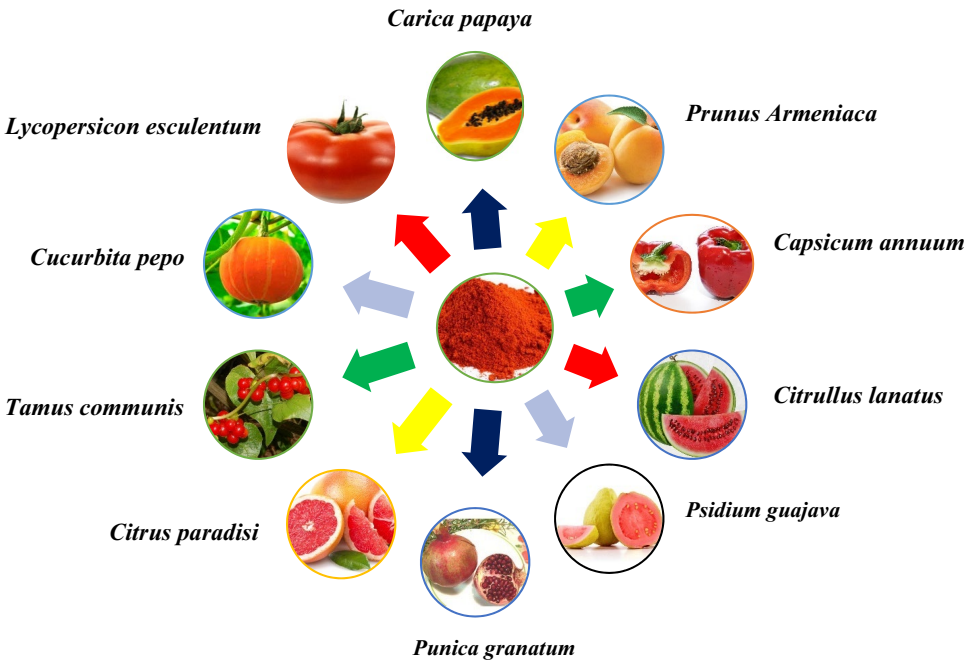

Fig. 2 The main sources of lycopene

seafood wholesale market (Nandan et al. 2021; Adelodun et al. 2022). The COVID-19 epidemic has infected practically every country and territory in the world (Tavakoli et al. 2020; Zhu 2019). Acute respiratory distress syndrome (ARDS) in COVID-19 patients is caused by the activation of a cytokine storm and inflammatory signaling pathways. The innate immune system is dysregulated when chemokines and pro-inflammatory cytokines are secreted in excess. This is observed in both COVID-19 and SARS, and viral load is unrelated to symptoms worsening in SARS (Mehta et al. 2020; Stebbing et al. 2020). A loss of beneficial lung surfactants, as well as increased oxidative stress and inflammation, characterizes ARDS (Wu et al. 2020).

A total of 6,324,112 deaths and 539,893,858 confirmed cases of COVID-19 have been reported to WHO as of June 23, 2022. SARS-CoV-2 is a single-stranded RNA virus with a genomic length of around 30,000 nucleotides belonging to the *Betacoronavirus* genus, one of four *Coronaviridae* genera that cause respiratory and enteric infections affecting both humans and animals (Zhu 2019). It has a modest substitution rate per site, ranging from 1.5 to 10^{-4}. A prevalence of cytosine (C) to uracil (U) transitions characterizes sequence alterations, which can be attributed to pyrimidine deamination. There is a nearly twofold excess of U over C, resulting in 32% uracil and 18% cytosine (Hou 2020). When compared to SARS-CoV, the nucleocapsid proteins and envelope of 2019-n CoV/SARS-CoV-2 are two evolutionarily conserved regions, with 89.6% and 96% of sequence identity, respectively (Hou 2020). SARS-CoV-2 primarily infects bronchial epithelial cells and alveolar epithelial angiotensin-converting enzyme-2 (ACE2) pneumocytes, while immunodetection and RNA sequencing have shown that vascular muscle cells (VSMC) contain ACE2 (Barbry et al. 2020; Hamming et al. 2004; Nicin et al. 2020; Thum 2020).

In the initial stages of COVID-19 infection, delayed cytokine production was observed in respiratory epithelial cells, macrophages, and DCs. Pericytes and microvascular smooth muscle cells, but not endothelial cells, express ACE2, which could reveal significant details about COVID-19 pathology (He et al. 2020). The receptor-binding domain (RBD) of SARS-spike CoV-2's protein was quite similar to

that of bat SARS-like coronaviruses. The discovery of several SARS-like COVs in bats has led to the hypothesis that these species serve as natural reservoirs for these viruses. Endocytosis of the SARS-CoV-2 virion is triggered by RBD binding to ACE2, exposing it to endosomal proteases (Wu et al. 2020b). A cytokine storm occurs in one out of every two fatal COVID-19 cases, with 82% of those over 60 years old (Paranjpe et al. 2020). Upregulation of several other pro-inflammatory mediators, including ACE2, is seen in the endothelial response to pericyte loss. Such pro-inflammatory endothelium changes, on the other hand, appear to occur even when there is no significant vascular inflammation. It's possible that if pericytes become infected with SARS-CoV-2, they'll become immunological targets. The increase in inflammation in severe COVID-19 cases could be due to the spread of microvascular inflammation (Varga et al. 2020).

Currently there are no treatment medicines that have been demonstrated to be effective against the virus (Ofuyatan et al. 2022). As a result of the pandemic, many supportive medications, such as ivermectin, and remdesivir which reduce viral RNA activity, were deployed. In combination with favipiravir, nafamostat mesylate therapy may allow for virus entry and replication suppression as well as prevention of the pathogenic host response, i.e. hyper-coagulopathy (Ikeda et al. 2020). The most promising antiviral agent is remdesivir, which has been licensed by the FDA for emergency use, although clinical trials are still underway (Mahboobipour and Baniasadi 2021; Wang et al. 2021a).

Immunotherapy can be employed in the most serious and life-threatening situations. Immunotherapy should not be given to patients who are currently unwell, such as those who have tuberculosis (Prattes et al. 2021).

The MERS and SARS outbreaks generated interest in such viruses, and researchers have found several antiviral targets, including polymerases, entry proteins, and viral proteases. However, more work is still needed to create drugs that target these pathways and can inhibit viral replication. Because SARS-CoV2 is an RNA virus, it can be detected using any of the existing RNA detection formats. When nasopharyngeal swabs are initially negative, repeat testing can be done to boost the chances of discovering SARS-CoV-2 in the nasopharynx (Loeffelholz and Tang 2020). Globally, COVID-19 treatment strategies are still limited. Vitamin (VA) has pharmacological efficacy in the treatment of pneumonia, it could be used in a SARS-CoV-2 antiviral treatment. VA's methods of action against SARS-CoV-2, according to bioinformatics research, include immunoreaction enrichment, inflammatory reaction suppression, and biological processes involving reactive oxygen species (Li et al. 2020b).

In humans, high amounts of lycopene can be found in the prostate, testes human plasma, and adrenal gland. It has been determined to be a safe substance for daily dietary use, with no adverse health effects even at the highest dose of 3 g/kg/day (Gupta et al. 2015). Lycopene was shown to improve the status of enzymatic activity in the cell and act as an important antioxidant—both enzymatic (catalase, glutathione reductase, and superoxide dismutase) and nonenzymatic (vitamins B, E, and C, carotenoids, and carnitines) antioxidants under normal operating conditions (Durairajanayagam et al. 2014). Lycopene is a natural antioxidant, anti-inflammatory, and antiviral agent that can help prevent and treat inflammatory diseases like COVID-19. Lycopene is a non-provitamin A and is well known for its antioxidant properties. Lycopene could be an effective pharmacological therapy for treating liver damage induced by long-term CS treatment (Rocha et al. 2021). In finishing pigs, dietary lycopene supplementation improved intestinal shape, and tight junction function inhibited inflammatory response and increased antioxidant capacity (Liu et al. 2021).

Currently, there is no effective anti-SARS-CoV-2 drug available to treat COVID-19 patients worldwide. In many diverse cultures, natural herbal treatments have been utilized for a long time to treat ailments. The effectiveness of traditional remedies produced from medicinal plants has contributed to the success of modern medicine. Antiviral drugs given early after the onset of symptoms can reduce viral shedding in patients' respiratory secretions, which lowers the risk of infection for contacts of those who are receiving treatment. The most prevalent clinical problems associated with the antiviral drug have been reported to be decreased appetite, constipation, and diarrhea (Ağagündüz et al. 2021). Remdesivir has been shown to have viral activity against coronaviruses in both Vitro and Vivo studies. Remdesivir inhibits SARS-CoV-2 (SARS-CoV-2 RdRp) replication, suppresses viral load, and protects animals infected with SARS-CoV-2 (Frediansyah et al. 2021). Therefore, the most promising Remdesivir antiviral drugs were taken into consideration to assess both their effectiveness and potential side effects on individuals with varying levels of COVID-19. Additionally, type I interferons are immunomodulatory medications that have been effective in treating COVID-19 early on because they have antiviral and pro-inflammatory properties (Hossain et al. 2021). The most common side effects of some patients who are taking remdesivir are increased aminotransferases and gastrointestinal symptoms (vomiting and/or nausea) (Fan et al. 2020). Understanding food-drug interactions are essential for improving the health of patients. Some antiviral drugs, including hydroxychloroquine, umifenovir, remdesvir, favipiravir, ribavirin, lopinavir, nitazoxanide, and oseltamivir, have the capability to interfere with food-drug and nutrition-drug interactions. However, it has been noted that the use of these drugs may have some negative adverse effects and comorbidities. Furthermore, the pharmacokinetic and pharmacodynamic

alterations generated by these supportive care drugs can impact nutrient metabolism both acutely and chronically (Ağagündüz et al. 2021).

The molecular docking analysis revealed that 20 naturally occurring molecules from popular Iranian medicinal plants (such as astragalin, adlumidine, chelidimerine, catechin gallate, rutin, fumariline, somniferine, etc.) have antiviral properties that could protect individuals from contracting SARS-CoV-2 due to their potent binding patterns to the pocket of SARS-CoV-2-RdRp. As a result, these molecules act as inhibitors of the SARS-CoV-2 M^{pro} and RBD receptors (Mousavi et al. 2021). Lycorine, gemcitabine, and oxysophoridine are examples of bioactive alkaloids extracted from Chinese herbal remedies that have antiviral activity against SARS-CoV-2. The three compounds have also been reported to inhibit SARS-CoV-2 replication in Vero E6 cells at noncytotoxic concentrations. (Zhang et al. 2020b). Phytochemicals extracted from *Avicennia officinalis* have excellent antioxidant and cytotoxic properties. Using molecular docking assays, the three compounds (hydrocinnamic acid, dihydroartemisinin, and phenethyl alcohol) reported the highest binding affinities against the main protease of SARS-CoV-2. As a result, *A. officinalis* fruit and leaf extract compounds could be employed therapeutically in response to COVID-19 (Mahmud et al. 2021). *Andrographis paniculate* extracts and their andrographolide component significantly inhibited the SARS-CoV-2 in Calu-3 cells through their anti-SARS-CoV-2 activities (Sa-Ngiamsuntorn et al. 2021). The phytochemicals extracted from *Oxalix pes-caprae* have antiviral potential, and molecular docking analysis revealed that four natural compounds (Caeruleanone A, vadimezan, matairesinol, and 2′,4′-Dihydroxy-2′′-(1-hydroxy-1-methylethyl) dihydrofuro [2,3-h] flavanone) are promising SARS CoV-2 M^{pro} (6LU7 M^{pro}) inhibitors due to their strong binding affinity (Gul et al. 2022). *Scutellaria baicalensis* Georgi, a traditional medicine with several pharmacological properties, contains the major active component baicalein. In hACE2 transgenic mice, baicalein (200 mg/kg/day) significantly decreased SARS-CoV-2 virus replication and increase body weight. As a result, baicalein may be a potential therapeutic solution for COVID-19 treatment (Song et al. 2021). Curcumin has antiviral and anti-inflammatory properties, and it could be used to treat COVID-19 patients by reducing pro-inflammatory cytokine levels in the blood (Amalraj et al. 2017; Pawar et al. 2021). Flavonoids and the medicinal plants from which they are derived have a wide range of biological applications, including antioxidants, antivirals, antifungals, antibacterial, anti-inflammatory agents, and so on. Flavonoids and antiviral drugs (mundulinol and luteolin) have the maximum binding affinity and can act as potential inhibitors for the M^{pro} and SP of SARS-CoV-2 as compared to the antiviral drugs that are being used in COVID-19 treatment (Abd El-Mageed et al. 2021). The polyphenols extracted from the leaves and bud of *Camellia sinensis* were found to have potent antiviral activities and powerful M^{pro} inhibitors. It has also been reported that a large number of *C. sinensis* polyphenols (such as theaflavin (TF1), theaflavin-3O-O-gallate (TF2a), theaflavin-3O-gallate (TF2b), theaflavin-3,3O-gallate (TF3), epicatechin-3-gallate (EGCG), myricetin, hesperidin, and quercetin) serve as SARS-CoV-2 RdrP inhibitors (Tallei et al. 2021; Wang et al. 2021b; Zhang et al. 2021). Isorhamnetin, a flavonoid derived from sea buckthorn berries, inhibited the entry of SARS-CoV-2 spike pseudo-typed virus into HEK293/ACE2 cells in vitro and could be a new treatment for COVID-19 control (Zhan et al. 2021). SARS-CoV-2 S protein enters 293/hACE2 cells predominantly by endocytosis, and virus entry requires TPC2, PIKfyve, and cathepsin L. Tetrandrine was found to inhibit the entry of SARS-CoV-2-S pseudoviruses into HEK293/ACE2 cells, most likely as a result of its ability to suppress TPC2, which may be involved in the SARS-CoV-2 endocytic pathway (Ou et al. 2020). Naringenin exhibited moderate anti-SARS-CoV-2 efficacy and its treatment potential for COVID-19 infection. It was observed that it reduced the expression of ACE2, SARS-CoV-2 3CLpro inhibition, and targeted TPCs in Vero E6 cells (Abdallah et al. 2021).

COVID-19 symptomatology, epidemiology, and pathogenesis

COVID-19 patients have been linked to a wide spectrum of symptoms, from moderate to severe. The most common are headache, cough, fever or chill, vomiting, difficulty breathing, lack of smell or taste, body aches, and fatigue. However, many patients also have congestion, dyspnea, cardiac damage, multi-organ failure, and shock. Symptoms emerge 2–14 days after exposure to the virus (Zhong et al. 2020). A nasopharyngeal or oropharyngeal swab is used to diagnose a patient, which permits the virus to be isolated and verifies the infection (Holshue et al. 2020; To 2020). Severe COVID-19 patients might suffer a second set of symptoms and problems later in the disease's progression, including neurological manifestations, pulmonary embolism, stroke, myocardial infection, acute renal injury, and venous and arterial thrombosis. In COVID-19, extrapulmonary symptoms have a substantially higher death rate than pulmonary signs (Diao et al. 2021; Helms et al. 2020; Mao et al. 2020; Mehta et al. 2020; Tang et al. 2020). When the virus enters the host, the viral RNA genome is released into the host cell cytoplasm and then replicates. The ACE2 receptor is being used by the SARS-CoV-2 virus to enter cells (Fig. 3). SARS-CoV-2 can be transmitted through direct (human-to-human) and indirect contact (airborne contagion and contaminated objects). This virus can persist in the human body for at least four days (Bandyopadhyay 2021; Chu et al. 2020; Li et al.

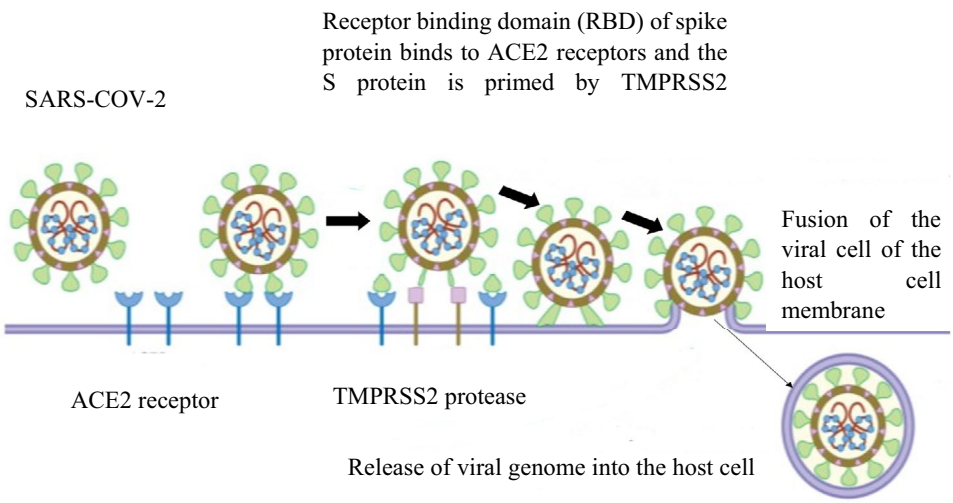

Fig. 3 SARS-CoV-2 binds to ACE 2 as the host target cell receptor, resulting in viral cell fusion with the host cell membrane via transmembrane serine protease 2

2020b). The spread of COVID-19 to healthcare personnel poses the greatest danger. Healthcare workers made up 21% of those infected by the SARS pandemic in 2002 (Chang et al. 2020). The spike protein's furin-cleaved S1 component binds directly to NRP1 on the cell surface, and utilizing a small-molecule inhibitor or monoclonal antibodies to block this interaction prevented virus replication in cell culture (Cantuti-Castelvetri et al. 2020; Daly et al. 2020; Haslberger et al. 2020).

The pathogenic characteristics of COVID-19 are strikingly similar to those of SARS and MERS coronavirus infections but have a lower overall fatality rate. In severe cases of COVID-19 infection, the cytokine storm could trigger a strong immune system attack on the host, resulting in ARDS, multiple organ failure, and death (Li et al. 2020b). Currently, it is considered that these coronaviruses can only survive for a few days outside of living cells in the environment, but this may be enough time for them to spread to other organisms, mutate and change their properties, and so on. For the foreseeable future, a variety of situations should be addressed (Núñez-Delgado 2020). In DT-induced mice, lycopene therapy improved mitochondrial performance by reducing oxidative stress, heart hypertrophy, cardiac fatty acid accumulation and viral infection (Wang et al. 2022). Lycopene has a protective effect against an increase in the serum level of creatine kinase MB in individuals undergoing percutaneous coronary intervention (PCI). This could point to lycopene's possible function in preventing PCI-induced myocardial damage (Arakeri et al. 2020).

Risk factors of COVID-19

Age, male gender, and underlying health issues like asthma, diabetes, cardiovascular disease, obesity, neurological, diabetes, hypertension, chronic lung diseases, and kidney diseases, all of which are thought to be the risk factors for COVID 19 (Table 1). The majority of the patients exhibited lymphopenia, thrombocytopenia, abnormal liver functions, and immune responses (Goyal et al. 2020; Lazzerini et al. 2020; Quartuccio et al. 2020). SARS-CoV-2 is mostly a respiratory infection, but it has the potential to impact other organ systems as well. COVID-19 has been demonstrated to disrupt practically every organ system, including the heart, brain, vascular, hematopoietic, liver, skin, and others, causing concerns such as abrupt cardiac failure, thrombosis, immunological dysfunction, and metabolic abnormalities (Li et al. 2021a). Diabetes, dyslipidemia, and oxidative stress are examples of proatherogenic stimuli that can cause endothelial dysfunction and, as a result, vascular dysfunction, leading to the development of atherosclerotic arterial disease, which can lead to coronary artery disease, acute coronary syndrome, stroke, and thrombosis. The disorders have also been linked to severe COVID-19 infections (Chistiakov et al. 2015; Fang et al. 2020; Stefan et al. 2020; Yuan et al. 2007). COVID-19 patients with severe CKD have a far higher risk of mortality than other known high-risk categories, such as those with obesity, hypertension, chronic heart disease, or lung illness (Gansevoort and Hilbrands 2020). Pregnant women are also at a high risk of contracting COVID-19, because the presence of ACE2 receptors in the placenta may further increase the risk of virus transmission from mother to baby. Normal pregnancy and COVID-19 both have decreased lymphocytes and NKG2A inhibitory receptors, as well as elevated ACE2 (Fig. 4), IL-8, IL-10, and IP-10 (Phoswa and Khaliq 2020). Obesity was linked to a threefold increase in the risk of COVID-19. Each unit of BMI increased the chance of severe COVID-19 by 12% (Alberca et al. 2021; Gao et al. 2020). Diabetes patients are more likely to develop an inflammatory storm, which leads to the rapid deterioration of COVID-19 (Guo et al. 2020). Increased levels of ACE 2 could be one of the mechanisms

Table 1 A risk factor for COVID-19

Risk factor	Virus	Mortality rate	Remark	Cited
Older age	SARS-CoV-2, SARS-CoV-1, MERS	10.0, vs. 4.9% among those with an age greater than 65 years	Elderly people have a higher risk of developing severe COVID-19	(Mehra et al. 2020; Petrilli et al. 2020; Williamson et al. 2020; Zhu 2019)
Cardiovascular diseases	SARS-CoV-2	10.2, vs. 5.2% among those without disease	COVID-19 mortality is significantly high in patients with cardiovascular disease	(Galbadage et al. 2020; Petrilli et al. 2020; Williamson et al. 2020; Zhu et al. 2020)
Coronary artery diseases (CAD)	SARS-CoV-2	15.3, vs. 5.6% among those without diseases	Patients with CAD had more severe conditions than non-CAD patients, according to studies	(Mehra et al. 2020)
Current vs former smoking	SARS-CoV-2	9.4, vs. 5.6% among former smokers or non-smokers	COVID-19 infection is more common in smokers	(Mehra et al. 2020; Williamson et al. 2020)
Cardiac arrhythmia	SARS-CoV-2	11.5, vs. 5.6% among those without arrhythmia	In patients with COVID-19, there is an increased risk of cardiac arrhythmia	(Mehra et al. 2020; Williamson et al. 2020)
Type 2 diabetes (T2D)	SARS-CoV-2	7.8 vs. 2.7%	Diabetes patients are more likely to have a severe COVID-19 clinical course and a higher mortality rate	(Williamson et al. 2020; Zhu et al. 2020)
Obesity	SARS-CoV-2	The case-fatality rate (CFR) was 2.3% among the 44,672, with obesity accounting for 7.3% (1,023) of the deaths with COVID-19	Through immunological, biochemical, and anatomical mechanisms, obesity is a highly risk factor for severe COVID-19	(Petrilli et al. 2020; Williamson et al. 2020; Yu et al. 2021b)
Sex	SARS-CoV-2, MERS	Men 60% versus 40% women	When compared to women, men have a higher risk factor for COVID-19	(Docherty et al. 2020; Galbadage et al. 2020; Williamson et al. 2020)
Kidney diseases	SARS-CoV-2, MERS	16% (2830 deaths out of 17,506 cases confirmed)	Chronic kidney disease was associated with higher mortality in hospitals	(Bhatraju et al. 2020; Cheng et al. 2020; Docherty et al. 2020; Williamson et al. 2020)
Hypertension	SARS-CoV-2, MERS	The CFR was 6.0 percent (1023 deaths out of 44,672 cases confirmed)	Hypotension might face a greater risk of developing into a critical or mortal condition	(Williamson et al. 2020; Wu and McGoogan 2020)
Cancer	SARS-CoV-2, MERS	The CFR was 5.6% (1023 deaths out of 44,672 confirmed cases)	Covid-19 causes severe problems in cancer patients	(Wu and McGoogan 2020) (Moni and Liò 2014; Williamson et al. 2020)

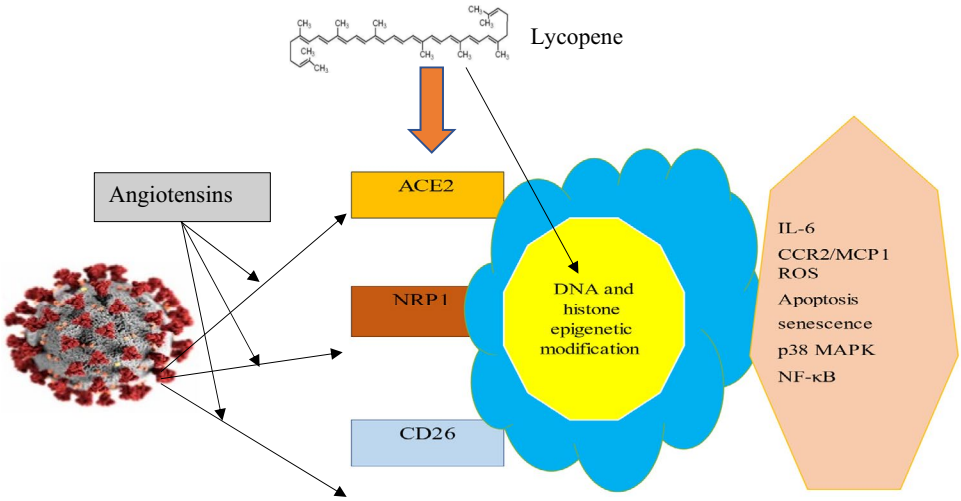

Fig. 4 This diagram demonstrates the entry of SARS-CoV-2 into the cell, as well as potential lycopene-based prevention measures (Cantuti-Castelvetri et al. 2020; Haslberger et al. 2020; Raha et al. 2020)

by which COVID-19 patients are affected by cardio-cerebrovascular illness. Patients with the cardio-cerebrovascular disease were more prone to developing a myocardial injury, increasing their risk of becoming critically ill and dying (Yu et al. 2021a). Severe patients had lower levels of hemoglobin, monocytes, lymphocytes, eosinophils, and platelet counts than non-severe patients while having higher neutrophil counts among the CBC indices. Severe and non-severe COVID-19 cases had significantly different renal function tests and liver, glucose levels inflammatory/infection indicators, and serum electrolytes (Feng et al. 2020). Innate and adaptive immunity in women is stronger, and they are more resistant to viral infections than men (Flanagan et al. 2017). In children with COVID-19, blood levels of TNF-α and IL-6 were increased at diagnosis than in children with other infectious illnesses. However, these cytokine levels did not correspond with disease severity, which is likely due to the fact that the small cohort included mostly moderate cases (Curatola et al. 2021). Children who contract the SARS-CoV-2 have better results than adults (Qian et al. 2021). Due to a less robust immune response, older age was linked to a higher risk of developing ARDS and death. Although the high temperature was linked to the development of ARDS, it was also linked to improved outcomes in ARDS patients. Furthermore, methylprednisolone medication may be advantageous for people who develop ARDS (Wu et al. 2020a).

Lycopene suppresses inflammatory reactions during COVID-19 infection

Severe COVID-19 infection is characterized by a large pro-inflammatory response or cytokine storm, which ultimately in ARDS and multi-organ failure. During COVID-19 infection, proinflammatory cytokines are released, causing infection of endothelial inflammation. When pro-inflammatory cytokines activate endothelial cells, they become more permeability to macromolecules that might cause extensive lung damage (Varga et al. 2020). The cytokine release syndrome (CRS) can occur directly as a result of viral damage or indirectly by overactivation of the immune system that triggers the infiltration of immune cells such as neutrophils and macrophages into the tissue. COVID-19 Patients may experience mild to moderate symptoms due to massive cytokine production, which typically leads to elevated inflammation markers, and disease severity (Darif et al. 2021; Griffith et al. 2014).

A cytokine release syndrome (CRS) was linked to COVID-19. The inflammatory pathway that promotes lung parenchymal injury and thromboembolic events appears to be triggered by CRS. Interleukin-6 is a key cytokine in the development of CRS, which causes hyper-inflammation, ALI, and, in some cases, irreversible lung tissue damage (Alharthy et al. 2020). SARS-CoV-2 infection increases the number of ACE2-positive endothelial cells in COVID-19-induced respiratory failure (ARDS). SARS-CoV-2 infection of endothelial cells produces endothelial cell swelling and disintegration, abnormal microvascular architecture, and endothelial dysfunction (Ackermann et al. 2020a). ACE2 is a protein found in various human organs that serves as a negative regulator of the renin-angiotensin system. Patients with aberrant pulmonary inflammation and immune responses can have either very high or very low ACE2 levels (Sodhi et al. 2019).

COVID-19 severity is linked to secondary haemophagocytic lymphohistiocytosis (sHLH), and several studies have found a significant increase in levels of various cytokines and chemokines such as TNF-α, IL-2, IL-7, macrophage inflammatory protein 1-α, interferon-γ inducible protein 10, granulocyte colony-stimulating factor, and monocyte chemoattractant protein 1 (Huang et al. 2020b). IL-6 is a key pro-inflammatory cytokine that also plays a role in inflammation, immune system modulation, and hematopoiesis. As a result,

IL-6 could be used to initiate therapies and monitor pro-and anti-inflammatory responses (Ritchie and Singanayagam 2020). Indeed, inhibiting the NF-κB pathway could regulate the number of NOS and NO content, as well as diminish the production of cytokines and chemokines (Li et al. 2017).

When the SARS-CoV-2 S protein binds to the ACE2 receptor, the pro-inflammatory pathway is activated, with the Ang II hormone directly activating pro-inflammatory responses and the release of cytokines. The SARS-CoV-2 virus has recently been shown to use the TNF-α pathway to release pro-inflammatory cytokines such as TNF-α and IL-6. TNF-α overproduction is caused by ADAM-17 angiotensin II overactivation, which is mediated by virus-induced ACE2 deficiency (Mahmud-Al-Rafat et al. 2020; Scialo et al. 2020).

NF-κB is a key transcription factor for a wide range of genes involved in cellular immunity and inflammation. Activated NF-κB is crucial for a full-fledged cytokine storm because it regulates the transcription and synthesis of chemokines and inflammatory cytokines that are involved in the acute inflammatory response (LIAO et al. 2005). As a result of cytokine storms and inflammatory responses, many COVID-19 patients may die. As a result, anti-inflammatory drugs may be able to reduce the severity of the condition and the rate of fatalities (Dhama et al. 2020; Huang et al. 2020a; Mehta et al. 2020). The release of IL-1β triggers the production of IL-6, a cytokine that raises C reactive protein (CRP) and has been associated with the COVID-19 cytokine storm as a significant proinflammatory factor (Qin et al. 2020; Zhang et al. 2020a). Patients with COVID-19 infection have been shown to have high amounts of pro-and anti-inflammatory cytokines in their blood than those with uncomplicated SARS. Airway epithelial cells infected with SARS-CoV also produce a high amount of CXCL-10, IL-6, CXCL8, IFN-α, and CCL5. Severe SARS patients, on the other hand, had relatively low levels of the anti-inflammatory cytokine IL-10 (Cameron et al. 2008; Huang et al. 2005; Zhang et al. 2004).

The inflammatory response was triggered by ATR (atrazine), which increased NO (nitric oxide) generation and caused heart injury. By regulating NO (nitric oxide) and NOS (nitric oxide synthase) generating systems and inhibiting the TRAF6-NF-κB pathway, supplement lycopene dramatically reduces heart damage (Li et al. 2017). Lycopene suppresses the production of proinflammatory cytokines and chemokines in macrophages (Lee et al. 2012; Marcotorchino et al. 2012). Lycopene improved blood cell and hepatic lipid function, boosted high-density lipoprotein cholesterol, reduced TNF-α and malondialdehyde, and increased hepatic antioxidant activity (Róvero Costa et al. 2019). Lycopene's anti-inflammatory actions are mediated via a reduction in TNF-α, NO, and IL-6 release, which leads to a reduction in uveal inflammation. Lycopene's anti-inflammatory and antioxidant properties may make it useful in the treatment of eye inflammation (Göncü et al. 2016). Lycopene's anti-inflammatory properties were linked to an M2-dominant phenotype in adipose and hepatic macrophages. Lycopene reduced HFD-stimulated insulin resistance and inflammation in epididymal white adipose tissues and the liver by easing M2-dominant polarization in adipose tissue macrophages (Chen et al. 2019). Interleukin-1, Interleukin-6, and NF-κB-p65 expression were downregulated in the PA control, but Interleukine-10 expression was elevated owing to lycopene therapy. Lycopene normalized severe brain vacuolation was seen in the histopathology of PA control rats (Ugbaja et al. 2021). Lycopene possesses anti-obesity and anti-diabetic properties in a variety of organs and tissues, including adipose tissue, liver, kidney, pancreas, brain, ovaries, stomach, and eyes. Several studies have revealed that lycopene consumption has antioxidant properties as well as immunological and inflammatory functions (Agarwal and Rao 2000; Zhao et al. 2020; Zou et al. 2013).

A dysfunctional immune response to COVID-19 could be enhanced by lycopene

COVID-19 disease, which is occurred by the SARS-CoV-2 virus, is linked to several physiopathological mechanisms that mobilize a wide range of biomolecules, most of which are immunological (Fig. 5). In its most serious conditions, hyperproduction of primarily proinflammatory cytokines, which preferentially target lung tissue, can significantly worsen the prognosis (Costela-Ruiz et al. 2020). During SARS-CoV2 infection, CD4 + and CD3 + T cells and the total lymphocyte count were low, and IL-6, ESR, and CRP were elevated, especially in severe COVID-19 patients (Iwamura et al. 2021). SARS-CoV-2 induces lymphopenia, dysfunction, lymphocyte activation, higher cytokine levels, as well as monocyte and granulocyte abnormalities, increase in immunoglobulin G (IgG) and total antibodies. As a result, decreasing inflammation and improving lymphopenia may be beneficial therapeutic methods for COVID-19 patients (Yang et al. 2020).

Both T and B cell responses to SARS-CoV-2 are identified in the blood approximately one week after the start of COVID-19 symptoms. CD4 + and CD8 + T cells are important in acute infection. COVID 19 has a hyper-inflammatory innate immune system and a defective adaptive immune system due to severe lymphopenia, decreased functioning, and exhausted T lymphocytes. CD8 + T cells are important for directly attacking and killing virus-infected cells, whereas CD4 + T cells are crucial for priming both B and CD8 + T cells and also for cytokine production to drive immune cell recruitment (Zheng et al. 2020). Severe COVID-19 patients have higher levels of ferritin, D-dimer, CRP, IL-6, and

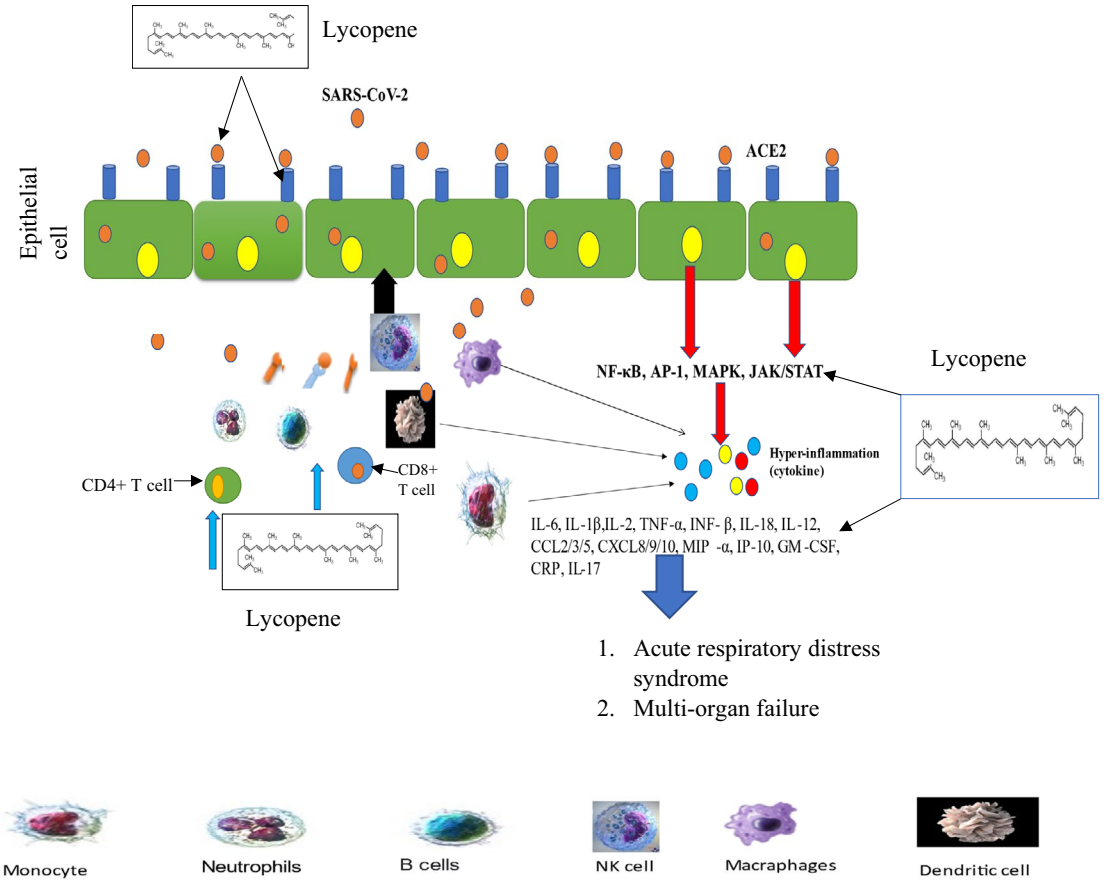

Fig. 5 A diagram showing COVID-19 pathogenesis can lead to ARDS and multi-organ failure. Lycopene can disrupt excessive inflammatory cytokine production

TNF-α in their blood, as well as a lower total number of NK cells, CD8 + cells, and CD4 + cells, as well as lower levels of basophils, monocytes, and eosinophils (Catanzaro et al. 2020; Janssen et al. 2021; Tay et al. 2020).

Furthermore, SARS-COV-2 was seen in the peripheral blood to impair components of host immunity, including an increase in fatigued CD8 + T cells and a decrease in CD4 + T cell activity, all of which point to a Th17 (Tay et al. 2020). When SARS-CoV-2 attaches to Toll-like Receptors (TLR), pro-IL1β is released, which leads to the production of mature IL-1β, which induces pulmonary inflammation, fever, and fibrosis. Most members of the IL-1 family of cytokines produce inhibitory cytokines such as IL-38 and IL-37. Immunological cells include B cells and macrophages. IL-38 is a cytokine that could be utilized to treat inflammation caused by viral infections, particularly coronavirus-19 infections. IL-37 performs its anti-inflammatory function via interacting with the IL-R5 or IL-18Ra receptors and may be explored as a therapeutic drug (Conti et al. 2020). The N-COV virus enters the cell by latching onto the protein receptor ACE2 and slinking within, after which it replicates and weakens our immune system. The lungs and colon have the most receptors. When the virus stays in the respiratory tract, it causes cough and cold, and when it inflames the hypothalamus, it causes diarrhea. When the virus inflames the hypothalamus, the fever rises (Koff and Williams 2020).

Innate immune cells have a vital role in activating a specific and effective immune response to SARS-CoV-2 infection, which is used as a biomarker for tissue damage in COVID-19 cases with severe tissue damage. The inflammatory response to SARS-CoV-2 has numerous clinical trials exploring the effectiveness of anti-inflammatory therapeutics against COVID-19. Lycopene also influences immunoglobulin production, increases IgA, IgG, and IgM levels in the blood, and boosts immunity (Kaneko et al. 2008), promoting cell-to-cell communication and increasing immunological response (Olson et al. 2008). Lycopene has immunomodulatory effects, as evidenced by the circulating percentage of lymphocytes, blood IgG concentrations, and ewe colostrum. Corn treated with lycopene increased the level of immunoglobulin G in sheep's blood, which facilitated passive immunity transfer to newborn lambs (Fallah et al. 2021).

Dietary lycopene supplementation may increase antioxidant activity and ameliorate AFB1-induced intestinal immune function and barrier function impairment in the intestinal mucosa (Sarker et al. 2021). In diabetic rats, lycopene has anti-anemic properties and improves immunity. Low platelet counts, a low neutrophil–lymphocyte ratio, steady albumin, a drop in neutrophil counts, and low globulin content were among the findings. Lycopene may aid in the regulation of basic hemato-physiological variables (Eze et al. 2019). Lycopene is an anti-inflammatory antioxidant with antioxidant effects. Lycopene reduced intestinal damage, intestinal immunoglobulin A depletion, and bacterial translocation when given before the ischemia–reperfusion event (İkiz et al. 2021). In severe COVID-19 cases, there was increased pro-inflammatory cytokine and chemokine production. Lycopene inhibits the synthesis of proinflammatory cytokines and chemokines in macrophages, reducing inflammation in a variety of organs (Lee et al. 2012; Marcotorchino et al. 2012). Aside from regulating chronic immunological and inflammatory processes and delaying dendritic cell maturation (Kim et al. 2004).

Oxidative stress of COVID-19

Severe COVID-19 frequently experiences respiratory distress that is treated by oxygen medication and may result in oxidative stress and ARDS. It has been reported that increased nitro-oxidative stress contributes to the development of ARDS (Mach et al. 2011; Park et al. 2009). Even in cases where people are dying from chronic ARDS, there is nitrosative stress. SARS-CoV-2 appears to be localized to macrophages and type I pneumocytes (Massaro et al. 1975). Nearly all patients with viral infections have chronic oxidative stress, which has an impact on disease pathogenesis including impaired immune function and inflammatory response (Nin 2012). According to some researchers, the development of severe lung damage in SARS-CoV patients is related to oxidative stress produced by cell activation, which may have a substantial effect on the pathogenesis of COVID-19. In general, cytokine production, inflammation, and cell death are linked to respiratory virus infections, which could be associated with oxidative (Delgado-Roche and Mesta 2020).

The Fenton reaction,

The first step: $Fe^{3+} + \bullet O2 - \rightarrow Fe^{2+} + O2$.

The second step: $Fe^{2+} + H2O2 \rightarrow Fe^{3+} + OH - + \bullet OH$ (Khomich et al. 2018; Sies 2020).

ROS is well-known for both its beneficial and harmful characteristics. Free radicals produced by RNA virus infections may have a function in a range of features of viral illness pathogenesis. During allergic and nonallergic inflammation, the inflammatory cells produce ROS (Chernyak et al. 2020).

However, ROS released by viral illness should not be regarded only as destructive agents, since they are crucial for the eradication of viruses phagocytosed by immune cells and also contribute to signaling between immune cells. Antioxidants may also help to reduce the viral load by minimizing oxidative stress. Most importantly, antioxidants tend to be appropriate during the stage of COVID-19 when inflammatory reactions must be inhibited. Such therapy is believed to protect organs and tissues from cytokine storms or oxidative stress (Assimakopoulos and Marangos 2020; Yang et al. 2013). ACE2 and TMPRSS2 gene expression has been found mostly in alveolar epithelial type II cells, which play a role in SARS-CoV pathogenesis (Sungnak et al. 2020; Ziegler et al. 2020). During COVID-19, increased levels of angiotensin-converting enzyme 2 (ACE2) served as an entrance receptor for SARS-CoV-2. Ang II is involved in the initiation and progression of inflammatory response. Low ANG II levels and high tACE2 levels give SARS-CoV-2 greater pathogenicity; a high ratio suggests the virus is less harmful and causes oxidative stress (free RONS) (Ackermann et al. 2020b; Fodor et al. 2021). When a patient is infected with SARS-CoV-2, phagocytes get activated, causing reactive oxygen species (ROS) to generate. Angiogenesis appears to be caused by endothelial dysfunction and hypoxia within lung injury foci during COVID19 (Varga et al. 2020).

Endothelial NOX2 is a prominent ROS producer, and AT1R is a key ATII receptor that stimulates multi-layered signaling in endothelial cells (Forrester et al. 2018). The possible causes of the pore opening of the mitochondrial permeability transition pore (mPTP), which is regulated by such a protein in the mitochondria, may increase the level of mtROS generated by NOX2. As a result, ATII increased mtROS generation, which in turn increased NOX2 activity (Bernardi et al. 2015; Wacquier et al. 2020).

Endothelial cells may undergo ROS-dependent apoptosis as a result of cytokine storms. The activation of endogenous antioxidant mechanisms is another strategy for combating oxidative stress during COVID 19. The transcription factor Nrf2, for example, regulates the production of antioxidants and other cell defense mechanisms (Zinovkin and Grebenchikov 2020). The generation of ROS is a typical element of cellular aerobic metabolism, which involves the respiratory and oxidizing of nutrients to generate energy. antioxidant mimetics or Nrf2 inducers could be used to treat viral-induced infections including respiratory problems and other infections that are correlated to a decrease in cellular antioxidative (Komaravelli and Casola 2014).

Hepcidin is important for maintaining iron homeostasis. Although iron is essential, its free form is likely to be involved in oxidation–reduction reactions, resulting in free radical production and oxidative stress (Daher et al. 2017;

Kell and Pretorius 2014). The hyperferritinemia seen in COVID-19 patients could be a result of inflammation. In an era of multidrug-resistant viruses, iron chelation appears to be a promising and logical adjuvant therapy for viral infections (Schmidt 2020).

Lycopene is an extremely strong antioxidant, and this is a key mechanism of lycopene action. Its exceptional ability to quench ROS is due to its eleven conjugated double bonds (Heber and Lu 2002). Lycopene's nutraceutical effects have been reported in cancer, infertility, metabolic syndrome, and liver damage patients (Grabowska et al. 2019). In the livers of obese rats, dietary lycopene (50 mg/kg) reduced oxidative stress, inflammation, and metabolic problems caused by long-term consumption of a high-fat diet (HFD) (Albrahim and Alonazi 2021). For the rise in the COVID-19-related risk of death, Nrf2 has powerful antiapoptotic effects and anti-inflammatory in endothelial cells. Lycopene reduced the oxidative damage caused by zearalenone (ZEA) in Sertoli cells (SCs) by increasing Nrf2 pathway expression and lowering autophagy and apoptosis in piglet SCs (Cao et al. 2021). In HFD-fed mice, lycopene (10 mg/kg) treatment had better anti-lipidemic and anti-antioxidant benefits than Moringa (400 mg/kg), most likely due to its ability to reduce oxidative stress (Greish et al. 2021). Lycopene alleviated palmitic acid (PA)-induced neuroinflammation in female Wistar rats through lowering oxidative stress and downregulation of NF-κB-p65 expression (Ugbaja et al. 2021).

During transient ischemia, lycopene has been proven to protect the brain from ischemia-induced damage. Lycopene protected SHSY5Y cells from oxygen–glucose deprivation (OGD)-induced autophagic death by decreasing oxidative stress-dependent activation of the AMPK/mTOR pathway (Li et al. 2021b). In vitro, neuronal damage was alleviated, reactive oxygen species generation was reduced, and cell viability was successfully increased by lycopene pre-treatment. As a result, lycopene can be useful in the treatment of oxidative stress-related AD (Huang et al. 2019).

Lycopene (20 mg/kg) therapy for 10 days reduced testicular function and produced oxidative stress in Swiss albino mice to reduce the adverse effects of ZEA exposure. In the kidneys and testes, ZEA decreased GST activity while increasing SOD activity in the liver (Boeira et al. 2014). The anti-inflammatory and antioxidant effects of lycopene have been demonstrated to reduce oxidative stress brought on by an excess of APAP and the ensuing liver damage in C57BL/6 mice (Bandeira et al. 2017). Lycopene can lower the risk of varicocele brought on by oxidative stress by boosting TAC levels and TAC enzymatic activities (Babaei et al. 2021) (Table 2).

Interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) interleukin-1β (IL-1β), interleukin-10 (IL-10), heme oxygenase (HO), monocyte chemotactic protein 1 (MCP-1), reactive protein (CRP), JNK (c-Jun N-terminal kinase), interferon-gamma induced protein-10 (IP-10), Quantitative polymerase chain reaction (qPCR), Enzyme-linked immunosorbent Assay (ELISA), Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), inducible nitric oxide synthase (iNOS), glutathione (GSH), Glutathione-S-transferase (GST), catalase (CAT), glutathione peroxidase (GSH-Px), malondialdehyde (MDA), non-alcoholic fatty liver disease (NAFLD), Overall case-fatality rate (CFR), SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), MERS (Middle East respiratory syndrome), RNA-dependent RNA polymerase (RdRp), main protease (M^{pro}) and receptors binding domain (RBD), two-pore calcium channel 2 (TPC2).

Clinical significance of lycopene

Lycopene has been suggested to have clinical efficacy in the treatment of diabetes. The average daily intake of dietary lycopene among diabetics was 0.04 mg/kg BW/d, and lycopene could lower oxidative stress and enhance the pathophysiology of T2DM (Leh et al. 2021). Lycopene's anticancer effects on oral cancer (OC) cells reveal that it might activate the PI3K/AKT/m-TOR signaling pathway to suppress EMT and induce apoptosis in OC cells. These data support the clinical use of lycopene in the treatment of OC (R. Wang et al. 2020). Lycopene (0.03 percent w/w of normal chow for five weeks) can reduce LPS-induced (0.25 mg/kg for nine days) neuroinflammation, oxidative stress, amyloidogenesis, and cognitive deficits in male C57BL/6 J mice, perhaps by modulating MAPKs, NFB, and Nrf2 signaling pathways, suggesting that LYC could be a nutritional preventive strategy in neuroinflammation-related disorders like Alzheimer's (AD) (Jia Wang et al. 2018a). In male mice, lycopene suppressed dependent MAPKs (ERK1/2, p38, and JNK1/ 2) and Akt/ GSK-3β signaling pathways to reduce oxidative stress and ameliorate cardiac hypertrophy. Therefore, it was considered that the antioxidant capabilities of lycopene would prevent cardiac hypertrophy (Zeng et al. 2019). Lycopene (5–10 mg/kg body weight/day for 10 days) in male SD rats could alleviate LPS-stimulated oxidative stress via enhanced total antioxidant and HDL-associated PON-1 activity, as well as down-regulating hepatocyte PCSK-9 expression via HNF-1α downregulation and plasma levels of inflammatory mediators (Alvi et al. 2017). In Wistar rats, lycopene (10 mg/kg/day) treatment prevented the angiotensin-II-induced remodeling of the cardiovascular system. Lycopene enhanced angiotensin-II-induced vascular superoxide anion, cardiac fibrosis, hypertrophy, lipid peroxidation, and antioxidant enzyme activity. Interestingly, lycopene showed antihypertensive potential without causing hypotension in normotensive rats (Ferreira-Santos et al. 2018). Mice were treated with lycopene (5 mg/kg) which significantly protected the heart against ATR-induced

Table 2 Various health benefits of lycopene

Model	Lycopene (route/dose)	Analysis	Main outcomes	Duration	Conclusion	Cited
Male C57BL/6 mice	25 and 50 mg/kg/day	ELISA	TNFα↓, IL-6↓, IL-10↓, ROS production↓, SOD↓, NF-κB↓	12 h	Lycopene, via reducing oxidative stress and inflammation, was effective in preventing liver damage induced by long-term CS exposure	(Rocha et al. 2021)
Male Sprague–Dawley rats	5 mg/kg BW	ELISA	↑CAT, ↑SOD, ↑GPx, TNF-α↓, CRP↓	10 weeks	In T2DM rats, lycopene could reduce oxidative stress by reducing glucose and lipid peroxidation, as well as reduce inflammatory events	(Zheng et al. 2019)
STZ-induced diabetic Wistar rats	10 or 20 mg/kg/BW	ELISA	SOD↑, GSH-Px↑, MDA↓	10 weeks	In diabetic rats, lycopene enhances glycolipid metabolism by reducing oxidative stress	(Yin et al. 2019)
Wistar male rats	4 mg/kg	ELISA, spectrophotometer	MDA↓, TOS↓, NF-κB↓, TNFα↓	3 months	Lycopene can alleviate inflammatory responses by reducing oxidative stress	(Icel et al. 2019)
Adult male Wistar albino rats	50 mg/kg	ELISA, spectrophotometer, qPCR	TNFα↓, iNOS↓, MPO↓, NO↓, GSH↑,	10 days	Lycopene prior treatment proved anti-inflammatory and antioxidant effects against acute pancreatitis (AP) rat	(El-Ashmawy et al. 2018)
Female Wistar–Albino rats	4 mg/kg/BW	Spectrophotometer	MDA↓, CAT↑, SOD↑, GPx↑, and GST↑	28 days	Lycopene possesses antioxidant properties that protect ovarian tissue against the toxicity of diabetic furans and non-diabetic	(Uçar and Pandir 2017)
Weanling ICR Male mice	60 and 1 mg/kg	ELISA, Immunoblotting	IL-1β↓, TNF-α↓, IL-6↓, HO-1↓	6–24 h	Lycopene can reduce LPS-induced inflammation and depression-like behavior by inhibiting the production of pro-inflammatory cytokines	(Zhang et al. 2016)
Male C57BL/6 mice	50 or 25 mg/kg/day	ELISA	IL-10↓, IFN-γ↓, TNF-α↓, SOD↑, CAT↑, GSH↑	60 days	lycopene has anti-inflammatory and antioxidant properties; it may be a promising novel treatment for acute lung inflammation and emphysema in mice exposed to CS	(Campos et al. 2019)

Table 2 (continued)

Model	Lycopene (route/dose)	Analysis	Main outcomes	Duration	Conclusion	Cited
Sprague–Dawley rats	25 or 50 mg/kg	ELISA, Western blotting	TNF-α↑, IL-1β↑, IL-6↑, and IL-8↑, HO-1↑, COX-2↓	14 days	The anti-inflammatory properties of lycopene may be used as a therapy to protect against spinal cord ischemia/reperfusion injury (SCII)	(Hua et al. 2019)
Male mice	20 mg/kg	ELISA, Western blotting	ALT↓, AST↓, TNF-α↓, IL-6↓, MDA ↓, SOD↑, Nrf2↑, COX-2↓, NF-κB↓	2 weeks	Lycopene has been reported to lessen the liver damage brought on by LPS by reducing oxidative stress and inflammatory damage	(Dong et al. 2019)
Adult male C57BL/6j mice	2 μM	Western blotting, luminex kit	IL-6↓, MCP-1↓, IL-1β↓, TNFα↓, NF-κB↑	24 h	Lycopene could prevent or reduce the prevalence of obesity-related diseases by reducing the expression of pro-inflammatory cytokines and chemokines in adipose tissues	(Gouranton et al. 2011)
Macrophage and adipocyte cells	0.5–2 μM	ELISA, Western blot	↓IL-1β, ↓TNF-α, ↓IL-6, JNK ↑, NF-κB↑	24 h	Lycopene has the potential to disrupt the vicious loop that occurs in adipose tissue between adipocytes and macrophages during obesity	(Marcotorchino et al. 2012)
Eight-week-old male C57BL/6 J mice	Powder	ELISA	TNFα↓, IL-6↓, CCL2↓, CCL5↓, MCP-1↓, NF-κB↓, IκB↓, p65↓	12 weeks	Lycopene has beneficial effects on inflammatory responses, obesity, and metabolic disorders	(Fenni et al. 2017)
Airway epithelial cells	2.5 μg/ml	ELISA	IL-6↓, IP-10↓, NF-κB↓	48 h	Lycopene may also be effective in reducing rhinovirus-induced airway inflammation	(Saedisomeolia et al. 2009)
Sprague–Dawley rats	2 or 4 mg/kg BW	ELISA	ALT ↓, MDA ↓, TNF-α ↓, GSH ↑, HSC activation ↓	Orally for 6 weeks	Lycopene supplementation may help to prevent the progression of steatohepatitis by reducing high-fat diet-induced oxidative stress in the cells	(Bahcecioglu et al. 2010)

Table 2 (continued)

Model	Lycopene (route/dose)	Analysis	Main outcomes	Duration	Conclusion	Cited
C57BL/6 mice	10 or 100 mg/kg	RT-PCR, spectrophotometer	CAT ↑, GSH ↑, TBARS ↓, IL1β ↓, Redox imbalance ↓	2 weeks	Lycopene can reduce the oxidative stress caused due to APAP overdose and subsequent liver damage in C57BL/6 mice	(Bandeira et al. 2017)
Sprague–Dawley rats	20 mg/kg diet		SOD ↑, CAT ↑, LDL ↓, GSHPX ↑	4 weeks	Lycopene's potential health advantages against non-alcoholic fatty liver disease (NAFLD)	(Piña-Zentella et al. 2016)
Sprague–Dawley rats	2.5, 5 mg/kg BW	Spectrophotometer	CAT ↑, MDA ↓, ALT ↓, AST ↓, LDH ↓		Lycopene's antioxidant properties protect against ischemia/reperfusion injury	(Bayramoglu et al. 2015)
Wistar rats and C57BL/6 mice	Rats: 1.1 mg/kg Mice: 1.1 mg/kg	Western blot, real time-PCR	IL-6 ↓, IL-1β ↓ IFNγ ↓,, Hepatic inflammatory foci ↓	4 and 3 weeks	Dietary lycopene powder can prevent alcohol-induced liver impairment and oxidative damage by inhibiting cytochrome p450	(Stice et al. 2015)
MI mice	10 mg/kg/day	Western blot, qPCR	TNFα ↓, IL-1β↓, NF-κB p65 ↓	4 weeks	Lycopene has been shown to have a cardioprotective effect by inhibiting local myocardial inflammation and apoptosis	(He et al. 2015)

environmental cardiology and alleviated cardiac injury via modulating the NO and NO-generating systems and blocking the TRAF6-NF-κB pathway (Zeng et al. 2019). Lycopene treatment (23 mg/kg BW per day) could alleviate oxidative stress-induced neuroinflammation and cognitive impairments via mediating Nrf2/NF-κB transcriptional pathway in CD-1 mice by improving neuronal damage, restoring antioxidant activities, and down-regulating inflammatory responses (Zhao et al. 2017). Lycopene (5–125 mg/kg for four weeks) treatment in hyperlipidemic rats could alleviate the damage to the blood–brain barrier and the loss of neurons in the brain induced by hyperlipidemia. These results suggest an inverse U-shape relation between dose and serum concentration of lycopene (Wang et al. 2018b). Mice treated with lycopene (10 mg/kg) exhibited inhibition of p38 activation and MMP-9 expression, which indicates that lycopene inhibits myocardial fibrosis to improve cardiac function and ventricular remodeling (Wang et al. 2014).

Lycopene (10 mg/kg/day) was given to the mice to inhibit the NFB signaling pathway, which attenuated the mice's inflammatory response and cardiomyocyte apoptosis post-MI. As a result, lycopene may have a cardioprotective impact by inhibiting local myocardial inflammation and apoptosis (He et al. 2015). Treatment with lycopene (5 mg/kg BW) in T2DM rats was able to reduce inflammation and oxidative stress, which protected against the progression of diabetes and associated consequences (Zheng et al. 2019). Lycopene (16 mg) treatment for individuals with oral submucous fibrosis considerably lowered the expression levels of the IGF1 pathway, suggesting that it could be a promising drug for the pre-treatment of oral squamous cell carcinoma (OSCC) and significantly induced cell apoptosis, which inhibits tumor growth and cell migration (Kumar et al. 2007). Lycopene exhibits suppressive inhibitory effects on WSU-HN6 and CAL-27 cells in vivo and in vitro, similar to prior findings. This study might treat oral squamous cell carcinoma with lycopene by acting as an anti-cancer agent (Tao et al. 2021).

Side effects/toxicity

A clinical disorder called lycopenemia is characterized by yellowish-orange skin pigmentation. It results from the overconsumption of lycopene resources obtained through diet or caused by the deposition of lycopene in the stratum corneum (Shaw and Koti 2009). The anti-oxidant lycopene does not prevent pre-eclampsia in healthy primigravidas, but it helps lessen pre-eclampsia and intrauterine development retardation. As a result, there have been more premature and underweight babies born. Therefore, it is advisable to refrain from using lycopene supplements as well as lycopene found in food during pregnancy and lactation (Banerjee et al. 2009; Sharma et al. 2006). Docetaxel with lycopene treatment was well tolerated, with no dose-limiting toxicities seen in the first six patients participating in the research. Two patients (15%) required dose reduction because of peripheral neuropathy. The most frequent side reactions (all low grade) that affected at least 15% of patients were diarrhea, nausea, vomiting, or both, peripheral neuropathy, weight loss, appetite changes, weariness, onycholysis, alopecia, and anemia (Zhuang et al. 2021). Lycopene is not benign. A significant number of individuals experienced gastrointestinal adverse symptoms such as nausea, vomiting, anorexia, flatulence, and abdominal distension. Although the majority of these were minor, they nevertheless highlight the fact that even natural, nutrition-based medicines might have unintended repercussions (Jatoi et al. 2007). Lycopene supplements were well tolerated. One patient discontinued treatment due to diarrhea (grade 2 toxicity) caused by lycopene supplementation. Other toxicities were observed, but these were unlikely to be caused by lycopene supplementation (Clark et al. 2006).

Lycopene has not been linked to any negative side effects. One patient reported an intense burning sensation and oral ulcers one week after starting treatment (Kumar et al. 2007). According to the Common Toxicity Criteria of the National Cancer Institute, none of the investigations found any serious toxicity or intolerance associated with lycopene supplementation (Kaba et al. 2004). Lycopene appears to be a perfectly safe dietary component from a safety point of view. It has no harmful effect on populations, ranging from an optimal dose of 12 mg/day to a very high dose of 150 mg/100 g (Przybylska and Tokarczyk 2022).

Conclusion

This review has presented the various mechanisms of SARS-CoV-2 infection along with the inflammatory, immunity, and oxidative properties of lycopene as COVID-19 preventative measures in light of the COVID-19 pandemic. COVID-19 cytokinemia differs from other kinds of pneumonia in that it causes organ failure and ICU hospitalization. SARS-CoV-2-induced hyper-inflammatory and immune responses are critical for not only understanding the pathogenesis of severe COVID-19 disease but also for vaccine evaluation and design. Many immunomodulatory, anti-inflammatory, and antiviral drugs have been tested in patients with COVID-19 as well. We conclude that lycopene could be used as a drug for treating the inflammation of COVID-19 infection because of its antioxidant, anti-inflammatory and antivirals properties.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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