



# Potential usefulness of Mediterranean diet polyphenols against COVID-19-induced inflammation: a review of the current knowledge

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## Abstract

The Mediterranean diet is a dietary pattern typical of the populations living in the Mediterranean basin during the 50s-60s of the last century. This diet has demonstrated beneficial effects in the prevention of several pathologies such as cardiovascular diseases, metabolic syndrome, or several cancer types, at least in part, due to its antioxidant compounds. Since the COVID-19 pandemic started, different authors have been studying the effects of certain dietary habits on the presence of COVID-19 and its severity, and the Mediterranean diet is one of them. This review gathers data from studies supporting the potential usefulness of the main phenolic compounds present in the Mediterranean diet, based on their antioxidant and anti-inflammatory effects, as preventive/therapeutic agents against COVID-19. The current evidence supports the potential benefits that hydroxytyrosol, resveratrol, flavonols such as quercetin, flavanols like catechins, and flavanones on the order of naringenin could have on COVID-19. This is due to the increase in the synthesis and translocations of Nrf-2, which increases the activity of antioxidant enzymes and thus reduces ROS production, the scavenging of free radicals, and the suppression of the activity of MMP-9, which is involved in the cytokine storm, and the inhibition of NF-κB.

**Keywords** Mediterranean diet · COVID-19 · Antioxidants · Polyphenols

Iñaki Milton-Laskibar and Jenifer Trepiana equally contributed to this work.

## Key points

Dietary patterns rich in polyphenols may benefit COVID-19 clinical outcomes.  
Polyphenol-mediated Nrf2 upregulation may reduce COVID-19-induced oxidative damage.  
NF-κB downregulation by polyphenols may attenuate COVID-19 derived inflammation.

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## Introduction

The Mediterranean diet is a traditional dietary pattern typical of the populations living in the Mediterranean basin during the 50s and 60s of the last century. This diet is characterized by a moderate fat intake, mainly from olive oil; a low consumption of meat; very low or null consumption of processed food; a variable consumption of fish and shellfish; and a high consumption of fibre, derived from vegetables, fruits, legumes, and whole-grain cereals. In adults, the Mediterranean diet may include a moderate consumption of

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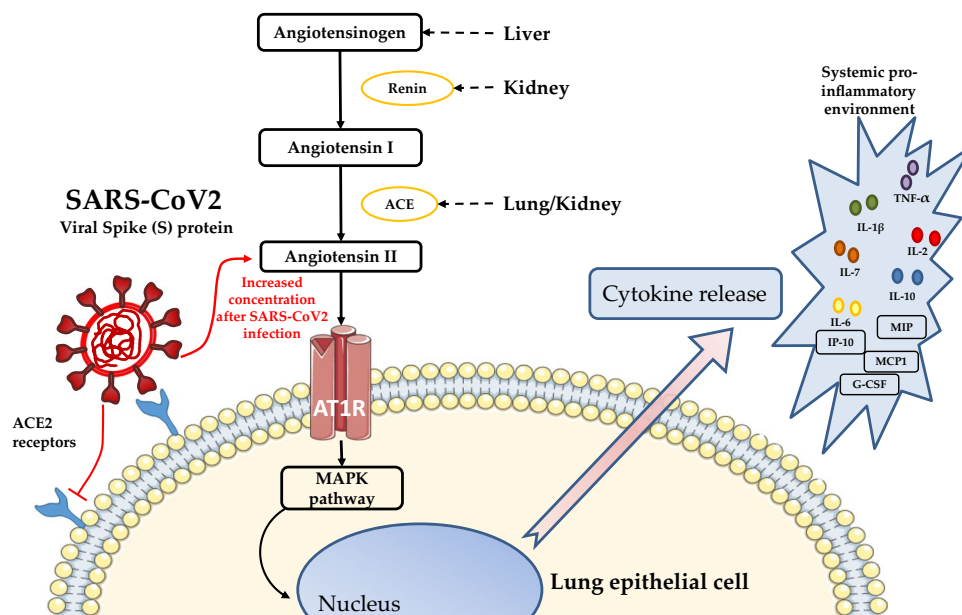
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red wine during meals. Consequently, it is a diet rich in many antioxidant compounds with potential health properties [50]. The Mediterranean diet has demonstrated to be associated with risk reduction for the common co-morbidities observed in COVID-19 patients such as cardiovascular diseases [50] and metabolic syndrome [26]. Consequently, it has been hypothesized that the Mediterranean dietary pattern, or at least some of its components, could be negatively associated with COVID-19 cases and related deaths.

One characteristic of viral infections is the great production of reactive oxygen species (ROS), which decreases patients' probability of overcoming the disease. Moreover, the oxidative stressful situations, where the individuals have lowered their antioxidant defence, increase the risk of infection, thus creating a vicious circle [66]. In addition, it is thought that the intracellular redox balance might alter the virus antigen presentation [65], as well as the expression of the angiotensin-converting enzyme 2 (ACE2) receptor [32], an enzyme highly expressed in adipocytes and potentially involved in the metabolism of the adipokine apelin [5], which reinforce that obesity is as a strong risk factor for COVID-19. In the case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it has been described that the ACE2 receptor, nuclear factor erythroid 2-related factor 2 (Nrf2), NLR family pyrin domain-containing 3 (NLRP3) inflammasome, toll-like receptors (TLRs), and bromodomain-containing protein 4 (BRD4) are modulated in COVID patients [42].

Coronaviruses use the spike glycoprotein to bind to the cellular receptors. The interaction of SARS-CoV spike protein with the ACE2 receptor induces changes which are essential for membrane fusion, therefore resulting in a critical initial step for SARS-CoV-2 to enter into target cells. In a normal situation, ACE2 receptor negatively regulates the function of ACE by converting Ang I to Ang 1–9 and Ang II to Ang 1–7. After SARS-CoV-2 infection, the virus interacts with ACE2 receptors, leading to their downregulation on endothelium of lung and, presumably, other organs, such as kidney. This downregulation of ACE2 leads to unopposed Ang II accumulation [15] and, consequently, to a MAPK-mediated increased release of proinflammatory cytokines (Fig. 1). Recently, elevated Ang II levels in plasma in COVID-19 patients with lung injury have been reported [46]. Moreover, increased levels of interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 (MIP1), and tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) have been found in severe COVID-19 patients [74]. These facts indicate that inflammation is an important feature of COVID-19, which plays a key role in the prognosis of the disease.

Taking all of the above in mind, it is plausible to think that the Mediterranean diet components may exert beneficial effects on COVID-19 outcomes. The benefits of this food pattern on the infection could be attributed, on the one hand, to the fact that it is a balanced diet, necessary for the



**Fig. 1** Proinflammatory response to the infection with SARS-CoV2. ACE2 receptor becomes unavailable to bind to Angiotensin II after viral infection. ACE, angiotensin-converting enzyme; AT1R, angiotensin II receptor type 1; G-CSF, granulocyte colony-stimulating factor; IL, interleukin; IP10, interferon gamma-induced protein 10;

MAPK, mitogen-activated protein kinase; MCP1, monocyte chemoattractant protein 1; MIP1, macrophage inflammatory protein 1; S, spike glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF- $\alpha$ , tumour necrosis factor  $\alpha$

**Table 1** Polyphenol content in several foods in the Mediterranean diet [54]

Polyphenol (CAS number)	Food	Content	Unit
<i>Hydroxytyrosol</i> (10,597–60-1)	Olive oil	0.35–0.77	mg/100 g FW
	Olive fruits	55.6–65.9	mg/100 g FW
	Wines	0.21–0.61	mg/100 mL
<i>Resveratrol</i> (501–36-0)	Wines	0.04–0.27	mg/100 mL
	Grapes	0.02–0.15	mg/100 g FW
	Nuts	0.02–0.11	mg/100 g FW
	Berries	0.35–3.00	mg/100 g FW
<i>Quercetin</i> (117–39-5)	Capers	76–1047	mg/100 g FW
	Onions	0.70–2.20	mg/100 g FW
	Broccoli	1.80–6.50	mg/100 g FW
	Apples	4.66–7.00	mg/100 g FW
	Berries	0.02–42.00	mg/100 g FW
	<i>Epigallocatechin-3-gallate</i> (989–51-5)	Nuts	1.10–2.30
Tea infusions		1.83–27.16	mg/100 mL
Beans		0.05–17.38	mg/100 g FW
<i>Naringin/naringenin</i> (10,236–47-2/480–41-1)	Oranges	11.00–11.90	mg/100 g FW
	Lemons	0.50–0.60	mg/100 g FW
	Citrus juices	8.48–45.05	mg/100 mL

The data include both the compound in its free state and in its conjugated state. All data have been obtained from the Phenol-Explorer platform (<http://phenol-explorer.eu/>). This database, developed at INRA in collaboration with AFSSA (incorporated into ANSES since 1 July 2010), the University of Alberta, the University of Barcelona, IARC, and In Siliflo, contains more than 35,000 content values for 500 different polyphenols in over 400 foods, derived from the systematic collection of more than 60,000 original content values found in more than 1300 scientific publications. *FW*, fresh weight

proper function of the immune system, and, on the other hand, to the fact that numerous studies have proved the anti-inflammatory, antioxidant, and immunomodulatory effects of the diet on diseases related to low-grade inflammation [51], mainly due to its polyphenol content (Table 1).

In addition to the beneficial effects on COVID-19 outcomes mediated by their antioxidant and anti-inflammatory effects, the Mediterranean diet polyphenols can also act through other mechanisms that are not addressed in this review article. For example, it has been revealed that these phenolic compounds might interfere with SARS-CoV-2 binding to its tissue-binding glucose-regulated protein 78 (GRP78) [20], a chaperone that is upregulated upon viral infection.

In contrast with the potential beneficial effects of Mediterranean diet, Western diets are related to systemic inflammation, increased oxidative stress and lower immune response, and thus may increase the severity of COVID-19 patients. These effects are due to their high content of saturated fat, refined carbohydrates and sugar, and to their low content of fibre. Moreover, the Western diets have been associated with different disorders such as metabolic syndrome or cardiovascular diseases, among others [19]. Furthermore, it is suggested that Western diets could worsen the evolution of COVID-19, due to the fact that it has been recently reported that a continuous high-fat high-sugar diet enhances the severity of symptoms of COVID-19 in Syrian hamster [55].

Unfortunately, to date, epidemiological data are extremely scarce. In an ecological study addressed in Spain and 23 OECD countries, Greene et al. (2021) observed an inverse relationship

between Mediterranean diet adherence and COVID-19 cases and related deaths [27] and concluded that the Mediterranean diet and other dietary approaches that reduce inflammation and risk for several chronic diseases might reduce the risk for severe COVID-19 pathology and mortality. In this scenario, the aim of the present review is to gather the reported scientific information supporting the potential usefulness of the main phenolic compounds present in the Mediterranean diet as preventive/therapeutic agents against COVID-19. For this purpose, this review article focuses on their antioxidant and anti-inflammatory effects. In this context, although we are fully aware that several polyphenols are present in the Mediterranean diet, this review gathers information on the main Mediterranean diet polyphenols for which scientific evidence can be found on their effects on this disease. Therefore, research studies concerning the simple phenol hydroxytyrosol, the stilbene resveratrol, and the flavonoids quercetin, catechin, and naringenin are compiled in the following lines. The data presented provide indirect evidences of the potential benefits of these compounds on SARS-COV-2 infection and COVID-19 development, and thus, conclusions concerning their actual usefulness should be taken with caution.

## Hydroxytyrosol

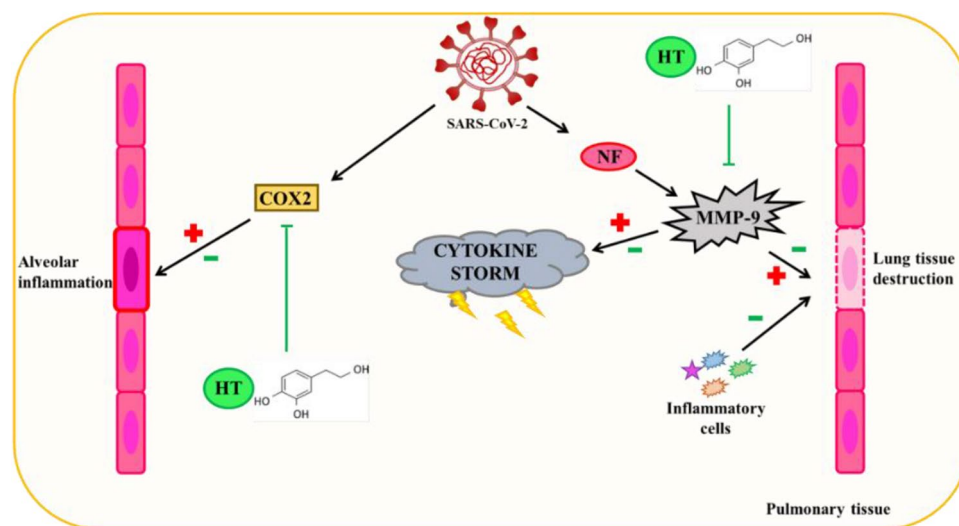
Olive oil is one of the most characteristic foods in the Mediterranean diet. In fact, it is the main source of added fat in this dietary pattern. As such, olive oil, and more precisely

extra virgin olive oil (EVOO), is an important source of nutrients and bioactive compounds that have shown beneficial health effects against several noncommunicable diseases, such as cardiovascular diseases, diabetes, and certain types of cancer [1]. Among these bioactive compounds naturally occurring in EVOO, polyphenols have attracted much attention, being hydroxytyrosol the one that has gained more attention. Indeed, within the health claims for olive oil authorized by the European Register of Nutrition and Health Claims, this polyphenol is considered to “contribute to the protection of blood lipids from oxidative stress” [21]. In addition, hydroxytyrosol has also been extensively studied due to its potential antiviral activity [1].

Hydroxytyrosol (4-(2-hydroxyethyl)-1,2-benzenediol), which is present in olives, increases during olive maturation as a result of oleuropein hydrolysis. It is extracted from olive leaves and fruits and is especially abundant in EVOO. The antiviral capacity of hydroxytyrosol is widely known, due in part to its anti-inflammatory effect. Different studies have demonstrated that this phenolic compound suppresses the activity of matrix metalloproteinase-9 (MMP-9) and cyclooxygenase-2 (COX-2) enzymes [24, 62]. Indeed, increased MMP-9 circulating level has been suggested as an early indicator of respiratory failure in patients with COVID-19 [67]. In this regard, it has been reported that, in acute lung injury (such as that occurring in COVID-19), MMP-9 is released from neutrophils, thus producing inflammation and degradation of the alveolar capillary barrier, which in turn promotes the migration of inflammatory cells resulting in further destruction of the lung tissue [16]. In addition, the involvement of MMP-9 in the so-called “cytokine storm” that

takes place in COVID-19 has also been proposed in studies using a network-based system biology approach [33]. Therefore, hydroxytyrosol-induced MMP-9 suppression may alleviate and/or partially prevent the lung injury produced by COVID-19 through this pathway. As far as COX-2 is concerned, its induction, as well as that of p38 mitogen-activated protein kinase (p38MAPK), is known to be involved in viral pulmonary alveolar inflammation [2]. Thus, the suppression induced by hydroxytyrosol in COX-2 might prove to be efficient in alleviating/preventing COVID-19-induced lung injury. Noteworthy, the capacity of hydroxytyrosol to decrease interleukin-6 (IL-6) and TNF- $\alpha$ , two cytokines that are known to be boosted in severe cases of COVID-19 as mediators of the “cytokine storm”, has been described in animal models (Fig. 2) [56].

As previously mentioned, the antioxidant properties of hydroxytyrosol have also been highlighted as contributors to its antiviral properties. In this regard, in vitro studies demonstrated that hydroxytyrosol acts by enhancing both Nrf2 synthesis and nucleus translocation, resulting in the transcription of genes encoding antioxidant response elements [77]. Nrf2 is a nuclear transcription factor that controls the expression and coordinated induction of a number of genes encoding detoxifying and antioxidant enzymes and proteins, thus a critically important mechanism for cell protection and survival. Interestingly, the suppression of Nrf2 pathway has been found in lung biopsies of patients with COVID-19 [53]. Therefore, the activation of Nrf2 has been postulated as a potential therapeutic target against this disease, since it is known to protect from lung injuries such as acute lung injury or respiratory distress syndrome [14].



**Fig. 2** Potential protective effects of hydroxytyrosol against SARS-CoV-2-induced damage in alveolar tissue through anti-inflammatory mechanisms. The red plus symbols represent the damage induced by SARS-CoV-2 in lung tissue. The green minus symbols represent the processes suppressed by hydroxytyrosol. The truncated green lines

represent the processes suppressed by hydroxytyrosol. HT, hydroxytyrosol; COX-2, cyclooxygenase-2; MMP-9, matrix metalloproteinase-9; NF, neutrophil; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

In summary, evidence from different *in vitro* studies demonstrates the mechanisms underlying the well-documented anti-inflammatory and antioxidant properties of hydroxytyrosol. Taking into account that a common feature of COVID-19 is an uncontrolled systemic inflammatory response, and that oxidative stress is involved in this infection, hydroxytyrosol might represent a compound of interest as therapeutic agent due to its anti-inflammatory properties.

## Resveratrol

Resveratrol is a polyphenol naturally present in low concentrations in different food sources, typical from the Mediterranean diet, that include grapes, red wine, berries, and nuts. In this sense, a recent meta-analysis of randomized controlled trials showed that resveratrol supplementation increased total antioxidant capacity [39]. Moreover, both *in vitro* and *in vivo* studies have shown that resveratrol has the potential to prevent different infections and inhibit many human respiratory viruses, including influenza viruses, by different mechanisms such as the inhibition of virus replication [18]. Consequently, this effect could also take place in the case of SARS-CoV2 virus.

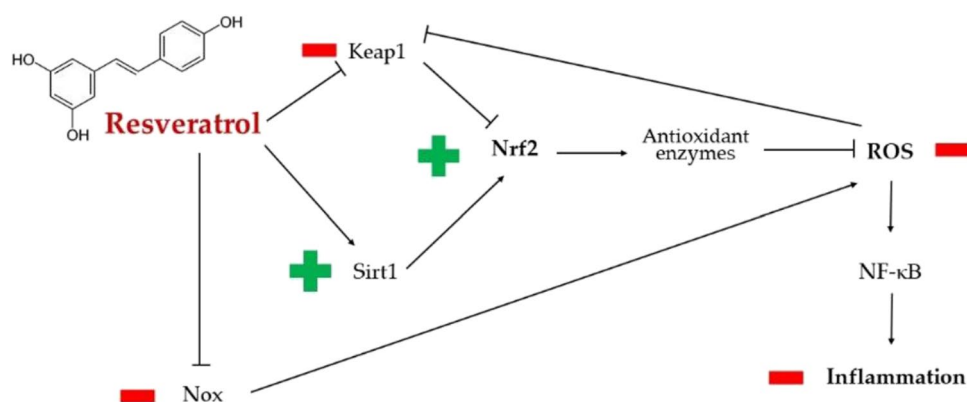
Resveratrol may interact with SARS-CoV-2, at least in part, by triggering Nrf2 [3], which, as explained before, results in the transcription of genes encoding antioxidant response elements [77]. Moreover, an important regulatory role of Nrf2 as a host defence mechanism against some respiratory virus diseases such as respiratory syncytial virus disease has been demonstrated [11]. The potentiation in Nrf2 signalling has been observed in both *in vitro* and *in vivo* studies. Thus, Hao et al. found that Nrf2 increased significantly in the heart tissue and the cultured cardiomyocytes

upon resveratrol treatment. They also observed that knock-down of Nrf2 expression in the cardiomyocytes made resveratrol no longer able to attenuate LPS-induced cellular toxicity, suggesting that Nrf2 indeed played a critical role in the cardioprotection of resveratrol [30].

This effect in Nrf2 is in part due to the activation of sirtuin 1 (SIRT1) and the decrease in the expression of Nrf2 inhibitor, Kelch-like ECH-associated protein 1 (KEAP1) (Fig. 3). The activation of Nrf2 by resveratrol increases the expression of Nrf2 target genes and antioxidant enzymes NAD(P)H quinone dehydrogenase 1 (NQO1) and glutathione S-transferase [75]. Another proposed mechanism by which resveratrol can lower ROS is the modulation of glutathione peroxidase. This enhances glutathione production and counteracts the oxidative stress-mediated tissue damage [75].

It has been observed that in rodents this polyphenol may also mitigate the severity of the infection by improving several endoplasmic reticulum stress markers like eukaryotic initiation factor 2 (eIF2 $\alpha$ ), which is associated with decreased levels of ROS. Furthermore, resveratrol inhibits the NOX family of superoxide-generating NADPH oxidases (NADPH oxidase), which are an important source of ROS and whose activation is associated with a more severe disease and thrombotic events in the new SARS-CoV-2-infected patients. In summary, resveratrol reduces ROS levels through the eIF2 $\alpha$  and NADPH oxidase pathway [3].

As it is known, hypertension and atherosclerosis are two risk factors in SARS-CoV-2 infection [9]. In this regard, the capacity of resveratrol to modulate SIRT1 and Nrf2 pathways, as well as ROS production, results in a greater nitric oxide (NO) bioavailability. Therefore, this resveratrol-mediated NO increase may well underly the vasodilator and antiplatelet effects attributed to the polyphenol [58, 71], which in turn could reduce the severity of COVID-19 in many patients.



**Fig. 3** Main potential protective effects of resveratrol against SARS-CoV-2-induced damage through antioxidant and anti-inflammatory mechanisms. The red minus symbols and the truncated lines represent the processes suppressed by resveratrol. The green plus sym-

bols and the arrows represent the processes activated by resveratrol. Keap1, Kelch-like ECH-associated protein 1; NF- $\kappa$ B, nuclear factor  $\kappa$ B; Nrf2, factor nuclear erythroid 2; Nox, NADPH oxidases; ROS, reactive oxygen species; Sirt1, sirtuin 1

Moreover, resveratrol is accumulated in the endothelial cells, and it is able to protect the endothelial barrier due to its potential antithrombotic effects [23]. In vitro, resveratrol decreases several thrombosis-related markers such as P-selectin, P-selectin glycoprotein ligand-1, and Von Willebrand factor, induced by  $H_2O_2$ , probably by activating the SIRT1 pathway [75]. Finally, due to its antioxidant activity, resveratrol can mitigate the inflammatory response related to ROS-mediated oxidative stress [3]. Lower ROS levels result in the inhibition of nuclear factor- $\kappa$ B (NF- $\kappa$ B) and extracellular signal-regulated kinases/mitogen-activated protein kinases (ERK/MAPK).

Finally, various meta-analysis of randomized clinical trials highlighted the anti-inflammatory effect of resveratrol in humans [29, 38], which could help to alleviate the so-called “inflammatory-storm”, characteristic of COVID-19 [73]. Moreover, a recent study explored the potential mechanisms underlying the effect of resveratrol in COVID-19 patients, using for this purpose a network pharmacological approach and bioinformatics gene analysis. This investigation revealed that resveratrol could mitigate SARS-CoV-2 produced excessive inflammation by inhibiting IL-17, TNF, and NF- $\kappa$ B signalling pathways [72].

In summary, the evidence described to date in in vitro and in vivo studies regarding the antioxidant, anti-inflammatory, and antithrombotic effects of resveratrol suggests that this polyphenol might exert beneficial effects on COVID-19 patients.

## Flavonoids

Flavonoids are secondary metabolites of plants, responsible for their colour and flavour. Depending on their chemical structure, level of oxidation and chemical substituents, they are classified into flavonols, flavanols, flavanones, flavones, isoflavonoids, chalcones, and anthocyanidins. The antibacterial and anticancer properties of flavonoids are widely known. Moreover, these compounds, commonly found in the Mediterranean diet, have the ability to sequester free radicals, since they are natural antioxidants derived from plants [51].

Furthermore, it has been shown that flavonoids activate the Nrf2-KEAP1 pathway, leading to a fall in cytokine production in an in vitro inflammatory model [12]. Therefore, flavonoids can be useful in SARS-CoV-2 therapy by activating the Nrf2 pathway and modulating the inflammatory process. Regarding TLRs and NLRP3 inflammasome, Liskova et al. [42] reviewed the potential role of flavonoids in the modulation of these inflammatory signalling pathways, thus affecting the production of IL-6 and IL-1, respectively. Lastly, the inhibition of BRD4 by flavonoids could decrease the inflammatory and immune process in COVID-19 patients [35].

To recapitulate, flavonoids might exert an antiviral and immunomodulatory role in COVID-19, but these effects ought to be evaluated in well-defined preclinical studies.

## Flavonols: quercetin

Quercetin is a flavonol found in abundance in several foods typical of the Mediterranean diet, specifically in some fruits (especially apples and grapes) and in some vegetables, for instance, onions. It represents the most abundant flavonoid in the human diet. The antioxidant, anti-inflammatory and antiviral effects of this polyphenol are well known. Several in vitro studies have revealed that this molecule inhibits TNF- $\alpha$ , IL-1, and IL-8 production, as well as COX and lipoxygenase (LOX) enzymes in different cell lines [40, 48].

It is well-known that patients with SARS-CoV-2 can present acute kidney injury (AKI), a renal disorder characterized by a diminished renal function, which can influence the prognosis of COVID-19, thus representing a critical complication and an increased risk of death [41]. Quercetin can be a therapeutic agent against COVID-19-associated AKI. In this regard, the nephroprotective effect of quercetin is related to both, its antioxidant and anti-inflammatory properties. As mentioned before, quercetin is effective in scavenging free radicals and in modulating the inflammatory response [64]. On the one hand, quercetin might exert control over the oxidant-antioxidant balance through inhibiting the downturn of glutathione peroxidase, superoxide dismutase, and catalase antioxidant activities observed in AKI. On the other hand, it has the potential of reducing the increment of lipid peroxidation found in AKI [7], as well as of modulating macrophage polarization, by means of NF- $\kappa$ B pathway downregulation. Furthermore, another proposed mechanism implicated on the antioxidant properties of quercetin against AKI is the inhibition of Nrf2 degradation [69]. This phenolic compound is a Nrf2 agonist, which allows this transcription factor to translocate to the nucleus, therefore promoting gene expression of antioxidant elements [49]. This polyphenol also lowers TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 levels in mice with AKI [37, 43]. In addition, it seems that quercetin might protect the renal function against the ischemic process by increasing AMP-activated protein kinase (AMPK) phosphorylation, inhibiting mTOR phosphorylation, and activating the autophagy-signalling pathway [8]. This data provides scientific evidence that supports the use of quercetin as a helpful therapeutic drug for the treatment of AKI, in order to avoid the short- and long-term morbidity as well as the fatal outcome of patients infected with SARS-CoV-2.

It is worth mentioning that, in a randomized placebo-controlled study, oral supplementation with quercetin up to 1 g/day for 3 months did not result in significant adverse effects [31]. Recently, several clinical trials have been carried out with the aim of evaluating the potential role of quercetin against COVID-19. In this context, in a prospective, randomized controlled cohort study, a daily 500 mg quercetin supplement was given to sixty healthy patients without COVID-19 infection during 3 months as a

preventive approach. The results showed that subjects not receiving the quercetin supplement had a 14% higher risk for being infected with COVID-19 than those who had taken the supplement [59]. In other study, a daily dose of 400 mg of quercetin was given to seventy-six subjects for 30 days with confirmed infection of SARS-CoV-2, but without severe COVID-19 symptoms. As a result, both the number of hospitalized patients and the hospitalization days were significantly lower in the quercetin group. Furthermore, the number of hospitalized patients who required oxygen, an entry in an intensive care unit (ICU) or died, were also lower with the polyphenol supplementation [17]. Other authors have also investigated the anti-inflammatory role of quercetin in COVID-19 patients. Therefore, a daily dose of quercetin (7 days with 600 mg and 7 days with 400 mg) was given to twenty-one COVID-19-infected subjects along with standard care. After 14 days of treatment, patients who received the quercetin supplement showed a faster amelioration of COVID-19-related symptoms. Additionally, inflammatory features such as lactate dehydrogenase (LDH), ferritin, C reactive protein (CRP), and IL-10 are death risk factors of COVID-19 [28]. Thus, it has been showed that LDH, ferritin, and CRP levels were diminished (−35.5%, −40%, and −54.8%, respectively) after the first week of supplementation with quercetin, being these blood markers were higher in patients who did not survive to SARS-CoV-2 infection [17].

Moreover, critical illness and mortality in patients with COVID-19 are associated with coagulopathy caused by this infection. This coagulopathy consists of microvascular and macrovascular thrombi, suggesting that an imbalance between coagulation and inflammation may lead to a hypercoagulable state. In this respect, quercetin, like other polyphenols, acts as a competitive inhibitor of thrombin, suggesting that it could be used to prevent this complication of the disease.

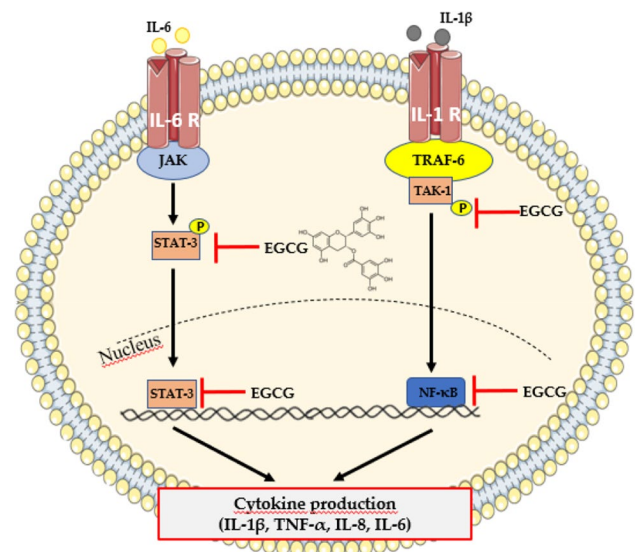
Taken together, the antioxidant and anti-inflammatory effects attributed to quercetin in preclinical studies suggest that this molecule can represent a suitable candidate for further investigation as a potential therapeutic agent against COVID-19.

### Flavanols: catechins

Epigallocatechin-3-gallate (EGCG) is a catechin present in green tea extract, as well as in nuts and beans. In fact, it is the most active and abundant phenolic compound in this extract. The potential positive effect of this phenolic compound seems to be related to the Janus kinase-signal transducer and activator of transcription protein (JAK/STAT). It is established that interferons (IFNs) can regulate the cellular entry of SARS-CoV-2 in host cells [60]. The potential role of IFNs has also been showed in *in vivo* models, due to the fact that type I and III IFNs signalling worsen lung diseases in SARS-CoV-infected mice [47].

Moreover, type III IFN not only increases lung damage in mice exposed to synthetic viral RNA, but it also reduces lung repair by inhibiting epithelial proliferation [4]. In this context, some authors have reported a IFNs-JAK/STAT pathway association, since IFNs trigger antiviral and immune responses through the JAK/STAT pathway [22], which in turn induces a cytokine storm [36]. For this reason, blocking JAK/STAT signalling with JAK inhibitors might be an attractive alternative in COVID-19 patients [68]. Thus, many clinical trials are testing the efficiency of JAK inhibitors in these patients [13]. The JAK/STAT pathway is activated not only by IFNs, but also by IL-6. The activation of the IL-6 receptor by this cytokine can in turn trigger JAK/STAT3, thus enhancing cytokine synthesis [25]. In fact, it has been reported that the worse prognosis for patients with COVID-19-associated cytokine storm can be due to high levels of IL-6 [61]. As shown in Fig. 4, EGCG is effective inhibiting the JAK/STAT3 signalling, because EGCG binds to the STAT3 SH2 domain, which leads to the inhibition of STAT3 phosphorylation. Moreover, EGCG suppresses STAT3 nucleus translocation, the subsequent STAT3-DNA-binding activity, and hence, cytokine production [70].

Furthermore, this catechin is also able to inhibit IL-1 $\beta$ -induced TNF-receptor-associated factor 6 - TGF $\beta$ -activated kinase 1 (TRAF6-TAK1) complex (Fig. 4). When EGCG



**Fig. 4** Potential protective effects of EGCG against SARS-CoV-2-induced hyper-inflammation. The black arrows represent the signalling pathways activated. The truncated red lines represent the processes suppressed by EGCG. EGCG, epigallocatechin-3-gallate; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-1 R, interleukin-1 $\beta$  receptor; IL-6, interleukin-6; IL-6 R, interleukin-6 receptor; IL-8, interleukin 8; JAK, Janus kinase; NF- $\kappa$ B, nuclear factor  $\kappa$ B; STAT-3, signal transducer and activator of transcription protein 3; TAK-1, TGF $\beta$ -activated kinase 1; TNF- $\alpha$ , tumour necrosis factor  $\alpha$ ; TRAF-6, TNF-receptor-associated factor 6

inhibits TAK1 phosphorylation, it prevents NF- $\kappa$ B entry into the nucleus and suppresses cytokine production. Indeed, NF- $\kappa$ B controls the induction of cytokines implicated in the cytokine storm, such as IL-1 $\beta$ , TNF- $\alpha$ , IL-8, and IL-6 [45].

To sum up, the anti-inflammatory properties of this catechin suggest that this molecule presents a potential interest as therapeutic agent against the cytokine storm induced by SARS-CoV-2.

### Flavanones: naringenin

Naringenin (4',5,7-trihydroxyflavanone) is a flavanone with antioxidant, anti-inflammatory, and antiviral properties. This molecule is the aglycone of naringin, which is the bitter component of some citrus fruits.

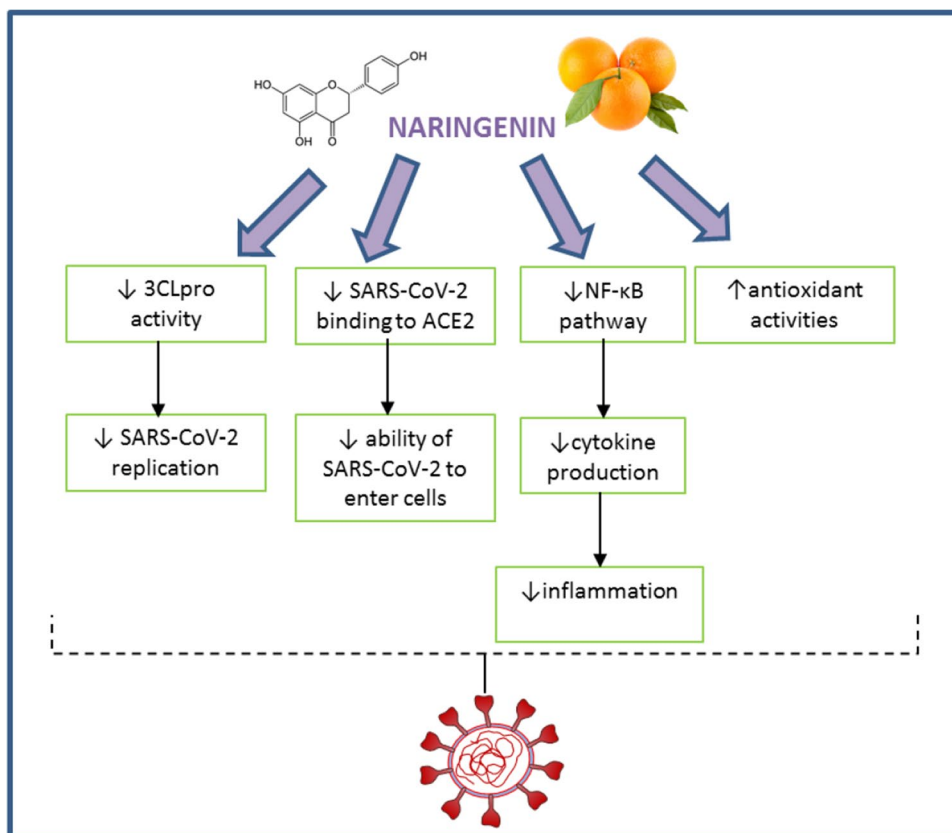
Numerous studies have reported the antioxidant activity of naringenin. Rashmi et al. (2018) showed that naringenin was able to scavenge free radicals, prevent lipid peroxidation in a dose-dependent manner, and increase the levels of reduced glutathione (GSH) in mice with streptozotocin-induced liver damage [57]. Moreover, Hernández-Aquino et al. concluded that the hydroxyl groups of its chemical structure had high reactivity against ROS [34]. Cavia-Saiz et al. [6] showed that naringenin was effective in increasing antioxidant enzymes in the liver of Wistar rats. With regard to the anti-inflammatory effect of naringenin, Zobeiri et al. reviewed that in

the liver, this compound could readily downregulate TNF- $\alpha$ , IL-1 $\beta$ , IL-6, TLR4, iNOS, and COX-2 through the attenuation of the NF- $\kappa$ B pathway and the activation of the AMPK [76] (Fig. 5). These two effects are useful in the prevention of respiratory infections such as COVID-19. Moreover, this molecule may attenuate pulmonary fibrosis, a feature of COVID-19, by means of reducing TNF- $\alpha$ , transforming growth factor- $\beta$  (TGF $\beta$ ), MMP-9, tissue inhibitors of metalloproteinases-1, hydroxyproline and malonaldehyde, results that have been observed in mice with acute lung injury and pulmonary fibrosis induced by paraquat [10]. According to these data, naringenin may be used as an alternative to diminish the expression of the proinflammatory cytokines in the treatment of patients with COVID-19 infection [44].

### Mechanisms of action of phenolic compounds

As a summary of that described in the previous sections, it can be pointed out that although the effects of the polyphenols present in the Mediterranean diet on COVID-19 have not been directly probed to date, these bioactive compounds show biological activities that can be useful to prevent this infection and/or to improve its prognosis. One of them is their antioxidant activity which,

**Fig. 5** Potential mechanism of action of naringenin against SARS-CoV-2. ACE2, angiotensin-converting enzyme 2 receptor; 3CLpro, 3-chymotrypsin-like cysteine protease; NF- $\kappa$ B, nuclear factor  $\kappa$ B; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2





according to the results obtained in *in vitro* experiments and animal models, can be mediated by the increase in the synthesis and translocation of Nrf-2, which boosts the activity of antioxidant enzymes, thus reducing ROS production and enhancing the scavenging of free radicals. The fact that a decrease in this gene has been observed in COVID-19 patients, gives support to this hypothesis.

On the other hand, the most severe cases of COVID-19 have been characterized by the so-called “cytokine storm”, which leads to a massive inflammatory process. Consequently, the well-known anti-inflammatory properties of the phenolic compounds could be useful to avoid this stage. This effect is mediated by the inhibition of the MMP-9 and COX-2 enzymes. The interest of reducing MMP-9 activity is clear because increased MMP-9 circulating level has been suggested as an early indicator of respiratory failure in patients with COVID-19. Moreover, the phenolic compounds inhibit the JAK/STAT3 signalling, thus reducing the production of proinflammatory cytokines. Finally, the reduction in ROS levels induced by these compounds results in the inhibition NF- $\kappa$ B, a transcription factor that controls the synthesis of proinflammatory cytokines.

Thrombotic events have also been described in SARS-CoV-2-infected patients. In this regard, some phenolic compounds can inhibit the NOX family of superoxide-generating NADPH oxidases (NADPH oxidase). This is an interesting effect because NOX activity sensitizes platelets and induces a state of hyper-responsiveness, which is a common feature in thrombotic diseases.

In addition to these effects, the phenolic compounds can prevent COVID-19 disease through other mechanisms that have not been described in this review since these are out of the scope of this journal. In this regard, polyphenols can induce changes in the enzyme ACE2, which acts as a receptor for the viral spike protein of SARS-CoV-2, thus facilitating its entry into the cell. In addition, phenolic compounds have also been reported to inhibit the activity of the dipeptidyl peptidase-4 (DPP4) co-receptor for SARS-CoV-2 (also used by other coronaviruses) [63]. Moreover, polyphenols can also inhibit the virus replication.

It is important to highlight that the dose level of phenolic compounds utilized in the clinical trials aimed to assess the effect of some of these molecules on COVID-19 patients is far greater than that found in Mediterranean diet foodstuffs. In view of this fact, potential synergistic or additive effect of a mixture of phenolic compounds at lower doses in increasing the inhibitory effect on SARS-CoV-2 has also been studied [52]. In fact, it has been suggested that the hydroxylation in C3', C4', and C5' in the B-ring; C3 in the C-ring; C7 in A-ring; the double bond between C2 and C3 in the C-ring; and glycosylation at C8 in the A-ring could contribute to this inhibitory effect.

## Conclusions

Due to the fact that COVID-19 is a very recent pandemic, to date, evidence regarding incidence of this infection and the evolution of COVID-19 patients among individuals following different dietary patterns is very scarce. Nevertheless, it is of utmost importance to collect all the available information concerning the effects that the components present in foods and foodstuffs characteristics of the Mediterranean diet, such as the polyphenols, can have on the infection process of SARS-COV-2 and the pathological events that occur during the development of COVID-19.

Indeed, to date, no direct evidence regarding the potential benefits of phenolic compounds on COVID-19 is available. Nevertheless, numerous studies have demonstrated that these molecules induce positive effects on several alterations induced by this disease, under conditions other than SARS-COV-2 infection, such as oxidative stress, inflammation, and thrombosis. This scientific information is valuable and suggests that the phenolic compounds of the Mediterranean diet may represent a potential protective factor against COVID-19, but caution must be taken when connecting preexisting data to this new infection. In view of this situation, further studies on this topic showing a direct relationship are required.

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## Declarations

**Conflict of interest** The authors declare no competing interests.

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