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QUERCETIN AND VITAMIN C: SYNERGISTIC THERAPY FOR THE PREVENTION AND TREATMENT OF COVID-19 RELATED DISEASE

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ABSTRACT

In December 2019, an epidemic of pneumonia of unknown etiology was detected in Wuhan City (China) and the etiological agent of the atypical pneumonia was isolated by the Chinese as novel coronavirus (2019-nCoV or SARS-CoV-2). The WHO announced this disease was to be known as "COVID-19." SARS-CoV-2 represents an emergent global threat which is straining worldwide healthcare capacity. As of May11 the disease caused by SARS-CoV-2 (COVID-19) has resulted in 16.2crore and 33 lakh deaths worldwide, with 24,372,007 total cases and 266,229 death in the India alone. It is important to study and develop pharmacological treatments useful for the prevention and treatment of COVID-19. We are trying to finding new antiviral compounds, knowledge of the main viral proteins is essential . The drug that is able targets of SARS-CoV-2 include 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), RNA-dependent RNA polymerase, and spike (S) protein. Quercetin is a flavonoid compound and their antiviral properties have been investigated in various study. Quercetin has capability to interfere with SARS-CoV-2 replication. Vitamin C (Ascorbic acid) is a essential vitamin necessary for functioning of the immune system. Numerous evidence show that vitamin C and quercetin co-administration exerts a synergistic antiviral action due to overlapping antiviral an immunomodulatory properties and the ascorbate has capacity to recycle quercetin, enhance its efficacy. We present the current evidence for the use of vitamin C and quercetin both for prophylaxis and for the treatment of COVID-19 patients as an adjunct to rising pharmacological agents such as Remdesivir or convalescent plasma.

KEYWORDS: COVID-19, infectious diseases, quercetin, SARS-CoV-2, vitamin C, quercetin, flavonoids, antiviral, Coronavirus, immunomodulation.

INTRODUCTION

The human coronaviruses such as HCoVs are severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), cause high mortality. In Saudi Arabia the SARS-CoV has infected 8098 individuals in 2002–2003 and whereas MERS caused 858 deaths .Recently discovered coronavirus (COVID-19) causes infectious disease. WHO originally called this infectious disease Novel Corona virus Infected Pneumonia (NCIP) and the virus had been named 2019 novel coronavirus (2019-nCoV). The virus is identified as the cause of an outbreak of pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019.ON 11 Feb2011, WHO officially renamed the diseases COVID-19 AS novel coronavirus (2019-nCoV). TO control the spread of disease, researchers are working to find out various drugs that inhibit virus-host interactions, such as ACE2 inhibitors, antibody-based therapeutic molecules, microRNAs, siRNA as therapeutic molecules, nucleoside analogs such as Azidothymidine, which contribute inhibition of reverse transcriptase action in human immune-deficiency virus (HIV), Aciclovir, ganciclovir that inhibit the infection of herpes simplex virus (HSV), Oseltamivir (Tamiflu), the drug that inhibit the viral budding in influenza. Many are trying to understand the cytokine profiling and attempting to inhibit the inflammation in the lung during COVID 19 infection phase.[1-13]

Pathophysiology of COVID-19

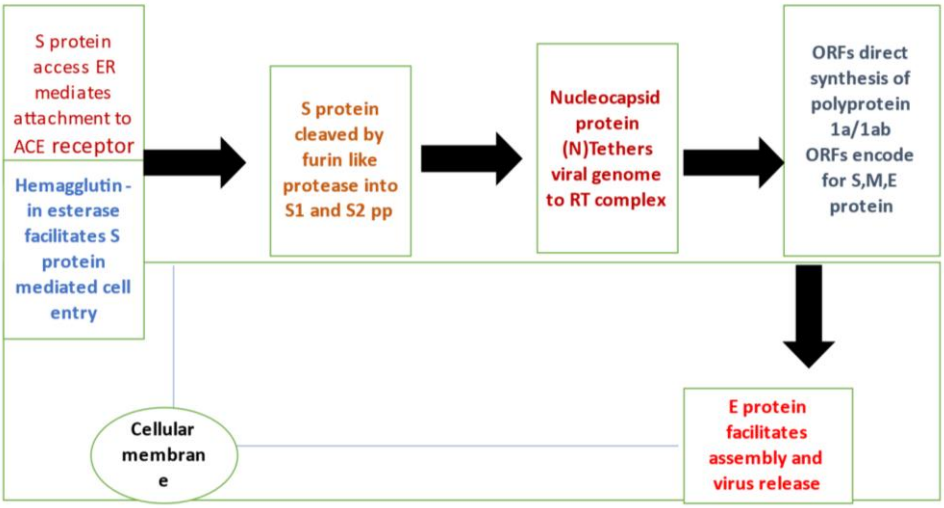

Fig: 1 pathophysiology of covid-19.

Table 1: Transmission ,symptoms and abnormalities of corona virus. (Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19).

Transmission	Symptoms	Abnormalities	Complication
Transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurs: 1. primarily via respiratory droplets from face-to-face contact 2. to a lesser degree, via contaminated surfaces. 3. Aerosol spread may occur, but the role of aerosol spread in humans remains unclear. 4. An estimated 48% to 62% of transmission may occur via pre- symptomatic carriers.	Common symptoms in hospitalized patients include: 1. fever (70%-90%), dry cough (60%-86%), shortness of breath (53%- 80%), fatigue (38%), myalgias (15%-44%), nausea/vomiting or diarrhea (15%-39%), headache, weakness (25%), and rhinorrhea (7%). 2. Anosmia or ageusia may be the sole presenting symptom in approximately 3% of individuals with COVID-19.	Among hospitalized patients include lymphopenia (83%), elevated inflammatory markers (eg, erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-α, IL-1, IL-6), and abnormal coagulation parameters (eg, prolonged prothrombin time, thrombocytopenia, elevated D-dimer [46% of patients], low fibrinogen	Among hospitalized patients with COVID-19 include : 1. pneumonia (75%); acute respiratory distress syndrome (15%) 2. acute liver injury, characterized by elevations in aspartate transaminase, alanine transaminase, and bilirubin (19%) 3. cardiac injury, including troponin elevation (7%-17%), acute heart failure, dysrhythmias, and myocarditis; prothrombotic coagulopathy resulting in venous and arterial thromboembolic events (10%-25%) 4. acute kidney injury (9%); neurologic manifestations, including impaired consciousness (8%) and acute cerebrovascular disease (3%); and shock (6%).

Sources of quercetin

Quercetin (also known as 3,3′ ,4′ 5,7-pentahydroxyflavone) is a member of the polyphenol family and is present in various vegetables and fruits, such as capers, lovage, dill, cilantro, onions, various berries (e.g., chokeberries, cranberries, and lingonberries), and apples.[8]Quercetin has viral infection due to its promising antiviral effects in inhibiting polymerases,[14] proteases,[15] reverse transcriptase,[16] suppressing DNA gyrase, and binding viral capsid proteins,[17,18]

Chemistry of quercetin

quercetin is produced from the phenylpropanoid pathway and is ultimately derived from phenylalanine. It is converted to 4-coumaroyl-CoA, via phenylalanine ammonialysate, to cinnamate-4-hydroxylase and 4-coumaroyl-CoA-ligase and combined with malonyl-CoA in a 1:3 ratio by 7,2′ - dihydroxy-4′methoxyisoflavanol

synthase to form tetrahydroxy chalcone. Then converted to naringenin and to eriodyctiol through flavonoid 3′ - hydroxylase. Finally, eriodyctiol is hydroxylated and converted to quercetin using flavanol synthase.[19]

Ascorbic acid(vitamin C)

Ascorbic acid is water soluble an essential vitamin with known antiviral properties.Citrus fruits such as orange and orange juice, peppers, strawberries ,broccoli, sprouts and potatoes. Vitamin C exerts its antiviral properties by promoting lymphocyte activity, increasing interferon-α production, modulating cytokines, reducing inflammation, improving endothelial dysfunction, and restoring mitochondrial function.[20–22] vitamin C may be directly viricidal.[23]

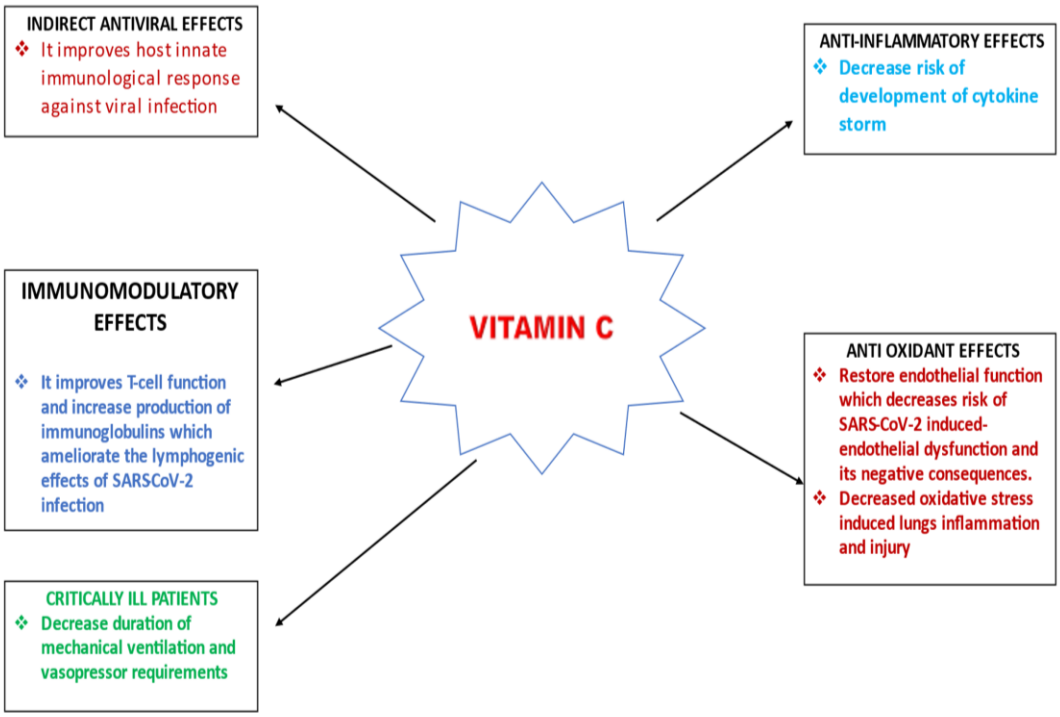

Fig 2: The beneficial effects of Vitamin C in management of COVID-19.

BIOLOGY OF QUERCETIN

Many researchers found that various flavonoid compounds, such as quercetins show their activity in affecting capillary wall resistance.[24] Dietary supplements differ, but contain the free form of quercetin—quercetin aglycone.[25] They found that if consumed, quercetin passes predominantly unaltered into the large intestine[26] and quercetin acts as a free radical scavenger, donating two electrons via o-quinone/quinone methide[27] both in vitro and in vivo,[28,29] quercetin as a potent antioxidant. Their antioxidant activity potentiate by vitamin C.[30] Quercetin also show anti inflammatory action and its diverse roles identified in in vitro and in vivo models including: inhibition of platelet aggregation,[31] inhibition of lipid peroxidation,[32] and its inhibitory effects on pro-inflammatory mediators such as lipoxygenase[33] and phospholipase A2.[34] This anti-inflammatory effect is primarily mediated by flavonoid activity on arachidonic acid metabolism and the associated leukotriene/prostaglandin pathways. 3-methylquercetin, a quercetin metabolite, showed stimulatory effects on nasal epithelial cell ciliary beat frequency, both in vitro and in vivo, when administered either alone or with absorption enhancer HP-β-CD.[35] Quercetin also affects the function of several lipids, protein tyrosine, and serine/threonine kinases,[36,37] such as phosphatidylinositol (PI)-3-kinase and inducible nitric oxide synthase (NOS2)[38,39]

Immunomodulatory properties

Vitamin C

Vitamin C play important role in improving the function of innate immunity and enhancing cellular and humoral immune response .Inadequate intake of micronutrients, including vitamin C, decreases resistance to infection and increases disease complications.[40] Vitamin C improves epithelial barrier integrity, which is the first line of defence against external pathogens.[41] Administration of vitamin C in high oral dose (60 mg/kg) enhanced natural killer cell activity, that's play an important role in the innate immunity against viral infection.[42] vitamin C accumulates intracellularly in neutrophils which show that vitamin C has a role in maintaining the normal function of leukocytes.[43] Administration of 1 g/day of IV vitamin C for 6 months to asthmatic children improved neutrophil chemotaxis.[44] Vitamin C in a dose of 200 mg to 1 g daily for 1–4 months improved the neutrophilic activity of

phagocytes. However, administration of 2 g of vitamin C on a daily basis for 2 weeks impaired bacterial killing activity of neutrophil.[45] Vitamin C reduces the release of proinflammatory cytokines that's play a role in mitigating cytokine storm in SARS-CoV-2 infection which leads to reduction of inflammatory-induced tissue damage.[46] In in vivo study, vitamin C supplement reduced lung inflammation induced by influenza A virus and pro inflammatory cytokine production in Gulo knockout mice.[47] In fact, SARS-CoV-2 infection has a greater negative impact on the immune system and leads to lymphopenia and reduced numbers of natural killer cells in addition to inducing excessive release of inflammatory mediators leading to cytokine storm and tissue damage.[48,46] Based on this evidence,vitamin C might have the potential to ameliorate the deleterious immunological effect of SARS-CoV-2 infection and that can make it a feasible treatment option in COVID-19.

Quercetin

Quercetin stimulates T-helper cells and produce (Th-1)-derived Interferon-γ (IFN- γ) and downregulates Th2-derived IL-4 then add to cultured blood peripheral mononuclear cells.[49] Many Studies showed that quercetin enhanced NK cell lytic activity, neutrophil chemotaxis, and lymphocyte proliferation in mice.[50,51]

Effect on SARS-COV-2

Various study confirmed that Quercetin has antiviral effect on several members of the Corona viridae family (Ling Yi and colleagues,) and "quercetin" a potential drug in the clinical treatment of SARS".[52] In 2003 SARS Coronavirus described as[53] it is a single-stranded RNA virus of ~29,700 nucleotides, which uses ribosome sites to encode two replicase glycoproteins, PP1a and PP1b, that mediate viral replication.[53,54] The precursor glycoproteins are synthesize 3C-like protease (3CLpro) plays a critical role in the lytic release of its replicates.[55] Quercetin 3β-galactoside binds SARS-Cov 3CL protease and inhibits its proteolytic activity with an IC50 of 42.79 ± 4.95μM.[56] The inhibitory action on 3CLpro is dependent on the hydroxyl group of quercetin which, shown as molecular modeling and Q189A mutation, recognizes Gln189 as a crucial site on 3CLpro responsible for the binding of quercetin.[56] Quercetin a compound able to block SARS-Coronavirus entry into Vero E6 cells with a half-effective concentration (EC50) of 83.4μM and with low cytotoxicity (CC50 3.32 mM).[98] SARS-CoV-2, the virus responsible for the 2020 COVID19 pandemic.[57] belongs to the genus Beta coronavirus and subgenus Sarbecovirus and, due to its similar receptor-binding domain, it has been assume, similarly to SARS-CoV, to infect type II pneumocytes entering via the angiotensin-converting enzyme II receptor[58] SARS-Cov-2 protease 3CL maintains the same Gln189 site[59] of SARS-Cov 3CLpro, which previously was identified as the binding site for the hydroxyl groups of quercetin and its derivates.[56] In vitro study showed that ascorbic acid treatment on chick-embryo ciliated tracheal organ cells (CETO) elevate resistance to Coronavirus infection but did not showed any effect on orthomyxovirus or paramyxovirus[60]

SYNERGISTIC ANTIVIRAL ACTION

Quercetin spontaneously oxidizes to form O-semiquinone and O-quinone/quinone methide (QQ), which can bind protein thiols forming toxic compounds.[61] Both the process anti- and pro-oxidant effects called as "quercetin paradox".[62] Although, QQ can be recycled into quercetin by electron donors like NADH or ascorbate, or form together, with glutathione either 6-glutathionyl-quercetin or 8-glutathionyl quercetin (GSQs).[69,63] Whenever ascorbate or glutathione levels are insufficient, quercetin may be shunted to QQ and exert prooxidant effects. So, the importance for its co-administration with vitamin C. However, even though QQ exhibits a higher affinity for glutathione than for vitamin C,[64] the methylated metabolites of quercetin show a higher preference for ascorbate than for thiols, a cycling of activity which will exert anti-oxidant effects.[66] Both GSQs[67] and QQ-protein thiols have unstable and transient -lasting for minutes and hours instead of days.[68] The intravenous administration (I.V 3 gr q6) are capable of free radical scavenging and electron donation, either by preventing quercetin or glutathione oxidation. The present scenario, ascorbate may exert antioxidant and immunoprotective effects, quercetin and its metabolites exert a coexisting antiviral response and, if quercetin-oxidized compounds are form, can be partially recycled by ascorbate and transported by glutathione, thus preventing their possible toxicity.[70]

QUERCETIN AND MOLECULAR DOCKING

To discover the new compounds expressing potential activity against SARS-CoV-2 viral targets, a number of studies reporting the use of computer modelling for screening purpose.[71] These models are help to determine the free energy of binding between a ligand and a receptor.[72] A lower binding free energy show a stronger ligand–receptor interaction. For obtaining comparable results via different modelling approaches can be a challenge[73] Computer base molecular docking allows visualisation of the relative binding affinity of thousands of molecules for the a viral receptors. The advantage of molecular docking screening is the reduction of the high costs related with physically screening the activity of large number of natural compounds.[74] Recently, the virtual screening[75] of 83 compounds used in Chinese traditional medicine for activity against the RNA-dependent RNA polymerase of SARS-CoV-2 identified the aflavin, an antioxidant polyphenol, as a potential inhibitor. The virtual screening of 115 compounds used within Chinese traditional medicine and focused 13 for further studies.[76] Some compounds are naturally occurring polyphenolic compounds such as quercetin and kaempferol, are for the treatment of other disease.[77] Many the study showed a significant inhibition by quercetin of 3CLpro and PLpro with a docking binding energy corresponding to

−6.25 and −4.62 kcal/mol, respectively[78] that's Smith and Smith (2020) determined quercetin a theoretical, but important, capability to interfere with SARS-CoV-2 replication. A target for structure-based drug discovery was identified the disruption of the viral S protein-ACE2 receptor interface. The computational docking model was repeated to identify small molecules that were able to bind to either the isolated viral S protein at its host receptor binding region or to the S protein–human ACE2 receptor interface, to potentially limit viral recognition of host cells and/or to disrupt host– virus interactions.

The researcher tested various natural compounds, among them quercetin was identified as the top scoring ligands for the S protein ACE2 receptor interface, and the confirmed its role as a promising antiviral agent. An in vitro molecular docking study was also observed to investigated the probability of molecular docking between quercetin and viral protease. Proteases play essential roles in viral replication, and specifically, 6LU7 was identified to be the main protease (Mpro) found in SARS-CoV-2[79] The SARS-CoV-2 genome is approximately 79% identical to that of SARS-CoV-1.[80] So quercetin showed an IC50 of 8.6 ± 3.2 μM against SARS-CoV-1 PLpro.[81] Recently various researchers confirmed that quercetin have antiviral activity with respect to SARS-CoV-1 by inhibiting also 3CLpro.[82]

BENEFICIAL EFFECTS OF VITAMIN C AND QUERCETIN IN VIRAL INFECTIONS (In vivo study)

Number of literature that supporting the antiviral properties of quercetin, in both in vitro and in vivo experiments. Quercetin has been proved that inhibits respiratory viruses in cultured cells.[83,84] It inhibits the cytopathic effects provoked by many serotypes of rhinovirus, echovirus type.[85, 86, 87, and 88] coxsackievirus (A21 and B1), and poliovirus (type 1 Sabin) at a minimal inhibitory concentration of 0.03 to 0.5μg/ml in Hela or WI-38 cells,[89] Quercetin also decrease the plaque formation by RNA and DNA viruses [Respiratory Syncytial Virus (RSV), Polio type 1, parainfluenza type 3, and Herpes Simplex Virus-1(HSV-1)] displaying anti-infective and anti-replicative properties [90]. It also inhibited the replication of cytomegalovirus (CMV) inoculated HeLa cells at a half inhibitory concentration (IC50) of 3.2 ± 0.8μM and with a selectivity index (SI) of 22.[91] This is confirm that quercetin has able to either block virus entry or inhibit viral replication enzymes such as viral polymerases.[92]

In vivo studies showed that when mice inoculated with meningoencephalitis virus are protected from lethal infection by quercetin (30 or 40 mg/Kg BID, po, for 4 days) in a dose dependent manner.[93] These effects are abolished if the compound is administered for < 3 days ,once per day or via subcutaneous injection. This study suggest that the antiviral effects may be dependent on a minimum inhibitory concentration or from some form of metabolic drug conversion.[93] Quercetin treatment also effective in immunocompetent mice infected with Mengo virus.[94]

Vitamin C is an essential nutrient involved in large number of immune functions. Reduced levels of ascorbate have been found in patients with viral infections,[95] sepsis,[96] sepsis-related ARDS,[97] and other critical illness.[98] At the time of infection vitamin C is necessary for neutrophil killing,[99] is concentrated within macrophages,[100] is responsible of T cell maturation[101] and promotes phagocytosis and apoptosis of spent neutrophils.[113] The viral infections, depending on their severity are related with an elevated level of metabolism and reduced circulating ascorbate.

Various investigators have confirmed the Vitamin C enhanced survival in different murine models of lethal infection. Mice infected with Venezuelan encephalitis virus and treated with vitamin C (50 mg/kg) exhibit half the mortality of controls with combined reductions in viral titers, lipid peroxidation products, and NO content.[102] Mice incapable of synthetizing vitamin C (L-Gulono-gamma-lactone oxidase nulls) were infected with influenza; mice not receiving supplemental vitamin C exhibited greater lung pathology scores despite no differences in viral titers.[103] In restraint-stressed mice with H1N1 viral-induced pneumonia, vitamin C lower mortality dose-dependently (100% vs. 80% vs. 50% at 0, 125, and 250 mg/kg/day) and decreased capillary-alveolar structural damage.[104] Mice inoculated with Rabies+ mouse brain cells and treated with daily 100 mg/kg IM vitamin C exhibited nearly half the mortality of controls.[105]

The study of vitamin C in human, patients with severe viral infection showed vitamin C supplementation (300 mg/day) protected from influenza-associated pneumonia.[106,107] Vitamin C administered at 1 g BID to 133 patients, reduced the risk (OR 0.25) of herpes simplex keratitis (HSK) recurrence.[108] The number of case reports related with virus acute respiratory distress syndromes (ARDS) suggest successful treatment with intravenous high doses of Vitamin C.[109, 110]

Recently researchers found that co-administration of quercetin (12.5 mg/kg/week) and vitamin C and B3 in a murine model of exercise-induced susceptibility to influenza H1N1 prolonged time-to-death (median time to death: placebo 9.0 ± 0.33 vs. quercetin 16.5 ± 1.2) and improved survival (mortality: placebo 74% vs. quercetin 52%) when compared to mice receiving only vitamins B3 and C.[111] An older, small clinical trial investigated the combination of flavonoids and ascorbic acid (1:1 ratio) as beneficial for respiratory infection (200 mg TID).[112]

SAFE PROFILE AND OPTIMAL DOSING

Quercetin oral supplementation up to 1 g/day for 3 months has not resulted in significant adverse effects.[114] Randomized placebo-controlled study was done with

quercetin and show 30 patients with chronic prostatitis were supplemented with oral quercetin (1 g/day) and only two reported mild adverse reactions (headache and temporary peripheral paresthesia).[115] Quercetin Intravenous administration in a phase I clinical trial for cancer patients resulted in nausea, vomiting, sweating, flushing, and dyspnea at doses >10.5 mg/Kg (756 mg per 70 Kg individual).[116] Only higher intravenously administered doses up to 51.3 mg/Kg (around 3,591 mg per individual) were associated with renal toxicity.[114] They proposed the following optimal dosing (Table 2). Further studies are need to examine and discuss the possible administration of quercetin for prolonged periods of time (>1 year). Up to 1 g/day for 3 months has not reported in significant adverse effects[114]

Table 2: Proposed multi-drug approach for either the prophylaxis for high risk population, and treatment of mild and severe cases.

	Quercetin	Vitamin c
Prophylaxis	250-500 mg BD	500 mg BD
Mild cases	250-500 mg BD	500 mg BD
Severe cases	500 mg BD	3gr q6 for 7 days

DISCUSSION

Quercetin and vitamin C may disrupt virus entry, replication, enzyme activity and protect the immune response by early IFNs production, promoting T cell maturation, and phagocytic activity. Quercetin and ascorbic acid co-administration represent strategy for prophylaxis and treatment of several respiratory viruses, such as SARS-CoV-2. In vitro study showed that quercetin retard viral membrane fusion for both influenza and SARS-Cov.[52] Quercetin targeted viral polymerases and may disrupted replication via the inhibition of reverse transcriptase enzymes. Quercetin inhibited SARS 3CL protease by binding to GLN189 site[56] and that indicated similarly by SARS-COV-2[59] and. Few in vivo models confirmed increase survival from lethal viral infection when treated with quercetin.[93,111] Various study proposed that oral administration and metabolic processing (methylation, conjugation, etc.) is necessary and have investigated quercetin derivates, as responsible for a cooperative antiviral activity. Vitamin C exerts immunomodulatory activity, enhancing interferon production through STAT3 phosphorylation,[90] limiting cytokine-induced organ damage,[103] promoting survival in lethal infections[102] and, importantly, is able to recycle oxidized quercetin,[63] increasing its antiviral effects. SARS-Cov-2 virus infection show a strong inflammatory and dysregulated reaction in the lung with an increased levels of IL-6 and a "cytokine-storm"[117] which has been shown to provoke either an asymptomatic, mild, or severe infections. In this scenario, Vitamin C and quercetin co-administration may represent a safe, effective, and inexpensive antiviral and immune modulative approach for both the prophylaxis of high risk populations and the treatment of both mild and severe cases. The side effects profile of these agents would also suggest that they may complement interventions which have shown potential benefits in treating Covid-19, such as Remdesivir[118] and convalescent plasma.[119,120] There are some limitations of their use in clinical studies. Both agents are present in varying degrees in individuals' diets and global recommendations for vitamin C intake vary extensively across the globe.[98]

CONCLUSION

The COVID-19 pandemic is the latest and is, so far, completely undetermined . In this time we wait the development of an effective Vaccine.The worldwide researchers focus their all efforts on selecting possible effective treatments, bearing in mind that the plant kingdom supplies chemical skeletons that, since ancient times, have provided humans with "drugs.The number of study that recommends quercetin as a potential molecule candidate for an anti-COVID-19 role. It show range of antiviral properties which can interfere at multiple steps of pathogen virulence -virus entry, virus replication, protein assembly.Due its poor pharmacokinetics profile, any galenic formulation aimed to improve its rate of absorption should be considered important.The therapeutic effects of quercetin can be augmented by the co-administration of vitamin C. Due to the lack of severe side effects and low-costs, we suggest the combined administration of these compounds for both the prophylaxis and the early treatment of respiratory tract infections, especially including COVID-19 patients.

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