# General overview on SARS-CoV-2 and potential role of natural compounds as antiviral drugs targeting SARS-CoV-2 proteins

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## Abstract

Purpose: The novel coronavirus disease namely COVID-19 is a viral disease induced by severe acute respiratory syndrome coronavirus (SARS-CoV-2). The cases were first reported in Wuhan, China, by the end of 2019 and subsequently spread worldwide. The virus can be transferred through direct or indirect contact and leads to several manifestations; the most common are fever, dry cough, pneumonia, and acute respiratory distress syndrome (ARDS). COVID-19 has caused massive human and economic losses, posing an ongoing threat. Understanding the current situation and developing a treatment which can be both safe and effective has become essential. In this regard, natural products could be an important resource in the development of treatment for COVID-19, as they have contributed to the treatment of other viruses in the past. This review aims to understand the cellular machinery of SARS-CoV-2 and to identify its drug targets.

Methods: Emphasis has been given on the literature survey based on in vitro, in vivo, and in silico studies of natural products as anti-SARS-CoV-2. The important role of these compounds in boosting the immune system was also highlighted.

Results: It was found that some natural products showed prominent antiviral activity against coronaviruses through impeding the main machinery used in their pathogenesis and replication cycle. Based on in vitro, in vivo, and in silico investigations, several classes of secondary metabolites, particularly polyphenols, have the ability to disrupt the interaction between SARS-CoV-2 S protein and the ACE2 receptor, resulting in virus entry inhibition. As well as the ability to block the activity of several enzymes involved in the virus replication cycle, including, 3CLpro, PLpro and RdRp. On the other hand, several vitamins and minerals can improve the immune response and are useful for COVID-19 prevention. Essential oils also show the ability to disrupt the fluidity of the virus envelope.

Conclusion: Many phytonutrients are counted as bioactive components against SARS-CoV-2, phenolic compounds by their potent mechanisms of action via the immune system rank first. Group B vitamins, vitamins A, C and E as well as minerals such as zinc, selenium and magnesium also play an important role in in preventing the attack by this virus.

**Keywords:** COVID-19, natural products, secondary metabolites, vitamins, minerals, SARS-CoV-2 proteins.

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## Introduction

Since the 1960s, coronaviruses were already known to humans(da Silva Antonio et al., 2020), they are classified into four types; alpha-CoVs and beta-CoVswhich can infect mammals whereas gamma-CoVs and delta-CoVs can infect birds. Seven coronaviruses have been discovered to be transmissible through human contact so far (Ezhilan et al., 2021), causing pneumonia-like symptoms (Wu et al., 2020).Among them, the two recent deadly forms are, SARS-CoV in China in 2002 and MERS-CoV in Saudi Arabia in 2012 (Boozari&Hosseinzadeh, 2021). In the 21st century, SARS-CoV-2 made history as the third coronavirus outbreak causing a dangerous disease called Covid-19 (coronavirus disease 2019) (Islam et al., 2021). The first appearance of this pathogen was in late November 2019 in Wuhan, China. It was postulated to be a result of a mutation in the bat virus (Wiktorczyk-Kapischke et al., 2021). By March 2020, the WHO has classified this disease as a global pandemic (Mouffouk et al., 2021) and issued a set of guidelines for preventing and controlling the spread of the disease (Cascella et al., 2021; Jahangir et al., 2020). Numerous reports have indicated the most common routes of transmission of covid-19 to the population, either directly via saliva or respiratory droplets; or indirectly via infected surfaces (Aghalari et al., 2021). The incubation time of SARS-CoV-2 is approximately 1 to 14 days, usually 3 to7 days(Liu & Liu, 2020). Patients infected with this pathogen can be divided into asymptomatic individuals and individuals with mild to severe symptoms which can lead to death (Wu et al., 2020). The most prevalent manifestations are fever, cough, headache, dyspnea, sore throat, myalgia, fatigue (Song et al., 2020) and loss of smell or taste (dos Santos, 2020). It was found that elder people and humans with low immunity and previous disorders have a higher danger of developing a serious illness (Liu & Liu, 2020). Currently, there are several commercial SARS-CoV-2 detection kits available. There are different methods available among which RT-PCR is the most used(Ezhilan et al., 2021). It characterized by a high sensitivity and specificity. In general, swabs are obtained from the back of the throat or the nasal cavity (Xu et al., 2020). Serological tests are another option for covid-19 diagnosis, they are based on the principle of targeting viral antibodies or antigens (Kobayashi et al., 2021). In addition to these examinations, CT scans are also often used (Behera et al., 2021).

As of 12 August 2021, more than 204,644,849 patients have been verified positive with a death rate of 4,323,139 (WHO, 2021). In the absence of any approved treatment (Liu et al., 2021), these numbers keep going up (Li et al., 2021). This state of emergency is giving priority to the search for new medicines and strategies to minimise the transmission of the virus and to find novel medical solutions that can be rapidly applied to the treatment of covid-19 (Quiles et al., 2020). Nature itself can be seen as a magic solution that provides molecules which can offer valuable opportunities. Over the last years, many medical disciplines have shown an increasing interest in naturally originating drugs. Furthermore, natural products are identified as an effective source of drug leads (Romeo et al., 2021).

The objective of this review consists of a contribution in a better understanding on the cellular machinery in SARS-CoV-2 and to identify its drug targets in the first section. The second section is based on in vivo, in vitro, and in silico studies of natural products effects against-SARS-CoV-2, considering their use in the treatment of previous coronaviruses. The important role of these compounds in boosting the immune system has been also highlighted.

**Classification and genomic structure of SARS-CoV-2**

Researchers introduced SARS-CoV-2 as a new enveloped RNA beta-coronavirus (Coperchini et al., 2020), from the Coronavirinae subfamily of the Coronavirdiae family (Liu et al., 2020). The genome sequence of the pathogen is more similar to SARS-CoV than MERS-CoV(Hu et al., 2021). Virion assembly is characterised by a spherical shape and a diameter of approximately 125 nm (Sofi et al., 2020).

The genome was identified as a single-stranded positive-sense RNA (+ssRNA) having a length of roughly 30 kb (Wang et al., 2020). It contains two extremities, a 5′ end cap structure which comprises the open reading frame 1ab (ORF1ab) and a 3′ poly (A) tail (Wiktorczyk-Kapischke et al., 2021). ORF1a/b is the first ORF, estimated to be about two-thirds of the genome's total length, it encodes 16 non-structural proteins (1-16 nsps), which most of them have a significant role in replication. The remaining third of the genome that is close to the 3' end contains other ORFs, which it is capable of encoding for four major structural proteins: spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid protein (N) (Zarandi et al., 2021).

The corona morphology of the virus is due to the presence of the spike glycoprotein on its surface (Wiktorczyk-Kapischke et al., 2021). The (S) protein is composed of S1 and S2 functional subunits. The first subunit attaches to the host cell receptor, while the second one merges the two membranes (Wang et al., 2020). The (E) protein gives the ring structure (Wiktorczyk-Kapischke et al., 2021) and takes a significant part in the viruses' release and in particular contributes to their pathogenicity (Zarandi et al., 2021). On the other hand, the (M) protein serves as a key organizer in assembly of coronavirus while the (N) protein is generally engaged in the ribonucleocapsid helical complex process.

SARS-CoV-2 has demonstrated a few modifications in the binding site compared to bat SARS-CoV, whereas 6 mutations were discovered after comparison with SARS-CoV. These alterations interrupt the important hydrogen bonds and change the receptor binding site (RBS) of SARS-CoV-2. Nevertheless, the emergence of repeated mutations may result in novel strains with altered virulence and that is one of the reasons why it is challenging to find an effective treatment to fight SARS CoV-2 (Bhuiyan et al., 2020).

**Life cycle of SARS-CoV-2**

Coronavirus entry mechanism into host cells is a significant determinant of viral pathogenicity; additionally, it is a key target for the immune system and human intervention strategies (Shang et al., 2020).

The SARS-CoV-2 entry into the cell is triggered by interactions between its spike protein (S1 and S2) and the angiotensin converting enzyme 2 (ACE2) (dos Santos, 2020). The S1 subunit have two domains, an N-terminal domain (NTD) and a C-terminal domain (CTD).The SARS-CoV-2 S1 CTD has shown a higher affinity for human ACE2 (hACE2) than SARS-CoV(Liu et al., 2020). The virus involves other cellular proteases such as furin and serine protease called transmembrane protease serine 2 (TMPRSS2) for the S protein as co-factors (Schultze & Aschenbrenner, 2021).

The envelope and capsid parts of the SARS CoV-2 are removed after the virion particle fuses with the host cell membrane. The virus injects its genetic material (RNA) into the cytoplasm of the cell, where it functions as mRNA for the translation of ORF1a and ORF1ab to generate the polypeptides (pp1a) and (pp1ab) (Bhuiyan et al., 2020), which they will be cleaved by the papain-like protease (PIpro) (dos Santos, 2020) and 3C-like

protease (3CLpro) (also named the main protease (Mpro)) (Machhi et al., 2020) to give 16 functional non-structural proteins, including: 3C-like protease (nsp5), papain-like protease (nsp3) , helicase (nsp13), RNA-dependent RNA polymerase (RdRp) (nsp12) , and other non-structural proteins. On the other hand, the subgenomic mRNAs are eventually translated into viral structural proteins S, M, and E proteins join the endoplasmic reticulum, and the N protein forms a nucleoprotein complex with positive-stranded genomic RNA (Liu et al., 2020). The virion precursors are then transported by vesicles to the Golgi apparatus then to the cell surface. Finally, the new virions are released from the infected cell via exocytosis and a novel replication cycle starts (dos Santos, 2020)(Figure 1).

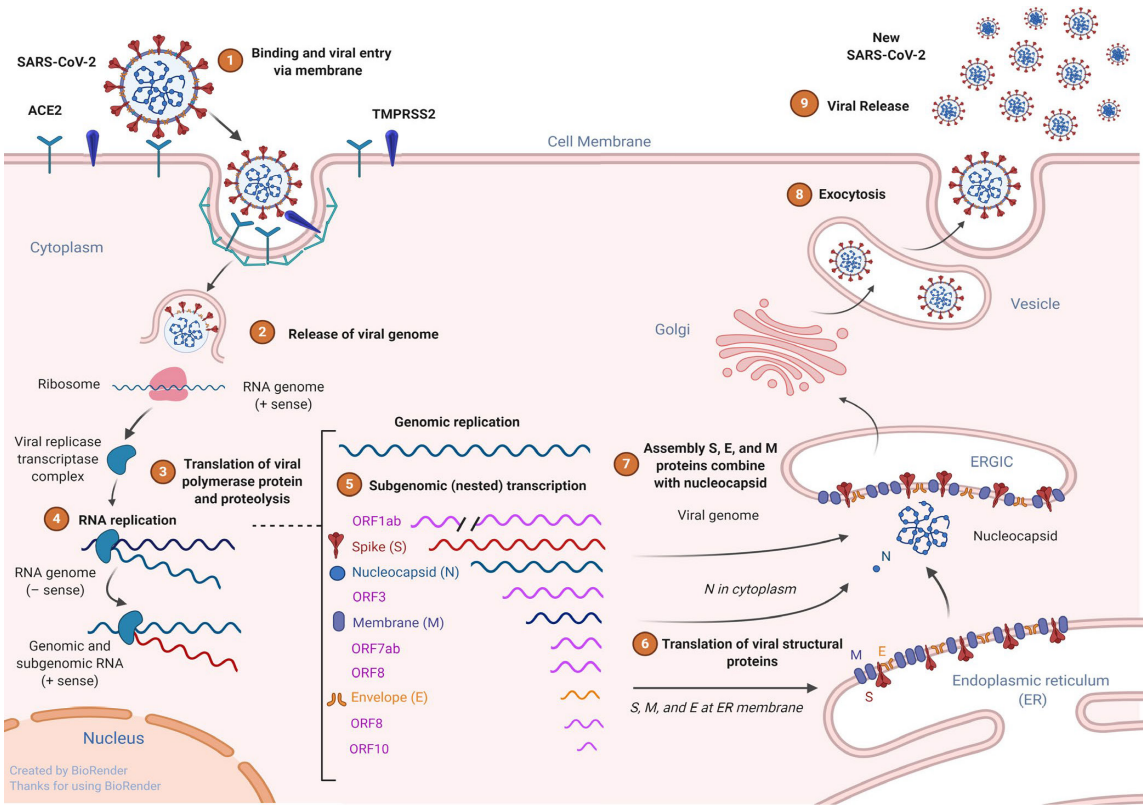


**Figure 1.** Virus binding, internalization to epithelial cells, and replication. Schematic representation of the genomic and subgenomic organizations of SARS-CoV and replication (Azkur et al., 2020).

## Immunity response

### 1. Innate immunity

Innate immunity uses different cells that express pathogen recognition receptors (PRRs) such as NOD-like receptors (NLRs), Toll-like receptors (TLRs), C-type lectin receptors, and RIG-I-like receptors (RLRs) (Hosseini et al., 2020). The PRRs detect released pathogen-associated molecular patterns (PAMPs) like viral RNA and damage-associated molecular patterns (DAMPs) such as ATP and DNA.

This recognition leads to an increased secretion of pro-inflammatory cytokines and chemokines including IL-6, MIP1α, MIP1β, IP-10 (Tay et al., 2020), IL-1, and TNF. These cytokines will stimulate NK and T cells to produce other pro-inflammatory cytokines, like GM-CSF, IL-2 and IFN-γ. The high concentration of pro-inflammatory cytokines will

attract immune cells to the infected sites, namely, neutrophils, macrophages and T cells (Hosseini et al., 2020). This may lead to an over-production of cytokines (Tay et al., 2020) and cause a cytokine storm (Chen et al., 2021). Furthermore, high levels of inflammatory monocytes CD16+ and CD14+ were detected in these infected people, causing the production of cytokines MCP1, MIP1 and IP10, all of which play an important role in the cytokine storm. Subsequently, the immune system initiates a massive attack against the lung and other infected organs, resulting in their damage and ARDS. At the beginning, the main objective of producing these cytokines is to trigger an anti-inflammatory and defensive response. However, the increased uncontrolled releasing perturbs the immune response and worsens the disease (Zarandi et al., 2021).

## 2. Adaptative immunity

As in the case of other disease, the adaptive immune response against viruses can be classified into humoral and cellular immunity. In the extracellular environment, neutralizing antibodies are the main defense actors, whereas in the intracellular environment CD8+ cytotoxic T cells play an important role against viruses. Both of them are regulated and controlled by antigen-specific CD4+ T cells (Mohamed Khosroshahi et al., 2021).

### 2.1. Humoral immunity

Neutralizing antibodies are efficient in totally inhibiting the virus from penetrating the host cells to reduce infection. They have an important preventive role in the later phases of the infection and avoid the relapse of the disease (Chowdhury et al., 2020). Days following infection, the majority of infected people with COVID-19 and those who have recovered show IgA, IgG and IgM responses to the virus. IgM and IgG antibodies are characterised by strong seroconversion (7-14) days after infection. IgA production was during the first week and reached the peak concentration at 20 to 22 days, while IgM antibodies peaked at 10-12 days and then decreased 18 days later. IgG titers increase in the first three weeks before starting to gradually decline until week eight. Other research on COVID-19 has published similar findings demonstrating that antibody responses following SARS-CoV-2 infection are short-lived (perhaps 3 to 4 months) (Poland et al., 2020).

### 2.2. Cellular immunity

Once the virus has entered tissue cells, like respiratory epithelial cells during SARS-CoV-2 infection, viral peptides are injected in CD8+ cytotoxic T cells via MHC class I proteins. This leads to the activation of CD8+ T cells which then begin to differentiate, undergo clonal expansion and generate virus-specific effectors and memory T cells. CD8+ T and NK cells can exhibit cytotoxicity to epithelial cells infected by the virus through their perforins and granzymes, and initiate apoptosis(Azkur et al., 2020)(Figure 2). Finally, macrophages phagocytose apoptotic cells and neutralize viruses (Tay et al., 2020).

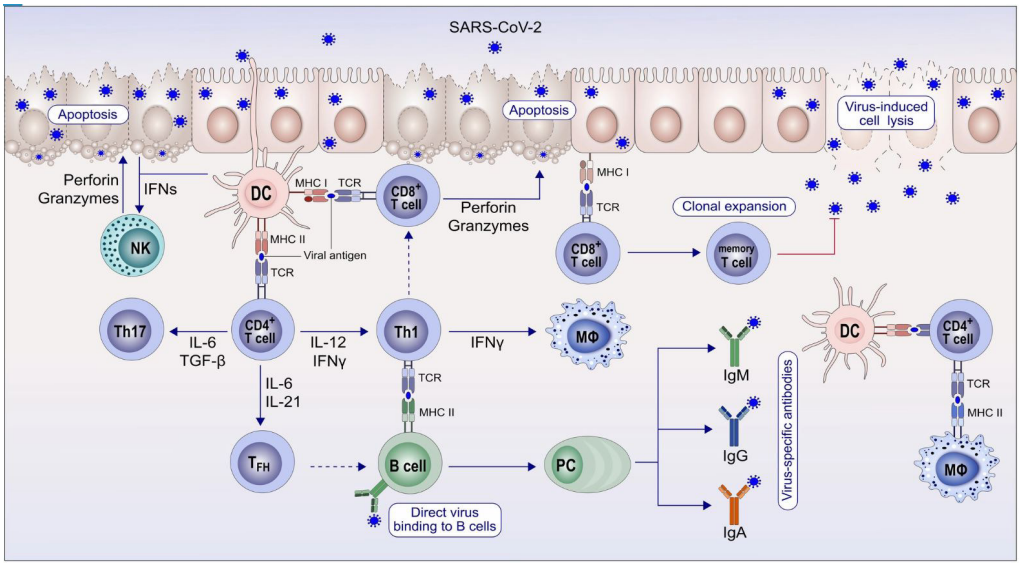


**Figure 2.** Immune response to SARS-CoV-2 and other Coronaviruses (Azkur et al., 2020).

It was observed that in infected patients with SARS-CoV-2 the total level of T cell counts, CD4 + and CD8 + T cells is significantly waned. Covid-19 is considered as a Cytokine storm disease, as described above. Some researchers signalled that cytokines, such as IL-10, TNF-α and IL-6 can induce apoptosis or necrosis of T cells, resulting in their reduction (Hosseini et al., 2020).

## Therapeutic targets of SARS-CoV-2

Drug targets are still one of the most significant criteria for both discovering novel molecules and determining the therapeutic effectiveness of current ones(Das et al., 2021). The strategy aims to target the cellular machinery at every stage of the virus pathway, from viral penetration and replication until their release (Prasansuklab et al., 2020) (Figure 3).

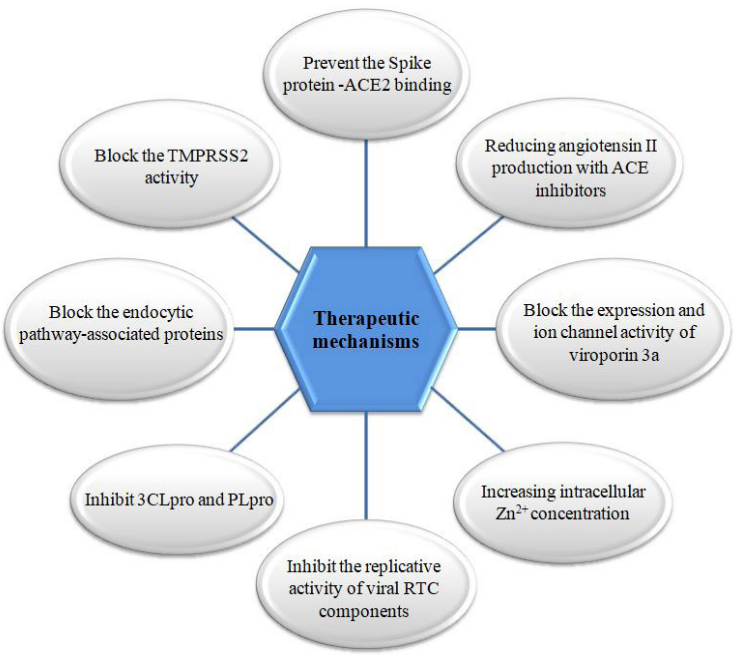


**Figure 3.** Schematic illustration of potential therapeutic mechanisms in SARS-CoV-2 infection

### Viral entry targets

The essential penetration point of SARS-CoV-2 into host cells is via the interaction between ACE2 and the S protein(Das et al., 2021). Many reports have mentioned that drugs targeting ACE2 and S-protein can block viral entry (Paraiso et al., 2020). The viral entry is also affected by the S protein by host cell TMPRSS2 activity and the capacity of this later to cleave ACE2, which makes it essential for the propagation and pathology of infected host tissues (Levy et al., 2020). Some researchers have reported that inhibition of TMPRSS2 activity can prevent SARS-CoV-2 infection (Prasansuklab et al., 2020).

According to several studies, one of the major pathways of entry into cells for many coronaviruses, including the novel SARS-CoV-2, has been identified as clathrin-mediated endocytosis. Following endocytosis into the host cell, the S protein of virus particle undergoes a cleavage at an acidic endolysosomal pH (3.0–6.5), which is mediated by a pH-dependent cysteine protease cathepsin L, and this ultimately leads to membrane fusion between the virus and the endosome, then the release of viral genetic material. As a result, targeting endocytic pathway-associated proteins is seen as one of the potential techniques for reducing SARS-CoV-2 entrance (Das et al., 2021; Prasansuklab et al., 2020).

### Viral replication targets

The 3CLpro enzyme (also known as the main protease (Mpro)) encoded in CoVsis important for proteolysis, viral replication, and infection (Boozari & Hosseinzadeh, 2021), making it an excellent target for antiviral treatment (Kiani et al., 2020). In addition to the role of PLpro in cleaving the N-terminal region of the polyprotein and releasing the non-structural protein 1, 2 and 3 (proteins necessary in correcting viral replication), it has other crucial roles include stripping ubiquitin, deISGylation from the host cell proteins for viral immune evasion processes. Hence, it could serve as another interesting target for drug discovery for the management of COVID-19 (Das et al., 2021). Furthermore, the coronavirus RTC (Replication/transcription complex) composed are responsible for both replication and discontinuous transcription of subgenomic RNA by involving multiple replicative enzymes such as RNA-dependent RNA polymerase (nsp12) and helicase (nsp13), which are currently being examined as possible COVID-19 treatment targets (Prasansuklab et al., 2020).

### Viral release targets

Viroporins are small accessory proteins encoded by viruses, which form pores and have ion channel activity that have been shown to play an important role in machinery of several viruses, including Coronaviruses. It has been mentioned that viroporin3a was only found in SARS-CoV and SARS-CoV-2, the reason that make them a possible therapeutic targets is their role in the regulation of viral budding and liberation from contaminated cells (Prasansuklab et al., 2020).

### Suppress the host inflammatory response

In some infected individuals, SARS-CoV-2 causes an ineffective host immune response, called cytokine storm that results in severe lung disease and mortality. The development of more efficient regulators of the immune response might decrease cytokine-induced hyper-inflammatory syndrome (Paraiso et al., 2020). ACE2 function is downregulated after binding to SARS-CoV-2 protein S, resulting in raised angiotensin II levels and

hyperactivation of AT1R signaling, inducing damages due to increased multi-tissue inflammation. As a result, reducing angiotensin II production with ACE blockers and inhibiting AT1R with angiotensin-receptor blockers (ARBs) can be beneficial in COVID-19 patients to improve Ang II/AT1R-mediated inflammation. Furthermore, in addition to their role in attenuating AT1R activation, ARBs have been shown to be capable of activating AT2R, thereby leading to a vasodilation advantage (Prasansuklab et al., 2020).

## Potential of natural compounds as drug candidates against COVID-19

To highlight an efficient and promising treatment against COVID-19 from natural products, the focus should be on molecules capable of interacting and binding with SARS-CoV-2 proteins that are capable of promoting virus infection (Omokhua-Uyi & Van Staden, 2021). Given the great resemblance between MERS-CoV, SARS-CoV and SARS-CoV-2, the action mechanism of the natural-based compounds will undoubtedly represent strong similarities (Chojnacka et al., 2020).

## Plant secondary metabolites

### 1. Polyphenols

Phenolic compounds or polyphenols are widely distributed secondary metabolites in the plant kingdom. These compounds are present in all parts of plants but with a heterogeneous quantitative distribution between different tissues. More than 8000 structures have been identified (Waksmundzka-Hajnos & Sherma, 2010). They have a wide distribution in medicinal and edible plants, such as vegetables, fruit, drinks, and extra virgin olive oil (Parrella et al., 2020).

Polyphenols have an important effect on the life cycle of SARS-CoV-2, inhibiting the interaction between the SARS-CoV-2 spike protein and the host cell ACE2 receptor, preventing viral penetration in the host cell and inhibiting viral RNA replication and protein processing (Paraiso et al., 2020)(Figure 4).Table 1 summarises some antiviral activities of natural polyphenols and their mode of action against certain coronaviruses.

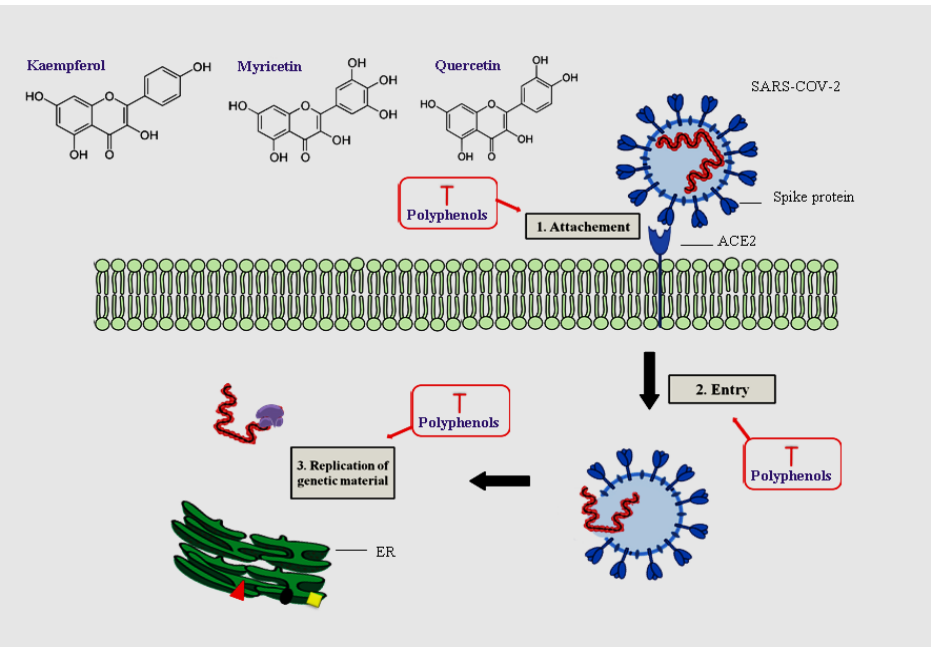


**Figure 4.** Polyphenols effect on the different steps of SARS-CoV-2 life cycle

**Table1.** Effect of polyphenolic compounds on SARS-CoV, MERS-CoV, and SARS-CoV-2.

| Polyphenolic classe | Example of molecule | Virus name | Mechanism of inhibition | Reference |
|---|---|---|---|---|
| **Phenolic acids** | Gallic acid | SARS-CoV | Bind with SARS-CoV spike protein | (Mehany et al., 2021) |
| | Hydroxy-benzoic acid | SARS-CoV-2 | Block entry and replication of 3CLpro | |
| **Flavanoids** | Kaempferol | SARS-CoV | Block ion channel 3a of CoVs and SARS-3CLpro activity | (Mehany et al., 2021) |
| | | MERS-CoV | Inhibit PLpro | |
| | Quercetin | SARS-CoV | Inhibit SARS-3CLpro activity and block the cellular entry of SARS-CoV | |
| | | SARS-CoV-2 | PLpro and 3CLpro enzyme | |
| | Myricetin | SARS-CoV | Block nsp13 by acting on the activity of ATPase | |
| | Herbacetin | SARS-CoV | Inhibit SARS-CoV 3CLpro by acting on its activity | |
| | Epigallo-catechin | SARS-CoV | Block activity of SARS-CoV 3CLpro | |
| | Luteolin | SARS-CoV | Bind with SARS-CoV spike protein | |
| **Anthra-quinones** | Emodin | SARS-CoV | Impede the S protein attachment to ACE2 | (Das et al., 2021) |
| **Coumarins** | Psoraldin | SARS-CoV | Act by inhibiting PLpro | (Das et al., 2021) |
| **Tannins** | Tannic acid | SARS-CoV-1 | Against 3CLpro | (Das et al., 2021) |

### 1.1. Polyphenols targeting the Spike protein and ACE2 receptor

Polyphenols have antiviral properties, among them preventing virus cell entry by impeding the interaction of SARS-CoV-2 S protein and ACE2 (El-Missiry et al., 2021). According to in silico and molecular docking studies polyphenols specifically flavonoids, caffeic acid, chrysin, rutin, myricetin, galangin, hesperetin, luteolin, pinocembrin, andphenethyl ester, have ACE receptor inhibitory properties and are thus promising phytochemicals for the treatment of covid-19 (Sohail et al., 2021).

Regarding the potential utility of quercetin against COVID-19, it was identified recently as a promising molecule in a study using supercomputer-based in silico drug-docking, due to its ability to minimize the attachment between the virus and the ACE2 receptor (Quiles et al., 2020). Quercetin demonstrated a stronger capacity to bind to the ACE2 than hydroxychloroquine and several antiviral medications, as well as excellent binding with S protein. Quercetin derivatives, including quercetin-3-O-glucuronide-7-O-glucoside, quercetin-7-O-galactoside and quercetin-3-O-vicianoside, were found to have a higher binding affinity to the ACE2 receptor than the reference molecule (Mouffouk et al., 2021).

Various virtual screening studies suggested the use of stilbenes as blockers of the entry

of SARS-CoV-2 by disrupting the S-ACE-2 complex interface. This includes resveratrol and piceatannol which have high binding capacity to this complex. Other stilbene derivatives such as trans-resveratrol, pinosylvin, and pterostilbene possess antiviral characteristics, however, with lower binding affinity than those noted previously(Das et al., 2021). Curcumin as well has a dual inhibitory effect, on both the viral spike protein and on the cell ACE2 receptor (Dourado et al., 2021). Several published reports have also shown that curcumin can modulate the angiotensin II levels in mice by targeting the renin-angiotensin system.

These findings indicate the possibility of polyphenols to control the severity of COVID-19 via modulating the abundance of ACE2. However, given the important role of ACE2 in pathophysiological processes, targeting the enzyme requires careful consideration to maintain a favourable benefit-risk balance (Paraiso et al., 2020). Hydroxytyrosol is a metabolite of oleuropein, the major polyphenolic constituent of olive derivatives it has an antiviral activity especially on viral envelope. Oleuropein and hydroxytyrosol can impede the virus penetration in the cell by blocking the fusion of their membranes. Based on these properties, it was suggested that Hydroxytyrosol may inhibit the endocytosis of SARS-CoV-2 (Kiani et al., 2020).

On the other hand, an in silico study showed that epigallocatechin gallate, herbacetin and other flavonoids bind strongly with S protein RBD (Paraiso et al., 2020). Other studies pointed out that phenolic compounds including ptérostilbène, kaempferol and curcumin particularly target and interact with the S1 domain of SARS-CoV-2 spike proteins while luteolin, quercetin, genistein, apigenin, isorhamnetin, fisetin, and resveratrol bind and target the S2 domain (Sohail et al., 2021). These compounds showed higher binding affinity than that of hydroxychloroquine.

The results obtained for different polyphenols and their antiviral properties, particularly on SARS-CoV-2 , are promising, but they need precaution in their treatment as most of the observations were based on an in silico study using bioinformatics (El-Missiry et al., 2021).

### 1.2. Polyphenols targeting TMPRSS2

Many natural products, particularly flavonoids, have been shown to inhibit the regulation of TMPRSS2, through an interesting binding with the active site of human TMPRSS2 (Omokhua-Uyi & Van Staden, 2021). This includes quercetin, luteolin, and kaempferol that have the capacity to suppress TMPRSS2 expression (Islam et al., 2021).

### 1.3. Polyphenols targeting 3CLpro and PLpro

Given the important antiviral role of flavonoids, it was found that puerarin, apigenin, quercetin, luteolin, amentoflavone, epigallocatechin, epigallocatechin gallate, and daidzein exhibited inhibition of SARS-CoV3CLpro (Sohail et al., 2021), whereas chalcones, kaempferol and isoliquiritigenin inhibit both of 3CLpro and PLpro(Paraiso et al., 2020). An in vitro study reported that the combination of epigallocatechin gallate and quercetin has an inhibitory effect with an IC50 of 73 µM (Noor et al., 2021).

Quercetin derivatives such as quercetin-3-b-galactoside also proven an inhibitory effect on SARS-CoV 3CLpro using the molecular docking methods and other bioassays. As SARS-CoV 3CLpro and SARS-CoV-2 have some characteristics in common, quercetin may have a preventive or curative effect against covid-19(Quiles et al., 2020). In addition

to this, some scientists demonstrated that curcumin inhibited SARS-CoV-2 3CLpro more effectively than the tested medications, such as chloroquine and hydroxychloroquine (Dourado et al., 2021).

### 1.4. Polyphenols targeting the RdRp, helicase and viroporin 3a

The inhibitory effect exerted by polyphenols on SARS-CoV-2 RdRp was highlighted by the effective role of resveratrol in blocking MERS-CoV replication in vitro through alteration of nucleocapsid protein and inhibition of RNA expression. Other polyphenols such as myricetin, quercetagetin and epi-gallocatechingallate also showed a strong interaction with RdRp of SARS-CoV and SARS-CoV-2 in silico (Paraiso et al., 2020). Furthermore, two molecular docking studies have revealed the ability of theaflavins to suppress the SARS-CoV-2 RdRp activity by blocking the active site (El-Missiry et al., 2021).

On the other hand, it has been shown that myricetin targets the activity of the SARS-CoV ATPase helicase, leading to its inhibition (Kiani et al., 2020). Whereas other flavonoids like kaempferol and its derivatives, particularly kaempferol 3-O-α-L-arabinopyranoside and glycoside juglanine were shown to be effective at inhibiting the ion channel function of the SARS-CoVviroporin 3a protein with an IC50 of 2.3 μm(Prasansuklab et al., 2020).

## 2. Terpenoids

Terpenoids are the largest and most diverse class of natural products. Part of these substances are aromas of plants and flowers, so important constituents of essential oils (Jan & Abbas, 2018). Their common plant sources are Spanish sage, tea, cannabis, thyme, and citrus fruits (Cox-Georgian et al., 2019).

Several reports have demonstrated that the protease activity of viruses can be suppressed by terpenoids by interacting with the associated amino acids. Indeed, terpenoids such as thymoquinone, forskolin, menthol, ginkgolide A, salvinorin A, bilobalide , noscapine, citral and beta-selinene have been recognized as effective inhibitors of viral proteases by binding to the amino acid sites aspartate, asparagine and phenylalanine (Sohail et al., 2021). Thymoquinone can disrupt the virus entry through a significant interaction with SARS-CoV- 2–ACE2 (El-Missiry et al., 2021).

In addition to that, various diterpenoids and triterpenoids containing salicylaldehyde and transmyrtanol derived from several medicinal plants have been reported to be potent agents as fumigants giving protection against COVID-19 (Sohail et al., 2021), as well as to the high binding affinity of triterpenoids with the spike protein- RDB (Omokhua-Uyi & Van Staden, 2021). The most potent inhibitory activities of SARS-CoV 3CLpro were given by iguesterin and pristimerin with IC50 of 2.6 μM and 5.5 μM respectively, as well as that of quinone-methide triterpenes isolated from Tripterygium regelii (Boozari&Hosseinzadeh, 2021).

## 3. Alkaloids

Alkaloids are organic substances of plant origin, nitrogenous and with an alkaline character (Cheng et al., 2020). Famous plants alkaloids in the human diet are present in coffee beans (caffeine), cocoa beans (theobromine and caffeine), tea leaves (theophylline, caffeine), tomatoes (tomatine) and potatoes (solanine) (Kurek, 2019).

DNA intercalators have the capacity of blocking the transcription, replication and the translation of the genetic material, in addition to their potential to stabilise the structure.

Alkaloids can be considered as DNA intercalators due to their structural properties. This includes sanguinarine, emetine, berberine(Sohail et al., 2021), quinine, hartmine, coptisine, tetradine, cinchonine, chelidonine and palmatin. Isoquinoline was also effective in human lung cells against SARS-CoV-OC43 spike protein and nucleocapsid protein, indicating that it might be used as a therapeutic candidate against SARS-CoV-2 (Das et al., 2021).

Several quinoline and isoquinoline alkaloids, such as dictamine, quinine, comma and space between the two words: cinchonine, skimmianine and β-carboline, have been shown to be effective in treating some virus's diseases, such as SARS-CoV-1. Moreover, chloroquine was tested in clinical trials and showed potent capacity in the treatment of COVID-19. It is therefore established that alkaloids from medicinal plants are interesting agents for the development of COVID-19 treatment (Sohail et al., 2021).

**4. Essential oils**

Essential oils are natural, volatile mixture of compounds with strong odour, ranged as secondary metabolites of aromatic plants.Previous studies demonstrated the capacity of essential oils to treat antiviral-resistant infection (Ma & Yao, 2020).

Essential oils begin their activity before host cell attachment by penetrating non-specifically into the lipid bilayer of the virus envelope, thereby disrupting the fluidity of the membrane (Khan et al., 2021). In several studies, the application of essential oil from the Eucalyptus and Corymbia species and its main compounds such as eucalyptol and citronellol has demonstrated significative antiviral properties. Thus, it has been suggested that the essential oils of both species, and their bioactive compounds, could act as a possible inhibitor of SARS-CoV-2 Mpro(Panikar et al., 2021). Another study has proven the antiviral potential of jensenone obtained from eucalyptus essential oil to inhibit Mpro of SARS- CoV-2 (Sharma & Kaur, 2020).Essential oils constitute an important group of phytochemicals that needs to be thoroughly investigated so as to find a new effective treatment for the severity of COVID-19 (Das et al., 2021).

**Vitamins as an adjunct treatment**

Vitamins are organic compounds with no energy value. They are obtained from food because humans cannot synthesise them in sufficient quantities (Hueda, 2017).

**1. Vitamin A**

Vitamin A is able to defend the body against various infections, mainly by controlling the proliferation and differentiation of immune cells (Akhtar et al., 2021). In respiratory diseases, it plays a crucial role in reducing severe complication and death rates. Isotretinoin is a vitamin A derivative which mediates ACE2 receptor downregulation. According to these findings, vitamin A plays a significant role in preventing SARS-CoV-2 entry and thus decreasing susceptibility to infections (Mahwish & Alothman, 2021). Green leafy vegetables, yellow-orange fruits and vegetables are the main source of plant vitamin A (Arruda de Souza Monnerat et al., 2020).

**2. Vitamin B Complex**

Numerous studies reported that vitamin B complex has the potential to control cytokine and chemokine production, it also mediates interaction with immune cells involved in inflammation and pathophysiological disorder (Jovic et al., 2020). This gives it a significant

role in improving the immune system of COVID-19 patients (Akhtar et al., 2021).

It has been found that adequate levels of thiamine (vitamin B1) are likely to enhance the antibody response against SARS-CoV-2. For Vitamin B3, niacin serves as a precursor to NADP and NAD, the latter of which has been shown to reduce pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β. Recent findings indicate that targeting IL-6 may help in the management of the inflammatory storm in patients with COVID-19. Furthermore, niacin has anti-inflammatory properties, as it reduces neutrophil infiltration in patients with ventilator-induced lung damage. In addition to the role of nicotinamide in reducing viral replication and strengthening the body's defense mechanisms, it could be applied as an adjunct treatment for patients infected with COVID-19. Some reports have shown that vitamin B6 as well as B2 and B9 up-regulate IL-10, a potent anti-inflammatory and immunosuppressive cytokine. It is possible that these vitamins may help to alleviate the cytokine storm and inflammation in many cases of infection by COVID-19 (Shakoor et al., 2021).

Folate (vitamin B9) is an indispensable agent for DNA replication and protein synthesis as well as in the adaptive immune response. Indeed, it was recently discovered that folic acid is an effective in inhibiting furin, thereby impeding the attachment of the SARS-CoV-2 spike protein, which prevents entry into the host cells. As a result, it was proposed that folic acid might be useful in the early stages of COVID-19-associated respiratory disease (Sheybani et al., 2020).

Vitamin B12 also functions as an immunomodulatory agent in cellular immunity, particularly in relation to cytotoxic cells such as CD8+, T-lymphocytes and natural killer cells. Therefore, it could be useful in preventing an excessive immune response, especially for COVID-19 patients (Mahwish & Alothman, 2021). Bananas, broccoli, carrots, spinach and oilseeds are considered as the most important source of theses vitamins(Arruda de Souza Monnerat et al., 2020).

**3. Vitamin C**

An adequate intake of vitamin C in the diet may be helpful in the prevention of COVID-19(Mahwish & Alothman, 2021). It is important in immunoregulation by minimizing the risk of respiratory tract infections through decreasing viral replication rates and pro-inflammatory cytokine concentrations (Mouffouk et al., 2021), like TNF-α and increase anti-inflammatory cytokines such as IL-10. This latter regulates inflammation and acts as a negative feedback mechanism with IL-6, which is critical in COVID-19 (Shakoor et al., 2021). Vitamin C is abundant in tomato, pepper , broccoli, cabbage, citrus fruits, strawberry, melon and pineapple (Arruda de Souza Monnerat et al., 2020).

**4. Vitamin E**

The role of vitamin E as a potent antioxidant contributes to protection against many viral infections by regulating host immune responses and its deficiency is related to impaired humoral and cellular immunity. It is important for enhancing antibody actions and the activity of natural killer cells, in addition to regulating the maturation of dendritic cells. Therefore, vitamin E should be recommended as a helpful nutrient to fight COVID-19 infection and associated disorders (Arruda de Souza Monnerat et al., 2020; Mahwish & Alothman, 2021). Vitamin E is abundant in wheat germ, dark green vegetables, vegetable oils and nuts which are the most important plant sources (Arruda de Souza Monnerat et al., 2020).

### The immune-stimulating role of minerals

Minerals are a large family of inorganic elements found in cereals, fruit, vegetables, nuts, etc. They are mainly classified in macrominerals and trace elements (Brezina, 2018). Trace minerals have been shown to play a role in maintaining and strengthening immunity, thereby reducing the risk of infection. It has been signalled that some trace elements help in preventing infections at different levels of immunity, as antioxidants among others; they can enhance the adaptive immune system, the innate immune system and antibody production. Some minerals play the role of cofactors for enzymes acting via the immune system (Thirumdas et al., 2021).

#### 1. Zinc

Because of its immunomodulatory and antiviral activities, zinc could be a supportive treatment for patients with COVID-19 (Shakoor et al., 2021). Due to the function of the zinc ion ($Zn^{2+}$) as a cofactor for many important viral enzymes such as PLpro and 3CLpro, increasing intracellular concentration inhibits these enzyme activities, particularly in the case of SARS-CoV (Prasansuklab et al., 2020) and SARS-CoV-2 (Mahwish & Alothman, 2021). Zinc deficiency results in decreased antibody production, which reduces the capacity of the immune system, for instance by affecting the activity of natural killer cells (Quiles et al., 2020).

#### 2. Selenium

Selenium exhibits antiviral activity by increasing the activation, proliferation and differentiation of CD4+ T cells. It has also been shown to play a key role in natural killer cell and CD8+ T cell function(Bae & Kim, 2020), as well as increasing macrophage activity and immunoglobulin production. Selenium deficiency leads to the development of pathogenicity in several viral infections by enhancing the production of pro-inflammatory chemokines (Mahwish & Alothman, 2021). With the rise of COVID-19 infections, it can be argued that selenium may have a protective and therapeutic role in improving mortality rates (Singh et al., 2020).

#### 3. Magnesium

Magnesium is also known to have a role in stimulating immune responses against viral infections by controlling many immune functions, including macrophages, immunoglobulin synthesis and the level of haemoglobin in the blood which distributes oxygen to all parts of the body from the lungs, which is useful during COVID-19 infection since the respiratory system is severely affected by SARS-CoV-2 (Mahwish & Alothman, 2021). Furthermore, magnesium has anti-thrombotic properties. Thus, it was suggested that magnesium deficiency in COVID-19 patients can result in disseminated intravascular coagulopathy (DiNicolantonio & O'Keefe, 2021).

## Conclusion

COVID-19 has caused a worldwide and serious threat to humankind since late December 2019, inevitably affecting a large population, particularly patients with pre-existing medical health conditions. Despite the imposition of preventive measures and the abundance of diagnostic equipment, the rapid spread of the virus and the weak immunity have forced health workers to seek an effective treatment for this disease. The good understanding

of the SARS-CoV-2 structure, life cycle and its pathogenicity has allowed determining the therapeutic targets. In this situation; our study was focused on some natural products that showed effective antiviral activity against coronaviruses via impeding the main processes followed in their pathogenesis and replication cycle. Based on in vitro, in vivo, and in silico investigations, the current study found that several classes of secondary metabolites, particularly polyphenols, have the ability to disrupt the interaction between SARS-CoV-2 S protein and the ACE2 receptor, resulting in virus entry inhibition. As well as the ability to block the activity of several enzymes involved in the virus replication cycle such as, 3CLpro, PLpro and RdRp. On the other hand, several vitamins and minerals are able for improving the immune response and are favorable for COVID-19 prevention. Essential oils also show the ability to disrupt the fluidity of the virus envelope. These natural products can reduce the gravity of COVID-19 manifestations and improve the immune response due to their wide range of biological activities.

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# نظرة عامة على فيروس سارس - كوفيد -2 والدور المحتمل للمركبات الطبيعية كأدوية مضادة للفيروسات تستهدف بروتينات سارس - كوفيد- 2

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## المُستَخلَص

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الهدف: مرض فيروس كورونا الجديد المسمى كوفيد 19 هو مرض فيروسي ناجم عن فيروس كورونا المتلازمة التنفسية الحادة الوخيمة. تم الإبلاغ عن الحالات لأول مرة في ووهان ، الصين، بحلول نهاية عام 2019 وانتشر بعد ذلك في جميع أنحاء العالم. يمكن أن ينتقل الفيروس عن طريق الاتصال المباشر أو غير المباشر ويؤدي إلى عدة أعراض؛ الأكثر شيوعًا هي الحمى، السعال الجاف، الالتهاب الرئوي ومتلازمة الضائقة التنفسية الحادة. تسبب كوفيد 19 في خسائر بشرية واقتصادية فادحة، مما يشكل تهديدًا مستمرًا. أصبح فهم الوضع الحالي وتطوير علاج آمنًا وفعالًا أمرًا ضروريًا. في هذا الصدد ، يمكن أن تكون المنتجات الطبيعية موردًا مهمًا في تطوير علاج كوفيد 19، حيث أنها ساهمت في علاج فيروسات أخرى في الماضي. تهدف هذه الدراسة إلى فهم الآلية الخلوية لفيروس كورونا وتحديد أهدافها الدوائية.

الطريقة: تم التركيز على الدراسة الببليوغرافية على أساس الدراسات في المختبر، في الجسم الحي، وفي دراسات حاسوب للمنتجات الطبيعية كمضاد لفيروس كورونا المتلازمة التنفسية الحادة الوخيمة ، كما تم تسليط الضوء على الدور المهم لهذه المركبات في تعزيز جهاز المناعة.

النتائج: وجد أن بعض المنتجات الطبيعية أظهرت نشاطًا مضادًا للفيروسات بارزًا ضد فيروسات كورونا من خلال إعاقة الآليات الرئيسية المستخدمة في دورة التسبب في المرض والتكاثر. استنادًا إلى التحقيقات في المختبر وفي الجسم الحي وفي السيليكو، فإن عدة فئات من المستقلبات الثانوية ، وخاصة البوليفينول، لديها القدرة على تعطيل التفاعل بين بروتين SARS-CoV-2 S ومستقبلات ACE2، مما يؤدي إلى تثبيط دخول الفيروس. بالإضافة إلى القدرة على منع نشاط العديد من الإنزيمات المشاركة في دورة تكرار الفيروس، بما في ذلك 3CLpro وPLpro وRdRp. من ناحية أخرى، يمكن للعديد من الفيتامينات والمعادن أن تحسن الاستجابة المناعية وهي مفيدة للوقاية من COVID-19. تظهر الزيوت الأساسية أيضًا القدرة على تعطيل سيولة غلاف الفيروس.

الإستنتاج: يتم احتساب العديد من المغذيات النباتية كمكونات نشطة بيولوجيًا ضد SARS-CoV-2، وتحتل المركبات الفينولية من خلال آليات عملها القوية عبر الجهاز المناعي المرتبة الأولى. تلعب فيتامينات المجموعة ب والفيتامينات أ، ج، هـ وكذلك المعادن مثل الزنك والسيلينيوم والمغنيسيوم دورًا مهمًا في منع هجوم هذا الفيروس.

**مفاتيح الكلمات:** كوفيد 19، منتجات طبيعية، مستقلبات ثانوية، فيتامينات، معادن، بروتينات SARS-CoV-2.