Plant bioactive compounds affecting biomarkers and final outcome of COVID-19

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Abstract

Herbal medicinal products are known for their widespread use toward various viral infections and ease of disease symptoms. Therefore, the sudden appearance of the Severe Acute Respiratory Syndrome-related Coronavirus 2 (SARS-CoV-2) and COVID-19 disease was no exception. Bioactive compounds from natural plant origin could act on several disease levels: through essential immunological pathways, affecting COVID-19 biomarkers, or by halting or modulating SARS-CoV-2. In this paper, we review the recently published data regarding the use of plant bioactive compounds in the prevention/treatment of COVID-19. The mode of actions responsible for these effects is discussed, including the inhibition of attachment, penetration and release of the virus, actions affecting RNA, protein synthesis and viral proteases, as well as other mechanisms. The reviewed information suggests that plant bioactive compounds can be used alone or in combinations, but upcoming, extensive and global studies on several factors involved are needed to recognize indicative characteristics and various patterns of bioactive compounds use, related with an array of biomarkers connected to different elements of inflammatory and immune-related processes of COVID-19 disease.

Keywords: plant bioactive, treatment, COVID-19, biomarkers

Introduction

The actual COVID-19 pandemic has incited many modifications in scientific research, redirecting research efforts in prevention, treatment, or supportive care of patients worldwide. Particular curative regimens and prescribed courses of medical treatment to prevail over morbidity and mortality are still needed in order to respond to this global health problem. Plants are rich sources of bioactive compounds that have been routinely and conventionally used to act toward bacterial, viral, fungal infections (1-3) for many centuries; thus, natural compounds with antiviral activity are a good starting point for finding suitable candidates in the fight against the SARS-CoV-2 virus.

Human coronaviruses include two very different types, SARS-CoV and the Middle East Respiratory Disease coronavirus (MERS-CoV), which are members of the genus that preceded the SARS-CoV-2 (4). SARS-CoV-2 is an envelope-covered virus with one RNA strand, nucleocapsid, and a phospholipid bilayer overlaid by "spike" glycoproteins (5). Its genome consists of nearly 30000 nucleotides coding 16 non-structural and 4 structural proteins (6). Part of these proteins is obligatory for the attachment (spike glycoprotein-protein S), approach and entrance into the host cell and replication of the virus. The point where S protein attaches to the host cell is the cellular membrane protein, angiotensin-converting enzyme 2 (ACE2). Consequently, the ACE2 receptor and the enzymes proteases degrading the spike protein can be good prospective therapeutic targets (7,8). Protein components presupposed in the replication and proliferation of the virus are valuable target points, while papain-like protease and chymotrypsin-like protease are recognized as important ones.

The manifestations of COVID-19 disease can vary between patients and the outcome is unpredictable. In addition, the late diagnosis of COVID-19 constitutes a major obstacle to effective disease management. Therefore, diagnostic tools with improved biomarkers and new treatments for COVID-19 are urgently needed.

The main objective of this review is to research and display the mode of (potential) action of bioactive compounds of plant origin, which includes essential immunological pathway involvement, influence on COVID-19 biomarkers, and halting or modulating SARS-CoV-2. Thus, in this review, we focus on the plant bioactive compounds that have been reported to interact significantly with coronavirus infection and investigate and describe the known biomarkers that are reported to be altered in this disease and are used in COVID-19 disease prediction and monitoring of disease progression. This study reviews the recently available data from studies focused on the capacity of some natural plant bioactive compounds positively described in terms of their anti-viral mechanisms of action, including the inhibition of attachment, penetration and release of the virus, actions that affect RNA, protein synthesis and viral proteases and other mechanisms.

It is significant to consider that, to this day, there has been no concrete and proven information in scientific literature showing how the nutrition status or patterns of food diet/herbal supplementation could help to minimize SARS-CoV-2 spread and the progression of COVID-19 (9). However, there has been some evidence, recently

published in relevant literature sources, which demonstrates the role of certain natural bioactive compounds in reducing the risk of COVID-19 (as well as other viral infections, e.g., influenza) (10,11).

Search strategy

The search strategy for the preparation of this review included exploring the PubMed database, using fundamental keywords related to biomarkers, immunological responses, COVID-19, and bioactive compounds (e.g., biomarkers, immune system, SARS-CoV-2, plants, bioactive compounds, polyphenols). This review included data published for the COVID-19 disease in the period from 2019 to 2021, as well as articles on the characteristics of bioactive compounds and immune biomarkers published from the 1990s up to recent date. No systematic assessment and statistical analysis were applied.

Immune response and COVID-19

Despite the fact that the immunological and pathological mechanisms associated with the COVID 19 disease have not been clarified in detail yet, there is evidence that not all people among the population exposed to the SARS-Cov-2 virus will develop an infection, and not all among them will manifest the most severe symptoms (12). The coherence of the human immune system and the suitable immune response is essential in managing and keeping at a minimum the life-threatening effects of the SARS-CoV-2 infection. The process of immune activation (5,13-15) is presented in Figure 1. If the interruption of the immune barrier occurs, and the expansion of the virus cannot be stopped, SARS-CoV-2 rapidly proliferates, mainly affecting the tissues that demonstrate a high expression of the angiotensin-converting enzyme 2 (ACE2), (e.g., kidneys, intestine, lungs, brain, and cardiovascular system) (16,17).
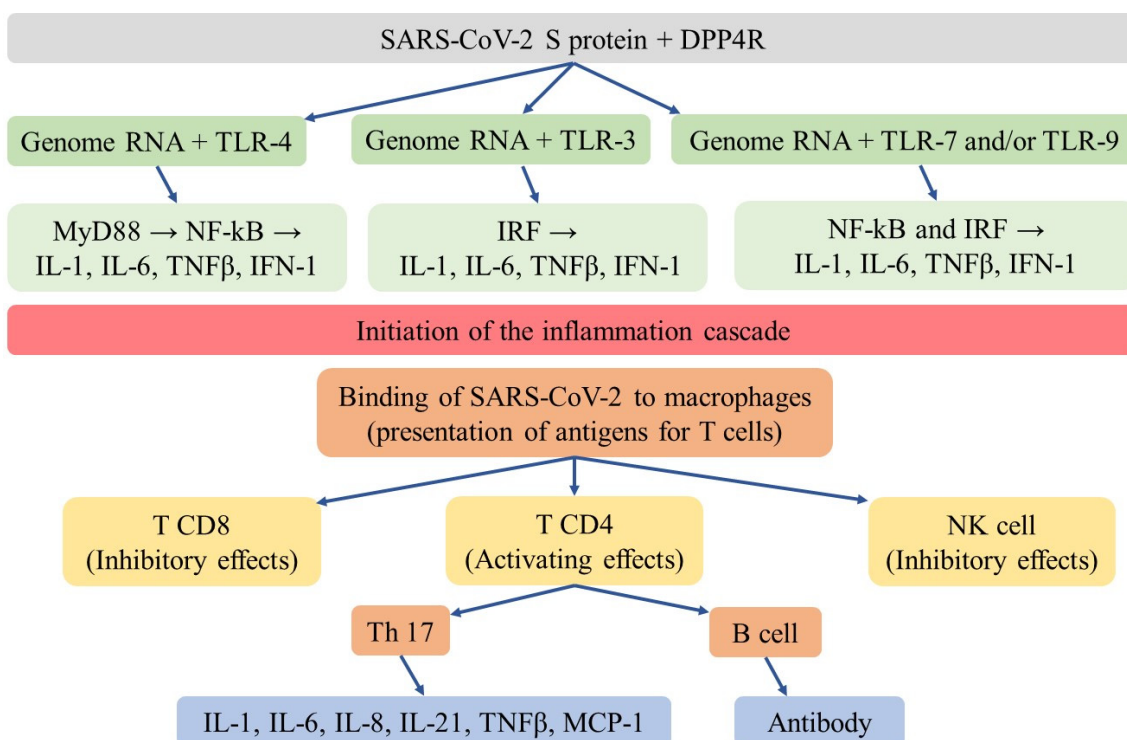
Figure 1. The main immune cells and cytokines involved in the immune defense response against SARS-CoV-2

Slika 1. Glavne imunološke ćelije i citokini uključeni u imunološki odbrambeni odgovor protiv SARS-CoV-2.

Legend: DPP4R Dipeptidyl peptidase-4 Receptor; TLR-4 Tool-like receptor-4; TLR-3 Tool-like receptor-3; TLR-7 Tool-like receptor-7; TLR-9 Tool-like receptor-9; MyD88 Myeloid differentiation factor-88; NF-kB Nuclear factor kappa; IL-1 Interleukin 1; IL-6 Interleukin 6; IL-8 Interleukin 8; IL-21 Interleukin 21; TNFβ Tumor necrosis factor β; IFN-1 Interferon; IRF Interferon regulatory factors; NK cell Natural killer cell; Th17 T helper type 17 cell; MCP-1 Monocyte chemoattractant protein-1;

Legenda: DPP4R receptor dipeptidil peptidaze-4; TLR-4 tolovidni receptor-4; TLR-3 tolovidni receptor-3; TLR-7 tolovidni receptor -7; TLR-9 tolovidni receptor -9; MyD88 Mijeloidni faktor diferencijacije-88; NF-kB Jezgreni faktor kapa; IL-1 Interleukin 1; IL-6 Interleukin 6; IL-8 Interleukin 8; IL-21 Interleukin 21; TNFb Faktor nekroze tumora β; IFN-1 interferon; IRF Regulatorni faktori interferona; NK cell- Ćelije prirodne ubice; Th17 T pomoćne ćelije tip 17; MCP-1 Monocitni hemoatraktantni protein-1;

Biomarkers of COVID-19

The manifestations of the COVID-19 disease can vary from very mild to very severe, resulting in death. The unpredictability of this disease has urged researchers and clinicians to designate biomarkers that can aid in prognosis and proper patient management. The experience gathered to-date regarding various laboratory examinations highlights several laboratory biomarkers that have been typically altered during infection

with COVID 19. No specific markers that can be assigned to this disease have been proposed to date, but the experience has shown that several groups of biomarkers can be employed to evaluate and form an opinion on the disease severity and prognosis. One group of markers refers to the immunological response, the other is related to cellular damage and inflammation, whereas the third is related to organ damage.

During these two years, plenty of laboratory data have been presented, analyzed and critically reviewed (18,19). Since the focus of this review is to address plant bioactive compounds that affect COVID-19 biomarkers, we will shortlist the ones that are highly associated with disease severity.

As a repercussion of an excessive immune response, increased values of pro-inflammatory cytokines have been noted in severe COVID-19, resulting in cytokine release syndrome. Initial research has detected an increase in pro-inflammatory cytokines (IL-6, TNF-α, IL-10, IL-2, IL-7) in the plasma of severe cases, related to inflammation and large-scale pulmonary tissue damage in patients with COVID-19 (20-22). Studies have shown that the levels of IL-6 are increased in patients with severe disease. However, some reports suggest that the levels of IL-6 can decrease after treatment with glucocorticoids, antibiotics, and antivirals, therefore questioning the adequacy of IL-6 as a marker of therapeutic response in COVID-19 (19,23).

White blood cell (WBC) count, neutrophil count (NC), lymphocyte count (LC), and especially neutrophil-to-lymphocyte ratio (NLR) are routinely assessed in patients with COVID-19. Many studies have reported that neutrophilia, lymphopenia, and NLR increase are associated with disease severity (24,25). However, other factors can affect these parameters, such as infections of bacterial or viral origin or glucocorticoid therapy, which makes their significance as prognostic markers unclear (24,26).

Acute-phase response plasma protein C-reactive protein (CRP) is produced by the liver, and its concentration rises in response to various inflammatory mediators such as IL-6. It is a non-specific marker that is typically elevated in various inflammatory conditions. However, it is noted that a rise in CRP levels and a rise in IL-6 levels are connected with an elevation of disease severity (22,27). A retrospective study by Luo et al. reported that this non-specific marker correlated with disease severity and was a good predictor of unfavorable outcomes (28).

D-dimer is formed by lysis of cross-linked fibrin and is a biomarker of fibrinolysis and activation of coagulation (29). It can be increased in various conditions, such as venous thromboembolism, inflammation, and pregnancy, so it is relatively nonspecific. Some literature reviews suggest D-dimer levels can be used as a prognostic marker and aid clinicians in determining the cases that are likely to become severe, especially together with prothrombin time (19,24). However, others state that, due to its low specificity, the variation in the units for D-dimer levels leading to unreliability, as well as the fact that D-dimer levels do not reveal the functional interactions among other players involved in coagulation processes, D-dimer levels can be regarded as a biomarker with low prognostic accuracy on its own (27).

Procalcitonin (PCT) is the pro-peptide of calcitonin that lacks hormonal activity. Physiologically, it is produced in the C-cells of the thyroid gland, with practically undetectable levels of < 0.1 ng/ mL in healthy subjects. However, during severe systemic infection, its levels may rise to over 100 ng/mL. It has a similar sequence to pro-inflammatory cytokines, which suggests that PCT is a mediator of inflammation (30). Its values may remain normal in non-complicated infections with SARS-CoV-2, but any substantial increase can suggest bacterial co-infection and further complications, therefore making it a marker for prognosis of serious disease (31). However, its value in COVID-19 is still ambiguous, especially in the initial prognosis, since it can stay within the normal range in the initial phase of the disease (19,32).

LDH is found in all human cells, especially in myocardial and liver cells. Its secretion can be triggered by necrosis of the cell membrane, suggesting a viral infection or lung damage, which is common in SARS-CoV-2 induced pneumonia (33). Literature reviews assessing various reported results found an increasing reliance on using LDH as a biomarker to measure the seriousness of SARS-CoV-2 infection (24).

Ferritin has immunosuppressive and pro-inflammatory action and is another molecular contribution to the cytokine storm responsible for the deterioration of COVID-19 disease outcomes. Studies have shown that ferritin can be regarded as a biomarker related to negative and health-endangering outcomes of the COVID-19 disease, since its values are increased, along with other pro-inflammatory markers in patients (32,34).

Cardiac troponin I (cTnI) is a necrotic biomarker for myocardial injury, and it is proposed to be a suitable marker of seriousness and mortality in COVID-19 patients (35). Myocardial injury can be triggered by the cytokine storm, as well as viral myocarditis. Since cardiovascular disease can occur in COVID-19 patients, many researchers regard cTnI as a good predictor of disease progression and mortality. Some authors claim cTnI is superior to D-dimer and lymphocyte count in predicting the severity of the disease (36).

Selected plant bioactive compounds that significantly interact with coronavirus infection

Due to the deficiency of specific drugs and typical therapeutic agents against COVID-19, the application of substances of natural origin as a potential solution against coronavirus was favored. Although herbal and traditional herbal medicines are generally disregarded as the first line of medicines, novel research in the treatment or prevention of SARS CoV-2 has indeed initiated from plant extracted bioactive compounds. Quinine, for example, an alkaloid obtained from the bark of *Cinchona oficinalis* has been used in the treatment of malaria since the 1960s (37). Chloroquine (Cq) and hydroxychloroquine (Hcq) as structural analogs of quinine were the first attempts of unfortunately unsuccessful therapy of the corona disease (38). Since naturally derived preparations and their active substances are most widely used in the Eastern Asian medicine, and the origin of this virus was initially reported in a Chinese province, it was expected that most of the recent studies combining the revealing of the mechanism of action of plant secondary metabolites and COVID-19 would be made by the researchers from this region (39). Thus,

scientists are increasingly intensifying research on the mechanism of action of bioactive compounds and their effect on COVID-19 biomarkers, mainly focusing on the use of traditional Chinese medicines, ethnobotanical herbs or drugs based on natural compounds, and other dietary supplements, some of which are currently in clinical trials (40-43).

The investigation of three large groups of secondary plant metabolites, polyphenols, terpenes, and alkaloids is still ongoing, and different effects and modes of action have been found to date. Knowing the details of viral attachment and penetration, and its ways of replication and invasion into the host cells, gives us some hints to predict the most common ways of their action. On the other hand, revealing and understanding the genome sequence of the virus, and the identification of its potential targets, bring about a possibility for examining the effectiveness of single bioactive molecules, as well as synergistic effects of the combination of different plant metabolites targeting few generally known modes of action. Therefore, there are several mechanisms of action of the plant bioactive compounds against SARS CoV-2 discussed in recent publications:

1. Affecting viral attachment and penetration in two ways:
- attachment of the plant bioactive molecules on the virus's spike protein
- inhibition of the attachment of the virus for the host cell, by occupying ACE2 receptors in the host cell and therefore inhibiting its cell penetration

2. Inhibition of virus release in the host cells by inhibition of its endocytosis in the host cell (by inhibiting cathepsin L (CTSL) or clathrin-based endocytosis)

3. Affecting RNA, protein synthesis and viral proteases in two ways:
- Anti-viral activity against RNA and protein synthesis of the SARS CoV-2 by the inhibition of RNA dependent RNA polymerase (RdRp).
- Inhibiting the viral proteases such as 3-chymotrypsin-like cysteine protease (3CLpro) and papain-like protease (PLpro)

4. Other mechanisms: for example, the modulation of a human immune response.

Plant bioactive compounds affecting virus spike protein attachment and penetration by inhibition

Coronavirus S protein is engaged in an important activity for viral fitting, fusion, and penetration into the cells, creating a prospective target for intervention. The S protein first binds on the surface of the host cells, utilizes the receptor-binding domain of the S1 subunit, and then fuses with cells through the S2 subunit by the host ACE2 receptor (7,44,45). Polyphenols such as (–)-epigallocatechin gallate (EGCG) and (–)-epicatechingallate (ECG), which are important catechin components of green tea, have high medicinal value against different viruses (46). One new docking study also unveils the present high binding affinity with the S protein of SARS-CoV-2 (47). The catechin molecule has an affinity to bind with the receptor-binding domain of the S protein of the

virus, and at the same time with the ACE2 of the host cell, and accordingly it may suppress and interfere with the coupling of the virus to cells.

Glycyrrhizin from licorice, *Glycyrrhiza glabra* L. has also been recognized as a bioactive plant compound that inhibits viral attachment and penetration of coronaviruses. Additionally, suppression of inflammation by downregulation of proinflammatory cytokines and other mediators has been demonstrated (41,48). This compound was analyzed against replication of SARS-CoV in isolates from clinical patients and compared with chemical substances and antiviral drugs (ribavirin, pyrazofurin, 6-azauridine) and effective selectivity index (SI) of over 67 was found (48), thus potential anti-SARS-CoV-2 activity was on site. SI is resolved by using the proportion of concentration of the extracts where cytotoxicity is on site or by using substance concentration that can inhibit 50% population of host cells (CC_{50}) to IC_{50} (inhibitory concentration of the compound that can cause 50% of virus inhibition). The higher value of SI for the compound indicates lower-grade cytotoxicity for the host cell, suggesting that glycyrrhizin is effective and safe for human application as a potential antiviral agent.

In this way, glycyrrhizin inhibited not only virus replication, but adsorption and penetration of the virus as well. Glycyrrhizin was less effective when added during than when added after virus adsorption (EC50 600 mg/L vs 2400 mg/L, respectively). Interestingly, in doses of EC50 300 mg/L it was most effective even when given during the adsorption period.

Luteolin is a polyphenolic flavone found in different plant species, used as a dietary supplement and in traditional Chinese medicine, due to its antiviral, anti-inflammatory, anti-oxidant, anti-cancer, and anti-apoptotic actions (49). There are studies showing the capability of luteolin to inhibit the entrance and fusion with human receptors of the SARS-CoV virus, Japanese encephalitis virus, Chikungunya virus, and Rhesus rotaviruses; accordingly, luteolin can have potential anti-SARS-CoV-2 activity (50,51). Back in 2004, in a study performed by Wu et al., among 121 plant compounds screened, luteolin and tetra-O-galloyl-β-D-glucose (TGG), from *Rhus chinensis* Mill. and *Veronica linariifolia* Pall. Ex Link, was discovered to have a high affinity to the S2 subunit of the S protein of the virus. For luteolin, an IC_{50} of 10.6 µM and SI of 14.62 were found (52).

Saponins, like saikosaponins A, B and D, are additional plant bioactive components that may inhibit binding, entrance, adsorption, and penetration of the virus into the host cell and possess an antiviral potential against poliovirus-2, HSV-1, influenza virus (saponin I, 5-10 mg/kg in mice), including SARS-CoV virus (53,54).

Emodin, an anthraquinone glycoside found in plants of genus *Rheum* and *Polygonum* (namely, the root tubers of *Rheum officinale* Baill., the root tubers of *Polygonum multiflorum* Thunb.), can inhibit the S protein and also ACE2 interconnection in a dose-dependent way. The IC50 value of emodin was found to be 200 µM. The promising blocking of the viral entry was shown by the inhibition of the S protein of the SARS-CoV virus in Vero E6 cells (55).

Caffeic acid is a phenolic compound, a product of secondary plant metabolism, and represents the predominant hydroxycinnamic acid found in the human diet. In the performed *in vitro* and *in vivo* studies, a number of beneficial effects of caffeic acid and its derivatives were shown, such as antibacterial, antiviral, antioxidant, anti-inflammatory, immunostimulatory, antidiabetic, antiproliferative/anticancer activity (56). There is a study that investigated caffeic acid isolated from the ethanol extract of *Sambucus formosana* Nakai, where prospective anti-coronavirus activity by interference with viral entrance in human coronavirus NL63 (HCoV-NL63) cells with IC_{50} of 3.54 μM (57) was demonstrated.

Details of bioactive plant compounds inhibiting SARS-Cov-2 attachment/interaction and penetration into ACE2 receptors are presented in Table I.

Affecting viral attachment and penetration into the cell by occupying ACE2 receptors in the host cell

Angiotensin converting enzyme 2 is a protein occurring across a cell membrane and is examined as the binding receptor for the spike protein of SARS-CoV-2. Many plant bioactive substances are known as possible blockers of the spike protein and potential ligands for ACE-2 receptors. In this way, they are effective candidates for reducing or blocking the viral attachment and penetration in the host cell (7).

In a recent study, Senthil Kumar et al. have noted that essential oils derived from *Pelargonium graveolens* L'Hér (Geraniaceae) and *Citrus limonum* L. Osbeck (Rutaceae) decreased human ACE2 levels in HT-29 cells. In concentrations of 1.43 ng/mL and 4.34 ng/mL, respectively, cytotoxic effects for the cells were not exerted. Using ELISA assay, they have shown that ACE2 protein values were notably diminished by the application of geranium and lemon essential oils. Moreover, qPCR analysis also confirmed that geranium and lemon essential oils indicated downregulated ACE2 and transmembrane protease serine 2 (TMPRSS2) mRNA levels (58).

The observation from another study has indicated that diverse herbal extracts from plant members of the Polygonaceae family inhibit the SARS-CoV S protein interaction with the ACE2 receptor. A good example is an anthraquinone also known as emodin, a bioactive compound isolated from genus *Polygonum* and *Rheum*, which has effectively obstructed the interconnection of S protein and ACE2 receptor (55,59).

These findings were confirmed by a molecular docking study examining the possibility of phytochemicals (hesperidin, emodin, anthraquinone, rhein and chrysin) binding to ACE-2 receptor and thus inhibiting the SARS CoV-2 virus. Results have shown that these bioactive substances can be linked with the host ACE2 as a non-competitive molecule and present their anti-viral action by disrupting spike protein binding (60).

A combination of different plant metabolites derived from 16 medicinal plants originating from China (used as Toujie Quwen Granules (TQG) for the treatment of coronavirus pneumonia 2019) has also been examined, and the results from molecular

docking indicated that other two flavonoids, astragaloside IV and rutin (quercetin-3-O-rutinoside, rutin has the quercetin as aglycon in its structure), coupled with ACE2 receptor the most (61).

Details of bioactive plant compounds inhibiting SARS-Cov-2 attachment and penetration into ACE2 receptors are presented in Table I.

Table I   SARS-CoV-2 protein S (structural protein) and ACE2 receptor inhibitors

Tabela I   SARS-CoV-2 protein S (strukturni protein) i inhibitori ACE2 receptora

Plant bioactive compound	Source	Class of compound	Target protein	References
Polyphenolic compounds				
(–)-epigallocate-chingallate (EGCG), (–)-epicatechin-gallate (ECG)	*Camellia sinensis* (Green tea)	Catechins	Binds to the receptor-binding domain of Protein S (also ACE2 of the host cell)	44, 46, 47
Luteolin	Different (*Citrus* sp. and other fruits)	Flavone	Bound to S2 subunit of the precursor of S protein	50, 62
Caffeic acid		Phenolic acid (hydroxycinnamic acid)	Protein S	45, 57
Astragaloside IV and rutin	Different plant species	Flavonoids	Inhibited ACE2 interaction	61
Quercetin	Different plant species	Flavonoids	Inhibited ACE2 interaction (also acting as antioxidant, anti-inflammatory, immunomodulatory agent)	79
Emodin	*Rheum* and *Polygonum* species	Anthraquinone glycoside	Inhibited the S protein and ACE2 binding (dose-dependent way)	51, 55, 59
tetra-O-galloyl-β-D-glucose (TGG) and luteolin	*Rhus chinensis* and *Veronica linariifolia*	Hydrolysable tannins and flavone	High affinity to the S2 subunit	50, 52
Terpenoid compounds				
Citronellol and limonene	Essential oils from *Pelargonium graveolens* and *Citrus limonum*	Monoterpenoids	Downregulated ACE2 of the host cell	58
Glycyrrhizin (or glycyrrhizic acid)	*Glycyrrhiza glabra* (licorice)	Triterpenoid saponins	Structural proteins, (also suppress inflammation through downregulation of proinflammatory mediators)	41, 45, 48 62
Saikosaponin A, B and D	*Bupleurum falcatum*	Triterpenoid saponins	Protein S (Inhibit the cellular attachment, entrance, adsorption, and penetration of a virus)	53, 54

Limiting viral release in the host cells by inhibition of its endocytosis (cathepsin L (CTSL) or clathrin based endocytosis)

Cathepsin L (CTSL) is a member of the lysosomal cysteine protease group involved in pathogen-induced endocytosis. Some *in vitro* studies have indicated that cathepsin L proteolysis of SARS CoV-1 blocks membrane merging of SARS-CoV-1 by degradation of its S protein by host CTSL (63). Interestingly, chloroquine is one of the possible drugs that can inhibit lysosomal cathepsins nonspecifically by increasing endosomal pH (64).

On the other hand, a selective cathepsin inhibitor, aurantiamide, an alkaloid structure, extracted from *Portulaca oleracea* L., a member of the Portulacaceae family, has been declared a suppressor of SARS-CoV endocytosis (65). Selective cathepsin inhibition can be one of the possible interventions to prevent SARS-CoV-2 release in the host cell. Therefore, in 2017 large screening was performed through molecular docking analysis on different traditional Chinese herbal medicines and published by Wang et al. They have confirmed that aurantiamide extracted from *Artemisia annua* L. has low-ranking docking binding energy (−50.767 kcal/mol). Consequently, there is a possibility for it to block virus entrance. These data represent a relevant activity of aurantiamide as a selective inhibitor of cathepsin L and suggest that this bioactive compound could be administered to restrain SARS-CoV-2 infection. However, there is a need for stricter examination in preclinical and clinical studies (66).

Although rare, studies exist that suggest the mode of entry of SARS CoV-2 can also include clathrin-dependent endocytosis (67). It has been well characterized that the endocytosis process employs growth factor receptors, including the transferrin receptor (TfR), epidermal growth factor receptor, and the keratinocyte growth factor receptor, to name a few (45). Zhuang et al. (2009) have investigated the inhibitory activity of procyanidins and cinnamon bark butanol extract in wild-type severe acute respiratory syndrome coronavirus (wtSARS-CoV). They have found that procyanidins alone could not influence the clathrin-dependent endocytosis pathway, but the extract of cinnamon bark has shown internalization of transferrin receptor (TfR) and inhibition of clathrin-dependent endocytosis (68).

Plant bioactive compounds affecting RNA, protein synthesis and/or viral proteases

As stated before, two modes of action have been proposed regarding affecting RNA, protein synthesis and/or viral proteases; namely, the inhibition of RNA dependent RNA polymerase (RdRp) or inhibition of the viral proteases, such as 3-chymotrypsin-like cysteine protease (3CLpro) and papain-like protease (PLpro).

RNA-dependent RNA polymerase (RdRp) is a crucial enzyme that accelerates the synthesis of complementary RNA of corona viruses by acting as a catalyst (69). Therefore, many scientists have examined this enzyme as one of the critical points for targeting the replication of SARS CoV-2. The discovery of RdRp structure has provided a newly arrived approach to detecting disease-preventive options for SARS-CoV-2

inhibition. The potential of some well-known medicinal plants, having quercetin, caffeine, ellagic acid, polyphenols of gallic and benzoic acid and/or resveratrol as secondary metabolites in their chemical composition, has been explored (70). The results have shown that all the examined bioactive substances have a binding affinity for the NSP12 co-factor, which further binds to the NSP7 and NSP8 co-factors that are key to the replication of SARS-CoV-2. *Houttuynia cordata* Thunb. has been found to interact with RdRp activity (71). In this evaluation study on the polymerase action performed with different concentrations of *Houttuynia cordata* Thunb. water extract (50, 100, 200, 400 and 800 μg/mL), a noticeable depletion in RdRp activity was shown. Methanol extracts from several other plants, such as *Cimicifuga racemosa* L., *Phellodendron chinense* C.K.Schneid., *Sophora subprostrata* Chun & T.Chen, *Phoradendron meliae* Trel., and *Coptis chinensis* Franch., were also found to inhibit RdRp action (72). Moreover, the *in silico* analyzes of Singh et al. (2020) have presented a number of bioactive substances (epigallocatechin gallate, theaflavin, theaflavin-3'-*O*-gallate, theaflavin-3'-gallate, theaflavin 3,3'-digallate) that vigorously attach to the active site of RdRp with a highly stable bound conformation (73).

Inhibiting some viral proteases such as 3CLpro and PLpro could be the next challenge for scientists working on SARS-CoV-2 extermination. It has been found that 3CL pro (also known as the main protease) is responsible for controlling viral replication. However, PL pro, which separates viral polypeptide chains a/b from SARS-CoV-2, is another enzyme essential for its survival and replication (74). Therefore, many studies, mainly *in silico* docking studies, have been fulfilled to assess the possible binding capacity of different plant bioactive compounds with 3CLpro or PLpro. However, unfortunately there are no recent experimental *in vitro*/*in vivo* analyzes that could confirm this *in silico* data.

Goswami et al. (2020) noted that an abundance of secondary metabolites found in *Alpinia officinarum* rhizomes, *Zingiber officinale* Roscoe and *Curcuma longa* L. inserted into the S3-S4 domains binds with a high affinity for PLpro, indicating their high potential as SARS-CoV-2 inhibitors (75). Additionally, an *in silico* docking analysis by Zhang et al. (2020) has found that some specific plant bioactive compounds, such as coumaroyltyramine, cryptotanshinone, kaempferol, and quercetin, are capable to interfere or inhibit both proteases (3CLpro and PLpro) (74).

The *in silico* analyses of flavonoids and their ability to bind to the 3CLpro have shown that herbacetin, rhoifolin and pectolinarin are effective blockers of the enzymatic activity of SARS-CoV 3CLpro. Moreover, their interactions were confirmed by the tryptophan-based fluorescence method, where induced-fit docking analysis identified S1, S2 and S3' sites responsible for binding to flavonoids (76).

Plant bioactive compounds with other modes of action

Alongside the enormous pool of ongoing studies on various plant bioactive metabolites through the referred mechanisms presented previously, there are certainly some medicinal plants that have been known as human immunomodulators acting

through an unspecific mechanism. Among them, *Echinacea angustifolia* DC*., Ligusticum* spp*. L., Andrographis paniculata* (Burm.f.) Nees*, Eupatorium perfoliatum* L.*, Thuja* spp*. L., Astragalus membranaceus* (Huangqi)*, Allium sativum* L.*, Pelargonium sidoides* DC., have been known to exhibit immunostimulatory effects to the unspecific immunological response (77).

The still-existing COVID-19 pandemic has demonstrated the necessity of reinforcing and consolidating the immune system as the principal way to prevent severe symptoms and complications from SARS-CoV-2. In this regard, specific bioactive compounds like curcumin, quercetin, and chosen representatives from stilbenes, flavonoids, and lignans that manifest immunomodulatory effects are strongly recommended for this purpose (78). Among these, quercetin is one of the most extensively used bioactive flavonoids, due to its proven antioxidant, antiviral, anti-inflammatory and immunomodulatory effects. Its activity was evaluated and proven in a randomized clinical study by Onal et al. in 2021 (79).

Future considerations and conclusions

There are a number of studies that cover plants/plant bioactive compounds used in Traditional Chinese medicine and Ayurveda with presumed anti-COVID 19 potentials. However, considering their abundance, they were not covered here, as this review only focuses on selected, common and available plants globally. Evidence from plant bioactive compound administration directed toward mitigating and controlling inflammation biomarkers could be an encouraging approach, with the potential to prevent and suppress detrimental health consequences. Regardless of the encouraging effect against SARS-CoV-2 displayed by selected plant bioactive molecules, a few limitations arose. In some cases, the information for bioactive substances or plant extracts is presented with deficient and incomplete data. Others offer no validated conclusions. Of course, there is an issue regarding the clinical effectiveness of these compounds that must be evidenced. Upcoming extensive and wide-reaching studies involving a number of factors are needed to enable straight estimation of the similarities or dissimilarities of various patterns of bioactive compound use in correlation to various biomarkers related to numerous inflammatory and immune-related processes of COVID-19 disease.

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Biljna bioaktivna jedinjenja koje utiču na biomarkere i konačni ishod COVID-19

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Kratak sadržaj

Biljni lekoviti proizvodi imaju dugu istoriju upotrebe u lečenju različitih virusnih infekcija i ublažavanju simptoma bolesti. Izbijanje pandemije koronavirusa 2 (SARS-CoV-2) i bolesti COVID-19 povezane sa teškim akutnim respiratornim sindromom nije bilo izuzetak od ovog trenda. Bioaktivna jedinjenja prirodnog biljnog porekla mogu da deluju na nekoliko nivoa bolesti: esencijalne imunološke puteve, utičući na biomarkere COVID-19, ili zaustavljajući ili modulirajući SARS-CoV-2. Ovaj rad pruža pregled objavljenih podataka o upotrebi biljnih bioaktivnih jedinjenja u prevenciji/lečenju COVID-19. Razmotreni su načini delovanja koji su odgovorni za ove efekte, uključujući inhibiciju vezivanja i penetracije virusa, inhibiciju RNK, sintezu proteina i virusnih proteaza, kao i druge mehanizme. Pregledane informacije sugerišu da se biljna bioaktivna jedinjenja mogu koristiti samostalno ili u kombinacijama, ali potrebne su veće studije koje uključuju više faktora kako bi se omogućilo direktno poređenje različitih obrazaca upotrebe bioaktivnih jedinjenja sa nizom biomarkera koji reflektiraju višestruke upalne i imunološki povezane puteve bolesti COVID-19.

Ključne reči: biljna bioaktivna jedinjenja, tretman, COVID-19, biomarkeri