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Phytochemicals containing biologically active polyphenols as an effective agent against Covid-19-inducing coronavirus

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ABSTRACT

The outbreak of Covid-19 disease caused by SARS-CoV-19, along with the lack of targeted medicaments and vaccines, forced the scientific world to search for new antiviral formulations. In this review, we describe the current knowledge about plant extracts containing polyphenols that inhibit Covid-19. Many plant-derived natural compounds (polyphenols) might provide a starting point for the research on the use of plant extracts in coronavirus treatment and prevention. Antivirus polyphenolic drugs can inhibit coronavirus enzymes, which are essential for virus replication and infection. This group of natural substances (betulinic acid, indigo, aloeemodine, luteolin, and quinomethyl triterpenoids, quercitin or gallates) is a potential key to designing antiviral therapies for inhibiting viral proteases. The known pharmacophore structures of bioactive substances can be useful in the elaboration of new anti-Covid-19 formulations. The benefit of using preparations containing phytochemicals is their high safety for patients and no side effects.

1. Introduction

At the end of 2019, the first cases of coronavirus disease were reported in the Chinese city of Wuhan. Acute respiratory tract inflammation caused by SARS-CoV-2 is an infectious disease, often fatal, that is characterized by the rapid and unexpected spread. In response to a series of virus outbreaks in other countries and continents, the World Health Organization (WHO) announced the Covid-19 pandemic on March 11 (Ho, Chan, Chung, & Leung, 2020). By July 14, WHO had reported 12,964,809 confirmed cases in 213 countries around the world, of which 4.40% were confirmed deaths. Fig. 1 shows the number of reported Covid-19 cases from January 11 to July 14, 2020 for individual WHO regions (Europe, the Americas, the West Pacific, the Eastern Mediterranean, Southeast Asia and Africa).

China was the first epicenter of Covid-19. The situation has (Mahmood et al., 2016) changed dramatically. At present, the Americas and Europe are struggling the most with the pandemic of Covid-19. By July 14, 3,286,063 coronavirus infections have been reported in the United States of America (39 times more than in China). The situation is also difficult in Europe, especially in the United Kingdom (290,137 cases), Spain (255,953 cases), Italy (243,230 cases), Germany (198,963 cases) and France (162,390 cases). In the Middle East, Iran and Turkey have also seen a significant sustained increase in particular infected with Covid-19 (259,652 and 214,001, respectively) (WHO, 2020).

The actual number of infected is probably much higher due to asymptomatic cases that may contribute to the development of the pandemic. Restrictions, such as the use of personal protective equipment (masks, gloves, antibacterial gels), self-isolation or quarantine, and even border closing to reduce the number of cases have been introduced in several countries. It is not known how long this situation will continue. Perhaps Covid-19 will turn out to be a seasonal virus and, like flu, there will be a significant decrease in infected people in the

Abbreviations: $3CL^{pro}$, 3C-like protease; ACE2, Angiotensin-converting enzyme 2; CBE, CBM, Herbal extracts from *Rhizoma Cibotii*; CC50, 50% cytotoxicity concentration; CDC, Cholesterol-dependent cytolysin; Covid-19, Coronavirus Disease 2019; CPE, Cytopathogenic effect; CTH, Herbal extract from *Cassiae Semen*; DBM, Herbal extract from *Dioscoreae Rhizoma*; DNA, Deoxyribonucleic acid; EC50, 50% effective concentration; FA, Fatty acid; FFA, Free fatty acid; GCG, Gallocatechin gallate; GSH, Herbal extract from *Gentianae Radix*; IC50, 50% inhibitory concentrations; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; M^{pro}, The major protease; MNP, Marine Natural Product; MTT test, Cytotoxicity test using 3- (4,5-dimethylthiazol-2-yl) −2,5-diphenyltetrazolium bromide; PL^{pro}, The papain-like protease; PLY, Pneumolysin; RNA, Ribonucleic acid; SARS-CoV, Severe Acute Respiratory Syndrome coronavirus; TCH, Herbal extract from *Loranthi Ramus*; WHO, World Health Organization

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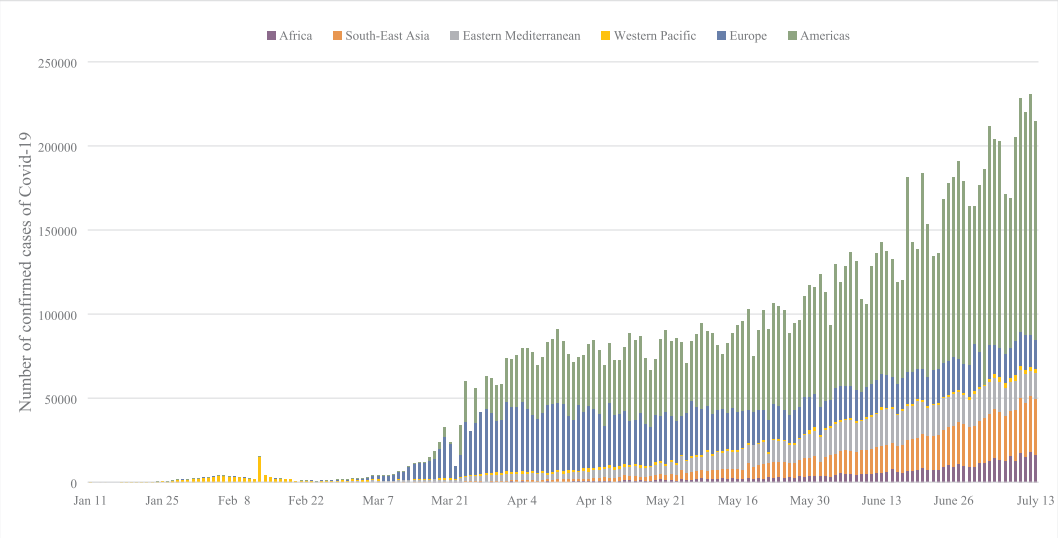

Fig. 1. Comparison of the number of confirmed cases of Covid-19 for WHO regions.

summer season. This would allow for better preparation for the next wave of the illness. The persistent state can lead to significant economic losses in all countries around the world, even those not affected by the virus. There are several scenarios for the progression of the pandemic, but there are still many unknowns (Johnson et al., 2020). Therefore, understanding how the virus operates and spreads is crucial in finding drugs or vaccines to fight SARS-CoV-2 infection.

SARS-CoV-2 is RNA virus with a genetic structure similar to that of SARS-CoV or MERS-CoV. The viral genome encodes a protease, which plays a crucial role in the production of viral proteins and controlling the activity of the replicase complex. This enzyme is necessary for virus replication and infection, making it a perfect target for designing antiviral therapies. Acute respiratory syndrome (SARS-CoV) coronavirus enzymes are one of the most promising targets for the discovery of anti-SARS drugs because of its key role in the life cycle of the virus. Natural inhibitors like betulinic acid, indigo, aloeemodine, luteolin, and quinomethyl triterpenoids, quercitin or gallates can be effective as antiviral preparations (Nguyen et al., 2012; Ryu et al., 2010). These substances act through the mechanism of enzyme inhibition. Enzymatic tests have shown that these natural molecules have IC50 values within the range from 3 to 300 μM. The studies were conducted on early SARS-CoV $3CL^{pro}$. Phytochemicals were isolated from medicinal plants, diterpenoids, biflavonoids - with SARS-CoV $3CL^{pro}$ inhibitory activity, by obtaining ethanol extracts. Biologically active compounds (quercetin, epigallocatechin gallate and galusatechin gallate (GCG)) showed good inhibition properties by binding to the $3CL^{pro}$ active site and the 3-OH galooyl group, which was required for virus inhibitory activity (Nguyen et al., 2012). Quercetin (Fig. 2a) is a polyhydroxy-flavonoid compound that supports body immunity and occurs in flowers, leaves and fruit of plants. In turn, gallic acid (Fig. 2b) has antiseptic properties and blocks carcinogenic processes.

Similarity between coronaviruses allowed Chinese scientists to test the possibility of using 26 herbal plants with the potential to inhibit SARS-CoV-2. The active compounds of these plants combined with the virus proteins showed potential antiviral activity (Zhang, 2020).

The SARS-CoV-2 genome is composed of approximately 30,000 nucleotides (Jin et al., 2020) and codes 16 non-structural and 4 structural proteins, among which some are necessary for entry into the host cell and replication (Jiménez-Alberto, Ribas-Aparicio, Aparicio-Ozores, & Castelán-Vega, 2020). At the infection stage, the virus attaches itself to the cell with a spike glycoprotein (protein S), which is located in the outer envelope. This protein consists of two subunits, responsible for cell attachment and subsequent fusion (Zhou, Fang, Xu, Ni, Shen, & Meng, 2020). The target of the binding is the cellular membrane protein, angiotensin-converting enzyme 2 (ACE2). The ability to bind the virus to the ACE2 membrane receptor is much stronger for SARS-CoV-2 compared to SARS-CoV, which has the same binding site (Liu et al., 2020). Protein S is hydrolysed by endosomal proteases (cathepsin or serine protease 2 (TMPRSS2)) which results in membrane fusion. (Quiros Roldan, Biasiotto, Magro, & Zanella, 2020). Both the receptor itself and the proteases cutting spike protein are potential therapeutic targets (Zhou et al., 2020). After fusion with a human cell, the virus releases its nucleotide into the cytoplasm and a number of molecular mechanisms are involved to produce the new RNA of the virus and the proteins that form its envelope. Key proteins involved in the replication and proliferation of the virus are an attractive target for antiviral compounds. Proteases, including papain-like protease (PL^{pro}) and chymotrypsin-like protease ($3CL^{pro}$), are identified as the most important targets. In view of the high similarity of SARS-CoV-2 with SARS-CoV and MERS-CoV, the mechanism of action of compounds of plant origin may be similar (Table 1).

Earlier outbreaks of SARS-CoV and MERS-CoV have provided us

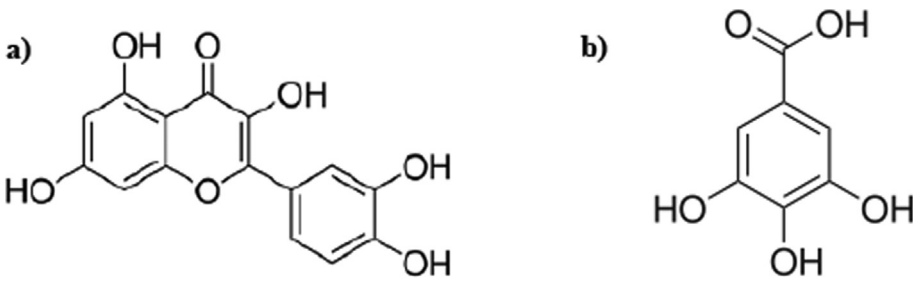

Fig. 2. The chemical formula of quercetin (a) and gallic acid (b).

Table 1
Bioactive compounds and their antiviral activity.

Plant	Active compounds	Virus type	Mechanism	References
Green tea	Epigallocatechin gallate, epicatechingallate and gallocatechin-3-gallate	SARS-CoV-2	Interaction with catalytic residues of major protease (M^{pro})	(Ghosh, Chakraborty, Biswas, & Chowdhuri, 2020)
Brown algae *Sergassum spinuligerum*	1,3,5-Trihydroxybenzene		Inhibits major protease (M^{pro})	(Gentile et al., 2020)
Brown algae *Ecklonia cava*	8,8′-Bieckol, 6,6′-Bieckol, Dieckol		Inhibits major protease (M^{pro})	(Gentile et al., 2020)
Broussonetia papyrifera	Polyphenols	SARS-CoV	Inhibition of cysteine proteases CoV	(Park et al., 2017)
Paulownia tomentosa	Geranylated flavonoids		Papain-like protease inhibition	(Cho et al., 2013)
root tubers of *Rheum officinale*	Emodine		inhibition of the S protein and ACE2 interaction	(T. Y. Ho, Wu, Chen, Li, & Hsiang, 2007)
	Flawonoids: herbacetin, rhoifolin pectolinarin		Inhibits SARS-CoV $3CL^{pro}$	(Jo, Kim, Shin, & Kim, 2020)
Traditional Chinese herbs	Tetra-O-galoyl-β-d-glucose (TGG) luteoline		The compounds bind to the SARS- CoV surface protein, hindering virus entry into its host cells	(Yi et al., 2004)
Toona sinensis leaves	Methyl gallate, gallic acid, kaempferol, quercetin, quercitrin, rutin, kaempferol-d-glucoside, (+)-catechin, (−)-epicatechin, beta-sitosterol, stigmasterol, beta-sitosteryl-glucoside, stigmasterol-glucoside, phytol and toosendanin		n.a.	(Chen et al., 2008)
Lycoris radiata	lycorine		n.a.	(Li et al., 2005)
Brown algae *Ecklonia cava*	Phlorotannins i.e. dieckol		Inhibits SARS-CoV $3CL^{pro}$	(Park et al., 2013)
	Quercetin-3-β-galactoside		Inhibits 3C-like protease ($3CL^{pro}$)	(Chen et al., 2006)
Radix *Sophorae*, rhrizome *Acanthopanacis*, radix *Sanguisorbae* and extract *Torilis* fructus		Mouse hepatitis virus (MHV)	Inhibits the effects on replication stages and/or their influence on cellular signal pathways	(Kim et al., 2010)
Rhrizome *Cimicifuga*, kory *Meliae*, rhrizome *Coptidis* and radix *Phellodendron*			Inhibits CoV production via reductions in viral RNA synthesis and viral protein expression	(Kim et al., 2008)
Houttuynia cordata Thunb	Flavonoids:quercetin, quercitrin and rutin	Mouse hepatitis virus (MHV) and DENV type 2	Inhibitory effects on the ATPase	(Chiow et al., 2016)
	(+)-Catechin	Transmissible gastroenteritis virus (TGEV)	Inhibiting effect on TGEV proliferation in vitro and associated with its anti-oxidation	(Liang et al., 2015)
Sambucus Formosana Nakai	Phenolic acids: caffeic acid, chlorogenic acid and gallic acid	HCoV-NL63	Inhibition of the replication of HCoV-NL63 in a cell-type independent manner	(Weng et al., 2019)
	Flavonoids: herbacetin, isobavachalcone, quercetin 3-β-d-glucoside and helichrysetin	MERS-CoV	Inhibits MERS-CoV 3C-like protease ($3CL^{pro}$)	(Jo et al., 2019)
Sambucus nigra	Flavonoid anthocyanins lectins	Avian infectious bronchitis virus (IBV)	Inhibition of virus replication	(Chen et al., 2014)
Green tea	Epigallocatechin gallate (EGCg)	Bovine coronavirus (BCV)	EGCg works in the first stage of viral infection, the interaction between EGCg and BCV spiked glycoprotein	(Matsumoto, Mukai, Furukawa, & Ohori, 2005)

with the data about antiviral phytochemicals with health beneficial activity. Coronavirus is an RNA virus, the genome of which encodes a protease essential in the production of viral proteins and controlling the activity of the replicase complex. This article reviews the possibility of using phytochemicals isolated from plants as water and ethanol extracts as a source of biologically active substances (e.g., quercetin and gallates), effective in inhibiting the development of Covid-19-inducing coronavirus. There is potential for the use of plant-derived polyphenols as functional foods and pharmaceutical preparations. The method of implementing such preparations is fast because the raw materials for their preparation, namely herbs and consumable plants, are approved for human consumption worldwide.

2. The potential use of plant extracts containing polyphenols to inhibit Covid-19-inducing coronavirus

The lack of Covid-19-oriented conventional therapeutic agents (vaccines, antibiotics) enforces the use of broad-spectrum antibiotics as well as widely known antivirals and corticosteroids. Supportive therapies, based on the agents of natural origin are also a solution of sorts. Extracts from natural products are a rich source of active compounds that can be used against coronavirus.

Herbal extracts from traditional Chinese medicine plants *Cibotium barometz, Gentiana scabra, Dioscorea batatas, Cassia tora and Taxillus chinensis* were found to inhibit SARS-CoV replication (Wen et al., 2011). The development of agents that inhibit coronavirus-associated respiratory syndrome (SARS-CoV) is important for both prevention and re-emergence of the disease. Wen et al. (2011) investigated over 200 extracts from Chinese medicinal herbs for inhibition of SARS coronavirus. Cellular tests were conducted that investigate SARS-CoV induced cytopathogenic effect (CPE) on Vero E6 cells under in vitro conditions. Herbal extracts, from *Gentianae radix, Dioscoreae rhizoma, Cassiae Semen* and *Loranthi Ramus* (designated as GSH, DBM, CTH and TCH, respectively) and *Rhizoma Cibotii* (designated as CBE and CBM) in the concentrations from 25 to 200 μg/ml proved to have potential inhibition effect on SARS-CoV. The concentrations of six extracts inhibited Vero E6 cell proliferation V (CC50) and virus replication (EC50) by 50%. The obtained selective index values (SI = CC50/EC50) for the most effective extracts from *Rhizoma Cibotii*, *Gentianae radix*, *Dioscoreae rhizoma*, *Cassiae Semen* and *Loranthi Ramus* and extracts were > 59.4, > 57.5, > 62.1, > 59.4 and > 92.9, respectively.

Rhizoma Cibotii and *Gentiana scabra* showed the most significant inhibition of SARS-CoV $3CL^{pro}$ activity. The IC50 values were 39 μg/ml and 44 μg/ml, respectively. Herbal extracts have been shown to have the potential as candidates for the development of SARS drugs or preventive preparations (Wen et al., 2011). Biflavonoids from *Torreya nucifera* inhibited the replication of SARS-CoV $3CL^{pro}$ (Ryu et al., 2010). Ryu et al. (2010) conducted research on the inhibitors among botanical sources of SARS-CoV $3CL^{pro}$. The authors studied ethanol extract from leaves of *Torreya nucifera*, a medicinal plant traditionally used in Asia. SARS-CoV $3CL^{pro}$ inhibitory activity (62% at 100 μg/ml) was found to be high. The authors identified eight diterpenoids and four biflavonoids by fluorescence resonance energy transfer analysis as potential inhibitors of the virus. Biflavone amentoflavone (IC50 = 8.3 μM) was the most effective against the virus. Also the activity of flavones (apigenin, luteolin and quercetin) was investigated. IC50 values were 280.8, 20.2 and 23.8 μM, respectively. The binding energy values by the molecular docking study confirmed the results of enzymatic tests. The stronger activity was related to the presence of the apigenin moiety at the C-30 position of flavones, since biflavone had an effect on $3CL^{pro}$ inhibitory activity (Ryu et al., 2010).

Chiow, Phoon, Putti, Tan, and Chow (2016) assessed the antiviral activity of ethyl acetate extract from *Houttuynia cordata* Thunb. containing quercetin, quercitrin and cyanserine in mouse coronavirus and dengue virus infections (Chiow et al., 2016) in *in vitro* tests. The flavonoids found in the extract (quercetin, quercitrin and rutin) were tested in terms of their efficiency against mouse coronavirus and dengue virus in virus neutralization tests and acute oral toxicity in C57BL/6 mice. The plant extract inhibited viral infectivity for up to 6 days. The 50% inhibitory concentrations (IC50) of extracts from *H. cordata* were 0.98 mg/ml for coronavirus and 7.50 mg/ml for dengue in the absence of cytotoxicity. Mice fed with plant extract in doses of up to 2000 mg/kg did not show signs of acute toxicity, with their major organs being histologically normal. The authors confirmed the synergistic efficacy of flavonoid combination of quercetin and quercitrin, and concluded that *H. cordata* has a great potential in the development of antiviral agents against coronaviruses and dengue infections (Chiow et al., 2016). Jo, Kim, Kim, Shin, and Kim (2019) characterized flavonoids as potential inhibitors of Middle Eastern Respiratory Syndrome – MERS-CoV 3 coronavirus – a zoonotic virus transmitted between animals and humans, characterized by a high mortality, for which no vaccine nor treatment was available. Since the antiviral activity of some flavonoids is well known, the authors used a flavonoid library to study inhibitory compounds against the MERS-CoV 3C-like protease ($3CL^{pro}$). The following compounds were found to block the enzymatic activity of MERS-CoV $3CL^{pro}$: herbacetin, isobavachalcone, quercetin 3-β-d-glucoside and helichristetine. The researchers conducted model tests on the binding of four flavonoids by the fluorescence-based tryptophan method. As a result, flavonol and chalcone were found to bind to the MERS-CoV $3CL^{pro}$ catalytic site. It was noticed that flavonoid derivatives with hydrophobic or carbohydrate groups attached to their core structures inhibit the virus. Such flavonoids can be used as templates to develop potential MERS-CoV $3CL^{pro}$ inhibitors (Jo et al., 2019). Nguyen et al. (2012) studied inhibition mediated by flavonoids against SARS coronavirus expressed in *Pichia pastoris*. 3C-like protease ($3CL^{pro}$) coronavirus associated with the acute respiratory syndrome (SARS-CoV) is essential for SARS-CoV replication and is a promising drug target. $3CL^{pro}$ was used for inhibition and kinetics tests in the presence of seven model flavonoid compounds. The IC50 for quercetin, epigallocatechin gallate and galusatechin gallate were 73, 73 and 47 μM, respectively. The most effective was galusatechin gallate (Ki 25 ± 1.7 μM), with the binding energy of −14 kcal/mol and the $3CL^{pro}$ active site (molecular docking experiments). It was found that for efficient inhibitory activity, the galooyl group should be present at the 3-OH position (Nguyen et al., 2012). Lv et al. (2020) investigated quercetin as a pneumolysin inhibitor that protects mice against *Streptococcus pneumoniae* infection. Pneumolysin (PLY) is the pore-forming cytotoxin and the major virulence determinant that belongs to the cholesterol-dependent cytolysin family (CDC) and is found in infections with *Streptococcus pneumoniae*. Pneumolysin that is released after killing bacteria with conventional antibiotics still has the ability to damage host cells. The most efficient is the pharmacological treatment that directly inhibits hemolysin activity. Hemolysis tests were used to confirm that quercetin can inhibit pneumolusin activity. Oligomerization assay was used to determine the mechanism of the quercetin inhibition of pneumolysin. Quercetin significantly reduced PLY-induced hemolytic activity and cytotoxicity through the inhibition of oligomers formation. Additionally, the survival rate of infected mice increased. The authors concluded that quercetin may be a new potential drug candidate in the treatment of clinical pneumococcal infections (Lv et al., 2020).

Park, Yoon, Kim, Lee, and Chong (2012) tested the synthesis and antiviral properties of 7-O-arylmethylquercetin derivatives against SARS-associated coronavirus (SCV) and hepatitis C virus (HCV). The antivirus compound aryl-diketo acid (ADK), the activity of which can be enhanced by aromatic aryl methyl substituent. Natural flavonoid (quercetin) contains the pharmacophore 3,5-dihydroxychromone. This is a bioisosteric compound containing the 1,3-diketoacid group of ADK. The authors tested the antiviral activity of quercetin derivatives containing an/the aryl methyl group − 7-O-arylmethylcercetin. The compound was effective against SARS-associated coronavirus (Park et al., 2012). Chen et al. (2006) studied the binding of quercetin-3-β-galactoside and its synthetic derivatives to SARS-CoV $3CL^{pro}$. Structure-

activity studies revealed significant pharmacophore characteristics. 3C-like protease ($3CL^{pro}$) of coronavirus is efficient with targets in the discovery of anti-SARS drugs because it plays a major function in the viral life cycle. A natural compound 3-β-galactoside-quercetin was found to play a key role as a protease inhibitor (by binding) by molecular docking, SPR/FRET-based bioassays and mutagenesis. The authors reported that quercetin-3-β-galactoside has the potential as an anti-SARS drug but also helps understand the mechanism of inhibition against the target enzyme (Chen et al., 2006). Song, Shim, and Choi (2011) showed that quercetin 7-rhamnoside reduces are replication of the epidemic diarrhea virus in pigs by an independent pathway of reactive oxygen species caused by viruses (Song et al., 2011). The antiviral effect of quercetin 7-rhamnoside (Q7R) flavonoid, which is not associated with antioxidant properties, was confirmed by the CPE reduction test. The production of the DNA fragment and reactive oxygen species (ROS) induced by infection was examined by the DNA fragmentation test and flow cytometry. Q7R inhibition of PEDV was not the result of its general antioxidant activity and was highly specific against PEDV infection (Song et al., 2011). Choi et al. (2009) showed the antiviral activity of quercetin 7-rhamnoside against the epidemic swine diarrhea virus (Choi et al., 2009). The epidemic swine diarrhea virus is the cause of severe entero-pathogenic diarrhea in pigs. It was found that Q7R actively inhibited PEDV replication at a 50% inhibitory concentration (IC50) of 0.014 μg/ml. The 50% cytotoxicity (CC50) concentration for Q7R was 100 μg/ml and the therapeutic index obtained was 7142. Structural analogs of Q7R, quercetin, apigenin, luteolin and catechin also showed anti-PEDV activity. Antiviral drugs and natural compounds have shown that ribavirin, interferon-, coumarin and tannic acid are relatively less effective compared to Q7R. It was found that Q7R can be considered as a compound in the development of guidelines for the design of other related antiviral agents (Choi et al., 2009).

The *Sambucus Formosana Nakai* extract showed a strong anti-HCoV-NL63 potential, mainly due to the activity of phenolic acid components, including coffee acid, chlorogenic acid and gallic acid (Weng et al., 2019). (+)-catechin, which is the main ingredient of green tea extract, shows antiviral activity against TGEV (Transmissible Gastroenteritis Virus). This compound reduces virus proliferation, or – to be precise – virus replication, by three $\log_{10}$ units (Liang et al., 2015). Green tea has an antiviral effect, mainly due to the presence of polyphenols, including (−)-epigallocatechin gallate (EGCG), (−)-epigallocatechin gallate, (−)-epicatechin gallate (−)-epicatechin and (+)-catechin (Mahmood et al., 2016). SARS-CoV inhibition was proven for *Toona sinensis Roem* leaf extract in nanoparticle form. The selectivity factor for SARS-CoV was 12–17. The extract contained a number of bioactive compounds, including methyl gallate, gallic acid, quercetin, (+)-catechin, (−)-epicatechin and others (Chen et al., 2008). *Houttuynia cordata* extract inhibited 3C-like protease ($3CL^{pro}$) and RNA-dependent polymerase RNA (RdRp) in severe coronaviral acute respiratory syndrome (SARS). Flavonoids present in *Galla chinensis* or *Veronica lin rrifolia* extract may bind to the surface of the spiky protein of the SARS virus, preventing virus particles from penetrating the cell (Wang & Liu, 2014). Phlorotannins extracted from brown algae show an inhibitory effect of SARS-CoV $3CL^{pro}$, which regulates the replication of the virus. In particular, dieckol showed a high inhibitory activity (IC 50 = 2.7 μM), characterized by a high association coefficient and the formation of strong hydrogen bonds, which was shown by molecular docking simulations (Park et al., 2013). Observations of the use of Chinese qingfei paidu decoction (QPD) indicated that the preparation mitigates the immune response and reduces inflammation caused by the virus. It has also been shown that traditional Chinese medicine, based on natural preparations containing bioactive compounds, can alleviate the symptoms of Covid-19 disease by reducing inflammation and stimulating the body to repair (Ren, 2020). The water extract from *Isatis indigotica* root, containing a number of phenolic compounds (indigo, sinigrin, aloeemodin and hesperetin in the micromolar range) showed anti-SARS-CoV $3CL^{pro}$. In particular, hesperetin (IC_{50}: 8.3 μM) and sinigrin (IC_{50}: 217 μM) may be potential inhibitors of this enzyme. (Lin et al., 2005). Two small particles from traditional Chinese herbs, tetra-O-galoilo-β-d-glucose (TGG) and luteolin have been proven to be active against SARS-CoV. TGG was characterized by activity against SARS-CoV (IC_{50} 4.5 μM) at selective index 240.0 The virus entry into the cell is a promising blocking site as it allows early inhibition of virus proliferation (Yi et al., 2004).

Plant extracts (*Lycoris radiata, Artemisia annua, Pyrrosia lingua* and *Lindera aggregate*) have shown antiviral activity of SARS-CoV with a 50% effective concentration (EC_{50}) within the range of 2.4–88.2 ng/ml. In particular, *L. radiata* extract proved to be a good candidate for an antiviral drug as it showed the highest efficacy (EC_{50} 2.4 μg/ml, SI > 300), mainly due to the lycorin component (Li et al., 2005). Extracts from *Sophorae* radix, *Acanthopanacis* bark, *Sanguisorbae* radix and *Torilis* fructus had the antiviral effect, while extract concentrations required to inhibit 50% replication were within the range of 0.8–3.7 μg/ml. The effect was induced by the inhibition of RNA-dependent RNA polymerase or protease activity required for RNA replication (Kim et al., 2010). Similarly, herbal extracts, *Cimicifuga* rhizomes, *Meliae* bark, *Coptidis* rhizome and *Phellodendron* bark also have an impact on coronavirus replication (Kim et al., 2008).

The significant aspect in the preparation of a drug for Covid-19 is also the discovery/design of major protease (M^{pro}) inhibitors. Through sequential matching, it has been proven that SARS-CoV-2 M^{pro} has approximately a 96% similarity to SARS-CoV-1 M^{pro} (Xu et al., 2020). The difference is in the 12 protein building amino acids and the size of the binding site, which in the case of SARS-CoV-2 is twice as small as in the case of SARS-CoV-1. It is also worth noting that one of the different amino acids (Ser 46) is located on the Cys44 - Pro52 loop, surrounding the binding site cavity (Bzowka et al., 2020). Therefore, there may be large differences in the matching of the appropriate inhibitor both in terms of availability to the cavity and shape matching. To identify Mpro inhibitors, a simulation was performed using Pharmit (N3/SARS-CoV-2 M^{pro}) and Marine Natural Product (MNP) library data. Seventeen potential SARS-CoV-2 M^{pro} inhibitors were identified. The inhibition of M^{pro} was attributed to compounds from the group of floronates, flavonoids and pseudo-opeptides. The most promising inhibitors of the virus were found to be oligomers of phloroglucin (1,3,5- trihydroxybenzene) derived from brown algae *Sergassum spinuligerum*. In turn, the most active inhibitors of SARS-CoV-2 are compounds from the florotannin group (8,8′-Bieckol, 6,6′-Bieckol, Dieckol) isolated from the brown algae *Ecklonia cava*. The simulation shows that compounds contained in plants may be a source of SARS-CoV-2 M^{pro} inhibitors and thus supress the proliferation of Covid-19 (Gentile et al., 2020).

Table 1 below presents bioactive substances obtained from various plants and their antiviral mechanism.

2.1. Bioactive extracts from acorns

Nuts of wild plants were a valuable food resource during times of crisis. Acorns, which are the fruits of *Quercus* trees, can also be food and highly nutritional feed. Their folk food applications for humans and in the feed are known, especially for poultry (Sekeroglu, Ozkutlu, & Kilic, 2017; Xu, Cao, Yue, Zhang, & Zhao, 2018). Indian Pomo Communities in America use acorns in traditional dishes such as acorn soup and dumplings (Meyers et al., 2007).

Acorns are used in the treatment of hemorrhoids, diabetes and kidney stones as a therapeutic agent in folk medicine. Acorns with their antibacterial, anti-ulcer, anti-helminthic, anti-inflammatory and antioxidant have been used in folk medicine to treat memorrhoids, diabetes, and kidney stones. They are also consumed as herbal coffee due to their characteristic aroma (Gezici & Sekeroglu, 2019).

Acorns are the fruit of several trees belonging to the *Fagaceae* family. For instance, in Central Europe, the dominant species of this family is *Quercus*. Although this nut has an appreciable effect on human nutrition, it is a key ingredient in the development of some typical

products with functional properties, such as Eichel Kaffe (acorn coffee), astringent and anti-diarrheal drink used as a traditional drug. What is more, during times of hunger, acorn flour was used to produce bread with good sensory properties and long shelf life. Natural flavor ingredients are currently in high demand in food. Currently acorns are used to make a coffee drink powder that has a coffee-like flavor but is free of caffeine and gluten, which satisfies because there is the great demand for it (Coelho et al., 2018).

As a food source, acorns have recently been discovered as a novel herbal product and functional food. Although acorn coffee is a historical and traditional hot drink, replacing real coffee, it has a potential as a commercial product. Because acorn-based extract contains useful minerals and low concentrations of heavy metals, acorn-based drinks can be consumed safely. As a functional food, it has health benefits in line with consumer preferences (Sekeroglu et al., 2017).

As demonstrated by Ishida et al. (2015), water and methanol extracts from acorns contain high concentrations of gallic acid and its derivatives. This explains the high concentrations of polyphenols in acorn coffee and the antioxidant activity of its infusions. In the study on acorn coffee, they showed twice as high concentrations of phenolic compounds than those in green coffees tested by Stelmach, Pohl, and Szymczycha-Madeja (2015), which conforms to the findings of this study. Coffee infusions prepared from acorns showed the highest antioxidant activity. EC50 values obtained for the capture of DPPH free radicals were 0.063 for acorn ginseng and 0.066 mg d.m./ml for acorn coffee (Samsonowicz, Regulska, Karpowicz, & Leśniewska, 2019).

The results showed that beverages based on *Quercus* have an antioxidant capacity related to the concentrations of phenols, mainly with ellagic acid as the main phenolic compound. This compound imparts to the drink antimutagenic properties. The main fatty acids were esterified lipids: oleic, linoleic, palmitic. Oleic and linoleic acids were found in the free fatty acid fraction (FFA). The heat treatment reduced the total fatty acid concentration in the TG and FFA fractions. It has been demonstrated that acorn smoking or coffee making does not cause genotoxic or cytotoxic compounds. This shows the potential of acorns to produce functional drinks i.e coffee substitutes. Since acorn coffee is not mutagenic, the cytotoxicity of these extracts was assessed by the MTT test. Ellagic acid is a phenolic compound with antimutagenic properties and is present in *Quercus* coffees as the main phenolic compound. Ellagic acid may also promote the release/formation of bioactive molecules on antimutagenic activity. Fatty acid composition (FA) analysis of raw samples of two species showed that in the triglyceride (TG) fraction the main acids are: oleic (C18: 1 c9), linoleic acid (C18: 2 c9c12), palmitic acid (C16), stearic acid (C18) and *cis*-vaccence (C18: 1 c11). In the free fatty acid (FFA) fraction, oleic, linoleic and palmitic acids were also characteristic compounds. The phenolic profile found ellagic acid and epicatechin gallate (−) gallate. The results showed that epicatechin gallate and gallic acid levels decreased together with heat treatment withan increase in ellagic acid concentrations (Coelho et al., 2018).

3. Future perspectives

This review provides a broad spectrum of information on the use of phytochemicals found in medicinal plants for the inhibition of coronavirus family. The examples clearly prove that the formulations with specific ingredients of herb extracts that have been developed for centuries in traditional medicine (e.g. Chinese medicine) can be beneficial as the source of anti SARS-CoV agents in the treatments and prevention of Covid-19. Natural compounds can act as antioxidants, direct enzyme inhibitors and throughout interaction-blocking virus surface protein receptors. Different medicinal plants can be used as a source of phytochemicals (polyphenols, sterols and lipids) with a broad range of biological activity (Coelho et al., 2018; Vinha, Barreira, Costa, & Oliveira, 2016). These compounds provide hope that extracts from different plants presented in this review may have antiviral properties, also against the coronavirus family.

The wide range of natural substances present in herbal extracts, which are underrated in conventional medicine, may constitute almost inexhaustible source of medicaments. The knowledge about their therapeutic properties and application has been handed down from generation to generation. The new trends in biotechnology and medicine have enabled the use of natural-origin compounds to a larger extent, than in the previous decades, mostly as the dietary supplements and nutraceuticals. Their toxicity together with consumption time are yet to be investigated by means of a multidisciplinary approach (omics science-genomics, proteomics, metabolomics) (Firenzuoli & Gori, 2007; Thomford et al., 2018). Also, new processing and formulation technologies might help optimize the solubility of antiviral bioactive compounds, their delivery strategies and therapeutic activities (Patra et al., 2018) to adapt them as antiviral functional foods (Lin, Hsu, & Lin, 2014; Zhong, Ma, & Shahidi, 2012) and drugs.

The studies performed so far have contributed to the knowledge of the chemical structure of antiviral compounds. Bioinformatic studies of the phyto-pharmacophores structures can (ul Qamar et al., 2020) can lead to designing new antiviral drugs. The use of herbal extracts might provide synergistic health beneficial effects (antioxidant, antiviral, antimutagenic, antiinflammation) between occurring phytochemical mixtures, which should be taken into account, but must be deeply explored (Yu et al., 2017).

4. Conclusions

Many examples show that nature offers the best solutions. A wide variety of plant species contain biologically active substances, which in synergistic combinations are effective in combating various diseases. They have been explored by folk or ancient medicine. Identifying individual compounds and determining mechanisms of action is very difficult. This hinders the standardization of products, especially since plant extracts contain a wide variety of different compounds, occurring in varying concentrations, with presumably synergistic effects. Despite many unknowns, scientific research unambiguously indicates that plant extracts inhibit the life cycle of coronavirus.

This review of literature indicates the great potential of plant extracts and phytochemicals in the development of functional foods enriched with polyphenols of plant origin or even pharmaceutical preparations. Laboratory model tests are needed to prove their efficacy in inhibiting coronavirus replication. The next step should be to conduct clinical trials on patients and observe the potential to reduce the multiplication of the virus in the patient's organism and thus improve clinical symptoms. It seems that the introduction of plant preparations into food and clinical practice should be relatively fast, because those are preparations of natural origin, obtained from plants authorized for use as herbs and food. It is necessary to conduct laboratory tests *in vitro* and *in vivo* on animals and patients to confirm their effectiveness in inhibiting Covid-19-inducing coronavirus replication. It is worth mentioning that the benefit of using these preparations is high safety for patients and no known side effects.

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Ethical statement

This paper does not conduct research on humans or animals.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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