Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Trends in Food Science & Technology 106 (2020) 1–11

Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: www.elsevier.com/locate/tifs

Review

anti-HCoV: A web resource to collect natural compounds against human coronaviruses

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ARTICLE INFO

Keywords:
SARS
MERS
Antiviral compounds-natural products
Web based resource
Viral fight

ABSTRACT

Background: A novel coronavirus, the SARS-CoV2, was revealed to be the cause of COVID19, the pandemic disease that already provoked more than 555.324 deaths in the world (July 10, 2020). No vaccine treatment has been defined against SARS-CoV2 or other human coronaviruses (HCoVs), including those causing epidemic infections, neither appropriate strategies for prevention and care are yet officially suggested.

Scope and approach: We reviewed scientific literature on natural compounds that were defined as potentially effective against human coronaviruses. Our desk research identified non-chemically modified natural compounds that were shown (in vitro) and/or predicted (in silico) to act against one or more phases of human coronaviruses cell cycle.

We selected all available information, merged and annotated the data to define a comprehensive list of natural compounds, describing their chemical classification, the source, the action, the specific target in the viral infection. Our aim was to collect possible compounds for prevention and care against human coronaviruses.

Key findings and conclusions: The definition of appropriate interventions against viral diseases need a comprehensive view on the infection dynamics and on necessary treatments. Viral targeting compounds to be exploited in food sciences could be of relevant interest to this aim.

We collected 174 natural compounds showing effects against human infecting coronaviruses, providing a curated annotation on actions and targets.

The data are available in *anti-HCoV*, a web accessible resource to be exploited for testing and in vivo trials. The website is here launched to favour a community based cooperative effort to call for contribution and expand the collection. To be ready to fight.

1. Introduction

1.1. Natural products as source of pharmacologically active molecules

Natural products (NPs) are defined as compounds found in nature and synthesized by living organisms (Osbourn & Lanzotti, 2009, pp. 1–597). They are secreted and can be extracted by prokaryotes, unicellular eukaryotes, fungi, plants and animals, or be part of them, like single cells, organs, tissues.

The capability of NPs to interfere or favour biological processes drives the interest for their exploitation for drug development, to search for proper ingredients with pharmacological or nutraceutical effects (Reed et al., 2018), for the use in traditional and modern medicine or as natural additives and ingredients for health and well-being.

NPs are divided in two main groups: the primary and the secondary metabolites. Primary metabolites are ubiquitous organic compounds considered essential for the organism life, including nucleic acids, proteins, carbohydrates, and lipids. Secondary metabolites are instead organic compounds, with a much more limited distribution in nature, that sustain the structure and the functional status of cells and overall organisms (Pietra, 1997). In particular, secondary metabolites such as flavonoids (Pietta, 2000), alkaloids (Cordell et al., 2001),

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https://doi.org/10.1016/j.tifs.2020.09.007
Received 18 April 2020; Received in revised form 29 July 2020; Accepted 14 September 2020
Available online 22 September 2020

phenylpropanoids (Korkina et al., 2011) and terpenes (Saito et al., 2016) are being extensively used as leading compounds because of their versatile functions and effects in health and wellbeing, for drugs and food design. Their chemical structures are chemically modified to reduce side effects and/or increase their bioavailability.

NPs can act in the organism at different levels. At intracellular level, they modulate signal transduction pathways through direct effects on the involved protein components (e.g enzymes, like kinases, regulatory proteins, membrane or intracellular receptors) (Harvey & Cree, 2010), on DNA damage prevention (Noroozi et al., 1998), on chromatin remodeling and epigenetic modifications (Rahman & Chung, 2010). At extracellular level, they help to control or reduce inflammatory status (Orlikova et al., 2014), cholesterol levels (Chen, Wesley et al., 2005), or act on components involved in specific diseases, like hypertension (Balasuriya & Rupasinghe, 2010).

For their broad spectrum of possible pharmacological and biological activities, NPs can be suitable candidate for their effects on multifactorial diseases, such as neurodegeneration and cancer (Balunas & Kinghorn, 2005). For example, the alkaloid colchicine, by inhibiting tubulin assembly, therefore suppressing microtubule formation and cell division, is able to block cell cycle leading to cell death (Kaplan et al., 1986). Other compounds inhibit the activity of DNA topoisomerases I (e.g. the alkaloid camptothecin) and II (e.g the antracicline doxorubicin), but also the activity of other key enzymes in DNA replication and transcription (Gamet-Payrastre et al., 2000).

Most drugs or ingredients deriving from prokaryotes are employed as antibacterial or antifungal agents, e.g. spectinomycin, rifamycin, kanamycin, daptomycin and tetracycline from *Streptomyces* species (Procópio et al., 2012), polymyxins from *Paenibacillus polymyxa* (Velkov et al., 2013), and rifamycins from *Amycolatopsis rifamycinica* (Riva & Silvestri, 1972).

Archaea have been also exploited as a source of enzymes-based drugs useful in food, chemical and pharmaceutical industries, where biotechnological processes frequently involve drastic conditions such as high temperatures, extreme pH, high salt concentrations, and/or high pressure. For example, the thermostable beta-glucosidase enzyme of *Pyrococcus furiosus* (an extremophilic species of Archaea domain) can be used to hydrolyze lactose in milk (Li et al., 2013).

Several anti-infective treatments are derived from fungi and include penicillins and cephalosporins. Another useful fungal metabolite, named lovastatin, isolated from *Aspergillus terreus*, is important for the production of anti atherosclerosis drugs (statins) (Subhan et al., 2016).

Animals also represent a source of bioactive NPs. In particular, venomous animals (snakes, spiders, scorpions, bees, wasps and frogs) have attracted much attention because of their constituents (proteins, nucleotides, lipids, biogenic amines etc.) often showing highly specific interactions with their target. Two examples for clinical use include ω-conotoxin (from the marine snail *Conus magus*) and ecteinascidin 743 (from the tunicate *Ecteinascidia turbinata*). The former is used to relieve severe and chronic pain, whereas, the latter is used to treat cancer (Lobo-Ruiz & Tulla-Puche, 2018).

Marine organisms are also of interests as source of NPs. Seaweeds, as an example, have been considered for their anti-tumor, anti-inflammatory, anti-lipidemic and anti-viral properties. It has been reported that some sulphated polysaccharides extracted from red algae show antiviral activity. In particular, galactan sulphate (from *Aghardhiella tenera*) and xylomannan sulphate (from *Nothogenia fastigiata*) exhibit antiviral activity against human immunodeficiency virus, herpes simplex viruses types 1, 2 and respiratory syncytial virus (Pal et al., 2014).

Several NPs extracted from plants were proven effective against viral infections, including those from coronaviruses (CoVs), coxsackieviruses, enterovirus 71, dengue, hepatitis B, hepatitis C, herpes simplex, human immunodeficiency (HIV-1) and influenza viruses (Lin et al., 2014). For example, secondary metabolites from green tea (Steinmann et al., 2013), cinnamon (Connell et al., 2016) and curcumin (extracted from turmeric) (Praditya et al., 2019), showed action against different viruses (HIV-1, human papillomavirus, hepatitis, influenza, chikungunya, herpes simplex 2, and Zika viruses (ZIKV)).

In the past two decades, coronaviruses have caused three epidemic diseases: SARS-CoV2 (Zhou et al., 2020), the severe acute respiratory syndrome (SARS) (Rota et al., 2003) and the Middle East respiratory syndrome (MERS) (Zaki et al., 2012). They have been, and in some cases continue to be, a threat to human lives, mainly triggering severe infections that are the leading causes of death, as communicated by the World Health Organization (website: https://www.who.int/).

The ongoing outbreak of the SARS-CoV2 raised again the problem of suitable treatments against dangerous viral infections and of appropriate care. Despite advances in immunization and drug development, at present, there are no effective preventive vaccine or efficient antiviral therapies to treat coronavirus infection diseases and to limit the main cause of death (Sanders, Monogue, Jodlowski, & Cutrell, 2020). Therefore, the identification of appropriate antiviral treatments that could inhibit or relief the effects of the human response to the infection is of fundamental importance for fighting COVID19 and similar possible diseases determined by Coronaviridae.

We reviewed all public scientific papers that describe natural compounds effective against coronaviruses infections, annotating their action, their chemical class and the source organism. Some of these compounds have been already proven for their action against SARS-CoV2, causing the current pandemic disease, other showed relevant effects against previously human infecting coronaviruses. Their functionality, revealed by in vitro experiments or predicted by in silico analyses, offers a relevant piece of information for further experimental validations and for in vivo trials that could drive towards proper food, ingredients and additives. Therefore, we considered useful to organize a web accessible collection, available at https://bigdatainhealth.org/letsbe/anti-HCoV.php, to share this knowledge with all the interested community. To be ready to face current and next challenges.

1.2. Coronaviruses

Coronaviruses are well known pathogens of the family Coronaviridae. They are enveloped viruses with a single-strand positive-sense RNA genome of 26–32 kilobases in size (Schoeman & Fielding, 2019). According to genetic criteria they have been divided into three groups, alfa, beta and gamma coronaviruses. They can infect also other animals, like birds and mammals. Alpha and beta coronaviruses are of particular interest because these strains can infect mammals and occasionally can cross the species barrier and become human pathogens (Schoeman & Fielding, 2019).

Indeed, only 7 coronaviruses have infected humans till now, SARS-CoV2 included. These viruses are indicated as HCoVs (human coronaviruses) and can be divided into four different lineages based on their genomic characterization. Alpha coronaviruses, including the strains 229E and NL63; beta coronaviruses lineage A, including strains OC43 and HKU1; beta coronaviruses lineage B, representing SARS-CoV and SARS-CoV2; beta coronaviruses lineage C, including MERS-CoV (Zaki et al., 2012).

The transfer from animals to humans happened in 2002–2003, when the epidemic SARS-CoV, which is a beta coronavirus, was transmitted from palm civets (in Guadong province, China) (Wang & Eaton, 2007). Moreover, the same event happened with Middle East respiratory syndrome (MERS-CoV), that started in 2015, when another beta coronavirus, belonging to a strain showing high similarity with SARS-CoV, was transferred to humans from dromedary camels in Saudi Arabia (Azhar et al., 2014). The new SARS-CoV2 was identified to be a beta coronavirus too (Zhou et al., 2020). It is closely related to the SARS-CoV virus, because of the high sequence similarity (94.4%) in the region of the seven conserved domains in the ORF1ab, coding for the viral replicases, that is in general used to classify CoV species (Yang & Wang, 2020).

In humans, coronaviruses can generate diseases ranging from upper respiratory tract infections to severe acute respiratory syndrome (SARS),

causing death. In particular, the high mortality rates among the infected population was the main reason that attracted worldwide attention versus SARS and MERS epidemic events (SARS caused a total of 774 patients died on 8096 diagnosed patients (total mortality rate, 9.6%) (Keum & Jeong, 2012). For MERS a total of 652 patients died on 1842 diagnosed patients (total mortality rate 35.4%) (Lin et al., 2017). SARS-CoV2 caused 555.324 deaths worldwide, up to now, with a 4% mortality rate on confirmed cases.

1.3. SARS-CoV2 genome

SARS-CoV2, together with SARS-CoV and MERS-CoV, are the major causes of severe pneumonia in humans caused by Coronaviridae. They all share common structural characteristics. Similarly, their genomic organization is typical of coronaviruses.

Looking at the genomic features of SARS-CoV2 it includes 6 open-reading frames (ORFs) and other accessory genes (Chan et al., 2020; Zumla et al., 2016). The main ORFs of the genomic RNA at the 5' end of the genome, ORF1a and ORF1ab, are used as templates to directly translate polyproteins 1a/1 ab (pp1a/pp1ab), respectively, which encode non-structural proteins (nsps) that form the replication-transcription complex (RTC) (Chen et al., 2020; Zumla et al., 2016). The two replicases are cleaved by two different proteases, the 3CLPro, that is also called the main protease (MPro), and the papain-like protease (PLPro) (Zhang, Lin et al., 2020). The 3CLPro operates as a dimer, each formed by 3 domains (I, II, III), sharing 96% sequence identity with the corresponding protein encoded by the SARS-CoV genome. 3CLPro can cleave at least 11 sites on the replicase 1 ab (Zhang, Lin et al., 2020). PLPro also takes part in this process, acting on secondary cleavage sites on PP1a and PP1ab. These events produce the two replicases and other enzymes involved in viral transcription and replication, including an RNA dependant RNA polymerase (RdRp) and an helicase (Hel) (Zumla et al., 2016).

At the 3' end of the genome there are other ORFs that encodes virus essential structural components: the spike glycoprotein (S), the envelope protein (E), the membrane protein (M) and the nucleocapsid protein (N), each of these serving different functions (Zumla et al., 2016).

The N protein functions primarily by binding the viral genome and organizing it as a nucleocapsid. Putatively, it can also contribute to the virion formation. The M protein defines the shape of the envelope, promotes the final viral assembly, and together with the E protein forms the envelope. The E protein is the smallest viral protein inside the infected cells, but only a small portion is incorporated into the virion envelope. The S protein mediates the attachment of the virus to the host cell membrane receptor (Xia et al., 2020). Because of its role in starting the viral infection, the S proteins are particularly of interest since they also determine the efficiency of the infection and its spreading (Zhou et al., 2020).

Spike proteins have two subunits, the amino-terminal receptor binding (S1) and the carboxy-terminal membrane fusion (S2) domains. The S1 domain includes the receptor binding domain (RBD), which is the region binding the host receptor, that determines tissue tropism and host range variability for different CoVs (Fig. 1). The cleavage at the junction between the S1 and the S2 domains activates membrane fusion, a process called the S protein priming, and that is crucial to determine the viral entry into the cell (Zhou et al., 2020).

1.4. HCoVs life cycle

Although the processes causing HCoVs entry into cells and viral particles formation still require deeper investigations, we here summarize the main aspects of Coronaviridae life cycle, distinguishing the main phases (Fig. 1) (de Wit et al., 2016).

HCoVs bind human cell receptors through the S1 domain of the S protein. The human receptor on the cell membranes for SARS-CoV, HCoV-NL63 and the newly discovered SARS-CoV2, is the angiotensin-converting enzyme 2 (ACE2) (Hoffmann et al., 2020). MERS-CoV enters the cell using the cell adhesion molecule 1 (CEACAM1) or the dipeptidyl-peptidase 4 (DPP4) (Wang et al., 2013).

When the virus binds its receptor, the S-priming, i.e. the cleavage of the S protein, may occur through specific transmembrane proteases, like protease serine 2 (TMPRRS2), with cathepsin B and L (CatB/L) also contributing in the process in SARS-CoV2 (Hoffmann et al., 2020). The entrance of the virus occurs via endocytosis or simply via membrane fusion, and the release of the viral genome into the cytosol appears to take place through acidification. Subsequently, the viral RNA overlapping ORFs forming the ORF1ab are translated, exploiting the host apparatus. The two resulting polyproteins, the replicases 1a (pp1a) and 1b (pp1b), undergo the autoproteolytic processing by 3CLPro and PLPro generating components of the replication/transcription complex (RTC): mature replicases and other non structural proteins. Once the RTC of the virus is assembled, it can start replication process. The replication

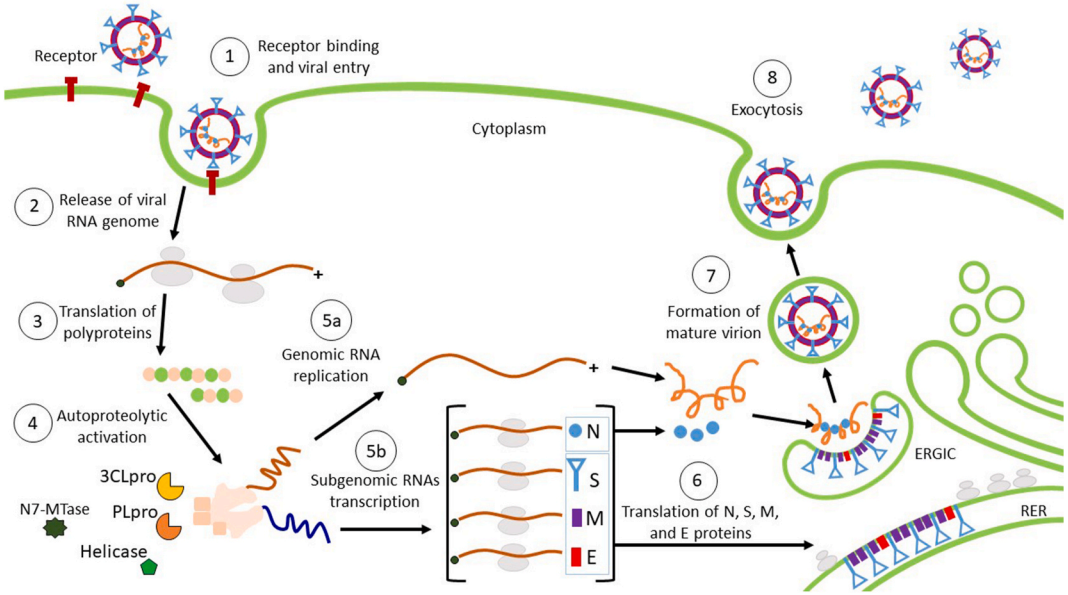

Fig. 1. Coronaviruses life cycle in the host cell and specific phases.

process gives rise to a full-length viral RNA genome which functions as a template for the new viral genomes and for subgenomic RNAs coding for viral structural proteins (Bergmann et al., 2006). Here copies of the viral genome, forming the nucleocapside with the N proteins, contribute to formation of the viral-like particles (VLPs), together with M and E proteins, that produce the CoV envelopes. Mature virions, included in cell endosomes are released by exocytosis.

1.5. Natural compounds anti HCoV-229E

In 2012, Chang et al. (Chang et al., 2012) extracted 22 triterpenoids from *Euphorbia neriifolia* that show an anti-viral role against HCoV-229E (Table S1). To this end, they performed anti-HCoV assays infecting viral susceptible MRC-5 fibroblast cells from lung, treating them with the extracted compounds for 2 h at 37 °C (Chang et al., 2012).

Interestingly, the bioactivity assays revealed a strong antiviral activity influenced by the chemical structure of the selected compounds. For instance, considering the friedelane derivatives, the antiviral activity of the two epimers, 3β-friedelanol and 3α-friedelanol, was substantially affected by a different orientation of the C-3 proton. Moreover, the comparison of 3β-friedelanol and 3β-acetoxy friedelane suggested the involvement of the acetyl group in the reduction of the activity.

1.6. Natural compounds anti HCoV-OC43

In 2019, Kim et al. (Kim et al., 2019) focused on the role of bisbenzylisoquinoline alkaloids extracted from *Stephania tetrandra.* Previous studies demonstrated that three variants of these compounds have effect on different viruses. In particular, tetrandrine (TET) has effect on herpes simplex and dengue viruses (Hu et al., 1997; Liou et al., 2008); fangchinoline (FAN) has effect on HIV-1 (Wan et al., 2012) and cepharanthine (CEP), possesses anti-viral activity against HIV-1 (Baba et al., 2001), herpes simplex (Liu et al., 2004) and Ebola viruses (Sakurai et al., 2015). The authors tested the same molecules against HCoV-OC43 infected MCR-5 cells (Kim et al., 2019). These treatments showed that TET, FAN and CEP, inhibited cell death induced by HCoV-OC43 (at IC_{50} values of 0.33 ± 0.03, 1.01 ± 0.07, and 0.83 ± 0.07 μM, respectively). Moreover, all the three compounds suppressed the expression of S and N proteins and the viral replication (Kim et al., 2019). In particular, the authors treated cells with TEN, FAN, and CEP at 24, 12, 6, and 3 h before HCoV-OC43 infection, during infection, and at 12, 24, and 48 h post-infection. They found that the three compounds had high antiviral activity from 3 h before the infection with HCoV-OC43. On the other hand, the treatments at 48 h post-infection revealed that the viability of cells was similar to that of the untreated group, for all the compounds, suggesting no antiviral effects after 48 h. Therefore, the authors suggested that TET, FAN, and CEP have antiviral activities in the range from 3 h before, to 48 h post HCoV-OC43 infection. These results indicate that three compounds are most effective at the early stages of the HCoV-OC43 life cycle. Moreover, the authors investigated the effects of the compounds on viral replication. They quantified the abundance of viruses in the supernatants and cell lysates by measuring the RNA levels of S and N proteins, revealing their decrease when comparing treated with non-treated cells.

1.7. Natural compounds anti MERS-CoV

In 2017, Lin et al. (Lin et al., 2017) described the role of stilbene derivatives against MERS-CoV infection. In particular, they focused on the role of resveratrol, as a natural compound present in different plants, including cranberry (*Vaccinium macrocarpon*), grape (*Vitis vinifera*) and Huzhang (*Polygonum cuspidatum*). Previous studies already demonstrated the antiviral role of resveratrol against SARS-CoV, but also positive effects against bacterial infections, only reduced in case of *Helicobacter pilory* (Zhang et al., 2015) and *Staphylococcus aureus* (Liu et al., 2016). Furthermore, it was demonstrated that resveratrol removes free radicals (Li et al., 2016), decreases the role of nitric oxide (Tsai et al., 1999), inhibits STAT3, (Baek et al., 2016), mTOR (Liu & Liu, 2011) and hedgehog signaling pathway (Gao et al., 2015), all relevant pathways in human cell surviving.

Lin et al. (Lin et al., 2017) expressed dipeptidyl peptidase 4 (DPP4) (receptor of MERS-CoV) (Raj et al., 2013) in mouse and tested mouse infection by MERS-CoV. They treated infected mouse with resveratrol and observed the inhibition of the cell death induced by the virus (Lin et al., 2017).

In 2017, Park et al. (Park et al., 2017) focused on the role of polyphenols extracted from *Broussonetia papyrifera* against MERS/SARS-CoV proteases. The authors expressed the viral 3CL and PLpro in *E. coli* and performed an inhibition assay to evaluate viral proteases activity after exposure to 10 plant root derived glucosidase inhibitors (Table S1). They found that all isolated polyphenols can inhibit both 3CL and PLpro proteases, and that, among them, papyriflavonol A has its highest activity against PLpro (IC_{50} = 3.7 μM) (Park et al., 2017).

1.8. Natural compounds anti SARS-CoV

In 2004, Chen et al. (Chen et al., 2004), tested in vitro the susceptibility of 10 isolates of SARS-CoV by commercially available antiviral agents and pure chemical compounds. They also confirmed the antiviral action of glycyrrhizin, together with baicalin, both belonging to the class of flavonoids and extracted from traditional Chinese herbs. These two molecules had been already reported to have also antimicrobial effects. The two molecules showed detectable antiviral activities on foetal rhesus kidney-4 (fRhK-4) infected with the 10 strains (EC_{50} for baicalin at 48 h was from 12.5 to 25 μg/ml). However, their activities showed a decrease after 48 h treatments (Chen et al., 2004).

Among the compound tested, the authors suggested the baicalin for both prophylaxis or treatment SARS-CoV infectious disease. The intravenous administration of a 360 mg dose of that compound in human can achieve an active serum concentration of 74 μg/ml. Despite its mechanism of action against SARS-CoV is not known, regarding HIV-1 infections, baicalin was shown to inhibit the infection process both at cellular entry and through the inhibition of HIV-1 reverse transcriptase. In particular, its binding with the chemokines MIP-1β and SDF-1α prevented the activation of both CCR5 and CXCR4 cellular receptors, which are essential for HIV-1 cellular entry.

In 2003, Cinatl et al. (Cinatl et al., 2003) tested glycyrrhizin against two clinical isolates of SARS-coronaviruses (FFM-1 and FFM-2). The glycyrrhizic acid is a triterpene glycoside extracted from the root of the licorice plant (*Glycyrrhiza glabra*), with many properties such as anti-inflammatory, anti-viral, hepatoprotective and anticancer activities. The authors also showed that the maximum effect of glycyrrhizin (EC_{50} = 300 mg/L) was obtained when administered during and after the viral adsorption in Vero E6 cells, the African green monkey kidney cell line. Despite the glycyrrhizin had never been tested against SARS-COVs infected patients, the administration of the compound effectively decreased the concentrations of P24 antigen and prevented the development of hepatocellular carcinoma in those infected by HIV-1 and chronic hepatitis C virus, respectively (Busia, 2017). Since side-effects were reported after several months of glycyrrhizin treatment, the authors suggested that the treatments should last for a short period. Despite the mechanism of the antiviral activity against SARS-CoV remains unclear, the authors suggested that it could be related to the upregulation of the inducible nitrous oxide synthase and, as a consequence, to the increased production of nitrous oxide that is proposed to be an inhibitor of SARS-CoV replication.

Results on the inhibition of viral adsorption were also found by Keyaerts et al., in 2007 (Keyaerts et al., 2007). The authors analyzed the role of plant lectins against SARS-CoV. Lectins are carbohydrate-binding proteins capable of specific recognition and reversible binding. The specificity of lectins versus different carbohydrates determines their anti-viral properties. Since SARS-CoV spike protein is heavily

glycosylated, the coronavirus infectivity can be inhibited by lectins, that specifically bind to glycans. The screening of many plant lectins tested on Vero E6 cells infected with SARS-CoV (Frankfurt 1 strain) led to the selection of SARS-CoV specific antiviral lectins. The lectins selected in the work included those specifically binding mannose, glucose, galactose, N-acetyl glucosamine and N-acetyl galactosamine. The highest anti-coronavirus activity was found among mannose-specific lectins. In the SARS-CoV spike protein there are 12 N-glycosylation sites. Two of the four sugars attached to four of these N-glycosylation sites were found to be mannose (Keyaerts et al., 2007). The presence of mannose can explain the potent anti-SARS-CoV activity of mannose-specific plant lectins (Keyaerts et al., 2007). To understand how lectins display an antiviral activity the authors used mannose-specific lectin from *Hippeastrum hybrid* agglutinins (HHA) ($EC_{50} < 5$ μg/ml), showing that lectins probably interfere with the glycans of the viral spike protein during both virus adsorption and virus release in the last phase of infection (phase 8 in Fig. 1) (Keyaerts et al., 2007).

Furthermore, in 2012, Keum et al. (Keum & Jeong, 2012) analyzed the activity of viral helicase. Firstly, they focused on the DNA unwinding activity of the helicase protein. In particular, they used the fluorescent resonance energy transfer (FRET) to find out the natural compounds that inhibit the DNA unwinding activity. They mixed the viral helicase protein with fluorescent-labeled double stranded DNA, each strand of which was labeled with different fluorescent dyes, (fluorescein (FAM) and carboxytetramethylrhodamine (TAMRA)) at the same terminus. Therefore, a constant FRET reaction between FAM and TAMRA occurred when the two DNA strands were base-paired; however, this interaction is lost as soon as the duplex is unwound by the viral helicase. Using this experimental approach, they excluded that the 64 natural compounds (that they screened) interfered with the DNA unwinding activity of the viral helicase protein. Subsequently, they examined the possible effects of the 64 natural compounds on the suppression of ATP hydrolysis by viral helicase. The ATP hydrolysis activity of viral helicase was measured using a long circular ssDNA as a template. The viral helicase protein is expected to continuously translocate along the ssDNA, unless the helicase separates from the DNA. The degree of ATP hydrolysis was examined by measuring the release of inorganic phosphate by colorimetric analysis. Usign this last approach, the authors found that two flavonoids, myricetin and scutellarein, inhibited the ATPase activity of the viral helicase (IC_{50} values: 2.71 ± 0.19 μM and 0.86 ± 0.48 μM, respectively), thus impacting on viral replication (Keum & Jeong, 2012).

In 2014, Sun et al. (Sun et al., 2014) tested the sinefungin activity against SARS-CoV. The sinefungin, isolated from *Streptomyces species*, known for its antifungal, antiviral and antiparasitic activity, is able to inhibit DNA methyltransferase. It was demostrated, in a yeast cell system, that sinefungin was more effective against coronavirus RNA guanine-N7-methyltransferase (expressed in *Saccharomyces cerevisiae* strain YBS40) than on human N7-MTase (yeast-based assays for the high-throughput screening of inhibitors of coronavirus RNA cap guanine-N7-methyltransferase) indicating its possible useful effect on the viral replication and subgenome expression (Sun et al., 2014).

Wu et al. (Wu et al., 2004) in 2004, tested many different compounds from traditional Chinese herbs for their activity against SARS-CoV (H.K. strain). Among the herbs tested, aescin, the major active principle of horse chestnut tree (*Aesculus hippocastanum*), and reserpine, an alkaloid produced by several members of the genus *Rauwolfi*, showed anti-SARS-CoV activities in term of reduced cytopathogenic effects in infected Vero E6 cell (EC_{50} values for reserpine and aescin were 6 μM and 3.4 μM, respectively).

These compounds shown protective effect against SARS-CoV without affecting the growth of not infected host cells. The decreased antiviral activity was then evaluated with an immunofluorescence assay to identify the presence of antibodies against viral antigens and with flow cytometry though the analysis of a decrease in the level of the viral spike protein.

Looking for others active compounds in their experiments on infected Vero E6 cells, Wu et al., 2004 found that ginsenoside-Rb1 (a derivative of both glycyrrhizin and aescin), extracted from Panax ginseng and *Lonicera japonica*, has antiviral activity at the concentration of 100 μM (Wu et al., 2004).

It is also important to mention that in 2006 Pyrc et al. (Pyrc et al., 2006), showed no detectable activity for both the glycyrrhizin and aescin against HCoV-NL63.

In 2005, Li et al. (Li et al., 2005) massively screened over 200 medicinal herbs, that were reported as useful against viral infection, looking for possible anti SARS-CoV medicaments. They infected Vero E6 and HepG2 cells, an immortal cell line derived from hepatocellular carcinoma, with two different strains of SARS-CoV (BJ001, BJ006). They found that the extracts *of Lycoris radiata, Artemisia annua, Pyrrosia lingua* and *Lindera aggregata* inhibited in a dose dependent way, the virus cytopathic effects (EC_{50} values of inhibition are 2.4 ± 0.2, 34.5 ± 2.6, 43.2 ± 14.1, and 88.2 ± 7.7 μg/ml, respectively). Because of its efficiency, the authors focused on *Lycoris radiate* extracts, demonstrating that the alkaloid lycorine (Table S1) has a high anti-viral activity (Li et al., 2005). The antiviral activities against SARS-CoV infected cells was evaluated using the MTS vitality assay in comparison with cells that were not infected by the virus. After the addition of active compounds, the viral infection and replication was sharply reduced resulting in and increased cell vitality. Nevertheless, the mechanism of antiviral activity of these active compounds has yet to be define.

In 2005, Chen et al. (Chen, Lin et al., 2005) showed that the tannic acid, 3-isotheaflavin-3-gallate (TF2B) and Theaflavin-3,3′-digallate (TF3) (polyphenols in black tea), selected from the pure Natural Products Library (https://www.nccih.nih.gov/grants/natural-product-libraries), are able to inhibit the 50% of the proteolytic activity of SARS-CoV 3CLpro (expressed in *E. coli*), at concentrations <10 μM ($IC_{50} = 3$, 3.7 and 9.5 μM respectively). Despite the mechanism of action of these extracts was still unknown, the authors suggested that TF2B and TF3 are inhibitors of SARS-CoV 3CLpro more effective than other compounds (i.e TF1) probably for the presence of a gallate group that could have an important role in directing their inhibitory effect against SARS-CoV 3CLpro.

Results on the inhibition role on SARS-CoV 3CLpro were also reported for quercetin-3-β-galactoside by Chen et al. (2006) The authors, though a virtual screening based firstly on molecular docking, found quercetin-3-β-galactoside to be a potent binder to the catalytic pocket of SARS-CoV 3CLpro. Then the results were also confirmed and supported by docking other techniques such as surface plasmon resonance and FRET bioassays but also and mutagenesis studies. Overall, the results showed that Gln189 plays a key role in allowing the binding of quercetin-3-b-galactoside to SARS-CoV 3CLpro. Quercetin is a water-soluble flavonoid that is known to have salutary effects on humans (Li et al., 2016).

In 2012, Park et al. (Park et al., 2012) studied the role of diarylheptanoids isolated from the stem bark of *Alnus japonica* were found to be inhibitors of SARS-CoV PLpro, using a recombinant vector expressed in *E. coli*. Interestingly, at the same concentration, no detectable inhibition of the other Coronavirus protease (3CLpro) was observed. The most effective inhibitor of PLpro was the hirsutenone (IC_{50} value of 4.1 μM). Moreover, differently from the others derivatives, hirsutenone resulted an efficient inhibitor of also the other protease, 3CLpro (IC_{50} value of 36.1 μM). The structure activity analyses revealed that catechol and α, β-unsaturated carbonyl moiety in the molecule were fundamental factors influencing its inhibitory actions against PLpro (Park et al., 2012).

In 2013, Cho et al. (Cho et al., 2013) showed that the 12 flavonoids extracted from *Paulownia tomentosa* have inhibitory activity against SARS-CoV PLpro. To investigate the inhibitory role of the 12 extracted flavonoids against SARS-CoV PLpro, they measured SARS-CoV PLpro activity in the presence or absence of test compounds using a fluorogenic assay. The SARS-CoV PLpro was expressed in *Escherichia coli* and purified by nickel affinity, ion-exchange and gel filtration chromatography.

In SARS-CoV PLpro inhibition assays, all of the 12 compounds tested displayed dose dependent inhibition (IC_{50} 5.0–14.4 μM). Of these, tometins had strong inhibitory activity against SARS-CoV PLpro. Tometins are characterized by a rare 3, 4-dihydro-2H-pyran motif. This structural arrangement was found to be more effective at inhibiting SARS-CoV PLpro enzyme than the parent compounds that were cyclization precursors (Cho et al., 2013).

Lastly, in 2007, Yang et al. (Yang et al., 2007) tested the coumarin anti-viral activity from the perennial plant *Boenninghausenia sessilicarpa*, known to be a coumarin-rich chinese herbal medicine. Coumarin derivatives of *B. sessilicarpa* were tested for antiviral activities in cells infected by SARS-CoV. Among the extracted compounds, leptodactylone showed a potent cell-protective effect and antiviral activity, while rutamarin exhibited weaker activity but the authors did not explain the mechanism of action of these compounds (Yang et al., 2007).

1.9. Natural compounds anti SARS-CoV2

In 2020, Li et al. (Li et al., 2020) performed a bioinformatics analysis to identify existing drugs that could be useful also against SARS-CoV2. In particular, their analysis of the genome sequence of SARS-CoV2 confirmed the higher sequence similarity with SARS-CoV (Zhou et al., 2020) followed by MERS and other human coronaviruses (Li et al., 2020). Using text mining and database searches, the authors identified 34 COVID19 related genes, identifying 24 disease-related human pathways and 78 potential drugs, that could be repurposed. They manually filtered the list of drugs based on their "mechanisms of action", "adverse effects", and "clinical approvals", yielding to a total of 30 drugs (Li et al., 2020). From their collection, we selected 11 natural compounds, (Table S1). Molecules were selected when they met the criteria of being natural, not chemically modified substances, with antiviral effect. For example, based on our criteria, compounds that were excluded are: monoclonal antibodies (like Adalimumab, Infliximab, Ruplizumab, Siltuximab, Ruplizumab, Ibalizumab, Golimumab, Afelimomab), synthetized or semi-synthetized chemical products (like Abacavir, Cefazolin, Epinephrine, Atiprimod, Thalidomide, Chloroquine, Clenbuterol), fusion proteins (like Etanercept), or those acting on the host immune system (like Olsalazine, N-Formylmethionine, Ketoprofen).

Moreover, Zhang et al. in 2020 (Zhang, Wu, et al., 2020), performed a literature search for natural compounds that resulted to be bioactive against SARS-CoV and MERS-CoV. They identified 13 natural compounds that were analyzed by protein structure computational approaches, based on the docking methodology, to identify possible direct interactions with SARS-CoV2 proteins and, therefore, possibly inhibiting their activity (Table 1a) (Zhang, Wu, et al., 2020). Independently, the authors reported the 26 herbs from the Traditional Chinese Medicine Systems Pharmacology database (http://www.tcmspw.com/browse.php?qc=herbs), the Encyclopedia of Traditional Chinese Medicine (http://www.nrc.ac.cn:9090/ETCM/) and SymMap (https://www.symmap.org/) that contained at least two of the natural compounds among those predicted with an antiviral activity, therefore identifying potential effective antiviral active herbs (Table 1b). The authors also evaluated the absorption, distribution, metabolism and excretion of the compounds, after boiling in water and oral assumption, based on the traditional chinese medical treatments (Zhang, Wu, et al., 2020). Since the authors did not list the specific compounds per herb in their work, we re-analyzed the different databases to identify the exact correspondence (Table 1b), so that we could report the complete list also in Table S1. Specifically, starting from the list of the 13 natural compounds identified by the authors we cross-searched for these compounds in the three databases they indicated in their work, i.e. the Traditional Chinese Medicine Systems Pharmacology database (http://www.tcmspw.com/browse.php?qc=herbs), the Encyclopedia of Traditional Chinese Medicine (http://www.nrc.ac.cn:9090/ETCM/) and SymMap (https://www.symmap.org/) that list bioactive compounds per herb. Then we re-associated the compounds to each of the 26 herbal plants

Table 1
Compounds per plant source from Zhang, Lin et al. (2020). a. List of the 13 compounds and their role against hCoVs infection. b. List of the 13 compounds associated to the respective plant sources.

a)	Molecular name	Targets or inhibition
	Betulinic acid	Replication, 3CLpro
	Coumaroyltyramine	PLpro and 3CLpro
	Cryptotanshinone	PLpro and 3CLpro
	Harmonil	Replication, 3CLpro, and entry
	Dihomo-γ-linolenic acid	3CLpro
	Dihydrotanshinone	Entry, and spike protein
	Kaempferol	PLpro and 3CLpro
	Lignan	Replication, 3CLpro
	Moupinamide	PLpro
	N-cis-feruloyltyramine	PLpro and 3CLpro
	Quercetin	PLpro and 3CLpro
	Sugiol	Replication, 3CLpro
	Tanshinone IIa	PLpro and 3CLpro

b)	**Molecular name**	**Targets or inhibition**	**Plants**
	Betulinic acid	Replication, 3CLpro	Peucedani radix - Licorice- Eriobotryae folium - Forsythiae Fructus - Hedysarum multijugum maxim. - Cortex mori - Tamaricis cacumen
	Coumaroyltyramine	PLpro and 3CLpro	Anemarrhenae rhizoma - Rhizoma fagopyri cymosi
	Cryptotanshinone	PLpro and 3CLpro	Herbal plants
	Harmonil	Replication, 3CLpro, and entry	*Fortunes bossfern rhizome*
	Dihomo-γ-linolenic acid	3CLpro	*Lepidii semen descurainiae semen*
	Dihydrotanshinone	Entry, and spike protein	Herbal plants
	Kaempferol	PLpro and 3CLpro	Cortex mori - Tamaricis cacumen - Asteris radix et rhizoma - Ardisiae japonicae herba- Anemarrhenae rhizoma - Radix bupleuri - Licorice - Lepidii semen descurainiae semen - Lonicerae japonicae flos - Inulae flos - Hoveniae dulcis semen - Houttuyniae herba - Ginkgo semen - Forsythiae fructus - Chrysanthemi flos - Floium mori - Farfarae flos - Euphorbiae helioscopiae herba - Eriobotryae folium - Epimrdii herba - Hedysarum multijugum maxim. - Erigeron breviscapus - Fortunes bossfern rhizome - Mori follum
	Lignan	Replication, 3CLpro	Licorice
	Moupinamide	PLpro	Coptidis rhizoma
	N-cis-feruloyltyramine	PLpro and 3CLpro	Peucedani radix
	Quercetin	PLpro and 3CLpro	Cortex mori - Coptidis rhizoma - Tamaricis cacumen - Asteris radix et rhizoma - Ardisiae japonicae herba - Rhizoma fagopyri cymosi - Radix bupleuri - Peucedani radix - Licorice - Lepidii semen descurainiae semen - Lonicerae japonicae flos - Inulae flos - Hoveniae dulcis semen - Houttuyniae herba - Ginkgo semen - Forsythiae fructus - Chrysanthemi flos - Floium mori - Farfarae flos - Euphorbiae helioscopiae herba - Eriobotryae folium - Epimrdii herba - Hedysarum multijugum maxim. - Erigeron breviscapus - Mori follum

(*continued on next page*)

Table 1 (*continued*)

b)	Molecular name	Targets or inhibition	Plants
	Sugiol	Replication, 3CLpro	Herbal plants
	Tanshinone IIa	PLpro and 3CLpro	Peucedani radix

identified in the work by Zhang, Wu, et al. (2020), and, therefore, we could report the compound and the corresponding herbal plants (Table 1b).

Moreover, in 2020, Wu et al. (Wu et al., 2020) analyzed all the proteins encoded by SARS-CoV2 genes, and predicted their structures by homology modeling. They identified a total of 21 targets (19 viral and 2 human targets) that were screened against an in house built database of 1066 natural products from traditional chinese herbs. In particular, they focused on 3CLpro, Spike, RNA-dependent RNA polymerase (RdRp) and PLpro, and identified 89 natural compounds potentially useful against SARS-CoV2 (Wu et al., 2020).

Last, in 2020, Islam et al. (Islam et al., 2020) provided a list of 123 natural compounds useful against CoVs infections. Thanks to a massive research with proper keywords in articles from public literature databases, they considered studies on crude extracts, fractions or preparations from plants, microorganisms or marine species, that demonstrated an action against CoVs. They excluded data duplication and titles or contents that did not meet the criteria of showing anti-viral activities against CoVs (Islam et al., 2020). From their list we selected the 78 natural compounds that act on the virus absorption and replication, among which 64 were new in our collection (Table S1).

1.10. Safety and clinical trials

Although it is not the main aim of this work, it is worthy to underline in this context that also for NPs the development of a new treatment, medicine, or any employment in food industry requires assessments of compounds safety, which is an important issue to be addressed in drug development and the cause of drug candidate attrition in the biopharmaceutical industry. Decision of any employment can only be made if both benefits and risks are addressed. The aim of safety tests, indeed, is to improve risk-benefit assessment at all stages of drug development (Roberts, 2018). Internationally accepted guidelines were developed to monitor drugs, foods and also environmental contaminants for adverse reactions and toxicity and to ensure their safety.

A drug's disposition depends upon the absorption process from a dosing site, the distribution to target and other systemic and peripheral tissues, and the elimination of unchanged drug by metabolism or excretion. These processes interact to characterize a drug by its pharmacokinetic profile and any alteration will have an impact on the drug safety and efficacy. Therefore, methods were developed by pharmaceutical chemists to predict drug absorption, distribution, metabolism, interaction and also the excretion of unchanged drug and the effect with potential adverse outcomes, thus compromising a drug's safety profile (Roberts, 2018).

The current preclinical tests used were determined 30 years ago by OECD and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) that indicated the guidelines for toxicity testing of pharmaceutical compounds to ensuring human drug safety (Guideline & others, 2009).

Over the past decades, efforts have been done by the pharmaceutical industry to the development, evaluation, and implementation of in vitro alternatives to animal testing in the hazard identification and risk assessment of preclinical drug candidates (Goh et al., 2015).

The safety assessment of drugs requires first testing in toxicology species prior to human studies (Guideline & others, 2009). Toxicological assessment and translational of toxicity data from animal species to human are often challenged since it was suggested that 70% of human-relevant toxicities are identified in toxicology species (Olson et al., 2000).

Although the detection of toxicity is dependent by organ and species, its absence in two different species is strongly predictive of the absence of toxicity in humans. In general, human adverse drug reaction (ADR) is associated mainly to hepatic, cardiovascular and neurological toxicities (Olson et al., 2000).

Drug-drug interaction (DDI) constitutes one of the potential mechanisms leading to often preventable ADR and health damage. In fact, multiple drug therapies are very common for the treatment of various medical illnesses thus being a potential source of DDI and of drug failure (Edwards & Aronson, 2000).

Thus, the understanding of the on-and off-target mechanisms that are responsible of ADR give the opportunity to evaluate target organ toxicity earlier in drug discovery and with a greater specificity.

Safety is also inherent the use of NP from raw materials for food formulation regarding their origin and synergy among ingredients (Abdel-Rahman et al., 2011). In the past years, the food industry has been involved in monitoring the NP safety on the market, supported by the US Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA). Such organizations act as a scientific guarantor in deciding what NPs are safe to be used as food.

Drug safety assessments in clinical trials involve experiments on humans, where a selected group of individuals is given the investigational product, generating crucial safety and efficacy data.

Among the compounds listed in Table S1, 19 are already included in the clinical trials database, ClinicalTrials.gov, for their exploitation as antiviral compounds (https://clinicaltrials.gov/) (Table S1). Among these, only the tannic acid, the curcumin and the aescin have been selected to undergo clinical trials for testing their efficacy in patients affected by human coronaviruses. In particular, they are all being tested for their efficacy against SARS-CoV2. In the randomized controlled trial on tannin specific natural extract (NCT04403646), the molecular complex ARBOX, composed by quebracho, Vit B12 and chestnut tannins extracts, is being tested as a dietary supplement in patient infected by SARS-CoV2 in addition to the conventional standard therapy (including antipyretics or lopinavir/ritonavir, azithromycin and hydroxychloroquine).

As for the tannin extracts, another ongoing trial using the compound aescin (NCT04322344) aims to evaluate its efficacy and safety as an adjuvant to conventional antiviral drugs in COVID-19 patients.

Another clinical trial started on May 8, 2020 exploiting a medical spray containing curcumin (20 mg/ml), artemisinin (6 mg/ml), frankincense (15 mg/ml) -and vitamin C (60 mg/ml) in micellar formulation against SARS-CoV2 infections (Table S1).

Moreover, on May 19th a clinical trails (NCT04394182) on patients affected by COVID-19 has started. In this trial, an experimental group with a poor or no response to standard medical treatment and without invasive mechanical ventilation are planned to receive an ultra low-dose lung radiotherapy (0.8 Gy single dose) in addiction with different drugs (including Piperacillin/tazobactam).

Furthermore, a clinical trial started on March 5 (NCT04308317), planned to combine the use of the tetrandrine (60 mg once a day), in tablets form, with the standard treatment of mild and severe neocoronary pneumonia. The aim is the slowing down the progress of the disease and therefore the improvement of patients' prognosis. All the information on these ongoing efforts is crosslinked with our collection in Table S1.

2. Discussion

Despite advances in prevention, immunotherapy and drug development, some infectious diseases still require effective vaccines or efficient antiviral therapies. As an example, coronaviruses, including SARS-CoV2 (Zhou et al., 2020), that is causing the current pandemic disease,

COVID19, as well as the other two epidemic coronaviruses, SARS (Rota et al., 2003) and MERS (Zaki et al., 2012), together with other coronaviruses, do not have suitable therapies or preventive treatments yet (Sanders et al., 2020). Therefore, the identification of appropriate antiviral effectors for drugs and food design is of fundamental importance to fight the COVID19 disease and all its side effects, to be ready for possible future challenges that can be determined by coronaviruses attacks (Osterholm, 2005).

Natural products (NPs) are compounds found in nature and synthesized by living organisms, that can be revealed to be potential bioactive compounds useful in drug discovery and food sciences (Kaplan et al., 1986; Noroozi et al., 1998; Rahman & Chung, 2010). According to their biological or pharmacological activities, they can act at intracellular (Harvey & Cree, 2010), as well as at extracellular levels (Orlikova et al., 2014), providing useful tools for treatments of infectious disease (Balunas & Kinghorn, 2005). NPs can target pathogen-host interaction or pathogen life cycle, inhibiting the infection, or behave as natural effectors that could ameliorate host health and, eventually, host resistance to the pathogen attack.

We performed a desk research and identified all natural compounds that appeared to inhibit human coronaviruses infections, as revealed by in vitro experiments, or predicted by in silico analyses (Table S1). Collecting information from several different reports, we selected the compounds that met the criteria of being natural, not chemically modified substances, and of being effective on one or more phases determining viral absorption and replication (Fig. 1) (de Wit et al., 2016), being therefore useful for the development of targeted pharmacological treatments or the identification of useful ingredients and additives that could favour proper food selection or its design.

We merged all the compounds from different species, or eventually active on different phases, or selected from different scientific efforts, into a unique list of 174 natural products, indicating all the relevant information and annotating the specific targets according to the viral replication cycle, when known, as well as the compound chemical classification (Table S1).

The compounds resulted to be all from plants, with the exception of framycetin and sinefungin from *Streptomyces*. All compounds were classified to be secondary metabolites, with major classes being represented by Flavonoids (48 compounds), Terpenes (32 compounds), Xanthenes (13 compounds), Alkaloids (9 compounds), Quinones (2 compounds).

In Fig. 2, we summarized the total amount of different classes per viral life cycle phase, also highlighting the classes representing the compounds acting on multiple phases (Fig. 2). It is evident that no active compounds were revealed for phases 2 (release of viral genome) and 3 (translation of polyproteins). All the details on specific compounds can be derived from Table S1 or consulting the website we organized to share the data in a user friendly accessible resource (https://bigdatainhealth.org/letsbe/anti-HCoV.php).

Among the different phases, as an example, phase 1 (receptor binding and viral entry) is the most critical for the overall infective process (Fig. 1). Among the different events that occur in this phase, we could find compounds that inhibit the Spike protein on the virus coat from interacting with the host receptor on the human cell membrane. Most representative classes acting against this phase are: Terpenes (3), Quinones (2) and Flavonoids (1) (Fig. 2 and Table S1). Chrysin (Islam et al., 2020) Cosmosiin (Wu et al., 2020) Luteolin (Islam et al., 2020) Neohesperidin (Wu et al., 2020), all belonging to the flavonoid class, were detected to be active in this phase but also on the autoproteolytic activation (phase 4) (Table S1).

Harmonyl, an alkaloid, appeared to be the only compound that could act on phase 1 and also on other two phases: the autoproteolytic activation and the genomic RNA replication. This action was revealed by an in silico prediction (Zhang, Lin et al., 2020) and, therefore, further experiment could reveal the effective multi target action of harmonyl against viral replication.

All the remaining compounds and target phases can be further investigated considering Table S1, in which we also indicated links to the ClinicalTrial.gov (https://clinicaltrials.gov/), to provide information on compounds under clinical trials. For a friendly consulting and further investigations, all the compounds here described, endowed with the respective accessory information, are available also through anti-HCoVS, a dedicated web based resource, available at https://bigdatainhealth.org/letsbe/anti-HCoV.php. This resource was designed to offer

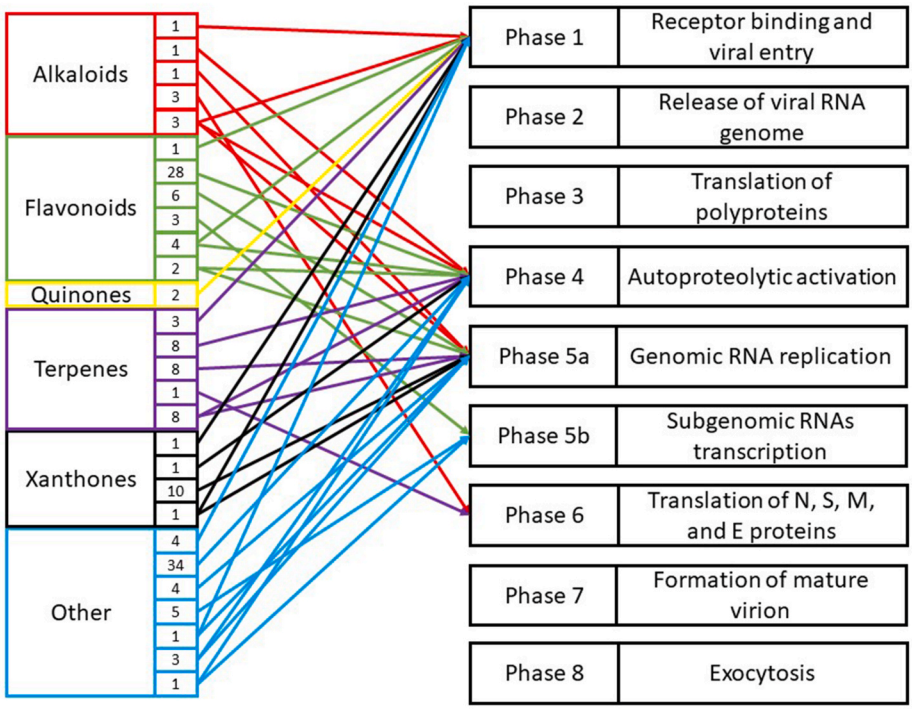

Fig. 2. Number of chemical classes per viral life cycle phases.

a comprehensive collection of natural compounds that resulted effective against human coronaviruses. The goal was to define a collection of natural compounds documented to be effective in coronaviruses absorption and replication. All data can be friendly searchable and all references are also crosslinked to the respective journal website. Moreover, compounds that can have multiple purposes can be easily identified, supporting validation of possible efficacy on multiple targets, but also to proof specificity of action.

3. Conclusion and future perspectives

We launched antiHCoV as a reference collection of natural compounds to be exploited against coronaviruses epidemics.

While expanding the collection to consider the host side perspective, the current resource aimed to collect all known compounds effective for natural treatments and proper food selection and design because of their action against viral absorption and replication. We annotated those that were in vitro tested and those predicted by computational analysis. We highlighted the action in the different viral life cycle phases also to identify compounds that could inhibit the absorption, since this is one of the major target that could help to fight the current and prevent the possible future coronaviral infections.

We aim to expand this collection with additional information on future results from novel testing and trials, enriching the dataset with more upcoming compounds, also relying on a possible community based support.

Formatting of funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The Emanuela Palomba PhD fellowship is founded by Stazione Zoologica Anton Dohrn (Italy) and by NOSELF s.r.l (https://www.noself.it/).

Francesco Monticolo is supported by a PhD fellowship founded by the Department of Agricultural Sciences, Università degli studi di Napoli Federico II.

University students under thesis gave their useful contribution to this community based collaborative effort with enthusiasm and this is why they are considered co-authors in the effort.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tifs.2020.09.007.

Coronavirus invasion starts with the interaction of the spike glycoprotein (S) on the viral coat with the receptor on the host cell membrane. The virus entry occurs through fusion with the host cell plasma membrane or by endocytosis (Phase 1: receptor binding and viral entry).

The viral RNA genome is released into the cytoplasm (Phase 2: release of viral RNA genome).

Translation of the viral genomic RNA produces two large polyproteins (Phase 3: translation of polyproteins) that undergo autoproteolytic processing performed by papain-like protease (PLPro) and 3C-like protease (3CLPro) to generate the constituents of the replication/transcription complex (RTC) (Phase 4: autoprotoeolytic activation). The RNA-dependent RNA polymerase, the key enzyme in the RTC, transcribes a newly synthesized full-length RNA genome (Phase 5a: genomic RNA replication) and subgenome RNAs (Phase 5b: subgenomic RNAs transcription). Translation of subgenomic RNAs gives rise to structural viral proteins (N, S, M and E) (Phase 6: translation of N, S, M, E proteins). The newly produced genomic RNA is encapsidated with the N proteins to form the nucleocapsid (N). The S, membrane (M) and envelope (E) proteins are inserted into the membrane of the rough endoplasmic reticulum (RER), transported to the ER–Golgi intermediate compartment (ERGIC) from where they combine with the RNA-encapsidated N proteins for the production of mature virions (Phase 7: formation of mature virion). Virus assembly occurs within Golgi vesicles, followed by virus release by fusion of virion-containing vesicles with the plasma membrane (Phase 8: exocytosis).

Image adapted from (de Wit et al., 2016).

Number of compounds per main chemical classes of natural compounds are indicated per phase of viral life cycle.

Compound name, their chemical Classification, their Source, their Phase of action according to Fig. 1, their target and methods of identification (In silico or In vitro) and, in case, Cell lines, Clinical trial number are indicated.

Note: the classification was obtained using PubChem (https://pubchem.ncbi.nlm.nih.gov/).

All compounds not present in PubChem are indicated with an index referring to the bibliographics reference necessary for the classification: (Buckingham & Munasinghe, 2015; Chang et al., 2012; Chen et al., 2005; Dai et al., 2015; González, 2015; Lipson et al., 2015; Mao et al., 2016; Rana & Rawat, 2005; Song et al., 2019; Torres et al., 2010; Ullah et al., 2018; Wan et al., 2013; Xu et al., 2015), website: https://www.medchemexpress.com.

References

Abdel-Rahman, A., Anyangwe, N., Carlacci, L., Casper, S., Danam, R. P., Enongene, E., Erives, G., Fabricant, D., Gudi, R., Hilmas, C. J., Hines, F., Howard, P., Levy, D., Lin, Y., Moore, R. J., Pfeiler, E., Thurmond, T. S., Turujman, S., & Walker, N. J. (2011). The safety and regulation of natural products used as foods and food ingredients. *Toxicological Sciences: An Official Journal of the Society of Toxicology, 123* (2), 333–348. https://doi.org/10.1093/toxsci/kfr198

Azhar, E. I., El-Kafrawy, S. A., Farraj, S. A., Hassan, A. M., Al-Saeed, M. S., Hashem, A. M., & Madani, T. A. (2014). Evidence for camel-to-human transmission of MERS coronavirus. *New England Journal of Medicine, 370*(26), 2499–2505. https://doi.org/10.1056/NEJMoa1401505

Baba, M., Okamoto, M., Kashiwaba, N., & Ono, M. (2001). Anti-HIV-1 activity and structure-activity relationship of cepharanoline derivatives in chronically infected cells. *Antiviral Chemistry & Chemotherapy, 12*(5), 307–312. https://doi.org/10.1177/095632020101200506

Baek, S. H., Ko, J.-H., Lee, H., Jung, J., Kong, M., Lee, J., Lee, J., Chinnathambi, A., Zayed, M. E., Alharbi, S. A., Lee, S.-G., Shim, B. S., Sethi, G., Kim, S.-H., Yang, W. M., Um, J.-Y., & Ahn, K. S. (2016). Resveratrol inhibits STAT3 signaling pathway through the induction of SOCS-1: Role in apoptosis induction and radiosensitization in head and neck tumor cells. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology, 23*(5), 566–577. https://doi.org/10.1016/j.phymed.2016.02.011

Balasuriya, N., & Rupasinghe, H. P. V. (2010). Plant flavonoids as angitensin converting enzyme inhibitors in regulation of hypertension. *Funct Foods Health Dis, 5*. https://doi.org/10.31989/ffhd.v1i5.132

Balunas, M. J., & Kinghorn, A. D. (2005). Drug discovery from medicinal plants. *Life Sciences, 78*(5), 431–441. https://doi.org/10.1016/j.lfs.2005.09.012

Bergmann, C., Lane, T., & Stohlman, S. (2006). Coronavirus infection of the central nervous system: Host-virus stand-off. *Nature Reviews Microbiology, 4*, 121–132. https://doi.org/10.1038/nrmicro1343

Buckingham, J., & Munasinghe, V. R. N. (2015). *Dictionary of flavonoids with CD-ROM*. CRC Press. https://books.google.it/books?id=jFW3BgAAQBAJ.

Busia, K. (2017). Fundamentals of herbal medicine: Major plant families, analytical methods. *Materia Medica, 2*.

Chang, F.-R., Yen, C.-T., Ei-Shazly, M., Lin, W.-H., Yen, M.-H., Lin, K.-H., & Wu, Y.-C. (2012). Anti-human coronavirus (anti-HCoV) triterpenoids from the leaves of Euphorbia neriifolia. *Natural Product Communications, 7*(11), 1415–1417.

Chan, J. F.-W., Kok, K.-H., Zhu, Z., Chu, H., To, K. K.-W., Yuan, S., & Yuen, K.-Y. (2020). Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections, 9*(1), 221–236. https://doi.org/10.1080/22221751.2020.1719902

Chen, F., Chan, K. H., Jiang, Y., Kao, R. Y. T., Lu, H. T., Fan, K. W., Cheng, V. C. C., Tsui, W. H. W., Hung, I. F. N., Lee, T. S. W., Guan, Y., Peiris, J. S. M., & Yuen, K. Y. (2004). In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *Journal of Clinical Virology: The Official Publication of the Pan American Society for Clinical Virology, 31*(1), 69–75. https://doi.org/10.1016/j.jcv.2004.03.003

Chen, L., Li, J., Luo, C., Liu, H., Xu, W., Chen, G., Liew, O. W., Zhu, W., Puah, C. M., Shen, X., & Jiang, H. (2006). Binding interaction of quercetin-3-beta-galactoside and its synthetic derivatives with SARS-CoV 3CL(pro): Structure-activity relationship studies reveal salient pharmacophore features. *Bioorganic & Medicinal Chemistry, 14* (24), 8295–8306. https://doi.org/10.1016/j.bmc.2006.09.014

Chen, C.-N., Lin, C. P. C., Huang, K.-K., Chen, W.-C., Hsieh, H.-P., Liang, P.-H., & Hsu, J. T.-A. (2005). Inhibition of SARS-CoV 3C-like protease activity by theaflavin-3,3'-digallate (TF3). *Evidence-based Complementary and Alternative Medicine: ECAM, 2*(2), 209–215. https://doi.org/10.1093/ecam/neh081

Chen, Y., Liu, Q., & Guo, D. (2020). Emerging coronaviruses: Genome structure, replication, and pathogenesis. *Journal of Medical Virology, 92*(4), 418–423. https://doi.org/10.1002/jmv.25681

Chen, J. T., Wesley, R., Shamburek, R. D., Pucino, F., & Csako, G. (2005). Meta-analysis of natural therapies for hyperlipidemia: Plant sterols and stanols versus policosanol. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 25*(2), 171–183. https://doi.org/10.1592/phco.25.2.171.56942

Cho, J. K., Curtis-Long, M. J., Lee, K. H., Kim, D. W., Ryu, H. W., Yuk, H. J., & Park, K. H. (2013). Geranylated flavonoids displaying SARS-CoV papain-like protease inhibition from the fruits of Paulownia tomentosa. *Bioorganic & Medicinal Chemistry, 21*(11), 3051–3057. https://doi.org/10.1016/j.bmc.2013.03.027

Cinatl, J., Morgenstern, B., Bauer, G., Chandra, P., Rabenau, H., & Doerr, H. W. (2003). Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *Lancet (London, England), 361*(9374), 2045–2046. https://doi.org/10.1016/s0140-6736(03)13615-x

Connell, B. J., Chang, S.-Y., Prakash, E., Yousfi, R., Mohan, V., Posch, W., Wilflingseder, D., Moog, C., Kodama, E. N., Clayette, P., & Lortat-Jacob, H. (2016). A cinnamon-derived procyanidin compound displays anti-HIV-1 activity by blocking heparan sulfate- and Co-receptor- binding sites on gp120 and reverses T cell exhaustion via impeding tim-3 and PD-1 upregulation. *PloS One, 11*(10), Article e0165386. https://doi.org/10.1371/journal.pone.0165386

Cordell, G. A., Quinn-Beattie, M. L., & Farnsworth, N. R. (2001). The potential of alkaloids in drug discovery. *Phytotherapy Research: PT, 15*(3), 183–205. https://doi.org/10.1002/ptr.890

Dai, J.-J., Tao, H.-M., Min, Q.-X., & Zhu, Q.-H. (2015). Anti-hepatitis B virus activities of friedelolactones from Viola diffusa Ging. *Phytomedicine, 22*(7), 724–729. https://doi.org/10.1016/j.phymed.2015.05.001

Edwards, I. R., & Aronson, J. K. (2000). Adverse drug reactions: Definitions, diagnosis, and management. *Lancet (London, England), 356*(9237), 1255–1259. https://doi.org/10.1016/S0140-6736(00)02799-9

Gamet-Payrastre, L., Li, P., Lumeau, S., Cassar, G., Dupont, M. A., Chevolleau, S., Gasc, N., Tulliez, J., & Tercé, F. (2000). Sulforaphane, a naturally occurring isothiocyanate, induces cell cycle arrest and apoptosis in HT29 human colon cancer cells. *Cancer Research, 60*(5), 1426–1433.

Gao, Q., Yuan, Y., Gan, H.-Z., & Peng, Q. (2015). Resveratrol inhibits the hedgehog signaling pathway and epithelial-mesenchymal transition and suppresses gastric cancer invasion and metastasis. *Oncology Letters, 9*(5), 2381–2387. https://doi.org/10.3892/ol.2015.2988

Goh, J.-Y., Weaver, R. J., Dixon, L., Platt, N. J., & Roberts, R. A. (2015). Development and use of in vitro alternatives to animal testing by the pharmaceutical industry 1980–2013. *Toxicology Research, 4*(5), 1297–1307. https://doi.org/10.1039/c5tx00123d

González, M. A. (2015). Aromatic abietane diterpenoids: Their biological activity and synthesis. *Natural Product Reports, 32*(5), 684–704. https://doi.org/10.1039/c4np00110a

Guideline, I. H. T., & others. (2009). *ICH guideline M3 (R2) on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals.* ICH, European Medicines Agency.

Harvey, A. L., & Cree, I. A. (2010). High-throughput screening of natural products for cancer therapy. *Planta Medica, 76*(11), 1080–1086. https://doi.org/10.1055/s-0030-1250162

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., … Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell, 181*(2), 271–280. https://doi.org/10.1016/j.cell.2020.02.052

Hu, S., Dutt, J., Zhao, T., & Foster, C. S. (1997). Tetrandrine potently inhibits herpes simplex virus type-1-induced keratitis in BALB/c mice. *Ocular Immunology and Inflammation, 5*(3), 173–180. https://doi.org/10.3109/09273949709116892

Islam, M., Sarkar, C., El-Kersh, D., Jamaddar, S., Uddin, S., Shilpi, J., & Mubarak, M. (2020). Natural products and their derivatives against coronavirus: A review of the non-clinical and pre-clinical data. *Phytotherapy Research*, 1–22. https://doi.org/10.1002/ptr.6700

Kaplan, M. M., Alling, D. W., Zimmerman, H. J., Wolfe, H. J., Sepersky, R. A., Hirsch, G. S., Elta, G. H., Glick, K. A., & Eagen, K. A. (1986). A prospective trial of colchicine for primary biliary cirrhosis. *New England Journal of Medicine, 315*(23), 1448–1454. https://doi.org/10.1056/NEJM198612043152304

Keum, Y.-S., & Jeong, Y.-J. (2012). Development of chemical inhibitors of the SARS coronavirus: Viral helicase as a potential target. *Biochemical Pharmacology, 84*(10), 1351–1358. https://doi.org/10.1016/j.bcp.2012.08.012

Keyaerts, E., Vijgen, L., Pannecouque, C., Van Damme, E., Peumans, W., Egberink, H., Balzarini, J., & Van Ranst, M. (2007). Plant lectins are potent inhibitors of coronaviruses by interfering with two targets in the viral replication cycle. *Antiviral Research, 75*(3), 179–187. https://doi.org/10.1016/j.antiviral.2007.03.003

Kim, D. E., Min, J. S., Jang, M. S., Lee, J. Y., Shin, Y. S., Song, J. H., Kim, H. R., Kim, S., Jin, Y.-H., & Kwon, S. (2019). Natural bis-benzylisoquinoline alkaloids-tetrandrine, fangchinoline, and cepharanthine, inhibit human coronavirus OC43 infection of MRC-5 human lung cells. *Biomolecules, 9*(11). https://doi.org/10.3390/biom9110696

Korkina, L., Kostyuk, V., De Luca, C., & Pastore, S. (2011). Plant phenylpropanoids as emerging anti-inflammatory agents. *Mini Reviews in Medicinal Chemistry, 11*(10), 823–835. https://doi.org/10.2174/138955711796575489

Li, W., Cao, L., Chen, X., Lei, J., & Ma, Q. (2016). Resveratrol inhibits hypoxia-driven ROS-induced invasive and migratory ability of pancreatic cancer cells via suppression of the Hedgehog signaling pathway. *Oncology Reports, 35*(3), 1718–1726. https://doi.org/10.3892/or.2015.4504

Li, S.-Y., Chen, C., Zhang, H.-Q., Guo, H.-Y., Wang, H., Wang, L., Zhang, X., Hua, S.-N., Yu, J., Xiao, P.-G., Li, R.-S., & Tan, X. (2005). Identification of natural compounds with antiviral activities against SARS-associated coronavirus. *Antiviral Research, 67*(1), 18–23. https://doi.org/10.1016/j.antiviral.2005.02.007

Lin, S.-C., Ho, C.-T., Chuo, W.-H., Li, S., Wang, T. T., & Lin, C.-C. (2017). Effective inhibition of MERS-CoV infection by resveratrol. *BMC Infectious Diseases, 17*(1), 144. https://doi.org/10.1186/s12879-017-2253-8

Lin, L.-T., Hsu, W.-C., & Lin, C.-C. (2014). Antiviral natural products and herbal medicines. *Journal of Traditional and Complementary Medicine, 4*(1), 24–35. https://doi.org/10.4103/2225-4110.124335

Liou, J.-T., Chen, Z.-Y., Ho, L.-J., Yang, S.-P., Chang, D.-M., Liang, C.-C., & Lai, J.-H. (2008). Differential effects of triptolide and tetrandrine on activation of COX-2, NF-kappaB, and AP-1 and virus production in dengue virus-infected human lung cells. *European Journal of Pharmacology, 589*(1–3), 288–298. https://doi.org/10.1016/j.ejphar.2008.04.056

Lipson, S. M., Ozen, F. S., Louis, S., & Karthikeyan, L. (2015). Comparison of α-glucosyl hesperidin of citrus fruits and epigallocatechin gallate of green tea on the Loss of Rotavirus Infectivity in Cell Culture. *Frontiers in Microbiology, 6*, 359. https://doi.org/10.3389/fmicb.2015.00359

Liu, M., & Liu, F. (2011). Resveratrol inhibits mTOR signaling by targeting DEPTOR. *Communicative & Integrative Biology, 4*(4), 382–384. https://doi.org/10.4161/cib.4.4.15309

Liu, X., Wang, Y., Zhang, M., Li, G., & Cen, Y. (2004). [Study on the inhibitory effect of cepharanthine on herpes simplex type-1 virus (HSV-1) in vitro]. *Zhong yao cai = Zhongyaocai = Journal of Chinese medicinal materials, 27*(2), 107–110.

Liu, Y., Zhou, J., Qu, Y., Yang, X., Shi, G., Wang, X., Hong, Y., Drlica, K., & Zhao, X. (2016). Resveratrol antagonizes antimicrobial lethality and stimulates recovery of bacterial mutants. *PloS One, 11*(4), Article e0153023. https://doi.org/10.1371/journal.pone.0153023

Li, B., Wang, Z., Li, S., Donelan, W., Wang, X., Cui, T., & Tang, D. (2013). Preparation of lactose-free pasteurized milk with a recombinant thermostable β-glucosidase from Pyrococcus furiosus. *BMC Biotechnology, 13*, 73. https://doi.org/10.1186/1472-6750-13-73

Li, Y., Yao, J., Han, C., Yang, J., Chaudhry, M. T., Wang, S., Liu, H., & Yin, Y. (2016). Quercetin, inflammation and immunity. *Nutrients, 8*(3), 167. https://doi.org/10.3390/nu8030167

Li, X., Yu, J., Zhang, Z., Ren, J., Peluffo, A., Zhang, W., Zhao, Y., Yan, K., Cohen, D., & Wang, W. (2020). *Network bioinformatics analysis provides insight into drug repurposing for COVID-2019*. https://doi.org/10.20944/preprints202003.0286.v1

Lobo-Ruiz, A., & Tulla-Puche, J. (2018). 2 - synthetic approaches of naturally and rationally designed peptides and peptidomimetics. In S. Koutsopoulos (Ed.), *Peptide applications in biomedicine, biotechnology and bioengineering* (pp. 23–49). Woodhead Publishing. https://doi.org/10.1016/B978-0-08-100736-5.00002-8.

Mao, X., Wu, L.-F., Guo, H.-L., Chen, W.-J., Cui, Y.-P., Qi, Q., Li, S., Liang, W.-Y., Yang, G.-H., Shao, Y.-Y., Zhu, D., She, G.-M., You, Y., & Zhang, L.-Z. (2016). The genus Phyllanthus: An ethnopharmacological, phytochemical, and pharmacological review. *Evidence-based Complementary and Alternative Medicine: ECAM, 2016*, 7584952. https://doi.org/10.1155/2016/7584952

Noroozi, M., Angerson, W. J., & Lean, M. E. (1998). Effects of flavonoids and vitamin C on oxidative DNA damage to human lymphocytes. *American Journal of Clinical Nutrition, 67*(6), 1210–1218. https://doi.org/10.1093/ajcn/67.6.1210

Olson, H., Betton, G., Robinson, D., Thomas, K., Monro, A., Kolaja, G., Lilly, P., Sanders, J., Sipes, G., Bracken, W., Dorato, M., Van Deun, K., Smith, P., Berger, B., & Heller, A. (2000). Concordance of the toxicity of pharmaceuticals in humans and in animals. *Regulatory Toxicology and Pharmacology: Regulatory Toxicology and Pharmacology, 32*(1), 56–67. https://doi.org/10.1006/rtph.2000.1399

Orlikova, B., Legrand, N., Panning, J., Dicato, M., & Diederich, M. (2014). Anti-inflammatory and anticancer drugs from nature. *Cancer Treatment and Research, 159*, 123–143. https://doi.org/10.1007/978-3-642-38007-5_8

Osbourn, A. E., & Lanzotti, V. (2009). *Plant-derived natural products: Synthesis, function, and application*. Springer. https://doi.org/10.1007/978-0-387-85498-4

Osterholm, M. T. (2005). Preparing for the next pandemic. *New England Journal of Medicine, 352*(18), 1839–1842. https://doi.org/10.1056/NEJMp058068

Pal, A., Kamthania, M., & Kumar, A. (2014). Bioactive compounds and properties of seaweeds—a review. *Open Access Library Journal, 1*. https://doi.org/10.4236/oalib.1100752

Park, J.-Y., Jeong, H., Kim, J., Kim, Y., Park, S. C., Kim, D., Park, K., Lee, W., & Ryu, Y. (2012). Diarylheptanoids from Alnus japonica inhibit papain-like protease of severe acute respiratory syndrome coronavirus. *Biological and Pharmaceutical Bulletin, 35*. https://doi.org/10.1248/bpb.b12-00623

Park, J.-Y., Yuk, H. J., Ryu, H. W., Lim, S. H., Kim, K. S., Park, K. H., Ryu, Y. B., & Lee, W. S. (2017). Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protease inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry, 32*(1), 504–515. https://doi.org/10.1080/14756366.2016.1265519

Pietra, F. (1997). Secondary metabolites from marine microorganisms: Bacteria{,} protozoa{,} algae and fungi. Achievements and prospects. *Natural Product Reports, 14*(5), 453–464. https://doi.org/10.1039/NP9971400453

Pietta, P. G. (2000). Flavonoids as antioxidants. *Journal of Natural Products, 63*(7), 1035–1042. https://doi.org/10.1021/np9904509

Praditya, D., Kirchhoff, L., Brüning, J., Rachmawati, H., Steinmann, J., & Steinmann, E. (2019). Anti-infective properties of the golden spice curcumin. *Frontiers in Microbiology, 10*, 912. https://doi.org/10.3389/fmicb.2019.00912

Procópio, R. E. de L., Silva, I. R. da, Martins, M. K., Azevedo, J. L. de, & Araújo, J. M. de (2012). Antibiotics produced by Streptomyces. *Brazilian Journal of Infectious Diseases: An Official Publication of the Brazilian Society of Infectious Diseases, 16*(5), 466–471. https://doi.org/10.1016/j.bjid.2012.08.014

Pyrc, K., Bosch, B. J., Berkhout, B., Jebbink, M. F., Dijkman, R., Rottier, P., & van der Hoek, L. (2006). Inhibition of human coronavirus NL63 infection at early stages of the replication cycle. *Antimicrobial Agents and Chemotherapy, 50*(6), 2000–2008. https://doi.org/10.1128/AAC.01598-05

Rahman, I., & Chung, S. (2010). Dietary polyphenols, deacetylases and chromatin remodeling in inflammation. *Journal of Nutrigenetics and Nutrigenomics, 3*(4–6), 220–230. https://doi.org/10.1159/000324358

Raj, V. S., Mou, H., Smits, S. L., Dekkers, D. H. W., Müller, M. A., Dijkman, R., Muth, D., Demmers, J. A. A., Zaki, A., Fouchier, R. A. M., Thiel, V., Drosten, C., Rottier, P. J. M., Osterhaus, A. D. M. E., Bosch, B. J., & Haagmans, B. L. (2013). Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature, 495*(7440), 251–254. https://doi.org/10.1038/nature12005

Rana, V. S., & Rawat, M. S. M. (2005). A new xanthone glycoside and antioxidant constituents from the rhizomes of Swertia speciosa. *Chemistry and Biodiversity, 2*(10), 1310–1315. https://doi.org/10.1002/cbdv.200590102

Reed, D., Raina, K., & Agarwal, R. (2018). Nutraceuticals in prostate cancer therapeutic strategies and their neo-adjuvant use in diverse populations. *NPJ Precision Oncology, 2*, 15. https://doi.org/10.1038/s41698-018-0058-x

Riva, S., & Silvestri, L. G. (1972). Rifamycins: A general view. *Annual Review of Microbiology, 26*, 199–224. https://doi.org/10.1146/annurev.mi.26.100172.001215

Roberts, R. A. (2018). Understanding drug targets: No such thing as bad news. *Drug Discovery Today, 23*(12), 1925–1928. https://doi.org/10.1016/j.drudis.2018.05.028

Rota, P. A., Oberste, M. S., Monroe, S. S., Nix, W. A., Campagnoli, R., Icenogle, J. P., Peñaranda, S., Bankamp, B., Maher, K., Chen, M.-H., Tong, S., Tamin, A., Lowe, L., Frace, M., DeRisi, J. L., Chen, Q., Wang, D., Erdman, D. D., Peret, T. C. T., … Bellini, W. J. (2003). Characterization of a novel coronavirus associated with severe acute respiratory syndrome. *Science (New York, N.Y.), 300*(5624), 1394–1399. https://doi.org/10.1126/science.1085952

Saito, A. Y., Marin Rodriguez, A. A., Menchaca Vega, D. S., Sussmann, R. A. C., Kimura, E. A., & Katzin, A. M. (2016). Antimalarial activity of the terpene nerolidol. *International Journal of Antimicrobial Agents, 48*(6), 641–646. https://doi.org/10.1016/j.ijantimicag.2016.08.017

Sakurai, Y., Kolokoltsov, A. A., Chen, C.-C., Tidwell, M. W., Bauta, W. E., Klugbauer, N., Grimm, C., Wahl-Schott, C., Biel, M., & Davey, R. A. (2015). Ebola virus. Two-pore channels control Ebola virus host cell entry and are drug targets for disease treatment. *Science (New York, N.Y.), 347*(6225), 995–998. https://doi.org/10.1126/science.1258758

Sanders, J. M., Monogue, M. L., Jodlowski, T. Z., & Cutrell, J. B. (2020). Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A review. *Journal of the American Medical Association, 323*(18), 1824–1836. https://doi.org/10.1001/jama.2020.6019

Schoeman, D., & Fielding, B. C. (2019). Coronavirus envelope protein: Current knowledge. *Virology Journal, 16*(1), 69. https://doi.org/10.1186/s12985-019-1182-0

Song, J.-G., Su, J.-C., Song, Q.-Y., Huang, R.-L., Tang, W., Hu, L.-J., Huang, X.-J., Jiang, R.-W., Li, Y.-L., Ye, W.-C., & Wang, Y. (2019). Cleistocaltones A and B, antiviral phloroglucinol-terpenoid adducts from cleistocalyx operculatus. *Organic Letters, 21*(23), 9579–9583. https://doi.org/10.1021/acs.orglett.9b03743

Steinmann, J., Buer, J., Pietschmann, T., & Steinmann, E. (2013). Anti-infective properties of epigallocatechin-3-gallate (EGCG), a component of green tea. *British Journal of Pharmacology, 168*(5), 1059–1073. https://doi.org/10.1111/bph.12009

Subhan, M., Faryal, R., & Macreadie, I. (2016). Exploitation of Aspergillus terreus for the production of natural statins. *Journal of Fungi (Basel, Switzerland), 2*(2). https://doi.org/10.3390/jof2020013

Sun, Y., Wang, Z., Tao, J., Wang, Y., Wu, A., Yang, Z., Wang, K., Shi, L., Chen, Y., & Guo, D. (2014). Yeast-based assays for the high-throughput screening of inhibitors of coronavirus RNA cap guanine-N7-methyltransferase. *Antiviral Research, 104*, 156–164. https://doi.org/10.1016/j.antiviral.2014.02.002

Torres, M. C. M., Braz-Filho, R., Silveira, E. R., Diniz, J. C., Viana, F. A., & Pessoa, O. D. L. (2010). Terpenoids from Croton regelianus. *Helvetica Chimica Acta, 93*(2), 375–381. https://doi.org/10.1002/hlca.200900201

Tsai, S. H., Lin-Shiau, S. Y., & Lin, J. K. (1999). Suppression of nitric oxide synthase and the down-regulation of the activation of NFkappaB in macrophages by resveratrol. *British Journal of Pharmacology, 126*(3), 673–680. https://doi.org/10.1038/sj.bjp.0702357

Ullah, M. F., Bhat, S. H., & Abu-Duhier, F. M. (2018). Nutraceuticals and natural product derivatives in the premises of disease prevention. *Nutraceuticals and natural product derivatives*. John Wiley & Sons, Ltd. https://doi.org/10.1002/9781119436713.ch5

Velkov, T., Roberts, K. D., Nation, R. L., Thompson, P. E., & Li, J. (2013). Pharmacology of polymyxins: New insights into an "old" class of antibiotics. *Future Microbiology, 8*(6), 711–724. https://doi.org/10.2217/fmb.13.39

Wang, L. F., & Eaton, B. T. (2007). Bats, civets and the emergence of SARS. *Current Topics in Microbiology and Immunology, 315*, 325–344. https://doi.org/10.1007/978-3-540-70962-6_13

Wang, N., Shi, X., Jiang, L., Zhang, S., Wang, D., Tong, P., Guo, D., Fu, L., Cui, Y., Liu, X., Arledge, K. C., Chen, Y.-H., Zhang, L., & Wang, X. (2013). Structure of MERS-CoV spike receptor-binding domain complexed with human receptor DPP4. *Cell Research, 23*(8), 986–993. https://doi.org/10.1038/cr.2013.92

Wan, Z., Lu, Y., Liao, Q., Wu, Y., & Chen, X. (2012). Fangchinoline inhibits human immunodeficiency virus type 1 replication by interfering with gp160 proteolytic processing. *PloS One, 7*(6), Article e39225. https://doi.org/10.1371/journal.pone.0039225

Wan, L.-S., Min, Q.-X., Wang, Y.-L., Yue, Y.-D., & Chen, J.-C. (2013). Xanthone glycoside constituents of Swertia kouitchensis with α-glucosidase inhibitory activity. *Journal of Natural Products, 76*(7), 1248–1253. https://doi.org/10.1021/np400082g

de Wit, E., van Doremalen, N., Falzarano, D., & Munster, V. J. (2016). SARS and MERS: Recent insights into emerging coronaviruses. *Nature Reviews Microbiology, 14*(8), 523–534. https://doi.org/10.1038/nrmicro.2016.81

Wu, C.-Y., Jan, J.-T., Ma, S.-H., Kuo, C.-J., Juan, H.-F., Cheng, Y.-S. E., Hsu, H.-H., Huang, H.-C., Wu, D., Brik, A., Liang, F.-S., Liu, R.-S., Fang, J.-M., Chen, S.-T., Liang, P.-H., & Wong, C.-H. (2004). Small molecules targeting severe acute respiratory syndrome human coronavirus. *Proceedings of the National Academy of Sciences of the United States of America, 101*(27), 10012–10017. https://doi.org/10.1073/pnas.0403596101

Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., … Li, H. (2020). Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharmaceutica Sinica B, 10*(5), 766–788. https://doi.org/10.1016/j.apsb.2020.02.008

Xia, S., Zhu, Y., Liu, M., Lan, Q., Xu, W., Wu, Y., … Lu, L. (2020). Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. *Cellular and Molecular Immunology, 17*(7), 765–767. https://doi.org/10.1038/s41423-020-0374-2

Xu, H.-B., Ma, Y.-B., Huang, X.-Y., Geng, C.-A., Wang, H., Zhao, Y., Yang, T.-H., Chen, X.-L., Yang, C.-Y., Zhang, X.-M., & Chen, J.-J. (2015). Bioactivity-guided isolation of anti-hepatitis B virus active sesquiterpenoids from the traditional Chinese medicine: Rhizomes of Cyperus rotundus. *Journal of Ethnopharmacology, 171*, 131–140. https://doi.org/10.1016/j.jep.2015.05.040

Yang, P., & Wang, X. (2020). COVID-19: A new challenge for human beings. *Cellular and Molecular Immunology, 17*, 555–557. https://doi.org/10.1038/s41423-020-0407-x

Yang, Q.-Y., Tian, X.-Y., & Fang, W.-S. (2007). Bioactive coumarins from Boenninghausenia sessilicarpa. *Journal of Asian Natural Products Research, 9*(1), 59–65. https://doi.org/10.1080/10286020500382397

Zaki, A. M., van Boheemen, S., Bestebroer, T. M., Osterhaus, A. D. M. E., & Fouchier, R. A. M. (2012). Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *New England Journal of Medicine, 367*(19), 1814–1820. https://doi.org/10.1056/NEJMoa1211721

Zhang, X., Jiang, A., Qi, B., Ma, Z., Xiong, Y., Dou, J., & Wang, J. (2015). Resveratrol protects against Helicobacter pylori-associated gastritis by combating oxidative stress. *International Journal of Molecular Sciences, 16*(11), 27757–27769. https://doi.org/10.3390/ijms161126061

Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., … Hilgenfeld, R. (2020). Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. *Science, 368*(6489), 409–412. https://doi.org/10.1126/science.abb3405

Zhang, D.-H., Wu, K.-L., Zhang, X., Deng, S.-Q., & Peng, B. (2020). In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. *Journal of Integrative Medicine, 18*(2), 152–158. https://doi.org/10.1016/j.joim.2020.02.005

Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., Zhu, Y., Li, B., Huang, C.-L., Chen, H.-D., Chen, J., Luo, Y., Guo, H., Jiang, R.-D., Liu, M.-Q., Chen, Y., Shen, X.-R., Wang, X., , … Shi, Z.-L., Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., Zhu, Y., Li, B., Huang, C.-L., Chen, H.-D., Chen, J., Luo, Y., Guo, H., Jiang, R.-D., Liu, M.-Q., & Ch. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature, 579*(7798), 270–273. https://doi.org/10.1038/s41586-020-2012-7

Zumla, A., Chan, J. F. W., Azhar, E. I., Hui, D. S. C., & Yuen, K.-Y. (2016). Coronaviruses - drug discovery and therapeutic options. *Nature Reviews Drug Discovery, 15*(5), 327–347. https://doi.org/10.1038/nrd.2015.37

Glossary

HCoVs: human coronaviruses
3CLPro: 3C-like protease
PLPro: papain-like protease
RTC: Replication/transcription complex
N7-Mtase: N7 methyltransferase
RER: rough endoplasmic reticulum
ERGIC: ER-Golgi intermediate compartment
N, S M and E: structural proteins
N: nucleocapsid
S: spike
M: membrane
E: envelope