



Starting Anti-COVID-19 Drug Discovery with Natural Products

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ABSTRACT

COVID-19 was characterized as a pandemic regarding its rapid international spread and severity on March 2020. The *Coronaviridae* family receives this name regarding the organization of the spike glycoprotein located in the envelope, which resembles a stellar corona when observed under a microscope. Coronaviruses undergo frequent mutations in their genome due to errors made by RNA-dependent RNA polymerase (RdRp). The SARS-CoV-2 was characterized by high infectivity and person to person transmission, with an incubation period of up to fourteen days. Potent antiviral activities of several natural products such as alkaloids, chalcones, triterpenoids have been reported but with unconfirmed efficacy or safety in the clinic as well as the complete underlying mechanisms. Also, CQ, HCQ and Ivermectin, remdesivir, lopinavir, ritonavir, favipiravir and pegylated interferon with ribavirin have been tested to develop both an effective therapy and a vaccine to treat COVID-19. This study investigated the antiviral effects of the natural products against SARS-CoV, HCoV-NL63, HCoV-229E and HCoV-OC43. Also, the Lycorine, Emodin, Promazine, Saikosaponins B2, Silvestrol, Cepharanthine, Fangchinoline, Tetrandrine, Caffeic acid, Chlorogenic acid, Gallic acid and Emetine are considered an important hit compounds for prospective anti-SARS-CoV-2 drug discovery.

Keywords: Coronaviruses; Drug Discovery; Natural Products; Transmission.

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In December 2019, a new coronavirus was detected in patients with a type of viral pneumonia who, coincidentally, had visited the seafood market in the city of Wuhan, Hubei Province, China (Gorbalenya et al. 2020). In December 2019, the *Severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) was reported by the World Health Organization (WHO). In January 2020, the disease caused by SARS-CoV-2 was called coronavirus disease 19 (COVID-19). The SARS-CoV-2 was characterized by high infectivity and person to person transmission, with an incubation period of up to fourteen days (Cheng et al. 2006). COVID-19 was characterized as a pandemic regarding its rapid international spread and severity (WHO 2020). According to the International Virus Taxonomy Committee (ICTV), SARS-CoV-2 is classified under the order of *Nidovirales*, family *Coronaviridae*, subfamily *Orthocoronavirinae*, genus *Betacoronavirus*, subgenus *Sarbecovirus* (de Groot et al. 2020). *Coronaviridae* is a family of positive-sense RNA viruses, enveloped with nonsegmented RNA genome (Fung & Liu 2019).

The *Coronaviridae* family receives this name due to the organization of the spike (S) glycoprotein located in the envelope, which resembles a stellar corona when observed under a microscope (Schoeman & Fielding 2019). This *Coronaviridae* family is subdivided into two subfamilies: *Letovirinae* and *Orthocoronavirinae*, comprising 26 subgenera, 46 species. The subfamily *Letovirinae* has one genus, *Letovirinae*, and the subfamily *Orthocoronavirinae* has four genera *Alphacoronavirus*, *Betacoronavirus*, *Deltacoronavirus*, and *Gammacoronavirus* (WHO 2020). *Alphacoronaviruses* and *Betacoronaviruses* infect or cause disease in mammals, including humans (Abolnik 2015), *Deltacoronaviruses* are related to diseases in birds and pigs (Paim et al. 2019), whereas *Gammacoronaviruses* are related to diseases in birds, dolphin, and whales (Mihindukulasuriya et al. 2008). Coronaviruses, like other RNA viruses, undergo frequent mutations in their genome due to errors made by RNA-dependent RNA polymerase (RdRp), presenting an average replacement rate of $\sim 3 \times 10^{-4}$ replacements per location per year (Fung & Liu 2019; Pyrc et al. 2006; Su et al. 2016). The high frequency of recombination is another important aspect in the genetics of coronaviruses that can have significant effects on the pathogenesis and epidemiology of these viruses (Makino et al. 1986; Su et al. 2016). Besides, the large genome of coronaviruses, in relation to other viruses, with single-stranded RNA allows plasticity in modifying the genome through mutations and recombination, increasing the probability of intra-species and interspecies variability (Su et al. 2016).

The SARS-CoV-2 is the result of viral recombination with the ability to break the biological barrier and escape the animal-animal cycle and infect humans by characterizing a zoonosis that, hypothetically, has the bat as the primary host (Q. Li et al. 2020). However, human to human transmission is what potentiates the epidemic characteristic of these infections (N. Zhu et al. 2020),

such as the epidemics caused by SARS-CoV and the Middle East respiratory syndrome (MERS)-CoV (Zhong et al. 2003). For the SARS-CoV-2 infection process to occur, glycoprotein S needs to be activated to bind to the incoming cell receptor. The initiation and activation process of glycoprotein S is mediated by host cell proteases, with the Transmembrane Protease Serine 2 (TMPRSS2) (Hoffmann et al. 2020) standing out and the angiotensin-converting enzyme receptor 2 (ACE2) is linked to the infection mechanism of some coronaviruses, among them SARS-CoV, responsible for the epidemic peak of this infection that occurred in China in 2002 (W. Li et al. 2003). The SARS-CoV-2+glycoprotein S complex very efficiently uses ACE2 to enter cells, mainly in lung cells, correlating with the rapid spread of SARS-CoV-2 among humans (Walls et al. 2020).

STRUCTURE AND BIOCHEMISTRY

Coronaviruses genomic RNA has approximately 30 kb in length, with 14 open reading frames (ORF). The ORF1a and ORF1ab comprise approximately two-thirds of the genome and encodes a complex replicase machinery. Genes for four structural proteins (Spike, Envelope, Membrane, Nucleocapsid) may be found at the 3' end of the virus genome (Romano et al. 2020). An envelope-anchored spike protein mediates coronavirus entry into host cells by first binding to a host receptor and then fusing viral and host membranes (Wan et al. 2020). Two receptors in humans cells have been described as possible routes of virus entrance, the angiotensin-converting enzyme 2 (ACE2) and CD147, both mediated by the spike (S) protein (Luan et al. 2020; K. Wang et al. 2020). The S protein is a multifunctional molecular machine that mediates coronavirus entry into host cells. It first binds to the ACE2 or CD147 receptors on the host cell surface through its S1 subunit and then fuses viral and host membranes through its S2 subunit (Wang et al. 2020). To engage a host cell receptor, the receptor-binding domain (RBD) of S1 undergoes hinge-like conformational movements that transiently hide or expose the determinants of receptor binding. Because of the indispensable function of the S protein, it represents a target for antibody-mediated neutralization, or its receptors may act as candidates for vaccine antigens (Wan et al. 2020; Shang et al. 2020).

The SARS-CoV-2 shares 79.6% of sequence identity to SARS-CoV and is 96% identical at the whole-genome level to BatCoV RaTG13 (a bat coronavirus) (Zhou et al. 2020). The SARS-CoV-2 shares the same receptor that SARS-CoV and RaTG13 (ACE2) in humans (Shang, Ye, et al. 2020; Wan et al. 2020; Li 2005). The crystal structure of the receptor-binding domain (RBD) of SARS-CoV-2 shows a more compact conformation in comparison to the SARS-CoV RBD. Moreover, several residue changes in the SARS-CoV-2 RBD stabilize two virus-binding hotspots at the RBD–ACE2 interface resulting in increased binding affinity (Shang Ye et al. 2020; Wrapp et al. 2020). Five out of six critical

amino acid residues in the spike protein for binding to ACE2 receptors differ between SARS-CoV-2 and SARS-CoV, as the RBD in the spike protein is the most variable part of the coronavirus genome (Zhou et al. 2020; Wrapp et al. 2020). The analysis of the ACE2-binding ridge in SARS-CoV-2 supports the notion that SARS-CoV-2 is associated with RaTG13 or a RaTG13-related bat coronavirus since both viruses contain a similar four-residue motif in that region. These features may have facilitated SARS-CoV-2 to transmit from bats to humans since small differences between the RaTG13 and SARS-CoV-2 spike proteins enhanced ACE2 recognition in the later (Shang Ye et al. 2020).

CORONAVIRUS GLYCOPROTEINS

The spike glycoprotein (S) called CoV S protein is the main structural protein in the coronavirus envelope. This protein forms projections about 20 nm in length and is the most polymorphic protein among coronaviruses organized as dimers or trimers. CoV S protein has two well-known functions, which are to fix and activate the fusion of the viral envelope with the host cell membrane, which contributes to the release of the viral genome into the cell (Bosch et al. 2003; Ou et al. 2020). CoV S protein has ~1,200aa of length and is cleaved post-translation into two subunits: amino-terminal S1 and carboxy-terminal S2, with about 500 and 600aa, respectively. The S protein is anchored by the carboxy-terminal portion of the S2 subunit in the viral envelope through a small hydrophobic transmembrane segment, forming the support of the spike, while the S1 subunit is globular and forms the part of the bulb present in the ectodomain of this protein (Binns et al. 1985; Spiga et al. 2003).

The S1 subunit contains the main epitopes targeted for the combination with neutralizing antibodies, which are made up of certain amino acid sequences that confer the serotype specificity to each viral strain (X.-J. Yu et al. 2003; Ou et al. 2020). Another characteristic of the S1 subunit is that it has regions in its sequence that have great variability, regions that are called: hypervariable region 1 (HVR I), delimited by amino acid residues 38 to 69; hypervariable region 2 (HVR II), delimited by amino acid residues 91 to 141; and the hypervariable region 3 (HVR III) comprising amino acid residue 250 to 387. Several studies have demonstrated the importance of these three hypervariable regions in the direct interaction with neutralizing antibodies and, therefore, constitute the serotype-specific determinants presented by the different strains of coronavirus (Takiuchi et al. 2007; Jaimes et al. 2020). Regarding viral protein structures are important tools on immunopathological understanding, the S1 subunit anchored in the ECA 2 receptor in pneumocytes II regulates transmissions between species and from human to human (Geng Li et al. 2020; W. Li et al. 2003).

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Angiotensin-converting enzyme 2 (ACE2) is an 805 amino acid metalloprotease that has considerable homology with ACE (Tipnis et al. 2000). ACE2 is a type I membrane protein that acts as a carboxypeptidase and not as a dipeptidyl carboxypeptidase like ACE (Guy et al. 2003). It is expressed in kidney cells, heart, blood vessels, gastrointestinal tract, liver, spleen, brain, placenta, and lungs (Gang Li, Hu & Zhang 2020). ACE2 is highly expressed in the kidneys and the cardiovascular and gastrointestinal systems, being expressed at lower levels in the central nervous system, lymphoid tissue, and lungs (Donoghue et al. 2000; Xudong et al. 2006; Valdés et al. 2006). In lungs, ACE2 is mainly expressed in the pulmonary AT2 alveolar epithelial cells, which are particularly prone to viral infections (Uhal et al. 2011).

ACE2 exhibits biochemical activities different from ACE, converting angiotensin I into angiotensin-(1-9) (Donoghue et al. 2000). Angiotensin-(1-9), whose actions have not yet been well defined, is hydrolyzed by ACE to angiotensin-(1-7). Another action of ACE2 is the hydrolysis of angiotensin II, with the removal of an amino acid, producing, from there, angiotensin-(1-7) (Crackower et al. 2002). The catalytic action of ACE2 is approximately 500x more efficient when the substrate is angiotensin II, compared to its action on angiotensin I. ACE2 is, moreover, 10–600x more potent than prolyl endopeptidase and prolyl-carboxypeptidase, respectively, to generate angiotensin-(1-7) from angiotensin II (Vickers et al. 2002). Several studies have shown that ACE2 expression in human tissues correlates with SARS-CoV and SARS-CoV-2 infection sites, including lung, kidney, and intestine (Sungnak et al. 2020; Zhao et al. 2020), which may be associated with complications in these organs resulting from the SARS-CoV-2 infection.

Similar to SARS-CoV infection, the S1 subunit of the CoV S protein contains a conserved Receptor-Binding Domain (RBD), which recognizes the host cell's angiotensin-converting enzyme 2 (ACE2). The CoV S protein is activated and cleaved by the the membrane-anchored serine transmembrane protease 2 (TMPRSS2), and the typically intracellular cysteine proteases cathepsin B/L, and/or furin, allowing the virus to release fusion peptides and fuse with the membrane. The co-expression of ACE2 and TMPRSS2, cathepsin, and/or furin is a key determinant for SARS-CoV-2 entry into host cells (Hoffmann et al. 2020; Kawase et al. 2012; Coutard et al. 2020). Thus, the virus promotes a decrease in the expression of ACE2, which would be responsible, physiologically, for protective actions of the lung due to its negative regulation on the activity of the renin-angiotensin system that is reported as harmful to the lungs. Thus, the decrease in ACE2 activity affects the exacerbation of atrophic, fibrotic, pro-oxidant, and vasoconstrictor processes in the lung (Zhao et al. 2020).

CORONAVIRUS PROTEASES

Similar to the SARS-CoV and the MERS-CoV, the SARS-CoV-2 genome encodes nonstructural proteins (such as papain-like protease (nsp3), 3-chymotrypsin-like protease (nsp5), helicase (nsp13), and RNA-dependent RNA polymerase (nsp12)), structural proteins (such as spike glycoprotein) and accessory proteins (Woo et al. 2010; Lai 1990). The four mentioned nonstructural proteins are key enzymes in the viral reproduction, and the spike (S) glycoprotein plays an essential role in the entry of the virus to the host cells. Accordingly, each of these five proteins is recognized as attractive targets to design and develop antiviral agents against SARS and MERS. The genome of SARS encodes two polyproteins, namely *pp1a* and *pp1b*. These polyproteins are cleaved to different functional proteins by the papain-like protease (PL^{pro}) and/or the 3-chymotrypsin-like protease (3CL^{pro}), which is frequently referred to as main protease (M^{pro}) (Ziebuhr, Snijder & Gorbalenya 2000).

Proteases are enzymes whose catalytic function is to hydrolyze peptide bonds of proteins. Based on the catalytic mechanisms, proteases are classified into nine different groups: metallo, aspartic, cysteine, serine, glutamic, asparagine, threonine, mixed catalytic type, and unknown catalytic type proteases (Rawlings et al. 2018). Coronavirus proteases belong to the cysteine protease class (Lai 1990). Cysteine proteases hydrolyze a peptide bond using the thiol group of a cysteine residue as a nucleophile. Hydrolysis usually involves a catalytic triad consisting of the thiol group of the cysteine, the imidazole ring of a histidine, and a third residue, in most of them, to orientate and activate the imidazole ring (Báez-Santos, St. John & Mesecar 2015). Although the primary function of PL^{pro} and 3CL^{pro} is to process the viral polyprotein in a coordinated manner, PL^{pro} has the additional role of stripping ubiquitin and ISG15 from host-cell proteins to aid coronaviruses in their evasion of the host innate immune responses. Therefore, targeting PL^{pro} with antiviral drugs may have an advantage in not only inhibiting viral replication but also inhibiting the dysregulation of signaling cascades in infected cells that may lead to cell death in the surrounding, uninfected cells (Anand et al. 2003).

SARS-CoV-2 PL^{pro} X-ray structure – unbound (Ratia et al. 2014) or inhibitor-complexed (Ghosh et al. 2009, 2010; Báez-Santos et al. 2014)- have been investigated by several authors. Báez-Santos et al. grouped the known SARS-CoV-2 PL^{pro} inhibitors into six different classes, one of them being the inhibitors of natural origin. Among the natural products, *tanshinones*, *diarylheptanoids*, and *geranylated flavonoids* were mentioned (Báez-Santos et al. 2014). Kim et al. found some phenolic components of ethanol extract of the seeds of *Psoralea corylifolia* to show high activity against the SARS-CoV PL^{pro} with an IC₅₀ value of 15 µg/ml (D. W. Kim et al. 2014). The structure of the compounds – belonging to the geranylated flavonoids class - are shown in Figure 1. Furthermore, Lee et al.

demonstrated that the MERS-CoV PL^{pro} blocking loop 2 (BL2) structure significantly differs from that of SARS-CoV PL^{pro}, where it has been proven to play a crucial role in SARS-CoV PL^{pro} inhibitor binding (H. Lee et al. 2015). The authors tested four SARS-CoV PL^{pro} lead inhibitors against MERS-CoV PL^{pro}. None of them were effective against MERS-CoV PL^{pro}. Recently, Arya et al. performed an in silico docking studies of several FDA approved drugs and the homology model of the SARS-CoV PL^{pro} enzyme. In this study, sixteen FDA approved drugs, including *chloroquine* and *formoterol*, was found to bind the target enzyme with significant affinity and proper geometry, suggesting their potential to be utilized against the virus (Arya et al. 2020).

The indispensable role of coronavirus main protease (Main^{pro}) in its essential role in processing the polyproteins that are translated from the viral RNA, makes it a popular target for drug design. Following the first SARS coronavirus outbreak in 2002, a series of inhibitors of Main^{pro} of the SARS-CoV was reported (Bacha et al. 2004; Jain et al. 2004; Wu et al. 2004). These early studies concentrated on (1) testing peptidomimetics, similar to the HIV protease inhibitors *ritonavir* and *lopinavir*, and (2) analogs of the natural products which had been reported to show antiviral and antimicrobial effects (L. Wang et al. 2015; Zaman et al. 2017). Wu et al., for example, used a cell-based assay to screen more than 10,000 compounds, all administered at 10 μ M, for inhibition of the cytopathic effect of the SARS-CoV virus. The authors found *valinomycin*, a peptide insecticide, to be the most effective of the screened compounds with an EC₅₀ of 0.85 μ M. *Beta-aescin* and *reserpine* were also found active. Compounds that are structurally similar to reserpine and beta-aescin were also tested, resulting in 10 new anti-SARS active compounds (Wu et al. 2004). Based on the high similarity of M^{pro}s in each CoV group, some wide-spectrum Michael acceptor peptidomimetic inhibitors (I2, N1, and N3) targeting SARS-CoV Main^{pro} enzymes (Figure 2) (Yang et al. 2005).

Yang and coworkers was first publishing the X-ray analysis of the SARS-CoV Main^{pro} holoenzyme and its complex with its inhibitor, chloromethyl ketone (CMK) (Yang et al. 2003). In contrast to common serine proteases, which have a Ser–His–Asp catalytic triad, SARS M^{pro} has a Cys–His catalytic dyad (Cys-145 and His-41), which is similar to the TGEV M^{pro} (Cys-144 and His-41) and the HCoV 229E M^{pro} (Cys-144 and His-41) (Anand et al. 2003). Jin et al. reported on the crystal structure of the SARS-CoV-2 M^{pro}-N3 complex, demonstrating a similar binding mode in the SARS CoV M^{pro}-N1 and the SARS CoV-2 M^{pro}-N3 complexes. The authors used a FRET assay to screen about 10,000 compounds, consisting of approved drugs, clinical-trial drug candidates, and natural products. The primary hits were seven compounds, including *disulfiram*, *carmofur*, and *ebselen* (Jin et al. 2020).

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Some docking studies to find homoisoflavanones and their thio analogs as inhibitors of the mutant coronavirus main protease enzyme SARS-CoV-2 M^{pro} were performed (Sepay et al. 2020). Based on the binding properties, they predicted the homoisothioflavone **7** (Figure 3) as a prosperous candidate for further investigations (Sepay et al. 2020). Furthermore, the structure-based virtual screening and molecular dynamic simulation indicated natural compounds with strong binding affinity and the ability to inhibit the SARS-CoV-2 Main^{pro} enzyme. The authors had a library of 1,048 natural compounds isolated from edible African plants. *Rhamnetin* (**8**) and *ellagic acid* (**9**) (Figure 3) showed a better therapeutic prediction than compound N3 used as standard (Azhagiya Singam et al. 2020).

HOST CELL PROTEASES

As for the natural product-based antiviral strategies, each step of the viral life cycle could be taken into consideration. The virus replication cycle can be divided into six structurally and biochemically different stages: (1) attachment of the virus to receptors on the host cell surface; (2) entry of the virus through the host cell membrane; (3) uncoating of viral nucleic acid; (4) replication, involving (a) synthesis of early regulatory proteins, (b) synthesis of new viral RNA or DNA; and (c) synthesis of late, structural proteins; (5) assembly (maturation) of viral particles; and (6) release from the host cell (Lindenbach 2013). Successful drug development can be seen considering each approach.

Coronaviruses can enter cells *via* fusion either directly at the cell surface or can be internalized through the endosomal compartment. The attachment of coronaviruses to the surface of the host cells is based on the formation of a coronavirus S protein and the ACE2 receptor of the host cell. The interactions, which result in the entry of the virus, also require activation of the S protein by the cellular proteinases (Kawase et al. 2012; Coutard et al. 2020). ACE2 is a metalloproteinase of which physiological function is hydrolytic cleavage of the protein angiotensin 2 (Tipnis et al. 2000; Heurich et al. 2014). It most often resides on the surface of epithelial cells that cover the surface of internal body cavities, such as the walls of the heart, intestines, and alveoli. However, not only angiotensin-2 but also the spike proteins of the SARS-CoV viruses can bind to the ACE2 receptors, making this receptor the key to viral cell infection. Inhibition of ACE2 enzymic activity by natural or synthetic inhibitors is not without risks. The main function of ACE2 is to inactivate angiotensin-2, the octapeptide with hypertensive activity. If we reduce the activity of ACE2, angiotensin-2 will build-up, which raises blood pressure and can trigger dangerous inflammatory processes (Heurich et al. 2014).

By this time, inhibition of the transmembrane protease serine 2 resulted in several prosperous results in blocking the attachment of coronaviruses in the surface of the host cells. TMPRSS2 facilitates human coronaviruses SARS-CoV and SARS-CoV-2 infections *via* two independent mechanisms, (a)

proteolytic cleavage of ACE2 receptor, which promotes viral uptake (Heurich et al. 2014), and cleavage of coronavirus spike glycoproteins which activates the glycoprotein for host cell entry (Hoffmann et al. 2020). Inhibition of the latter activity of TMPRSS2 by *camostat mesylate* (NI-03) (Figure 4), proved to be a clinically approved approach to block entry of the SARS-CoV 2 virus into mammalian cells and might constitute a treatment option (Hoffmann et al. 2020).

CORONAVIRUS RNA-DEPENDENT RNA-POLYMERASE

Molecular biological studies indicated that all structural proteins (including the spike (S), envelope (E), membrane (M), hemagglutinin-esterase (HE), and nucleocapsid (N)) show considerable structural variations among the different CoVs (Woo et al. 2005; Shen et al. 2019; Marra et al. 2003; Rota et al. 2003). On the contrary, protein structural analyses suggest that key binding pockets of the RNA-dependent RNA-polymerase (RdRs) enzymes are likely to be conserved across the three CoV viruses. Therefore, it is reasonable to use data from agents already assessed for activity against SARS/MERS CoVs to extrapolate to SARS-CoV-2. Accordingly, the RNA-dependent RNA-polymerase (similar to RNA helicase, and the main proteinase (M^{pro,20}) constitute attractive nonstructural protein targets for the development of wide-spectrum anti-coronavirus drugs.

Coronaviruses are single-strained, positive-sense, nonsegmented RNA viruses (Class IV) according to the Baltimore scheme (Baltimore 1971). They can use their genome both as genomic and mRNA. One of the viral genes expressed yields an RNA-dependent RNA-polymerase (or RNA replicase), which creates minus-strand RNA from the plus-strand genome. The minus-strand RNA can be used as a template for more plus-strand RNA, which can be used as mRNA or as genomes for the newly forming viruses. Present-day inhibitors of such activities of RNA-dependent RNA-polymerases are nucleoside analogs. The approved nucleoside analogs *favipiravir* and *ribavirin* have been tested against SARS and MERS and shown to have antiviral effects *in vitro*. Clinical results have suggested that *favipiravir* affected patients with COVID-19, and it has been added to the list of potential therapies there (Cai et al. 2020). *Ribavirin* is a guanosine analog with *in vitro* activity against a large number of highly lethal emerging viruses (Figure 5). *Ribavirin* inhibits RNA synthesis by viral RdRp as well as inhibiting mRNA capping. Studies demonstrated, however, that while SARS-CoV, MERS-CoV, and HCoV-OC43 were sensitive to ribavirin *in vitro*, doses that significantly inhibited CoV replication exceeded ribavirin concentrations attainable by typical human regimens (Falzarano et al. 2013).

Remdesivir (Figure 5) was initially studied as a possible treatment for Ebola but was not particularly effective in comparison to other agents investigated in these outbreaks. It is effective in *in vitro* tests and animal models of SARS and MERS. Additional studies demonstrated that *remdesivir*

decreased viral titers and viral RNA in *in vitro* models of both SARS-CoV and MERS-CoV infection of HAEs (Sheahan et al. 2017).

Furthermore, Yin *et al.* (Yin et al. 2020) reported the structure of the SARS-CoV-2 RdRp either in the apo form or in complex with a 50-base template-primer RNA and *remdesivir* (GS-5734). The complex structure revealed that the partial double-stranded RNA template was inserted into the central channel of the RdRp, where remdesivir is incorporated into the first replicated base pair and terminates the chain elongation (Yin et al. 2020). The results can provide a rational basis to design even more potent SARS-CoV RdRs inhibitors. One of the prosperous candidates is *galidesivir* (BCX4430). It has broad-spectrum antiviral effectiveness against a range of RNA virus families, including coronaviruses (SARS and MERS) (Zumla et al. 2016).

CORONAVIRUS RNA HELICASE

To convert a closed double-stranded DNA or RNA helix into two open single strands, so that other protein machinery can manipulate the polynucleotides, the cells require helicases. Helicases are small molecular motors that use energy derived from ATP hydrolysis. They are classified into six superfamilies SF1-SF6 and participate in almost every aspect of nucleic acid metabolism. DNA helicases play key roles in DNA replication, recombination, and repair. Cells need RNA helicases for transcription, translation, and RNA splicing. Earlier, several potent antiviral drugs were discovered that inhibit an essential herpes simplex virus (HSV) helicase complex, and this discovery inspired many others to study helicases as drug targets (Guang Xi 2007; Kwong, Rao & Jeang 2005; Shadrack et al. 2012).

The majority of helicases prefer only one type of nucleic acid (i.e., either RNA or DNA) as an unwinding substrate (Frick 2003). Regardless of their functional diversity, helicases all contain core domains that hydrolyze nucleoside triphosphates. The enzymatic core is formed either by the tandem RecA-like domains within the same polypeptide chain (SF1-SF2 superfamilies) or between subunits of the functional oligomer of the helicase (SF3-SF6 superfamilies) (Singleton, Dillingham & Wigley 2007). Sequence conservation analysis indicates that SARS CoV helicase belongs to the SF1 superfamily, including Rep, UvrD, PcrA, RecD, Pif1, Dda, Upf1-like helicases, and many positive ss RNA virus helicases (Gorbalenya & Koonin 1989).

Hao and co-workers first reported on the X-ray structure of MERS CoV helicase (Hao et al. 2017). The authors found that MERS-CoV helicase has multiple domains, including an N-terminal Cys/His rich domain (CH) with three zinc atoms, a beta-barrel domain, and a C-terminal SF1 helicase

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core with two RecA-like subdomains. It was found that while the domain organization of helicases (nsp13 proteins) is conserved throughout nidoviruses, the individual domains of them are closely related to the equivalent eukaryotic domains of Upf1 helicases. Earlier, Yu and co-workers conducted *in vitro* biochemical experiments to find out which natural compounds might suppress either (1) the DNA unwinding activity or (2) the ATPase activity of the SARS CoV helicase. The authors demonstrated that selected naturally-occurring flavonoids, including *myricetin* (**12**) and *scutellarein* (**13**) (Figure 6), might serve as SARS-CoV chemical inhibitors (Yu et al. 2012).

Tanner and coworkers (Tanner et al. 2005) have found that *bananin* (**14**) (Figure 7) and its three derivatives function as noncompetitive SARS-CoV helicase inhibitors at a site different from the ATP and nucleic acid binding site, causing inhibition probably through an allosteric mechanism. Lee et al. discovered a novel chemical compound, (*E*)-3-(furan-2-yl)-N-(4-sulfamoylphenyl)acrylamide (**15**) (Figure 7) that suppresses the enzymatic activities of SARS coronavirus helicase. The authors performed ATP hydrolysis and double-stranded DNA unwinding inhibitory assays and found IC₅₀ values of the μM range (Lee et al. 2017). Pillaiyar et al. recently published a comprehensive survey on the chemical structures that have proved to be effective against SARS and MERS viruses according to the different potential targets. In their review, they did not mention any helicase inhibitors approved for antiviral therapy. The most promising candidate has been a synthetic 1,2,4-triazole derivative **16** (SSYA10-001) that inhibited the viral NTPase/helicase of both SARS-and MERS-CoVs (Pillaiyar, Meenakshisundaram & Manickam 2020). Based on the results, compound **16** (Figure 7) could serve as a potential lead for the development of effective broad-spectrum anti-coronavirus drugs.

NATURAL PRODUCTS

For centuries, the natural products and their derivatives have been recognized as inexhaustible sources of therapeutic agents (Rodrigues et al. 2016; Zhi et al. 2019; Molinari 2009). The molecular structures and supramolecular arrangements of natural products have continued to inspire the development new drug entity (Molinari 2009; Viegas, Da Silva Bolzani & Barreiro 2006). The treatment of viral infections has witnessed the use of extracts, formulations, active principles of plant origin (S. Hu et al. 2019). For instance, plant species rich in quinoline alkaloids belonging to the Rutaceae family (*Almeidea coerulea*, *Araliopsis tabouensis*, *Boronella koniambiensis*, *Brombya* sp. nov., *Esenbeckia pentaphylla*, *Evodia fargesii*, *Haplophyllum sieversii*, *Melicope bonnickii*, *Melicope semecarpifolia*, *Philotheca deserti* var. *deserti*, *Pilocarpus grandiflorus*, *Ruta chalepensis*, *Spathelia excelsa*, *Spiranthera odoratissima*, *Toddalia aculeata*, *Zanthoxylum ailanthoides*, *Zanthoxylum heitzii*) possesses antiviral property (da Silva et al. 2013).

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Potent antiviral activities of several alkaloids, chalcones, triterpenoids have been reported (Islam et al. 2020). In the previous study, alkaloids that were isolated from the root bark of *Z. ailanthoides* inhibited viral replication in H9 lymphocyte cells without significant impact on the growth of uninfected H9 cells (Chouhan et al. 2014). In order to ensure therapeutic success of plant extract or isolates in the treatment of COVID-19, the screening for antiviral activities needs to take account of the coronavirus machinery for replication and pathophysiological mechanistic. The extracts with phytoconstituents that exhibit activities against coronavirus as shown in Table 1.

Current challenges with the therapeutic application of extracts and active principles of plant origin in the treatment of coronavirus infection include unconfirmed efficacy or safety in the clinic as well as the complete underlying mechanisms (Li et al. 2005). The emergence and spread of resistant strains, as well as the high rates of mutations in microorganisms, reduced the effectiveness of antiviral drugs (Gerrish and García-Lerma 2003). Altogether, there are needs to continually develop new antiviral therapies with wide or narrow spectrum in order to solve drug resistance problems or find new molecules and novel mechanisms of action in the treatment of viral diseases.

SYNTHETIC DERIVATIVES

Chloroquine (**17**) and hydroxychloroquine (**18**) are synthetic derivatives of quinine (**19**), a quinolinic alkaloid that was isolated from the bark of a *Cinchona* tree by pharmacists Pierre Joseph Pelletier and Joseph Caventou, around 1920 (Figure 8). For decades the salts of chlorate or phosphate of chloroquine (CQ) and hydroxychloroquine (HCQ), both 4-aminoquinolines, have been used to treat malaria, an infectious disease caused by species of *Plasmodium spp.* CQ has been known since 1934 and HCQ was synthesized in 1946 by introducing an *N*-hydroxy-ethyl side chain in place of CQ's *N*-diethyl group (Monteiro et al. 2020). HCQ proved to be (~40%) less toxic (McChesney 1983) during its prolonged use (for months or even years), allowing the application of higher doses than QC (Marmor et al. 2016) (25 mg/kg for 3 days). Therefore, HCQ is recommended for the treatment of autoimmune diseases, such as: lupus erythematosus systemic and rheumatoid arthritis (Lim et al. 2009).

Although they are generally safe substances when used to treat malaria and autoimmune diseases, the safety, efficacy, and benefit of these drugs in the treatment of COVID-19 (SARS-CoV-2) have been analyzed by several research groups around the world. The CQ acts on lung cell receptors and interferes with the glycosylation of the angiotensin receptor by converting enzyme 2 (ACE2), thus, impairing the entry of viruses into cells, since SARS- CoV-2 invades lung cells by endocytosis through the ACE2 receptor (W. Li et al. 2003). According to Hu and collaborators, QC induces the suppression of phosphatidylinositol binding clathrin assembly protein (PICALM), preventing, in this way,

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endocytosis (Hu, Frieman & Wolfram 2020). The alkalization of lung cells promoted by 4-aminoquinoline also hinders viral replication, as it impairs the function of the endosome, inhibits the fusion of autophagosomalysoma, in addition to inactivating enzymes that are essential for viral replication (Savarino et al. 2003).

The *in vitro* antiviral activity of QC (Inglot 1969) was first verified in the late 1960s, when the ability of this drug to inhibit the synthesis of encephalomyocarditis virus was demonstrated. Currently, there are *in vitro* studies that have suggested an anti-SARS-CoV activity (Keyaerts et al. 2004) of the QC and HCQ salts. Liu et al (Yao et al. 2020) recommend using HCQ sulfate (400 mg given twice a day, followed by 200 mg twice a day for another 4 days) to treat patients infected with SARS-CoV-2. Considering the usage history of these drugs, their safety and their low cost, these authors recommended that clinical studies be carried out to evaluate the effects of the drug in patients infected with COVID-19.

The effectiveness of QC phosphate in humans for the treatment of severe acute respiratory syndrome caused by the coronavirus was initially reported by Chinese scientists Gao and collaborators. However, this publication, available in Preprints repositories, does not present scientific data to support such findings and, therefore, cannot be taken as conclusive (Gao, Tian & Yang 2020). Despite this, the Republic of China, through the National Health Commission, included QC in its sixth edition of the Guidelines for the prevention, diagnosis, and treatment of pneumonia induced by the new coronavirus (Dong, Hu & Gao 2020). Chinese guidelines recommend using doses of 300 mg to 500 mg (twice daily) of QC phosphate over a period of 10 days. A preliminary clinical study conducted in the south of France verified the efficiency of HCQ sulfate 600 mg/d (200 mg, three times per day, during ten days) in reducing viral load in patients diagnosed with COVID-19. Gautret and collaborators reported that the elimination of the virus was more efficient when azithromycin was associated with HCQ (Gautret et al. 2020).

In Brazil, a randomized, double-blind trial, conducted by Borba and colleagues, with 81 hospitalized patients due to SARS-CoV-2 infection, showed that the highest dose of chloroquine (600mg CQ twice daily for 10 days) should not be recommended for critically ill patients with COVID-19 for safety reasons due to prolonged QTc interval and increased lethality (Borba et al. 2020). The study also found that the potential risk to safety (safety hazards) of patients increases, especially when QC is administered in combination with azithromycin and oseltamivir. Despite the effectiveness of QC or HCQ in laboratory studies, reports in the literature (Wang et al. 2015) describe the difficulty and even the disappointment when transposing it to a clinical scale. The complex pharmacokinetics of 4-

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aminoquinolines justify these differences between the results of laboratory and clinical trials (Lim et al. 2009; Smit et al. 2020). 4-aminoquinolines demonstrate high basicity, high half-life (around 40-45 days), lead to accumulation in lysosomes, in addition to having a high volume of distribution and long renal clearance.

The main adverse effects related to the use of CQ and HCQ are related to retinopathy (Saurabh et al. 2013) which can occur even after discontinuation of treatment. Another reported adverse effect is cardiovascular toxicity, due to its electrical instability, characterized by the prolongation of the QT interval, that is, the time spent for ventricular depolarization and repolarization. This mechanism is related to the blocking of the hERG potassium channel, which prolongs ventricular repolarization and the duration of action potentials, triggering ventricular arrhythmias. Studies by Shi et al and Guo et al demonstrate that patients who suffer from cardiovascular diseases and are infected with SARS-CoV are more likely to develop ventricular arrhythmias (Shi et al. 2020; Guo et al. 2020).

Therefore, given the lack of sufficient scientific evidence (Geleris et al. 2020) to prove the efficacy and safety of CQ and HCQ to treat patients infected with coronavirus (COVID-19), the World Health Organization has temporarily suspended clinical trials with these drugs. Despite this, countries like China and Brazil (Rosenberg et al. 2020; Mahévas et al. 2020; Tang et al. 2020) maintain guidelines and protocols that suggest they authorize the use of these drugs to treat patients with SARS-CoV-2. Another derivative synthesized, obtained in 1975, and that comes from natural products, is ivermectin. It derives from avermectin, a product that comes from the fermentation of the actinomycete *Streptomyces avermitilis*, through catalytic hydrogenation of a single double bond. Ivermectin (anti-parasitic) has greater potency and less toxicity than avermectin, which is used for its insecticidal and anthelmintic action. Ivermectin inhibited SARS-CoV-2 in laboratory cultures of infected cells (Vero-hSLAM cells) (Caly et al. 2020).

Ivermectin probably interacts with transmembrane transporters (Impae Impb1) thus preventing the virus from entering the cell nucleus. Consequently, viral multiplication would be inhibited and this would result in decreased infection, as there would be a reduced inhibition of antiviral responses, leading to a more efficient antiviral response. However, the results presented in monkey kidney cell cultures were relatively high ($IC_{50} = 2,5 \mu\text{m}$), requiring extremely high doses for therapeutic effects in humans and, consequently, already proving not to be an effective drug for the treatment of Covid-19 (Momekov & Momekova 2020). In addition, previous experiments in cell cultures have shown to be effective in treating Dengue virus infection, but have failed in animal

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models. Finally, on April 10, 2020, the FDA's Center for Veterinary Medicine (FDA Letter to Stakeholders: Do Not Use Ivermectin Intended for Animals as Treatment for COVID-19 in Humans FDA n.d.) advised not to use ivermectin that is intended for animals as a treatment for Covid-19 in humans. In addition to CQ, HCQ and Ivermectin, other drugs (not derived from natural products) are being considered, such as: remdesivir, lopinavir, ritonavir, favipiravir and pegylated interferon with ribavirin (Ahn et al. 2020) are also being tested in a constant and global effort by research laboratories and institutions to develop both an effective therapy and a vaccine to treat emerging infectious contagious diseases, such as COVID-19, which is currently unsolved.

ARTIFICIAL INTELLIGENCE DRIVEN DRUG DISCOVERY

Although there are already several drugs being assessed clinically for SARS-CoV-2 (Beigel et al. 2020; García et al. 2020; Irvani et al. 2020; Irie et al. 2020), the continuous efforts to discover new drug candidates more effective, safe, and inexpensive remain necessary. However, the accelerated discovery of new anti-COVID-19 drugs represents a major challenge, since this demand is incompatible with current drug discovery pipelines, which require long cycle times of research, and present limited success in clinical trials (Nosengo 2016). To make this process faster and efficient, academics, startups and big pharmaceutical companies are exploring the potential of artificial intelligence (AI) systems to help streamline their research and development (R&D) process (Ekins et al. 2019).

With the recent advances in computer technology, solid progress in AI-drive drug discovery field has been made by using machine learning (ML) techniques. These techniques enable the development of mathematical models from various data types. Once having learned from the data, the ML model can be used to make predictions or decisions without being explicitly programmed to do so. The possibilities of ML seem virtually unlimited, with applications ranging from automation of whole organism assays (Singh, Carpenter & Genovesio 2014), lead identification and optimization (Neves et al. 2018; Chen et al. 2018), early accessing of pharmacokinetics and toxicological (ADME/Tox) profile of compounds (Goh, Hodas & Vishnu 2017), formulation design (Alves et al. 2019), as well as clinical trial recruiting, design and optimization (Gayvert, Madhukar & Elemento 2016). Applying ML to discovery NP with potential anti-SARS-CoV-2 activity is a sequential process that involves the use of algorithms to learn from datasets of compounds with bioactivity data (Figure 9) (Lavecchia 2015).

Initially, chemical and biological data are collected from bioassay databases and the literature and curated using standardized protocols (Fourches et al. 2010; Alves et al. 2016). In this sense, thousands of compounds with experimental ADME/Tox properties, and bioactivity data for SARS-

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CoV-2 are publicly available on databases such as ChEMBL (Gaulton et al. 2012) and PubChem Bioassay (Y. Wang et al. 2012). Then, molecular descriptors (i.e., final result of a mathematical procedure which transforms chemical structure into a useful number) are calculated on different levels of representation (1D to nD) of chemical structures (Chuang, Gunsalus & Keiser 2020). In the learning phase, a ML technique is applied to discover an empirical function that can achieve an optimal mapping between the molecular descriptors and experimental property. To date, Support Vector Machine (SVM) (Vapnik 2000), Random Forest (RF) (Breiman 2001), and Deep Neural Networks (Lusci, Pollastri & Baldi 2013) are the most popular and effective ML methods for modeling quantitative structure-activity relationships. At the end of this step, the ML model must be subjected to rigorous statistical validation to determine its predictive power (Cherkasov et al. 2014). Once presenting a satisfactory statistical performance, ML models may be applied as filters in virtual screening (VS) of libraries of natural and semisynthetic compounds (i.e., 10³ to 10⁴ chemical structures) (Cherkasov et al. 2014).

In principle, VS is often compared to a funnel, where a large number of natural products in chemical libraries (i.e., 10³ to 10⁵ compounds) are reduced to a smaller number of virtual hits that will be tested experimentally (i.e., 10¹ to 10² compounds) (Tanrikulu, Krüger & Proschak 2013; Kar & Roy 2013). Although in principle, ML models are the most useful tools for the identification of bioactive compounds, complementary computational methods can be incorporated into VS as a multi-step filtering process, including: (i) sets of empirical rules (e.g., Veber (Veber et al. 2002) and Lipinski's (Lipinski et al. 1997) rules, pan-assay interference rules and models (Baell & Holloway 2010; Jasiel et al. 2018)); (ii) chemical similarity cutoffs; (iii) ADME/Tox filters (Braga et al. 2015); (iv) and molecular docking (Kitchen et al. 2004). In this sense, the integration of different methods increases reliability in predictions and the hit rate in VS.

Generally, typical hit rates from experimental VS typically range between 1% and 40%, while the hit rates of experimental random screening approaches range between 0.01% and 0.1% (T. Zhu et al. 2013). Despite the high hit rate, the expectation that ML-based VS can completely replace experimental assays is overoptimistic. So, *in vitro* experimental validation of computational hits should be performed as the most important step of the study. After experimental validation of virtual hits, ML models can still play a key role in the hit-to-lead and lead optimization design of semisynthetic compound series. In this sense, models can be used as a multi-parameter optimization decision system to find the compounds with adequate balance between potency, selectivity and ADME/Tox properties (Neves et al. 2018).

CONCLUSION

This study investigated the antiviral effects of the natural products against SARS-CoV, HCoV-NL63, HCoV-229E and HCoV-OC43. Also, the Lycorine, Emodin, Promazine, Saikosaponins B2, Silvestrol, Cepharanthine, Fangchinoline, Tetrandrine, Caffeic acid, Chlorogenic acid, Gallic acid and Emetine are considered an important hit compounds for prospective anti-SARS-CoV-2 drug discovery. Further hit-to-lead analyses are required to transform these potential inhibitors into clinical drugs. We anticipate that the insights gained in the present work may prove valuable for exploring novel natural products as anti-COVID-19 therapeutic agents in the future.

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Iniciando a Descoberta de Drogas Anti-COVID-19 com Produtos Naturais

RESUMO

COVID-19 foi caracterizada como uma pandemia por sua rápida disseminação internacional e gravidade em março de 2020. A família Coronaviridae recebe esse nome devido à organização da glicoproteína de pico localizada no envelope, que se assemelha a uma coroa estelar quando observada ao microscópio. Os coronavírus sofrem mutações frequentes em seu genoma devido a erros cometidos pela RNA polimerase dependente de RNA (RdRp). O SARS-CoV-2 foi caracterizado por alta infectividade e transmissão pessoa a pessoa, com período de incubação de até quatorze dias. Atividades antivirais potentes de vários produtos naturais, como alcalóides, chalconas, triterpenóides, foram relatadas, mas com eficácia ou segurança não confirmadas na clínica, bem como nos mecanismos subjacentes completos. Além disso, CQ, HCQ e ivermectina, remdesivir, lopinavir, ritonavir, favipiravir e interferon peguilado com ribavirina foram testados para desenvolver uma terapia eficaz e uma vacina para tratar COVID-19. Este estudo investigou os efeitos antivirais dos produtos naturais contra SARS-CoV, HCoV-NL63, HCoV-229E e HCoV-OC43. Além disso, licorina, emodina, promazina, saikosaponinas B2, silvestrol, cefarantina, fangchinoline, tetrandrina, ácido cafeico, ácido clorogênico, ácido gálico e emetina são considerados compostos de sucesso importantes para a descoberta de drogas anti-SARS-CoV-2.

Palavras-Chave: Coronavírus; Descoberta de drogas; Produtos naturais; Transmissão.

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