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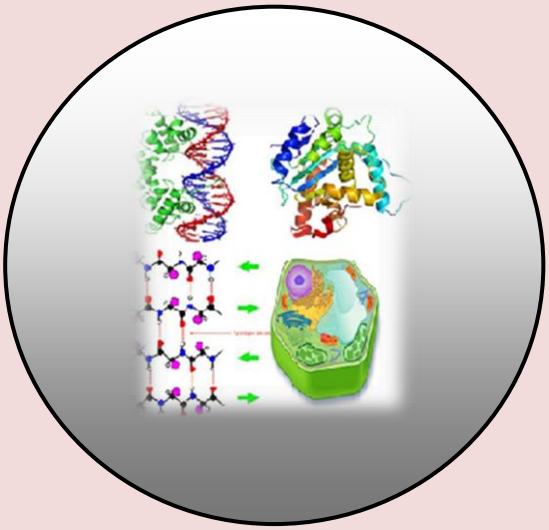
ISSN 2319-3077 Online/Electronic
ISSN 0970-4973 Print

Index Copernicus International Value
IC Value of Journal 82.43 Poland, Europe (2016)
Journal Impact Factor: 4.275
Global Impact factor of Journal: 0.876
Scientific Journals Impact Factor: 3.285
InfoBase Impact Factor: 3.66

J. Biol. Chem. Research
Volume 38 (1), 2021 Pages No. 97-107



Journal of Biological and Chemical Research

An International Peer Reviewed / Referred Journal of Life Sciences and Chemistry

Indexed, Abstracted and Cited in various International and National Scientific Databases

Published by Society for Advancement of Sciences®

J. Biol. Chem. Research. Vol. 38, No. 1, 97-107, 2021
(An International Peer Reviewed / Refereed Journal of Life Sciences and Chemistry)
Ms 38/01/4149/2021

ISSN 2319-3077 (Online/Electronic)
ISSN 0970-4973 (Print)

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REVIEW ARTICLE
Received: 08/09/2020 Revised: 10/02/2021 Accepted: 11/02/2021

Natural and Synthetic Compounds as Treatment Alternatives for COVID-19: A Current Review

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ABSTRACT

Coronavirus disease (Covid-19) caused by SARS-CoV-2 virus has put a world in a big and historical crisis since its outbreak in December 2019. The search for potent anti-viral drug and vaccines has begun immediately after the outbreak, considering high transmission and mortality rate of the novel virus. A number of antiviral drug trials are being made, but nothing is proved to be an exact therapy to date. Currently, researchers around the world are evaluating various natural and synthetic products against the main protease of SARS-CoV-2 to find antivirals specific to the virus. Many compounds either separately or in combination showed high binding efficacy and strong inhibitory activity through different interactions mainly hydrogen bonding and hydrophobic interactions although the mechanism of the activity is not fully understood. This review summarizes compounds with potential efficacy against SARS-CoV-2 to identify highly promising candidates that can greatly help to develop a drug or a vaccine for the novel virus.

Keywords: Coronavirus, COVID-19, Novel Coronavirus Main Protease (SARS-Cov-2 Mpro), Amino Acid Residues, Hydrogen Bonding and Hydrophobic Interactions.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019 is caused by novel corona virus disease 2019 (COVID-19) become a global pandemic and has since spread worldwide (Zhu et al., 2020. The disease is making the world to go through a historical crisis which is likely to continue for the coming couple of years. The outbreak of SARS-CoV-2 was considered to have originally started via a zoonotic transmission associated with the seafood market in Wuhan, China. However, human to human transmission was recognized as the main role in the subsequent outbreak afterward (Li et al., 2020). COVID-19 pandemic is distributed to 212 Countries and Territories around the world and as of 09 May 2020, 3 898 658 cases including 274, 290 deaths have been reported (ECDPC, 2020). Coronaviruses can infect diverse animals including livestock, companion animals and birds, causing serious respiratory enteric, cardiovascular and neurologic disease (Amer, 2018, Saif, 2004).

In humans, CoVs mostly cause respiratory and gastrointestinal symptoms ranging from the common cold to more severe disease such as bronchitis, pneumonia, severe acute respiratory distress syndrome (ARDS), coagulopathy, multi-organ failure and death, even though it was only thought that Coronaviruses cause mild, self-limiting respiratory infections in humans before the SARS-CoV outbreak (Cabeça et al., 2013, Vabret et al., 2003, Esper et al., 2010, Vabret et al., 2006 Patrick et al., 2005). Human coronaviruses (HCoVs) have also been associated with exacerbations of chronic obstructive pulmonary disease, (Geoffrey et al., 2009 cystic fibrosis (Luiz et al., 2012) and asthma (Susan et al., 2005, McIntosh et al., 1973). The novel virus is stronger in its transmission ability than other coronaviruses. The confirmed transmission modes of SARS-CoV-2 include respiratory droplets and physical contact, and the incubation period for the virus is approximately 3 to 7 days, but it can be as long as 24 days (Yang et al., 2020).

The life cycle of the virus with the host consists of the following 5 steps: attachment, penetration, biosynthesis, maturation and release. Once viruses bind to host receptors (attachment), they enter host cells through endocytosis or membrane fusion (penetration). Once viral contents are released inside the host cells, viral RNA enters the nucleus for replication. Viral mRNA is used to make viral proteins (biosynthesis). Then, new viral particles are made (maturation) and released (Berend et al., 2003). Coronaviruses have pricky spikes that project from their surface through which they are attached to the host cell to begin infection.

Once they are attached, a proteolytic enzyme of the host cell cleaves and activates the receptor-attached spike macromolecule. The cleavage and activation which varies based on the host cell proteolytic enzyme available facilitate cell entry through endocytosis or direct fusion of the viral envelope with the host membrane (Ahmad et al., 2020). Full understanding of their life cycle in the host cells is believed to have a great contribution in designing specific drug.

Today, absence of a distinct drug and vaccine for the novel virus and the rise of new cases and deaths all over the world make COVID-19 pandemic the leading international concern. The only option to minimize its damage to date is the prevention and control modes. The three strategies to control the spread of COVID-19 include:- reduce the number of infectious individuals; reduce the number of susceptible individuals and reduce contact between susceptible and infectious individuals (WHO, 2020, Hellewell et al., 2020, Bedford et al., 2020). However, available control strategies are not adequate when absence of a vaccine or effective treatment is taken into account.

Presently, the major concern regarding Covid-19 pandemic is to develop a vaccine and/or specific drug to save the lives of millions of people globally. Several drugs including lopinavir-ritonavir, remdesivir, hydroxychloroquine, and azithromycin have been tested in clinical trials (Cao et al., 2020, Gautret et al., 2020, Zhou et al., 2020), but nothing is proved to be an exact therapy to date. Testing is continued hardly in clinical trials to get a drug for this devastating pandemic and reduce its damage. A number of natural compounds from medicinal plants and synthesized compounds are showing good inhibitory activity against SARS-CoV-2 virus either separately or in combination. Thus, the binding efficacy of these compounds is summarized in this review.

Natural and Synthetic compounds as anti SARSCoV- 2 agents

There are many therapeutic alternatives to treat viral infections, but the high rate of virus mutation makes their full understanding and efficient antiviral drug synthesis challenging (Ahmed and Ibrahim, 2015). But, presently many natural and synthesized compounds are showing good anti SARS-CoV-2 virus activity. Withaferin-A (Wi-A), Withanone (Wi-N) (active withanolides of Ashwagandha) and Caffeic acid Phenethyl Ester (CAPE, bioactive ingredient of propolis) was tested against highly conserved protein, M^{pro} of SARS-CoV-2. These are natural products with a proved antiviral activity even though the mechanism of the activities has not been fully understood.

It was found from the investigation that Wi-N and CAPE inhibited efficiently to the level of N3 protease inhibitor. The strong binding ability and similar activity with N3 protease inhibitor might be attributed to relatively similar structure between them, making likewise mode of binding.

This indicates the potential available in natural compounds and the emphasis to be given in designing efficient drugs either by modifying or mixing them with synthetic products (Kumara et al., 2020). Andrographolide, a compound extracted and isolated from *Andrographis paniculata* plant was tested against SARS-COV-2 using silico approach. The compound showed strong binding ability to the site of SARS-CoV-2 Mpro. It was also proved by Computational approaches as andrographolide have good solubility, pharmacodynamics property and target accuracy. The structure (Figure 1) of the bioactive compound andrographolide has several –OH which might the reason behind its good activity by forming hydrogen bonding interactions (Enmozhia et al., 2020). In comparison to other synthetic compounds like disulfiram, tideglusib and shikonin, andrographolide showed great binding efficacy (Jin et al., 2020).

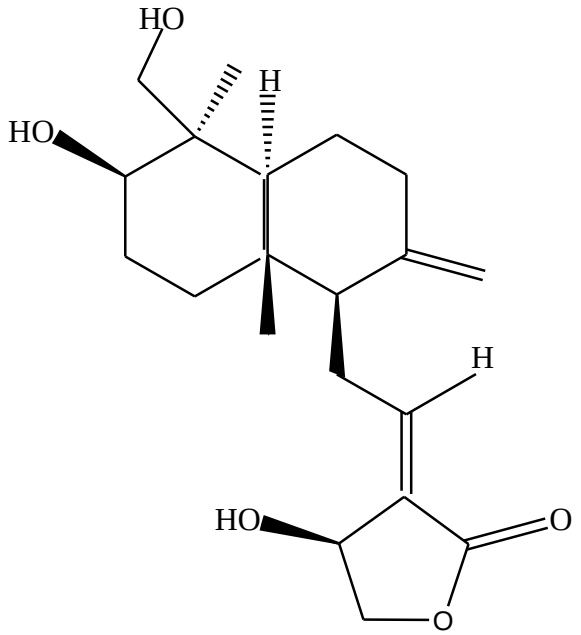


Figure 1. Structure of Andrographolide (Enmozhia et al., 2020).

A number of flavonoids from a created library were studied for their inhibition potential against SARS-CoV 3CLpro using FRET method. These polyphenolic secondary metabolites are reported as good antioxidants and anticancer (Burak and Imen, 1999, Ovando et al., 2009, Lee et al., 2009) while some flavonoids also have antiviral activity (Zakaryan et al., 2017).

Herbacetin, rhoifolin and pectolinarin inhibited SARS-CoV 3CLpro in excellent manner, showing better activity than previously reported flavonoids (Ryu et al., 2010, Nguyen et al., 2012, Schwarz et al., 2020). High binding activity of herbacetin might be associated with the presence of additional 8-hydroxyl group in its structure that creates higher number of hydrogen bonding for stronger interaction with S1 and S2 sites. The carbohydrate groups on the S1 and S2 sites of rhoifolin and pectolinarin may be related to their high affinity towards SARS-CoV 3CLpro since the –OH groups on the carbohydrates groups also form hydrogen bonding interactions. The finding of this study indicated a combination of biochemical assay and docking prediction resulted better inhibitory flavonoid derivatives which need attention for designing a drug for Covid-19 (Seri et al., 2020).

Arbidol is an approved antiviral agent in China and Russia in treating influenza, SARS, and Lassa viruses (Cheng et al., 2020, Xu et al., 2020). A few reports indicated that lopinavir/ritonavir and arbidol helped patients with COVID-19 to recover successfully (Lim et al., 2020, Wang et al.), but the mechanism remains controversial (Kim et al., 2020). Integrating lopinavir/ritonavir and arbidol appeared as a likely preferred option in a retro- spective study with a small sample size (Deng et al., 2020).

Lopinavir/ritonavir and arbidol were evaluated for their antiviral efficiencies with the 2019-nCoV disease (COVID-19) on fifty patients (lopinavir/ritonavir group, 34 cases and arbidol group, 16 cases). Arbidol showed higher activity than lopinavir/ritonavir in treating COVID-19 since it had a shorter duration of positive RNA test (Zhu et al., 2020).

A structure-based drug design approach was used to produce drug candidates from the existing pool of FDA-approved drugs and evaluated against the SARS-CoV-2. From the results, it was identified that Glecaprevir and Maraviroc (MVC) are the best inhibitors of SARS-CoV-2, playing the role through binding to the substrate-binding pocket of SARS-CoV-2 with non-covalent interactions. This may strongly support for the urgent and critical drug search to treat COVID-19 (Anas et al., 2020).

The potential of chloroquine and hydroxychloroquine was tested against SARS-CoV-2–infected Vero cells. Chloroquine and its analogue hydroxychloroquine were reported to have anti–SARS-CoV activity in vitro (Wang et al., 2020, Biot et al., 2020). Although there is no clinical evidence to support the use of Chloroquine and hydroxychloroquine for SARS-CoV-2 infection treatment, hydroxychloroquine was found to show better in vitro anti–SARS-CoV-2 activity (Yao et al., 2020). As it is clearly observed from the structures of the two compounds, the presence of –OH group (Figure 2.) is the most likely reason behind its better activity as it increases the hydrogen bonding interactions between the molecule and the amino acid residues of SARS-CoV-2.

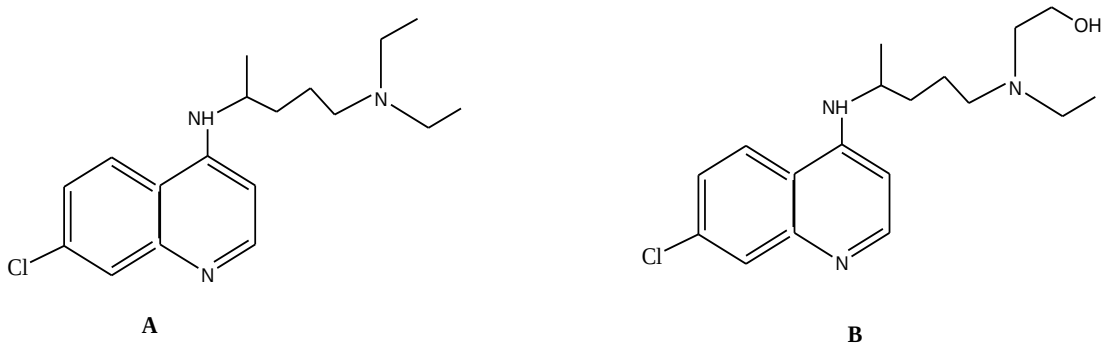


Figure 2. Structure of chloroquine (A) and hydroxychloroquine (B) (Yao et al., 2020).

A comparative study between Favipiravir (FPV) and Lopinavir (LPV)/ritonavir (RTV) was done in COVID-19 treatment based on changes in chest computed tomography (CT), viral clearance, and drug safety between two groups of patients. FPV showed a significantly higher improvement rate in chest imaging which is autonomously related to its faster viral clearance ability. The finding of the study announces a promising candidate that showed good control of the disease progression of COVID-19 by inhibiting the SARS-CoV-2 (Cai et al., 2020).

Forty antiviral phytochemicals were selected and evaluated against the main protease of SARS-CoV-2- Mpro using Auto Dock Vina and GOLD with the main protease as a standard.

Five of the candidates including hypericin, cyanidin 3-glucoside, baicalin, glabridin, and a-ketoamide-11r showed high binding affinity supported by noncovalent interactions with the binding site residues, hypericin showing the highest through pi-alkyl interaction with the catalytic binding residue Cys145. It is also predicted from the principal component analysis (PCA) of QSAR that L3 (a-ketoamide-11r) shows the lowest residuals because of the presence of the -CONH- and C=O groups in its chemical structure which enhances its stability through resonance stabilization, minimizing its interaction with SARS-CoV-2 Mpro Protein (PDBID- 6Y84) active site. These five selected phytochemicals can be used as potential inhibitors against the SARS-CoV-2 for the future (Islam et al., 2020). Chemical compounds from Indian spices were screened as potent inhibitors of SARS-CoV-2 main protease by applying bioinformatics method while α–ketoamide was used as a positive control (Umesh et al., 2020).

From the 45 compounds considered, four small molecules (Alpha-ketoamide, Carnosol, Rosmanol and Arjunglucoside-I) showed a great binding affinity to the defined (Owen et al., 2020) SARS-CoV-2 Mpro Protein (PDBID- 6Y84) active site and. The highest binding affinity was exhibited by Carnosol which may be attributed to formation of hydrogen bonds with Leu141, Ser144 and Cys145 and hydrophobic interactions with His41, Thr25, Asn142, Phe140, Glu166, Met165 amino acid residues of the active site. This compound also showed stable movement in the active site of SARSCoV-2 Mpro, forming a stable complex in the dynamic state. Both Rosmanol and Arjunglucoside-I also exhibited a strong binding affinity. The strong affinity of Rosmanol, a natural compound isolated from *Rosmarinus officinalis* might be related to its hydrogen bonds formation with Leu141, Gly 143, Ser144 and Cys145 and hydrophobic interactions with Thr25, 26, His41, Phe140, His163, and Leu27. The strong binding ability of Arjunglucoside-I might be related to its hydrophobic interaction with His41, 164 and Cys145 and further hydrogen bonding interaction with Thr25, Thr26, His163, and Glu166. Relatively the lower number of amino acid residues interacting with Arjunglucoside-I through hydrophobic and hydrogen bonding interactions might be the reason behind weaker affinity than Carnosol and Rosmanol. Carnosol and Rosmanol have the properties which can further exploited and investigated for drug candidate against SARS-CoV-2 (Umesh et al., 2020).

GC–MS analysis was used to identify eighteen compounds from garlic essential oil by molecular docking technique, out of which seventeen are organosulfur compounds. The inhibition ability of these compounds was tested against the host receptor angiotensin-converting enzyme 2 (ACE2) proteins in the human body. The interaction of cyclic octatomic sulfur (T18) was not demonstrated due to its lowest content in the essential oil and its bulky structure, since the later complicates the interaction with the ACE2 protein. Diallyl tetradisulfide(T5) showed the highest inhibiting activity which might be associated to presence of higher number nucleophilic sulfur atoms that can donate electron charges towards electrophilic sites, facilitating the condition for the π-electrons present at both ends of the compound for strong π-interactions with the ACE2 protein. Inhibition of ACE2 protein leads to prevention of protein maturation of the virus and the spread of infection. Trisulfide, 2-propenyl propyl (T11) showed similar activity with diallyl tetradisulfide (T5). The two leading compounds in percentage in the oil (allyl disulfide and allyl trisulfide) also showed strong inhibition activity. The order of the whole activity of the compounds is Diallyl tetradisulfide (T5) = Trisulfide, 2-propenyl propyl (T11) > Allyl disulfide = Allyl trisulfide > Allyl methyl trisulfide (T4) > 2-Vinyl-4H-1,3-dithiine (T8) >3- Vinyl-1, 2- dithiadicyclohex-4-ene (T9)> Methyl allyl disulfide (T12) > Diacetonalcohol (T13) > Trisulfide, (1E)-1- propenyl 2-propenyl (T14) >Allyl sulfide (T15) > Allyl (E)-1-propenyl disulfide (T3) > Allyl (Z)-1-propenyl disulfide (T7) > Carvone (T10) > 1-propenyl methyl disulfide (T16) > Trisulfide, (1Z)-1- propenyl 2-propenyl (T17) > 1, 2-Dithiole (T6). The finding of the study indicated the capability of the compounds in inhibiting ACE2 and resisting SARS-CoV-2 which shows the attention to garlic in searching specific and potent drug for the disease (Thuy, 2020).

A number of ayurvedic antitussive medicines, anti-viral phytochemicals and synthetic anti-virals were screened against SARS-CoV-2 MPro. The phytochemicals under study contain alkaloids, flavonoids, glucosinolates, phenolics, terpenes and terpenoids, which are prepared from available structures (Kim et al., 2019). Many molecules such as d-Viniferin, myricitrin, chrysanthemin, myritilin, taiwanhomoflavone A, Lactucopicrin 15-oxalate, nympholide A, afzelin, biorobin, herperidin and phyllaemblicin B exhibited great binding affinity with SARSCoV-2 targets including MPro, RdRp and hACE-2. Most of these compounds are natural products, indicating how much bioactive phytochemicals can be a baseline for designing and developing a drug against SARS-CoV-2 (Joshi et al., 2020).

Chinese medical herbs that are confirmed in having anti-sever acute respiratory syndrome coronavirus were screened and 13 candidates were tested against SARS-CoV-2 targets such as 3CLpro, PLpro and spike protein using docking analysis.

The selected compounds showed strong inhibition ability (Zhang et al., 2020), Coumaroyltyramine, Cryptotanshinone, Kaempferol, Moupinamide, N-cis-feruloyltyramine, Quercetin and Tanshinone IIa showed great affinity towards PLpro which might be associated to interfere occurred when the substrate enters the enzyme's active sites (Ratia et al., 2006). Those showed strong inhibition on 3CL pro including Betulinic acid, Coumaroyltyramine, Cryptotanshinone, Desmethoxyreserpine, Dihomo-c-linolenic acid, Kaempferol, Lignan, N-cis-feruloyltyramine, Quercetin, Sugiol and Tanshinone IIa by entering the region between domains 2 and 3, blocking dimmer formation (Anand et al., 2003). Good inhibition activity of Dihydrotanshinone I might be related to blocking viral entry to bound the fusion cone of spike which is required for viral membrane fusion protein (Xu et al., 2006).

Anti SARS-CoV-2 activity of thousands of phytochemicals was screened by in-silico method. Withanone compounds, root extracts of *W. somnifera* (Chaurasiya et al., 2008) showed good binding activity to ACE2-RBD interface aided by hydrogen bonding interaction between the phytocompound and Tyr16 of ACE2 and Tyr175 of RBD. Inhibition potential of the phytocompound was more enhanced by its movement towards the centre of the binding interface as a result of other hydrogen bonding interaction with ACE2 N15, ACE2 Q19 and RBD R78. The stronger ionic interaction at the binding interface of the modeled ACE2 receptor and RBD of 2019-nCoV greatly strengthens the binding affinity of the Withanone compounds. This is another highlight for the importance of natural compounds in controlling COVID-19 entry into host cells and further investigations on *W. somnifera* plant may help in searching a drug manage and control COVID-19 infection (Balkrishna et al., 2020).

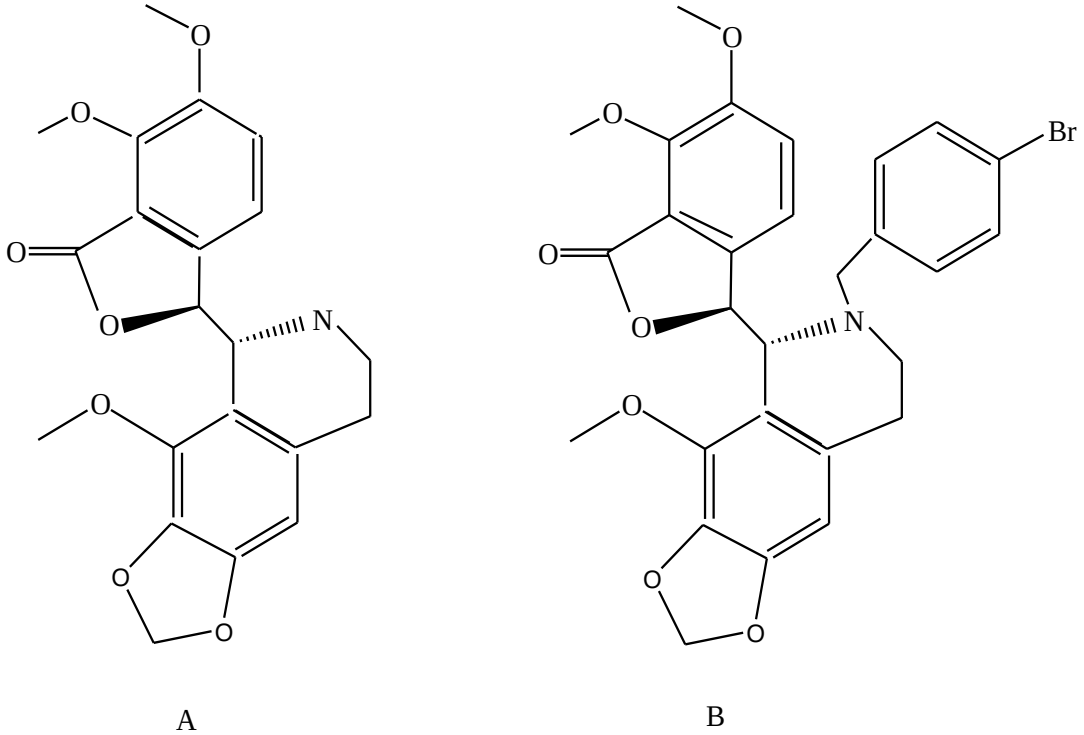
The potential of FDA-approved thiol-reacting disulfiram with its metabolites and captopril in inhibiting essential viral enzymes of SARS-CoV-2 was checked by an in silico approach. Disulfiram (DSF) including its metabolites and captopril showed strong binding affinity through the irreversible and preferable covalent interaction. The mechanism of action for antiviral compounds is not well understood, but it is shown here that the inhibitory potential of these compounds on 3CLpro is a two-step; initial binding to the protein followed by a nucleophilic attack by thiol group of Cys1459 (Lobo-Galo et al., 2020).

Three drugs (lopinavir, oseltamivir and ritonavir) obtained from Drug Bank (Wishart et al., 2018) were analysed against SARSCoV-2 protease by computational methods both separately and in combination. The combined drugs exhibited a better binding than the individual drugs with improved binding energy. Hydrogen bonding and hydrophobic interactions between SARS-CoV-2 protease and the combined drugs are responsible for strong binding. For SARS-CoV-2 protease–lopinavir complex, hydrophobic interactions are dominant. In SARS-CoV-2 protease-oseltamivir and ritonavir complexes both hydrogen bonding and hydrophobic interactions participate without dominating each other. The highly effectiveness of the combined drugs lopinavir, oseltamivir and ritonavir against SARSCoV-2 protease emphasizes as combining active compounds is among the major ways to obtain the successful inhibition of COVID-19 (Muralidharan et al., 2020.

A FRET-based enzymatic assay was applied to evaluate the inhibition potential of boceprevir, GC-376, rupintrivir and calpain inhibitors II, and XII on SARS-CoV-2 main protease (Mpro). Boceprevir (IC_{50} = 4.13 μM) and narlaprevir (IC_{50}=4.73 μM) strongly inhibited Mpro in a better manner than simeprevir (IC_{50}=13.74 μM). It is suggested that these two compounds are not non-specific cysteine protease inhibitors. MG-132 showed better binding affinity (IC_{50}= 3.90 μM) towards SARS-CoV-2 main protease (Mpro) than Boceprevir and narlaprevir. Calpain inhibitor II(IC_{50}= 0.97 μM) and XII(IC_{50}= 0.45 μM) were found to better inhibitors by far, Calpain XII showing the best inhibitory activity (Ma et al., 2020).

Ten essential oils were evaluated for their inhibitory activity against the angiotensin-converting enzyme 2 (ACE2) receptor targeting for a search of compounds capable to block cell entry of SARS-CoV-2. A significant inhibition activity was observed for all essential oils from which geranium and lemon oils displayed better ACE2 inhibitory effects in epithelial cells although it is dependent in HT-29 cells (Kumar et al., 2020). The mechanism of action of these oils and their components were found to be mainly through inhibition of viral replication (Loizzo et al., 2008).

The binding affinity of noscapines (23B)-protease ligand and its derivatives to form a complex with the active site of SARS-CoV-2 thereby by inhibiting the novel virus was evaluated using generic evolutionary method (GA). Noscapine is an alkaloid based on benzylisoquinoline with various applications including anticancer (Kumar et al., 2019).



A B

Figure 3. Noscapine (A) and CMPD23B (B) (Kumar et al., 2020).

All Noscapine derivatives showed good binding affinity which might be attributed to different interactions like hydrogen bonding, vdW, electrostatic interactions, π-π stacking, etc. between the ligands and the aminio acid residues such as ARG40, TYR54, CYS85, PHE181, ARG188, ARG40, TYR54, GLU55, MET82 and ASN84 With CMPD23B showing the best of all. In the case of CMPD23B extra stacking occurs in electrostatic favorable regions and van der Waals interactions in the region of steric favorable with protease of coronavirus contributed for its highest binding affinity and makes the difference to the others. CMPD23B fulfills all criterias of drug likeness with only one violation, indicating high probability for this chemical to be a drug for the novel virus which leaves a hopeful open door for further investigations (Kumar et al., 2020).

CONCLUSION

Coronavirus is a series threat all over the world today. A huge effort is being applied from researchers extensively, but nothing is proved to be specific drug or a vaccine yet. The search for effective treatment has been continued to minimize the mortality of SARS-CoV-2 with some natural and synthetic compounds showing a promising inhibition against SARS-CoV-2 protease. Although the mechanism of the action is still doubt, the irreversible covalent interactions, hydrogen bonding, hydrophobic interactions, π-π stackings and van der Waals interactions between the ligands and the amino acid residues were found to contribute a lot. The inhibition potential of some compounds was found to be enhanced when combined, indicating the emphasis to be given for combining the potent compounds. Combination of active natural compounds with synthesized compounds may help to reach on persuasive treatments for SARS-CoV-2 rapidly.

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