Review Article

Thai Journal of Pharmaceutical Sciences

Probable selective compounds for inhibition of SARS-CoV-2 infection: A review

Nagaraju Rajendraprasad

Department of Chemistry, JSS College of Arts, Commerce and Science (An Autonomous Institute of University of Mysore), Mysuru, Karnataka, India

Corresponding Author:
Nagaraju Rajendraprasad, Department of Chemistry, JSS College of Arts, Commerce and Science (An Autonomous Institute of University of Mysore), Mysuru, Karnataka, India.
Mobile: +91-9880547493.
E-mail: prasadtnpur@gmail.com

Received: Aug 13, 2020
Accepted: Jan 11, 2021
Published: Dec 16, 2021

ABSTRACT

The world is severely facing the pandemic COVID-19 Corona viral disease. Many people died and more than five millions are fighting for their life in the world. The viral candidate has become to play villain role for the real life due to non-availability of medication. In this background attempt is made to present a review report on the probable and effective compounds to inhibit the viral activity of SARS-CoV-2. The works on the use of plant-based and synthetic compounds to suppress the viral functioning is summarized. Wherever possible, the mechanism of action with the results and effect of dose are described. Compounds showing exemplary abilities to inhibit viral functioning including those associated to SARS, Ebola, MERS, etc., were highlighted. The mechanism of action and inhibitory ability of the candidate compounds have been highlighted so that the choice to undertake further research to identify effective anti-viral drugs to treat COVID-19 decease. This review will definitely make researchers to raise the hope for use or modification of existing medications to treat this epidemic COVID-19 disease.

Keywords: Corona virus, COVID-19, pandemic, SARS-CoV-2, therapeutic compounds

INTRODUCTION

The coronavirus, a third pathogenic human corona virus (HCoV) [Figure 1], named as 2019 novel Corona Virus (SARS-CoV-2), was found reported in Wuhan of China[1] very recently. Corona virus, denoted by SARS-CoV-2, is a similar virus to the severe acute respiratory syndrome (SARS) virus that became responsible organism for an outbreak in 2003[2] and to the Middle-East respiratory disease virus (MERS-CoV) that emerged in 2012 which led to global epidemics with high morbidity and mortality.[3]

These HCoVs cause high-morbidity lower respiratory tract conditions, such as pneumonia, bronchiolitis, and croup, especially in the elders and young children.[4-6]

The SARS-CoV-2 is a single-stranded RNA genome (size range between 26.2 and 31.7 kb, positive sense), largest among all RNA viruses, with an enveloped structure[7,8] bearing the club-shaped projections of glycoproteins (diameter 80–120 nm).[7] The number of open reading frames in the CoV genome ranges from six to ten.[8] Its genetic material is susceptible for frequent recombination process, which can give rise to new strains with alteration in virulence.[9]

The spike (S) trimeric, membrane (M), envelop (E), and the nucleocapsid (N) proteins are principal chemical blocks in the structure of SARS-CoV-2. These along with glycoproteins have to be destroyed by targeted molecules to cure COVID-19 disease. Chemically, either N-linked or O-linked glycoproteins with sugar residues enriched with hydroxymethyl or hydroxy groups are more active in viruses, and these groups are taken into account to suppress the viral infection. Thus, with the chemical and biological background one must be keen to identify the target molecule in discovering the vaccine or a drug to cure COVID-19 disease.

The literature survey revealed non-availability of a definite therapy for COVID-19 disease. However, from the contributions of past and present researchers the way of finding the remedy to cure the pandemic disease can be made bit convenient. In this direction, a review has been undertaken to present the efforts put by various workers on synthesis and study of antiviral activity of some chemical compounds and to propose the probable active compounds to treat COVID-19.

DISCUSSION

Edible Oils with Antiviral Properties

Ayurveda has been proved as one of the best medication methods to treat many diseases right from ancient days. Rajesh *et al.*[10] presented a review for methods available to

the preventive management of novel H1N1 Flu pandemic, which is also a viral disease. The glycoproteins of viruses are targeted to neutralise with coconut oil (Cocos nucifera oil) as therapeutic agent. Coconut oil, as an Ayurvedic medicine in India, is used to treat abscesses, alopecia, amenorrhea, asthma, blenorrhagia, bronchitis, bruises, burns, cachexia, calculus, colds, constipation, cough, debility, dropsy, dysentery, dysmenorrhea, earache, erysipelas, fever, flu, gingivitis, gonorrhea, hematemesis, hemoptysis, jaundice, menorrhagia, nausea, phthisis, pregnancy, rash, scabies, scurvy, sore throat, stomachache, swelling, syphilis, toothache, tuberculosis, tumors, typhoid, venereal diseases, and wounds[11] because the medium chain fatty acids (MCFA), and their derivatives (e.g., monoglycerides) display potent antiviral properties.[12] After C. nucifera oil is consumed, the resulted lauric acid, a MCFA, is expected to kill or inactivate pathogenic microorganisms inside the body by reacting with the hydroxyl groups of glycoproteins in a process of esterification. The process is also for solubilizing the lipids and phospholipids in the envelope of the pathogenic organisms causing the disintegration of their outer membrane [Figure 2].

The MCFA is also expected to interfere with the organism's signal transduction,[13] and thus the deactivation of virus[14] can be initiated. As an alternate to the C. nucifera oil, the ground nut, mustard or palm oil are also useful because they too undergo breakdown to produce required fatty acids. The mutation of virus is reasonably avoided by rinsing throat and applying the nose and eyes with suitable amount of oil.

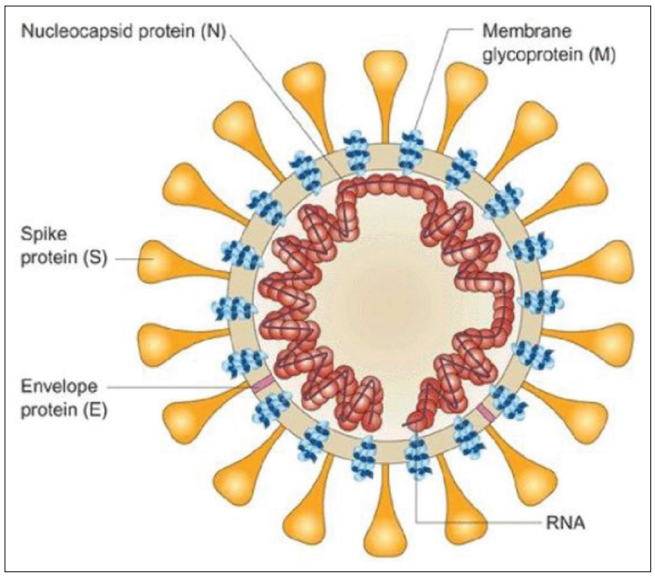


Figure 1: Structure of HCoV

Further, lauric acid (C12) and monolaurin, its derivative, have been known for many years to have significant antiviral activity. Lauric acid is a MCFA, which makes up about 50% of coconut oil; monolaurin is a metabolite that is naturally produced by the body's own enzymes on ingestion of coconut oil and is also available in pure form as a supplement. Sodium lauryl sulfate, a common surfactant that is made from lauric acid, has been shown to have potent antiviral properties. Lauric acid, monolaurin, and sodium lauryl sulphate (SLS) are used in a wide range of products for their antiviral properties. The antiviral activities of lauric acid and monolaurin were first noted by Sands *et al*.[15] and later by Hierholzer and Kabara.[16] In particular, Hierholzer and Kabara[16] showed that monolaurin was able to reduce infectivity of 14 human RNA and DNA enveloped viruses in cell culture by >99.9%, and that monolaurin acted by disintegrating the virus envelope. Thormar *et al*.[17] confirmed the ability of lauric acid and monolaurin to inactivate viruses by disintegration of the cell membrane. SLS has been shown to be able to solubilize and denature the viral envelope.[18,19]

The Junin virus (JUNV) is the causative agent of Argentine hemorrhagic fever. In a comparison among the saturated fatty acids from C10 to C18 against JUNV infection, Bartolotta *et al*.[20] showed that lauric acid was the most active inhibitor. From mechanistic studies, it was concluded that lauric acid inhibited a late maturation stage in the replicative cycle of JUNV. From transmission electron microscope images, JUNV is an enveloped virus featuring glycoproteins that are embedded in the lipid bilayer forming viral spikes;[21] this is similar to SARS-CoV-2.

Hornung *et al*.[22] showed that in the presence of lauric acid, the production of infectious vesicular stomatitis virus was inhibited in a dose-dependent and reversible manner: after removal of lauric acid, the antiviral effect disappeared. They observed that lauric acid did not influence viral membrane (M) protein synthesis, but prevented the binding of viral M proteins to the host cell membrane.

The coconut oil is quite good enough as agent to fight against viral functions in humans and animals because of its composition with lauric acid and monolaurin.[23] Monolaurin was reported to treat influenza virus,[24] Simean immunodeficiency virus,[25] and human immunodeficiency virus (HIV).[26] SLS was also found reported for use to inactivate viruses in milk of farm animals.[27] Coconut oil itself was shown to have anti-HIV properties in small clinical studies.[28,29] With

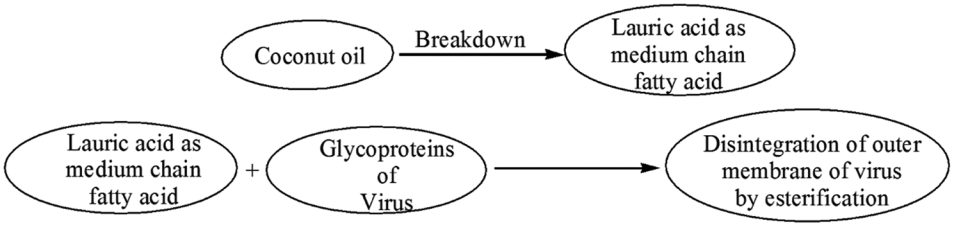


Figure 2: Probable pathway of disintegration of virus by coconut oil

these backgrounds, as a hydrophobic substance, the coconut oil has the ability to destroy the viral structure. Therefore, drug discovery researchers can emphasise to study the efficacy *in vivo*, dosage, regimen and administrative routes, and to decide its therapeutic use to cure COVID-19 disease caused by SARS-CoV-2.

In a typical report, the inactivation of enveloped viruses and killing of cells using fatty acids and monoglycerides was described.[17] It is prevalent to understand that the medium-chain saturated and long-chain unsaturated fatty acids are highly active against the enveloped viruses at very high concentrations. Monoglycerides of these fatty acids are also highly antiviral at a concentration 10 times lower than that of the free fatty acids. Antiviral fatty acids affect the viral envelope, causing leakage and at higher concentrations, a complete disintegration of the envelope and the viral particles. It was also described the disintegration of the plasma membranes of tissue culture cells resulting in cell lysis and leads to death. Linoleic and other fatty acids were found suited to destroy the poliovirus. At very low concentrations of moanocaprin (2 mM) and monolaurin (0.9 mM), the inactivation of virus was found appreciable. The effective antiviral functioning of stored milk due to lipoprotein lipase was also highlighted in this article. On storing of milk, the released fatty acids were found highly responsible in disintegrating the virus activity. Thus, a clear indication can be obtained from this report that the fatty acids and milk proteins or other products may be considered to investigate as inhibitors of SARS-CoV-2.

Pyrazolone Group of Compounds as SARS-CoV 3C Like Protease Inhibitors

Exactly a decade ago an article[30] on synthesis and evaluation of pyrazolone compounds as SARS-CoV 3C like protease inhibitors (SARS-CoV $3CL^{pro}$) was published. The SARS-CoV is a positive-strand RNA virus that uses a complex set of enzymes to replicate the largest RNA genomes at present known for RNA viruses and synthesize an extensive set of 5' leader-containing subgenomic mRNAs that encode the viral structural proteins and several species-specific proteins with unknown functions. The features and the symptoms of diseases caused by SARS CoV and SARS-CoV-2 are somewhat similar one to another, and hence, the molecules could be challenged to check their capability in reducing the SARS-COV-2's mutation. The authors presented the efficiency of synthesized compounds with varied functional groups toward the inhibition of SARS-CoV $3CL^{pro}$ along with the comparison of 3,5-dioxopyrazolidine (Compound 1) [Scheme 1] as SARS-CoV inhibitor which was reported by Chen *et al*.[31] They described the significant functioning of three (Compound 2, 3 and 4) [Scheme 1] out of 21 compounds toward the inhibition of SARS-CoV $3CL^{pro}$. The structural formulae of the compounds presented in Scheme 2 reveals that the greater inhibition of SARS-CoV $3CL^{pro}$ is majorly due to the presence of carboxyl group, which is expected to involve in arresting the mutation of virus. The cytotoxicity was studied by MTT assay for compounds 2 to 4. From the data of computer model and docking study, it was observed the formation of hydrogen bond between oxygen of carboxy group of compounds and side chain of Gln-192 [Figure 3]. This clued that the carboxy group containing pyrazolidine compounds found effective to inhibit SARS-CoV 3 CL^{pro}.

Lopinavir (LPV) and Other HIV-1 Protease Inhibitors

The molecular docking study of LPV [Scheme 2], an HIV-1 protease inhibitor was reported[32] for showing its potency against CoV infection.[33] The other approved HIV-1 protease inhibitors, namely, tipranavir (TPV), saquinavir (SQV), ritonavir (RTV), nelfinavir (NFV), indinavir (IDV), darunavir (DAR), atazanavir (ATV), and amprenavir (APV) [Scheme 2] were also tested by docking experiments by ArgusLab software. A polypeptide substrate with TVLQSGFR sequence was constructed in Argus-Lab Software and subjected to find enzyme binding site. The substrate was docked to optimize coordinate structure of Mpro in Hex software. The crystal structure of Mpro with PDBID of 1UK3 was used as a starting structure throughout this study. Serial and triplicate docking experiments were carried out and calculated the binding energy, and fitness of the inhibitors to the enzyme active site was ascertained. The extraction of binding sites was also optimized in the study. The resulted data indicated that binding energies of inhibitors fitness are in the order LPV > SQV > TPV > RTV > IDV > ATV >DAR > NFV > APV. The binding between the compound and the tertiary structure of enzyme observed in the study is showed in Figure 4. In this investigation the calculated RMSD, RMSF, MSD, dipole moment, diffusion coefficient, binding energy, and binding site similarity indicated effective binding of inhibitors to SARS proteinase resulting in their structural changes, which coincide with proteinase inhibition. By experiments, the authors draw the outcome that LPV and SQV were the most and the least powerful inhibitors of coronavirus proteinase, respectively. A most recent report[34] outlined that a non-critical SARS-CoV-2-infected patient was treated with LPV/RTV on the 8th day of admission, after which the clinical symptoms improved and the coronavirus load began to decrease until undetectable. It was also showed that LPV/RTV could inhibit the replication of MERS-CoV and SARS-CoV *in vitro*.[35] In primate models, animals treated with LPV/RTV for MERS were found to have a better prognosis than untreated animals. Thus, LPV/RTV

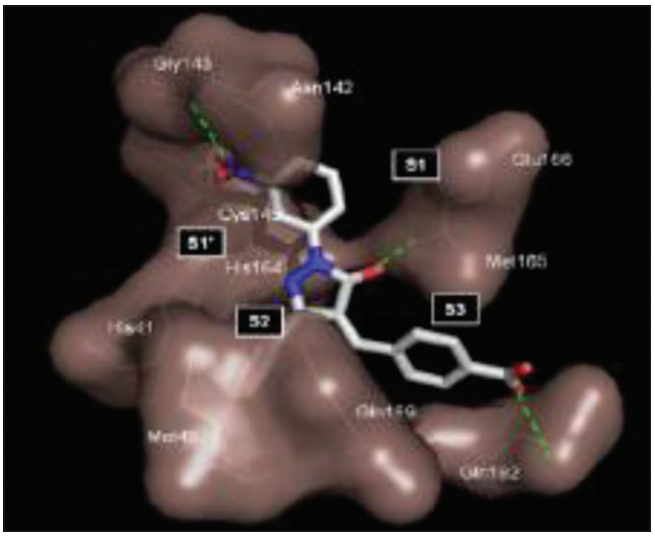
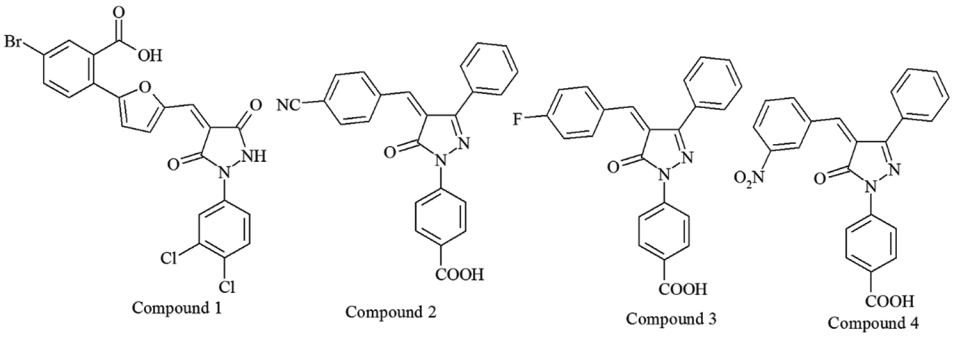
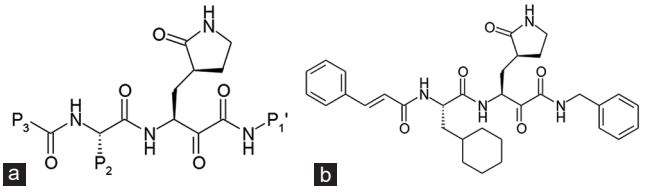


Figure 3: Docking studies for showing the compounds' binding in the active site of SARS CoV $3CL^{pro}$



Scheme 1: Chemical structures of SARS-CoV 3CL^{pro} inhibitors



Scheme 2: Chemical structures of a) α-ketoamides with P1', P2 and P3 substituents and b) P1′= benzyl, P2 = cyclohexylmethyl, and P3 = cinnamoyl substituted α-ketoamide.

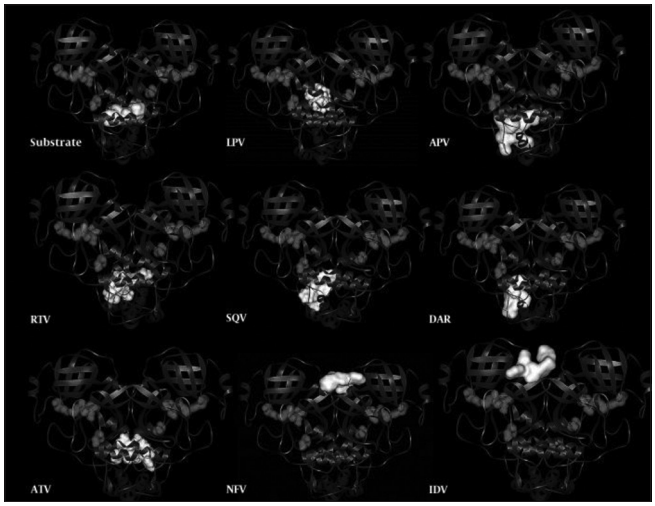


Figure 4: Representation of binding between the targeted compounds (LPV, SQV, TPV, RTV, IDV, ATV, DAR, NFV and APV to the nnzyme tertiary structure

can be the most prominent target compounds to disinfect SARS-CoV-2.

α-Ketoamides as Inhibitors of Coronavirus and Enterovirus Replication

A group of researchers from China, Germany, Belgium, and Netherlands have reported[36] synthesis of 11 α-ketoamides [Scheme 2] and tested their ability to the inhibition of coronavirus and enterovirus replication. The structure-based design of peptidomimetic α-ketoamides as inhibitors of main and 3C proteases was proposed. Authors used a 5-membered ring (γ-lactam) derivative of glutamine (Gln-Lactam) as the P1 residue (His at the Nsp13/Nsp14 cleavage site) in the α-ketoamides. This moiety was found to be a good mimic of Gln and enhance the power of the inhibitors by up to 10-fold, most probably because compared to the flexible Gln side-chain, the more rigid lactam leads to a reduction of the loss of entropy on binding to the target protease.[37,38] The substituents at the P1', P2, and P3 positions of the α-ketoamides were optimized and subjected to check the effect of them to inhibit coronaviral activity. The synthesized compounds were subjected to study of crystal properties. From the keen observation of behavior of synthesized organic α-ketoamides, only two compounds showed acceptable character toward the effective functioning against the HRV2, HRV14, and EV-D68 in HeLa (Rh) cells.

As per the results of structure-based optimization inhibition study, the compound with benzyl (P_1'), cyclohexylmethyl (P_2), and cinnamoyl (P_3) substituted α-ketoamide [Scheme 2] exhibited very good inhibitory activity against the SARS-CoV Mpro as well as the enterovirus 3Cpro, and its performance in the SARS-CoV and enterovirus replicons was found convincing. The compounds were tested for antiviral activity against HCoV NL63 in LLC-MK_2 and $CaCo_{2\ cells}$. The results substantiated that low- or sub-micromolar EC_{50} values in LLC-$MK_{2\ cells}$ but were largely inactive in $CaCo_{2\ cells}$. The compounds were inactive with EC50 >87 μM against Coxsakievirus B3 in Vero cells, but they were found better active in Huh T-7 cells. The compound with benzyl (P_1'), cyclohexylmethyl (P_2), and cinnamoyl (P_3) substituted α-ketoamide also exhibited similar activities against MERS-CoV and SARS-CoV. The same compound evolved with excellent activity against MERS-CoV when Huh7 cells were the host cells (400 pM), the activity was weaker by a factor of up to 12,500 when Vero cells were used (EC_{50} = 5 μM). Besides, it also exhibited excellent anti-MERS-CoV activity in human Calu3 lung cells. The EC_{50} value of this compound while inhibiting SARS-CoV was found as 2.1 μM revealed the activity of this molecule. However, a clear fail to show activity against viruses in Vero cells. However, authors failed to present the complete termination or disintegration of viral functioning by the synthesized compounds. In spite of this, researchers could be interested to take up further investigation to study the interaction of these molecules with viral glycoproteins.

Triazole Derivatives as Potential CoV Helicase Inhibitors

Triazole derivatives have been synthesized[39] and subjected for docking experiments to the study of potential CoV helicase

inhibition capacity. Sixteen 1,2,4-triazoles were synthesized by following simple, straight forward, and solvent free reactions using 4-amino-5-hydrazino-4H-1,2,4-triazole-3-thiol as a starting material. The structural features of the resulted compounds were compared with the lead compound SSYA10-001 [Scheme 3]. All the characterized compounds were subjected to check the ability to the inhibition of helicase MERS-CoV enzymatic activity.

The starting compound, 4-amino-5-hydrazino-4*H*-1,2,4-triazole-3-thiol inhibited the M-nsp 13 helicase and ATPase activity with IC_{50} value of 12.4 and 8.9 μM, respectively. This prompted the authors to further investigate the synthesized compounds. Only two of 16 compounds, namely, 4-(cyclopent-1-en-3-ylamino)-5-[2-(4-iodophenyl) hydrazinyl]-4*H*-1,2,4-triazole-3-thiol and 4-(cyclopent-1-en-3-ylamino)-5-[2-(4-chlorophenyl) hydrazinyl]-4*H*-1,2,4-triazole-3-thiol were the most effective MERS-CoV helicase inhibitors with ATPase IC_{50} values of 0.47 and 0.51 μM, respectively. From the results of molecular docking study, it was emerged that 4-(cyclopent-1-en-3-ylamino)-5-[2-(4-iodophenyl) hydrazinyl]-4*H*-1,2,4-triazole-3-thiol and 4-(cyclopent-1-en-3-ylamino)-5-[2-(4-chlorophenyl) hydrazinyl]-4*H*-1,2,4-triazole-3-thiol were the most potent against target protein M-nsp 13 in the active binding site of 5WWP with very low binding energies. The resulted docking of these two effective and potent molecules into inhibitor binding pocket of MERS-CoV (5WWP) resembled with that of SSYA10-001 [Figure 5], and it is said to prevail the suitability of these compounds to resist the virus functioning. The difference in binding affinity of the compounds was due to the substituents in the structures. The binding study was also reported the binding interaction with active pockets, namely, Tyr 159, Tyr 7, Tyr 171, and Arg 163. Thus, the work reached to the conclusion that the activity of these compounds to inhibit CoV was due to the presence of cyclopentene group.

Drug Combinations Targeting SARS-CoV and SARS-CoV-2: Repurposable Drugs

An article reported[40] the network-based methodologies for rapid identification of candidate repurposable drugs and potential drug combinations targeting the inhibition of SARS-CoV-2 acitivity. The inspection was undertaken by following the bioinformatics validation of drug-induced gene signatures and HCoV-induced transcriptomics in human cell lines. The mechanisms were postulated for the action in a specific HCoV for which repurposing was proposed. From the phylogenetic analyzes using the genome sequence data from 15 HCoVs to inspect the evolutionary relationship of SARS-CoV-2 with other HCoVs, it was found that the genomes of SARS-CoV-2 had ~99.99% nucleotide sequence identity across three diagnosed patients. A 79.7% of nucleotide sequence identity by SARS-CoV-2 with SARS-CoV among the six other known pathogenic HCoVs, revealed the conserved evolutionary relationship between SARS-CoV-2 and SARS-CoV. More than 2000 molecules were subjected to construct the drug-target network and out of which 135 were found associated with the HCoV–host interactive. The network proximities were calculated to validate the bias of the pooled cellular proteins from six CoVs, namely, SARS-CoV, MERS-CoV, HCoV-229E, HCoV-NL63, mouse MHV, and avian IBV.

The calculated Z-scores showed consistency among the pooled 119 HCoV-associated proteins and four other individual CoVs. The Pearson correlation coefficients of the proximities of all the drugs for the pooled HCoV were reported to be satisfactory. These network proximity analyzes put the authors to become frontline to propose repurposable candidates to prevent or curing of HCoVs.

All 135 drugs were subjected for gene set enrichment analysis (GSEA) using transcriptome data of MERS-CoV and SARS-CoV infected host cells and the drug-gene signatures were generated. The further investigation led the researchers to end up with several interesting compounds. In the analysis mesalazine (anti-inflammatory drug), sirolimus (immunosuppressor), and equilin (agonist of the estrogen receptor for menopausal symptoms) achieved the highest GSEA scores of 3, followed by paroxetine and melatonin with GSEA scores of 2. The other high-confidence repurposable

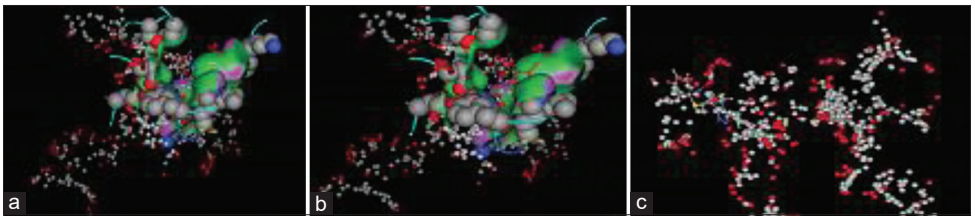
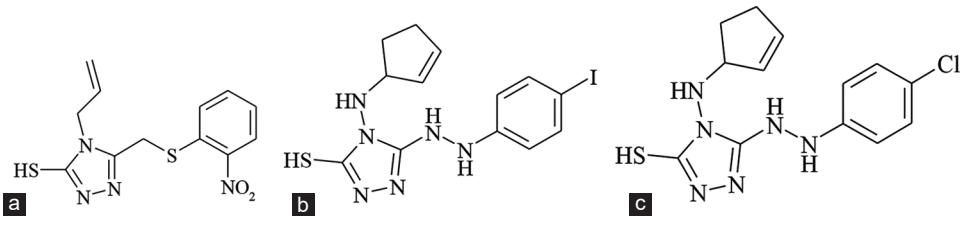


Figure 5: Molecular docking interaction images of (a) 4-(Cyclopent-1-en-3-ylamino)-5-[2-(4-iodophenyl)hydrazinyl]-4H-1,2,4-triazole-3-thiol, (b) 4-(Cyclopent-1-en-3-ylamino)-5-[2-(4-chlorophenyl)hydrazinyl]-4H-1,2,4-triazole-3-thiol and (c) SSYA10-001 into inhibitor binding pocket of MERS-CoV (5WWP)



Scheme 3: Chemical structures of lead and active compounds: a) SSYA10-001; b) 4-(cyclopent-1-en-3-ylamino)-5-[2-(4-iodophenyl) hydrazinyl]-4H-1,2,4-triazole-3-thiol; and c) 4-(cyclopent-1-en-3-ylamino)-5-[2-(4-chlorophenyl) hydrazinyl]-4H-1,2,4-triazole-3-thiol.

drugs, namely, irbesertan (antihypertensive), toremifene (antineoplastic), camphor (antipruritic, anti-infective), mercaptopurine (antimetabolite and antineoplastic), sirolimus (immunosuppressive), carvedilol (beta-blocker), colchicine (anti-inflammatory), dactinomycine (antineoplastic), quinacrine (antimalarial and antibiotic), eplerenome (diuretic), emodin (anthraquinone) and oxymetholone (anabolic steroid) were also selected to study their inhibition capacity against HCoVs based on their features to bind with the target proteins and specifically literature-reported antiviral evidence. The chemical structures of 16 compounds selected for study are presented in Scheme 4. The medicinal uses of each of these compounds were described based on the literature evidence for their biological functioning. Besides, the antiviral behavior of each of these target compounds also postulated.

The roles of toremifene in blocking the viral infections from MERS-CoV, SARS-CoV, and Ebola virus in established cell lines[41,42] and in destabilising the membrane protein of virus and inhibition of l replication,[43] the behavior of equilin in inhibiting the entry of Zaire Ebola virus glycoprotein and HIV,[41] the potency of irbesertan in inhibiting hepatitis B virus and the hepatitis delta virus, ability of sirolimus to block viral protein expression and to cure H1N1 pneumonia,[44] the selective inhibition ability of mercaptopurine for SARS-CoV and MERS-CoV[45,46] and antiviral properties of melatonin[47-49] and eplerenone[50] were described based on the literature evidence and the obtained Z-scores.

The effect of combination drugs, with increased efficacy, on inhibition of SARS-CoV-2 was also reported. Sirolimus plus dactinomycin were proposed a combination regiments to treat HCoV. These regiments were assumed to inhibit mTOR signaling and RNA synthesis pathway (including DNA topoisomerase 2-alpha and DNA topoisomerase 2-beta) in HCoV-infected cells. From the network analysis and the literature knowledge,[43,51-54] it was found that the combination of toremifene plus with emodin might be a suitable and potential therapeutic approach for SARS-CoV-2. Mercaptopurine's ability to inhibit SARS-CoV and MERS-CoV by targeting papain-like protease and antiviral property of melatonin judged as a selective medicament for SAR-CoV-2.

With all the above possibilities, the article put probable therapeutic agents to treat SARS-CoV-2 either using single or combined medicaments out of the drugs undertook in the study. These candidatures have to be confirmed further by thorough clinical studies and to be adjudged factually.

Hydroxychloroquin and Chloroquin as SARS-CoV Inhibitors

As a highly valuable outcome of the research,[55] the results of intake of hydroxychloroquine (HCQ) [Scheme 5] for inhibition of SARS-CoV-2 were found satisfactory. The pharmacological activities of chloroquine (CQ) [Scheme 5] and HCQ were tested on SARS-CoV-2 infected Vero cells by following PBPK model using five different dosages. The results of inhibition, EC_{50} values of 0.72 and 5.47 μM for HCQ and CQ, respectively, indicated the former drug is more potent than the latter. A dose of 200 mg each twice a day for 4 days was recommended for inhibition of SARS-CoV-2 infection. The potency will be substantial when given 500 mg twice daily for 5 days in advance. The CQ was found to inhibit SARS-CoV by elevation of endosomal pH and altering the terminal glycosylation of ACE-2 and ultimately interfere with the virus receptor binding to stop the mutation.[56] The mechanism of action of HCQ is same as that of CQ; however, the same for SARS-CoV-2 is yet to be found. A ray of hope with HCQ could be the remedy, provided the negligible side effects, to treat SARS-CoV-2 infections. Although there the caution from United States Food and drug Administration and World Health Organization for using HCQ in curing the COVID-19 disease because of serious cardiac adverse events and other potential serious side effects in patients, the issues may be fixed by throwing interest to further clinical investigations.

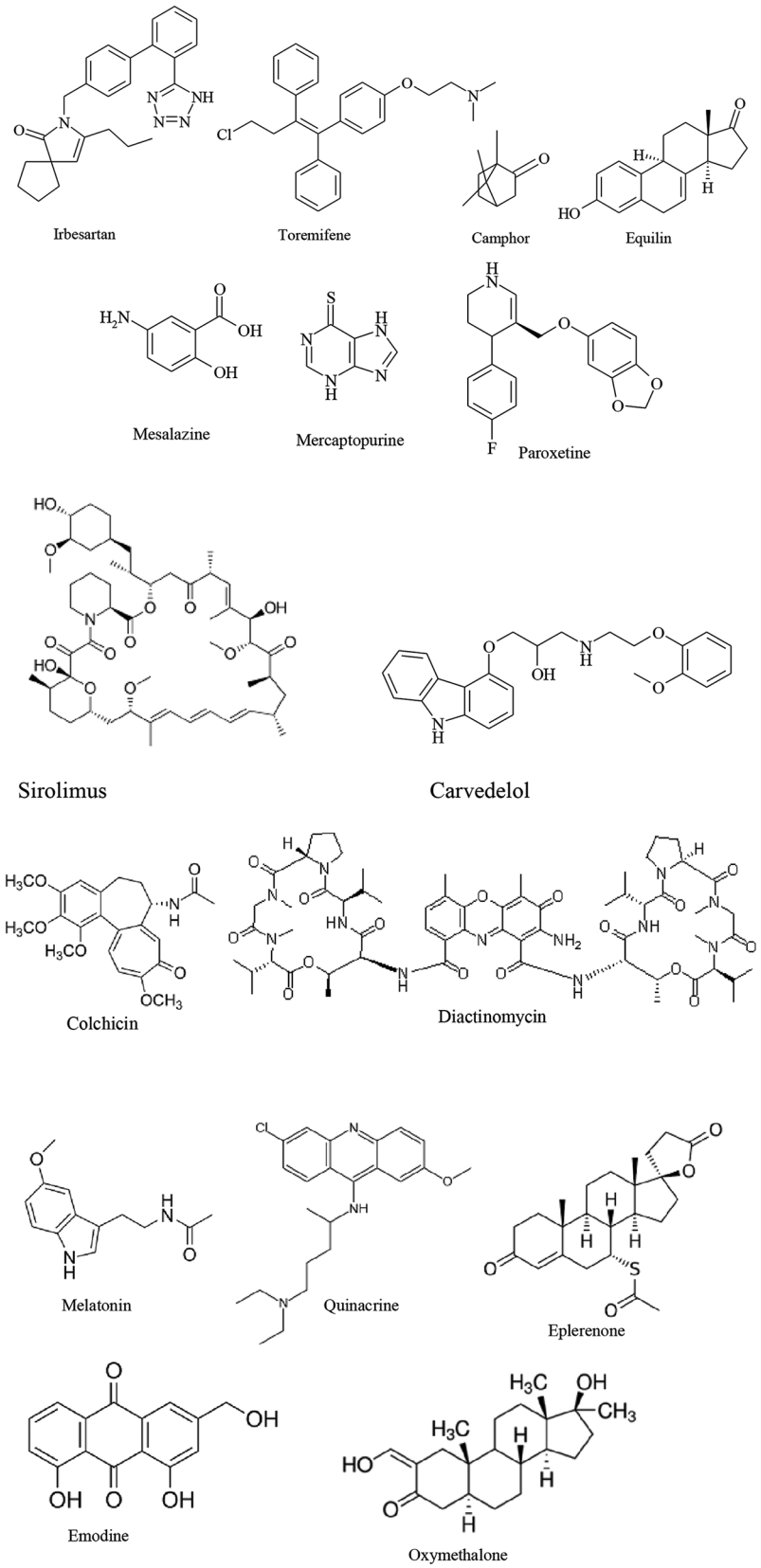
Amiodarone to Inhibit CoV

In their systematic review, a group of researchers from India have brought out the probable drug targets for SARS-CoV-2.[57] The review was framed after trapping a total 392 articles for preliminary investigations. A full text screening was carried out to reach 122 articles which were found relevant to the context of the review. The importance of spike proteins, S1 domain for N and C terminals as major antigens, S2 subunit with HR1, HR2 and hydrophobic fusion peptide, the envelop, membrane and nucleocapsid proteins, 3C-like, papain like protease, hemagglutinin esterase and NTPase helicase in identification of target group is presented. The biological and therapeutic use of amiodarone (ADN) [Scheme 6], a benzofuran derivative, anti-arrhythmic drug to inhibit CoV infection in Vero cells[58] has been described. It was understood from the mechanism of action that ADN alters late endosomes and inhibits SARS-CoV infection at a post-endosomal level. The test was undertaken on Vero cell monolayers infected with SARS-CoV by pre-treating with 0–50 μM ADN for 2 h. Cells were washed with PBS and incubated overnight in the presence of ADN. Virus released in the supernatant was titrated on Vero cells and $TCID_{50}$ calculated. The trypsin treatment was also done for the cells. The results showed that ADN affected the life-cycle of SARS-CoV in a concentration-dependent manner. A 5 μM ADN induced a significant diminution of the virus titer; 10 μM ADN decreased the virus titer 10 times; 50 μM ADN brought the virus titer below the detection limit, which was 10 $TCID_{50}$/ml in the assay.

SARS 3CL^{Pro} Inhibitors

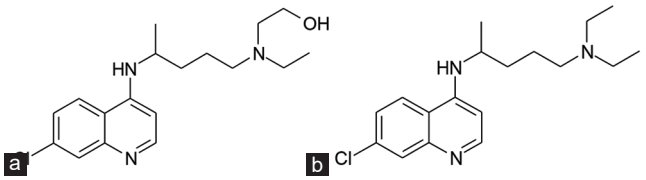
The inhibition ability of several compounds was also accounted in this review. The fused ring structured decahydroisoquinoline scaffolds were described toward the inhibition of SARS 3CL^{Pro}.[59] Two compounds, namely, (S)-2-[({(3S,4aR,8aS)-2-[(biphenyl)-4- carbonyl]decahydroisoquinolin-3-yl}methyl)amino]-3-(1H-imidazol-4-yl)propanal and (S)-2-({[(3S,4aR,8aS)-2-(4-bromobenzoyl)decahydroisoquinolin-3-yl]methyl}amino)-3-(1H-imidazol-4-yl)-propanal were indicated as potent molecules to inhibit SARS 3CL^{Pro}. The type of interaction, binding and other characteristic features of these compounds are described.

Four interesting compounds, viz, (R)-N-(3-fluorobenzyl)-1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxamide, (R)-N-(3-acetamidobenzyl)-1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxamide,



Scheme 4: Chemical structures of projected compounds as SARS-CoV-2 inhibitors

(R)-N-(4-fluorobenzyl)-1-(1-(naphthalen-1-yl)ethyl) piperidine-4-carboxamide, and (R)-N-((2-methoxypyridin-4-yl) methyl)-1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxamide [Scheme 6] were reported to show acceptable



Scheme 5: Chemical structures of: a) HCQ and b) CQ

inhibition to SARS-CoV PL^{pro}[60] with IC_{50} values of 0.15, 0.39, 0.49 and 0.35 M, respectively, in Vero cells. None of these compounds exhibit cytotoxicity or off-target inhibitory activity of a series of human DUB and cysteine protease enzymes. Besides, these inhibitors did not bind to human serum albumin. The first compound was reported with most potency and less metabolic stability when compared to other three.

Papain-like Protease Inhibitor

The design of a most able coronavirus papain-like protease inhibitor, 1-[(R)-1-(1-naphthyl)ethyl]-4-[3,4-(methylenedioxy) benzylamino]carbonylpiperidine [Scheme 6], was reported[61] a decade ago. From the lead optimization and structure activity study the said compound emerged as a good potent PL^{pro} inhibitor and showed antiviral activity against SARS-CoV infected Vero E6 cells. The IC_{50} and antiviral EC_{50} values of 0.32 and 9.1 μM, respectively, gave a clue that the molecule is going to be considered as forthcoming therapeutic candidate to inhibit HCoV activity.

Peptidomimetic Compounds as SARS-CoV $3CL^{Pro}$ Inhibitors

Nitrile-based broad-spectrum peptidomimetic inhibitors for coronavirus 3C-like proteases were proposed by Chi-Pang *et al*.[62] Three peptidomimetic SARS-CoV $3CL^{Pro}$ inhibitors, namely, "Mic-AVLQ-CN," "Boc-AVLQ-CN," and "Cbz-AVLQ-CN" [Scheme 6] were tested with the results of extreme suitability to treat said disease. Besides, authors described the synthesis and biological evaluation of hexapeptide inhibitor "Cbz-TSAVLQ-CN" for effective functioning against the SARS-CoV $3CL^{Pro}$ [Scheme 6] as a potent peptide. The reported IC_{50} values of 49 ± 2, 49 ± 2, 4.6 ± 0.2 and 39 ± 1 μM, for Mic-AVLQ-CN, Boc-AVLQ-CN, Cbz-AVLQ-CN and Cbz-TSAVLQ-CN, peptides, respectively. In respect to Cbz containing peptide, the inhibition ability was found 10 times greater than the rest of the peptides. These four typical inhibitors were found displayed broad-spectrum inhibition against $3CL^{pro}$ from all groups of coronaviruses. The structural features, binding activities, and other required characteristics of these peptides were described. These peptides, since they are derived to be proteins, may be promising target molecules with observed inhibition ability toward CoV.

A Synthetic Peptide as HCoV Inhibitor

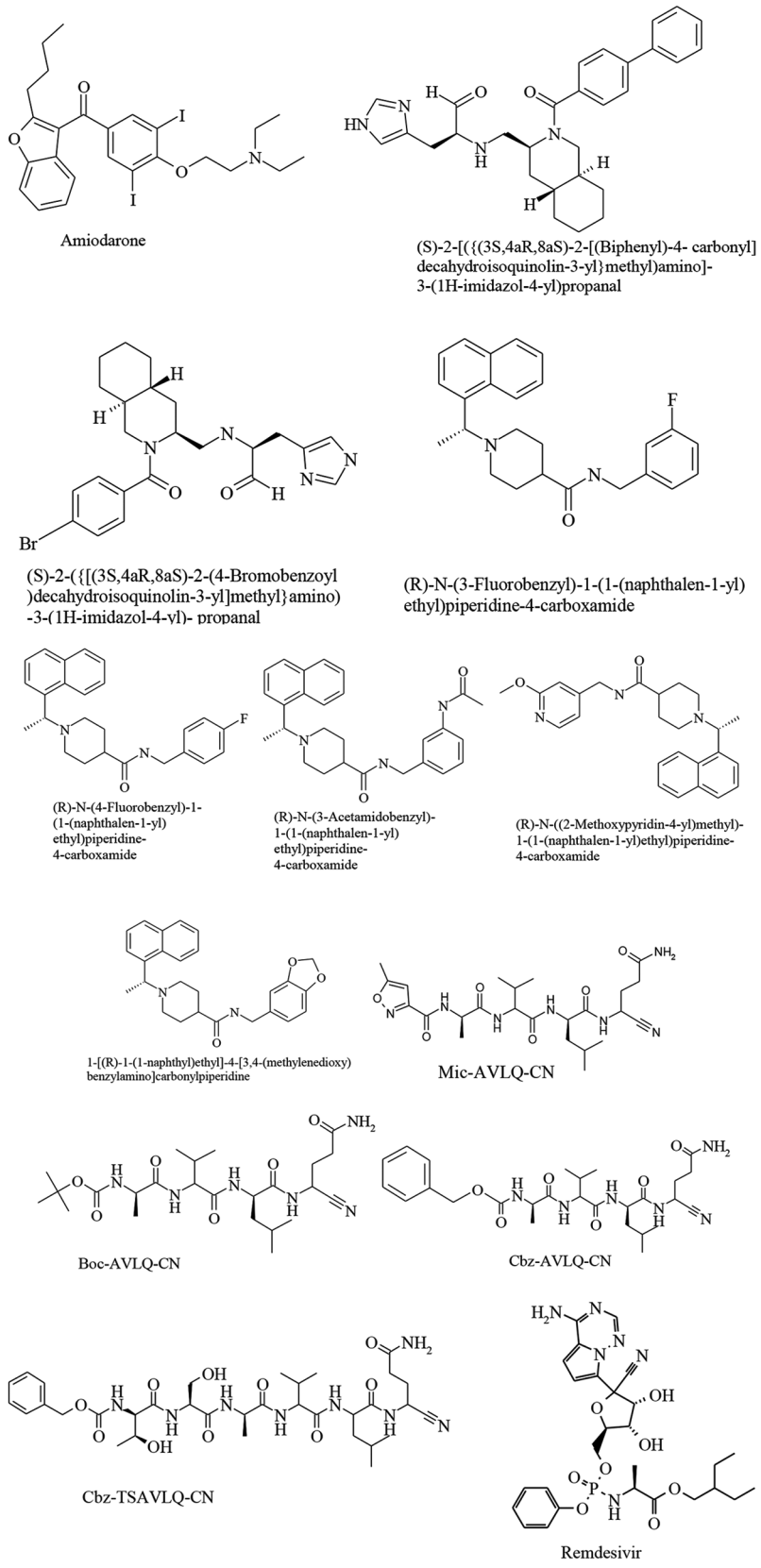
A very recent report dedicated the research outcome of use of modified OC43-HR2P peptide for having showed broad-spectrum and potent fusion inhibitory activity against both α-HCoV and β-HCoV S-mediated cell-cell fusion.[63] The studies on the inhibition of this peptide against MERS-CoV, SARS-CoV, and OC43, were systematically carried out and the resulted IC_{50} values of 0.39, 0.54, and 0.66 μM, respectively, revealed the peptides' selective use to disinfect HCoV. The improved fusion inhibitory activity and increased solubility revealed the antiviral effect of the peptide. Different peptides, EK0-1, EK0-2, EK0-3, and EK1, showed gradually increased solubility and excellent inhibitory activity in cell-cell fusion assays. The last peptide, EK1, exhibited the greater potency to pan-CoV antiviral fusion activity with IC_{50} values in the range of 0.19–0.62 μM. EK1 peptide emerged as a highly potent one to HCoV cell-cell fusion than MERS-HR2P and SARS-HR2P peptides. The ability of EK1 peptide to block various pseudotyped and live CoV infection, its anti *in vivo* HCoV activity, and safety and low immunogenicity, it may be employed as highly essential mode to treat the CoV-19 after necessary clinical approvals.

Remdesivir (RDV): A Significant Candidature to Inhibit SARS-CoV Infections

RDV [Scheme 6], a nucleotide analogue inhibitor of RNA-dependent RNA polymerases, was reported to be as antiviral compound against RNA viruses.[64] The triphosphate form of the inhibitor (RDV-TP) competes with its natural counterpart ATP. The study of inhibition of RNA synthesis by RDV-TP revealed that there was reduction of the 14-mer product due to RNA synthesis arrest at position i+3 with increasing concentrations of RDV-TP. The IC_{50} for RDV-TP of 0.032 μM, 1.5-fold higher than the ATP concentration, was resulted under optimized conditions. This pointed RDV-TP's use as an efficient inhibitor of CoV. Increasing concentrations of ATP caused a corresponding increase in IC_{50} values for RDV-TP, which shows that RDV-TP is a competitive inhibitor. Besides, RDV alone was also found to inhibit the infection of SARS-CoV-2 virus, with an EC_{50} (half-maximal effective concentration) of 0.77 μM and a selectivity index of >129.87.[65] Significant improvement in CoV-2 patient's condition was also reported[66] after giving the injection of RDV for a day. RDV was showed the ability to reduce MERS-CoV replication, improve pulmonary function and reduce pulmonary lesions in Calu-3 cells and mouse models.[67] Due to the structural resemblance between SARS-CoV-2 and MERS-CoV,[2,68] RDV must possess greater potentiality against SARS-CoV-2. The anti-RNA virus activity of RDV against Ebola virus, Marburg virus, Nipa virus and Hendra virus was reported[69-71] earlier. The mechanism of action of RDV with novel expression for the inhibition of SARS and MERS-CoV was also proposed in different reports.[67,72-74] The *in vitro* preventive and therapeutic effects against MERS-CoV and SARS-CoV was also found exhibited by RDV, as per the reports of de Wit group of workers[75] and Agostini *et al*.[76] The backgrounds and the results of study of selectivity of RDV and its ATP-analogues in the same context revealed the suitability of them as selective members to inhibit SARS CoV-2 activities.

Synthetic 1-Thia-4-azaspiro[4.5]decan-3-one Derivatives for Inhibition of HCoV

A series of seven 1-thia-4-azaspiro[4.5]decan-3-one derivatives [Table 1] were synthesized and their biological activities were studied for inhibition of HCoV.[77] A compound, N-(2-methyl-8-tert-butyl-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl)-3-phenylpropanamide



Scheme 6: Chemical structures of some reported anti-CoV compounds

(Derivative 6), exhibited most activity with an EC50 value of 5.5 μM, comparable to the known coronavirus inhibitor, (Z)-N-[3-[4-(4-bromophenyl)-4-hydroxypiperidin-1-yl]-3-oxo-1-phenylprop-1-en-2-yl]benzamide (K22). The cytotoxic

activities of each derivative were also presented and that too indicated the Derivative 6's most potency as antiviral compound for human coronavirus 229E in HEL 299 fibroblast cells.

Ribavirin: A Guanosine Analogue to Show HCoV Inhibition Ability

A description for the treatment of several viral infections, including respiratory syncytial virus, hepatitis C virus, and some viral hemorrhagic fevers using ribavirin (RVN) (1-(β-D-ribofuranosyl)-1H-1,2,4-triazole-3-carboxamide), a guanosine analogue, an antiviral compound is found in the literature.[78,79] RVN is, although an effective antiviral drug, it is seldom used alone otherwise in combination with other drugs such as interferon.[80] However, RVN reported to reduce the hemoglobin concentration in the human body and this made the drug as limited one for use as antiviral agent. RVN works to inhibit RNA synthesis and replication of MERS-CoV and HCoV-OC43.[81] The effective functioning of RVN against viral growth may be the positive orientation for taking it for investigation of reducing the CoV-2 infection rate with its therapeutic application.

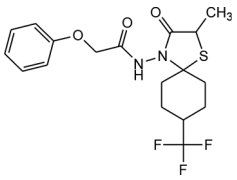
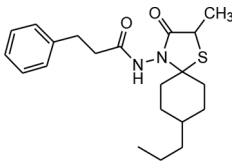
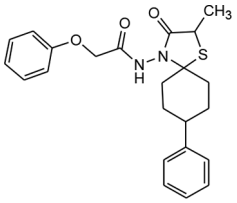
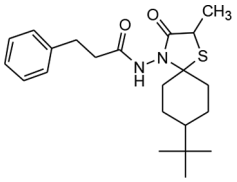
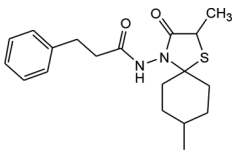
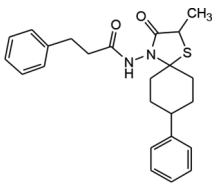
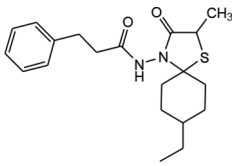
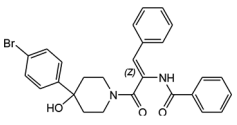
Compounds of Indian Spices to Inhibit SARS-CoV

Some of the Indian spices compounds have been channelized to bioinformatics investigation and the outcome revealed Arjunglucoside-I, carnosol and rosmanol as the good candidatures to show anti-SARS-CoV-2 activity.[82] The compounds have been subjected to study of classical molecular dynamics simulation and absorption, distribution, metabolism, and excretion properties. The results of the study of various kinds of interaction between the amino acids near the active site of SARS-CoV-2 main protease with the test compound, respective inhibitor constant (K_i) and biological source and binding energy revealed that the satisfactory role as anti SARS-CoV-2 agents can be expected from the cited three compounds. The excellent activity as indicated by the inhibition constants (K_i) of 0.96, 1.38 and 1.67 μM, give a clue of their suitability to stop the propagation of SARS-CoV-2.

Able Anti-SARS-CoV-2 Inhibitors

A group of researchers proposed a pair of compounds as antiviral agents targeting SARS-CoV-2 protease by structure-based design.[83] After the compounds were synthesized subjected to fluorescence resonance energy transfer-based cleavage assay to determine the IC_{50} values. The results revealed excellent inhibitory potency with IC_{50} values of 0.053 ± 0.005 μM and 0.040 ± 0.002 μM, for author's reported compounds 11a and 11b respectively. The X-ray crystallographic data was used in order to elucidate the mechanism of inhibition of SARS-CoV-2 M^{pro}. The capability of these compounds to inhibit SARS-CoV-2 *in vitro* was checked using plaque-reduction assay. The pharmacokinetic properties and other relevant required investigation were carried out and the obtained data of results is presented in Table 2. According to the data presented in Table 2, the authors reached the conclusion of the utmost suitability of these couple of compounds to inhibit the SARS-CoV-2 activity.

Table 1: Chemical structures and inhibition constants of 1-thia-4-azaspiro[4.5]decan-3-one derivatives

Derivative	Structure	EC_{50}, μM	Derivative	Structure	EC_{50}, μM
1		31±1	5		8.1±2.2
2		12±1	6		5.5±0.7
3		28±0	7		6.1±0.2
4		18±5	K22		3.3±1.0

Plants Extracts with Antiviral Compounds Toward SARS-CoV

Quite a number of articles describing the use of plant extracts as antiviral medicaments are also found in the literature. Saikosaponins are group of oleanane derivatives behaves as glucosides and are found in *Bupleurum* spp, *Heteromorpha* spp, and *Scrophularia scorodonia*. The extracts of these plants, usually with Saikosaponins, have been reported to possess various biological activities, specifically antihepatitis, antinephritis, antihepatoma, anti-inflammation, immunomodulation and antibacterial effects. Anticoronaviral activity of saikosaponins (A, B_2, C and D) and their mode of action using 2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-5-[(phenylamino) carbonyl-2H-tetrazolium hydroxide] and XTT assay procedure were described.[84] Saikosaponins B_2 [Scheme 7] exhibited most potency toward the inhibition of corona viral activity. The experimental IC_{50} value of 1.7 ± 0.1 μM with cytotoxic CC_{50} value of 383.3 ± 0.2 μM revealed its super anti-corona activity. A 6 μM Saikosaponins B_2 was reported to be the required concentration to inhibit corona viral function.

Antiviral activity of lycorine [Scheme 7], the compound in the extract of Lycoris radiate Chinese plant, against SARS-CoV in Vero cell-based CPE/MTS screening was presented.[85] The extracted, fractionated and purified plant extract was subjected to anti-SARS-CoV activity study. The results with EC_{50} value of 15.7 ± 1.2 nM and CC_{50} value of 14980.0 ± 912.0 nM in cytotoxicity assay and a selective index >900 indicated the expectation of the extract for a fruitful outcome in the inhibition of SARS-CoV activity. The researchers of this work clearly revealed that lycorine is a candidate for the development of new anti-SARS-CoV drugs.

The popularity of Chinese medicines is not restricted for use to cure any kind of the disease. The antiviral properties of some Chinese plants extracts are presented and the result from the literature seems the suitability of the proposed extracts to treat SARS-CoV-2. Baicalin [Scheme 7], the extract of Scutellaria baicalensis Georgi, has showed antiviral activities for SARS coronavirus which was tested using the fetal rhesus kidney-4 (fRhK-4) cell line, with an EC50 12.5 ug/ml at 48 h, and selectivity index of 4–8.[86] The EC_{50} of 11 ug/ml was found from the plaque reduction assay.[86] These results bring the compound baicalin has anti-SARS CoV-2 agent. The inhibition ability, as reported with IC_{50} value of 2.24 mM *in vitro*[87] of baicalin toward ACE also suggests its ability as anti-SARS CoV compound.

Scutellarin [Scheme 7] is another compound from the extract of Chinese plant, Erigeron breviscapus (Vant.) Hand Mazz. Scutellarin, has also exhibited the properties and by which the expectations are obvious to treat the current pandemic. Scutellarin is being used as including anti-inflammation, anti-oxidant, anti-platelet, anticoagulation and for vascular relaxation agent.[88] A study showed that scutellarin treatment could reduce the expression and activity of ACE in brain tissue *in vivo*.[89] The IC_{50} value against ACE was 48.13 ± 4.98 μM. These values are approachable to consider the compound as anti-SARS CoV-2 candidature.

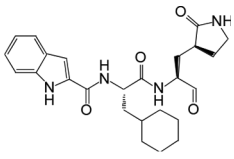
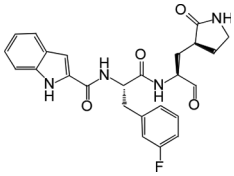
A compound with name Hesperetin [Scheme 7], present in the extract of citrus aurantium and Citri Reticulatae Pericarpium, was showed to inhibit the cleavage activity of 3C-like protease ($3CL^{pro}$) of SARS-coronavirus in cell-free and cell-based assays, with an IC_{50} value of 8.3 Mm.[85] The ability of hesperetin to inhibit SARS-coronavirus may be en-cashed to inhibit SARS-CoV-2 infections.

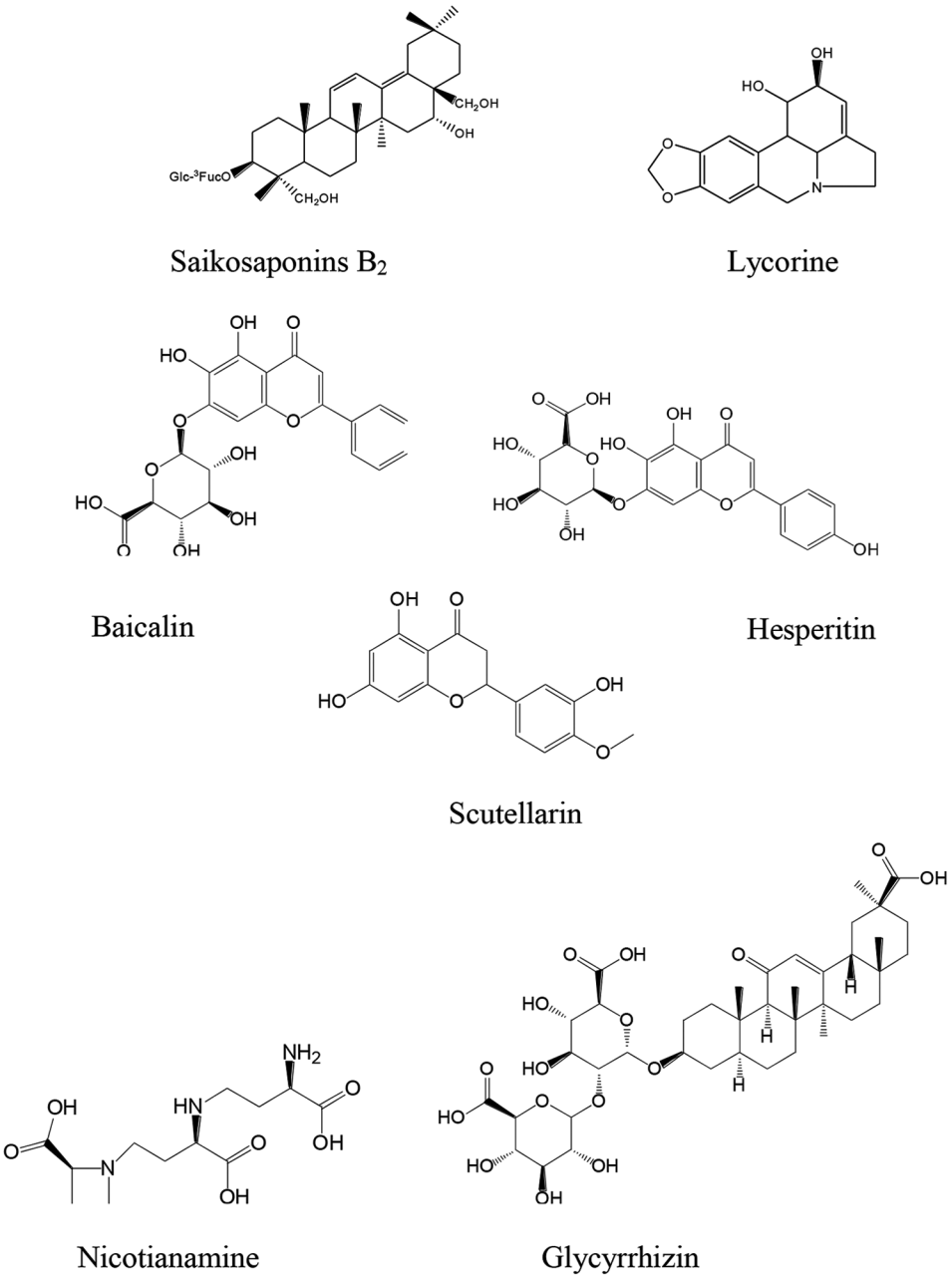
Nicotianamine [Scheme 7], a highly abundant compound found in soyabean, was reported its use as a potent inhibitor of ACE2, with an IC_{50} value of 84 nM.[90]

Another promising compound for SARS treatment is glycyrrhizin [Scheme 7].[91,92] Glycyrrhizin plant product isolated from Chinese herb liqorice root. It was reported to show the inhibition of viral adsorption and penetration and was found most effective when administered both during and after the viral adsorption period.[93]

The plant extracts such as Isatis indigotica root and phenolic Chinese herbs have played pivotal role during the SARS crisis in China, Hong Kong, and Taiwan. Antiviral effects of I. indigotica root were found against influenza, hepatitis A and Japanese encephalitis.[94,95] I. indigotica root is expected to contain indigo, indirubin, indican (indoxyl-β-d-glucoside), β-sitosterol, γ-sitosterol and sinigrin, etc.[96] Indigo and indirubin were identified as the promiscuous chymotrypsin inhibitors.[97] The anti-influenza virus effect of indirubin was demonstrated by group of researchers.[98] In addition, several

Table 2: Chemical structure and results of study of anti-SARS-CoV-2 activities of chemical compounds proposed by authors

Compound	Chemical structure	Inhibitory activity against SARS-CoV-2 Mpro, IC_{50} in μM	*In vitro* inhibition activity against SARS-CoV-2, EC_{50} in μM	Cytotoxicity using CCK8 assays, CC_{50} in μM	Bioavailability, %
11a		0.053±0.005	0.53±0.01	>100	87.8
11b		0.04±0.002	0.72±0.09	>100	80.0

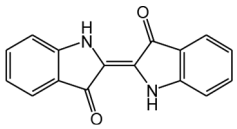
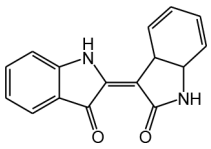
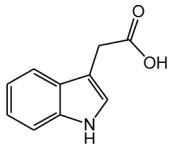
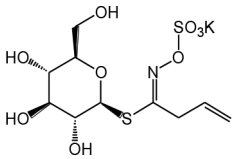
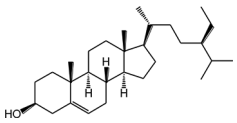


Scheme 7: Structures of chemical compounds of plant extracts showing anti-SARS CoV-2 property

herb-derived phenolics aloeemodin, hesperetin, quercetin, and naringenin were also recognized with antiviral effects against poliovirus, vesicular stomatitis virus, Sindbis virus, herpes simplex virus types 1 and 2, parainfluenza virus, and vaccinia virus.[99-102] A report on the anti-SARS-CoV $3CL^{pro}$ effect of the water extract of I. indigotica root, I. indigotica root-derived compounds, and herb-derived phenolics using a cell-free cleavage and cell-based cleavage assay is also found in the literature.[103] The results of assay indicated that I. indigotica root was a dose-dependent anti-$3CL^{pro}$ effect with an IC_{50} of 53.8 ± 4.2 μg/mL at 50% inhibitory concentrations. The *in vitro* cytotoxicity assay was also checked using Vero cells and the CC_{50} of cell death was reported as >5000 μg/mL. The article also presented the anti-SARS-CoV $3CL^{pro}$ action of five major compounds of the I. indigotica root, namely, indigo, indirubin, indican, sinigrin, and beta-sitosterol. The data in Table 3, as presented by the authors, indicated that sinigrin, beta-sitosterol and indigo dose-dependently inhibited cleavage activities of the $3CL^{pro}$ in cell-free and cell-based assays. The results also concluded the most effective functioning of sinigrin in inhibiting SARS-CoV $3CL^{pro}$ activity. Thus on conducting further experiments to assure the anti-CoV-2 properties of these reported plant extracts, conclusions on their usage can be made possible.

Although sinigrin, an antioxidant, was reported to possess inhibitory effects on quinine reductase and glutathione S-transferase, antiproliferative effects against cancer cells, and antimicrobial activity against Bacillus subtilis and Saccharomyces cerevisiae,[104-106] the results presented in the

Table 3: The results of inhibitory study of *I. indigotica* root extract on cell-free and cell-based cleavage activity of the SARS-CoV $3CL^{pro}$

Compound	Chemical Structure	IC_{50} (cell-free cleavage), µg/mL	IC_{50} (cell-based cleavage), µg/mL	CC_{50}, µg/mL
I. indigotica root	-	53.8±4.2	191.6±8.2	>5000
Indigo		37.3±8.1	190±2.6	917±18
Indirubin		81.3±5.2	Not reported	Not reported
Indican		33.1±1.2	Not reported	Not reported
Sinigrin		50.3±1.5	90.1±4.2	>5000
β-Sitosterol		47.8±8.6	502.1±2.9	613±9

I. indigotica: Isatis indigotica

above Table 3 indicates the significant property of that in blocking the cleavage processing of a viral protease.

CONCLUSION

The globe is in search of a perfect SARS-CoV-2 inhibitor and there is a big challenge is posed to drug discovery laboratories. Since SARS-CoV-2 is a virus with glycoproteins and nucleocapsid proteins, it is very clear that the chemical functioning of the compound must definitely derived in inhibiting the mutation of virus. Variety of compounds reported in the literature with their specific activity with anti-viral functions for SARS-COV-1, MERS-CoV, etc. With the existing knowledge and the present requirement the molecular structure has to be designed so as to suppress the viral activity of SARS-CoV-2. The most relevant and appropriate articles were identified and the review was undertaken to extract out the probable and effective therapeutic compounds with antiviral activity. These compounds are well suited to treat SARS-CoV-2 based on the mechanism of action proposed by the researchers and they are left to further studies by clinical trials. The structural and biological activities are summarized so that this script may be equipped one to pin out the lead compound out of all reported antiviral compounds. The discovery scientists may extend the studies on use of plant extracts, traditional oils, which are triglyceryl esters and leads to give rich short or long chain fatty acids after hydrolysis for arresting the activity of glycoproteins in SARS-CoV-2. Straight investigations with MCFA will also for greater consequences in the inhibition of HCoV. This is going to be most ease and effective treatment because of absence of side effects. The old medicaments used to treat malaria, H1N1, Ebola, and various other diseases are definitely to be tested because of the evidences for their antiviral activities. The promising action of quite a few compounds such as lauric acid, LPV, ritonavir, remdesivir, etc., have been marked with the data of results for the convenience of drug discovery researchers. The antiviral ability of the compounds is either against SARS-CoV or MERS-CoV and thus the binding ability is comparable with that of the present panic COVID-19 disease. It is put front that there is a wide scope and opportunity to utilise the compounds as such or after modification of the functional behavior toward SARS-CoV-2.

ACKNOWLEDGMENT

The author is grateful to the authorities of JSS Mahavidyapeetha, Mysuru and Principal of JSS College of Arts, Commerce and Science, B N Road, Mysuru, India, for providing the facilities to undertake this work.

REFERENCES

1. Nanshen C, Min Z, Xuan D, Jeming Q, Fengyun G, Yang H, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507-13.
2. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W. A pneumonia

outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3.
3. Paules CI, Marston HD, Fauci AS. Coronavirus infections-more than just the common cold. JAMA 2020;323:707-8.
4. Van der Hoek L. Human coronaviruses: What do they cause? Antivir Ther 2007;124:651-8.
5. Gaunt ER, Hardie A, Claas EC, Simmonds P, Templeton KE. Epidemiology and clinical presentations of the four human coronaviruses 229E, HKU1, NL63, and OC43 detected over 3 years using a novel multiplex real-time PCR method. J Clin Microbiol 2010;488:2940-47.
6. Pene F, Merlat A, Vabret A, Rozenberg F, Buzyn A, Dreyfus F, *et al*. Coronavirus 229E-related pneumonia in immunocompromised patients. Clin Infect Dis 2003;377:929-32.
7. Yang H, Bartlam M, Rao Z. Drug design targeting the main protease, the Achilles' heel of coronaviruses. Curr Pharm Des 2006;12:4573-90.
8. Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses 2012;4:1011-33.
9. Hilgenfeld R. From SARS to MERS: Crystallographic studies on coronaviral proteases enable antiviral drug design. FEBS J 2014;281:4085-96.
10. Rajesh A, Chawla R, Rohit M, Arora P, Sharma RK, Vinod K, *et al*. Potential of complementary and alternative medicine in preventive management of novel H1N1 Flu Swine Flu pandemic: Thwarting potential disasters in the Bud. Evid Based Complement Alternat Med 2011;2011:586506.
11. Fiore C, Eisenhut M, Krausse R, Ragazzi E, Pellati D, Armanini D, *et al*. Antiviral effects of *Glycyrrhiza* species. Phytother Res 2008;222:141-8.
12. Emojevwe V. Cocos nucifera (coconut) fruit: A review of its medical properties. Adv Agric Sci Eng Res 2013;3:718-3.
13. Kabara JJ. The Pharmacological Effect of Lipids. Champaign, USA: American Oil Chemist's Society; 1978.
14. Projan SJ, Skrobot SB, Schlievert PM, Vandenesch F, Novick RP. Glycerol monolaurate inhibits the production of beta-lactamase, toxic shock toxin1, and other staphylococcal exoproteins by interfering with signal transduction. J Bact 1996;176:4204-9.
15. Sands JA, Landin P, Auperin D, Reinhardt A. Enveloped virus inactivation by fatty acid derivatives. Antimicrob Agents Chemother 1979;151:27-31.
16. Hierholzer JC, Kabara JJ. In-vitro effects of monolaurin compounds on enveloped RNA and DNA viruses. J Food Safety 1982;41:1-12.
17. Thormar H, Isaacs CE, Brown HR, Barshatzky MR, Pessolano T. Inactivation of enveloped viruses and killing of cells by fatty acids and monoglycerides. Antimicrob Agents Chemother 1987;311:27-31.
18. Piret J, Déseomeaux A, Bergeron MG. Sodium lauryl sulfate, a microbicide effective against enveloped and nonenveloped viruses. Current Drug Targets 2002;31:17-30.
19. Piret J, Lamontagne J, Bestman-Smith J. *In vitro* and *in vivo* evaluations of sodium lauryl sulfate and dextran sulfate as microbicides against herpes simplex and human immunodeficiency viruses. J Clin Microb 2000;381:110-9.
20. Bartolotta S, Garcí CC, Candurra NA, Damonte EB. Effect of fatty acids on arenavirus replication: Inhibition of virus production by lauric acid. Arch Virol 2001;1464:777-90.
21. Grant A, Seregin A, Huang C, Kolokoltsova O, Brasier A, Peters C, *et al*. Junín virus pathogenesis and virus replication. Viruses 2012;4:2317-39.
22. Hornung B, Amtmann E, Sauer G. Lauric acid inhibits the maturation of vesicular stomatitis virus. J Gen Virol 1994;75:353-61.
23. Baltić B, Starčević M, Đorđević J, Mrdović B, Marković R. Importance of medium chain fatty acids in animal nutrition. IOP Conf Series Earth Environ Sci 2017;85:012048.
24. van der Sluis W. Potential Antiviral Properties of Alpha-monolaurin. Poultry World. Available from: https://www.poultryworld.net/Nutrition/Articles/2015/12/Potential-antiviral-properties-of-alpha-monolaurin-2709142W.
25. Li Q, Estes JD, Schlievert PM. Glycerol monolaurate prevents mucosal SIV transmission. Nature 2009;4587241:1034-8.
26. Kirtane AR, Rothenberger MK, Frieberg A. Evaluation of vaginal drug levels and safety of a locally administered glycerol monolaurate cream in Rhesus macaques. J Pharm Sci 2017;1067:1821-7.
27. De Sousa AL, Pinheiro RR, Araújo JF. Sodium dodecyl sulfate as a viral inactivator and future perspectives in the control of small ruminant lentiviruses. Arq Inst Biol 2019;86:e0752018.
28. Dayrit CS. Coconut Oil in Health and Disease: Its and Monolaurin's Potential as Cure for HIV/AIDS. Chennai, India: 37 Cocotech Meeting; 2000.
29. Widhiarta KD. Virgin coconut oil for HIV positive people. Cord 2016;321:50-7.
30. Ramajayam R, Kian-Pin T, Hun-Ge L, Po-Huang L. Synthesis and evaluation of pyrazolone compounds as SARS-coronavirus 3C-like protease inhibitors. Bioorg Med Chem 2010;18:7849-54.
31. Chen L, Chen S, Gui C, Shen J, Shen X, Jiang H. Discovering severe acute respiratory syndrome coronavirus 3CL protease inhibitors: Virtual screening, surface plasmon resonance, and fluorescence resonance energy transfer assays. J Biomol Screen 2006;118:915-21.
32. Meynard JL, Moinot L, Landman R, Morand-Joubert L, Besseghir A, Kolta S. Week 96 efficacy of lopinavir/ritonavir monotherapy in virologically suppressed patients with HIV: A randomized non-inferiority trial ANRS 140 DREAM. J Antimicrob Chemother 2018;73:1672-6.
33. Mohammad RD, Sara TG, Mohammad SD. Lopinavir: A potent drug against coronavirus infection: Insight from molecular docking study. Arch Clin Infect Dis 2017;124:e13823.
34. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ. Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: The application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR. J Korean Med Sci 2020;35:e79.
35. Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J Infect Dis 2015;212:1904-13.
36. Linlin Z, Daizong L, Yuri K, Yong N, Qingjun M, Jiang W, *et al*. α-Ketoamides as broad-spectrum inhibitors of coronavirus and enterovirus replication: Structure based design, synthesis, and activity assessment. J Med Chem 2020;63:4562-78.
37. Tan J, George S, Kusov Y, Perbandt M, Anemuller S, Mesters JR, *et al*. 3C protease of enterovirus 68: Structurebased design of Michael acceptor inhibitors and their broad-spectrum antiviral effects against picornaviruses. J Virol 2013;87:4339-51.
38. Dragovich PS, Zhou R, Skalitzky DJ, Fuhrman SA, Patick AK, Ford CE, *et al*. Solidphase synthesis of irreversible human rhinovirus 3C protease inhibitors. Part 1: Optimization of tripeptides incorporating N-terminal amides. Bioorg Med Chem 1999;7:589-98.
39. Nashwa HZ, Mohammed IM, Abdullah YA. Design, synthesis and molecular docking of novel triazole derivatives as potential CoV helicase inhibitors. Acta Pharm 2020;70:145-59.
40. Dyall J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, *et al*. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob Agents Chemother 2014;58:4885-93.
41. Lisa MJ, Jennifer MB, Sue ED, Charles JS, Andrea S, Calli L, *et al*. FDA-approved selective estrogen receptor modulators inhibit Ebola virus infection. Sci Transl Med 2013;5:190ra179.

42. de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, *et al*. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother 2014;58:4875-84.
43. Yuguang Z, Jingshan R, Karl H, Daniel MJ, Antra Z, Thomas AB, *et al*. Toremifene interacts with and destabilizes the Ebola virus glycoprotein. Nature 2016;535:169-72.
44. Chun HW, Tsai CF, Shu ML, Shu YH, Chun LC, Kang YL, *et al*. Adjuvant treatment with a mammalian target of rapamycin inhibitor, sirolimus, and steroids improves outcomes in patients with severe H1N1 pneumonia and acute respiratory failure. Crit Care Med 2014;42:313-21.
45. Chen X, Chou CY, Chang GG. Thiopurine analogue inhibitors of severe acute respiratory syndrome-coronavirus papain-like protease, a deubiquitinating and deISGylating enzyme. Antivir Chem Chemother 2009;19:151-6.
46. Cheng KW, Cheng SC, Chen WY, Lin MH, Chuang SJ, Cheng IH, *et al*. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. Antivir Res 2015;115:9-16.
47. Tan DX, Manchester LC, Terron MP, Flores LJ, Reiter RJ. One molecule, many derivatives: A never-ending interaction of melatonin with reactive oxygen and nitrogen species? J Pineal Res 2007;42:28-42.
48. Tan DX, Korkmaz A, Reiter RJ, Manchester LC. Ebola virus disease: Potential use of melatonin as a treatment. J Pineal Res 2014;57:381-4.
49. Galano A, Tan DX, Reiter RJ. On the free radical scavenging activities of melatonin's metabolites, AFMK and AMK. J Pineal Res 2013;54:245-57.
50. Xiao J, Shimada M, Liu W, Hu D, Matsumori A. Anti-inflammatory effects of eplerenone on viral myocarditis. Eur J Heart Fail 2009;11:349-53.
51. de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, *et al*. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother 2014;58:4875-84.
52. Cong Y, Hart BJ, Gross R, Zhou H, Frieman M, Bollinger L, *et al*. MERS-CoV pathogenesis and antiviral efficacy of licensed drugs in human monocyte-derived antigen-presenting cells. PLoS One 2018;133:e0194868.
53. Schwarz S, Wang K, Yu W, Sun B, Schwarz W. Emodin inhibits current through SARS-associated coronavirus 3a protein. Antivir Res 2011;90:64-9.
54. Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antivir Res 2007;74:92-101.
55. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, *et al*. *In vitro* antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 SARS-CoV-2. Clin Infect Dis 2020;71:732-9.
56. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, *et al*. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:69-9.
57. Manisha P, Phulen S, Nishant S, Pramod A, Shweta S, Hardeep K, *et al*. Drug targets for corona virus: A systematic review. Indian J Pharmacol 2020;52:56-65.
58. Stadler K, Ha HR, Ciminale V, Spirli C, Saletti G, Schiavon M, *et al*. Amiodarone alters late endosomes and inhibits SARS coronavirus infection at a post-endosomal level. Am J Respir Cell Mol Biol 2008;39:142-9.
59. Shimamoto Y, Hattori Y, Kobayashi K, Teruya K, Sanjoh A, Nakagawa A, *et al*. Fused-ring structure of decahydroisoquinolin as a novel scaffold for SARS 3CLprotease inhibitors. Bioorg Med Chem 2015;23:876-90.
60. Baez-Santos YM, Barraza SJ, Wilson MW, Agius MP, Mielech AM, Davis NM, *et al*. X-ray structural and biological evaluation of a series of potent and highly selective inhibitors of human coronavirus papain-like proteases. J Med Chem 2014;57:2393-412.
61. Arun KG, Jun T, Kalapala VR, Kiira R, Rima C, Debbie CM *et al*. Severe acute respiratory syndrome-coronavirus papain-like novel protease inhibitors: Design, synthesis, protein-ligand x-ray structure and biological evaluation. J Med Chem 2010;5313:4968-79.
62. Chuck CP, Chen C, Ke Z, Wan DC, Chow HF, Wong KB. Design, synthesis and crystallographic analysis of nitrile-based broad-spectrum peptidomimetic inhibitors for coronavirus 3C-like proteases. Eur J Med Chem 2013;59:1-6.
63. Xia S, Yan L, Xu W, Agrawal AS, Algaissi A, Tseng CK, *et al*. A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. Sci Adv 2019;5:eaav4580.
64. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem 2020;29515:4773-9.
65. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus 2019-nCoV *in vitro*. Cell Res 2020;30:269-71.
66. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929-36.
67. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11:222.
68. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
69. Lo MK, Jordan R, Arvey A, Sudhamsu J, Shrivastava-Ranjan P, Hotard AL. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and paramyxoviruses. Sci Rep 2017;7:43395.
70. Brown AJ, Won JJ, Graham RL, Dinnon KH, Sims AC, Feng JY. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antiviral Res 2019;169:104541.
71. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 2016;531:381-5.
72. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017;9396:eaal3653.
73. Lucey DR. New treatments for Ebola virus disease. BMJ 2019;366:l5371.
74. Mulangu S, Dodd LE, Davey RT, Tshiani MO, Proschan M, Mukadi D. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 2019;381:2293-303.
75. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T. Prophylactic and therapeutic remdesivir GS-5734 treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A 2020;117:6771-6.
76. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, *et al*. Coronavirus susceptibility to the antiviral remdesivir GS-5734 is mediated by the viral polymerase and the proofreading exoribonuclease. mBio 2018;9:e00221-18.
77. Çağla BA, Nesrin C, Annelies S, Lieve N, Zafer C. Synthesis and anti-coronavirus activity of a series of 1-thia-4-azaspiro[4.5]decan-3-one derivatives. Arch Pharm Chem Life Sci 2019;352:1800330.
78. Falzarano D, de Wit E, Martellaro C, Callison J, Munster VJ, Feldmann H. Inhibition of novel β coronavirus replication by a

combination of interferon-α2b and ribavirin. Sci Rep 2013;3:1686.
79. Arabi YM, Shalhoub S, Omari AA, Mandourah Y, Al-Hameed F, Sindi A, *et al*. Effect of ribavirin and interferon on the outcome of critically ill patients with MERS. Am J Respir Crit Care Med 2017;195:A6067.
80. Falzarano D, De Wit E, Rasmussen AL, Feldmann F, Okumura A, Scott DP, *et al*. Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat Med 2013;1932:1313-7.
81. Shen L, Yang Y, Ye F, Liu G, Desforges M, Talbot PJ. Safe and sensitive antiviral screening platform based on recombinant human coronavirus OC43 expressing the luciferase reporter gene. Antimicrob Agents Chemother 2016;60:5492-503.
82. Umesh, Debanjan K, Chandrabose S, Sanjeev KS, Vikash KD. Identification of new anti-nCoV drug chemical compounds from Indian spices exploiting SARSCoV-2 main protease as target. J Biomol Struc Dyn 2021;39:3428-34.
83. Wenhao D, Bing Z, Xia-Ming J, Haixia S, Jian L, Yao Z, *et al*. Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. Science 2020;368:1331-5.
84. Pei-Win C, Lean-Teik N, Lien-Chai C, Chun-Ching L. Antiviral effects of saikosaponins on human coronavirus 229E *in vitro*. Clin Exper Pharm Phys 2006;337:612-6.
85. Li SY, Chen C, Zhang HQ, Guo HY, Wang H, Wang L, *et al*. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Res 2005;671:18-23.
86. Chen F, Chan K, Jiang Y, Kao R, Lu H, Fan K, *et al*. *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2004;311:69-75.
87. Deng YF, Aluko RE, Jin Q, Zhang Y, Yuan LJ. Inhibitory activities of baicalin against renin and angiotensin-converting enzyme. Pharm Biol 2012;504:401-6.
88. Wang L, Ma Q. Clinical benefits and pharmacology of scutellarin: A comprehensive review. Pharmacol Ther 2018;190:105-27.
89. Wang W, Ma X, Han J, Zhou M, Ren H, Pan Q, *et al*. Neuroprotective effect of scutellarin on ischemic cerebral injury by down-regulating the expression of angiotensin-converting enzyme and AT1 receptor. PLoS One 2016;111:e0146197.
90. Saori T, Taku Y, Kumiko Y-K, Toshihiro S. Nicotianamine is a novel angiotensin-converting enzyme 2 inhibitor in soybean. Biomed Res 2015;363:219-24.
91. Hoever G, Baltina L, Michaelis M, Kondratenko R, Baltina L, Tolstikov GA. Antiviral activity of glycyrrhizic acid derivatives against SARS-coronavirus. J Med Chem 2005;48:1256-9.
92. Pilcher H. Liquorice may tackle SARS. Nature 2003;7:16.
93. Cinatl J. Antiviral activity of glycyrrhizic acid derivatives against SARS-coronavirus. J Med Chem 2005;484:1256-9.
94. Qin GW, Xu RS. Recent advances on bioactive natural products from Chinese medicinal plants. Med Res Rev 1998;18:375-82.
95. Wu XY, Qin GW, Cheung KK, Cheng KF. New alkaloids from *Isatis indigotica*. Tetrahedron 1997;53:13323-8.
96. Gilbert KG, Maule HG, Rudolph B, Lewis M, Vandenburg H, Sales E, *et al*. Quantitative analysis of indigo and indigo precursors in leaves of *Isatis* spp. and *Polygonum tinctorium*. Biotechnol Prog 2004;20:1289-92.
97. McGovern SL, Shoichet BK. Information decay in molecular docking screens against holo, apo, and modeled conformations of enzymes. J Med Chem 2003;46:2895-907.
98. Mak NK, Leung CY, Wei XY, Shen XL, Wong RN, Leung KN, *et al*. Inhibition of RANTES expression by indirubin in influenza virus-infected human bronchial epithelial cells. Biochem Pharmacol 2004;67:167-74.
99. Semple SJ, Pyke SM, Reynolds GD, Flower RL. *In vitro* antiviral activity of the anthraquinone chrysophanic acid against poliovirus. Antiviral Res 2001;49:169-78.
100. Andersen DO, Weber ND, Wood SG, Hughes BG, Murray BK, North JA. *In vitro* virucidal activity of selected anthraquinones and anthraquinone derivatives. Antiviral Res 1991;16:185-96.
101. Paredes MA, Mendez J, Rodriguez-Ortega M. Anti-Sindbis activity of flavanones hesperetin and naringenin. Biol Pharm Bull 2003;26:108-9.
102. Kim HK, Jeon WK, Ko BS. Flavanone glycosides from Citrus junos and their anti-influenza virus activity. Planta Med 2001;67:548-9.
103. Lin CW, Tsai FJ, Tsai CH, Lai CC, Wan L, Ho TY, *et al*. Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds. Antiviral Res 2005;681:36-42.
104. Brabban AD, Edwards C. The effects of glucosinolates and their hydrolysis products on microbial growth. J Appl Bacteriol 1995;79:171-7.
105. Munday R, Munday CM. Selective induction of phase II enzymes in the urinary bladder of rats by allyl isothiocyanate, a compound derived from *Brassica* vegetables. Nutr Cancer 2002;44:52-9.
106. Smith TK, Lund EK, Parker ML, Clarke RG, Johnson IT. Allyl-isothiocyanate causes mitotic block, loss of cell adhesion and disrupted cytoskeletal structure in HT29 cells. Carcinogenesis 2004;25:1409-15.