RESEARCH ARTICLE

Computational Drug Repurposing for SARS-CoV-2 Targeting RNA-dependent RNA Polymerase: Old Wine in a New Bottle

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ABSTRACT

The emergence of the novel coronavirus (COVID-19) pandemic caused by SARS-CoV-2 has caused worldwide health emergency. Resulting in millions of deaths and confirmed cases globally, the critical demand for effective remedies remains paramount. This study explores the molecular biology of SARS-CoV-2, focusing on its structural and accessory proteins, as well as potential targets for drug intervention. Drug repurposing, an attractive strategy in drug discovery, is extensively discussed, including drugs targeting various stages of the virus lifecycle and mitigating the after-effects of COVID-19 infection. Additionally, natural phytoconstituents are explored as potential agents against COVID-19. Moreover, a study on database screening for effective antiviral drug molecules for SARS-CoV-2 through molecular docking techniques is presented, identifying promising lead molecules. We delve into the virtual screening of antiviral drug databases, prioritizing the RNA-dependent RNA polymerase (RdRp) enzyme as a promising target. Utilizing molecular docking techniques, we analyse protein-ligand interactions and assess hit molecules through MM-GBSA binding energy calculations. This comprehensive approach seeks to advance the development of effective therapies to eradicate this deadly global pandemic.

Keywords: COVID-19, Drug repurposing, Molecular docking, RNA-dependent RNA polymerase (RdRp), SARS-CoV-2

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INTRODUCTION

The unexpected and unpredictable surge of novel Coronavirus (COVID-19) disease caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) has left the entire globe to a halt. COVID-19, first detected in Wuhan, impacted all age groups globally with significant fatalities [1]. As per the W.H.O. statistics, over 7 million deaths and more than 776.8 million COVID-19 cases worldwide: the pandemics staggering toll as of November 10, 2024, with the number continuously escalating. The symptoms embrace fever, breathing difficulty, cough, and invasive lesions on the lungs in the patient. People are said to be 'asymptomatic' when they test positive for COVID-19 but no symptoms are generated or rather the symptoms are not developed to any noticeable extent. The generally accepted incubation period for COVID-19 is up to 14 days, representing the interval between initial viral exposure and symptom onset. Some people can get tested positive for the virus 1-3 days before symptom onset, and are referred to as 'pre-symptomatic'. In both asymptomatic and pre-symptomatic people, onwards transmission of the virus is believed to be still possible and contagious. Hence, they are sometimes dubbed as 'silent-carriers'[2, 3]. The challenges posed in combating this deadly virus are deficiency of effective and licensed drugs, vaccines, inadequate hospital services and medical supplies, logistics, and many more. that have alleviated with the cohesion worldwide[1]. SARS-CoV-2 is a positive-sense single-stranded RNA (order Nidovirale) belonging to the family *Coronaviridae*, and subfamily *Coronovirinae*. The genomic structure of the virus is represented [4] in **Fig. 1**. Viral entry into the host cell occurs through a two-step process: first, the spike protein binds to the ACE2 receptor, tailed by membrane fusion or endocytic uptake. Following endocytosis into target cell, pH-dependent cysteine protease cathepsin L causes cleavage of S protein at an acidic endo-lysosomal pH (3-6.5) [5]. Host cell protease TMPRSS2 activates the viral S protein, enabling direct fusion with the cell membrane. On the viral RNA is released into the cytoplasm, it is translated into two precursor polyproteins, pp1a and pp1ab. These proteins are subsequently processed by viral proteases, including 3CLpro and PLpro, to generate a variety of nsps essential for viral replication. The two non-structural proteins (nsps) consist of two key replicative enzymes: nsp-12 i.e., RNA-dependent-RNA-polymerase and nsp13 i.e., helicase [6]. The viral replication-transcription complex (RTC), formed by nsps, enables genomic RNA replication and subgenomic mRNA transcription. Newly assembled virion, comprising structural proteins and viral genome, are released via viroporin-mediated budding [7]. Extensive mutation is commonly observed in RNA viruses during replication due to the absence of proofreading activity in most viral RNA-dependent RNA polymerase (RdRp). Recent investigations indicate the novel corona virus SARS

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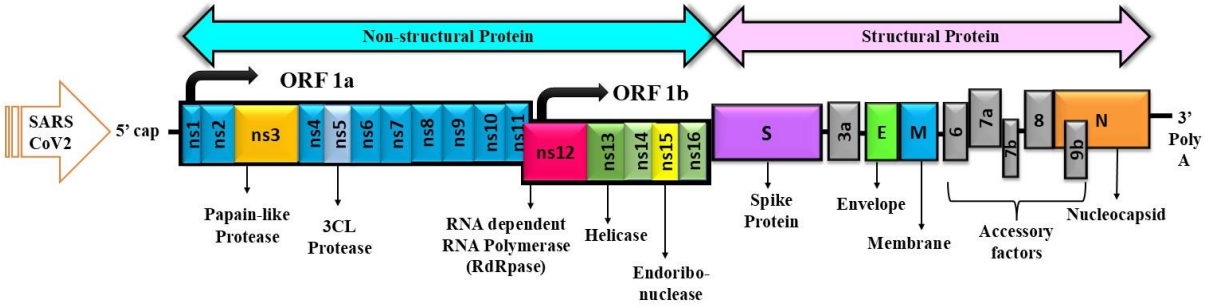

Fig.1 Representation of genomic structure of SARS-CoV-2 highlighting the position of ns1-ns16, S, E, M and N genes

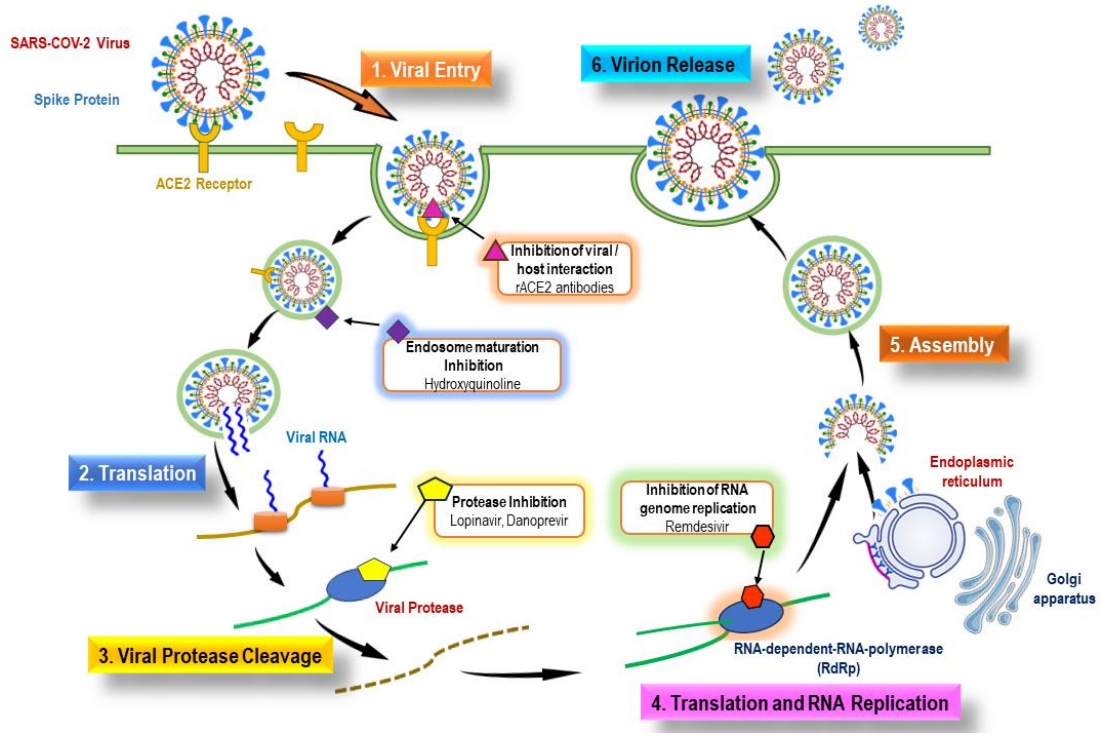

Fig. 2. SARS-CoV-2 life cycle depicting the stages and potential targets of inhibition

CoV-2 possess some proofreading activity which reduces the error rate and pace of mutation [8-10]. The SARS-CoV-2 viral life cycle depicting the stages and anticipated targets of inhibition is shown in **Fig. 2.**

Drug repurposing

Drug repurposing, searching new indications for the existing drugs, is believed to reduce both the money and time involved in the prolonged and inflated ADMET evaluation of candidate molecules, often in case of developing drugs de novo [11]. Recycling old drugs in the wake to treat new diseases, salvaging deferred drugs and intensifying patents' lives contributes to drug repurposing (also called drug repositioning) and makes it an attractive strategy in drug discovery [12-15]. The seemingly never-ending COVID-19 pandemic has caused a rush to repurpose existing drugs. Constitutively, the drugs that are currently in testing phase for repurposing in COVID-19 can be characterized as (1) potential drugs inhibiting one or more stages of COVID-19 virus lifecycle and (2) potential drugs countering the after-effects COVID-19 infection like augmented immune response and immense cytokine release, posing a risk of both ARDS (Acute Respiratory Distress Syndrome) and coagulopathy.

Drugs inhibiting stages of COVID-19 lifecycle

Virus attachment and entry

The molecules that are supposed to cause the down-regulation of ACE-2 receptors along with TMPRSS2 inhibitors have been proposed as potential molecules to be considered in the treatment for SARS-CoV-2 patients [16, 17]. The drugs under consideration for repurposing against SARS-CoV-2's initial stage of infection, specifically viral attachment and entry (Stage 1), are presented in **Fig. 3**. The proposed molecules include estradiol **(1)**, spironolactone **(2)**, isotretinoin **(3)** and retinoic acid **(4)** as down-regulators of ACE-2; and bicalutamide **(5)**, camostat mesylate **(6)** and nafamostat **(7)** as TMPRSS2 inhibitors. Additionally, binding of virion to the host cell has been targeted and attained much attention that has led to two antiviral molecules considered as potential inhibitors of binding: umifenovir **(8)** (blocking the activation of S protein); and

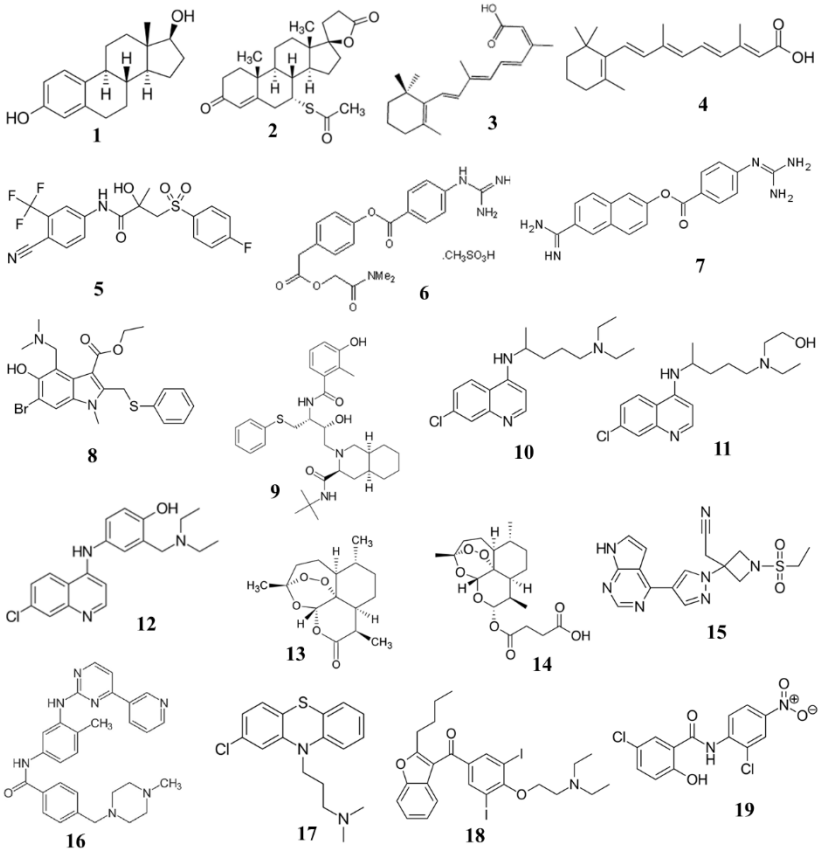

Fig. 3: Structures of drugs considered for repurposing at stage 1 (viral attachment and entry) of COVID-19 virus life cycle

nelfinavir **(9)** (binds to the activated S protein further inhibiting the membrane fusion process). Furthermore, drugs inhibiting endocytosis are also considered for drug repurposing strategy in treatment of COVID-19. These include antimalarials like chloroquine **(10)**, hydroxychloroquine **(11)**, amodiaquine **(12)**, artemisin **(13)** and artesunate **(14)**, baricitinib **(15)**, imatinib **(16)**, chlorpromazine **(17)**, amiodarone **(18)** and niclosamide **(19)** [18]. Out of these, hydroxychloroquine (HCQ) is currently in Phase III of clinical trials against COVID-19. The proposed mechanisms of action of HCQ are: (1) raises pH in endosomes and accumulation in acid vesicles thereby preventing viral fusion and entry; and (2) inhibits terminal ACE-2 glycosylation and prevents SARS-CoV-2 S protein [19-21].

Viral replication

Drugs that inhibit the viral RdRp, a crucial enzyme in replication of virus, hold promise for repurposing in the treating COVID-19 [16]. Drugs considered are remdesivir **(20)** (broad-spectrum anti-viral drug) [22], favipiravir **(21)** (anti-influenza drug in Japan) [23], sofosbuvir **(22)** (drug used in Hepatitis C) [24], emtricitabine **(23)** (nucleoside reverse-transcriptase inhibitor (NRTI) in treatment of HIV/AIDS) [25], galidesivir **(24)** (broad-spectrum adenosine nucleoside antiviral drug) [26] and clevudine **(25)** (pyrimidine analogue against Hepatitis B) [27]. Remdesivir is currently in the Phase III trials and is approved as treatment option for COVID-19 in Japan [28-31]. It is a ProTide (Prodrug of nucleoTide) and is believed to be a chain terminator blocking the transcription process. Its reactive 3'-hydroxyl group forms a phosphodiester bond with the next subsequent nucleotide. Additionally, research demonstrates that cyano group at position 1 of remdesivir have steric clashes with RdRp (residue S861) upon chain elongation perturbing the RNA positioning, ultimately hampering translocation to the remdesivir [32, 33]. Drugs that inhibit proteases, currently used in HIV/AIDS treatment, are also being investigated for their ability to combat SARS-CoV-2 such as lopinavir **(26)**, ritonavir **(27)**, danoprevir **(28)**, atazanavir **(29)** and darunavir **(30)**. Metalloproteinases required for cell fusion and virus replication in coronavirus are also considered as potential target and thus, tetracycline derivatives such as doxycycline **(31)** has been significantly considered as potential molecules for repurposing in COVID-19 [34-36].

Virion assembly, budding and progeny release

The antiviral drugs used in this step of viral replication along with immunosuppressants like sirolimus **(32)** (also known Rapamycin, macrolide compound) [37] are considered for drug repurposing proposed for SARS-CoV-2 [16]. Oseltamivir **(33)** (neuraminidase inhibitor anti-influenza drug inhibiting the release of progeny influenza virus) [38] and daclatasvir **(34)** (potent inhibitor of non-structural protein 5A used in treatment of hepatitis C) [39] are considered as anti-COVID drugs [40-43]. The drugs considered for repurposing at stage 2 and stage 3 i.e., viral replication,

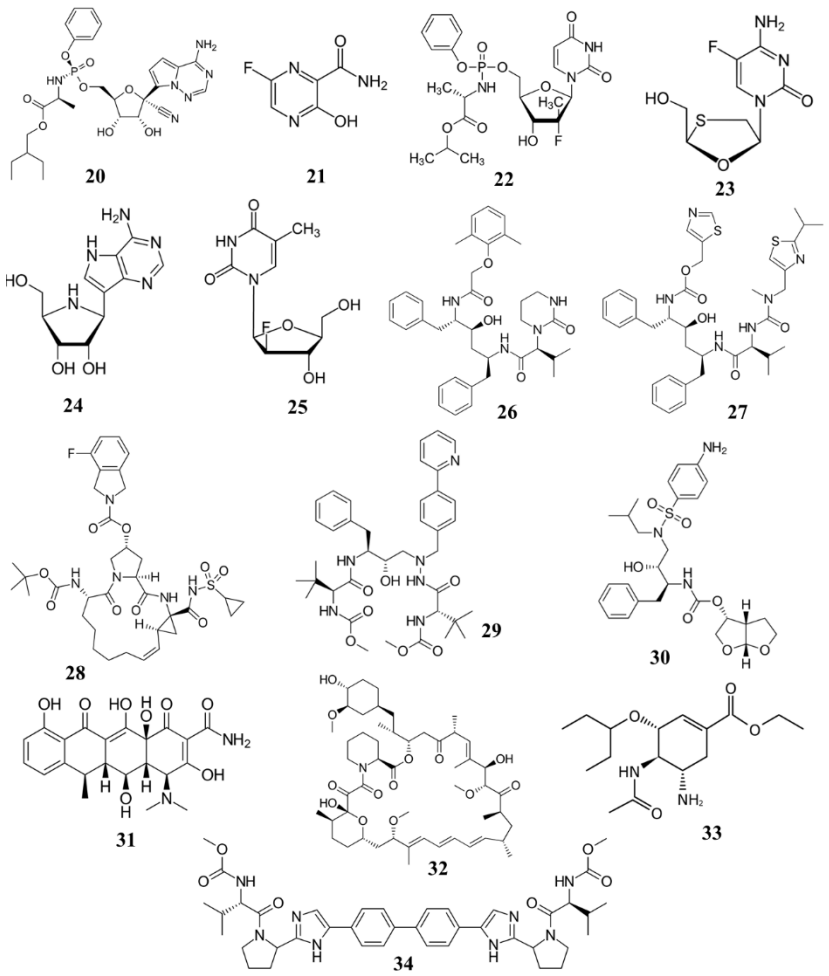

Fig. 4: Structures of drugs considered for repurposing in stage 2 (viral replication) and stage 3 (virion assembly, budding and progeny release) of COVID-19 virus life cycle

viral assembly, budding and progeny release respectively, of SARS-CoV-2 life cycle are depicted in **Fig. 4**.

Drugs countering the after-effects of COVID-19 infection

As discussed above, COVID-19 infection is linked with augmented immune and inflammatory response thereby leading to immense cytokine release causing severe cytokine storm. The implications of cytokine storm such as ARDS, coagulopathy, lymphopenia represents considerate targets to develop an efficacious treatment for COVID-19 [44]. A lot many anti-inflammatory and immunomodulatory drugs such as glucocorticoids viz. methylprednisolone **(35)**, prednisone **(36)**, hydrocortisone **(37)** and dexamethasone **(38)** [45]; non-steroid anti-inflammatory drugs (NSAIDs) i.e., nonselective cyclooxygenase (COX) inhibitors like ibuprofen **(39)**, aspirin **(40)**, diclofenac **(41)**, naproxen **(42)** along with selective COX2 inhibitors like celecoxib **(43)**, rofecoxib **(44)**, etoricoxib **(45)**, valecoxib **(46)** [46]; interleukin antagonists viz. tocilizumab **(47)** (blocks the interleukin-6 signal transduction pathway) [47]; and kinase inhibitors viz. imatinib **(48)**, abemaciclib **(49)**, gilteritinib **(50)** and osimertinib **(51)** [48] are proposed for COVID-19 drug repositioning. Several trials have been carried on the use of dexamethasone to assess its ability against effects of SARS-CoV-2 viral infection. In patients with critical COVID-19 illness, dexamethasone reduced 28-day mortality [49]. Macrolide antibiotics like azithromycin **(52)** and clarithromycin **(53)** are also being considered against inflammatory and immunomodulatory effects of SARS-CoV-2 viral infection [50]. Drugs being explored for repurposing to treat post-acute sequelae of SARS-CoV-2 are depicted in **Fig. 5**.

Natural Phytoconstituents in repurposing as potential agents combating COVID-19

The journey of drug development is expensive and time-consuming. The similarity between the plant-based anti-viral screening and synthetic drugs testing procedure establish a better link between *in-vitro* & *in-vivo* findings. These results might accelerate their approval procedure [51, 52]. It has been long known about the plant's contribution in healing and in a series of cases, different phytoconstituents have been identified in past that hamper the replication of number of viruses [53], still natural phytoconstituents-based treatment has been largely ignored. This opens up a highly significant area for exploratory study in development of potential phyto-anti-COVID drugs. Various natural phytoconstituents have demonstrated efficacy in forestalling the entry of SARS-CoV-2 in host cells [7]. The

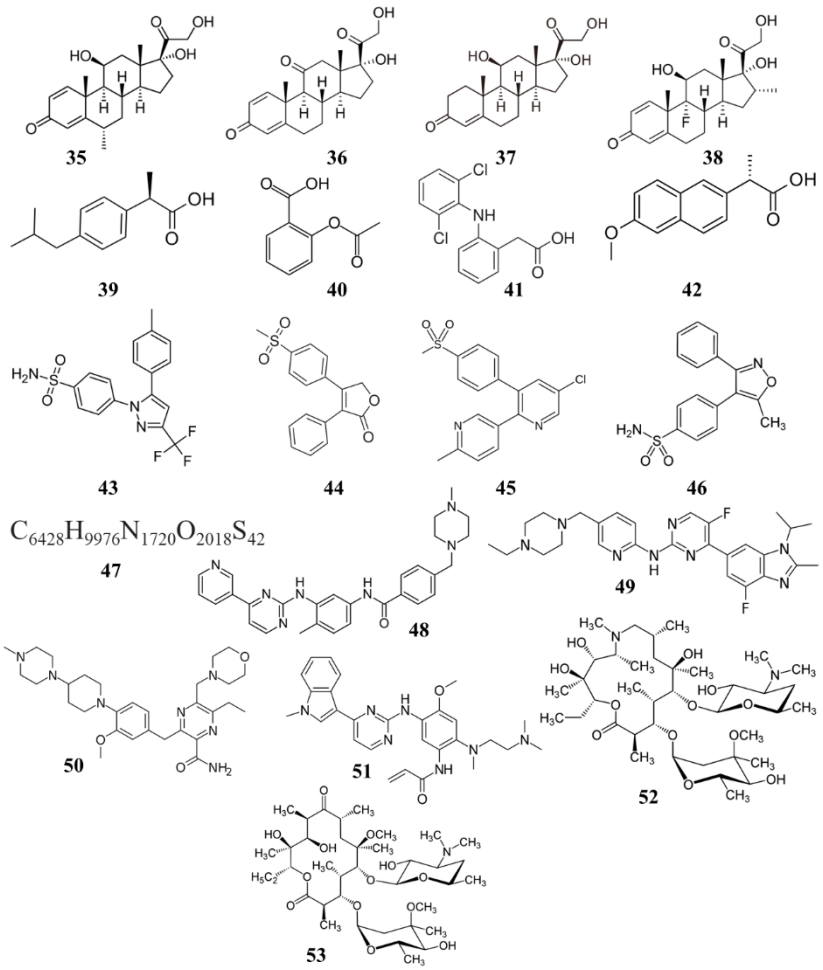

Fig. 5: Structures of drugs for repurposing countering the after-effects of COVID-19 infection.

development of an anti-SARS-CoV-2 medication requires a fusion enzyme-based and cell-based *in-vitro* and *in-vivo* studies. **Fig. 6** highlights natural phytoconstituents being considered for repurposing in COVID-19 therapy. Recent research demonstrated dose-dependent effectiveness of emodin **(54)**, an anthraquinone derivative, in hampering the binding of S protein to host receptor ACE2 [54]. Numerous Chinese herbal extracts containing small antiviral molecules exhibit strong S protein binding, disrupting viral entry [55]. Apart from various synthetic drugs, discussed in the previous sections, inhibiting TMPRSS2 activity, it was reported that Xanthoangelol G **(55)** isolated from *Angelica keiskei* demonstrated inhibition of TMPRSS2 (IC50 = 51.6 μM) [56]. Next, targeting the proteins involved in endocytic pathway of virus are considered as encouraging strategy in inhibiting SARS-CoV-2 entry [57]. Several natural compounds are reported to act through this strategy viz. terpenes/terpenoids [58-61] and alkaloids [62-64], via two pathways: one involving cathepsin inhibition, the other involving increased lysosomal pH, both resulting in protein breakdown in endolysosomes, an intracellular vesicles.

The phytoconstituent extracted from liquorice roots (Glycyrrhiza radix) viz. Glycyrrhizin **(56)** (triterpene glycoside glycyrrhizic acid) was proved to be more efficacious than ribavirin (licensed drug for respiratory syncytial virus) against SARS-CoV [65]. It is believed that glycyrrhizin causes increased production of nitrous oxide synthase that leads to inhibition of viral replication [65, 66]. After additional studies on glycyrrhizin derivatives and careful analysis of the obtained results indicated that incorporation of different functional groups led to 10-70 folds increase in anti-SARS activity; at the same time safety was compromised due to increased cytotoxicity [67]. These findings open avenues for glycyrrhizin modification for enhanced anti-COVID activity, although cytotoxicity needs to be addressed. Reports suggested various plants and their extracts showing curative strategy intended for MERS-CoV and SARS-CoV a consequence of immune response modulation. Extracts from a range of plants, including *Linder aggregate*, *Pyrrosia lingua*, *Artemisia annua,* and *Lycoris radiata* demonstrated better activity against SARS-CoV compared to glycyrrhizin, out of which *Lycoris radiata* was reported to be the most efficacious medicine (EC50: 2.4 ± 0.2 mg/L) [68]. Furthermore, extracts of eucalyptus, *Lonicera japonica* and *Radix ginseng* exhibited anti-SARS-CoV activity, with *Radix ginseng* specifically reducing acute lung injury by targeting inflammatory signaling [69]. The proteases, 3CLpro and PLpro have been considered as the promising targets to develop agents against SARS and MERS. The tannic acid compounds, theaflavin-3,3'-digallate (TF3) **(57)** and 3-isotheaflavin-3-gallate (TF2B) **(58)** present abundantly in black tea extracts were proven to be potent inhibitors of 3CLpro determined by HPLC proteolytic assay [70]. In addition, Quercetin **(59)**

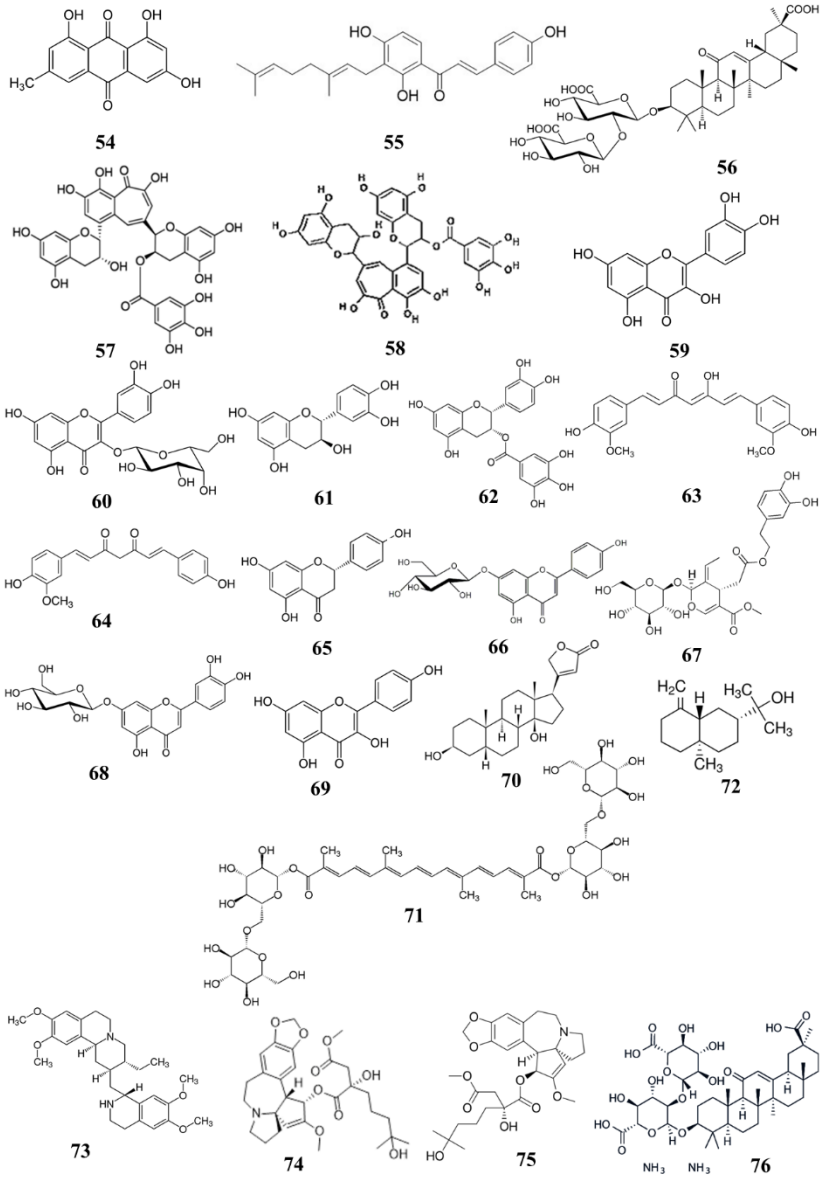

Fig. 6: Natural phytoconstituents: A repurposing strategy for COVID-19.

and its derivative quercetin-3-β-galactoside **(60),** a plant flavonoid, also inhibited SARS-CoV 3CLpro replication, where the inhibitory action was believed to be due to the sugar moiety [55, 71, 72]. The RdRp was reported to be inhibited along with 3CLpro of SARS-CoV by an extract of the traditional Chinese medicine, *Houttuynia cordata* [73]. Along with 3CLpro inhibition, there have been reported extracts showing greater inhibition of SARS-CoV PLpro [74]. Carbinolamide motif present in cinnamic amide extract of *Tribulus terrestris* fruit demonstrated IC50 = 15.8 µM targeting SARS-CoV PLpro [75].Owing to the significant protein resemblances amid MERS-CoV, SARS-CoV, and SARS-CoV-2 [76] suggest that plants and their phytoconstituents effective against first two viruses could also effective against COVID-19. Evidence suggests that the 95%-100% homology in SARS-CoV-2 proteins in comparison to SARS-CoV except two proteins i.e., orf8 and orf10 [77]. There is a 95% similarity found in 3'-5' exonuclease, nsp7, 8, 9, 10, helicase, 3CLpro and RdRp of both SARS-CoV-2 and SARS-CoV, [76] a comparison drawn from Blastp search. The nucleocapsid (N) protein also exhibits approximately 90% amino acid identity. These similarities and identities form the basis in utilizing the above-mentioned phyto-inhibitors, that show anti-SARS-CoV activity, for COVID-19 too along with various other phytoconstituents reported in the databases. While it has not been possible to provide definite clinical data of these potential phytoconstituents targeting SARS-CoV or MERS-CoV in past to bring them to an effective antiviral therapeutic, it poses disadvantage in the existing scenario of COVID-19. Most of the recent investigations based on potential plants and their phytoconstituents aimed at COVID-19 emphasis mainly on two approaches: 1) use of bioinformatic tools like molecular docking; and 2) molecular farming i.e., production of vaccines and antibodies [78, 79]. Molecular docking of various molecules of herbal origin have been reported that shown inhibition of proteins viz. spike proteins, PLpro, 3CLpro, and viral

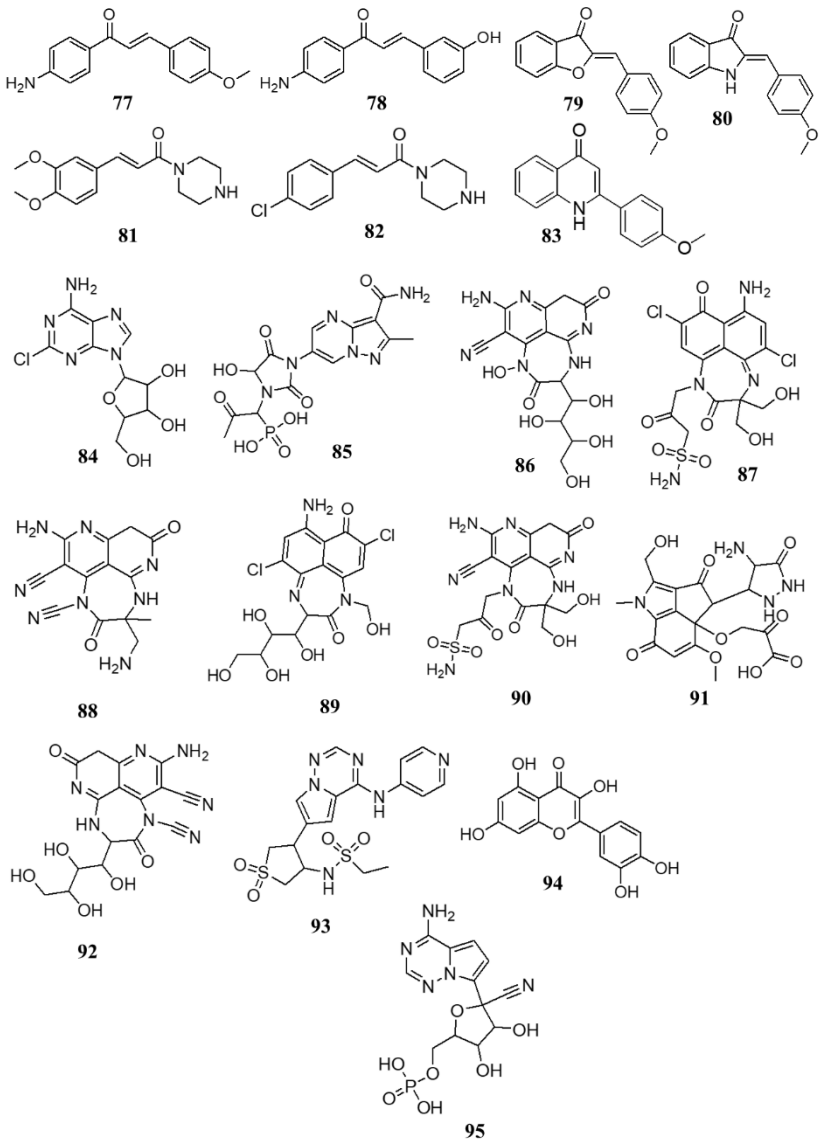

Fig. 7: Structures of Set 1 (77-83) consisting of non-nucleoside analogues from our developed antiviral dataset; Set 2 (84-93) consisting of nucleoside analogues from similarity search datasets; and Quercetin (94) screened from natural molecules dataset; Remdesivir (95) used as standard.

replication pertaining to SARS-CoV-2 [79]. A recent study based on molecular docking considering nelfinavir and lopinavir as standards suggested that certain molecules extracted from medicinal plants, viz. catechin **(61)**, epicatechin-gallate **(62)**, curcumin **(63)**, desmethoxycurcumin **(64)**, naringenin **(65)**, apigenin-7-glucoside **(66)**, oleuropein **(67)**, luteolin-7-glucoside **(68)**, kaempferol **(69)** and quercetin, have strong binding with main protease of COVID-19. Thus, they have been proposed as inhibitors targeting main protease [80]. Another study employing molecular docking study revealed that digitoxigenin **(70)**, crocin **(71)** and β-Eudesmol **(72)** isolated from *Nerium oleander*, *Crocus sativus L* and *Lauris nobilis*, has the potential to inhibit the Spike protein [81].

In-vitro experiments are another key aspect in the search for therapeutic phyto-inhibitors against SARS-CoV-2. Due to poor oral bioavailability (as suggested by *in-vitro* studies), these phyto-inhibitors are expected to show different clinical efficacy *in-vivo.* Emetine extracted from roots of ipecac *(Psychotria ipecacuanha)* **(73)** was shows viral replication inhibition at 0.5 μM [82]. Furthermore, another reported effective antiviral drug Homoharringtonine **(74)**, isolated from *Cephalotoxus fortunei*, against porcine epidemic diarrhoea coronaviruses and murine hepatitis demonstrated to inhibit SARS-CoV-2 at EC50 value of 2.10 μM. Interestingly, the therapeutic plasma concentration (0.066 μM), of a semi-synthetic homoharringtonine, omacetaxine **(75)**, after 11 days of treatment found to be significantly lower than its *in-vitro* EC50 value against SARS-CoV-2 [82]. Diammonium glycyrrhizinate **(76)**, liquorice root extract and Vitamin C tablets were approved for clinical trials and were prescribed for COVID-19 [83]. These significant results confirm the effectiveness of potential plant-derived therapeutics combating SARS-CoV-

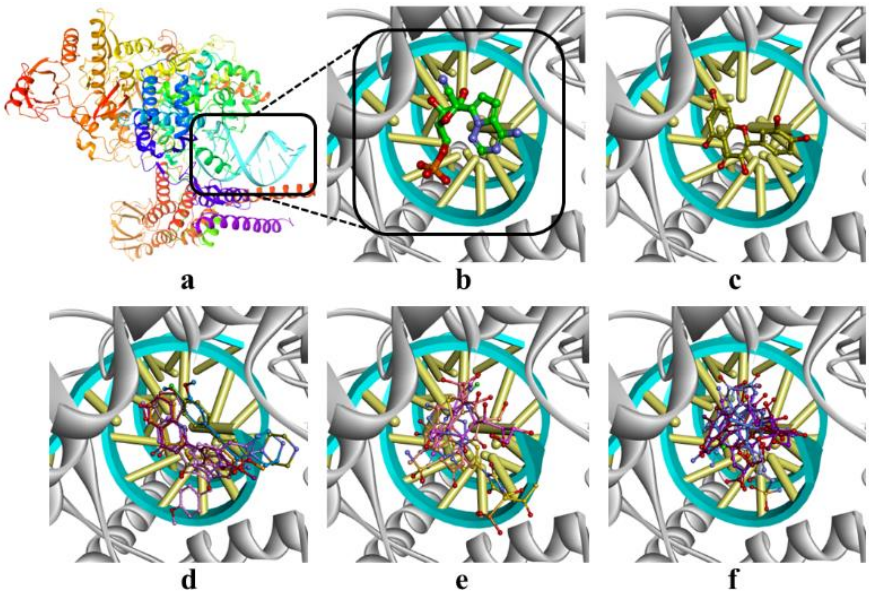

Fig. 8: (a) 3D crystal structure of RdRp enzyme, PDB ID: 7C2K, RNA complex is depicted

2 and hence, should proximately be taken into consideration for dose optimization. These exciting outcomes make us expectant towards the utility of these broad-spectrum Phyto antivirals against sudden viral outbreaks in future.A systematic avenue, combining *in-silico in-vitro,* and *in-vivo* procedures, can ease clinical trials of promising plants and active phytoconstituents.

MATERIALS AND METHODS

Preparation of ligands

Based on the backdrop, we present here a study cantered on the screening of various databases to gain insight towards the scaffold generation/selection that could be employed to generate leads to be developed against COVID-19.

Five databases were selected for virtual screening comprising of synthetic and natural origin viz. Asinex (6827 molecules), an antiviral database of synthetic small molecules and macrocycles; Enamine (3200 molecules), database containing nucleoside mimetics as antiviral agents; Natural product like similarity search (913 molecules), 2D fingerprint similarity search against Specnet, Timetek, Selleck, Analyticon; ChemDiv (4000 molecules), database of natural-product-based library. It was based on similarity search using Remdesivir as standard with the help of BioSolveIT (for similarity search). The fifth database was comprised of our lab designed, synthesized, and evaluated antiviral dataset comprised of scaffolds derived from natural origin like chalcones, aurones, indolinones, quinolones and cinnamic acid-piperazine derivatives. Our developed antiviral dataset was comprised of sixty non-nucleoside molecules, evaluated against pandemic H1N1 using *in-vitro* techniques. the ligand energy minimization was accomplished using the MMFF94 force field. The resulting energy-minimized ligands were then prepared for molecular docking by converting them to pdb format.

Preparation of Protein

RdRp (RNA-dependent RNA polymerase) 3D crystal structure (PDB ID: 7C2K) was retrieved from RCSB protein data bank [84]. Biovia Discovery Studio was used for preparation of protein for molecular docking. The co-crystallized ligand was detached from the protein structure followed by addition of polar hydrogens, water molecules, and charges.

Virtual screening of antiviral drug databases

Molecular docking

Virtual screening of altogether 15,000 molecules was carried out by molecular docking technique using Maestro Glide (for HTVS and docking) software with the enrichment factor calculated from Maestro EF 1% = 11. Standard Precision Glide was employed on top screened 1103 molecules based on best interactions with important amino acid residues. Next, Extra Precision Glide docking was performed on the screened top 100 molecules from them and the molecules were further screened by rescoring them with MM-GBSA calculations in Maestro for binding energy.

An RMSD of 0.46Å for co-crystallized ligand's binding pose validated the docking protocol. The screened molecules were then divided into two sets. The first set comprised of non-nucleoside analogues (7 molecules, **77-83**). The other set composed of nucleoside analogues (10 molecules, **84-93**) with structural similarity to Remdesivir **(95)**, along with quercetin **(94)** screened form the natural database as shown in **Fig. 7.**

RESULTS AND DISCUSSION

The selection of analogues highlights possibility of two mechanisms. One mechanism similar to Remdesivir, is proposed for nucleoside analogues dataset while the other proposed mechanism is for non-nucleoside analogues [85-87]. We studied the interactions of the screened molecules with amino acid residues of NSPs (viral proteins) complexed with RdRp that plays a fundamental role in the incorporation of RNA into the genome. The standard drug remdesivir triphosphate **95** showed three hydrogen bond and a van der Waals interaction with pyrimidine base U31257, two hydrogen bond interactions with A1261,

Table 1: The MM-GBSA binding energy (kcal/mol) of screened non-nucleoside and nucleoside analogues

Compound	Chemical Name of Compound	MM-GBSA binding energy (kcal/mol)
77	(E)-1-(4-aminophenyl)-3-(4-methoxyphenyl) prop-2-en-1-one	-37.645
78	(E)-1-(4-aminophenyl)-3-(3-hydroxyphenyl) prop-2-en-1-one	-34.838
79	(Z)-2-(4-methoxybenzylidene) benzofuran-3(2H)-one)	-33.582
80	(Z)-2-(4-methoxybenzylidene)indolin-3-one)	-33.145
81	(E)-3-(3,4-dimethoxyphenyl)-1-(piperazin-1-yl)prop-2-en-1-one	-34.249
82	(E)-3-(4-chlorophenyl)-1-(piperazin-1-yl)prop-2-en-1-one	-36.334
83	2-(4-methoxyphenyl)quinolin-4(1H)-one	-36.325
84	(2R,3R,4S,5R)-2-(6-amino-2-chloro-9*H*-purin-9-yl)-tetrahydro-5-(hydroxymethyl) furan-3,4-diol	-44.951
85	6-(4-hydroxy-2,5-dioxo-3-(2-oxopropyl) imidazolidin-1-yl)- 2-methylpyrazolo[1,5-a] pyrimidine-3-carboxamide	-37.073
86	9-amino-1,2,3,4,6,7-hexahydro-3-(1,2,3,4-tetrahydroxybutyl)-2,6-dioxo-1-hydroxy-[1,4]diazepino[5,6,7-de][1,6]naphthyridine-10-carbonitrile	-43.795
87	4-((1E)-8-amino-6,10-dichloro-2,3-dihydro-2,2-bis(hydroxymethyl)-3,7 -dioxonaphtho [1,8-ef][1,4]diazepin-4(7H)-yl)-2-oxopropane -1-sulphonamide	-43.505
88	9-amino-3-(aminomethyl)-3,4,6,7-tetrahydro-3-methyl-2,6-dioxo-[1,4]diazepino[5,6,7-de][1,6]naphthyridine-1,10(2H)-dicarbonitrile	-40.296
89	(4E)-7-amino-5,9-dichloro-3-(1,2,3,4-tetrahydroxybutyl)-1-(hydroxymethyl) naphtho[1,8-ef] [1,4]diazepine-2,8(1H,3H)-dione	-43.153
90	4-(9-amino-10-cyano-3,4,6,7-tetrahydro-3,3-bis(hydroxymethyl)-2,6-dioxo-[1,4]diazepino [5,6,7-de][1,6]naphthyridin-1(2H)-yl)-2-oxopropane-1-sulphonamide	-40.867
91	3-(6-(4-amino-5-oxopyrazolidin-3-yl)-3,5a,6,7-tetrahydro-1-(hydroxy methyl)-5-methoxy-2-methyl-3,7-dioxo-2H-cyclopenta[cd] indol-5a-yloxy)-2-oxopropanoic acid	-41.381
92	9-amino-3,4,6,7-tetrahydro-3-(1,2,3,4-tetrahydroxybutyl)-2,6-dioxo-[1,4]diazepino [5,6,7-de] [1,6]naphthyridine-1,10(2H)-dicarbonitrile	-41.119
93	N-(4-(4-(phenylamino)pyrrolo[1,2-f][1,2,4] triazin-6-yl)sulpholan-3-yl) ethansulphonamide	-40.784
94	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one (Quercetin)	-39.381
95	(2S)-2-{(2R,3S,4R,5R) [5-(4-Amino pyrrolo [2,1-f] [1,2,4]triazin-7-yl) -5- cyano-3,4-dihydroxy-tetrahydro -furan-2-ylmethoxy]phenoxy-(S)-phosphorylamino} propionic acid 2-ethyl-butyl ester (Remdesivir)	-47.224

hydrogen bond interactions with Ser683, Thr688 and Asp761; and phosphate group having salt bridge interaction with Lys546 and Arg556. All the nucleoside analogues showed interactions with above-mentioned base pairs and active amino acid residues of RdRp enzyme. The significant binding energies, ranging from -37.073 to -47.224 kcal/mol, suggest that these compounds can effectively mimic the action of remdesivir. Notably, compounds **84** and **86** exhibited the good binding energy (-44.951 and 43.795 kcal/mol, respectively), indicating its potential as effective inhibitor of the RdRp enzyme.

Interestingly, the non-nucleoside analogues also showed interaction with U31257 and above-mentioned important amino acid residues of the RdRp enzyme, albeit with slightly lower binding energies compared to nucleoside analogues (-33.145 to -37.645 kcal/mol). These interactions suggest a different but potentially effective mechanism of inhibition, providing an alternative pathway for therapeutic intervention.

Furthermore, Quercetin, a well-known natural phytoconstituent demonstrated a notable binding energy of -39.381 kcal/mol. This suggests that it can effectively interact with RdRp enzyme, albeit not as strongly as the nucleoside analogues. However, its binding energy is significantly better than all non-nucleoside analogues analyzed, indicating its potential utility in drug repurposing as an antiviral agent. The poses for molecules in RdRp enzyme of SARS-CoV-2 has been depicted in **Fig. 8**.

in cyan colour (base pairs in ladder form yellow colour) and highlighted in a box; (b) remdesivir triphosphate pose interacting with RNA; (c) pose of quercetin screened from natural phytoconstituents database; (d) non-nucleoside analogues 77-83 from our antiviral dataset; (e) nucleoside analogues 84-88; and (f) nucleoside analogues 89-93 from screened databases.

The MM-GBSA binding energy analysis provided a quantitative measure of the binding affinities of the screened compounds. The MM-GBSA binding energies

show that nucleoside analogues generally exhibit higher binding affinities compared to non-nucleoside analogues. Notably, compounds 84-95 shows significantly lower binding energies, suggesting stronger interactions with the enzyme**. Table 1** represent the details of the MM-GBSA binding energies of screened molecules.

The overall study gave us eighteen hit molecules. Our study underscores the potential of both nucleoside and non-nucleoside analogues in targeting SARS-CoV-2 RdRp enzyme. The distinct mechanism of action and strong binding affinities of these compounds provide a robust foundation for further experimental validation and development of effective antiviral therapies. The ability of nucleoside analogues to closely mimic the interactions of Remdesivir supports their potential in antiviral therapy. Additionally, the distinct interaction profile of non-nucleoside analogues offers a complementary approach that could be explored further. Computational drug repurposing thus offers a rapid and efficient approach to identifying promising candidate for combating COVID-19 pandemic. Further, we can explore these analogues by appropriate structural modifications to get an exclusive breakthrough molecule which can be used in combat strategy against the deadly coronavirus. It is hoped that this study will stimulate further investigations in this field.

CONCLUSION

The drug development targeting the novel coronavirus is emphasized in this study. The virus has created havoc in the globe and it is infamously cited as COVID-19 - a devastating pandemic 2019. Various targets based on the stages in lifecycle of coronaviruses were reviewed and explored for the evaluation of various known drugs from synthetic as well as phytochemical origins, that have been considered for repurposing to develop much awaited lead to combat COVID-19 crisis. In this ocean, we tried to add a drop by doing virtual screening using molecular docking technique on reported antiviral (specifically RNA virus) based drug databases. The primary focus was on the most promising target viz., RNA-dependent-RNA-polymerase (RdRp) enzyme. From the computation of protein-ligand interactions, we arrived at scaffolds **84** (binding energy - 44.951 kcal/mol) and **86** (binding energy - 43.795 kcal/mol) which showed potential to be lead against this virus similar to Remdesivir (binding energy - 47.224 kcal/mol). One big learning of this pandemic was to make use of drug repurposing strategy which is nothing but like filling old wine in a new bottle, indeed came to rescue of mankind in this challenging time.

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