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MINIREVIEW

Novel Targets of SARS-CoV-2 and Potential Inhibitors against the Viral Targeted Proteins: A Review

G. KOTESWARA REDDY*, V. RENUKA, A. CHANDANA and K.S.Y. NAVYA

Department of Biotechnology, Koneru Lakshmaiah Education Foundation (Deemed to be University), Green Fields, Vaddeswaram-522502, India

*Corresponding author: E-mail: koteswarareddy@kluniversity.in

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The world-wide pandemic emerged due to severe-acute-respiratory-syndrome coronavirus-2 (SARS-CoV-2) causing viral respiratory disease (COVID-19). An insight into coronavirus drug, vaccine targets and their controlling agents are necessary and important for exploring new drugs and vaccines against the viral activities. Recent drug targets identified includes RNA-dependent-RNA polymerase (RdRp), papain-like proteases (PLpro), helicases, 3-chymotrypsin-like protease (3CLpro) are the proteins which are responsible for the viral replication and viral RNA synthesis. Most of the studies focussed on vaccine targets including spike protein (S), envelope protein (E), nucleocapsid protein (N) and membrane protein (M) to mitigate the proliferation and concentration of viral particles from infected one to others. Recent works revealed a strong awareness about the use of FDA approved drugs favipiravir, remdesivir, galidesivir, lopinavir, itraconazole, acyclovir and fleximer as repurposed drugs and few phytochemicals were also screened against the activity of viral enzymes to treat the complexity of the viral disease.

Keywords: SARS-CoV-2, COVID-19, Drug targets, Vaccine targets, Phytochemicals.

INTRODUCTION

The severe acute-respiratory infectious disease which is caused due to SARS-CoV-2 viral agent has appeared as a "world-wide pandemic" declared by WHO on 11th March 2020 resulting in nearly 15 million infections by July, 2020 globally [1,2]. This virus is more transmissible having an enveloped, positively sensed single-stranded RNA of ~30 kb genome length and included in the genus β-coronavirus [3]. It consists of 16 non-structural, 27 structural and 9 accessory proteins encoded by 14 open reading frames [4,5]. Recent research and clinical studies described the importance of drugs in contrast to the mechanisms of SARS-CoV-2 virus. Researchers reported the use of FDA approved drugs as repurposed drugs to treat the complexity of this viral disease. To study this, the knowledge of viral structure, drug targets or proteins, vaccine targets and their activities is necessary for exploring new drugs against the viral activities [2].

Recent works revealed strong awareness about the RNA-dependent-RNA-polymerase (RdRp), papain-like proteases (PLpro), helicases, 3-chymotrypsin-like protease (3CLpro) are the proteins responsible for the viral replication and viral RNA synthesis [2]. The inhibitors such as favipiravir, remdesivir, galidesivir, lopinavir, itraconazole, acyclovir, fleximer, *etc.*, were discovered in which some were repurposed drugs used against the activity of viral enzymes or proteins [6]. The functional amino acids, active residues of each protein were discussed by different experimental, molecular docking and clinical approaches. The vaccine targets of viruses like spike-(S), envelope-(E), nucleocapsid-(N) and membrane-(M) proteins are also studied for drug designing purposes [6,7]. The discussion of the clinical phase of each inhibitor molecule can be helpful in noticing the drug performance against the virulence in patients [8]. Screening of phytochemicals extracted from the medicinal plants have a key role in uncovering the potential anti-coronavirus natural compounds. Current studies disclosed that the 3CLpro takes a vital role in viral replication hence it acts as a potential drug-target against COVID-19 [9]. The phytochemical named diosgenin was found to be potential

anti-COVID unaffected compounds compared to lopinavir [10]. The discovered drug targets, vaccine targets, inhibitors and phytochemicals are discussed.

The current mini-review is divided into four parts, in which the first part dealt with the drug-targets of viral proteins, the second part explained the vaccine targets of SARS-CoV-2, the third one summarized the existing drugs of viral enzymes and the subsequent part discussed the phytochemicals screened from various plant sources and summarized against of SARS-CoV-2 viral proteins.

Drug-targets against SARS-CoV-2

RNA-dependent-RNA-polymerase (RdRp): RdRp, a protein which is conserved in covid-19 is also known as Nsp12 (non-structural-protein). It is an important enzyme for viral RNA transcription and translation. It has a domain located at C-terminus with Ser-Asp-Asp conserved motif [3]. The role of RdRp enzyme involves proof reading in such a way that the core domain of helicase binds to ATP and the zinc-binding domain is required for replication and transcription [7]. The inhibitors such as favipiravir, remdesivir, penciclovir, galidesivir, *etc*. are used as drugs having inhibition property of RdRp enzyme activity (PDB Code: 6XQB) [1,2,11].

Papain like protease (PLpro): It is a protease of cysteine encoded by Nsp3 protein. PLpro is very essential for activities of deubiquitinating and interferon antagonism required for viral RNA synthesis and replication [4]. It consists of a domain located at the *N*-terminal part with 1a and 1ab polyproteins. Lopinavir, ritonavir and disulfiram are the drugs, which are used as inhibitors that inhibit viral replication by blocking Mpro and PLpro activities (PDB code: 7D47) [4].

Helicases: These are the multi-purpose proteins with a metal-binding-domain (MBD) at *N*-terminal and a helicase-domain (Hel). The Zn binding domain is formed by *N*-terminal whereas the helicase domain is formed by the C-terminal with a preserved motif and take part in unwinding the double-stranded (ds) viral DNA and RNA along the 5′–3′ direction in a nucleoside-triphosphate-dependent way [12]. A report states, the Nsp13 protein which encodes helicases is essential for the replication, transcription and translation processes of coronavirus [13]. The inhibitors like bananins, 5-hydroxychromone derivative, ADKs and SSYA10-001 are observed as they retard the helicase activity of SARS-CoV-2, which are under preclinical studies (PDB Code: 5RL6, 6XEZ, 7KRO) [14].

3-Chymotrypsin-like-protease (3CLpro): It is also known as the main protease (Mpro) encoded by Nsp5 and occupies an vital role in viral replication and NSPS-maturation which are predominant for the viral life-cycle. This is divided from polyproteins to produce mature enzymes and cleaves at 11 sites to release Nsp4-Nsp16 downstream. This protein consists of conserved active site residues at Cys145 and His41 [15]. This enzyme is responsible at early infection stage for step-by-step release of other enzymes. For functional testing of these proteins, many biochemical assays are used. Due to high similarity of 3CLpro/Mpro, repurposed drugs were also discovered (PDB code: 6LU7, 7DPV, 7DPP) [16,17]. The molecules such as GC376 and its analogue GC373 were observed as 3CLpro inhibitor proteins of SARS-CoV-2 [18]. Other drugs like lopinavir and ritonavir, which were repurposed drugs and also observed as best inhibitors against 3CLpro activity. Many phytochemicals like licoleafol, amaranthin, *etc*. have been discovered, which can target the activity of 3CLpro by inhibiting proteolytic and ATPase activities [2,16]. The list of possible drug targets of SARS-CoV-2 are summarized in Table-1.

Vaccine targets against SARS-COV-2

Spike-protein (S): The clove shaped glycosylated spike protein is an immune response inducer of the host system. It is a type-I *trans*-membrane-protein with ectodomain, *trans*-membrane and intracellular domains [29]. The conserved amino acid residues of this protein are Cys480 and Cys488. In addition to this, the similarity between the structure of S-protein receptor-binding-domain (RBD) of both SARS-CoV-2 and SARS-CoV is observed to be unbelievable [29,30]. There is a receptor-binding S1 and a membrane-fusion S2 domains where the cleavage is required at S1-S2 junction for membrane fusion and activation of viral entry. Hence the spike-protein has a major role in viral and cell receptor (ACE2) interaction and is a major target for antiviral agents (PDB code: 6ZGH, 7BNM, 7BNN) [29,31,32].

Envelope-protein (E): E-protein, which is around 8-12kDa, is a very important component in assembly, release and virulence phases of the life cycle of viruses. It is composed of 75 amino acid residues with N-terminal *trans*-membrane (TM) and C-terminal domains. It consists of His, Leu amino-acid residues that replace Pro at 37 and 72 positions (PDB code: 7K3G, 7AD1) [6].

Nucleocapsid-protein (N): The organization of this protein structure is complex. It owns three highly conserved-domains; an *N*-terminal, an RNA-binding and a C-terminal domain. It was observed that these domains may together participate in RNA binding and its phosphorylation status is a prerequisite to trigger the structural dynamism that facilitates the affinity of viral *versus* non-viral RNA [7]. N protein consists of 9 serine and 4 arginine amino acid residues in the conserved region. It involves RNA packaging in a string of beads type of conformation. Even though it contributes its role in viral genome organization, it also promotes viral assembly and enhances efficiency of virus transcription amongst others (PDB code: 6M3M, 6WKP, 7N0S) [30].

Membrane protein (M): Membrane protein is common within the viral membrane and essential for the budding process of viruses. It can bind to all other structural-proteins. This helps in viral-assembly completion by stabilizing N protein-RNA complex. It interacts with S-protein during cell attachment and entry. Ser, Arg, Gly are the conserved amino acid residues at position 89 among coronaviruses (PDB code: 7B27) [6,7].

Drugs against the targeted viral proteins

Favipiravir: Favipiravir, an RNA-dependent-RNA-polymerase (RdRp) inhibitor, is used against SARS-CoV-2 activity that is involved in hindrance during viral replication. This drug was developed by Fujifilm company and it was a repurposed drug, which was initially used for treating influenza virus and Hepatitis C virus (HCV) infections. No adverse effects have

TABLE-1
LIST OF PROBABLE DRUG TARGETS AGAINST SARS-CoV-2

Classification of viral proteins	Drug targets	Biological function	Functional amino acids/Active site residues/Motifs	RCSB/PDB code	Ref
Viral RNA synthesis and replication	RNA-Dependent-RNA-Polymerase (RdRp)	Transcription and replication of RNA	Ser-Asp-Asp motif	6XQB	[2,4]
	Papain-Like Protease (PLpro)	Deubiquinating and interferon antagonism activities	N-terminal part of polyproteins 1a and 1ab	7D47	[1,2,19]
	Helicases	dsDNA and RNA replication, transcription and translation.	Zn binding domain	5RL6 6XEZ 7KRO	[1,3,4,17]
	3-Chymotrypsin-Like Protease (3CLpro)	Maturation of Nsps for viral life cycle.	Cys145 and His41	6LU7 7DPV 7DPP	[2,11,20,21]
Viral structural proteins	Spike protein	Membrane fusion and viral entry activation	Cys480 and Cys488	6ZGH 7BNM 7BNN	[2,12,19]
	Envelope protein	Structural unity and host virulence	His, Leu replaces Pro at 37 and 72 positions	7K3G 7AD1	[2,6,17,22]
	Nucleocapsid protein	Intracellular localization (modulation of cell processes), virus transcription and assembly	9 serine and 4 arginine residues	6M3M 6WKP 7N0S	[3,16,23]
	Membrane protein	Maintenance of viral envelope shape	Ser, Arg, Gly at position 89	7B27	[2,7]
Host-specific receptor or enzymes	ACE2- RNA binding domain (RBD)	Mediates viral entry and virus infection (pathogenesis)	V445, F486 and Y505	6M17 7B3O	[24]
	trans-Membrane-protease-serine 2 (TMPRSS2)	Triggers viral infection into host cells	HIS296, ILE346 and SER441	1Z8G 6K5D 3T2N 5CE1	[25]
Viral virulence factors	Nsp1	Triggers host mRNA degradation Inhibits type-I interferon	Lysine, Leucine and Proline	7K3N 7K7P 7EQ4	[2,26]
	Nsp3c	Resists host innate immunity	H120 and F121	7B62 2RNK	[2,27]
	ORF7a	DNA replication, RNA processing	Glu26	6W37 7C01 7JN5	[5,28]

been reported till now for this drug and showing better results against COVID-19. Currently, this drug is in Phase-II clinical studies [8,33].

Ribavirin: The RdRp inhibitor which inhibits the synthesis of viral RNA and capping of mRNA has the capability of decreasing the viral load in the host system. This drug is in phase-II of development phase. Bausch Health Pharmaceutical company progressed this drug for treating covid patients. Ribavirin was used in combination with lopinavir/ritonavir (that inhibits the 3CLpro activity) during the first epidemic of SARS CoV showed better results in patients but was not recommended for SARS CoV-2 treatment [8,34].

Penciclovir: This drug was found to be near results of activation energies like remdesivir that can exhibit antiviral activity by inhibiting the nsp12 of RdRp protein. Penciclovir, a repurposed drug, which was used initially for the treatment of Herpes virus, did not show satisfactory results against Covid-19 activity. Company named Fujifilm, Toyama chemicals established this drug which was FDA approved but still in preclinical phase [8,35].

Disulfiram: It is developed by a trade name called Antabuse. It can be used as anti-covid drug as it can obstruct the Mpro and PLpro proteins which resulted in inhibition of viral replication. This drug is in Phase-2 clinical trials. The molecular mechanisms of disulfiram include depletion of the effect of inflammation and suppression of nsp13 ATPase activity in addition to Mpro and PLpro inhibitions. Generally, this drug is advised to the alcohol-addicted patients [36,37]. The list of possible drugs and their details against target viral proteins of SARS CoV-2 is summarized in Table-2.

Phytochemicals screened to treat SARS-COV-2 patients

5,7,3,4-Tetrahydroxy-2′-(3,3-dimethylallyl)isoflavone: It is extracted from the plant called *Psorothamnus arborescens*. The medicinal use of this phytochemical compound is to treat stomach troubles and repurposed for the SARS CoV2 disease treatment by targeting the activity of 3CLpro [54]. Previous studies state that this phytochemical has higher binding efficiency as it inhibits the proteolytic activity of virus by interacting strongly with Cys-His catalytic residues through hydrogen bond formation [9].

TABLE-2
LIST OF DRUGS AGAINST TARGETED-VIRAL-PROTEINS/LIST OF COMPANIES ACTIVELY INVOLVED IN DEVOLVING DRUGS TO TREAT SARS-CoV-2 PATIENTS

Target protein	Inhibitor	Mechanism of action/Target site	Current status	Company/ Organization	Development phase	Ref.
RNA-Dependent RNA Polymerase (RdRp)	Favipiravir	RNA-dependent-RNA-polymerase inhibitor, Interferes with viral replication	Being Used as treatment for Influenza and experimental analysis for Covid-19	Fujifilm	Phase - II	[8,33,38]
	Ribavirin	Inhibits viral-RNA synthesis and mRNA-capping	Approved for treatment of HCV and RSV not recommended for Covid treatment	Bausch Health	Phase – II	[8,34]
	Penciclovir	Inhibits nsp12 of RdRp and exhibits antiviral activity	Used against Herpes Virus but not showed better results against Covid 19 treatment in *in vitro*	Fujifilm Toyama Chemical	Preclinical trials	[8,35]
	Remdesivir	Analogue of nucleotide; Broad- spectrum; many viral-infections, can inhibits viral-RNA synthesis	It's now being tested in five Covid-19 clinical trials that have been set up at lightning speed	Gilead	Phase - III	[8]
	Galidesivir	Inhibitor of RNA polymerase and premature termination of RNA transcription	Used for yellow fever under clinical investigation for Covid-19	BioCryst	Phase - I	[39]
	Itraconazole	Antifungal drug exhibits invitro antiviral activity by inhiting viral replication	Clinical studies are going on for treatment against SARS-CoV-2	Janssen Pharmaceuticals	Randomized clinical trials	[40]
	Novobiocin	Anti-bacterial drug that may also exhibits antiviral activity by inhibiting RdRp	Used for treating lower respiratory tract problems of pneumonia patients and also problems caused due to SARS-CoV2 proteins	N/A	N/A	[41]
	Chenodeoxycholic acid	Primary bile acids having anti-inflammatory properties by binding with RBD of S-glycoprotein of SARS-CoV2	Used for covid patients to facilitate the absorption of other drugs	N/A	N/A	[42]
	Cortisone	Corticosteroid works against pathogens that effects lung diseases (anti-allergic effect)	Currently using only for advanced pneumonia covid patients (not highly recommended)	Merck & Co.	Randomized clinical trials	[43]
	Idarubicin	Inhibitor of topoisomerase-II that inhibits endoribonuclease enzyme of nsp15 useful for viral life cycle	Anti-cancer drug used rarely for Covid-19 patients	N/A	Randomized clinical trials	[44-46]
	Silybin	Inhibits viral invasion by binding to ACE2 receptor	Hepatoprotective drug used for covid patients too	N/A	N/A	[44]
	Pancuronium Bromide	Provides muscle relaxation by interacting with neuroreceptors	Prescribed sometimes for covid treatment	N/A	N/A	[44]
	Dabigatran etexilate 6'-fluorinated-aristeromycin analogues	Inhibition of viral induced cellular injury, hepatotoxicity for arterial and venous thrombotic problems	First-line choice for oral anticoagulant at discharge after covid treatment	N/A	Phase - III	[8,47]
	Acyclovir	Inhibition of viral DNA polymerase responsible for RNA synthesis	Approved for treatment of HCV and HSV not recommended for Covid treatment	N/A	Preclinical trials	[8,48]
	Fleximer	Combined with acyclovir for inhibiting viral nucleoside polymerase	Antibody drug conjugate still in clinical development	N/A	Preclinical trials	[49]
Papain like protease (PLpro)	Disulfiram	Inhibits viral replication by blocking Mpro protease and reduces hyperinflammation in cells	Prescribed in particular doses to alcohol dependents	Antabuse	Phase - II	[36,37]
	Lopinavir	Inhibits 3CLpro activity	Approved for HIV treatment but NIH is against for covid-19 treatment	AbbVie	Phase - III	[8]
	Ritonavir	Inhibits 3CLpro activity	Approved for HIV treatment but NIH is against for covid-19 treatment	AbbVie	Phase - III	[8]

Helicases	Bananins	Inhibits viral invasion and replication	Used as Anti-corona-RNA-viral agents	biostep GmbH	N/A	[50]
	5-Hydroxy-chromone derivative	Inhibits helicase activity	Anti-viral activity against HCV and SCV and used for covid treatment	N/A	N/A	[51]
	ADKs	Inhibits the helicase activity of NTPase/helicase	Approved for HIV-1 and HCV and in clinical studies for SARS-CoV2	N/A	N/A	[51,52]
	SSYA10-001	Inhibits viral replication by blocking helicases	Used as replication inhibitors of SARS,MERS,Hepatitis viruses	N/A	N/A	[53]

Myricitrin: The plant source of myricitrin is *Myrica cerifera*. It is useful for medicinal, ayurvedic and homeopathic purposes for treating various hepatic diseases. Recently, this compound is repurposed for the use of covid treatment as it mainly targets Mpro, 3CLpro viral proteins by inhibiting their ATPase activities. The molecular docking studies of this compound particularly highlights its importance for covid treatment [9,55].

Methyl rosmarinate: A natural compound methyl rosmarinate is taken out from the plant named *Hyptis atrorubens Poit* which contains the antiviral activity. It is useful to help for the covid patients' treatment as it inhibits the activity of 3CLpro in the host system. Current research reveals that the myricitrin and methyl rosmarinate showed stable fluctuations and folding results suggesting the better phytochemical compounds against 3CLpro activity [9].

Diosgenin: Diosgenin is a phytochemical compound found in a rhizome plant named *Rhizoma polygonati*. It helps in treating SARS CoV2 disease by inhibiting viral replication by docking with the angiotensin-converting-enzyme-II of the host cell target. Studies proved that it targets the spike protein, 3CL-hydrolase, RNA-dependent-RNA-polymerase viral proteins helping in Covid-19 treatment. The binding or docking scores of diosgenin showed better results when compared to other chemical drug targets like lopinavir. It is also present in medicinal plants like smilax and heterosmilax species [10].

(+)-Syringaresinol-O-β-D-glucoside: This phytochemical compound is also found in *Rhizoma polygonati*, a rhizome plant. The mechanism of action of this compound is similar to diosgenin, which is useful for the COVID-19 treatment. The molecular weight of (+)-syringaresinol-O-β-D-glucoside is more than diosgenin but the molecular docking results of both are said to be similar. This compound inhibits viral replication by targeting the ACE2, spike proteins of the host the target cell [10]. The list of top ranked phytochemicals screened and their plant sources are summarized against the viral proteins in Table-3.

Conclusion

The review focussed on SARS CoV-2 drug, vaccine targets and their controlling agents are necessary and important for exploring new drugs and vaccines against the viral activities. Recent drug targets identified including RNA-dependent-RNA-polymerase (RdRp), papain-like proteases (PLpro), helicases, 3-chymotrypsin-like protease (3CLpro) are the proteins accountable for the viral-replication and viral-RNA synthesis. The FDA drugs such as favipiravir, remdesivir, galidesivir, lopinavir,

TABLE-3
TOP RANKED PHYTOCHEMICALS SCREENED TO TREAT SARS-CoV-2 PATIENTS

PubChem ID	Phytochemical name	Plant source	Mechanism of action/Target site	Target protein	Ref.
11610052	5,7,3,4-Tetra-hydroxy-2'-(3,3-dimethylallyl) isoflavone	*Psorothamnus arborescens*	High-binding affinity and inhibits proteolytic activity	3CLpro	[9,54]
5281673	Myricitrin	*Myrica cerifera*	Inhibits ATPase activity	3CLpro, Mpro	[9,55]
6479915	Methyl-rosmarinate	*Hyptis atrorubens* Poit	Inhibits proteolytic activity	3CLpro	[9]
NPACT00105	3,5,7,3',4',5'-hexahydroxy-flavanone-3-O-β-D-glucopyranoside	*Phoseolus vulgaris*	Inhibits reverse transcriptase activity	3CLpro	[9,56]
10930068	(2S)-Eriodictyol-7-O-(6"-O-galloyl)-β-D-glucopyranoside	*Phyllanthus emblica*	Inhibits viral replication	3CLpro	[9]
5318606	Myricetin 3-O-β-D-glucopyaranoside	*Camellia sinensis*	Antiviral activity	3CLpro	[9,55]
11111496	Licoleafol	*Glycyrrhiza uralensis*	Antiviral activity	3CLpro	[9,55]
6123095	Amaranthin	*Amaranthus tricolor*	Antiviral activity	3CLpro	[9,55]
64143	Nelfinavir	Drugs used as control	Bind to receptor binding site	3CLpro	[9]
65947	Prulifloxacin	Drugs used as control	Bind to receptor binding site	3CLpro	[9]
5311054	Colistin	Drugs used as control	Bind to receptor binding site	3CLpro	[9]
99474	Diosgenin	*Rhizoma polygonati* (rhizome)	Inhibition of viral replication	ACE2, spike protein (3CL hydrolase)	[10]
443024	(+)-Syringaresinol-O-β-D-glucoside	*Rhizoma polygonati* (rhizome)	Inhibition of viral replication	ACE2, spike protein (3CL hydrolase)	[10]

itraconazole, acyclovir and fleximer in which some were repurposed drugs used against the activity of viral enzymes or proteins. Most of the studies are focussed on vaccine targets including spike-protein (S), envelope-protein (E), nucleocapsid-protein (N) and membrane-protein (M) to mitigate the proliferation and concentration of viral particles from infected one to others. Recently, few phytochemicals were screened from the plant sources and summarized against SARS-CoV-2 includes 5,7,3,4-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone, myricitrin, methyl-rosmarinate, 3,5,7,3,4,5-hexahydroxy flavanone-3-O-β-D-glucopyranoside, (2S)-eriodictyol, licoleafol, amaranthin, nelfinavir, prulifloxacin, colistin, 7-O-(6″-O-galloyl)-β-D-glucopyranoside, diosgenin and (+)-syringaresinol-O-β-D-glucoside. This review will be useful for the researchers community to explore the new drugs and vaccines against the viral proliferation of SARS CoV-2.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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