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Corresponding Emails:
subrots6@gmail.com

DARSGAH-E-AHLEBAIT

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Prediction Study Proposing a Novel Strategy (Car-Tv) and Drug against Sars-Cov-2 Virus [A Review]

Subrot Sarma*

Editor of International Journal of Anatomy and Research and Independent Researcher and Scholar, P.O. Nazira, 785685, India

Abstract

Introduction: SARS-CoV-2 virus is responsible for inflicting COVID-19 pandemic. Considering virulence towards health & its economic effect on the population, suitable drug developmental strategy should be devised. An evaluation is provided here in the form of minireview dissecting the available therapeutic strategies, drugs and their mode of action against ssRNA+ viral infection including SARS-CoV-2 virus. The aim turned into to enlist the call of the antiviral agents and mechanisms associated with a viral life cycle that may be exploited probably to be used as therapeutic means to neutralize the SARS-CoV-2 viral infection. Methods: Using an online database like PubMed, MEDLINE, Embase, Google scholar, a systematic literature search was performed following key-word: antiviral agents, inhibitor ss RNA+, mechanism of antiviral activity, SARS-CoV-2, viral life-cycle, In silico/In vivo/In vitro. Results: The data identified and highlighted in the present assessment could be used for developing a novel therapeutic strategy against SARS-CoV-2 that can be categorized into 3 clusters. Cluster I- unique (for SARS-CoV-2) endocytic antiviral mechanism as potential drug target that may be exploited for drug design using both computational and In vivo approach. Cluster II- a total of 7 medicaments is hypothesized to

act as an antiviral agent against SARS-CoV-2 affecting multiple steps of viral entry and endocytosis. Molecular simulation and In vivo analysis of the compounds are put forward for further analysis. Cluster III- a total of 21 physic used as an antiviral drug against SARS-CoV-2 in the In-silico setup calls for In vivo and In vitro analysis. Miscellaneous- Computational and In vivo investigation against SARS- CoV-2 viral infection using novel targets of CD147, Vimentin as an antiviral strategy. Novelty - CAR-TV- (chimeric antigen receptor -T cell-virus) therapy against SARS-CoV-2 virus is predicted with its potential receptor blueprint. Conclusion: Antiviral drug targets and therapeutic agents examined against ssRNA+ virus should get the priority to design medicine (In silico, In vivo, In vitro) against SARS-CoV-2. Novel draft of CAR-TV cell therapy with its proposed design of the receptor/antibody has the potential to be used as an effective drug development strategy against SARS-CoV-2 viral infection including any antimicrobial infection showing unique antigenic characteristics.

Keywords: ssRNA+, RNA dependent RNA polymerase, Endocytosis, Molecular simulation, CAR-T

Introduction

Coronavirus sickness 2019 (COVID-19) might be a malady brought about by extreme intense respiratory disorder coronavirus 2 (SARS-CoV-2) which causes mortality and morbidity [1]. The genome wide examination uncovered the presence of two sorts of coronavirus strain L(aggressive) and S strain (less aggressive) [2]. The current pandemic causing (human SARS-CoV-2- contamination) has a place with the β-coronavirus family indicating genomic character to bat coronavirus [3]. The SARS-CoV-2 virus is a positive-strand single-stranded RNA (ss RNA+) virus having a place with subgenus Sarbecovirus, Orthocoronavirinae subfamily [4, 5, 6]. Clinical manifestation includes fever, exhaustion, and different diseases related with lungs [3]. Till now the number of people infected with the virus has ascended to 870,000 and death of 43,000[7, 8, 9]. One can treat the infection either by utilizing already available drugs in the viral infection field effectively or devise novel medication targets or utilize an elective novel medication improvement system. In this hypothetical survey, a couple of expectations have been utilized to build up drugs against SARS-CoV-2 viral disease with its potential component of activity along specifying new helpful targets. The review finishes up with the suggestion of utilizing a creative methodology for treating SARS-CoV-2 viral infection defined as CAT-TV.

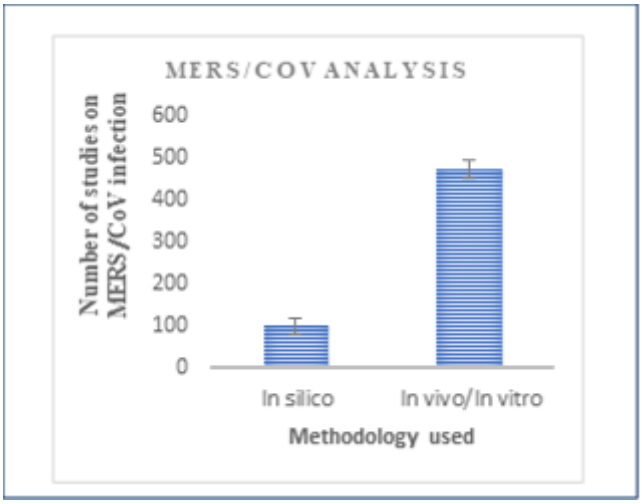


Fig. 1. Relative distribution of research publication focused on previously identified corona viral infection caused by MERS-CoV and SARS-CoV-2. Compared to In silico analysis, number of studies using In vivo/In vitro has increased drastically over the years. Source: PubMed, Uniport, ExPasy (Table 1)

Genomic Organization of the Sars-Cov-2 Virus

It is of high significance to decipher the genomic and proteomic profile of the SARS-CoV-2 virus to investigate and plan novel medications. SARS- CoV-2 virus has specific spike protein (S glycoprotein) receptors [10]. In silico analysis have indicated the antigenic explicitness of S1 spike proteins towards the host cell receptor of ACE2 (angiotensin-converting enzyme- 2) [11,12]. Other important auxiliary proteins incorporate Envelope (E), Matrix (M) and Nucleocapsid (N) including a few frill proteins, a positive-sense ssRNA [13] with the variable ORF (1-16) coding for non-structural proteins [14]. Aside from a couple of amino corrosive replacements, SARS-CoV-2 virus shows huge similitude with previously recognized

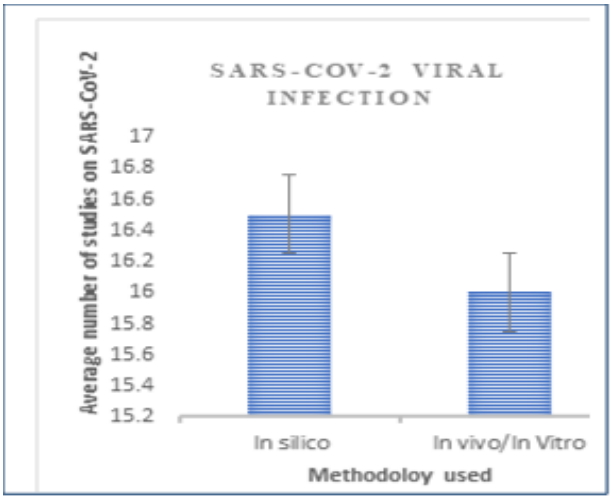


Fig. 2. Distribution of In silico and In vivo/In vitro approaches investigated against SARS-CoV-2 viral infection. Drastic increase in the number of In vivo/In vitro analysis is expected in the near future representing the graph to be more like Fig1 (Table 1) Source: PubMed, Uniport,ExPasy.

SARS-CoV [15]. Transformative arrangement investigation and varieties of the medication focus to be utilized for the restorative methodology assumes a significant job in building up the plan or structure of the immunization to make it increasingly viable and efficient [16]. Along these lines, examining the developmental preoccupation of the infection from the set-up strain (SARS-CoV) could give intimations about the inclination of the viral genome for its frequency of mutation and possible hot spots for amino acid substitution and help to design better drug strategy against SARS-CoV-2 infection [17]. As the current infection is harmful and pathogenic, checking the viability of established drug/drug mechanism against ss RNA + viral infection may become basis for the concerned agents chipping away at SARS-CoV-2 infectivity.

SARS-Cov-2 VIRAL PATHOGENESIS

The virus enters the host through fecal, oral, and respiratory course lastly settling and reproducing in the pneumocyte type II covering the alveolar cells [18]. SARS-CoV-2 spike protein S1 1 subunit -ACE2 interaction is fol- lowed by viral attachment, membrane fusion and endocytosis with the release of viral genome in the intracellular space of the alveolar cells [15]. Viral translation, polyprotein processing and viral replication utilizing host ribosomes, replicase, and protease are associated with ss RNA virus life cycle like SARS- CoV-2 [19].

Results

To suggest and propose novel therapeutic agents against a particular SARS- CoV-2 infection, it is essential to have the fundamental data, for example, the study of disease transmission, etiology, viral life cycle, pathogenesis, drugs used, drug targets focused and ailment of studied viral infection and to compare with previously identified strain of SARS-CoV virus infection. So there is urgent need of coordination among basic and clinical research in this field. In the vast majority of the medication advancement plans structured against a particular infection like SARS-CoV-2, In silico examination along with molecular docking reads may help which would make the therapeutic strategy more effective and plausible in the In vivo set up [20, 21, 22, 23, 24].

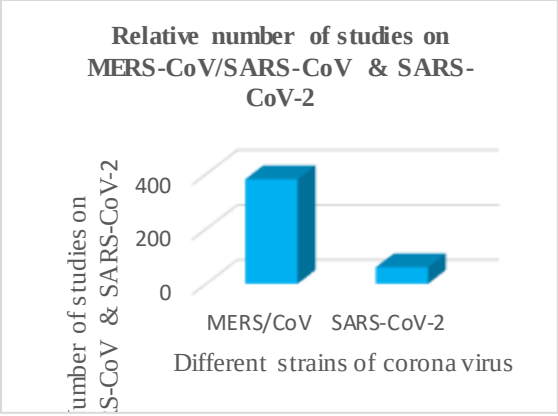


Fig. 3. Total number of studies performed in MERS-CoV/SARS-CoV as compared to SARS-CoV-2 viral infection. The data generated in the case of MESR-CoV/SARS-CoV could be used as a framework for future therapeutic approaches that can applied for SARS-CoV-2 drug development programme. Note that the above data comprises both In silico, In vivo and In vitro analysis. PubMed, Uniport, ExPasy (Also see Table 1).

Till date, more In vitro/In vivo antiviral studies have been done in the case of MERS- CoV [25] and SARS-CoV [26] as compared to the In-silico analysis (FIG 1). The reverse is true for the studies done with SARS-CoV-2 viral infection [27, 28] (FIG 2). This result is important that emphasize and corroborate previous studies on drug development against microbial infection indicating relevance of In silico approach that form the foundation for future In vivo/In vitro and clinical studies. As more data gets generated from SARS-CoV-2 infection studies, prediction could be made that FIG 2 would transition to become more like FIG 1 in the near future. This finding isn't unexpected as the human genomic/proteomic information and along with modern programming software are increasingly accessible for data analysis. Relative number of studies performed on MERS-CoV/SARS-CoV and SAR-CoV-2 (FIG 3) using both In silico and In vitro/In vivo strategy indicates availability of large date set (MERS-CoV/SARS-CoV) that can provide the foundation for studies to be done with SARS-CoV-2 viral infection (Table 1). Information regarding limitation, efficiency and overall impact on the health (available drugs) could be extracted from the database on MERS-CoV/SARS-CoV.

Antiviral Medication and Its Objectives Strcutured against Basic Component of Viral Life Cycle

The drug targets used for drug development strategy against viral infection covers components of replication, translation, receptor biology, focusing on enzymes and other critical proteins [Table 2 (Cluster III), FIG 4]. Multiple projects have identified different types of antiviral agents to be effective against MERS-CoV/SERS-CoV viral infection that has been successfully examined both and In /In set up (FIG 4) [29, 30, 31]. The data also represents antiviral study investigated against other +. Inhibitor of RNA dependent RNA followed by inhibitor followed by inhibitor has been focused of analyzing antiviral activity in the case of most +viral infection [17, 32, 33].

Table -1

			MERS-CoV		
Methods	**Data-1**	**Data-2**	**Data-3**	**Total***	**Average**
In silico	**20**	**18**	**20**	**58 (1-10*)**	**19.33**
In vitro/In vivo	**83**	**177**	**43**	**303 (11-26*)**	**101**
SARS-CoV					
Methods	**Data-1**	**Data -2**	**Data-3**	**Total***	**Average**
In silico	**13**	**12**	**16**	**41 (3, 27-35*)**	**13.66**
In vitro/In vivo	**41**	**97**	**30**	**168 (16, 20, 36-50*)**	**56**
			MERS-CoV/SARS-CoV		
In silico				**99(51-78*)**	
In vivo/In vitro				**471(25, 78-94*)**	
****References***					
			Key words		
Antiviral agents	**MERS/SARS-CoV Viral Infection**	**ssRNA+/computational drug design**	***In silico/Docking***	***In vitro***	**In Vivo**
			SARS-CoV-2		
	Data-1	**Data -2**	**Data- 3**	**Total**	**Average**
In silico	**20**	**9**	**4**	**33(51-60, 66, 72, 95-102*)**	**16.5**
In vivo/In vitro	**20**	**11**	**1**	**32(25, 78-86, 103-112*)**	**16**

Table. 1. Using online database like NCBI-Pubmed, above mentioned key word were used in order to find relevant publication in the field of SARS-CoV-2 viral infection. Same approach was used for MERS-CoV, SARS-CoV. The parameters were slightly altered in the search engine and 3 data data-set was used to find the average for number of publications in the field and plotted vs different methodologies. Representative citation enlisted for the references screened in the PUBMED for MERS-CoV, SARS-CoV, SARS-CoV-2 in the In silico and In vivo/In vitro set-up.

Analysis of the papers associated with antiviral studies reveal one critical aspect that none of the drugs are targeted against pathway proteins in case of SARS-CoV-2 viral drug development

strategy (FIG 5). See details below as the pathway is dissected in terms of therapeutic strategy for SARS-CoV-2.

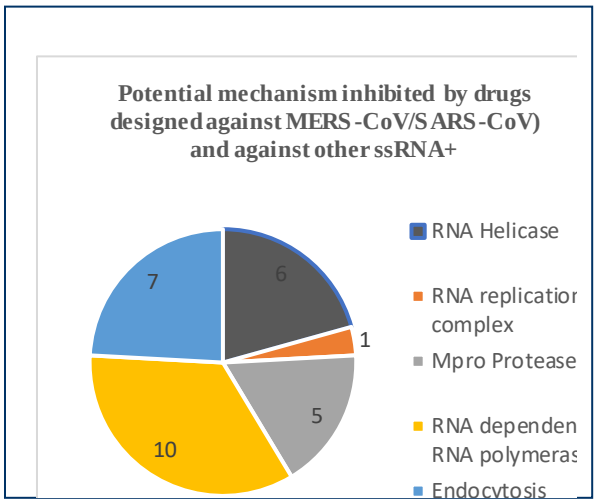


Fig 4 In silico/In vitro/In vivo antiviral strategies studied targeting multiple aspects of RNA life cycle. Numbers indicate relative number of antiviral investigations performed against specific viral mechanism. The analysis included antiviral research against the ssRNA + viral infection along with MERS-CoV and SARS-CoV infection. Source: PubMed, Uniport, ExPasy

Antiviral Medications Researched Both in Vivo/In Vitro against Sars-Cov-2 Viral Infection

Chloroquine is by and large broadly used for the treatment of different viral diseases including HIV [34, 35]. Additional function includes suppression of pro- inflammatory response and subsequent release of cytokines like IL-1, IL-6. The utilization of zinc added substances with expands the productivity of the treatment against SARS-CoV-2 [36] (see Table 2, Cluster III).This drug is the most widely used therapeutic agent available in the field that has undergone In silico, In vitro and clinical trials [37, 38]. RNA dependent RNA polymerase inhibitor has been successful in the treatment of SARS-CoV-2 viral infection and is in the clinical trial process. In Silico and In Vivo analysis showed promising outcome to use it as an antiviral drug [39, 40].

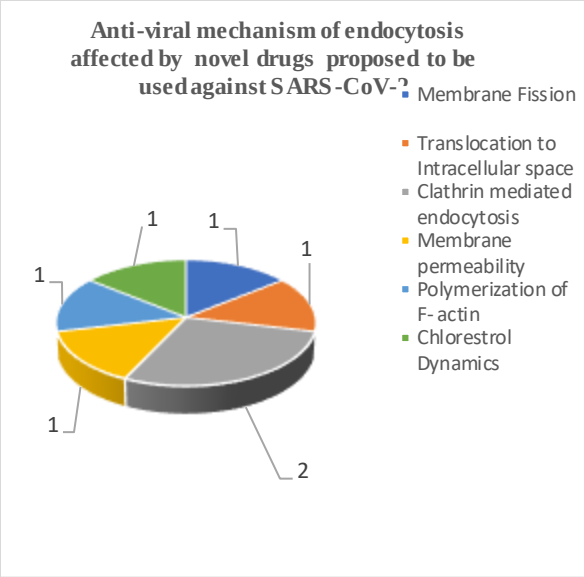


Fig 5 [Cluster I) Multiple steps of endocytic mechanism research that has been target of antiviral drug design scheme explored against ssRNA+. Both In silico & In vivo studies have been represented. These mechanisms could be investigated for future therapeutic examination to be used against SARS-CoV-2 viral infection. Note that endocytic pathway has never been studied against SARS-CoV-2 viral infection for its potential inhibitory antiviral activity

Antiviral Medications That Have Been Utilized Effectively Against Infection In Silico Proposed To Be Utilized Against Sars-Cov-2 Viral Diseases In Silico And In Vitro

In silico and In vivo investigation has uncovered the antiviral capacity of specialist drugs like Benzotriazole, Imidazole, Imidazodiazepine, Phenothiazine, Quinoline, Anthracycline [40,41]. Despite the fact that there has been discussion with respect to its instrument of activity hindering the movement of and has been recommended. These could be utilized in both In Silico, In Vivo, and In Vitro examination as potential antiviral against the SARS-CoV-2 infection (Table 2, also see Cluster III).

Positive Correlation Of Antiviral Activity Of Drugs Against Double Stranded Positive RNA Virus Using In Silico Virus.

Compounds like Benzotriazole, Imidazole, Imidazodiazepine, Phenothiazine, Quinoline, Anthracycline has been reported to show antiviral activity against RNA+ viral infection supported by an In silico analysis [41, 42]. The mechanism of action is not very clear but preliminary analysis reveals its potential anti- enzymatic activity against the which is critical factor for translation of the viral genome (Table 2, also see Cluster III). Second group of drugs identified in a computational modelling analysis indicate possible therapeutic activity against SARS-CoV- 2 which includes viniferin, myricitrin, taiwanhomoflavone, lactopicrin 15-oxalate [43]. These drugs affect the activity of the critical enzyme involved in viral translation and propagation. Moreover, antiviral activity of, Ribavirin, Sofasbuvir and Galidesivir has been explored against RNA viral infection in an In Silico analysis [44-46]. The computational docking study was targeted against

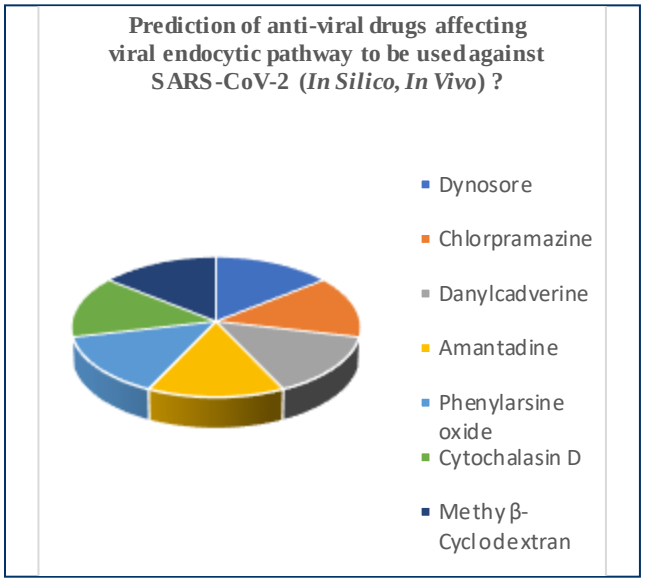
SARS-CoV-2 viral enzyme of RNA dependent RNA polymerase. All these compounds (see Table 2, Cluster III) are potentially good candidate to be used as antiviral agent or therapeutic drug that may be investigated in the In vivo and In vitro set- up specially against SARS-CoV-2 viral infection.

Novel Drugs Target Mechanism to Be Explored Against Sars-Cov-2.

The crucial process of viral entry into the host cell is aided by the process of endocytosis using clathrin dependent or independent mechanism [47]. It is a complex process involving biomolecules GTPase, PTPase, cholesterol dynamics and so on and so forth [48] (Table 3, Cluster I/II). The multistep process takes into consideration The process takes into consideration the fission of the membrane, translocation of the clathrin to the intracellular space, polymerization of F-actin etc [49]. Hindering these crucial steps may be a novel mechanism to configure the drugs against SARS-CoV-2 (FIG 5). These drugs would hamper the entry of the SARS-CoV-2 virus into the host cell (FIG 6; Cluster II). List of the drugs that can be investigated applying In silico, and In vivo/In vitro approach against SARS-CoV-2 viral infection is proposed in this review (FIG 6; Table 3, Cluster II).

Miscellaneous Receptors like Cd147 as an Potential Medication Target against Sars-Cov-2.

ACE 2 shows high affinity for SARS-CoV-2 virus [17, 50] aided by spike protein S1 subunit and this interaction of receptor binding domain with the ACE2 has been target of many



pharmaceutical investigations in both computational and in cell culture laboratories. Other viruses like rhinovirus shows high affinity for CD147 receptor and its activity is interrupted by inhibitors like azithromycin [51].

Fig. 6. [Cluster II] List of therapeutic drugs proposed to be investigated against various components of endocytic pathway in both In vivo and In silico against SARS-CoV-2 viral

infection. Computational simulation and molecular simulation studies followed by in vivo study for its antiviral activity against SARS-CoV-2.

Both SARS-CoV-2 virus and rhinovirus belongs to the same class of ssRNA + sharing crucial component of the spike protein features. Primary sequence analysis and homology modelling, screening of conserved domains, 3D rendering and protein -protein interaction studies between ACE2, CD147 with RBD (receptor binding domain) of SARS-CoV-2) may provide information on the receptor diversity used by SARS-CoV-2 virus for its entry and propagation [52].

Drug target	Mechanism of action	Inhibitor (Cluster III)	In silico/In vivo	
RNA helicase [39, 52]		1.*Benzotriazole* *2.Imidazole* *3.Imidazodiazepine* *4.Phenothiazine* *5. Quinoline* *6. Anthracycline*	*In Vivo*	Studied on non-SARS-CoV-2 *In vivo* studies against SARS-CoV-2 required
ssRNA+ replication complex [53] (pH dependent)	RNA replication	Chloroquine*	*In Vivo*	Studied for SARS-CoV-2
Mpro (protease)[40, 54, 55]	Polypeptide processing	1.*δ-viniferin* *2. myricitrin* *3.taiwanhomoflavone A 4. lactucopicrin 15-oxalate* *5.nympholide A*	*In Silico*	*In vivo* studies required against SARS-CoV-2
RNA dependent RNA polymerase (RdRp)[56, 43]	Viral Translation	Remdesivir* *Theoflavin* *1.Ribavirin* *2.Remdesivir* *3. Sofosbuvir* *4. Galidesivir 5.Tenofovir*	*In Vivo* *In Silico* docking study *In Silico* docking study	SARS-CoV-2 study *In Vivo* study needs to done against SARS-CoV-2. *In Vivo* study to be done against SARS-CoV-2 viral infection
RdRp[40]		*1.afzelin* *2. biorobin* *3. Hesperidin 4.phyllaemblicin B*	*In Silico* docking study	*In Vivo* study to be done against SARS-CoV-2 viral infection

*- Not in the cluster (III)

Physic proposed to be investigated as antiviral agent against SARS-CoV-2

Table 2 List of novel potential drugs and In silico approach used against SARS-CoV-2 viral infection proposed for further investigation with molecular simulation and In vivo analysis. (Cluster III) Prediction of drugs and its targets affecting the process of viral replication/translation as a potential anti-viral drug against SARS-CoV-2

Prediction of A Novel Methodology Of Car-Tv As An Antiviral Strategy To Counter The Sars-Cov-2 Viral Infection

CAR-T (chimeric antigen receptor-T cell) therapy for the tumor treatment got a gigantic lift as of late where T cell modified receptor cells are designed to counter-act the tumor antigen and re-infused back to the patient thus eliminating the tumor based on antigen-antibody neutralization mechanism [4, 53].

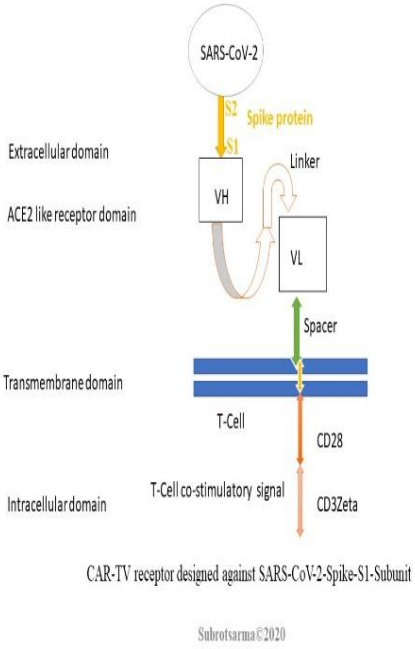


Fig. 7. A schematic portrayal of essential plan of the T-Cell explicit receptor depicted The difference between CAR-TV (proposed in this review) and traditional CAR-T(50). The tumor antigen specificity and S1 subunit spike protein specificity make the both approach different. Inactivating virus (50, 63) expressing ACE2 like receptor (based on genomic manipulation) transfused back into the patient infected with SARS-CoV-2 viral infection triggering cytotoxic T-Cell/T-helper/APC/MHC-II and thus neutralizing the virus. Drug design and blue-print of the CAR-TV receptor against SARS-CoV-2 virus. Modified form of CAR-TV devised from [64].

A comparable methodology has been proposed in this review CAR-TV (virus) for the treatment of SARS- CoV-2 infection with the exception that antigen is SARS-CoV-2 virus infection explicit instead of tumor explicit. As the antigen specificity is already deciphered in the case of SARS- CoV-2 spike protein, manipulation for the expression of receptors /antibody in the T immune cell along with the aid of T-cytotoxic cells, MHC-II, APC etc specific for the virus

should not be technically difficult to develop in the laboratory. Schematic representation of the basic design and blue print of the modified T cell receptor is described here (FIG 7). The novel procedure proposed here could be applied to other microbial disease sedate improvement that shows species explicit antigenic highlights (e.g., organism explicit antigen) and should be focus of the future investigation in the field of microbial pharmacology.

Drug Target (Cluster I)	Function	Mechanism	Inhibitor (Cluster II)	Remarks
Dynamin GTPase [57]	Membrane fission during endocytosis	GTPase activity of dynamin in endocytosis	Dynosore*	*In Silico*/*In Vivo*/ to be investigated against SARS-CoV-2 as anti-viral agent*
Clathrin /AP2 [58]	Translocation to intracellular space	Clathrin mediated endocytosis	Chlorpromazine*	*In Silico*/*In Vivo*/ to be investigated against SARS-CoV-2 as anti-viral agent*
Clathrin Coated Vesicle [59]	Clathrin mediated endocytosis	endocytosis	Dansylcadaverine/ amantadine*	*In Silico*/*In Vivo*/ to be investigated against SARS-CoV-2 as anti-viral agent*
PTPase [60]	membrane-permeable protein-tyrosine phosphatase	endocytosis	Phenylarsine oxide*	*In Silico*/*In Vivo*/ to be investigated against SARS-CoV-2 as anti-viral agent*
F-actin [61]	Polymerization of F-actin	endocytosis	Cytochalasin D*	*In Silico*/*In Vivo*/ to be investigated against SARS-CoV-2 as anti-viral agent*
Cholesterol [62]	Cell membrane dynamics of cholesterol during endocytosis	endocytosis	methyl β-cyclodextran*	*In Silico*/*In Vivo*/ to be investigated as anti-viral agent against SARS-CoV-2*

*Drugs predicted to act as antiviral agents for SARS-CoV-2(not been explored both In silico/In vivo.

Table 3 Components of the endocytosis that are predicted to act as an anti-viral against SARS-CoV-2 viral infection

Discussion

7 drugs screened (targeting endocytosis) through virtual process should be examined In silico/In vivo set up for its antiviral activity against SARS- CoV-2 infection. 16 drugs focused in

this review may be investigated In vivo for its antiviral activity against SARS-CoV-2. The proposed CAR-TV cell therapy research can be examined further against SARS-CoV-2 viral infection and for other antigen-specific infection. Computational receptor biology should get the focus in order to identify alternative receptors (against SARS-CoV- 2 virus).

Homology modelling of ACE2 like receptors should be examined by studying sequence homology (www.ebi.ac.uk,www.molbol-toosls.ca), creating 3D domain (SWISS- PROTEIN respiratory) and using 3D interaction tools (SPRINT-Scoring Protein INTeration, Struct2Net [54]. Receptors like vimentin and CD147 may be used by the SARS-CoV-2 viral for its entry into the cell that may be explored both In silico and In vivo to study alternative viral entry routes which could become focus of drug development strategy against SARS-CoV-2 viral infection.

Conclusion

In this mini-review, an effort has been made to predict few possible drug target mechanisms (endocytosis) which could be exploited in order to develop novel drugs against SARS-CoV-2 viral infection. Also, in this review approximately 21 drugs have been documented and proposed that can be investigated in In vivo/In vitro set up for its potential role as an antiviral agent against SARS-CoV-2 infection. Moreover, novel antiviral strategy of using CAR-TV cell therapy against viral infection like SARS-CoV-2 has been introduced for the first time in this review with its feasible design that may be improved and improvised by the experts in the field of virology and pharmacology. This new proposition has the potential for paradigm shift for future studies not only against SARS-CoV-2 virus but all the infection showing unique antigenic features that may be countered by altering the genomic set-up of the receptor biology of the T-cells. By overcoming the limitation of this novel strategy (CAR-TV), the proposed modification can have tremendous implication in the field of personalized medicine.

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Methods

Literature survey

A multidisciplinary approach has been used extensively for analyzing, interpretation, and post interpretation of the data (gene and protein) from the available database which includes NCBI-Pubmed, Expasy etc.

Software

For referencing, Endnote X9 software was extensively used and format was altered based on the journal policy. Plagiarism checker was useful in detecting any kind of unintentional plagiarism. Grammarly software was used for improving the quality of the manuscript writing.

Microsoft Word, Excel, and Power point helped in the schematic representation of the data including Tables and graphs. Manuscript was generated in the BioMed Central's TeX template.

List of Abbreviations

ACE2: angiotensin Converting enzyme CAR-T: chimeric antigen receptor T cell CAR-TV: chimeric antigen receptor T cell against virus, F-actin: filamentous actin, GTPase: guanosine triphosphate, INFγ: interferon γ.MERS-CoV: middle east respiratory syndrome corona virus. PTPase: protein tyrosine phosphatase, hydrolase enzyme. RdRp: RNA dependent RNA polymerase. ROS: reactive oxygen species. SARS-CoV: severe acute respiratory syndrome corona virus. ss RNA+: positive sense single stranded ribonucleic acid TNF α: tissue necrotic factor.

Availability of data and materials.

All data generated and analyzed during the study are included in this published article (and its supplementary information files).

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