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Review Article

Preventive Medicinal Plants and their Phytoconstituents against SARS-CoV-2/COVID-19

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ABSTRACT

Pandemic coronavirus disease-2019 (COVID-19) is an infectious disease caused by the newly discovered virus "Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2)". Considering the present scenario of COVID-19 outbreak and its impact on humankind, holistic remedies with respect to herbal medicine validated from ethnopharmacological rationale are now targeting approaches globally as a preventive care against SARS-CoV-2. **Aim:** This review is primarily focused on to deliver a concise fact of the coronaviridae family, pathophysiology, mechanism of action, ethnopharmacological validated Indian herbs for inhibiting the virus with possible targets. **Experimental procedure:** In this study, science mapping tool Bibliometrix R-package was used to perform bibliometric analysis and building data matrices for keywords co-occurrence investigation, country-wise scientific production; collaboration between the countries worldwide, co-word analysis on topic "keywords associated with SARS-CoV-2 and medicinal plants". **Results and Conclusion:** Our findings is to deliver a concise knowledge about the coronaviridae family, pathophysiology, possible targets for managing the SARS-CoV-2, in addition to potential medicinal plants and their phytoconstituents against COVID-19. Target-specific inflammatory pathways due to post infection of SARS e.g. NLRP3, p38-MAPK, Metallopeptidase Domain 17; endocytosis pathways e.g. Clathrin, HMGB1 pathways are primarily highlighted along with relevant interleukins and cytokines, which directly/indirectly triggering to immune system and play a significant role. Based on selective pathways and potential lead, the outcome of our elaborated study put forward selected Indian medicinal plants that hold a very high probability as preventive care in this global crisis.

Key words: COVID-19, SARS-CoV-2, Coronavirus, Phytoconstituents, Medicinal Plants, Biblioshiny.

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INTRODUCTION

Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2) is a newly discovered virus responsible for pandemic infectious disease "COVID-19". The causative virus is very minute in size (65-125 nm in diameter) but upraised health-related concerns globally.[1] It is believed that early spreading of this zoonotic virus (normally exists in animals but that can infect humans being also) is from Wuhan, China but the origin of the SARS-CoV-2 is still ambiguous.[2] The International Committee on Taxonomy of Viruses (ICTV) adapted a new taxonomic nomenclature in 2019[3] and SARS-CoV-2 positive-sense single-stranded RNA virus (+) ssRNA virus (Figure 1) belongs to the family Coronaviridae and classified under the subfamily Orthocoronavirinae.[4–6]

The virion schematic has a nucleocapsid (N) composed of genomic ssRNA (Gen) with approximately 30,000 nucleotides covered by the spike major structural proteins: spike glycoprotein (S), an integral membrane protein (M), small envelope protein (E) in the Lipid membrane (MEM).

In the current classification system subfamily Orthocoronavirinae is organized into four genus viz. alpha (α), beta (β), delta (δ) and gamma (γ)[7] corresponds to their respective groups 1, 2, 3 and 4. In all the four genus, total forty-five (45) unique species of coronaviruses (Table 1) are included based on their specific genetic sequences.[5] SARS-CoV-2 belongs to the second group betacoronavirus (2-b) with the non-segmented helical genetic material, size ranging 30kbs, bearing the largest genome among known RNA viruses. The genome of SARS-CoV-2 shares nucleotide similarity 89.10% when compared to SARS-CoV genes, whereas another study indicates that SARS-CoV-2 has a 96.2% structural similarity with a coronavirus CoV RaTG13 identified in bats.[6,8] Presently the virus exists into the two major variants; L type (~70%) and S type (~30 %). L type is more aggressive and infectious in

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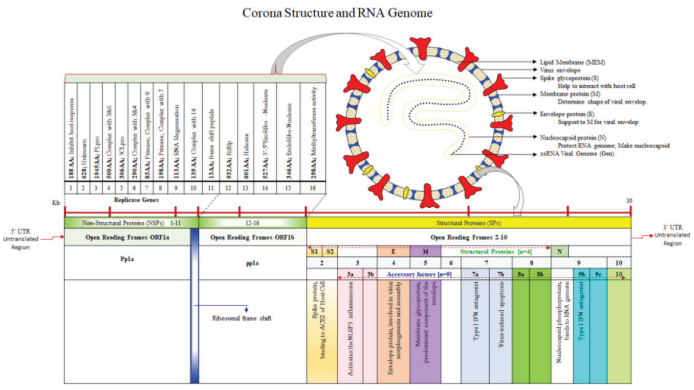

Figure 1: Diagrammatic representation of the virion of a coronavirus and associated genome.

comparison to S type.[9] Genus CoVs α and β mainly infect mammals whereas species from CoVs δ and γ genus mainly affect birds.[4] CoVs replicate inside the host cell and develop the conditions i.e. bronchitis, hepatitis, gastroenteritis and systemic diseases, that are answerable for fatality in many species of birds, rodents and animals including humans.[10] Severe Acute Respiratory Syndrome related coronavirus (SARSr-CoV) and Middle East Respiratory Syndrome related to Coronavirus (MERSr-CoV) are the two lethal viruses other than SARS-CoV-2, that out broke in 2003 and 2012, respectively[11] are also severe to health especially for respiratory illness.[10] They remain asymptomatic in early stages[4] and are accountable for significant morbidity and also for mortality[12] once it reaches to severe conditions e.g. severe pneumonia, renal insufficiency.[13,14] Besides these three species, Alphacoronavirus NL63 is also believed to cause bronchiolitis in children, whereas Alphacoronavirus 229E[4] and betacoronavirus HKU1 are associated with the Acute Respiratory Distress Syndrome (ARDS) in healthy adults.[15,16] Many other families of viruses like e.g. rhinoviruses, influenza parainfluenza and respiratory syncytial virus (RSV), enteroviruses and adenovirus commonly infects the upper respiratory tract[17,18] but in some patients can also challenge the lower respiratory tract.

When compared to other viruses in coronaviridae, SARS-CoV-2 is more severe and the rate of transmission is also much higher than SARS-CoV.[1] The history of COVID-19 was reported by WHO China officially declared cases of pneumonia of unknown etiology on 31th December, 2019.[19] In Thailand, the first COVID-19 case was recorded outside of China confirmed by WHO.[20] Shang *et al.* was among the first authors to report about the COVID-19 pandemic, with around 500 reported cases and 17 fatalities in January 2020. The numbers have increased at an exponential level from there, so confining the pandemic statistics at this moment seems impractical. As of, 5:10pm CEST, 23 September, 2021 globally number of 229 858 719 confirmed cases are reported and a death toll of 4,713,543 have been confirmed globally.[21]

To overcome this pandemic situation, existing antiviral drugs[2] are not sufficient. As of now, limited clinically/FDA approved drugs, or vaccines are available in the world market against COVID-19[22]. Researchers are using *in silico* computational docking tools to screen and find virtual ligand complexes from existing molecular databases to find out the solution from synthetic or natural product derived molecules.[22,23] At present some of the possible therapeutic options include antiviral, antimalarial, antibacterial, anthelmintic drugs, Interferon, amniotic fluid cells, monoclonal antibodies and mesenchymal stem cells (MSCs), and Convalescent Plasma Therapy for COVID-19 are widely explored.[2,24] Alternately, natural products and dietary supplements based on the traditional systems of medicine are also open worldwide for exploring possible answers to this intricate problem. Some authors have focused on traditional medicine, which have a broad spectrum of antiviral activities,[25,26] while others are focused on a parallel approach i.e. molecular docking on natural products and their derivate gives relevant solutions. Considering the above facts, a number of articles have recently been reviewed for the possible treatment, cure and/or against pandemic coronavirus;[27] however, further inputs are still required to bring the scientific outcomes and relevant information to the scientific community, which will be inevitable in the fight against the virus outbreak and enlighten the dark. To get a more lucid solution, it is necessary to understand the nature of the virus, viral diversity, pathophysiology and body consequences post-infection and controlled clinical studies etc. Keeping all the pertinent information in mind, this review is primarily focused on to deliver a concise fact of the coronaviridae family, pathophysiology, mechanism of action, possible targets for inhibiting the virus. To draw the findings from attentive knowledge, our effort was to deep dive about the existing Elsevier Scopus database knowledge on traditional medicine and to explore bibliometric analysis on phytomedicine(s)/phytoconstituent(s)/phytomolecule(s). These studies help for managing coronavirus induced symptomatic various respiratory disorders such as cough and cold. The present outcome aids to enlighten the current state of affairs and to explore the imminent direction of ethnopharmacological validated natural product research for identifying novel and fruitful approaches as a prevention remedies against COVID-19. This study also contributed the knowledge to the research community on the subject matter of futuristic approaches from traditional medicine against SARS-CoV-2 outbreak.

MATERIALS AND METHODS

Bibliographic tool for data generation between SARS-CoV-2 and phytoconstituents/phytomedicine

Globally, more than 150 countries participated in COVID-19 research in a period of 2020-21, and out of them top 10 countries accounted 82.93% of global research.[28] The Elsevier's Scopus abstract and citation online database https://www.scopus.com/home.uri was used to search the title "SARS-CoV-2" and a total number of 12,109 documents were obtained. To limit the objectives of the study, string was used as *"(Title (SARS-CoV-2 or Coronavirus or COVID-19) and Title-Abs-Key (phytomedicine or phytoconstituent or phytomolecule or traditional medicine or ethnomedicine or ethnopharmacology) and (Limit-to (Doctype, article) or Limit-to (Doctype, review) and (Limit-to (Language, English).* The comprehensive published literature of 960 documents were retrieved from the database, which explored the beneficial effect of an array on phytomedicine/phytoconstituents from medicinal plants as preventive remedies against SARS-CoV-2 infections. All attributes on retrieved data e.g., author(s), titles, years, source title, cited by, digital object identifier (DOI), affiliations, abstract, keywords and references of documents, published from 2020 to 2021 were selected and were exported in .csv format. The maps were created based on bibliometric data by utilizing VOSviewer (http://www.vosviewer.com) and biblioshiny app.

Assessments and consolidation of information

Based on the data, this review is categorised majorly in four sections to give consolidated information as follows:

- *Bibliometric analysis*
- *Morphological characteristics, structure of the SARS-CoV-2 and replication process*
- *Therapeutic targets for SARS-CoV treatment*
- *Medicinal plants: Futuristic approach as preventive care*

Table 1: Classification of coronavirus species based on the International Committee on Taxonomy of Viruses (ICTV).[3]
Family: Coronaviridae; Subfamily: Orthocoronavirinae
Genome: Linear, Single Segmented ssRNA; Genome replication by Enzyme: Viral RdRp at Intracellular site-Cytoplasm.

Genus	S. N.	Species	Reservoir hosts and Target site in Human
Alpha-coronavirus	1	Bat coronavirus CDPHE15 (BtCoV-CDPHE15)	Bats
	2	Bat coronavirus HKU10 (BtCoV-HKU10)	Bats
	3	Rhinolophus ferrumequinum alphacoronavirus HuB-2013 (BtRfCoV-HuB13)	Bats
	4	Human coronavirus 229E (HCV-2293)	Human (Mild respiratory disease)
	5	Lucheng Rn rat coronavirus (LRNV)	Rat
	6	Mink coronavirus 1 (MCoV)	Mink
	7	Miniopterus bat coronavirus 1 (BtMiCoV-1)	Bats
	8	Miniopterus bat coronavirus HKU8 (BtMiCoV-HKU8)	Bats
	9	Myotis ricketti alphacoronavirus Sax-2011 (BtMy-Sax11)	Bats
	10	Nyctalus velutinus alphacoronavirus SC-2013 (BtNy-Sc13)	Bats
	11	Pipistrellus kuhlii coronavirus 3398 (BtCoV/P.kuhlii/Italy/3398)	Bats
	12	Porcine epidemic diarrhea virus (PEDV)	Pig
	13	Scotophilus bat coronavirus 512 (BtScCoV-512)	Bats
	14	Rhinolophus bat coronavirus HKU2 (BtRhCoV-HKU2)	Bats
	15	Human coronavirus NL63 (CoV-NL63)	Human (Mild respiratory disease, Bronchiolitis and pneumonia)
	16	NL63-related bat coronavirus strain BtKYNL63-9b (BtKYNL63)	Bats
	17	Sorex araneus coronavirus T14 (SoArCo-T14)	Shrew
	18	Suncus murinus coronavirus X74 (SmCo-X74)	Shrews
	19	Alphacoronavirus 1 (Transmissible gastroenteritis virus) (TGEV)	Pig
Beta-coronavirus	1	Betacoronavirus 1 (Human coronavirus OC43) (HCoV-OC43)	Human (Fever, cough upper respiratory tract infections and Fatal Encephalitis)
	2	China Rattus coronavirus HKU24 (RtCoV-HKU24)	Rat
	3	Human coronavirus HKU1 (HCoV-HKU1)	Human (Respiratory tract infections; pneumonia and Flu-like symptoms)
	4	Murine coronavirus (MHV)	Mouse
	5	Myodes coronavirus 2JL14 (MrufCoV 2JL14)	Rodent Myodes
	6	Bat Hp-betacoronavirus Zhejiang2013 (BtHpCoV-ZJ13)	Bats
	7	Hedgehog coronavirus 1 (EriCoV-1)	Hedgehog
	8	Middle East respiratory syndrome-related coronavirus (MERSr-CoV)	Human (Shortness of breath, pneumonia, gastrointestinal symptoms and diarrhea)
	9	Pipistrellus bat coronavirus HKU5 (BtPiCoV-HKU5)	Bats
	10	Tylonycteris bat coronavirus HKU4 (BtTyCoV-HKU4)	Bats
	11	Eidolon bat coronavirus C704 (Ei-BatCoV C704)	Bats
	12	Rousettus bat coronavirus GCCDC1 (BtEoCoV-GCCDC1)	Bats
	13	Rousettus bat coronavirus HKU9 (BtRoCoV-HKU9)	Bats
	14	Severe acute respiratory syndrome-related coronavirus (SARSr-CoV)	Human (Severe respiratory distress, Lower respiratory tract illness, fever, chills, cough shortness of breath)
Delta-coronavirus	1	Wigeon coronavirus HKU20 (WiCoV-HKU20)	Bird
	2	Bulbul coronavirus HKU11 (BuCoV-HKU11)	Bird
	3	Common moorhen coronavirus HKU21 (CMCoV-HKU21)	Bird
	4	Coronavirus HKU15 (PoCoV-HKU15)	Pig
	5	Munia coronavirus HKU13 (MuCoV-HKU13)	Bird
	6	White-eye coronavirus HKU16 (WECoV-HKU13)	Bird
	7	Night heron coronavirus HKU19 (NHCoV-HKU19)	Bird
Gamma-coronavirus	1	Goose coronavirus CB17 (CB17)	Bird
	2	Beluga whale coronavirus SW1 (BWCoV-SW1)	Whale
	3	Avian coronavirus (IBV)	Bird
	4	Avian coronavirus 9203	Bird
	5	Duck coronavirus 2714 (DK2714)	Duck

RESULTS

Bibliometric analysis

The holistic trends of global publications were retrieved from Elsevier Scopus database on pandemic SARS-CoV-2 with respect to medicinal plants and their phytoconstituents and were represented in Table 2.

Keywords co-occurrence investigation

The keywords used profoundly by the research community in the various disciplines were selected as a study tool for the in-depth analysis of subject area on SARS-CoV-2. Biblioshiny app executed two key disciplines "*Keywords Plus*" and "*Author's Keywords*" containing 7005 and 2327 numbers respectively. Top 200 keywords that had maximum strength were selected from the list of each sequential key discipline and were presented in the form of WordCloud (Figure 2). In the "*Keywords Plus*", the maximum occurrences were observed with the keywords "*coronavirus*" (630) followed by "*molecular docking*" (207) then "*traditional chinese medicine*" (F-92) (Figure 2A); whereas in case of "*Author's Keywords*", the maximum occurrences were observed with the keywords "*sars-cov-2*" (760) followed by "*coronavirus*" (419) then "*molecular docking*" (128) (Figure 2B).

Further, to investigate the co-occurrence network, top 100 keywords were selected through VOSviewer tool[29] and were represented in nine clusters (Figure 3).

Table 2: Holistic representation of global publications research on SARS-CoV-2 retrieved through web interface biblioshiny app.

Description	Counts and rates
Main Information about Data	
Timespan (Four Decades)	2020:2021
Sources	433
Articles (Original research Papers/Reviews)	960
Average year from publication	0.83
Average citation per article	7.005
Average citations per year per article	3.537
Total References in publications	71409
Articles	
Article	565
Review	395
Article Contents	
Keywords Plus; Identification (ID)	7005
Author's Keywords; Description (DE)	2327
Authors	
Authors	4625
Author Appearances	5851
Authors of single-authored articles	67
Authors of multi-authored articles	4558
Authors Collaboration	
Individual article	68
Article per author	0.208
Authors per article	4.82
Co-Authors per article	6.09
Collaboration Index (CI)	5.11

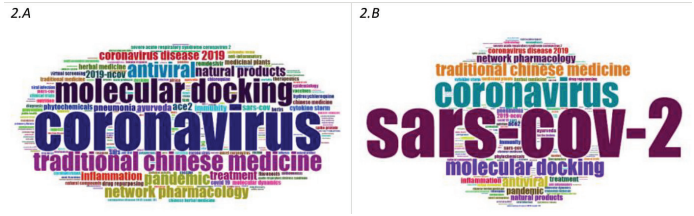

Figure 2: WordCloud of top 200 keywords.
2A: Graphical Parameters of "Keyword Plus"; 2B: Graphical Parameters of "Author's Keywords" by biblioshiny app.

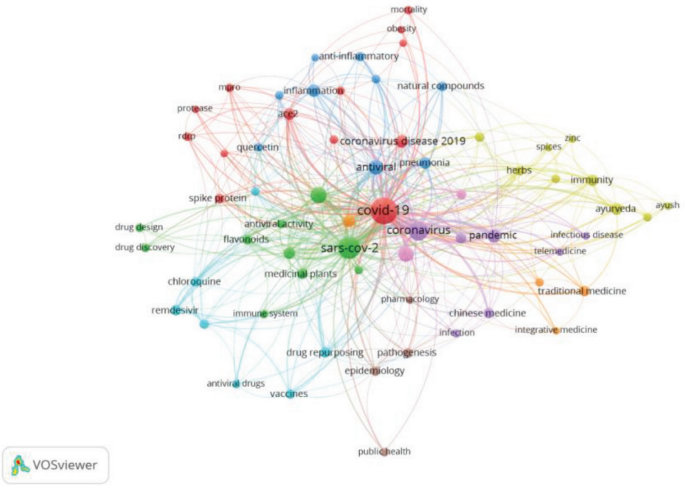

Figure 3: Network representing the relationship among the top 100 keywords.

Analyses based on the Elsevier's Scopus citation database from 2020 to 2021. An artwork generated with VOSviewer tool. Cluster-1 red color; cluster-2 green color; cluster-3 blue color; cluster-4 bellow color; cluster-5 purple color; cluster-6 aqua color; cluster-7 orange color; cluster-8 brown color; cluster-9 pink color.

Red coloured cluster-1 was found to be a total 20 keywords; with dominated keyword "*covid-19*" (Occurrences 590; Links 64; TLS 861). Green coloured cluster-2 showed a total 15 keywords; with dominated keyword "*sars-cov-2*" (Occurrences 278; Links 60; TLS 548). Blue coloured cluster-3 represented a total 13 keywords; with dominated keyword "*antiviral*" (Occurrences 48; Links 33; TLS 116). Yellow coloured cluster-4 explored 13 keywords; with dominated keyword "*ayurveda*" (Occurrences 22; Links 14; TLS 44). Purple coloured cluster-5 described a total 10 keywords; with dominated keyword "*coronavirus*" (Occurrences 141; Links 55; TLS 321). Aqua coloured cluster-6 was found to be 10 keywords; with dominated keyword "*remdesivir*" (Occurrences 15; Links 10; TLS 37). Orange coloured cluster-7 showed a total 08 keywords; with dominated keyword "*natural products*" (Occurrences 32; Links 16; TLS 59). Brown coloured cluster-8 explored total 08 keywords; with dominated keyword "*epidemiology*" (Occurrences 11; Links 12; TLS 21) whereas, pink coloured cluster 9 shown only 3 keywords; with dominated keyword "*traditional chinese medicine*" (Occurrences 59; Links 22; TLS 95).

Scientific collaboration (Worldwide)

The research scholars, academicians, scientists, and subject experts work together to synergize their research knowledge and quality findings, visibility of their publications, and improve the professional prestige together with socio-economic benefits under a common platform. The

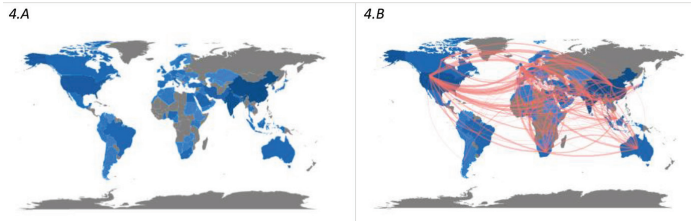

Figure 4: Country maps.
4.A: Country scientific production; 4.B: Country collaboration map.

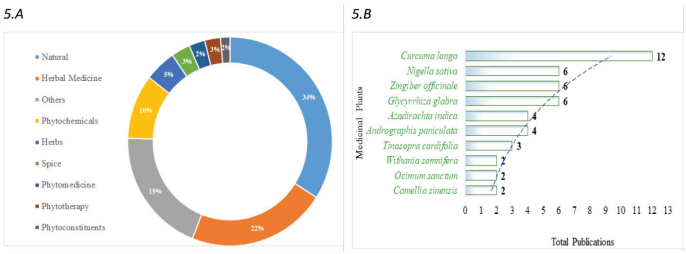

Figure 5: Pie chart for frequently used natural product derived keywords.
5A: Frequently used words associated natural product based drug discovery against SARS-CoV-2. 5B: Publications of Indian Medicinal plants on title.

cross country-wise scientific production was generated through biblioshiny app, which provides different shades for distinguishing the patterns of publications in Figure 4A.

Dark blue shade signifies high productivity whereas blue signifies the different productivity rate; grey shade no contribution. The top 21 countries were actively engaged in publishing research on "*SARS-CoV-2*" associated with medicinal plant or natural phytoconstituents. China was the leading country with 950 frequencies followed by India and the USA with their numbers 619 and 233 respectively.

Country wise co-authorship pattern is presented in Figure 4B, which indicates the collaboration between the countries to increase the amount of publications as compared to single approach.

The higher frequency of collaboration with the other countries was observed in the United States (181 frequency) followed by India and the United Kingdom (136 and 133 frequency) and then Italy and China (67 and 44 frequency).

Article associated with SARS-CoV-2 and Ethnomedicinal plants

Retrieved data from "*Authors keyword*", indicated that the word "natural" and "herbal medicine" together contribute around 56%, whereas in individually they support 34% and 22% respectively. Phytochemical, herbs, spices, phytomedicine, phytotherapy and phytoconstituents are the other words frequently used by authors while publishing the articles associated with SARS-CoV-2 and finding out the preventive medicine from traditional/natural product derivatives shown in Figure 5A.

Further, medicinal plants that frequently used in 960 articles titles including their common name were scanned and ten medicinal plants that are traditionally used in Indian System of medicine were selected for further investigation as shown in Figure 5B, i.e. *Andrographis paniculata, Azadirachta indica, Camellia sinensis, Curcuma longa, Glycyrrhiza glabra, Nigella sativa, Ocimum sanctum, Tinospora cordifolia, Withania somnifera* and *Zingiber officinale.* Individual roles and their contribution are described in this review separately; however, before getting the answer from Indian medicinal plants and their derivatives, it is necessary to understand morphological characteristics of SARS-CoV-2 and its pathophysiology that is summarized here.

Morphological characteristics and structure of SARS-CoV-2

The morphology and genetics of SARS-CoV-2 has significant differences from MERS-CoV and SARS-CoV. All the betacoronaviruses genome contains 5'-untranslated region (UTR) and around ten open reading frames (ORFs). Out of all 14 ORFs, ORF1a encodes 1-11 Non-structural proteins (NSPs), whereas ORF1b encodes 12 to 16 NSPs. ORF1a and ORF1b translate polypeptides pp1a and pp1ab via Replicase-transcriptase activity that is after cleaved by virus-encoded proteinases, e.g. papain-like protease (PLpro) and chymotrypsin-like proteins (CLpro) like 16 proteins. One of enzymatic protein RNA-dependent RNA polymerase (RdRp), is involved to form Replication Transcription Complex (RTC), which synthesizes (-)ssRNA. This template translates genetic information (+) ssRNA and necessary structural proteins,[30] which comprise 4 operational proteins specifically spike (S) protein (180-220 kDa), envelope (E) protein (9-12 kDa), membrane (M) protein (23-35kDa), and distinct protein nucleocapsid (N) (inside the structural envelope 50-60kDa) with several other unknown non-structural genes and at the end 3'UTR.[31] The S, M and E proteins help to form a viral coat; control viral assembly and their release from host cells, whereas N protein takes part to pack the RNA genome and transfer genetic information to other virions.[23] One very specific protein hemagglutinin esterase (HE) is present in some of the betacoronaviruses species, however in SARS-CoV, it was unidentified.[32] Every structural protein has its own specific role in the replication process. Trimeric spike (highly glycosylated) protein[33] composed of two subunits (S1 with 394 glutamine residues and S2)[1] helps to attach and promote fusion of virion-cell membrane, maturate and exit from the host cells.[34] Morphologically, spikes have club-shaped surface projections on the top that gives crown or coronet (Latin corona) like appearance to this virion; therefore the name coronavirus coined for it.[8]

Replication of SARS-CoV-2 inside the host cells

Viruses comply with several stages to multiply their numbers inside the host cell including attachment, penetration, uncoating, biosynthesis, maturation, and release as follows:

1. Association of viral S protein to host receptors - endocytosis.
2. The endosomal membrane infused with virus membrane (probably mediated by S2),
3. Release of genetic sequence ssRNA(+) into the host cytoplasm.
4. Activation of proteolytic enzymes and replicase polyprotein.
5. Replication and development of new ssRNA(+) genomes.
6. Synthesis of structural proteins.
7. Binding of structural and nucleocapsid proteins at endoplasmic reticulum (ER)
8. ER-Golgi intermediate compartments
9. Release of newly formed virions - exocytosis.
10. Pathophysiological symptom

The life sequence of CoV in the host cell is depicted in Figure 6 and is described here to understand as follows:

Host cell interactions

Several studies have mentioned that bats carry major alpha and beta-CoV species that may spill over to the human populations and can result in viral outbreaks.[4] Once CoVs are exposed to human reservoir host cell mostly through respiratory secretions, virus's spike proteins attach to the host cell via surface receptors known as angiotensin-converting enzyme-2 (ACE2),[6] which are highly expressed in the human lungs and if locally increased, it triggers to pulmonary edema.[35] Spike proteins of SARS-CoV and MERS-CoV interact to host cells through two different surface receptors via ACE2 and dipeptidyl peptidase 4 (DPP4) respectively.[36] ACE20 is the key modulator of the Renin-Angiotensin

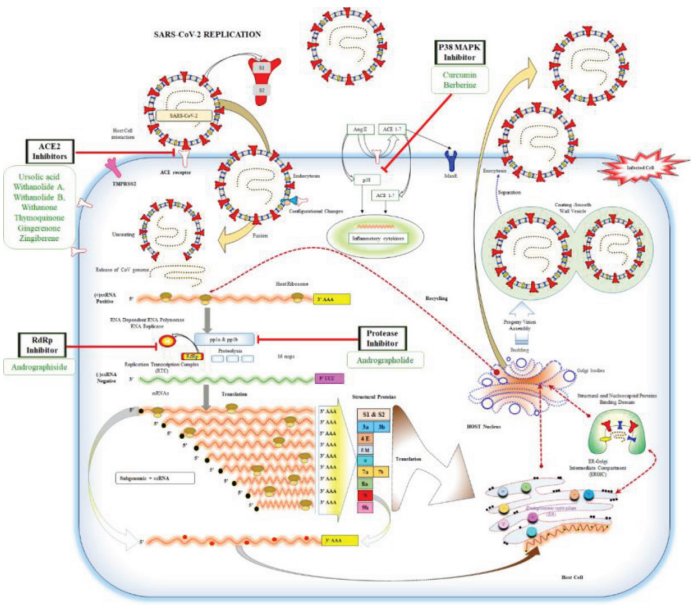

Figure 6: CoV life cycle in the host cells.

Attachment of the viral S protein to the host receptors - endocytosis, A fusion of virus membrane with the endosomal membrane (mediated by S2), Release of genetic sequence ssRNA(+) into the host cytoplasm, Activation of proteolytic enzymes and replicase polyprotein, Replication and development of new ssRNA(+) genomes, Synthesis of structural proteins, Binding of structural and nucleocapsid proteins at endoplasmic reticulum (ER), Budding at membranes of the ER-Golgi intermediate compartments, Release of newly formed virions exocytosis; Inflammatory pathways-p38-MAPK, TLR4 Pathways.

System and plays a major role in modulating hypertension, diabetes, and cardiovascular disease.[35]

Presently scientific reports support that ACE2 helps to bind coronavirus to the host cells via receptor recognition. It also helps to set off chemical changes that effectively infuse with the host membranes, resulting in viruses along with its genomic structure that can easily permeate into the cells. Spike protein S plays a very important role in the interaction phase. The viral surface is composed of the N-terminal domain named as S1 proteins, which guide how to associate with the host receptors, while another C-terminal is composed of S2 proteins, which helps to change the configuration and incorporate the genome into the host cells. Structural proteins plays crucial role in viral pathogenicity as it aids to viral assembly. SARS-CoV and SARS-CoV-2 gene sequences were compared and were analyzed the transmembrane helical segments particularly ORF1a. It was reported that, amino acids serine and proline in SARS-CoV-2 are replaced with glycine and isoleucine in SARS-CoV at positions 723 and 1010 respectively.[37] The above changes with respect to viral mutations are the key factor for the severe transmission of SARS-CoV-2 that is associated with the genetic recombination of S protein in receptor binding domain (RBD). These are some of the grey areas, where further investigation is still required to explain mechanisms of viral pathology.

Fusion of genome into the host cell

Viral S protein mainly contains three clusters, named as ectodomain, a single-pass transmembrane anchor and a short intracellular tail. Large ectodomain RBD-S1 recognizes the human ACE2 receptor, which has lysine 31 residues to bind with virion particles. ACE2 is a G protein-coupled receptor existing in two variants namely Ang II type 1 receptor (AT1-R), commonly associated with cardiovascular/renal-related functions in adults and Ang II type 2 receptor (AT2-R), passively associated with the same activities.[38] After binding successfully, a series of enzymatic modifications started due to the protein Transmembrane Serine Protease 2 (TMPRSS2), that is associated with the ACE2 receptor as well.[2] Due to these conformational modifications, viral membranes fuse with the plasma membrane and allow viral genomes to enter into the host cells. Replication processes start when the virus genome and its related nucleocapsid are released into the host cytoplasm.[39] This particular step is highly pH-dependent and most lysosomal cysteine proteases modify the virion particles to fuse their genetic materials into the cells. This could be a target-oriented step to control the entry of the virus inside the host.

Replication (transcription and translation)

The genome that contains two genes ORF1a and ORF1b produce two replicase polyproteins (pps) namely pp1a and pp1b.[39] These pps help to control the host ribosomes for their own translation process. Both pp1a and pp1b contribute to the formation of the replication transcription complex (RTC). Protease cleavages the proteins and produces 16 predicted non-structural proteins (NSPs1-16). All NSPs have their own specific functions, required for replication and transcriptions, however, some of them have not been described yet. Structural proteins synthesized by the translation process and have a functional role in virus pathogenicity. The RNA polymerase (RdRp), an enzyme, which replicates the viral genome, whereas CLpro and PLpro proteases are involved in the processing of viral surface proteins.

Exit from the host cell

To make the structure envelope of the virion, above-mentioned proteins enter into the endoplasmic reticulum (ER)-Golgi intermediate compartment (ERGIC) complexes. In parallel, the ribonucleoprotein (RNP) complex is also formed due to binding of the replicated genome to the N protein. The ERGIC body combines all the necessary and required proteins and develops a pre-developed virion particle, which enters into the Golgi complex to develop smooth wall vesicles. Both the complete virion particles with the plasma membrane leach into the extracellular matrix. Apart from exocytosis, matured virion also starts a number of replications inside the host cell and generates multiple copies of infectious particles.

Possible therapeutic targets against SARS-CoV

SARS-CoV and MERS-CoV, which are responsible for unexpected human disease in the 21st century, originated from the bats and studies suggested that the bats are resistant to corona virus protein-mediated modulation of antiviral responses.[40] Keeping in mind the exceptional life span and CoV resistance power of bat species, it is much required to focus on site-specific targets for the preventive measure of SARS-CoV-2. Since "Prevention is better than cure," therefore our target was to emphasize on finding the remedies, which closely interacts with the pathophysiology of SARS-CoV-2 infection. After careful assessment, we have focused our research on two separate approaches; the first approach was associated with the virus structure, morphology and how it interacts to the host cells, whereas another approach was dedicated mainly to observe the consequences and pathophysiological symptoms on the human body, post-viral infection.

Virus targeted approaches

Proteolysis targets

Based on existing knowledge of structural configuration and pathophysiology of SARS-CoV-2, it is known that structural proteins S1 and S2 domains are the potential targets for the selection of preventive remedies and also for designing the new drugs.[41] The genes that encoded above

proteins could be the possible targets for preventive care.[32] Wu *et al*. (2020) performed target-based virtual ligand screening for different proteins namely 3-chymotrypsin-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp), and papain-like protease (PLpro).[23] The 3C-like protease (3CLpro) is an important target for the drug development against SARS-coronavirus as it coordinates the processing of the proteolytic mechanism of replicase polypeptides 1a and 1ab to generate the liable functional proteins.[42] These inhibitors could be the benchmark objective for comprehensive research, symptomatic management, and supportive therapies.

Respiratory tract infections (RTIs)-antiviral targets

Upper respiratory tract infection (URTI) includes nasopharyngitis (common cold), tonsillitis, Pharyngitis, laryngitis, and sinus infection whereas lower respiratory tract infection (LRTI)[43,44] comprises pneumonia, acute bronchitis and chronic obstructive pulmonary disease/chronic bronchitis (AECB).[45,46] Presently more than five families of infectious viruses are responsible for the URTIs and LRTIs which are classified[3] based on genus and presented in Table 3. Researchers are now focusing on understanding the viral genome, which is very close to the corona virus family and are trying to find the cure.

Post-viral infection targeted approaches

Anti-inflammatory targets

SARS-CoV and MERS-COV infection enhances the chemokine's and pro-inflammatory cytokines inside the cells that cause damage to lung tissues. Studies demonstrated that humans and mice have inflammation triggering protein "NLR family pyrin domain containing 3 (NLRP3)" that reacts in the presence of stress and infection conditions.[56] Surprisingly, when compared to humans and mice this protein is dampened in bats population, even at the presence of high loads of viral strain.[40] Studies addressed that the bats have a longer lifespan and have a greater capability to servive along with a number of virus reservoirs[57] without any infection.[58] Pathogen associated molecular patterns (PAMPs) binds to TLR receptor and modulates the Mitogen-activated protein kinases (MAPKs), p38, transcription factor NF-kB, and extracellular signal-regulated protein kinase (ERK1) pathways[59] through the MyD88 modulator to release cytokines namely Pro-IFN-1β

Table 3: Human respiratory viruses and treatment plants.[3]

S. No.	Family	Genus	Virus Species	Type Species	Genome Composition	Medicinal Plants	Ref.
	Adenoviridae	*Mastadenovirus*	*Human mastadenovirus A-G HAdVs*	*Human mastadenovirus C*	dsDNA	*Cymbopogon citratus (lemongrass) and Cymbopogon nardus (citronella grass)*	[47]
	Herpesviridae	*Cytomegalovirus*	*Human betaherpesvirus 5*	*Human betaherpesvirus 5*	dsDNA	*Ginkgo biloba*	[48]
	Orthomyxoviridae	*Alphainfluenzavirus*	*Influenza A A/PR/8/34 (H1N1)*	*Influenza A (IAV)*	ssRNA(-)	*Polygonum chinense*	[49]
		Betainfluenzavirus	*Influenza B B/Lee/40*	*Influenza B (IBV)*	ssRNA(-)	*Sambucus nigra*	[50]
		Gammainfluenzavirus	*Influenza C C/Ann Arbor/1/50*	*Influenza C (ICV)*	ssRNA(-)	-	-
		Deltainfluenzavirus	*Influenza D*	*Influenza D (IDV)*	ssRNA(-)	-	-
	Paramyxoviridae	*Morbillivirus*	*Measles morbillivirus*	*Measles morbillivirus*	ssRNA(-)	*Acacia arabica*	[51]
		Respirovirus	*Human respirovirus 1 or Human parainfluenza virus 1 (HPIV-1)*	Murine respirovirus	ssRNA(-)	-	-
			Human respirovirus 3 or Human parainfluenza virus 3 (HPIV-3)		ssRNA(-)	*Viscum album*	[52,53]
	Picornaviridae	*Enterovirus*	*Rhinovirus A*	Enterovirus C or Coxsackievirus A21	ssRNA(+)	*Zanthoxylum piperitum and Zanthoxylum schinifolium*	[54]
			Rhinovirus B		ssRNA(+)		
			Rhinovirus C		ssRNA(+)		
			Enterovirus A-L (Total -12)		ssRNA(+)		
	Pneumoviridae	Metapneumovirus	*Human metapneumovirus (hMPV)*	*Human orthopneumovirus*	ssRNA(-)	*Limnocitrus littoralis*	[55]
		Orthopneumovirus	*Human orthopneumovirus or Human respiratory syncytial virus (hRSV)*		ssRNA(-)	*Rosmarinus officinalis*	[17]
	Corona-viridae	Classified separately in Table 1					

and Pro-IFN-18.[60] Further ATP dependent NLRP3 inflammasome triggers these two pro signaling proteins into the active forms IFN-1β and IFN-18 with the help of Apoptosis-associated speck-like protein containing a CARD (ASC) and controlled caspase-1 proteins,[61] which further stimulates the NLRP3 inflammasomes and induce interleukins e.g. IL-1β through MyD88 pathway (Figure 7). In the respiratory tract, T cells and B cells secrete inflammatory cytokines[62] that regulate the NLRP pathway and further various inflammatory mediators and erythrocytes are passes into the lungs alveoli, leads to symptomatic conditions on dyspnea and respiratory failure.[62] Mechanism and regulation of NLRP3 activation remains ambiguous,[60] however NLRP3 could be the target for the preventive care against SARS-CoV-2 as it is speculated that NLRP3 proteins in bats are associated to control viral-induced and age-related inflammations.[58]

One of the studies on the p38 MAPK inhibition mechanism suggested that the p38 MAPK pathway could be the target for developing an encouraging therapeutic lead against COVID-19.[63] It was noticed that, Angiotensin-converting enzyme 2 (ACE2), which is primarily mediate in the lungs and heart is directly associated with the p38 MAPK activated pro-inflammatory cytokines release, such as IL-6, TNF-α and IL-1β by disrupting the conversion of Ang II into Ang 1-7 during the virus entry. Once this conversion is interrupted Ang II level is increased and Ang II dependent p38 MAPK pathway is activated, resulting in a high level of pro-inflammatory cytokines. Another side, cytokines level, which are counterbalanced by Ang 1-7 mediators through Mas binding receptor, is also down regulated. Due to this combined approach of Ang II and Ang 1-7, high loads of inflammatory response are produced in the host cell. It is noticed that p38 MAPK pathway also activates ADAM Metallopeptidase Domain 17 (ADAM17) protein, which is directly associated with the generation of TNF-α.[64] It has proved that chloroquine (CQ) affects the activation of the p38 MAPK ERK pathway, which is associated with replication of HCoV-229E in human fetal lung cell line.[65]

Outcome of the above facts indicates that inhibition of p38 and ADAM17 pathways could be the potential targets for preventing this virus and therefore now getting attention from the researchers.

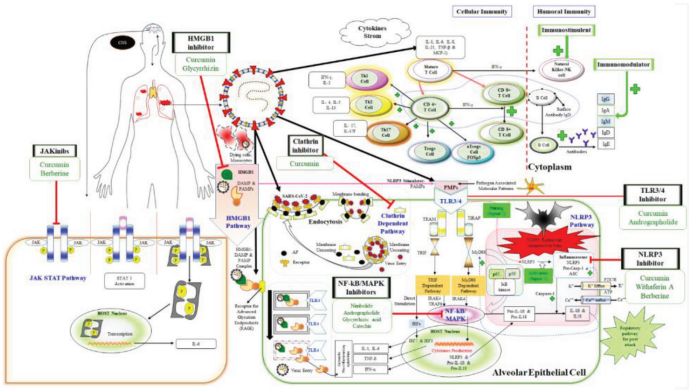

Figure 7: Possible sites for preventive consequences post-infection.

Virus infected Alveolar Epithelial Cell responding through various approaches

Immunity: Adopted cellular immunity via CD4 and CD8+ T Cells; humoral immunity via Immunoglobulins IgG and IgM

Inflammatory pathways: NLRP3, Metallopeptidase Domain 17; NF-kB/MAPK; JAK/STAT Pathway

Endocytosis pathways: Clathrin Pathways; DAMP and PAMP dependent HMGB1 pathways.

Immunomodulatory targets-immune boosters against week immunity

Human system is built up with multi-level immune architectures that maintain a steady-state of homeostasis and defense from pathogens/foreign particles.[66] Once pathogens successfully enter into the body, our immune system addresses them and eliminates pathogens or infectious particles via specific immune pathways i.e. acquired or adaptive in nature.[67] This system is entangled with inflammatory pathways. Study specified that the SARS-CoV-2 mainly infect alveolar epithelial type 2 cells (AEC2) via surface receptors ACE2. The existing studies so far available seem to indicate that due to the viral infection, host cells produce excessive pro-inflammatory cytokines 'cytokine storm'[9] leading to extensive tissue damage and acute respiratory distress syndrome by various pathways (Figure 7) including the JAK-STAT pathway.[38] SARS-CoV-2 activates the innate immune system, which increases the count of macrophages, neutrophils and leukocytes in the extracellular matrix. During SARS-CoV-2 infection, flushing of the high level of pro-inflammatory cytokines and antigen presenting cells APC (mainly dendritic cells), synergistically works on activating the adaptive immune system. Viral-mediated response interfere with the existing level of T lymphocytes including $CD4^+$ T and $CD8^+$ T lymphocytes, regulatory T (T reg) cells, antigen-specific memory T cells, natural killer cells (NK cells), B-lymphocyte (B cells), that are necessary for regulating the viral replication, bound to virus for the spreading, and also for cleaning the infected cells.[9] SARS-CoV infection increases lymphocytopenia in the peripheral blood system via lymphocyte sequestration and thereby levels of T lymphocytes are decreased.[68] Affected $CD4^+$ T lymphocytes rapidly activate pathogenic Th1 cells, which further activates monocytes with high expression of IL-6. The highly expressed IL6 acts as a key player and further induces cellular proliferation and differentiation of B-lymphocytes to control thermoregulation.[69] This could be one of the targets to control body temperature and central nervous system activities during SARS-CoV-2 infection. Additionally, Th1 cells are regulated through JAK-STAT pathway that predominantly found in the nervous system, cardiovascular system and in cellular level at renal proximal tubular and hepatocytes cells. It plays a major role in the immune system triggering through the Ang II receptor. Presently JAK family consists of four subdivisions s e. g. JAK1, JAK2, JAK3, and Tyk2 whereas STAT family is comprises with total numbers seven i.e. STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6.[38] Out of all JAK families, JAK3 is connected with hematopoietic activity and regulates lymphocyte function. Pro-inflammatory cytokines, especially IL-6 and IL-10 that are remarkably high in COVID-19 are unregulated via JAK1 and JAK2 signaling pathways respectively. Likewise, JAK1 is also stimulated by the blood growth factor "granulocyte-colony stimulating factor (G-CSF)". Other interferon factors like IFN- β and IFN-γ modulate the Tyk2 and JAK2 pathways and regulate the SARS-CoV related activities. Interfering and/or inhibition of the above JAK-STAT sub-families and type I/II cytokine receptors through JAK inhibitors (JAKinibs) could be the alternative tool for preventing and controlling the 'cytokine storm'.[38] Furthermore, lungs cells are having regulators like AP2-associated protein kinase-1 (AAK1; Adaptor-associated protein kinase 1) and cyclin G-associated kinase (GAK), which regulates clathrin-mediated endocytosis (CME) and helps to metabolites, hormones, proteins and in some cases infectious cells including viruses particle for the entering inside the cell.[70] Again this could be a unique target for drug discovery for preventing SARS-CoV-2 infections as the drugs as Baricitinib has already been reported to interrupts clathrin-dependent endocytosis via disrupting AAK1 signaling pathway and reduces the inflammation in SARS-CoV-2 patients.[71] One more extracellular protein High-Mobility Group Box 1 (HMGB1) is also interesting to the researcher as it is one of the novel therapeutic targets that activates the innate immune system

and treats the severe pulmonary inflammation including COVID-19.[72] It is reported that a number of herbal therapies inhibits HMGB1 secretion effectively.[73] In addition to that, the NF-kB signaling pathway is involved directly or indirectly to produce various pro-inflammatory cytokines due to activation of T helper cells as well. At a site of infection, cytokines IL-17 remediate monocytes and neutrophils and triggers the down streaming of cytokine and chemokine cascades i.e. IL-1, IL-6, IL-8, IL-21, TNF-β (lymphotoxin-alpha) and member of the C-C chemokine family known as Monocyte Chemoattractant Protein-1 (MCP-1).[7]

T cells are essential for adaptive immunity against viral infections. Anti-viral $CD4^+$ helper T cells (Th) helps to produce virus-specific antibodies by B cells, while $CD8^+$ cytotoxic T cells (Tc) can kill virus-infected host cells. Study on severe and critical COVID-19 patients demonstrated that, infected patient had remarkably increased pro-inflammatory cytokine levels i.e. IL-2, IL-4, IL-6, IL-10, and TNF-α. Out of all, IL-6 and IL-10 both were exceptionally high and played a key role in the cytokine storm whereas total lymphocytes i.e. total T cell, $CD4^+$ T, $CD8^+$ T, Beta and NK cells levels, which secrete IFN-γ and TNF-α were found very low. These observations conclude that targeting cytokines could be an effective and preventive therapeutic strategy against COVID-19 outbreak. An elevated level of IFN-α, and IFN-γ signified that high levels of pro-inflammatory cytokines contribute to more infectious and severe diseases.[74] IL-6 and IL-10 were also found high in number in other reports too[62,63,75,76] and therefore the above facts concluded that these are the noteworthy interleukins and could be the prime targets to inhibit and reduce the infection associated with SARS-CoV-2 patients.

Humoral immune response to COVID-19 has not been yet explored much and still remains a mystery.[77] Remedies that can support the generation of IgG and/or IgM antibodies could be the target for the interest. One study on 285 patients of SARS-CoV-2 were found positive for virus-specific immunoglobulins IgG and/or IgM within nineteen days after first symptom appears.[78,79] Hou *et al*. also found that the same antibodies (IgG and IgM) were high in 338 hospitalised patients, however the increased levels of both the immunoglobulins were not maintained with respect to time. In most of the patients, IgM level was increased after first week of SARS-CoV-2 infection, reached the peak in two weeks and then reduced to original levels whereas IgG level was detectable only after 1 week and this level was maintained for a long period.[77]

Therefore, there is an open space to bring out strategies that are closely associated with the production of immunoglobulins as preventive care medication. Bats are having strong tolerance against virus allied diseases and studies demonstrated that Interferon-α may protect bats from virus-associated infections.[80]

With the above-mentioned facts, Immunomodulators[81] are one of the important targets for the designing of preventive medicine against SARS-CoV-2, which are classified based on clinical symptoms as follows:

***Immunoadjuvants*:** True modulators, which boost efficacy of the immune system (exploit and support to very specific type cells), e.g. helper T1 cells (Th1) and helper T2 cells (Th2), Immunoglobulins.

***Immunostimulants*:** Immunotherapeutic agents, which enhances the basic level of the immune response against infections (characteristically non-specific and act on innate and adaptive immune responses) e.g. immunopotentiators.

Immunosuppressant's: Immunocompromised drugs, which concomitantly administered to support organ transplants.[67,82]

Present scenario: Insilco approaches and existing treatments

At present, a number of modern systems of medicine e.g. antiviral and antimalarial drugs and other potential therapeutic options are available to control this serious problem.[2] Vellingiri *et al*. (2020) described in detail the commercially available antiviral drugs and ongoing clinical trials for the management of COVID-19.[83] They classified medicines based on the mechanism of action e.g. Ribavirin interfere and bind the target site of RdRp; Sofosbuvir works via inhibiting nucleotide polymerase enzyme; whereas Lopinavir/Ritonavir inhibits protease enzyme; Remidesivir (anti-viral peptide) terminates the nascent viral RNA.[84] Chloroquine/hydroxychloroquine that falls under the drug category antimalarial, increases endosomal pH that is prerequisite for viral infusion with host cells. Anti-HIV drugs, monoclonal antibodies like other treatments are also in practice; however, these are target specific medicines.[83] Some of Angiotensin II receptor (ACE-II) blockers (ARBs) i.e. losartan, telmisartan, valsartan, and candesartan are in practicing now but the suggested treatments are reported with some contradicting outcomes.[38] Another approach is associated with the IL-6 antagonists from the modern system of medicine e.g. Tocilizumab, sarilumab, siltuximab[9] for SARS-CoV-2 treatment. Therapeutic neutralizing antibodies (NAbs) is another option against SARS-CoV-2.[85]

Apart from the existing drugs/target molecules and sites, researchers are also finding newer targets and molecules for SARS-CoV-2 with the help of computational tools. These studies focus on identifying target proteins and binding sites, where active ingredients/ derivatives/lead molecules may be able to interact, distress the different infectious stages of SARS-CoV-2, and answers as preventive remedies for the COVID-19.

Medicinal plants for preventive care

As mentioned, the number of medicinal plants, phytoconstituents and their derivatives were explored against COVID-19 based on molecular docking, however, some interesting ethnopharmacological validated medicinal plants and respective phytoconstituents are identified based on *in vitro* and *in vivo* research outcomes and also considering *in silico* molecular docking approaches and highlighted in Table 4. Medicine plants, practiced from ancient time and derived phytoconstituents are now choices to the researchers and industrial interest for managing COVID-19 infection.[86–89]

Highly cited ten Indian medicinal plants, which refined from the Elsevier Scopus database are summarized here for understanding their mechanism of action against SARS-CoV-2:

Andrographis paniculata

Andrographolide diterpenoid derived from *Andrographis paniculata* (family: Acanthaceae) is used to treat various serious ailment including cancer. Recently an *in silico* prediction study including target analysis, toxicity and ADME prediction, revealed about Andrographolide molecule, that inhibit Mpro protease activity and targeted as potential candidate against SARS-COV-2,[112] which help to digest the polyprotein and helps in the cleavage of the genome, pp1a and ppa1b.[113] Andrographolide is the molecule having broad spectrum antiviral activity over various viral strains[114] i.e. herpes simplex virus type-1, Chikungunya,[115-117] etc. Studies revealed that the strains of influenza viruses e.g. H9N2, H5N1 and H1N1 are also inhibited via andrographolide and its various derivatives.[118] Apart from the antiviral activities, andrographolide also exhibited anti-inflammatory activity.[119] Tumor Necrosis Factor Ligand Superfamily Member 14 (TNFSF14) that exhibits inflammatory activities in lung fibroblast[120] is remarkably down-regulated up to 12 folds in the presence of andrographolide.[119] Shen *et al*. supported the anti-inflammatory properties of andrographolide and proved that it inhibits extracellular signal-regulated kinase (ERK), activator protein (AP)-1 cellular pathway along with IκB kinase ε (IKKε), interferon regulatory factor (IRF)-3 pathways.[121,122] Another molecule Andrographiside inhibits RNA-dependent RNA polymerase (RdRp) and could be the target for drug discovery.[23]

Table 4: Medicinal plants and potential targets.

S. No.	Scientific Name	Common Name	Family	Plant Part	Phytoconstituents	Mechanism of Action	Reference
			Cell surface and Proteolysis Targets:				
1	*Bupleurum* spp., *Heteromorpha* spp. *and Scrophularia scorodonia*	Chai Hu; Figwort	Apiaceae, Scrophulariaceae	Root	Saikosaponins (A, B2, C and D)	Antiviral activity against HCoV-229E by Inhibiting viral attachment and penetration; 0.25-25 μmol/L	[90]
2	*Camellia sinensis*	Tea	Theaceae	Leaves	Theaflavin-3,3′-digallate (TF3)	Inhibits the 3C-like protease (3CLPro) and suppresses the viral replication on SARS-CoV	[91]
3	*Cimicifuga foetida*	Foetid Bugbane	Ranunculaceae	Rhizome	Cimicifugin	Interfere viral attachment to the host cell and internalization steps; stimulates IFN-β secretion	[92,93]
4	*Clerodendrum inerme Gaertn*	Glory Bower	Verbenaceae	Leaves	Protein CIP-29	Inactivate ribosome and interfere the protein synthesis	[94]
5	*Galla chinensis*	Chinese gall	Anacardiaceae	Nutgall	Tetra-*O*-galloyl-β-D-glucose	Avidly binds with surface spike protein of SARS-CoV	[95]
6	*Houttuynia cordata*	Chameleon Plant	Saururaceae	Aerial parts	Genistein	SARS-CoV 3CLpro (protease inhibitor); RNA-dependent RNA polymerase (RdRp)	[13]
7	*Isatis indigotica*	Dyer's woad	Brassicaceae	Root	Aloe emodin and Hesperetin	Inhibit cleavage activity of the 3CLpro (protease inhibitor); IC_{50} 366 μM IC_{50} 8.3 μM	[42]
8	*Rheum palmatum*	Rhubarb	Polygonaceae	Rhizomes	RH121	Inhibit SARS-3CLpro activity; IC(50) 13.76 μg/mL; inhibition rate 96%	[96]
9	*Scutellaria baicalensis*	Baikal skullcap	Lamiaceae	Root	Scutellarein; Myricetin	SARS-CoV helicase enzyme inhibitor (nsP13); Virucidal activity; suppresses the viral adsorption and replication	[97,98]
10	*Strobilanthes cusia*	Chinese Rain Bell	Acanthaceae	Leaves	Tryptanthrin	Alters structure of viral spike proteins and inhibits the cleavage activity of PLP2 against CoV-NL63	[99]
11	*Terminalia chebula*	Chebulic myrobalan	Combretaceae	Fruits	Chebulagic acid (CHLA) and Punicalagin (PUG)	Abrogate host cell binding and penetration	[100]
12	*Toona sinensis* Roem	Cedrela sinensis	Meliacceae	Leaves	Quercetin and TSL-1	Inhibit the cellular entry of SARS-CoV	[101]
13	*Torreya nucifera*	Japanese nutmeg-yew	Taxaceae	Leaves	Amentoflavone	Inhibit cleavage activity of the chymotrypsin-like protease 3CLpro (protease inhibitor); IC_{50} 8.3μM; Suppressed the formation of a molecular complex including ERK and c-Fos.	[102,103]
Anti-inflammatory and Immunity boosting targets:							
14	*Boerhaavia diffusa*	Punarnava	Nyctaginaceae	Root	Punarnavine	Reduce Pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α; Inhibits angiotensin-converting enzyme and xanthine oxidase; Modulate oxidative stress and down-regulating NF-kB and transforming growth factor β1	[104,105]
15	*Brassica nigra*	Mustards	Brassicaceae	Seeds	Sinigrin (allyl-glucosinolate or 2-propenyl-glucosinolate)	Inhibit the levels of TNF-α and IL-6; Blocked phosphorylation of JNK and p38. Significantly suppresses the expression of p65 and NLRP3	[106]
16	*Punica granatum*	Pome-granate	Punicaceae	Fruits	Punicalagin	Inhibit ATP-induced IL-1β release following NLRP3 inflammasome activation	[107]
17	*Nigella sativa*	Black caraway	*Ranunculaceae*	Seeds	Thymoquinone, Dithymquinone	Increase $CD4^+$ to $CD8$ T^+ cells ratio, and a 30% increase in natural killer (NK) cell function; Inhibit of NF-kB, reduced mRNA expression of cytokines and chemokines, mainly TNF-α	[69;108]

Continued...

Table 4: Medicinal plants and potential targets.

S. No.	Scientific Name	Common Name	Family	Plant Part	Phytoconstituents	Mechanism of Action	Reference
Respiratory tract infection and associated antiviral actives:							
18	*Aloe vera*	Aloe	Asphodelaceae	Leaves	Aloe emodin	Antiviral activity against influenza A virus via galectin-3 up-regulation	[109]
19	*Taraxacum officinale*	Dandelion	Compositae	Aerial Part	Aqueous extract	Inhibits viral nucleoprotein synthesis at RNA levels and polymerase activity against influenza virus type A, human A/PR/8/34 and WSN (H1N1)	[110]
20	*Terminalia chebula*	Chebulic myrobalan	Combretaceae	Fruits	Chebulagic acid (CHLA) and Punicalagin (PUG)	Abrogate host cell binding and penetration	[100]
21	*Vitis vinifera*	Grapes	Vitaceae	Fruits	Resveratrol	Control Toll-like receptor 3 (TLR3) expression, inhibited the TRIF signaling pathway, and induced M2 receptor expression Down-regulate IFN-γ levels in RSV infection	[111]

Azadirachta indica

Neem (*Azadirachta indica*) is an Indian traditional medicinal plant (family: Meliaceae) widely used in treatment of various diseases. Every part of the plant is sources for numerous phytochemicals, which have various therapeutic benefits. Neem leaf inhibits herpes simplex virus (HSV) glycoprotein D regulated viral fusion and polykaryocytes; exhibits antiviral activity over Herpes simplex virus type 1 infections.[123] Neem leaf extract cures pulmonary inflammation via inhibiting the inflammatory cells and via regulating the chemotactic factor-Monocyte Chemoattractant Protein-1 (MCP-1). The extract also activates central inflammatory cytokines e.g. TNF-α and IL-6 via various signaling cascades directly and indirectly. The study revealed that neem leaf extract modulates the release of these pro-inflammatory cytokines in bronchoalveolar lavage fluid[124] of Chronic obstructive pulmonary disease (COPD)[125] and therefore it could be promising targets for COVID-19 mediated pneumonia. Additionally, one of the active compounds known as nimbolide present in leaf extract also inhibits the cytokine storm and protects endotoxin-induced acute respiratory distress by interfering with toll-like receptor 4 and inhibiting the TNF-α mediated NF-κB pathway. It inhibits Histone deacetylase 3 (HDAC-3) protein and affects nuclear translocation in ARDS experimental model.[126] Essentially HDAC-3 is a protein-coding gene,[127] which also activates IL-1-induced inflammatory signaling pathway[128] for maintaining the equilibrium between both pro and anti-inflammatory gene expression, and furthermore conquers lung inflammation.[129] Due to strong antiviral activities and cytokine storm inhibiting activity, neem leaf is an important choice for further discovery to get the answer for preventive medicine against SARS -CoV -2.

Camellia sinensis

This plant also referred to as green *tea* (family: Theaceae) is worldwide one of the best antioxidants to treat various ailments. It is enriched with various phytoconstituents including polyphenols i.e. Catechin (C), Epicatechin (EC), Epigallocatechin (EGC), and Epigallocatechin gallate (EGCG).[130] Green tea has the ability to inhibit protease family Matrix metalloproteinase, which significantly activates chemokine and degrades the myelin proteins responsible for generation of auto-antigens.[131] In recent studies on molecular docking, a selective polyphenols i.e. theafavin, (−)-epigallocatechin 3-gallate, Genistein, 1-O-cafeoylquinic acid, and Ethyl trans-cafeate are considered as matrix metalloproteinase inhibitors; where 2, 9, and 12 are the recognised MMPs docked with above green tea molecules.[132] *Camellia* extract increases natural killer cells and regulates IL-2 and IFN-g secretion.[133] EGCG, ECG, and theaflavin-3,3'-digallate prevented tumor necrosis factor superfamily 14-induced ERK, JNK, and NF-κB activation.[134]

Curcuma longa

Curcumin, the major curcuminoid of the spice turmeric "also known as "Indian saffron" (family: Zingiberaceae) with a diverse range of therapeutic attributes is obtained from the rhizome of *Curcuma longa* (family: Zingiberaceae).[135] Curcumin "Indian Solid Gold"[136] was used first as an anti-inflammatory agent dating back to nearly 4000 years.[137] It is now widely used as a potential herb for the prevention and/or treatment of chronic diseases including cancer[138] because to its anti-oxidative and anti-inflammatory properties.[139] Curcumin inhibits diverse signaling pathways e.g. NF-κB, NLRP3, cyclooxygenase-2 (COX-2), TNF-α, metalloproteinase-9 (MMP-9), MAPK/ERK, signal transducer and activator of transcription-3 (STAT3-transcription factors) and interleukins pathways.[140-144] It acts as a potential anti-inflammatory candidate against numerous conditions i.e. neurodegenerative disorders, cardiovascular complications, pulmonary oedema, metabolic syndrome, autoimmune and also for neoplastic diseases.[143] Presently, anti-inflammatory properties of curcumin are well studied and globally accepted and suppresses inflammation through multiple pathways.[143] Majorly, anti-inflammatory activity of the curcumin is due to pro-inflammatory transcription factor NF-κB and also via IκB kinase signaling pathway.[142,145] Curcumin inhibits IL-6 and TNF-α expression also at both RNA and protein levels.[146] Interestingly, it is clearly demonstrated that curcumin inhibits the release of inflammasome NLRP3.[147] It is the result of down-regulated inflammatory cytokines.[148] Curcumin inhibits ATP sensitive ion movement; K^+ efflux and Ca^{++} influx through P2X7 receptor, which responsible for triggering and activating the NLRP3 inflammasomes and further induces the expression of the inflammasome components (Figure 7) e.g. the conversion of inactive cytokine precursor pro-IL-1β to active IL-1β.[59] Other signaling pathways such as NFκB, p38, and ERK1 also expresses NLRP3 and pro-IL-1β modulation. One study on pulmonary infection model suggests that NLRP3 and Apoptotic Speck-like protein containing a Card (ASC) works via inflammasome-dependent and independent pathways and NLRP3 and ASC control the release of IL-1β and HMGB1.[149] Recently it was found that, extracellular HMGB1

could be the therapeutic target to treat pulmonary inflammation considering with SARS-CoV-2.[72] It is highly possible that HMGB1-assisted transport system helps to SARS-CoV-2 virus for entering of its RNA into the host cytosol. Infected macrophages releases pro-inflammatory factor HMGB-1[150] which, binds to the extracellular mediators, DAMP and PAMPs. Further, HMGB1encourages the endo-cytosis process with the help of protein receptor "Receptor for Advanced Glycation Endproducts (RAGE)" and modulates the induction of cytokine IL-1. Curcumin is the molecule which can directly reduce HMGB-1 release[151] diminish cathepsin B leakage, modulating the HMGB1 proteins, and finally down regulate the elicited inflammatory cytokines i.e. IL-1, IL-1β and IL-18. Interestingly, anti-viral treatment combined anti-HMGB1 and mAb will be another target for the protection of lungs tissue against any decease[151-154] in SARS-CoV infection.[72]

In addition to NLRP3 inflammasomes, curcumin also reduces cytokines mRNA expressions i.e. COX-2, IL-6, IL-12, TNF-κ, and IL-1β. Abe *et al.* showed that curcumin suppresses IL1β, IL8, TNF-α, MCP1 and macrophage inflammatory protein-1α (MIP1α) interfering with the release of alveolar macrophages and monocytes cells.[155] From the above outcome and strong correlation between the inhibiting pathway, it can be concluded that Curcumin will be a futuristic approachable molecule against SARS-CoV-2 infection.

Glycyrrhiza glabra

This plant is also known as licorice (family: Fabaceae) and has a lot of medicinal properties and therefore it is known as the grandfather of herbs.[156] The dried unpeeled root of *Glycyrrhiza glabra* is the source of numerous secondary metabolites, which are having various medicinal benefits. Primarily two triterpenoid saponins glycyrrhizic acid and glycyrrhetinic acid are used as an anti-bacterial and anti-viral candidate against numerous infectious disease. Glycyrrhizic acid inhibits various virus strains at the stage of replication, including SARS-CoV, Influenza viruses, H1N1[157] and H5N1.[158,159] Apart from virus replication, glycyrrhizin can also inhibit the adsorption and penetration of the viruses.[156]

Glycyrrhizin was reported for strong antiviral activities on patients with SARS when compared with four other compounds ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid,[160] however the mechanism by which, glycyrrhizin's works against SARS-CV is quite ambiguous. From the virus structural configuration, it proves that spike proteins (S-protein) of coronaviruses are highly glycosylated and are important to helps enter the viral genome into the host cells via the adjoining of S-protein to ACE2 surface receptors.[153,161] It was speculated that adding of N-acetyl-glycosamine residue into GL molecules would increase the hydrophilic nature of the GL molecule and further it would help to interact with viral proteins. Resultant inhibition of viral entry into the host. Keeping the above facts in mind, fifteen derivatives of glycyrrhizin (GL) glycopeptides were evaluated for the antiviral activity to find out more potent compounds against SARS-CoV.[162] Out of all, interestingly seven derivatives have shown antiviral activity against SARS-CoV replication when compared to GL at a lower concentration. The first derivative, 2-acetamido-β-D-glucopyranosylamine was developed by a coupling reaction between GL and N-acetyl-β-D-glycopyranosylamine shown a 10-fold increased anti-SARS-CoV activity. Effective concentration (EC_{50}) and cytotoxicity concentration (CC_{50}) was found to be 40 ±13 μM and >3000 μM respectively. On the other hand, compounds i. e. amides and amino acid conjugates of glycyrrhizin were also increased activity up to 70-fold, however higher cytotoxicity concentrations decreased their selectivity interest.[162] Considering the experimental data, modification into the GL molecule could be the lead for drug discovery programs to find anti-SARS-CoV-2 drugs from natural product derivatives. Another study indicated that glycyrrhizin, its aglycone metabolite was also able to up-regulate nitrous oxide synthase, which mediated nitrous oxide production and responsible for inhibition of the virus's replication.[160,163] Glycyrrhizin was able to inhibit adsorption and penetration of the virus during the early steps of the replicative cycle In addition to inhibition of virus replication. The mechanism of the activity of glycyrrhizin against SARS-CoV is unclear. Glycyrrhizic acid has also exhibited strong anti-inflammatory properties. It also modulates Protein kinase C, casein kinase II (CK-2), transcription factor-activator protein 1 (AP-1) and NF-kB etc cellular signaling pathways.[160] Glycyrrhizin is also a strong HMGB1 receptor inhibitor, which binds directly to high mobility group boxes in HMGB1[164] and gives a protective effect against SARS-CoV. Besides above-targeted activity, *Glycyrrhiza glabra* is also able to enhance immune activities via increasing levels of serum IgA, IgG and IgM.[165]

Nigella sativa

This plant usually called as black cumin (family: Ranunculaceae) is marked as "magical condimental" against various disease due to most pharmacologically active ingredient Thymquinone (TQ).[166,167] One of the molecular docking study, Thymoquinone was observed high binding affinity towards active sites 6LU7, ACE2 and Heat Shock Protein A5 where as another study, molecule dithymoquinone (DTQ) was shown high binding affinity towards the ACE2 interface (8.6 kcal/mol) as compared to positive control chloroquine (7.2 kcal/mol). It was revealed that these compounds could be possible inhibitors, which disrupt the interactions between host epithelial cell and viral protein, associated with the outer surface and presenting the adhesion.[167-169] In another interesting study, it was found that one of the alkaloid nigellicine from nigella helps Zn ion uptake to pneumocytes cells and interfere the viral pathogenesis and reported that *Nigella sativa* in combination with Zn could be a possible complement against COVID-19 treatment.[170] One more compound α-hederin from same plant was found to active by interfering the interleukin secretion pathways (IL-13)[166] Nigella increase the level of helper T4 and natural killer (NK) cell whereas suppress T8 level.[171] Because of above facts it is in a high priority candidate against SARS-CoV-2.

Ocimum spp.

Holy Basil/ Sacred herb/Tulsi/ Herb royale (family: Lamiaceae) tagged as "*the incomparable one*" is the choice of a large number of remedies for the treatment of numerous respiratory problems, common cold virus's diseases and believed to promote longevity.[172,173] This legendary "*Queen of Herb*" is classified in genus *Ocimum* and belongs to the family Lamiaceae.[174] Recently, some researchers did *in silico* investigations and mentioned this herb as a protease inhibitor against SARS-CoV-2.[22,175,176] Out of the selected 16 compounds from *Ocimum sanctum* (OB) majorly oleanolic acid, ursolic acid, rosmarinic acid, apigenin, gave promising results against SARS-CoV-2 through different key approaches e.g. significant high binding affinity to ACE2 receptor, NSP15 Endoribonuclease inhibition, binding affinity to nucleocapsid domain, CLpro protease inhibition, spike protein inhibition, etc.[22] However, these are *in silico* data and more focused research is required to prove the claim. Chiang *et al.* (2005) studied possible antiviral activities on the selective viruses i.e. herpes viruses (HSV), adenoviruses (ADV), hepatitis B virus (HBV) and on RNA viruses i.e. coxsackievirus B1 (CVB1) and enterovirus 71 (EV71) and found that ursolic acid was having the strongest activity as compared to crude extracts along with selected other two purified compounds, namely apigenin and linalool. The crude aqueous extract was found to possess a moderate broad-spectrum antiviral activity, whereas, ursolic acid was shown the strongest antiviral activities on RNA viruses i.e. coxsackievirus B1 (CVB1) and enteroviruses 71 (EV71) with the selectivity index ($SI = CC_{50}/EC_{50}$) greater or equal to 200. Antiviral activity of Ursolic acid was associated majorly with the infection process and replication phase.[177] Above mentioned antiviral study results encourage that ursolic acid, which is also *in silico* predictive

molecule against SARS-CoV-2 due to its high binding efficacy against surface spike[176] could be the future target for controlling the RNA virus's infection including SARS-CoV-2.

Tinospora cordifolia

Tinospora cordifolia (family: Menispermaceae) is also known as Heart-leaved moonseed/Giloy/Guduchi or in Sanskrit 'Amrita', which means 'the root of immortality'. It is generally used as a single drug or as in a "Rasayana" (refers to nourishment or nutrition) herb for the management of numerous diseases and ailment.[178-180] Due to its immense applications e.g. rejuvenating effect, nourishing and replenishing activities, immunity-boosting strengths and longevity properties, the plant is used for a number of traditional preparations to maintain "wellness of life" which is the principle of Ayurveda.[180,181] The plant could also be a choice for preventive medicine against SARS-CoV-2,[22] due to one of the alkaloid Barberine, which exhibit strong antiviral,[182] anti-inflammatory and immunomodulatory activity through various pathways i.e. p38 MAPK,[183] NLRP3,[184] MEK/ERK,[185] and NFkB[186] IFN-α.

Barberine, Tinosporide and Tinocordioside are the molecules for the *in silico* predictive tool for the SARS-CoV-2 treatment.[22] Berberine, an isoquinoline alkaloid exert antiviral activity against influenza A/FM1/1/47 (H1N1) on A549 cells and also in mouse lungs and p38 MAPK activity is implicated in infection by the virus's replication process. Results support that berberine can suppress the symptoms induced by viral infections like pulmonary inflammation and edema etc.[182,187] Considering all of the mentioned facts, *Tinospora Cordifolia* is a prominent plant for developing therapeutic solutions against SARS COV-2 outbreak.

Withania somnifera

This well acknowledged and widely accepted plant (family: Solanaceae) is also known as "Indian measure winter cherry" and "Indian ginseng.[188] The steroidal alkaloids and steroidal lactones are the major class of compounds studied well with molecular docking tools and predicted that they could be the strong candidate against SARS-CoV-2. These molecules could give a positive indication either via interacting with viral receptor binding domain (S-protein)[189] or via inhibiting the main protease Mpro.[22,175,190] Ziauddin *et al*. (1996) mentioned the immunomodulatory effects of Ashwagandha.[191] Recently, the molecular dynamics simulations study on 100 numbers molecules were performed on target non-structural proteins (NSP) and found that nine phytochemicals, majorly from this plant active against SARS-CoV-2 for.[192]

Presently researchers are also mainly focusing on immunity boosters from medicinal plants, spices, and oleoresins. However, apart from above-highlighted plants, some relevant phytoconstituents act via various different pathways, which also are compiled here to get the knowledge for futuristic approaches.

Zingiber officinale

Ginger (family: Zingiberaceae) is extensively used in folk medicine as a digestion aid, against nausea and sore throat. One of the molecular docking studies revealed that zingiberenol and zingiberol compounds inhibit SARS-CoV-2 main protease (M^{pro}).[193] Similarly, nine out of forty-two active constituents were also analysed through the molecular docking studies and was found to be active through main protease inhibitory activity.[194] Further, one more ligand-binding docking study, Chakotiya and Sharma reported Gingerenone and Zingiberene are the remarkable compound with spike protein ACE2 inhibitor mechanism while compared with Chloroquine.[195] Ginger enriched extract was also reported for inhibitory expression of inflammatory responses i.e. iNOS and COX-2 activity together with IκB-α phosphorylation.[196] The above findings support this plant as a preventive candidate for Covid-19.

DISCUSSION

Most antiviral drugs induce forced mutations; however, the inherent nature of coronaviridae family is able to resist such mutations and capable to translocate their RNA to other viruses in the same family, resultant potent virus strains developed, which aid them to infect other cells as well.[197] By keeping in mind all the associated studies over the current pandemic scenario of COVID-19 outbreak and its impact on human-kind, an alternate holistic approach in research is very much needed to aids enhanced immunity, in addition to focusing resources to develop a magic formula for curing the disease. All these facts call up for the need for a holistic approach, which works on improving immunity.

In this study, we used science mapping tool Bibliometrix R-package to perform bibliometric analysis and building data matrices for keywords co-occurrence investigation, country-wise scientific production; collaboration between the countries worldwide, co-word analysis on topic "keywords associated with SARS-CoV-2 and medicinal plants".

Keywords Plus is the word and/or phrases, which indicate about the article in a concise way and present in the reference title instead of title of an article. Author's keywords are the keywords that comprehensively represent the article's and its contents and overview of scientific knowledge. Author's keywords more closely describe the article then the Keywords Plus.[198] From results, it was observed that Ayurveda, Natural Products and Traditional Chinese Medicine are dominating words for searching the phytoconstituents that are driven from medicinal plants. Plants and their derivatives are extensively used as remedies and are very popular in the indigenous system of medicine since long. These systems of medicines are based on traditional and ethnic knowledge and are mostly backed by strong scientific background. Herbal medicines, which are standardized with specific makers (standard), are very useful as preventive medicine against SARS-CoV-2.[199] Phytoconstituents are early line of defence systems to fight against the number of pathogenic viruses including SARS-CoV through the various pathways. They are able to alter SARS-CoV related pathophysiological consequences, post-viral infections; however, herbal medicines and extracts usually are not consumed in very pure form. In addition, they have a number of molecules and active components and thereby they work on different receptors and give multi-targeted therapeutic effects. A more focused research approach is required on specific plants and derived molecule(s)/actives, for their safe usage and potential effects through modern scientific technologies.

Inflammation triggering protein NLRP3 that responds against SARS-CoV is not actively functioning in bats and thereby bats survive even in the presence of high loads of viral strain. This could be one of the key factors for long lifespans of the bats. SARS-CoV and MERS-COV cause proliferate pro-inflammatory cytokines and chemokines, which infect lung tissue and affect humankind. Presently there is no vaccine in the market and existing drugs are having some complications. As discussed a target-specific approach would be beneficial considering the ability of phytoconstituents of the discussed herbs to act especially on different anti-inflammatory/immune response pathways. A number of natural products and derivatives are now in the interest of researchers globally due to these activities. e.g. andrographolide suppress the inflammatory activities down-regulating by TNFSF14 pathway; nimbolide inhibits induced acute respiratory distress by TLR3/4 and resultant inhibition of TNF-α mediated NF-κB pathway; *Camellia* increases natural killer cells; *Curcuma longa* one of the best-known anti-inflammatory agent suppresses the inflammation by NLRP3 protein; glycyrrhizic acid modulates the protein kinase C, casein kinase II, and activator protein 1 (AP-1) and regulate NF-kB like cellular signaling pathways; Nigella increase the level of helper T4 and natural killer (NK) cell whereas

suppress T8 level; *Ocimum* species is also inhibits the NF-κB pathway; Likewise *Tinospora cordifolia,* known as "the root of immortality and longevity" have some very potent molecules like berberine, tinosporide and tinocordioside also suppress the symptoms induced by viral infections like pulmonary inflammation through p38 MAPK pathways; Ginger. In addition, *Withania somnifera* has anti-inflammatory activity and it can inhibit the production of prostaglandins and inflammatory cytokines. Numerous publications coined that plant extracts or phytoconstituents, exhibit potential immune-stimulating effects through phagocytic enhancement, required for attenuating viral load, and prevent the spreading of infection. However, some of the key points are needed to be considered for accepting the plant extracts and botanicals as remedies against COVID-19 including quality of botanicals, claim, dose, time of ingestion, health condition, specified treatment etc.

The outcome of our elaborated study put forward that the number of medicinal plants and their derivatives such as *Andrographis paniculata, Azadirachta indica, Curcuma longa, Glycyrrhiza glabra, Ocimum sanactum, Tinospora cordifolia, Withania somnifera* and so on could be the potential candidates as preventive remedies; however extensive research on individual plants are much required for the claim.

CONCLUSION

The phytoconstituents of the identified plants hold the remarkable potential to fight against viruses. There are many unexplored territories in the field of phytochemicals, especially to develop superior ethnopharmacological validated herbal products with enhanced efficacy and limited toxicity that needs to be explored. The derivatives of the mainstream phytochemical, which are already exploited, may hold the key for better solutions against SARS-CoV. After computational data derived from molecular docking on the natural products and their derivatives, clinical studies are very much valuable and required since the demand for the antiviral remedies for SARS COV-2 are an exigent necessity. Target-specific inflammatory pathways and development of therapeutics for enhanced immunity are much advocated since they are preventive care and can have a significant role especially on global pandemics like COVID-19.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

3CLpro: 3C-like protease; **ACE2:** angiotensin-converting enzyme 2; **ADAM17:** ADAM metallopeptidase domain 17; **ARDS:** Acute respiratory distress syndrome; **ASC:** Apoptosis-associated speck-like protein containing a CARD; **CD4+:** Cluster of differentiation 4+; **CD8+:** Cluster of differentiation 8+; **COVID-19:** coronavirus disease 2019; **DNA:** Deoxyribonucleic acid; **ERGIC:** endoplasmic reticulum-Golgi intermediate compartment; **ERK:** Extracellular signal regulated protein kinase; **HCoV:** Human coronavirus; **HDAC-3:** Histone deacetylase 3; **HIV:** human immunodeficiency virus; **HMGB1:** High-Mobility Group Box 1; **IL:** Interleukin; **INFα:** Interferonα; **JAK-STAT:** Janus kinase/signal transducer and activator of transcription; **LRTI:** Lower respiratory tract infection; **MAPK:** Mitogen-activated protein kinases; **MCP1:** Monocyte Chemoattractant Protein-1; **MCP-1:** Monocyte chemoattractant protein-1; **MERS:** Middle East respiratory syndrome; **MERS-CoV:** Middle East respiratory syndrome coronavirus; **NF-kB:** Nuclear Factor kappa-light-chain-enhancer of activated B-cells; **NLRP3:** Nod-like receptor protein 3; **NSPs:** Nonstructural proteins; **ORF:** Open reading frame; **PAMPs:** Pathogen associated molecular patterns; **PHEIC:** Public Health Emergency of International Concern; **PLpro:** Papain-like protease; **RBD:** Receptor binding domain; **RdRp:** RNA dependent RNA polymerase; **RNA:** Ribonucleic acid; **RSV:** Respiratory syncytial virus: **RTC:** Replicase transcriptase complex; **RTI:** Respiratory tract infection; **SARS:** Severe acute respiratory syndrome; **SARS-COV-2:** Severe acute respiratory syndrome coronavirus-2; **TMPRSS2:** Transmembrane Serine Protease 2; **TNF-α:** Tumor necrosis factor α; **TNFβ:** Tumor necrosis factor β; **TRAF3:** TNF receptor associated factor 3; **TRS:** Transcriptional regulatory sequence; **URTI:** Upper respiratory tract infection.

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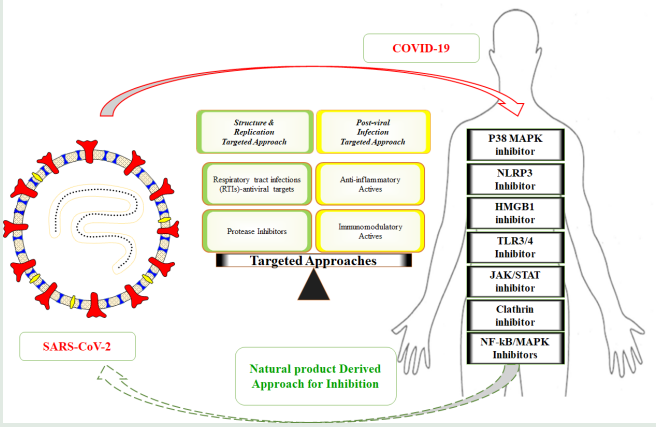
GRAPHICAL ABSTRACT



SUMMARY

This article is primarily reviewed and delivered a concise fact of the coronaviridae family, pathophysiology, mechanism of action, ethnopharmacological validated Indian herbs for inhibiting the virus with possible targets. Science mapping tool Bibliometrix R-package was used to understand bibliometric analysis on keywords associated with SARS-CoV-2 and medicinal plants. The outcome of our elaborated study put forward that the number of medicinal plants such as *Andrographis paniculata, Azadirachta indica, Curcuma longa, Glycyrrhiza glabra, Ocimum sanactum, Tinospora cordifolia* and *Withania somnifera* etc and their derivative phytoconstituents act on various pathways e.g. NLRP3, p38-MAPK, Metallopeptidase Domain 17; endocytosis pathways, HMGB1 triggers immune system directly/indirectly against SARS-CoV-2/COVID-19 and could be the potential candidates as preventive remedies.

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