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A Comprehensive Review and Perspective of Herbal Medicines in the Treatment of COVID-19

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: An emergent COVID-19 outbreak originated in Wuhan City, in December 2019. The COVID-19 contamination has swiftly unfold from Wuhan to maximum different provinces and different 24 countries. WHO declared a public health emergency of global concern over this worldwide COVID-19 outbreak on 30th January 2020. Manifold research has been intensely initiated for immunization and drug development for COVID-19 till date no specific vaccine or approved drugs are accessible for COVID-19. Alternatively, therapy consists of supportive care and non-specific anti-viral, anti-malarial, and antibiotics are being testedas drugs for COVID-19.

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Though, novel approaches could play a crucial role to combat mortality rate and patient recovery in the treatment of COVID-19.
Objective: To reveal the epidemiology, pathophysiology, and comparison of promising synthetic and natural drug targets to avert and cure of COVID-19.
Method: This article sets a brief understanding of the viral characteristics, its life cycle, infection to humans, and the pathophysiology of the disease. It also throws light on the currently used synthetic medicines. we have reviewed the effect of natural products to prevent or treat COVID-19 infection. Their mechanisms of action have been elaborately discussed. literature research was undertaken using PubMed, Google Scholar, Scopus, and WHO website. The different herbal products (extracts) and their moieties which are promising as anti-SARS-CoV-2 by direct inhibition of the virus replication or entry has also been discussed.
Results and Conclusion: In conclusion we have highlighted that natural therapeutics either alone or in combinationcould be used as alternative medicines to treat/prevent COVID-19 infection. Moreover, their structures may offer clues for the development of anti-SARS-CoV-2 drugs.The integration of nanocarriers for effectively delivering the conventional as well as the herbal drugs becomes a key point for their efficacy and safety.

Keywords: COVID-19; life cycle; epidemiology; pathophysiology; chinese system of medicine; nanocarriers.

1. INTRODUCTION

Coronavirus (CoVs) is a protein covered single-stranded RNA virus that is zoonotic and majorly targets the human respiratory system causing symptoms ranging from high body temperature, cold, cough, exhaustion, chills and breathing problems. The examination of the chest X-ray of the lungs of the infected person showed diffused infiltration with gridding shadow [1]. Previous out breaks of coronavirus included the Severe Acute Respiratory Syndrome (SARS)-CoV and Middle East Respiratory Syndrome (MERS)-CoV. In the latter half of December 2019, a cluster of patients reported pneumonia caused by an unidentified organism of animal origin in Wuhan city, China [2,3]. Based on the initial reports and estimated reproduction number range (1.4-6.4) the predicted onset potential CoVs was much higher than SARS-CoVs [4].World Health Organization (WHO) named CoVs as COVID-19 on 11th February 2020.

WHO and a medical journal Lancet hosted by Johns Hopkins University [5], reported 2,006,523 infected cases with 1,28,886 confirmed deaths as of 15th April 2020. At the same time,617,628 confirmed cases were reported from the United States (US) alone with 26,977 deaths. Besides, COVID-19 was found infecting population spread across 179 countries globally.Ten countries have shown confirmed cases>10,000 and while 32 nations have reported 1000-10,000 confirmed cases/million people. On 27th March the US surpassed China in terms of infected cases count [6].

Despite the progress in the field of drug development and immunization, COVID-19 lacks preventive vaccines and effective drug therapies due to the viral escape mutants. There is a need for the identification of effective anti-viral drugs and natural compounds for the preventing and curing of COVID-19. Also, clinical practice suggests Chinese herbal medicine as an alternative therapy[7]. Medicinal plants are now receiving more consideration than ever as they have the perspective of providing huge profits to society or undeniably to all mankind, particularly in the track of medicine. By decreasing the deadliness and the adverse influences of drugs at the same time, herbal treatment aids in increasing the calming value and biodiversity [8,9].

For the development of novel formulations, herbal medicines were not considered due to the absence of scientific explanation and handling complications. Scientific needs of herbal medicines such as pharmacokinetics, mechanism of action, dose, dosage form,etc. can be solved by modern phytopharmaceutical research and can be incorporated in novel drug delivery systems such as solid dispersions, solid lipid nanoparticles, nanoparticles, liposomes, micro-emulsions, etc. With enhanced efficacy, herbal drugs can be applied in an improved procedure by integrating them into contemporary dosage systems. By designing novel drug

delivery systems, this can be achieved for herbal constituents [10,11].

This review aims to present the pathogenesis, risk factors, transmission, life cycle and diagnosis of COVID-19, current treatment reports of synthetic drugs, traditional herbal medicine for the cure of COVID-19, identification of anti-COVID-19 moieties from herbal medicine, clinical trials of herbal medicine and possible dosage forms to target the disease.

2. SEARCH METHODOLOGY AND SELECTION CRITERIA

The identification of articles was accomplished using a systematic search in the **PubMed (National Library of Medicine), MEDLINE** (International Literature on Health Sciences), **SciELO** (Scientific Electronic Library Online), **Lilacs** (Latin American and Caribbean Literature on Health Sciences),PubMed, LitCovid, COVID-Evidence, Clinical Trials, and Science Direct. The relevant search strategy and keywords (such as "Novel coronavirus" or "COVID-19" or "SARS-CoV-2") were used to collect information on the novel coronavirus. Additional keywords (such as "natural products and COVID-19" or "Role of ACE-2 in SARS-CoV-2" or "COVID-19 and chinese medicines") were used to collect all useful information for this review. The search was carried out systematically for the screening of the related content as shown in Fig. 1. Initially, a total of 351 publications were retrieved from different databases and 82 articles were deleted due to duplication. The remaining articles have been carefully reviewed in order to determine the eligibility and methods used. 141 articles were referred for the present review work.

3. UNDERSTANDING PATHOGENESIS, RISK FACTORS AND DIAGNOSIS OF COVID-19

It was reported that COVID-19 is an acute respiratoryinfection, but the severity is characterized by substantial alveolar damage and a progressive respiratory failure with a case fatality rate of 4.65% (Fig. 1). The pathological features greatly resembled SARS and MERS upon obtaining the biopsy samples of the major end organs. Both lungs exhibited bilateral diffused alveolar damage accompaniedby cellular fibromyxoid discharge, the formation of hyaline membrane, and desquamation of pneumocytes which indicated acute respiratory distress syndrome (ARDS). Also, inflammatory infiltrates dominated by the lymphocytes were present in the interstitium. Various cellular pathological transformations were visible in the intra-alveolar spaces characterized by symplasm, the cytoplasm was granular withprominent nucleoli.

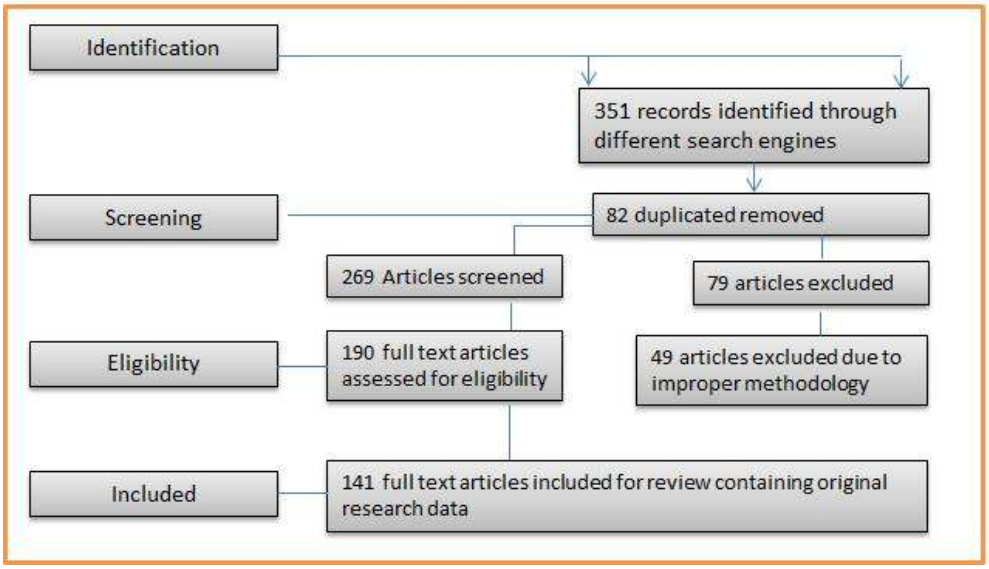

Fig. 1. Search methodology and selection criteria

Liver biopsy indicated moderate infiltration of liver cells with fat associated with disturbed

metabolism, signifying liver damage or injury which may be drug-induced or due to infection. Apart from the inflammatory infiltrates in the interstitium there was no major damage to the heart tissue. Upon analyzing the peripheral blood through cytometric analysis CD4 and CD8 T-cells count decreased with associated hyperactivity which wasindicted by increased amounts of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%). Also, CD8 T-cells were discovered to accommodate cytotoxic granules in high concentrations where the cells were 64.2% granulysin positive, 31.6% perforin positive, and 30.5% double positive with granulysin and perforin. Furthermore, pro-inflammatory CCR6+ Th17 was enhanced in CD4 T-cells which was due to the overactivity of T-cells causing severe immune injury to the patient. Patients also demonstrated lymphopenia in common which may be a major factor in the severity of the disease and mortality rate[12].

Various cytokines and chemokines like Interleukin (IL) 7, 8, 9, 10, IL1-β, IL1RA, basic Granulocyte-macrophage colony-stimulating factor (GMCSF), Interferon (IF)γ, Fibroblast growth factor (FGF) 2, Granulocyte colony-stimulating factor (GCSF), etc. Showed increased serum levels COVID-19 patients. Serious cases admitted in the intensive care unit (ICU) also exhibited marked levels of pro-inflammatory cytokines like GCSF, IP10, TNFα, IL10, IL2, IL7, MCP1, and MIP1α which may be involved in the severity of the disease [13,14].

The higher Multisystem Organ Failure (MSOF) numberand d-dimer greater than 1 µg/mL increased the risk of mortality. A uni-variable analysis in the hospital setup demonstrated that the mortality was higher in a patient with heart disease and diabetes mellitus. Other factors such as elevated levels of procalcitonin, prothrombin time, creatinine, high sensitive cardiac troponin (hscTn) 1, d-dimer, IL-6, lactate dehydrogenase, serum ferritin and Alanine transaminase (ALT), conditions such as lymphocytopenia, Age and leucocytosis also enhanced the mortality rate [15].

COVID-19 RNA detection method involves sampling from the respiratory tract or the throat swab and analysis by quantitative fluorescence polymerase chain reaction method (PCR). Other methods include the detection of the positive nucleic acid of COVID-19 by real-time PCR (RT-PCR) method by analyzing the sputum, throat swabs, and secretions of the respiratory tract. Also,the detection of flu antigens A, B, H7N type leads to early detection but has enhanced false-negative rate. New sequencing and electron microscopy techniques are deficient due to the lack of specific nucleic acid detection technology [16].

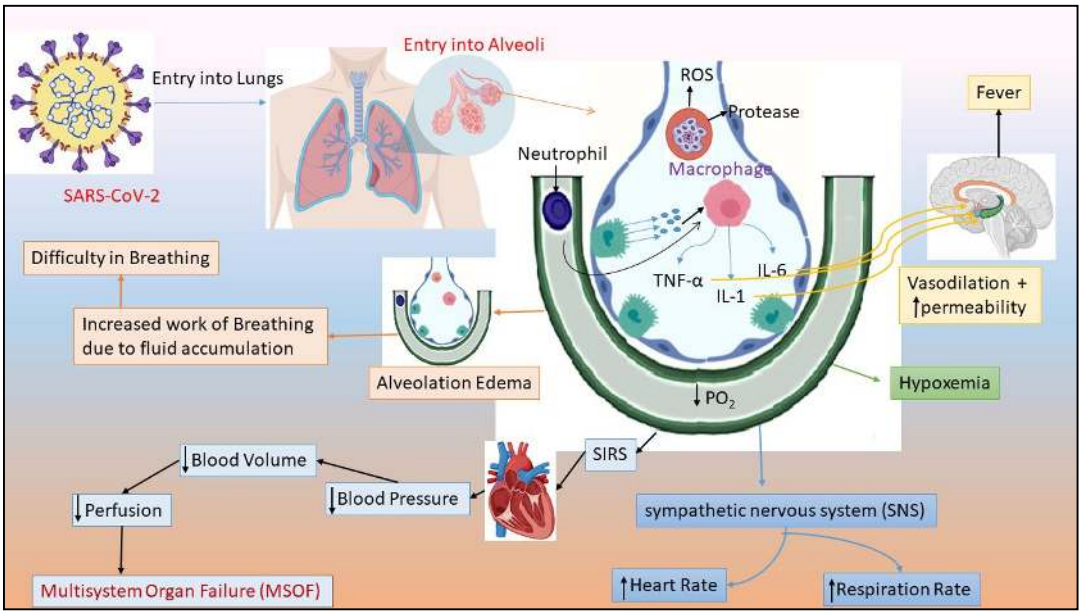

Fig. 2. Schematic representation of Pathophysiology of COVID-19

4. TRANSMISSION AND LIFE CYCLE OF COVID-19

Research to find out the possible host reservoir or intermediate carriers for the probable infection was recognized as two species of snakes that could be the reservoir. However, to date no concluding evidence has been found other than birds and mammals [17,18]. COVID-19 viral genomic sequence analysis showed 88% similarity with earlier coronaviruses whose origin was a bat, that was responsible for severe acute respiratory syndromes (SARS) [19,20] indicating that mammals being the likely link between virus and humans. Reports also indicated that person-to-person spread is the most probable route for spreading COVID-19 infection. This is because it was observed among people who did not have any exposure to the wet animal market in Wuhan yet suffered from the infection [21,22]. Infection from Person-to-person spreads by direct contact or through droplets generated on coughing or sneezing from an infected subject or through fecal contamination (Fig. 2). A limited study was conducted on infected women howoever delivering babies through cesarean; the test confirmed no transmission from mother to child. However, no study was done to confirm for transmission occurring during vaginal birth.

SARS-CoV-2 belongs to the *β* genus, Nidovirales order of the Coronaviridae family. It is enveloped, with single (+) stranded RNA, with symmetric helical nucleocapsid [23]. The virus encrypts twenty different proteins including four main structural proteins (S: spike; E: envelope; M: membrane; N: nucleocapsid) (Fig. 4), and several nonstructural proteins such as RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLpro) [24].

The binding of a receptor expressed by the host cell is the initial process of viral infection. This is followed by attachment and penetration into the host cell. Lung epithelial cells are the primary target for the virus. Human-to-human spread of COVID-19 occurs when the receptor-binding domain of virus spikes interacts with cellular receptors,here it is recognized as angiotensin-converting enzyme 2 (ACE2) receptor [25]. Importantly, the sequence of COVID-19 binding interaction is similar to that of SARS-CoV. Results strongly suggest that access to the individual patient cells is through to ACE2 receptor [20].

COVID-19 S-protein binds ACE2 cellular receptor resulting in a conformational change of S protein causing the viral envelope to fuse with the cell membrane followed by the release of RNA into the host cell. Now this released RNA is translated and replicate polyproteins such as PP1A and 1AB which are further cleaved into smaller viral proteinases. Polymerase enzyme cleaves the genome RNA to subgenomic mRNAs by the transcription process and further translation leads to the formation of viral proteins. The assembling of generated viral proteins and genome RNA into virions takes place within the endoplasmic reticulum and Golgicomplex which then ejected out of the host cell via vesicles (Fig. 5) [18].

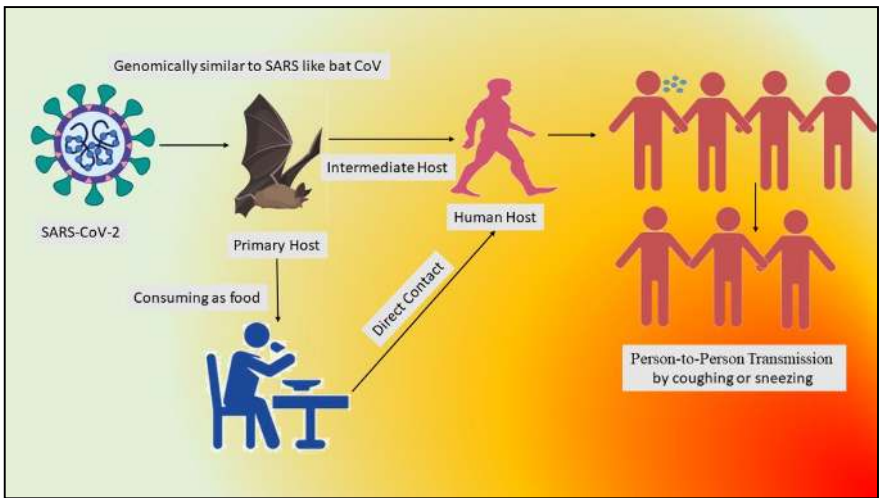

Fig. 3. Transmission of COVID-19

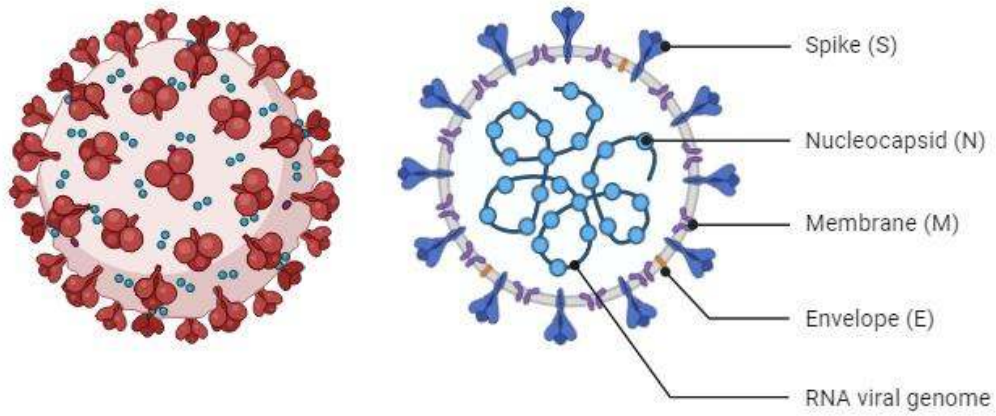

Fig. 4. Structure of corona virus

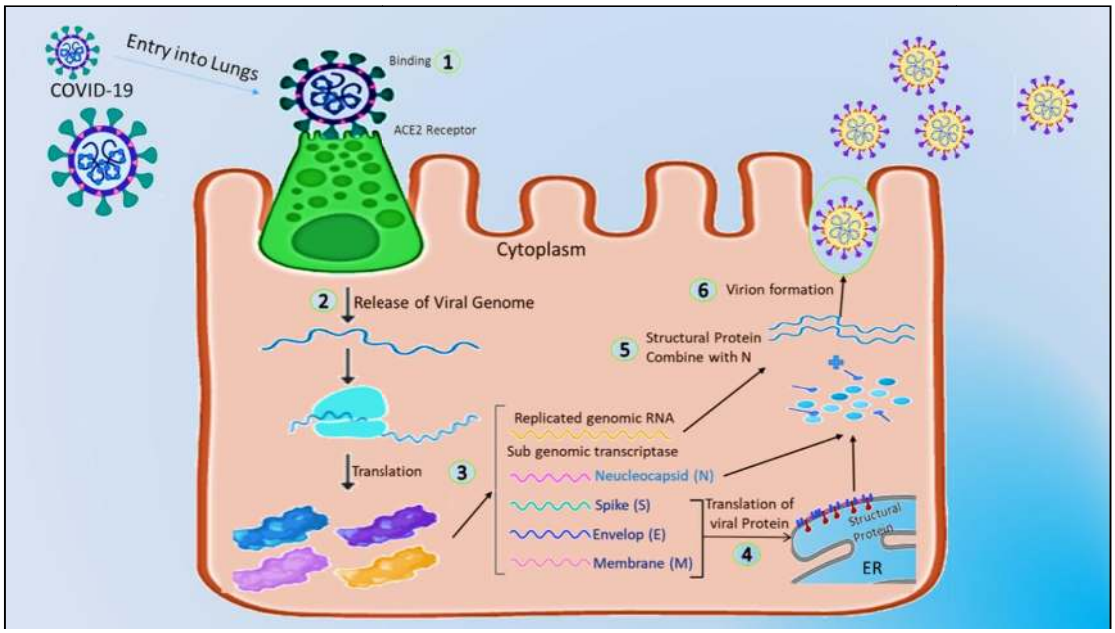

Fig. 5. Life Cycle of COVID-19

5. CURRENT TREATMENT REPORTS USING SYNTHETIC DRUGS

The current worldwide pandemic COVID-19 brought about by the SARS-CoV-2 infection has just dispensed unconquerable harm both to the human lives and worldwide economy.

COVID-19 infected patient is isolated followed by the administration of various antiviral and antibiotic regimens. No specific vaccines or antiviral drugs are treating this infection. The current treatment being adopted is broad-spectrum antiviral therapy that includes nucleoside analogs and HIV-protease inhibitors that could assuage virus infection until the specific antiviral becomes available [38]. The treatment protocolincluded 75 patients who were administrated existing antiviral drugs that included twice a day oral therapy of 500 mg lopinavir, 75 mg oseltamivir, 500 mg ritonavir along with intravenous administration of 0.25 g ganciclovir for 3–14 days [39]. Another study reported chloroquine and broad-spectrum antiviral remdesivir are extremely helpful in vitro control of COVID-19 infection. The exciting antiviral drugs for human consumption have established safety data, hence they can be considered to treatment of this infection [40].

Table 1. Approaches for drug disclosure focusing on SARS-CoV-2

Approach	Method	Molecules targeted	Limitation
Repurposing of antiviral compounds	tracking antiviral compounds ,its activities and estimate their effect on viral replication and packaging	interferon alpha, beta and gamma, ribavirin and chemical inhibitors of cyclophilin 8 have shown to exhibit anti viral effect [26].	lack specificity against SARS-CoV-2, have severe adverse effects [27,28].
High-throughput screening of compounds	Library screening methodology that constitute compounds targeting transcriptional machinery of various cell lines	Search from libraries involving 'drug-likely' chemical compounds having antiviral effects [29–33].	Could have immunosuppressive or cytotoxic effects at higher concentrations. The concentration could be more than EC 50 value to exhibit the pharmacological effect [34].
Inhibition of SARS-CoV-2 replication mediated by siRNA	Targeting novel agents resulting from genomic research and and pathophysiology of SARS-CoV-2	siRNA molecules shich inhibits specific viral enzymes involved in viral duplication,attacking the host receptor ACE-2 [35].	Lack of specific drug delivery of these molecules paucity in siRNA-based therapy [36,37].

Another non-randomized small sample-sized clinical trial conducted using 600mg of hydroxychloroquine daily along with azithromycin based on the clinical condition was tested for the viral load using nasopharyngeal swabs with the negative controls. After 6 days of the treatment 6 patients showed no symptoms, while 22 and 8 patients had upper respiratory tract and lower respiratory tract infection suggesting its potential in the treatment of COVID-19. Also, hydroxychloroquine action was strengthened by azithromycin which resulted in the reduction or removal of viral load [41]. Furthermore, newer compounds are being developed. Clinical candidate EIDD-2801 has shown good therapeutic potential against seasonal and pandemic influenza virus infections that can be considered for the treatment of COVID-19 [42]. Along these lines, until more specific therapeutics become available, it is reasonable to consider more broad-spectrum antivirals such as Lopinavir/Ritonavir, RNA synthesis inhibitors, peptide (EK1) and Neuraminidase inhibitors. To develop pre-and post-exposure prophylaxis suitable animal models are needed to understand viral replication. Scientists are trying to develop a nonhuman primate model to study COVID-19 infection for evaluation of novel therapeutics and testing potential vaccines in addition to better understand virus-host interactions[14].

In SARS-CoV [43,44] and MERS-CoV [45] corticosteroids were made use to reduce the levels of cytokines however there is no evidence of reduced mortality upon the usage of corticosteroids [46] and are not suggested for systemic use in infected patients [46]. Earlier, for the treatment of influenza or SARS-CoV convalescent plasma therapy was used which reduced the viral load and mortality [47,48] and this is being applied for COVID-19 treatment in China [49]. Its safety and efficacy need to be carefully evaluated for its clinical use. Based on several authentic reports and findings, WHO also concluded that there no specific recommended medicine to date prevention and treatment COVID-19" [50].

Traditional Herbal Medicine (THM) or herbal medicines through Ayurveda or Siddha and Unani have been widely used to manage and treat infectious diseases from ages. These herbal medicines can also be an alternative therapy to synthetic drugs. Reports suggest that patients suffering from COVID-19 have been benefited from THM [51] by reducing the adverse events [52]. These reports suggest that THM can serve as valuable weapons in the armory against COVID-19.

6. KNOWLEDGE FROM SARS: PHARMA-COLOGICAL ARBITRATIONS

The take home message from pervasiveness of SARS and MERS can be used to develop certain medicines for SARS-CoV-2 pollution [53]. As of

late antiviral drugs like oseltamivir, peramivir, zanamivir, ganciclovir, acyclovir and ribavirin are not proposed for COVI-19 treatment [54,55]. Also, major corticosteroid treatment, for instance, methylprednisolone isn't recognized as a treatment decision for SARS-CoV-2 infected patients [56]. In such a circumstance, similiarity of SARS-CoV and MERS disease to SARS-CoV-2 infection, a comprehension into the treatment decisions for SARS and MERS could drive us to gain knowledge on pharmaceutical agents with anti SARS-CoV-2 [57].

7. PARADIGM SHIFT IN THETREATMENT OF COVID-19 BY TRADITIONAL HERBAL MEDICINE

Traditional Herbal Medicine (THM), is an ancient system of medicine that includes the Chinese system of medicine (CSM), the Indian system of medicine-Ayurveda, a Korean system of medicine-Kampo, Unani andhomeopathic system of medicine. (Table 1) [58]. In many practices, they may have certain short comings, but they are still an appreciable source of medicinal information. Lau et al, stated that, throughout the SARS outbreak, 1063 volunteers covering 926 hospital workers and 37 laboratory technicians employed in high-risk environments were on this herbal formulation- *Sang Ju Yin* plus *Yu Ping Feng San* and interestingly, in comparison to 0.4% of infection among the control group, nobody was infected. Moreover, the evidence stated that *Sang Ju Yin* plus *Yu PingFeng San* could potentially alter T cells to augment host protection capability[59,60]. But Liu and his colleagues established other sets of literature data suggesting no advantage of adjuvant treatment with herbal medicines observed in terms of mortality [61]. Owing to these outcomes, systematic clinical trials employing potential THM for the treatment of COVID-19 should be essentially conducted.

7.1 COVID-19 Management through Clinical Trials of Herbal Medicines

Herbal traditional medicines have been utilized in China since the outbreak of the COVID-19 episode. Without a doubt, these customary medications showed promising results in 90% of the 214 patients treated [70]. Comparative promising outcomes were accounted for in Zhejiang Province – China. Chinese customary meds known as ShuFengJie Du and Lianhuaqingwen have been prescribed because of their showed adequacy against previous influenza A (H1N1) or SARS-CoV-1. A gathering of specialists from the Zhongnan Hospital of Wuhan University remembered the utilization of conventional prescriptions for the rules for the treatment and anticipation of COVID-19. A few strategies utilizing restorative plants were suggested for the counteraction of COVID-19. Additionally, to treat the sickness, the specialists suggested the utilization of various natural blends as indicated by the illness stage [71].

CSM is greatly appreciated by China in its fight to overcome and eliminate SARS-CoV-2. For instance, the Health Commission of china has authenticated in 26 capitals that, CSM must be employed along with allopathic drugs in the treatment. China's National Health Commission on February 17, 2020, recounted 60,107 confirmed cases (85% of confirmed cases) were treated with CSM [72]. According to another clinical trial report on 1st March 2020, they were a total of 303 uncompleted clinical trials trying to assess the effectiveness and safety of

Table 2. Traditional medicinal system around the world

Tradition System of Medicine	Origin
A Chinese system of Medicine (CSM) [62]	China (2,200 years ago)
Ayurveda [63] and Unani medicine [64]	India (4000 BC–1500 BC)
Kampo (Japanese traditional medicine) [65]	In 5th/ 6thcentruryKampo was actually instigated from China through the Korean peninsula
Sasang constitutional medicine (SCM) Traditional Korean medicine (TKM), [66]	SCM is a division of Korean traditional medicine. In the mid-19th century, it was introduced for usage
Traditional Aboriginal medicine [67]	Australia
Traditional medicine in Africa [68]	Africa
Russian herbal medicine [69]	Russia , 10th century

treatments on patients. Clinical trials on the use of CSM for therapy accounted for 16.5% (50/303trials), while 4.6 %(14/303 trials) studied the combined therapeutic effect of CSM with allopathic medicine. The self-prepared herbal formulations such as *Xin Guan-1 Formula*, *Xin Guan-2 Formula,*and *Qing Yi-4* were examined which accounted for 7.3% (22/303 trials). Additionally, 4.6%(14/303) other trials were evaluated for commercially existing preparations such as *Tan Re Qing Injection* and *LianHua Qing Wen Capsule* are studied (Table 2). To date, 6 Guidelines editions of Diagnosis and Treatment for this decease have been published by NHC [16]. Depending on the phase of the disease and symptom diversity, THM has been recommended for the COVID-19 therapy from the fourth edition [73]. The latest edition states that the patients during the period of medical observation CSM are recommended with these Chinese herbal products as a preventative measure (14):*Lian Hua Qing Wen Capsule, Huo Xiang Zheng Qi Shui*, S*hu Feng Jie Du Capsule* and *Jin Hua Qing Gan Granule*. During the treatment period, *Tan Re Qing Injection, Qing Fei Pai Du Tang*, *Xi Yan Ping Injection*, *Re Du Ning Injection, Xing Nao Jing Injection, Xue Bi Jing injection*, and further Chinese herbal formulations should be selected [72]. Also, in a serious condition of the patients, *Shen Mai Injection, Sheng Mai Injection, Shen Fu Injection*, *An Gong Niu Huang,*and *Pill Su He Xiang Pill* have to be administered (Table 5). Luo, et al. after critical assessment of the frequency of usage in 23 provinces established that *Astragalus membranaceus, Lonicerae Japonicae Flos,Glycyrrhiza euralensis, Rhizoma Atractylodis Macrocephalae, Saposhnikoviaedivaricata, Fructus forsythia, Atractylodis Rhizoma, Radix platycodonis, Cyrtomium fortune J. Sm*, and *Agastacherugosa* were most often used Chinese herbs in the COVID-19 therapy [74]. Xu, et al., have reported that *Yu Ping Feng* and *Astragalusmembranaceus* were employed in the 13 deterrence programs (in Beijing, Tianjin, et al.) for "reinforcing vital *qi*", the terminology used in that is like enhancing host protection capacity. *Scrophularianingpoensis* and *Ophiopogon japonicas* were regularly used herbs for "nourishing *yin*" in northern China, while *Atractylodis Rhizoma, Agastacherugosa* along with other Chinese herbal medicine with "aromatic dehumidification" property was frequently employed in southern China [75] (Table 6). Up to 5th February 2020, 214 infected cases were treated by administering with *Qing Fei Pai Du Tang* in Shanxi, Hebei, and Heilongjiang Shaanxi Provinces with success rate ≥ 90%. The signs and symptoms among the majority of cases (≥60%) were significantly improved, while the infection was stabilized among 30% of cases [76]. Later, 701 reported cases were administered with *Qing Fei Pai Du Tang* in ten provinces of China. At the end of the treatment 130 patients (18.5%) were cured. 51 patients (7.27%) with characteristic symptoms such as fever and cough were disappeared. 268 patients (38.2%) showed improvement and 212 patients (30.2%), condition was stabilized [62]. *LianHua Qing Wen Capsule* was retrospectively analyzed for its clinical effectiveness in the healing of confirmed and suspected cases by Yao, *et al*. and Lu, *et al.,*. The results showed that the herbal formulation could noticeably relieve symptoms such as cough and fever prompting early recovery [77,78]. But there is no data on its safety and clinical effectiveness and the same needs to assessed. It was also noted that this preparation was not suggested by HNC's Guideline [79]. Receptor ACE2 is the primary route for entering the body for SARS-CoV and SARS-CoV-2 [80]. Hypothetically, blockade of this ACE2 can prevent the infection of SARS-CoV-2. Molecular docking experiment by Chen and Du found that CSM derived compounds, made up of scutellarin, baicalin, nicotinamideglycyrrhizin, and hesperetin, could interact with ACE2 [81]. Hence, these compounds, as well as formulations containing these herbal actives, might potentially inhibit the infection of SARS-CoV-2.

8. IDENTIFICATION OF ANTI-COVID-19 MOIETIES FROM HERBAL MEDICINE

Herbal medicines employed in CSM can be exploited as potential drug candidates for COVID-19 therapy. In the last few decades research is been done to identify therapeutic moieties having activity against various viruses and in particular the corona family. Additionally, the phytoconstituents responsible for the activity in the herbs were also studied (Table 3). Similarity in SARS-CoV and SARS-CoV-2, prompt us to study the potential use of natural herbs that have a positive therapeutic effect on SARS-CoV for their potential effects on SARS-CoV-2.The 3- chymotrypsin-like protease (3CLpro) is very much important for viral replication which indicates itself as a potential drug target for the drug development for SARS-CoV and SARS-CoV-2.

Table 3. Current status of clinical trials for COVID-19 management

Drug	No. Enrolled	NCT NO.	Phase	Study Design	Outcome	Status
-	400	NCT04292327	-	Observational and Retrospective	Morality, The time interval of Nucleic acid detection become negative	Active, Not yet recruiting
CSM Prescription	340	NCT04306497	-	Cohort	The relief rate of main symptoms. Virus antigen-negative conversion rate	Recruiting
CSM Prescription	50	NCT04323332	III	Non-Randomized	Length of hospital stay (days) Duration (days) of supplemental oxygenation CT imaging changes	Not yet recruiting
T89	120	NCT04285190	-	Randomized	The degree of remission of symptoms of patients, including fatigue, nausea, vomiting, chest tightness, shortness of breath, etc.	Not yet recruiting
YinHuQingWenDecoction	300	NCT04278963	II,III	Randomized	Viral load curve has shown COVID-19 viral load reduction in specimen of upper respiratory tract	

Table 4. Traditional uses of the medicinal species and mixtures with possible anti-SARS-CoV-2 effects

S.No.	Herbal drug	Biological source and Family	Whole extract/Active Principle	Therapeutic target or IC 50 value (µg/ml)	Ref
	Chinese *Rhubarb* extracts	The dried rhizome of *Rheumpalmatum Linn*. and *Rheum Officinale*Baillon Family: *Polygonaceae.*	Water extract	13.76±0.03	[82]
	Houttuyniacordata	A perennial herb, member of the genus Houttuynia Family:*Saururaceae*	Water extract	NA	[83,84]
	litchi seeds	Family*: Sapindaceae*	Flavonoids	NA	[85]
	Isatisindigotica	A flowering plant Family: *Brassicaceae*	Beta-sitosterol (root extract)	IC50: 1210µM	[86]
	Sinigrin	Family:*Brassicaceae*	Sinigrin	IC50: 217µM	
	Indigo			IC50: 752µM	
	Aloe-emodin	Family:*Asphodelaceae*	Aloe-emodin	IC50: 366 µM	
	Hesperetin	Naturally occurring flavanone-glycoside found in many citrus fruits.	4'-methoxy derivative of eriodictyol, a flavanone.	IC50:8.3 µM	
	Quercetin	A plant pigment	Flavanid	IC50: 73µM	[87]
	Epigallocatechingallate	A polyphenol found in tea	Epigallocatechingallate	IC50: 73µM	
	Gallocatechingallate	A polyphenol found in tea	Gallocatechingallate	IC50: 47 µM	
	Herbacetin	A flavonoid found in flaxseed	Flavonol	SARS 3CLpro activity	[88]
	Rhoifolin	isolated from plant Rhus succedanea	Rhoifolin		
	Pectolinarin	Isolated product from Cirsium isolate	Pectolinarin		
	Herbacetin	Isolated from flaxseed hulls	Herbacetin		
	Isobavaschalcone	Chinese herbal formulation			
	Quercetin 3-β-D-glucoside	A glucoside	Quercetin 3-β-D-glucoside		
	Helichrysetin			InhibitsMERS-CoV 3CL protease enzymatic activity	[89]
	Scutellarein	A flavone that can be found in Scutellarialateriflora	Scutellarein	Potently inhibited the nsP13 (SARS-CoV helicase protein) by altering the ATPase activity	[90]
	Myricetin	A flavonoid of polyphenolic compounds			
	Kang Du Bu Fei Tang	Chinese herbal formulation		IC50:471.3 µg/mL	[83,84]

S.No.	Herbal drug	Biological source and Family	Whole extract/Active Principle	Therapeutic target or IC 50 value (µg/ml)	Ref
	Sinomeniumacutum	Chinese herbal formulation		IC50:198.6 µg/mL	
	CoriolusVersicolor	Polypore mushroom Family:*Polyporaceae*	Whole extract as a component of Chinese herbal formulation	IC50:108.4 µg/mL	
	Ganodermalucidum	Family:*Ganodermataceae*	Whole extract as a component of Chinese herbal formulation	IC50:41.9 µg/mL	
	Panax ginseng	Family:*Araliaceae*	Whole extract as a component of Chinese herbal formulation	Blocked SARS-CoV replication at therapeutic concentrations	[91]
	Rauwolfiaserpentina	Flower in the milkweed Family: *Apocynaceae*	Whole extract as a component of Chinese herbal formulation		
	Lonicera japonica	Family:*Caprifoliaceae*	Whole extract as a component of Chinese herbal formulation		
	Emodin	Isolated from rhubarb Family:*Polygonaceae*	A component of Chinese herbal formulation		[92]
	Baicalin	Flavone glycoside	A component of Chinese herbal formulation		[93]
	Nicotianamine	It is synthesized by the enzyme nicotianamine synthase	A component of Chinese herbal formulation		[94]
	Scutellarin	A Flavanoid found in Scutellariabarbata and S. lateriflora Family:*Lamiaceae*	A component of Chinese herbal formulation		[95]
	Veronicalinariifolia	No label identified	Whole extract as a component of Chinese herbal formulation	Blocked the interaction of ACE2 and SARS-CoV S-protein	[96]
	Juglanin	A flavonol found in Polygonumaviculare.	A component of Chinese herbal formulation		[97]

S.No.	Herbal drug	Biological source and Family	Whole extract/Active Principle	Therapeutic target or IC 50 value (µg/ml)	Ref
	Saikosaponins	A flavonoid from Bupleurumfalcatum Family:*Apiaceae*	A component of Chinese herbal formulation		
	Glycyrrhizin	A sweet-tasting constituent from glychraizaglabra Family: *Fabaceae*	A component of Chinese herbal formulation		[98]
	*Toonasinensis*Roem	Family: *Meliaceae*	A component of Chinese herbal formulation		[99]
	*Loniceraejaponicae*Flos,	Family:*Caprifoliaceae*	Whole extract as a component of Chinese herbal formulation	Inhibit SARS-CoV-2	[100]
	Scutellariae radix	Is a root Family:*Lamiaceae*	Whole extract as a component of Chinese herbal formulation		
	Fructus Forsythia,	Dried fruit of *Forsythia suspense* Family:*Oleaceae*	Whole extract as a component of Chinese herbal formulation		
	Indirubin	A constituent of the Chinese herbal medicine "Qing-Dai,"	A component of Chinese herbal formulation	Strong antiviral and Immunomodulatory effects	[101]
	Lycoris radiate	Is a plant in the amaryllis Family:*Amaryllidaceae*	Whole extract as a component of Chinese herbal formulation	Anti-HCoV-229E activity.	[102]
	Artemisiaannua	Family:*Asteraceae*	Whole extract as a component of Chinese herbal formulation		
	Pyrrosia lingua	Family:*Polypodiaceae*	Whole extract as a component of Chinese herbal formulation		
	Lindera aggregate	Family:*Lauraceae*	Whole extract as a component of Chinese herbal formulation		
	Calophyllumblanco	Family:*Caryophyllaceae*	Whole extract as a component of Chinese herbal formulation		

9. NATURAL COMPOUND THERAPEUTICS AS ACE 2-BLOCKERS (Fig. 6)

The coronavirus encodes more than a dozen of proteins, some of which are essential to viral entry and replication. Among these proteins, the most well-studied are **papain-like protease (PLpro), 3C-like protease (3CLpro) and spike protein**. theseproteins make attractive targets for drug development.

The entrance of the SARS-CoV-2 genome into the host cells happens because of the SARS-CoV-2 spike protein binding to receptors [103]. By utilizing phylogenetic examination and basic site of ACE 2 structure, various animals, for example, feline, pigeon, and sheep were anticipated to be transmitters for SARS-CoV-2 [104]. Hoffmann et al. exhibited that the ACE2 receptor is utilized by SARS-CoV-2 to enter human cells [105].

Studies have indicated that TMPRSS2 inhibitors may be a promising alternative against SARS-CoV-2. TMPRSS2 is a transmembrane serine protease that separates both ACE2 and the S protein. Ortega et al. [106] used silico approaches suggested association between changes in SARS-CoV-2 Spike protein and ACE2 receptor. They displayed similarities of SARS-CoV-2 spike protein towards human ACE2 in comparison to that of the Bat-CoV spike and ACE2. This assessment concluded that the ACE2 receptor may be the key "connect" used by SARS-CoV-2 to contaminate people. Chen et al. [107] confirmed that not withstanding the way that SARS-CoV and SARS-CoV-2 RBD of spike glycoprotein had 72% of essential similarities, SARS-CoV-2 RBD indicated higher correspondence with ACE2. ACE2 inhibitors are thought to alter RBD restricting site and thus block SARS-CoV-2 disease. Additionally, Wrapp et al. [108] found that the SARS-CoV-2 spike demonstrated a higher affection to ACE2 than SARS-CoV. Adedeji et al. [109] indicated that early blocking of SARS-CoV with ACE2 inhibitors was one of the segments used by SARS drugs. It has been showed up in three progressing assessments on COVID-19 that hypertension and diabetes mellitus triggers the danger of COVID-19 infection, inspite of utilizing ACE2 inhibitors. ACE2 inhibitors, angiotensin II type-I receptor blockers, and ibuprofen lead to ACE2 upregulation which legitimizes the urgent need to utilize as well as distinguish elective ACE2 blockers. Along these lines, therapeutic plants could be considered as alternative medicine to exhibit anti SARS-CoV-2.

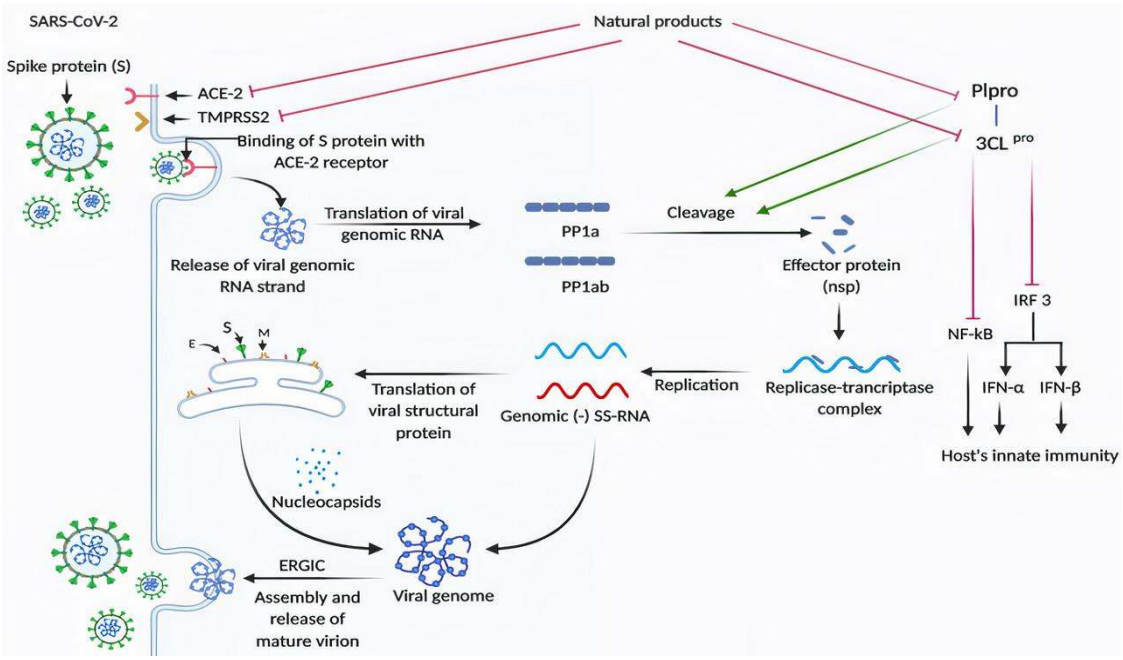

Fig. 6. Mechanism of anti SARS cov2 from natural products

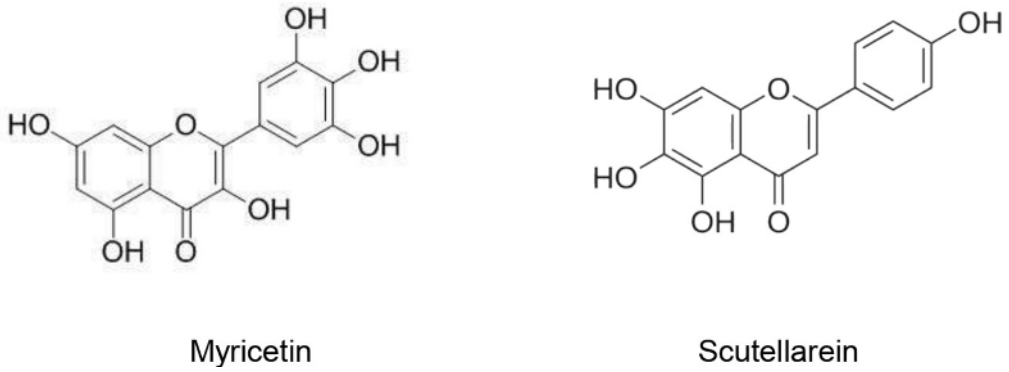

Fig. 7. structure of anti SARS CoV-2 drugs

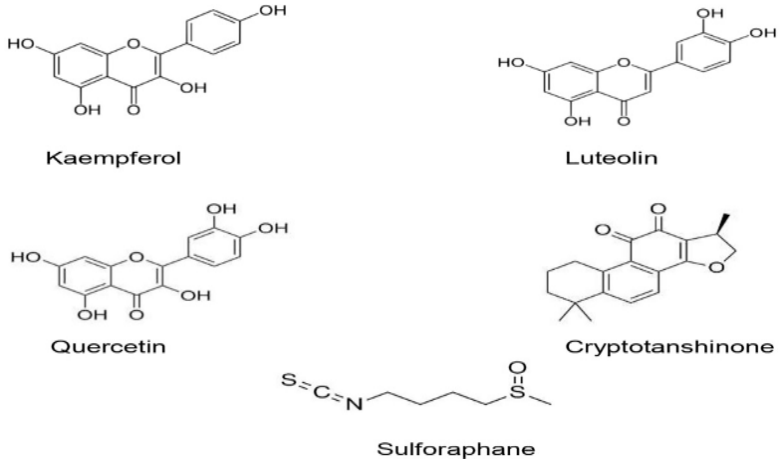

Fig. 8. Supression of TMPRSS2 by flavonoids

SARS-CoV-2 related proteins are areas of interest as targets for antiviral drugs.SARS-CoV helicase still forms the target of novel antiviral medications. 64 regular particles from 15 therapeutic plant species were assessed with respect to their inhibitory movement of SARS-CoV helicase. Myricetin and scutellarein (Fig. 1) fundamentally supressed the SARS-CoV helicase movement. At 10 μM, myricetin (IC50 = 2.71 ± 0.19 μM) and scutellarein (IC50 = 0.86 ± 0.48 μM) had the option to hinder 90% of the ATPase movement of the SARS-CoV helicase. Appropriately, Myricetin and scutellarein were recommended to be promising alternative for anti SARS drugs (Fig. 7) [110].

9.1 Supression of TMPRSS2 by Natural Products

Recently, Hoffmann et al. [105] reported that SARS-CoV-2 could also utilize TMPRSS2 for binding to S protein. TMPRSS2 is a transmembrane serine protease that cleaves both ACE2 and the S protein. After the association between the S spike protein (SARS-CoV-2) and the ACE2 (host cell), the complex is severed by the TMPRSS2 to encourage viral passage [111]. Matsuyama et al. [112] found that a significant TMPRSS2 articulation in cells makes them vulnerable to SARS-CoV-2.

Researchers have reported that the use of TMPRSS2 inhibitors could be a treatment altenative against SARS-CoV-2.

Since SARS-CoV-2 viral entry is dependent ACE2 receptor, the latter should be attached to the TMPRSS, alternatives to suppress the TMPRSS2 expression in human cells could represent a promising therapeutic or preventive approach [113]. It has been demonstrated that kaempferol had the option to inactivate TMPRSS2 articulation by 49.14 and 79.48% at 5 and 15 μM, (Da et al., 2019). Moreover,

sulforaphane (an isothiocyanate) was found to inhibit TMPRSS2 articulation via translocation of the Nrf2 (atomic factor (erythroid-inferred 2)- like 2) [114]. Mamouni et al. (2018) found that flavonoids including luteolin, quercetin, and kaempferol inhibited TMPRSS2 articulation (Fig. 8). In spite of positive and synergisitc effects attributed to the three flavonoids, at low concentrations, the efficacy and safety of these compounds in COVID-19 patients is still unclear [115].

9.2 Natural Products Targeting the Papain-Like Proteinase (Plpro)

PLpro is one of the nonstructural proteins within the SARS-CoV-2 genome. Also, PLpro has been discovered to be an antagonist of the host's natural protection.PLpro was shown to focus on the interferon creation by obstructing the IRF3 phosphorylation, dimerization, and atomic movement and NF-κBsignalling pathways (by forestalling IκBα debasement) [116]. These impacts were appeared to happen in Toll-like receptor 3 and retinoic acid-inducible gene 1 pathways. Studies shown that SARS-CoVPLpro represses the TLR7 pathway by means of inactivation of TRAF3/6-TBK1-IRF3/NF-κB/AP1 signalling pathways (Fig. 9) [117].

Recently, Arya et al. (2020) screened FDA-affirmed drugs for their in silico inhibitory capability of PLpro. They showed that sixteen FDA-endorsed drugs (Biltricide, Cinacalcet, Procainamide, Terbinafine, Pethidine, Labetalol, Tetrahydrozoline, Ticlopidine, Ethoheptazine, Levamisole, Amitriptyline, Naphazoline, Formoterol, Benzylpenicillin, Chloroquine, and Chlorothiazide) displayed significant affinity to SARS-CoV-2 proposing their conceivable adequacy as hostile to SARS-CoV-2 [118]. Some of the compounds which exhibits anti Plpro effect has also been identified (Fig. 9).

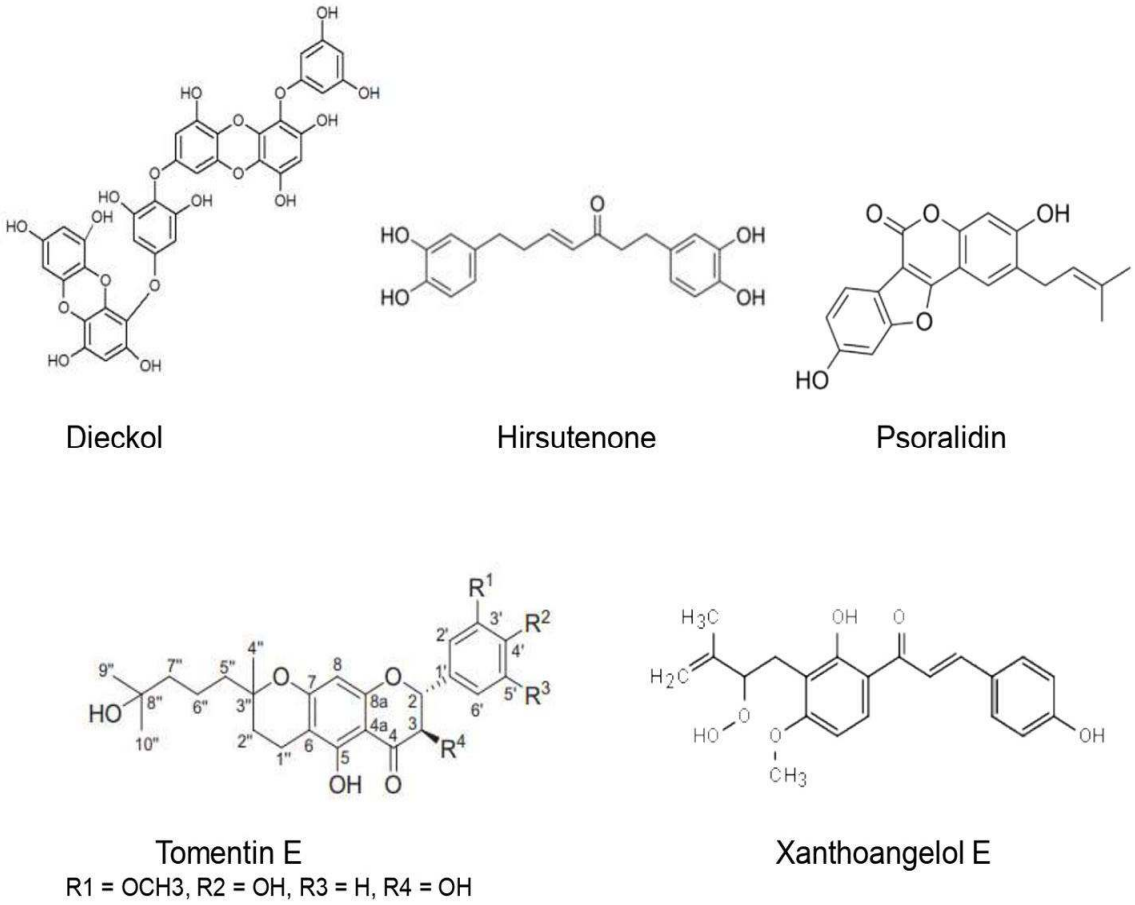

Fig. 9. Natural compounds as inhibitors of PLpro.

9.2.1 PLpro inhibitory impacts of *cinnamic amides*

Song et al. (2014) concluded that six cinnamic amides (N-trans-Feruloyloctopamine, N-trans-Coumaroyltyramine, N-trans-Caffeoyltryamine, Terrestrimine, N-trans-Feruloyltryamine, and Terrestriamide) removed from Tribulusterrestris L had affinitiy to SARS-CoVPLpro in a dose dependent manner. PLpro inhibitory IC50 of these mixes were discovered to be 15.8–70.1 µM. Terrestrimine [(E)- N-(1-hydroxy-2-(4-hydroxyphenyl)- 2-oxoethyl)- 3-(4-hydroxy-3-methoxypheny) acrylamide] indicated antagonistic action of SARS-CoVPLpro with an IC50 of 15.8 ± 0.6 µM. The presence of a polar substituent (ketone or liquor) on the methylene gatherings (C8'and C7') was indicated to exhibit inhibitory action [119].

9.2.2 Anti PLpro activity of Flavonoids From *Cullen corylifolium* (L.) Medik

Cullen corylifolium (L.) Medik. Seeds extracted from ethanol, indicated a significant inhibitory activity of SARS-CoVPLpro with an IC50 of 15 µg/ml. Besides, six flavonoids present in the concentrate (Bavachinin, neobavaisoflavone, isobavachalcone,40 – O-methylbavachalcone, psoralidin, and corylifol A) supressed SARS-CoVPLpro action in a dose dependent manner with IC50 assessed to be 4.2–38.4 µM. The most elevated inhibitory impact was applied by psoralidin (IC50 = 4.2 ± 1.0 µM) and isobavachalcone (IC50 = 7.3 ± 0.8 µM) [120].

Five new geranylated flavonones, tomentinA, tomentin B, tomentin C, tomentin D, tomentin E from the ethanolic concentrate of Paulownia tomentosa (Thunb.) Steud. organic products as were also promising as demonstrated by Cho et al. [121] brought about critical restraint of SARS-CoVPLpro in a dose dependent manner with IC50 of 5.0 and 14.4 µM. Tomentin E displayed the most noteworthy inhibitory impact with an IC50 of 5.0 ± 0.06 µM. It has been discovered that atoms with 3,4-dihydro-2H-pyran moiety had higher hindrance.

10. NATURAL PRODUCTS TARGETING THE CHYMOTRYPSIN-LIKE PROTEASE [3CL(PRO)]

3CL(pro) forms a part of 16 nonstructural proteins of the SARS-CoV-2. 3CL(pro) is considered a potential therapeutic target for anti-COVID-19 drugs [122] as it contributes towards SARS-CoV-2 replication process. Some of the natural compounds also exhibited anti 3CL(PRO) effect (Fig. 10).

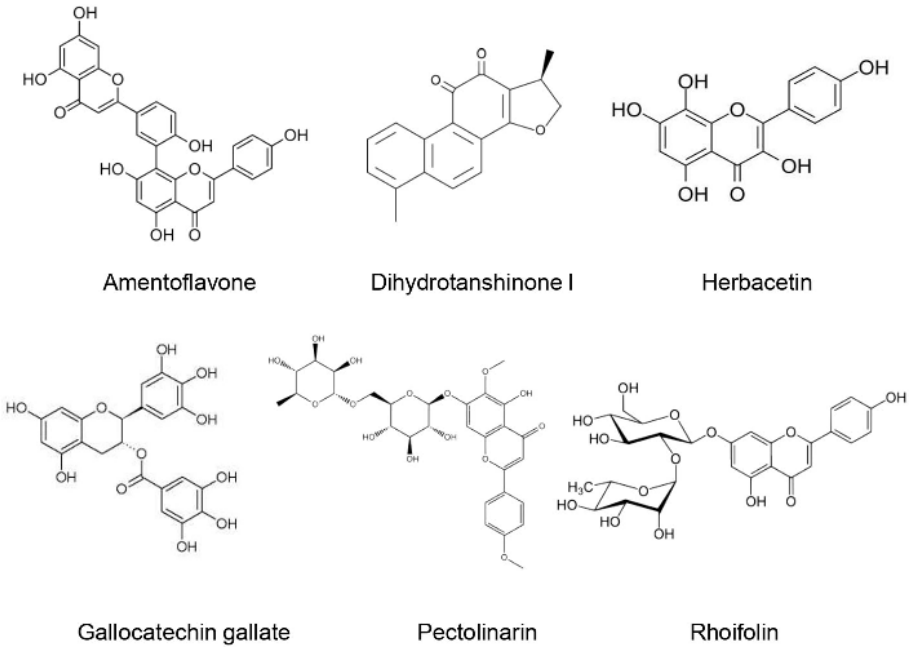

Fig. 10. Anti SARS-CoV-3CL(pro) mediators from natural products

10.1 Inhibitory Potential of Alkylated Chalcones as anti SARS-CoV-3CL(pro)

Inhibitory potential toward of alkylated chalcones and coumarins extracted from Angelica keiskei (Miq.) Koidz was explored utilizing a fluorescence resonance energy transfer (FRET) method. Except for coumarins, alkylated chalcones showed promising inhibitory impacts in a dose dependent pattern. IC50 ran from 11.4 ± 1.4 to 129.8 ± 10.3 μM. Also, xanthoangelol E (Figure 5) was discovered to be the most powerful SARS-CoV-3CL(pro) inhibitor. Motor investigations demonstrated that both alkylated chalcones were serious inhibitors. Since xanthoangelol E was additionally found to hinder SARS-CoV-PLpro it could be a promising competitor in the remedial methodology against COVID-19[123].

10.1.1 Inhibitory potential of Phlorotannins From *Ecklonia cava* (Algae)as anti SARS-CoV-3CL(pro)

From ethanolic concentrate from earthy colored Alga Ecklonia cava nine phlorotannins were isolated by Park et al. [124]. These phlorotannins were investigated for their inhibitory impacts towards SARS-CoV-3CL(pro) via without cell based assay. Eight phlorotannins (triphloretolAn, eckol, dioxinodehydroeckol, 2-phloroeckol, 7-phloroeckol, fucodiphloroethol G, dieckol, and phlorofucofuroeckol A) were demonstrated to be serious inhibitors of SARS-CoV-3CL(pro) in a dose dependent manner. IC50 went from 2.7 ± 0.6 (dieckol) to 164.7 ± 10.8 μM (triphloretol A). Besides, six phlorotannins (dioxinodehydroeckol, 2-phloroeckol, 7-phloroeckol, fucodiphloroethol G, dieckol, and phlorofucofuroeckol A) brought about a critical micromolar dose dependent portion inhibition of SARS-CoV-3CL(pro) cis-cleavage action. It was further supported by Molecular docking studies which showcased that diekcol had the most reduced restricting vitality (11.51 kcal/mol) towards SARS-CoV-3CL(pro). Diekcol was appeared to frame solid H bonds to the reactant dyad (Cys145 and His41). The bioavailability of phlorotannins with respect to their utilization is as yet a considerable constraint to approve their convenience. [125]. Also, their configuration with assorted variety of basic linkages and the distinctive auxiliary and conformational isomers for a similar sub-atomic weight, and the absence of clear connection between their structure and bioactivity might be another restriction to their clinical use [55].

10.1.2 Inhibitory potential of Tanshinones From *Salvia miltiorrhiza* Bunge as anti SARS-CoV-3CL(pro)

The inhibitory capability of Salvia miltiorrhiza Bunge towards SARS-CoV-3CL(pro) was evaluated by Park O. K. et al. (2012). It was concluded that ethanolic extricate Salvia miltiorrhiza Bunge (30 μg/ml) could cause 60% hindrance of SARS-CoV-3CL(pro). Moreover, they exhibited that six tanshinones of the plant (lipophilic portion) caused hindrance of SARS-CoV-3CL(pro) in a percentage though not in a time dependent manner. IC50 was assessed at 14.4–89.1 μM. Dihydrotanshinone I showed the most significant inhibitory impact with an IC50 of 14.4 ± 0.7 μM. With respect to the dynamic system of SARS-CoV-3CL(pro) hindrance, Salvia miltiorrhiza Bunge tanshinones were discovered to be noncompetitive inhibitors [126].

10.1.3 Inhibitory potential of BiflavonoidsFrom *Torreyanucifera* (L.) Siebold & Zucc. as anti SARS-CoV-3CL(pro)

Ethanol concentrate of Torreyanucifera (L.) Siebold and Zucc. leaves revealed four biflavonoids (amentoflavone, bilobetin, ginkgetin, and sciadopitysin) and were assessed for their anti SARS-CoV-3CL(pro) by utilizing a FRET strategy. All biflavonoids displayed a marked inhibitory impact of SARS-CoV-3CL(pro) with IC50 of 8.3–72.3 μM. The mechanism of action was because of eight diterpenoids disconnected from the T. nucifera extricate (IC50: 49.6–283.5 μM). Amento flavone showed most significant inhibitory activity with least IC50 (8.3 ± 1.2 μM). Additionally, its inhibitory potential was a higher priority than that of apigenin (IC50 = 280.8 ± 21.4 μM), quercetin (IC50 = 23.8 ± 1.9 μM) and luteolin (IC50 = 20.0 ± 2.2 μM). Atomic docking exhibited that amento flavone indicated a decent liking with SARS-CoV-3CL(pro) and framed solid hydrogen bonds. An apigenin moiety at position C-30 of flavones was recommended to be liable for a superior inhibitory impact [127].

11. POSSIBLE DOSAGE FORMS TO TARGET COVID-19

The action of herbal medicines relies on the complete utility of the variability of dynamic components, as all the elements offer synergists action and therefore improve the healing rate [128]. Every function plays an essential role which is related to each other that possesses the

insoluble character which is resulting in lesser bioavailability and increases systematic approval necessitating repetitive administration or higher dose, which lets the drug be a minor candidate for the use of treatment [129]. Nano-dosage forms (Polymeric Nanoparticles) are developed in Phyto-formulation research that includes Liposome, Solid Liquid Nanoparticles (SLNs), Proliposomes which have several advantages for herbal drugs that are the improvement of bioavailability and solubility, improvement of pharmacological action, safeguarding from venomousness, improving tissue macrophages dissemination, improvement of constancy, increased physical-chemical stability there preventing easy degradation and sustained delivery, etc. [130]. For improving the activity and overpowering issues that are connected with plant medicines, Nano drug delivery systems (NDDSs) of natural drugs have a great potential in future drug therapy. In the traditional medicine system, integration of the nano-carries as an NDDS that is essential to conflict more chronic diseases such as cancer, asthma, diabetes, and so on [131].

12. FUTURE PERSPECTIVES AND CONCLUSION

Globally, numerous herbal medicines of Indian, China, Western and Arabic origin are marketed. These medicines with unique insights carry the experience of thousands of years in preventing, controlling the prevalence of wide-ranging diseases, and enhancing the immunity of the body. The crucial key in COVID-19 treatment is early intervention to curtail disease progression, shorten the course of the disease and improve the cure rate thereby decreasing the overall mortality rate using herbal medicine. The main reason behind the effectiveness of these herbal medicines is not only to prevent the virus growth but also to regulate and enhance one's immune system of the body that alters the various inflammatory responses there by promoting the early repair of the body. More in-depth research needs to be done on CSM that have definite curative effects to understand their mechanism of action for enhanced effective utilization in the treatment of the disease. Recently, some studies have been conducted on these aspects of herbal medications against COVID-19 [132-135].

The herbal drugs have several drawbacks such as poor bioavailability, instability, low solubility, low oral absorption, and unpredictable toxicity. Growth of herbal therapies in several institutes that have been carried out at basic and clinical trial levels. Further research should be directed for developing the concept of herbal nanoparticles for COVID-19 delivery in suitable animal models for studying the entire viral life cycle.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

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CONFLICT OF INTEREST

The authors assert no conflict of interest.

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