Journal of the Indian Chemical Society 99 (2022) 100244

Contents lists available at ScienceDirect

Journal of the Indian Chemical Society

journal homepage: www.editorialmanager.com/JINCS/default.aspx

Brief survey on phytochemicals to prevent COVID-19

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ARTICLE INFO

Keywords:
Phytochemical
Molecular docking
COVID-19
Traditional plant

ABSTRACT

Background: The recent pandemic by COVID-19 is a global threat to human health. The disease is caused by SARS-CoV-2 and the infection rate is increased more quickly than MERS and SARS as their rapid adaptation to varied climatic conditions through rapid mutations. It becomes more severe due to the lack of proper therapeutic drugs, insufficient diagnostic tool, scarcity of appropriate drug, life supporting medical facility and mostly lack of awareness. Therefore, preventive measure is one of the important strategies to control. In this context, herbal medicinal plants received a noticeable attention to treat COVID-19 in Indian subcontinent. Here, 44 Indian traditional plants have been discussed with their novel phytochemicals that prevent the novel corona virus. The basic of SARS-CoV-2, their common way of transmission including their effect on immune and nervous system have been discussed. We have analysed their mechanism of action against COVID-19 following *in-silico* analysis. Their probable mechanism and therapeutic approaches behind the activity of phytochemicals to stimulate immune response as well as inhibition of viral multiplication discussed rationally. Thus, mixtures of active secondary metabolites/phytochemicals are the only choice to prevent the disease in countries where vaccination will take long time due to overcrowded population density.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are causative agent of COVID-19, which create global pandemic situation since December 2019. According to World Health Organization (WHO) corona virus are spread in most of the all countries in the world and occurred huge death during 2020 [1]. During corona infection many associated diseases viz. pneumonia, kidney infection, coughing, cardiac disease, central nervous system disease acute and chronic respiratory, enteric disease etc. attack to human body [2]. Although many anti-viral drugs should be used for the treatment of corona but any one is not yet been established appropriate therapy for the treatment of this disease [3]. Now a days in the field of medical science we cannot prepare life-saving medicines without chemicals. For that reason, we are suffering from other destructive side effects on human beings and ultimately disturb biodiversity and sustainable ecosystem of earth. (see Fig. 4)

In this fearful situation, we may be dependent on herbal medicines for corona treatment. Various types of tribal people are living in several states of India including Jharkhand, Sikkim, Nagaland, and Karnataka etc. Most of the time people also depend upon local herbs for the treatment of any infectious diseases [4]. After the creation of the world, life was originated and at the same time the nature has created FLORA i.e., vegetation kingdom/plant kingdom. The animals including human also being dependent upon natural vegetation. Not only India, many countries of world partially depend upon the herbal product for their live hoods [5]. Even many herbal based companies have been developed in India like Patanjali, Himalaya, Dabour etc. several years ago [6]. According to the famous books 'SUSHRUT SAMHITA' and 'CHARAK SAMHITA' ancient people used the different parts of plants to cure themselves from several infectious disease [7]. The very special books were the pioneers or pathfinders and we owe to them in the modern age also. We can also refer 'The Ramayana' in regarding medicinal plant. It is also a common picture today that some carnivorous animals like dog, mongoose etc. eat

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https://doi.org/10.1016/j.jics.2021.100244
Received 1 July 2021; Received in revised form 3 November 2021; Accepted 3 November 2021

Abbreviation

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
MS	Multiple sclerosis
HCoV	Human CoV
WHO	World Health Organisation
BSO	Black seed oil
MCMV	Murine cytomegalovirus
RSV	Respiratory syncytial virus
HCMV	Human cytomegalovirus
RRV	Ross River virus
HRV	Human rotavirus
HCoV	Human CoV
SARS-CoV	Severe acute respiratory syndrome coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus
HAA	Himalayan Amchi Association
RIPs	Ribosome-inactivating proteins

some plants or grass to cure diseases [8].

Previously reported that *Toona sinensis* leaves contain many important bioactive compounds such as gallic acid, methyl gallate, quercetin, kaempferol, rutin, stigmasterol glucoside, quercitrin, (+)-catechin, kaempferol-*d*-glucoside, (−)-epicatechin, stigmasterol, beta-itosterol, beta-sitosteryl-glucoside, phytol and toosendanin [9]. Among them quercetin is a powerful antiviral activity against HIV-luc/SARS [10]. Beside synthetic drug, herbal treatment plays front line defence against COVID -19 infection in many developed countries even china [11].

Ubiquitously expressed that since antiquity Licorice is one of the most widely used medicinal plants [12]. The use of the herbal plants can be traced back from ancient Assyrian, Egyptian, Chinese and Indian cultures that was appreciated by ancient Greeks and Romans. From ancient time Licorice was used in Arabic medicine during the Middle Ages, as documented by the Canoneof Ibn Sina (980–1037 AD), a summary of Hippocrates and Galen's medicine. This plant use in respiratory viral infections such as hoarse voice or dry cough and including hepatitis infection (Fiore et al., 2008). Beside traditional use a few numbers of herbs specifically interact with surface protein or viral intracellular enzymes which can promote viral infection [13]. The chamomile plant called *Anthemis hyalina*inhibit replication of virus [14].

During globalization civilized human face global worming including air pollution for mainly isolation from tree. At that time if we want to save our planet from several epidemics and also biodiversity with ecosystem for proper existence of human beings, so, we need to follow the path way of great, ancient Indian physician's Charak and Sushrut during focus on the herbal medicines in our daily life [15]. The main objective of this study is to investigate the effects of phytochemicals against COVID-19.

2. Corona virus

CoV's have four genera in Coronavirinae subfamily such as A-CoV (Alpha-CoV), B–CoV (Beta-CoV), D-CoV (Delta-CoV) and G-CoV (Gamma-CoV) [16]. Crown shaped spike surrounded protein envelope that responsible for mainly respiratory diseases but few enteric diseases in many hosts like cat, human, rodent and pig etc. [17]. Different genotypic character containing Human CoV (HCoV) act on humans, those are included HCoV-OC43, HCoV-229E, Middle East Respiratory Syndrome CoV (MERS-CoV) and Severe Acute Respiratory Syndrome CoV (SARS-CoV) [18]. COVID-19 viruses have 27–32 kb non segmented (+) ssRNA, which has diameter about 60–160 nm and genome RNA modified by 3′-poly A tail and 5′-cap [19]. The genome of COVID-19 virus able to code four structural proteins and more non-structural proteins included mainly on two ORFs (ORF1a and ORF1b) that will ultimately be fragmented into about 16 proteins [20]. The non-structural proteins are involved modification of host immune system and they can participate the viral genome replication [21]. Envelope (E), Nucleocapsid (N), membrane (M) and spike (S) proteins are synthesis from 3′-end of ORF whereas 5 ′-end of ORF encode sixteen non-structural proteins (nsp1 to nsp16). The M, E, and S protein present mainly envelope of corona virus, those are responsible for viral assembly pathogenesis and invade of target cells [22].

3. Common therapy for COVID -19

3.1. Traditional phytotherapy

Traditional allopathic treatments are not available to people everywhere all over the world. When human is a fight over COVID-19, it is either an expensive or insufficient infrastructure or absence of trained physicians even ratio of doctors and patient should be high [23]. Prior study reported that one physician was recruited per 30,000–100,000 people in Nepal. On the other hand, huge number of ethno-medicinal plants were available in higher in the mountains of Himalayas [24]. Herbal treatments which are easier than others mainly depend upon oral administration of living or dried plant extracts, or in tablets or capsules form. For that reason, mainly tribal people or rural are also fully or partially depends upon herbal medicine. The control of viral infection used by medicinal plant has largely historical and anecdotal evidence. Among several developing countries, some area of Indian people also depends upon Ayurvedic, flock medicine, Unani and Siddha, for control infectious disease including jaundice. Not only India, China also depends upon Ayurvedic plant beside traditional drug [25]. Several viral diseases controlled by many medicinal plant extract [26–28]. Thyagarajan et al. (1988, 1990) reported that dried milled *Phyllanthus amarus* was successful in clearing hepatitis B surface antigen (HBsAg) from blood positive carriers in Madras, India. The potential of medicinal herbs *Acacia nilotica, Boswellia carterii, Embeliaschimperi, Piper cubeba, Quercus infectoria, Trachyspermumammi* and *Syzygiumaromaticum*extracts were investigated in vitro and a significant inhibiting activity against HCV protease were reported [29]. Andrographis paniculate produce andrographolide which significantly arise $CD4^+$ lymphocyte level of HIV patient [30] (Fig. 1 & Table-1).

3.2. Route of administration of phytotherapy by traditional plants

The main route is ingestion of plant material that may be living or dried [11]. Several parts of plant were used for ethno-medicinal preparations that were fruit, bark, flower, leaf, stem, seed, root, rhizome, wood, and even whole plant. Several underground parts were frequently used, and this was recognized to availability of dominant bioactive compounds [31]. Bioactive plant product also applied as juice, oil, powder, latex, vegetable, paste, raw/fresh and resin. Plant juice (39.13%) was most commonly used, followed by decoction (13.04%), paste (10.86%), etc. The most popular forms of medicinal preparations in western Nepal are juice, decoction, paste, infusion, and powder [32] (Fig. 2 & Fig. 3).

4. Overview of traditional medicinal plants worldwide

Virus are randomly mutated with respect to environment and resistance towards antiviral agents [33]. In this critical situation viral diseases prevention is the global issue for safeguard of public health. Regardless lack of suitable immunization and appropriate medicine preparation are vital hindrance in our society [34]. At that time ethno-medicine is an alternative way to control viral infection. Although, the usage of medicinal herbs is an old-age practice but modern traditional therapeutics also stimulated by natural ethno-medicine for the control of many diseases. The medicinal plants have potent therapeutic value due to

Fig. 1. Traditional plants help to rescues from viral illness.

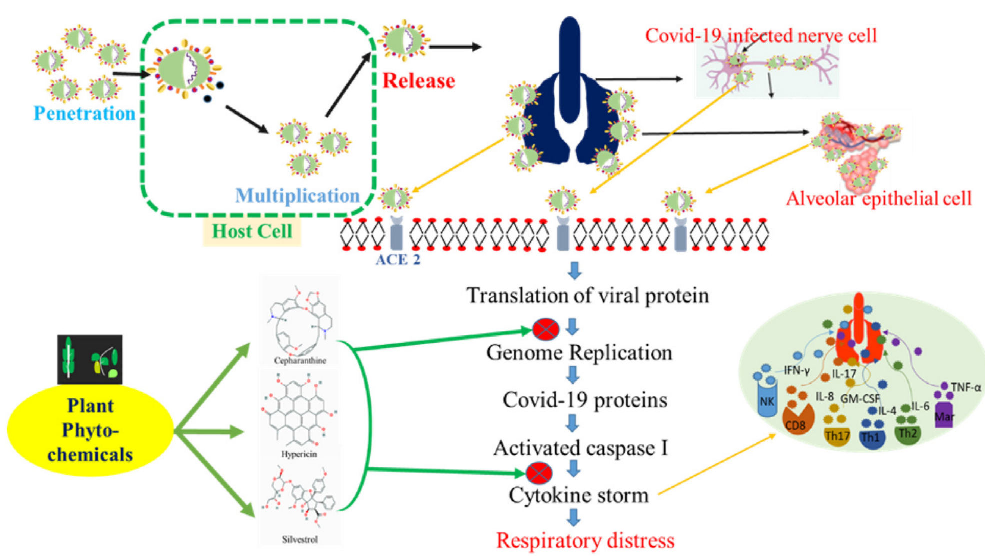

Fig. 2. Controlling path way of viral infection by phytochemicals.

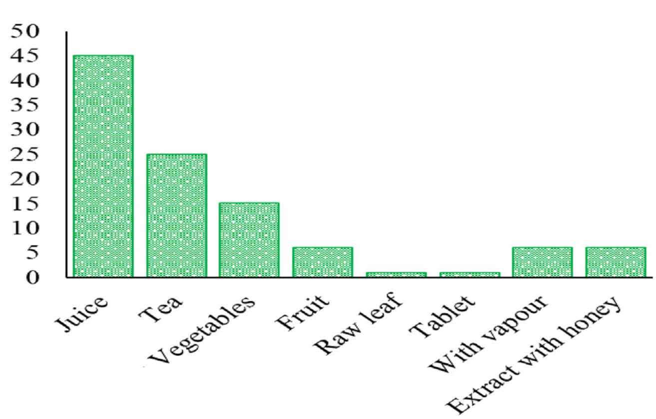

Fig. 3. Different modes of preparations use for therapies.

synthesis of several important bioactive metabolites include flavonoids and phenols (antioxidant), alkaloids (antibacterial, antimalarial, anti-parasite, analgesic and anti-allergenic) and terpenoids (anti -helminthic, anti-virus, anti-bacteria, anti-inflammatory, and antimalarial, anticancer) activity [35]. In this age of globalization, people are abandoning synthetic drugs as in ancient times and relying on trees for proper treatment. At present, various types of medicinal herb are available in tropical portion of earth those are rich in huge useful phyto-chemicals that have not only antimicrobials (namely, antiviral, antibacterial and antifungal) activity but also use in several purpose like cardiovascular treatment, neuronal treatment, diabetes etc. [36]. In this circumstance various researchers of Europe, Asia even America have given commitment to development of antiviral drug from their native traditional herbs. At present many herbal based companies were developed and they marked world basis through formulating new type of herbal based medicine. Medicinal plants have a several types of potent chemical constituents, which able to inhibit the replication and penetration of a group of RNA or DNA containing viruses [37]. Several bioactive

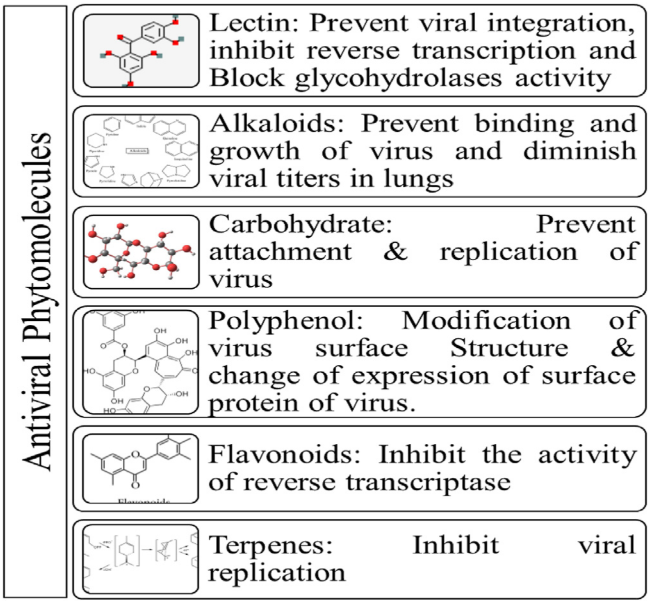

Fig. 4. Molecular mechanism of phytochemicals.

phytochemicals are strong common antiviral agent such as polysaccharides, alkaloids, lectins, proteins, terpenes, flavonoids, polyphenols, etc. but their mode of action are different. Among strong bioactive compound polysaccharides, prevent viral attachment and replication but lectins can block viral entry inside of host, alkaloid prevents viral growth, terpene (saponins) inhibits the replication of virus and flavonoids able to inhibit reverse transcriptase.

Previously reported that glycosides have antifungal and antibacterial activities; but saponins have anti-inflammatory, antiviral activities [35]. On the other hand, topotecan and irinotecan (derived from *Camptotheca acuminate*), taxol (derived from *Taxus brevifolia*), vinblastine and vincristine (derived from *Catharanthus roseus*), teniposide and etoposide (derived from *Podophyllum peltatum*), silymarin flavonoid (derived from *Silybum marianum*) curcumin (derived from *Curcuma longa*) prominently show anti-malignant tumour activity [38]. β-sisosterol and campesterol, have anti-viral activities those found in Aloe Vera plant. *Ocimum sanctum have* strong aesthetic value of Hindu religion and *used* as common antifungal and anti-bacterial plant for synthesis of bioactive phytochemicals (e.g., apigenin, citral, taxol and ursoli acid). *Berberis vulgaris* act as antimicrobial agent but they use for preparation of antidiabetic, hepatoprotective drug [39].

Lin et al., in 2014, reported that many herbal compound acts upon dengue virus, enterovirus 71 (EV71) human immunodeficiency virus (HIV), hepatitis C virus, hepatitis B virus, herpes simplex virus, measles virus, influenza virus, respiratory syncytial virus and even Corona virus [40]. *B*eside infectious diseases, genetic diseases also control by herbal treatment e.g., extract of *Withania somnifera* use to treatment of Alzheimer's and Parkinson's disease [41].

5. The common class of antiviral phytochemicals derived from traditional herbs

From many years several plant oil or extract have been recognized. The oil of *Melaleuca alternifolia* (tea plant) has extensive use as antimicrobial agent for the preparation of pharmaceutical cosmetics that use externally such as hand and face washes, vaginal creams, pimple gels, shampoos, foot powders, conditioners and different skin care products [42]. Beside antibacterial activity of *Melaleuca alternifolia* and eucalyptus oil exhibited high level of in-vitro antiviral activity against HSV-2 and HSV-1 virus [14]. *Santolina insularis* is an Italian medicinal plants which have antiviral effects on HSV-2 and HSV-1 that also prevent cell-to-cell transmission of viruses [43]. Whereas Sandalwood oil, derived from *Santalum album* (L.), which displayed a dose dependent effect of HSV-1 but not HSV-2 [44]. Black seed oil (BSO) from *Nigella sativa* has antiviral effect of murine cytomegalovirus (MCMV) [45]. The leaf extract of *Shepherdia argentea* inhibit reverse transcriptase enzyme of HIV-1 and polyphenols inhibit viral replication enzymes (e.g., RNA polymerase of influenza virus and Reverse transcriptase of HIV and enzymes poly (ADP-ribose) glycohydrolase [46].

Fruits extract of *Terminalia chebula* have the antiviral action by inhibiting the reverse-transcriptase on human immune deficiency virus-1, anti-herps simplex virus (HSV) and anti-cytomegalovirus (CMV), also chebulinic and chbulagic acids extract of *T. chebula* have the strong antiviral efficacy against HSV-2 [47]. Ethanolic extracts of *Aegle marmelos* fruits have the various antiviral effects such as in Ranikhet viral disease and also in human coxsackie viruses B1–B6 [47,48]. Homoharringtonine, an alkaloid compound derived from the *Cephalotoxus fortuei* which is used as an antiviral compound against the coronavirus, herpesvirus and rhabdovirus virus, also this compound able to inhibit the viral replication in Vero E6 cells of SARS-CoV-2 virus [49,50]. Hirsutenone, Xanthoangelol and Betulinic acid are active compounds extracted from the medicinal plants *Alnus japonica, Angelica keiskei* and *Betula pubescens* respectively which have the antiviral activity against the SARS-CoV by inhibiting the 3-chymotrypsin-like protease ($3CL^{pro}$) and papain-like protease (PL^{pro}) activity [51]. *Urtica dioica* agglutinin (UDA) an active compound derived from the *Urtica dioica* plant species which prevents the viral attachment to cell through binding with the glycoprotein of SARS-CoV virus [52]. Earlier study suggested that traditional Chinese medicinal (TCM) plans *Scutellaria baicalensis* Georgi, used globally as a broad spectrum antiviral compound, which also have the anti-Covid-19 $3CL^{pro}$ activity in in-vitro study [53]. Luteolin (flavonoid) and resveratrol (terpenoid) are extracted from *Veronica linariifolia* plants and strongly inhibited entry of coronavirus by interfering with spike protein and ACE2 receptor of SARS-CoV [53,54].

6. Antiviral activity of herbal medicine against selected viruses

Many traditional medicinal plants have been reported to have strong antiviral activity and some of them have already been used to treat animals and people who suffer from viral infection [55–58]. Research interests for antiviral agent development was started after the Second World War in Europe and in 1952 the Boots drug company at Nottingham, England, examined the action of 288 plants against influenza A virus in embryonated eggs. They found that 12 of them suppressed virus amplification [59]. During the last 25 years, there have been numerous broad-based screening programmes initiated in different parts of the globe to evaluate the antiviral activity of medicinal plants for in vitro and in vivo assays. Canadian researchers in the 1970s reported antiviral activities against herpes simplex virus (HSV), poliovirus type 1, coxsackievirus B5 and echovirus 7 from grape, apple, strawberry and other fruit juices [60,61]. One hundred British Columbian medicinal plants were screened for antiviral activity against seven viruses [62]. Twelve extracts were found to have antiviral activity at the concentrations tested. The extracts of *Rosa nutkana* and *Amelanchier alnifoliawere* very active against an enteric corona virus. A root extract of Potentilla arguta and a branch tip extract of *Sambucus racemosa* completely inhibited respiratory syncytial virus (RSV). An extract of *Ipomopsis aggregata* demonstrated good activity against parainfluenza virus type 3. A *Lomatiumdissectum* root extract completely inhibited the cytopathic effects of rotavirus. In addition to these, extracts prepared from *Cardamine angulata*, *Conocephalum conicum, Lysichiton americanum*, *Polypodium glycyrrhiza* and *Verbascum Thapsus* exhibited antiviral activity against herpes virus type 1. The extracts of 40 different plant species have been used in traditional medicine and were investigated for antiviral activity against a DNA virus, human cytomegalovirus (HCMV), and two RNA viruses, Ross River virus (RRV) and poliovirus type 1, at noncytotoxic concentrations [63]. The most active extracts were the aerial parts of *Pterocaulons phacelatum*

(Asteraceae) and roots of *Dianella longifoliavar. grandis* (Liliaceae), which inhibited poliovirus type 1 at concentration of 52 and 250 lg ml)1, respectively. The same authors concluded that the extracts of *Euphorbia australis* (Euphorbiaceae) and *Scaevola spinescens* (Goodeniaceae) were the most active against HCMV whilst, extracts of *Eremophilalatrobei* subsp. glabra (Myoporaceae) and *Pittosporum phylliraeoidesvar.* microcarpa (Pittosporaceae) exhibited antiviral activity against RRV. The human rotavirus (HRV), RSV and influenza A virus were susceptible to a liquid extract from *Eleutherococcussenticosus* roots. In contrast, the DNA viruses, adenovirus and HSV type 1 virus (HSV-1) were not inhibited by the same plant extract [64]. They concluded that the antiviral activity of *Eleutherococcussenticosus* extract is viral RNA dependant. Related studies also showed that influenza RNA was inhibited by a water-soluble extract of *Sanicula europaea (L.)* [65]. In a later study of Karagoz et al. (1999) it was shown that an acidic fraction obtained from the crude extract of *Sanicula europaea* was the most active fraction in inhibiting human parainfluenza virus type 2 replication at noncytotoxic concentrations [66]. By comparison, ethanol extraction abolished the antiviral activity. The plausible explanation is that the antiviral activity could disappear during the course of fractionation. Another example, *Myrcianthescis platensis* showed in vitro anti-RSV but not anti-HSV-1 or anti-adenovirus serotype 7 (DNA virus) [67]. In contrast, other medicinal plants, for example *Nepeta coerulea, Nepetanepetella, Nepeta tuberosa*, *Sanguisorba minor magnolii* and *Dittrichia viscose* showed clear antiviral activity against DNA and RNA viruses, i.e., HSV-1 and VSV in addition to poliovirus type 1 in the case of *Dittrichiaviscose* [68]. The *Azadirachta indica* leaf extract was found to be active against a number of viruses such as smallpox (DNA), chicken pox (DNA), poxvirus (DNA), poliomyelitis (RNA) and herpes viruses (DNA) [69,70]. An extract of the cactus plant *Opuntia streptacantha* inhibited intracellular DNA and RNA virus replication and inactivated extracellular virus, such as HSV, equine herpes virus, pseudorabies virus and influenza virus [71]. The *Bergenialigulata, Nerium indicum* and *Holoptelia integrifolia* plants exhibited considerable antiviral activities against influenza virus (RNA) and HSV (DNA) [72] (Fig. 5).

7. Anti-viral activity of medicinal herbal phytochemicals against SARS-CoV-2

Many people can use various plant simultaneously with several drug. Although all over world can suffer corona virus but infectivity rate significantly slow in many tribal based states of India like Sikim, Nagaland, Himachal Pradhesh, Jharkhand etc., [73]. On the other hand, few people of Bankura and very less people of Purulia district West Bengal can suffer by COVID-19. Beside Purulia, Sikim, Nagaland, Meghalaya and many other regions cover by mainly tribal community. They also depend upon various medicinal plant for treatment of any disease. When total world uses chemical drugs then tribal people based on the selective plant for precaution and treatment of corona infection [74]. Plants selected by three basic steps (1) The plants were selected by survey report from tribal people (2) Verified by PubMed for those herbs conventionally used to

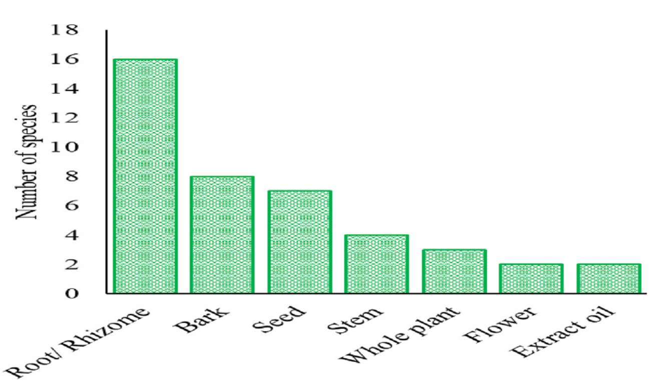

Fig. 5. Plant parts for antiviral preparation.

treatment viral respiratory infections. (3) In vivo, general effect prediction with network pharmacology analysis. Bacteria and viruses, pandemic diseases are spreading. It seems to us out of control and we think ourselves helpless, unsafe. So, we are now in endangered position for human civilization. Many would be glad to learn that the much common villagers and the tribal people strictly use herbal medicine to cure disease [75]. They are healthier than others. According to survey report from tribal zone of Purulia district, West Bengal, India several plants use as traditional herbs for treatment of COVID-19 and influenza, those are including in Table 1.

SARS is a positive-sense single-stranded RNA (+ssRNA) virus of the Coronaviridae family that covered by protein envelope. Several species of the CoV family act on especially upper respiratory tract and gastrointestinal tract of mammals and birds. In case of human's common cold occur generally but pneumonia and SARS to be difficult for treatment [76]. A group of human CoV (HCoV) like HCoV-229E, -OC43, -NL63, -HKU1, and severe acute respiratory syndrome coronavirus (SARS-CoV) triggered a global threat with high mortality. In 2012, the World Health Organization (WHO) chosen a sixth type of HCoV infection identified as the Middle East respiratory syndrome coronavirus (MERS-CoV) which is related with high fatality [77]. There are no exact treatments for CoV infection and defensive vaccines are still being explored. Thus, the conditioner produces the need to grow active antivirals for prophylaxis and treatment of CoV infection. Previously informed that saikosaponins (A, B2, C, and D) which are naturally happening triterpene glycosides inaccessible from medicinal plants such as Bupleurum spp., Heteromorpha spp., and Scrophularia scorodonia, applyas antiviral activity against HCoV-22E9 [78]. Upon co-challenge with the virus, these natural compounds successfully prevent the early stage of HCoV-22E9 infection, including viral attachment and penetration. Citations from *Artemisia annua, Lycoris radiata, Pyrrosia lingua,* and *Lindera aggregata* have also been recognized to show anti–SARS-CoV effect from a showing analysis using hundreds of medicinal herbs [79]. Natural inhibitors against the SARS-CoV enzymes, such as the nsP13 helicase and 3CL protease, have been recognized as well and contain myricetin, scutellarein, and phenolic compounds from *Torreya nucifera* and *Isatisindigotica* [80–82]. Other anti-CoV natural medicines contain the water extract from Houttuynia cordata which has been experiential to exhibit several antiviral mechanisms against SARS-CoV, such as preventing the viral protease and blocking the viral RNA-dependent RNA polymerase activity [83] (Table 2).

8. Mechanism and targeting site of COVID: potential herbal compound

A group of herbal derived chemical compounds have potential antiviral properties, but the mechanisms of action are different. The first target sites are glycoproteins of virus envelope that leading to as nonspecific binding to host cells (human cell receptors of respiratory cells ACE2) [84]. However, the actual chemical constituent in the research used to treat the infection was not identified. There are different types of plant flavonoids may be used to treat the symptoms of SARS-CoV3CL by inhibition of essential protein synthesis process of the virus [85]. After the entries of virus into host cell, +ss RNA attach to the host ribosome during translation of two kinds of large, co-terminal polyproteins that are necessary for packaging new virions [86]. Herbal therapeutics able to target spike, RdRp, 3CLpro, and PLpro of SARS-CoV-2 [87,88]. SARS-CoV-2 shares about 82% resemblance of genomic sequence identity with SARS-CoV's and more than 90% resemblance of sequence identity in several essential enzymes [89]. Several natural herbal compounds such as theaflavin and cepharanthine repressed SARS-CoV-2 by defeating RdRp and ACE activities; hirsutenon e and tanshinones I–VII showed antiviral action against SARS-CoV via obliging the PLpro activity, while pristimererin, celastrol, iguesterin, tingenone, chalcones I–IX and quercetin-3-β-galactoside were able to inhibit SARS-CoV by defeating the 3CLpro activity [90] (Table 2).

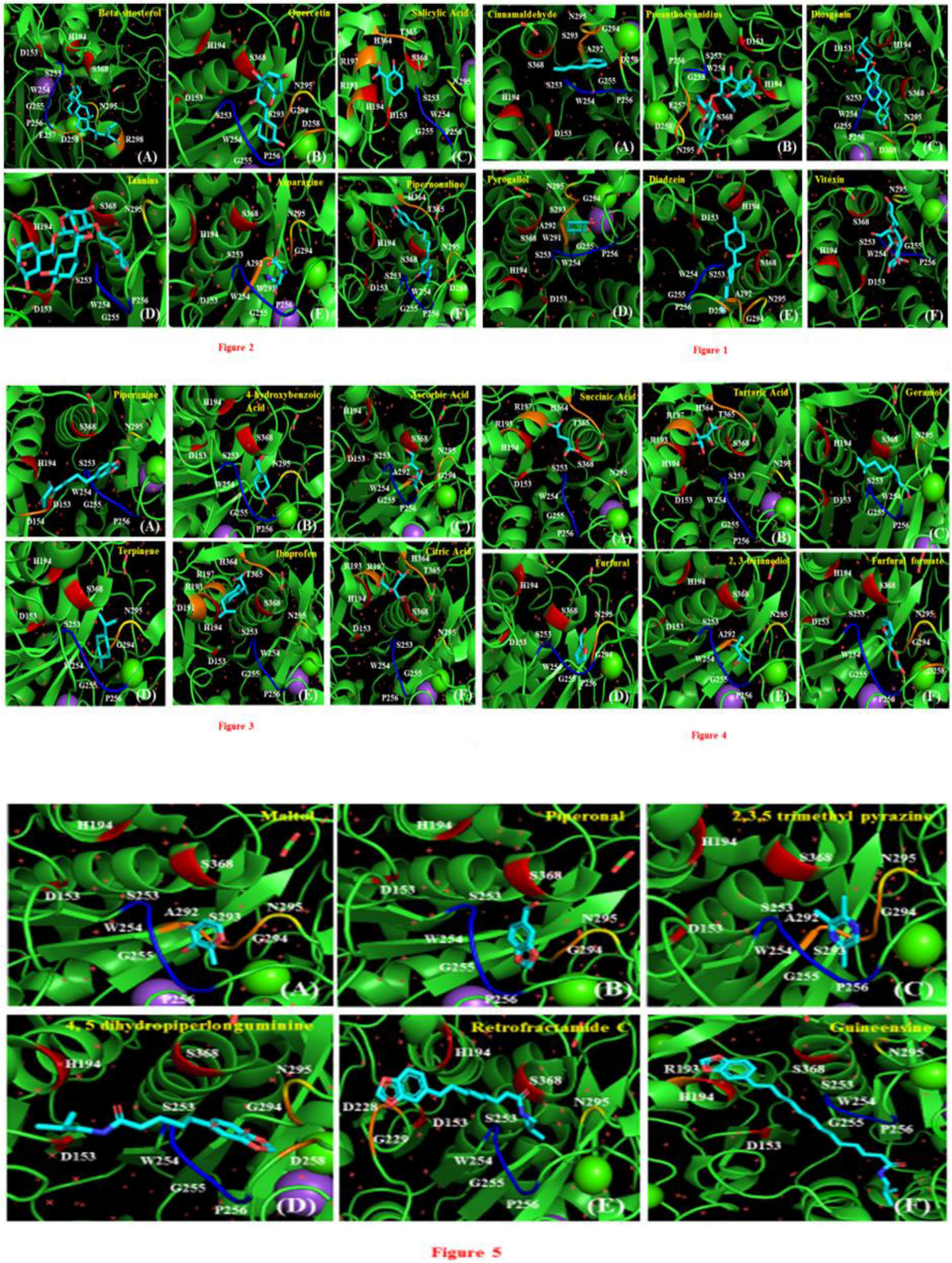

Fig. 6. Images are representing the docking interactions between herbal compounds with Human Furin (4RYD).

Table 1
List of traditional Indian plants including their therapeutic uses as antiviral agents.

Sl. no.	Botanical Name & family	Local name	Part used	Method of use in	Treatment for	References
1	*Cinnamomum zeylanicum* Blume (Lauraceae)	Cinnamon	Bark	1 teaspoon natural honey+1/4 tea spoon bark dust	Influenza, HSV-1 viruses, Parainfluenza virus	Patil et al., 2020
2	*Jatropha curcas* L. (Euphorbeaceae)	Physic nut/varenda	All parts, mainly latex	Latex with candy	Influenza, HIV	Agrawal et al., 2020
3	*Glycyrrhiza glabra* L. (Fabaceae) + Honey	Licorice Licorice	Root Root dust	Extract Mixture	Influenza Influenza +covid 19	Huaccho-Rojas et al., 2020
4	*Piper chaba*Trel. &Yunck.(Piperaceae) +*Zinziberofficinale*Roscoe(Zinziberaceae)	Pippali or long Pepper ginger	Fruit, + Rhizome	Juice (certain quantity)	Influenza	John et al., 2020
5	*Piper nigrum* L. (Piperaceae) + *Syzygiumaromaticum* (L.) Merr. &L.M.Perry (Myrtaceae) + (Buch. -Ham.) T.Nees&C.H.Eberm. (Lauraceae)+ *Camellia sinensis* (L.) Kuntze (Theaceae)	Black pepper Cloves Cinnamom Green tea	Fruit (piper)+Flower bud (syzygi)+Leaf (Cinnamo) +Leaf (Camell)-	As tea (certain quantity)	Influenza	Narkhede et al., 2020
6	*Oxalis carniculata*L. (Oxalidaceae)	Amruli	Mainly leaf, steam	As vegetables	Influenza	Ding et al., 2021
7	*Averrhoa carambola* L. (Oxalidaceae)	Starfruit	Green and ripe fruit	As fruit	Influenza	Barile et al., 2020
8	*Nigella sativa* L. (Ranuculaceae)	Kalonji/Black cumin	Seed	Mixed with honey (certain quantity)	Influenza	Islam et al., 2021
9	*Adhatodavasica* Nees (Acanthaceae)+*Ocimum sanctum* L. (Lamiaceae)	Bakash + Holybasil	Leaf (adhato.) +Spadix (ocim.)	As juice (certain quantity)	Influenza	Chernyshov et al., 2020
10	*Zinziber officinale* Roscoe (Zinziberaceae) + *Allium cepa* L. (Liliaceae) + *Capsicum frutescens* L. (Solanaceae)	Ginger, Onion&Chilli	Rhizome, Scale leaf&Green fruit	As fruit (certain quantity)	Influenza	Pal et al., 2019
11	*Allium sativum* L. (Liliaceae)	Garlic	Raw scale leaf	(certain quantity)	Influenza	Rouf et al., 2020
12	*Citrus limon* (L.) Osbeck (Rulaceae)	Lemon	Fruits	Mixed with tea or water	Influenza	Hakim et al., 2020
13	*Oxalis corniculata*L. *(Oxalidaceae)*	Amruli	Mainly leaf and steam	As vegetables	COVID-19	Navarro-Leon et al., 2020
14	*Azadirachtaindica*A.Juss.(Maliaceae)	Neem	Leaf	As vegetables	COVID-19	Borkotoky et al., 2020
15	*Daucuscarota* L.(Apiaceae)	Carrots	Root	As vegetables	COVID-19	Haryanto et al., 2021
16	*Moringa* sp(Moringaceae)	Drumstick tree	Leaf and fruit	As vegetables	COVID-19	Meireles et al., 2020
17	*Momordica charantia*L. (Cucurbitaceae)	Karela	Leaf and fruit	As vegetables	COVID-19	Fedoung et al., 2020
18	*Ficushispida*L.f.(Moraceae)	Fig	Fruit	As vegetables	COVID-19	Hassan et al., 2020
19	*Glinusoppositifolius*(L.) Aug.DC.(Molluginaceae)	Cuisine/Gima	Leaf	As vegetables	COVID-19	Wiart et al., 2020
20	*Spinacia oleracea* L.(Amaranthaceae)	Spinach	Leaf	As vegetables	COVID-19	Chaachouay et al., 2021
21	*Nyctanthes arbour-tristis* L.(Oleaceae)	Night jasmine/Sueli	Leaf	As vegetables	COVID-19	Bharshiv et al., 2016
22	*Mangifera indica* L. (Anacardiaceae)	Mango	More sour green fruit	As Fruit	COVID-19	Yang et al., 2020
23	*Ananascosmosus* (L.) Merr.(Bromeliaceae)	Pineapple	Fruit	As juice/fruit	COVID-19	Kumar et al., 2020
24	*Spondias pinnata* (L.f.) Kurz(Anacardiaceae)	Amrha	Fruit	As vegetables	COVID-19	Li et al., 2020
25	*Tamarindus indica* L. (Fabaceae)	Tamarind	Fruit	As vegetables	COVID-19	Borquaye et al., 2020
26	*Emblica officinalis* L. (Phyllanthaceae)	Emblica	Fruit	As vegetables	COVID-19	Akbar et al., 2020
27	*Citrus limon*(L.) Osbeck(Rulaceae)	Lemon	Fruit	As juice	COVID-19	Yousaf et al., 2018
28	*Aegle marmelos*(L.) Corrêa(Rutaceae)	Stone/golden apple	Fruit, Leaf	As fruit, juice	COVID-19	Akbar et al., 2020
29	*Chebulic myrobalan* (*Terminalia chebula*) Retz. (Combretaceae)	Haritaki	Fruit	Fruit dust	COVID-19	Haque et al., 2021
30	*Oxalis corniculata* L.(Oxalidaceae)	Amruli	Mainly leaf and steam	As juice	COVID-19	Villela et al., 2021
31	*Tinospora cordifolia* (Thunb.) Miers(Menispermaceae)	Giloy/guduchi	Mainly leaf and steam	As juice	COVID-19	Singh et al., 2021
32	*Corica papaya* L. (Caricaceae)	Pawpaw	Mainly leaf; Latex from fruit with candy (certain quantity)	As juice	COVID-19	Barooah et al., 2020
33	*Andrographis paniculata* (Burm.f.) Nees(Acanthaceae)	Kalmegh	All parts	As juice and tablet	COVID-19	Dharmadasa et al., 2020

(*continued on next page*)

Table 1 (*continued*)

Sl. no.	Botanical Name & family	Local name	Part used	Method of use in	Treatment for	References
34	*AzadiractaindicaA*.Juss.(Maliaceae) + *Curcuma longa* (Zinziberaceae)	Neem Turmeric	Mainly leaf and fruit Rhizome	As juice	COVID-19	Tillu et al., 2020
35	*Momordica charantia*L. (Cucurbitaceae)+ *Vitex negundo* L.(Lamiaceae) + *Nyctanthesarbor-tristis* L. (Oleaceae) + Honey	Karela Chinese chaste Night jasmine/sueli	Leaf Leaf Leaf Leaf	As juice	COVID-19	Divya et al., 2020
36	*Piper nigrum* L. (black)(Piperaceae)+ *Syzygiumarometicum*(L.) Merr. &L.M.Perry(Myrtaceae)+ *Cinnamomum tamala*(Buch. -Ham.) T.Nees&C.H.Eberm. (Lauraceae)+ *Camellia sinensis* (L.) Kuntze (Theaceae)+*Salt*	Black pepper Cloves Tejapatta/tejpat Green tea	Fruit dust 1 teaspoon Flower bud dust 1teaspoon +4th Tejpat +1 teaspoon 2 cups → Boiling 1cup	As tea	COVID-19	Tazeen et al., 2021
37	*Piper nigrum* L. (Piperaceae) + *Cinnamomum zeylanicum* Blume (Lauraceae) + *Ocimum sanctum* L.(Lamiaceae) + *Zinziber officinale* Roscoe(Zinziberaceae)+ water+ Salt	Black piper Cinnamon Holybasil(tulsi) Ginger	Fruit dust 1 teaspoon Bark dust 2 teaspoons Leaf dust4 teaspoon Rihizome dust 2 teaspoons 2 cups → Boiling1 cup	As tea	COVID-19	Sulaiman et al., 2021
38	*Terminalia chebula*Retz.(Combretaceae) + *Piper nigram*L.(Black) (Piperaceae) + *Zinziber officinale* Roscoe(Zinziberaceae) + *Cinnamomum zeylanicum* Blume (Lauraceae) + *Ocimum sanctum* L. (Lamiaceae)+ Water+Salt	Haritaki + Blackpepper + ginger + cinnamon + Holybasil (tulsi)	Fruit dust 1 teaspoon Fruit dust 1 teaspoon Rhizome dust 2 teaspoons Bark dust 2 teaspoons Leaf dust 4 teaspoons 2 cups → Boiling 1cup	As tea		Patel et al., 2021
39	*Glycyrrhiza glabra* L. (Fabaceae)+ *Cinnamomum zeylanicum* Blume (Lauraceae)+ *Terminalia chebula*Retz.(Combretaceae)+ *Amomum subulatun*Roxb.(Zinziberaceae)+ *Ocimum sanctum* L. (Lamiaceae)+Water+Salt	Licorice Cinnamon Haritaki Cardamom Holybasil(tulsi)	Root dust 1 teaspoon Bark dust 2 teaspoon Fruit dust 1 teaspoon Seed dust 2 teaspoon Spadix dust 2 teaspoon 2 cups → Boiling1cup	As tea	COVID-19	Hejazi et al., 2021
40	*Cinnamomum cassia* (L.) J.Presl(Lauraceae)+ *Citrus limon* (L.) Osbeck(Rutaceae)/*Zinziber officinale* Roscoe(Zinziberaceae)+ Water + Salt	Cinnamon Lemon Ginger	Bark dust 2 teaspoon 1 teaspoon 2 teaspoons 2 cups → Boiling 1cup	As tea	COVID-19	Chaachouay et al., 2021
41	*Amomumsubulatum* Roxb.(Zinziberaceae) + *Cinnamomum cassia* (L.) J.Presl(Lauraceae)+ *Zinziber officinale* Roscoe (Zinziberaceae)+ *Allium sativum* L.(Amaryllidacae)+ *Citrus limon* (L.) Osbeck(Rutaceae) +*Brassica nigra* L. (Brassicaceae)+Water	Cardamom Cinnamon Ginger Garlic Lemon Mustard oil	Big 10 Few Some piece of Some 2 big (juice) few	As vapour and drinking mixture.	COVID-19	Shah et al., 2020
42	*Negella sativa* L.(Ranunculaceae)+ *Glycyrrhiza glabra* L. (Fabaceae)+ *Piper nigrum* L. (Piperaceae)+ *Cicer arietinum* L.(Fabaceae)+ *Amomum subulatum* Roxb.(Zinziberaceae)+ *Ferula asafoetida* L. (Umbellifereae)+ *Vitis vinifera* L. (Vitacae)+ Honey	Blackcumin/kalonji Licorice Blackpepper Chickpea Black cardamom Hing Grapevine	Seed dust (Ne) + Root dust (Gly) + Fruit dust (Pi) + Seed dust (Ci) + Seed dust (Am) + Hing (Fe) + Fruit (Vi) Certain quantity	As mixture	COVID-19	Joshi et al., 2021
43	*Allium sativum*L.(Amaryllidaceae)+ *Zinziber officinale* Roscoe (Zinziberaceae)+ *Piper nigrum* L. (Piperaceae)+ *Daucus carota*L.(Apiaceae)+ *Foeniculum vulgare* Mill.(Apiaceae)+ *Ocimumsanctum* L. (Lamiaceae)+ *Vigna radita*(L.) R. Wilczek(Fabaceae)+Honey	Garlic Ginger Blackpepper Carrots Sweet fennel mungbean	Scale leaf (Alli) + Rhizome (Zin) + fruit (pipe) + root (dau) + fruit (foe) +Spadix/ Seed (oci)+seed (vig) Certain quantity	As mixture	COVID-19	Daniell et al., 2021
44	*Ferula asafoetida* L. (Umbellifereae)+ *Glycyrrhiza glabra* L. (Fabaceae)+ *Cinnamomum cassia* (L.) J.Presl(Lauraceae)+ *Cinnamomum camphora* (L.) J.Presl.(Lauraceae)+ Honey	Hing Licorice Cinnamon Camphor	Turpentine oil Root Bark dust Turpentine oil (Certain quantity)	As mixture	COVID-19	Fazil et al., 2020
45	*Jatropacurcas*L.(Euphorbiaceae)	Jatropa	Leaf and Stem extract	As Extract	HIV	Syaht et al., 2020
46	*Glycyrrhiza glabra* L. (Fabaceae)	Licorice	Root	Root Extract	HIV, HSV1&2	Jalali et al., 2021
47	*Cocos nucifera* L.(Arecaceae)	Coconut tree	Kernel, Water	Husk fiber	HSV-1, ACVr	Singh et al., 2020

9. Energy minimization and molecular docking of phytochemicals derived from traditional plants

Medicinal plants always provide useful benefits to humankind. Here we have studied an in-silico docking experiment among the compounds of medicinal plants with human furin protease (PDB: 4RYD). The purpose of the study is to establish how the components of medicinal plants help us to develop immunity in our body. Protein Data Bank file for Human Furin (PDB ID: 4RYD) was used as receptor molecule and list of herbal compounds isolated from different medicinal plants were taken as ligand molecule for docking. Each molecule was undergone energy minimization using ChemBio3D Ultra 13.0 software, a high-quality workstation where MM2 energy minimization of each molecule was identified with stable molecular conformation. Minimum RMS gradient was taken as 0.010. The iGEMDOCK v2.1 software was used for the docking studies of those herbal compounds with Human Furin. The iGEMDOCK software

Table 2
Principle compounds of the selected medicinal plants used as antiviral agents.

Sl no	Name of plant	Major compound	Reference
1	*Cinnamomum zeylanicum*	Cinnamaldehyde, Pro anthocyanidins, Eugenol	Asif et al., 2020
2	*Jatropha curcas*	Tannic acid, diosgenin, Phorbol esters, gallic acid, pyrogallol rutin, myricetin and daidzein, apigenin and its glycosides, vitexin and isovitexin, stigmasterol, β-sitosterol] ellagic acid, quercetin, coumaric acid, benzoic acid and salicylic acid.	Oskoueian et al., 2011
3	*Glycyrrhiza glabra*	Asparagines, tannins, glycosides, resins, sterols, volatile oils, Glycyrrhizin (glycyrrhizic acid; glycyrrhizinate), triterpenoid aglycone, glycyrrhetic acid (glycyrrhetinic acid; enoxolone), Glycyrrhizin and glycyrrhetic acid, glycyrrhetic acid, Carbenoxolone (18-βglycyrrhetinic acid hydrogen succinate), e liquirtin, isoliquertin, liquiritigenin and rhamnoliquirilin. Five new flavonoids- glucoliquiritinapioside, shinflavanone, shinpterocarpin, prenyllicoflavone A, and 1-methoxypha-seolin, glabridin and hispaglabridins A and B, both glabridin and glabrene have estrogen-like activity, many volatile components are present in roots e.g., geraniol, pentanol, hexanol, terpinen-4-ol, α-terpineol. Isolation of various compounds like propionic acid, benzoic acid, furfuraldehyde, 2,3 butanediol, furfurylformate, maltol, 1-methyl-2-for-mylpyrrole, trimethylpyrazineetc from the essential oil is also reported	Monica et al., 2014
4	*Piper chaba*	Piperonal, Methyl piperate, Piperchabamide A, Piperchabamide A, Piperanine, Piperine, Piperoleine B, Piperocaine, Piperchabamide B, PiperundecalidinePiperchabamide C, Dihydropiperlonguminine, Piperlonguminine, Piperchabamide E, Retrofractamide C, Retrofractamide A, Piperchabamide D, Retrofractamide B, Guineensine, Brachystamide B, *N*-Isobutyl-(2E,4E)-decadienamide, *N*-Isobutyl-(2E,4E)-dodecadienamide, *N*-Isobutyl-(2E,4E)-octadecadienamide, *N*-Isobutyl-(2E,4E,14Z)-eicosatrienamide	Hisashi et al., 2008
5	*Zingiber officinale*	6-Shogaol, 6-Gingerol,8-Gingerol,10-Gingerol, Curcumin, Citric acid, Malic acid, Oxalic acid, Succinic acid, Tartaric acid	Hsiang-yu Yeh et al., 2014
6	*Piper nigrum*	Pinoresinol, guineesine, Chavicine, 1-[(2E, 4Z,8E)-9-(3,4-mehtylenedioxy-phenyl)-2,4,8-nonatrienoyl] pyrrolidine, Pipercide, Sesamin, Piperarborenine E, Piperarborenine D, Piperarborenine C, Dehydropipernonaline and piperrolein B,	Mgbeahuruike et al., 2017
7	*Piper longum*	Longumosides A (1) and B (2), erythro-1-[1-oxo-9(3,4-methylenedioxyphenyl)-8,9-dihydroxy-2E-nonenyl]- piperidine (3), and threo-1-[1-oxo-9(3,4-methylenedioxyphenyl)- 8,9-dihydroxy-2E-nonenyl]-piperidine (4) were isolated, besides two new natural products 3b,4a-dihydroxy-2-piperidi-none (5), 5,6- dihydro-2(1H)-pyridinone (6) (Fig. 1). Compounds 2–6, together with the isolates previously obtained with a large amount from P. longum involving piperine (7),3,7 1-[1-oxo-5(3-methoxyl-4-hydroxyphenyl)-2E-pen-tenyl]-piperidine (8),6,10 guineesine (9),3,5 (2E,4E)-*N*-isobutyleicosa-2,4-dienamide (10),3 piperlonguminine	Fatima et al., 2021
8	*Cinnamomum tamala*	Monoterpenes (65.6%). The predominant monoterpenes were *trans*-sabinene hydrate (29.8%), (Z)-β-ocimene (17.9%), myrcene (4.6%), α-pinene (3.1%) and β-sabinene (2.3%). Among 21 sesquiterpenes (32.9%).	Showkat et al., 2004
9	*Camellia sinensis*	Polyphenols epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG), caffeine, theanine, myricetin, quercetin, and kaempferol, which are examples of alkaloids, amino acids, and flavonols,	Vanara et al., 2018.
10	*Citrus bergamia*	(−)-linalyl acetate (−)-linalool (+)-limonene γ-Terpinene, β-Pinene α-pinene α-terpinene	Selvarani et al., 2014.
11	*Oxalis carniculata*	Two isolated **compounds** 5-hydroxy-6,7,8,4′-tetramethoxyflavone (1) and 5,7,4′-trihydroxy-6,8-dimethoxyflavone (2) tannins, palmitic acid, a mixture of 8 oleic, linoleic, linolenic and stearic acids. glycosides, phytosterols, phenolic compounds, flavonoids, proteins (12.5%), amino acids and volatile oil.	Kishor et al., 2017
12	*Nigella sativa*	Thymoquinone (TQ), dithymoquinone, thymohydroquinone, thymol, carvacrol, nigellimine-*N*-oxide, nigellicine, nigellidine, and alpha-hederin	
13	*Adhatoda vasica*	2-(4-(but-2-yl) phenyl) propanoic acid, N, *N*-dimethylglycine n-hexadecanoicacid. Ibuprofen, n-hexadeconic acid, N, N dimethylglycine.	Sharly et al., 2017
14	*Cimum sanctum*	Eugenol (1-hydroxy-2-methoxy-4-allylbenzene, euginal (also called eugenic acid), urosolic acid, (2,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydro-1H-picene-4a-carboxylic acid, carvacrol (5-isopropyl-2-methylphenol, linalool (3,7-dimethylocta-1,6-dien-3-ol, limatrol, caryophyllene (4,11,11-trimethyl-8-methylene-bicyclo [7.2.0] undec-4-ene, methyl carvicol (also called Estragol: 1-allyl-4-methoxybenzene	Priyabrata et al., 2010
15	*Allium cepa*	Quercetin, fructose, quercetin-3-glucoside, isorhamnetin-4-glucoside, xylose, galactose, glucose, mannose, organosulfur compounds, allylsulfides, flavonoids, flavenols, *S*-alk(en)yl cysteine sulfoxides, cycloalliin, selenium, thiosulfinates, and sulfur and seleno compounds	Loredana et al., 2017
16	*Capsicum frutescens*	Ester, terpenoids, noncarotenoids, lipoxygenase derivatives, carbonyls, alcohols, hydrocarbons 8, capsaicin, dihydrocapsaicin 4, capsiconinoid 11, capsinoid, 8-methyl-*trans*-6-nonenoic acid (capsaicin), 8-methylnonanoic acid (dihydrocapsaicin), 7-methylnonanoic acid (nordihydrocapsaicin), 9-methylde-canoic acid (homodihydrocapsaicin) and 9-methyldec-*trans*-7-enoic acid (homocapsaicin).	Antonio et al., 2018
17	*Allium sativum*	Allicin, diallyl disulphide, *S*-allylcysteine, and diallyl trisulfide, diallyl disulphide (DDS), *S*-allylcysteine (SAC) and diallyl trisulfide (DTS)	Peyman et al., 2013
18	*Oxalis corniculata*	5-hydroxy-6,7,8,4′-tetramethoxyflavone (1) and 5,7,4′-trihydroxy-6,8-dimethoxyflavone, *β*-sitosterol, betulin, 4-hydroxybenzoic acid, ethyl gallate, methoxyflavones, apigenin, and 7-*O*-β-D-glucopyranoside, palmitic acid, oleic,	Sharma et al., 2014.

(*continued on next page*)

Table 2 (*continued*)

Sl no	Name of plant	Major compound	Reference
		linoleic, linolenic and stearic acids. flavonoids, iso vitexine and vitexine-2″-O- beta – D- glucopyrunoside.	
19	*Azadirachta indica*	Glycosides, limonoids, tetranortriterpinoids, coumerins, isocoumerins, kaempferol, quercetin, myricetin, 5,7,4 trihydoxyflavone, apigenin 7,0 glucoside. Azadirachtin A, B, D, H, I, Desacetylnimbin, Azadiradione, Nimbin, Salanin, Azadirone, Nimbolin, Nimbinene, Nimbolide.	Mohammad et al., 2007
20	*Daucus carota*	*p*-hydroxybenzoic acid; caffeic acid; chlorogenic acid; and the anthocyanins. phenolics, carotenoids, polyacetylenes, and ascorbic acid,	Ahmad et al., 2019
21	*Moringa* sp	Phenolic acids, flavonoids, isothiocyanates, tannins and saponins, N, α-L-rhamnopyranosylvincosamide, 4-(α-L-rhamnopyranosyloxy) phenyl acetonitrile (niazirin), pyrrolemarumine 4″-*O*-α-Lrhamnopyranoside, 4′-hydroxy phenylethanamide-α-Lrhamnopyranoside (marumoside A) and its 3-*O*-β-Dglucopyranosyl-derivative (marumoside B) and methyl 4-(α-L-rhamnopyranosyloxy)-benzylcarbamate, 4-*O*-(α-L-acetylrhamnopyranosyloxy)-benzyl glucosinolates, deoxy-niazimicine (*N*-benzyl, Sethylthioformate)	Singh et al., 2017
22	*Momordica charantia*	Momordicolide ((10E)-3-hydroxyl-dodeca-10-en-9-olide, 1), monordicophenoide A (4-hydroxyl-benzoic acid 4-*O*-beta-D-apiofuranosyl (1→ 2)-*O*-beta-D-glucopyranoside, 2), dihydrophaseic acid 3-*O*-beta-D-glucopyranoside (3), 6,9-dihydroxy-megastigman-4,7-dien-3-one (blumenol, 4)	Li et al., 2009

was implemented with generic evolutionary algorithm (GA) to carry out automated molecular dockings. AutoDock Vina software was also used for the docking analysis. The software can work through Auto Dock Tools (ADT) or Pyrex tools [91]. The macromolecules were cleaned from water residues and Gasteiger charges were calculated. The ligands and macromolecules were uploaded in the Pyrex tool [92]. Finally, the receptor and ligand files were converted into pdbqt format.

While performing docking experiment of different herbal compounds isolated from different medicinal plants like *Cinnamomum zeylalanicum, Jatropha curcas, Glycyrrhiza glabra, Piper chaba, Zingiber officinale, Piper nigrum, Piper longum, Cinnamomum tamala, Ocimum sanctum* etc. screening of all these essential compounds present in these plants is our main maim of study. Here we have docked 66 different compounds with human furin protease. Out of 66 compounds, 30 compounds were shown not only strong binding affinity but also binds to the active site of the receptor molecule.

In silico docking study of cinnamaldehyde with furin protein clearly depicts a binding affinity of −64.25 kcal/mol (Table 3). Cinnamaldehyde interacts with the following residues D258, W254, G255, A292, S293, G294 of furin protein. Docking of proanthocyanidins with furin protein shows strong binding affinity of −125.73 kcal/mol. Pro-anthocyanidins binds with the residues H194, S253, G255, N295, S368, W254, E257, D258 of furinprotein (Fig. 6 & Table 3).

From the results of molecular docking, it is very much evident that all these herbal compounds have significant role in binding with furin protein thus preventing the viral entry with the human body.

10. Aspects of synergetic combination of medicinal plants with orthodox drugs for alleviating viral infection:

Strikingly it was seen that some patients of the Far East are use combination of orthodox medical drugs and herbal medicine for improving illnesses [93] as well as reduce the side effects of orthodox medical drugs, to extent better treatments. Although pharmacological appliances of the combinations are not well-studied but efficacious treatments by amalgamation of plant products with orthodox drugs were reported [94]. Acyclovir combines with *Geranium robertianum*, Actium *lappa, Calendula officinalis and* shows better results of ulcer [95]. Combined application of Verbascum thapsiforme (Scrophulariaceae) flowers and three amantadine derivatives enhance the inhibitory effect of influenza virus [96].

11. Biotechnology and high-tech herbal medicine

The many uses of medicinal plants need have led to encounter and overexploitation. An account of the multipurpose uses of ethno-medicinal plants in turn to be threaten for overharvesting in several countries including India [97]. Frequent forest fires and early harvests jeopardise existing populations of medicinal plants. The institution Himalayan Amchi Association (HAA), aimed at maintenance traditional knowledge about health care is enthusiastic to guard medicinal plants and strengthen the knowledge of several plant species including *Amchi healers* [98]. Due to climate change and exploitation of soil the quality and quantity of medicinal plants have been lost. Excess-harvesting was a tremendous threat to many indigenous medicinal plant species, like *N. grandiflora*, *Z. armatum*, *A. rivularis* etc [99]. Today biotechnology is an emergent ground all over world. It has numerous industrial applications, principally in health care sector, agriculture field, food industries and involve the maintenance of eco-sustainable environment. Microbes and phytochemicals are both sue as raw materials of biomedical industries. But all medicinal plants incapable to grow in any climate at selective season. So, mainly tissue culture technology can fulfil the crisis of phytochemicals. Plant secondary metabolites easily produce by tissue culture technique in adverse situation (loss of plant, habitat degradation). By this technique extinct species should be culture.

12. Future prospects

Now viral diseases are still serious, although few under control by proper life-prolonging drugs. But these more expensive drugs are still far beyond the developing countries. Perhaps, the expansion of innocuous, active and cheap antiviral drugs act as RT inhibitors (HIV and hepatitis) that are not yet curable. In spite of fact that, significant attention requires for screening of various medicinal plant and extraction of bioactive compound those act on especially viral diseases. Beside screening programme genus of species wise identification require and proper detection of useable parts of plant and optimise bioactive phytochemicals extraction method also most essential. Ultimately monitoring require for growth pattern and season (s) during deposition or maturation of materials as well as details of administration of phytochemicals [55]. Some herbs contain ribosome-inactivating proteins (RIPs) which can alter function of ribosome of infected cell and block viral protein synthesis [100].

13. Conclusion

Based on the more resemblance of the receptor and the genome of SARS-Cov and SARS-Cov2 this report tried to recommend potential plant species that might be involved as anti-SARS-Cov2 agents. Plant species can deliver a purely natural, low cost and with less side effects approaches of drug development strategy against COVID-19. Our study suggested the several plant species such as *Oxalis corniculata*, *Ocimum sanctum*, *Cinnamomum zeylanicum, Moringa* sp. etc might encounter the

Table 3
Energy minimization of ligands and determination of binding free energy of docking interactions between herbal compounds with Human Furin (4RYD) using iGEMDOCK.

Sl. No.	Receptor	Ligand	Energy Minimization of Ligand	Ligand Binding site	Binding Free Energy (kcal/mol)	Plant source
1	Human Furin:A (PDB:4RYD)	Cinnamaldehyde (PubChem CID: 637511)	5.373	D258, W254, G255, A292, S293, G294	−64.25	*Cinnamomum zeylanicum*
2	Human Furin:A (PDB:4RYD)	Proanthocyanidins (PubChem CID:122173182)	46.1570	**H194,** S253, G255, **N295, S368,** W254, E257, D258	−125.73	*Cinnamomum zeylanicum*
3	Human Furin:A (PDB:4RYD)	Eugenol (PubChem CID: 3314)	8.9422	N310, Q488, A532, G307, S311, Y313	−67.36	*Cinnamomum zeylanicum*
4	Human Furin:A (PDB:4RYD)	Piperchabamide B (PubChem CID: 44453655)	26.9485	D233, P266, A267, W531, A532	−81.24	*Piper chaba*
5	Human Furin:A (PDB:4RYD)	Diosgenin (PubChem CID: 99474)	69.3497	**N295**, **D153**, **H194,** W254, G255, D258	−83.51	*Jatropha curcas*
6	Human Furin:A (PDB:4RYD)	Phorbol ester (PubChem CID: 22833501)	80.1299	G307, Q488, N529, V231, G265, P266, E271, R490, W531	−90.75	*Jatropha curcas*
7	Human Furin:A (PDB:4RYD)	Gallic Acid (PubChem CID: 370)	2.4714	N310, I312, Q488, G307, S311, W531	−65.83	*Jatropha curcas*
8	Human Furin:A (PDB:4RYD)	Pyrogallol (PubChem CID: 1057)	1.0761	W254, W291, A292, G255, S293, G294	−73.30	*Jatropha curcas*
9	Human Furin:A (PDB:4RYD)	Rutin (PubChem CID: 5280805)	39.8640	K261, G265, R490, R498, G527, N529, T262, V263, D264, F528, D530, W531	−118.61	*Jatropha curcas*
10	Human Furin:A (PDB:4RYD)	Myricetin (PubChem CID: 5281672)	13.5507	A412, T413, R512, T514, H537, H422, T511	−100.80	*Jatropha curcas*
11	Human Furin:A (PDB:4RYD)	Diadzein (PubChem CID: 5281708)	16.2532	A292, **S368, H194,** S253, W254, G255, D258, G294, **N295, S368**	−86.60	*Jatropha curcas*
12	Human Furin:A (PDB:4RYD)	Apigenin (PubChem CID: 5280443)	20.6339	N310, N529, A532, G307, S311, W531	−86.53	*Jatropha curcas*
13	Human Furin:A (PDB:4RYD)	Vitexin (PubChem CID: 5280441)	37.1296	G255, **N295**, W254, P256	−100.39	*Jatropha curcas*
14	Human Furin:A (PDB:4RYD)	Stigmasterol (PubChem CID: 5280794)	57.5356	S311, I312, G307, N310, N529, W531, A532	−95.87	*Jatropha curcas*
15	Human Furin:A (PDB:4RYD)	Beta-sitosterol (PubChem CID: 222284)	61.7182	W254, G255, E257, D258, **N295**, R298	−76.61	*Jatropha curcas*
16	Human Furin:A (PDB:4RYD)	Quercetin (PubChem CID: 5280343)	19.2953	S253, W254, D258, S293, G294, **N295**, **S368**, G255, P256	−92.62	*Jatropha curcas*
17	Human Furin:A (PDB:4RYD)	Coumarinic Acid (PubChem CID: 5280841)	8.7769	N310, S311, I312, Q488, G307, W531	−61.24	*Jatropha curcas*
18	Human Furin:A (PDB:4RYD)	Benzoic Acid (PubChem CID: 243)	5.1257	S311, I312, Q488, G307, N310	−51.31	*Jatropha curcas*
19	Human Furin:A (PDB:4RYD)	Salicylic Acid (PubChem CID: 338)	5.9864	R197, R193, H364, **H194**, T365	−66.84	*Jatropha curcas*
20	Human Furin:A (PDB:4RYD)	Tannins (PubChem CID: 250395)	30.5261	**H194**, L227, S253, W254, G255, D258, **N295, S368, D153,** G294	−126.02	*Glycyrrhiza glabra*
21	Human Furin:A (PDB:4RYD)	Asparagine (PubChem CID: 6267)	0.6768	W254, P256, D258, W291, A292, **N295**, D306, G255, G294	−73.96	*Glycyrrhiza glabra*
22	Human Furin:A (PDB:4RYD)	Piperine (PubChem CID: 638024)	22.3105	H405, Q129, D131, N133, D430	−83.07	*Piper chaba*
23	Human Furin:A (PDB:4RYD)	Pipernonaline (PubChem CID: 9974595)	25.6848	G255, D258, H364, **H194**, W254, **N295**, T365	−83.42	*Piper chaba*
24	Human Furin:A (PDB:4RYD)	Sterol (PubChem CID: 1107)	46.5331	R391, V444, A445, V278, S279, T389, W390, Q447	−71.34	*Glycyrrhiza glabra* *Oxalis carniculata* *Jatropha curcas* *Oxalis carniculata*
25	Human Furin:A (PDB:4RYD)	Glycyrrhizin (PubChem CID: 128229)	147.4117	H364, R193, R197, N295, Q346, Q350, T365, G366, W328	−106.91	*Glycyrrhiza glabra*
26	Human Furin:A (PDB:4RYD)	Triterpenoid (PubChem CID: 451674)	83.8831	R268, Q488, P266, E271, G307, S311, Y313, R490, W531, A532	−102.97	*Glycyrrhiza glabra*
27	Human Furin:A (PDB:4RYD)	Piperanine (PubChem CID: 5320618)	23.9457	**D153**, D154, **N295, H194,** S253, W254, G255	−64.86	*Piper chaba*
28	Human Furin:A (PDB:4RYD)	Carbenoxolone (PubChem CID: 636403)	94.1615	R498, D264, G307, N310, Q488, V263, G265, P266, D526, W531	−106.93	*Glycyrrhiza glabra*
29	Human Furin:A (PDB:4RYD)	4-hydroxybenzoic Acid (PubChem CID:	6.1428	**N295, S368,** S253, W254, G255	−68.95	*Oxalis corniculata*
30	Human Furin:A (PDB:4RYD)	Caffeic Acid (PubChem CID: 689043)	7.9915	D174, D177, D179, D181, Y186, R225, Q183, P184, R185	−65.75	*Daucus carota*
31	Human Furin:A (PDB:4RYD)	Chlorogenic Acid (PubChem CID: 1794427)	24.4496	D264, G265, P266, E271, N310, Q488, G307, W531	−93.48	*Daucus carota*
32	Human Furin:A(PDB:4RYD)	Ascorbic Acid (PubChem CID: 54670067)	10.0206	S253, W254, G255, A292, **S368,** G294	−81.68	*Daucus carota*
33	Human Furin:A (PDB:4RYD)	Terpinene (PubChem CID: 7462)	8.8331	W254, G255, G294, **N295**	−52.65	*Citrus bergamia*
34	Human Furin:A (PDB:4RYD)	Ibuprofen (PubChem CID: 3672)	13.1030	R197, H364, T365, D191, R193, **H194**	−67.43	*Adhatodavasica*

(*continued on next page*)

Table 3 (*continued*)

Sl. No.	Receptor	Ligand	Energy Minimization of Ligand	Ligand Binding site	Binding Free Energy (kcal/mol)	Plant source
35	Human Furin:A (PDB:4RYD)	Beta-pinene (PubChem CID: 14896)	42.4570	K402, H405, L428	−47.44	*Cinnamomum tamala*
36	Human Furin:A (PDB:4RYD)	Alpha-pipene PubChem CID: 6654)	40.2085	G307, W531, A532	−47.00	*Cinnamomum tamala*
37	Human Furin:A (PDB:4RYD)	Shogoal (PubChem CID: 5281794)	14.4742	G307, S311, Y313, Y571, G265, Q488, W531	−85.21	*Zingiber officinale*
38	Human Furin:A (PDB:4RYD)	Gingerol (PubChem CID: 442793)	13.5860	R490, R498, G527, N529, A532, V263, W531	−81.42	*Zingiber officinale*
39	Human Furin:A (PDB:4RYD)	Curcumin (PubChem CID: 969516)	16.2009	N310, S311, D530, W531, A532, E271. G307, R490, Y313,	−101.55	*Zingiber officinale*
40	Human Furin:A (PDB:4RYD)	Citric Acid (PubChem CID: 311)	10.4725	R193, R197, H364, **H194**, T365	−81.18	*Zingiber officinale*
41	Human Furin:A (PDB:4RYD)	Malic Acid (PubChem CID: 525)	4.0677	R193, R197, H364, T365	−73.63	*Zingiber officinale*
42	Human Furin:A (PDB:4RYD)	Oxalic Acid (PubChem CID: 971)	3.4268	R193, R197, H364, T365	−67.47	*Zingiber officinale*
43	Human Furin:A (PDB:4RYD)	Succinic Acid (PubChem CID: 1110)	5.5864	R197, R193, H364, T365, **S368**, **H194**	−64.50	*Zingiber officinale*
44	Human Furin:A (PDB:4RYD)	Tartaric Acid (PubChem CID: 875)	1.5444	R193, **H194**, R197, H364, T365	−77.01	*Zingiber officinale*
45	Human Furin:A (PDB:4RYD)	Geraniol (PubChem CID: 637566)	6.3964	P256, S253, W254, G255	−62.52	*Glycyrrhiza glabra*
46	Human Furin:A (PDB:4RYD)	Pentanol (PubChem CID: 6276)	3.5892	W291, A292, D306, W254	−47.22	*Glycyrrhiza glabra*
47	Human Furin:A (PDB:4RYD)	Hexanol (PubChem CID: 8103)	4.2305	S302, L515, A517, H422, T514	−48.81	*Glycyrrhiza glabra*
48	Human Furin:A (PDB:4RYD)	Terpinen-4-ol (PubChem CID: 11230)	11.9362	N310, A532, G307, W531	−53.53	*Glycyrrhiza glabra*
49	Human Furin:A (PDB:4RYD)	Alpha-terpineol (PubChem CID: 17100)	10.3419	R512, H537, A412, T413, T511	−60.28	*Glycyrrhiza glabra*
50	Human Furin:A (PDB:4RYD)	Propionic Acid (PubChem CID: 1032)	2.2108	S293, G294, T367	−42.62	*Glycyrrhiza glabra*
51	Human Furin:A (PDB:4RYD)	Furfural (PubChem CID: 7362)	16.7451	**N295**, W254, G255, G294	−54.76	*Glycyrrhiza glabra*
52	Human Furin:A (PDB:4RYD)	2, 3 butanediol (PubChem CID: 262)	2.2703	W254, A292, G255	−54.22	*Glycyrrhiza glabra*
53	Human Furin:A (PDB:4RYD)	Furfuryl formate (PubChem CID: 556916)	19.4771	D258, W254, G255, G294, **N295**	−56.77	*Glycyrrhiza glabra*
54	Human Furin:A (PDB:4RYD)	Maltol (PubChem CID: 8369)	1.5977	W254, A292, G255, S293, G294	−62.88	*Glycyrrhiza glabra*
55	Human Furin:A (PDB:4RYD)	Piperonal (PubChem CID: 8438)	14.3266	D258, **N295**, S253, W254, G255, G294	−75.95	*Piper chaba*
56	Human Furin:A (PDB:4RYD)	2, 3, 5 Trimethyl pyrazine (PubChem CID: 26808)	6.2161	W254, A292, G255, S293, G294	−66.09	*Piper chaba*
57	Human Furin:A (PDB:4RYD)	Methyl piperate (PubChem CID: 9921021)	17.1656	G265, I312, Q488, G307, S311, Y313, W531	−80.98	*Piper chaba*
58	Human Furin:A (PDB:4RYD)	Piperundecalidine (PubChem CID: 44453654)	25.5185	S311, Q488, R498, E271, Y313, N529	−84.87	*Piper chaba*
59	Human Furin:A (PDB:4RYD)	Piperchabamide C (PubChem CID: 44454018)	26.7749	H395, R483, T573, A436, N440, W441, T442, V444	−86.33	*Piper chaba*
60	Human Furin:A (PDB:4RYD)	4, 5 Dihydropiperlonguminine (PubChem CID:12682184)	8.4121	D258, G294, S253, W254, G255	−81.69	
61	Human Furin:A (PDB:4RYD)	Piperlonguminine (PubChem CID: 5320621)	5.1772	G126, H405, V127, Q129, D131, N133, L428	−83.73	*Piper longum*
62	Human Furin:A (PDB:4RYD)	Retrofractamide C (PubChem CID: 25255091)	7.3032	R185, D228, G229, **N295**, **S368**, **H194**, W254	−78.59	*Piper chaba*
63	Human Furin:A (PDB:4RYD)	Piperchabamide D (PubChem CID: 16041827)	11.4058	D301, A332, R512, H300, D410, H422	−85.95	*Piper chaba*
64	Human Furin:A (PDB:4RYD)	Guineensine (PubChem CID: 6442405)	7.0806	R193, D264, **H194**, E236, W254, G255, Y308	−91.46	*Piper chaba*
65	Human Furin:A (PDB:4RYD)	Brachystamide B (PubChem CID: 10047263)	8.3768	K419, T400, K402, P403, R418, L437, Q439, N440	−88.28	*Piper chaba*

defence, treatment against COVID-19 disease. However, the key composite in those species to obstruct SARS-CoV is still unclear but in recent years many bio-active compounds have been purified from natural herbs including methyl gallate, gallic acid, quercetin, quercitrin, rutin, (+)-catechin, (−)-epicatechin, kaempferol, betasitosterol, stigmasterol, kaempferol-*d*-glucoside, beta-sitosteryl-glucoside, phytol and toosendanin [101]. Among such plant product, lectins (Urticarious agglutinin) and secondary metabolites such as Baicalin and Glycyrrhizin have shown promising results in SARS-CoV as well as an encouraging in-silico outcomes in the COVID-19 disease (Table 4). On the other hand, quercetin, has been reported to have antiviral activity against HIV-luc/SARS [102]. Meanwhile, numerous studies have tried to practice the plants as a bioreactor to express the SARS vaccinal agents or to overexpress the vaccinal agents. Overall, further studies are required in order to more assess the anti-viral capability of plant species. Such plant derived compounds might be a better choice for further research toward finding a novel herbal-based treatment approach. In this study, among more than 40 number of herbal plants along with their composition analysis,

Table 4
Identified major compounds including their source.

Binding free energy	Compound name	Source of the compound
−126.02	Tannins	*Glycyrrhiza glabra*
−125.73	Proanthocyanidins	*Cinnamomum zeylanicum*
−118.61	Rutin	*Jatropha curcas*
−106.93	Carbenoxolone	*Glycyrrhiza glabra*
−106.91	Glycyrrhizin	*Glycyrrhiza glabra*
−102.97	Triterpenoid	*Glycyrrhiza glabra*
−101.55	Curcumin	*Zingiber officinale*
−100.80	Myricetin	*Jatropha curcas*
−100.39	Vitexxin	*Jatropha curcas*

Glycyrrhiza glabra is the best one as they have the principals compounds like tannins, carbenoxolone, triterpenoid and glycyrrhizin which showed the highest binding ability with furin protease, followed by *Cinnamomum zeylanicum* and *Jatropha curcas*. The knowledge of numerous native plants from village elderly and local healers can be of massive significance to the local people and herbal medicinal researchers.

Author's contribution

Sanjoy Pal, Trinath Chowdhury, Kishalay Paria, Sounik Manna, Sana Parveen, Pralay Sharma and Sk Saruk Islam collected the data and wrote the manuscript. Santi M Mandal and Sk Md Abu Imam Saadi supervised and corrected the manuscript. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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