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Natural medicinal plant products as an immune-boosters: A possible role to lessen the impact of Covid-19

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ABSTRACT

Transmissible Covid-19, caused by novel corona virus since last of 2019 has outspread widely until now. Where, India was the second most affected country and 3rd in mortality rate. In world ancient history, medicinal plants were played a crucial role to cure several diseases. In present study, we show some novel natural medicinal plant metabolites as the potential inhibitors against papain-like protease (PLpro), main protease (Mpro) and RNA-dependent RNA polymerase (RdRp), transmembrane proteinase Serine 2 (TMPRSS2) and angiotensin converting enzyme-2 (ACE-2) of Covid-19. Plant metabolites were having been proven to inhibit SARS-CoVs, which also actively walkable against Covid-19.

1. Introduction

Coronavirus disease (Ccvid-19) is an acute respiratory infectious disease caused by SARS-CoV-2 a novel coronavirus strain that has emerged a pandemic issue and greatly effects public health widely in 2019–20 [1,2,3]. First case of Covid −19 was initially reported in Wuhan capital of Hubei Province of China and then it spread widely in 215 countries [4,5]. The World Health Organization (WHO) declared Covid-19 as a Public Health Emergency of International Concern in 30th January (https://www.who.int/), [6]. This disease spread has led to more than 108,153,741 affirmed cases and 2,381,295 passed away around the globe on February 14, 2021, and India was the second most affected country (10,904,940 affirmed cases) and 3rd position in deaths (1,55,642) cases (https://covid19. who.int/table) in February 14, 2021. Still to date the number of affected cases in Covid-19 was steadily increasing across the globe, and so far, due to its high mortality rate and rapid transmission by human-to-human connection (WHO, 2020) [7,8,3]. After SARS-CoV in 2002 and MERS-CoV in 2012, Covid-19 ranked third disease epidemic situation in human population during 21st century [9,10,11]. Covid-19 are identified as β-coronavirus, enveloped, positive ss-RNA viruses with varied genome size ranging from 26 to 32 kilobase pairs and genome sequence similarity with MERS-CoV and SARS-CoV [12,5,3]. Nomenclature of Covid-19 based on its 82% identity to the SARS-CoV genome sequence by the taxonomists Coronavirus Study Group (CSG) under the aegis of International Committee on Taxonomy of Viruses (ICTV) [13]. In Indian subcontinent history, herbal medicinal plants were used to cure various diseases based on health healing systems. It was established that various medicinal plant such as: *Angelica keiskei* inhibit cysteine proteases of SARS-CoV [14], *Ecklonia cava* as a SARS-CoV 3CLpro inhibitor [15], *Salvia miltiorrhiza* effects on cardiovascular system during SARS-CoV [16], *Torreya nucifera (L.)* acts as a SARS-CoV 3CLpro inhibition [17], *Isatis indigotica* an Anti-SARS coronavirus 3C-like protease inhibitor [18] and *Lycoris radiata* have antiviral activities against SARS-associated coronavirus [19] were used for disease cure through ayurveda treatments. It was reported that, different compounds extracted from medicinal plant like steroids, polysaccharides, alkaloids, glycosides, etc have anti-viral, anti-bacterial, anti-fungal, anti-inflammatory, analgesic, anti-diabetic, anti-stress, anti-tumourneuro protective, rejuvenating, cardioprotective and

Abbreviations: ACE-2, angiotensin converting enzyme-2; Covid-19, corona virus disease-2019; CSG, Coronavirus Study Group; E, small envelope protein; ICTV, International Committee on Taxonomy of Viruses; N, nucleocapsid protein; M, matrix protein; Mpro, main protease; nsps, non-structural proteins; PLpro, papain-like protease; RBD, receptor binding domain; RdRp, RNA-dependent RNA polymerase; S, spike protein; ST, swine testicular; TMPRSS2, transmembrane proteinase Serine 2; WHO, world health organization; IC, Inhibitory concentration.

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immunomodulatory effects in several disease [20,21,22,23,24]. From the beginning of Covid-19 outbreak in china, traditional herbal medicines were used to cure the viral disease. It was found that out of 214 Covid-19 patients, 90% of patients were recovery from the Covid-19 viral disease by using the traditional herbal medicines in China [25,26]. Furthermore, to cure these viral diseases, specialists recommended different herbal medicinal plant for Covid-19 patients based on their disease-stage and symptom differentiation [27]. In present review, we summarize the proposed plant derived metabolites to suppress the causative agent of Covid-19 i.e., severe acute respiratory syndrome coronavirus-2. Hence forward, we explored the effect of some plant metabolites like emodin, lopinavir, lycorine, oseltamivir, hypericin, etc against the Covid-19 disease. So, present review emphases on the probable uses of herbal medicinal plant metabolites and natural products to prevention or treatment of Covid-19 infection.

2. Role of plant metabolites to suppress the Covid-19

By effectively completing joint examination, the structure of Covid-19 encodes key proteases such as papain-like protease (PLpro), main protease (Mpro) and RNA-dependent RNA polymerase (RdRp) have been established in Nature & Science [28]. These proteases are engaged with the proteolytic handling of the polyproteins into individual non-structural proteins (nsps) to control the viral genome articulation and replication [29]. A started program of consolidated structure helped is utilized for drug plan, virtual medication screening and high throughput screening to recognize new medication drives that focus on the Covid-19 infection principal protease was planned. For this outbreaks situation to discover active compounds to suppress the causal microbes, scientists and researchers discover some inhibitor like N3, through docking-based drug designing process and subsequently design the structure of Covid-19 virus protease i.e., Mpro (3CLpro) interacted with that compound [30]. RdRp, (namely nsp12) is the focal segment of coronaviral transcription and replication apparatus and shows up. Specialists likewise report that cofactors nsp8 and nsp7 complex with the cryo-EM structure of Covid-19 infection full-length nsp12 at 2.9 Å resolution. A relative investigation model established how Remdesivir ties to that polymerase. The structure gives a premise to the plan of new antiviral therapeutics focusing on viral RdRp [31]. The study only focuses on the antiviral potential of medicinal plants against human SARS coronaviruses since the Covid-19 pandemic by SARSCoV-2 has become the greatest catastrophe event in the 21st century, and until now, there is no specific medication discovered to treat patients infected by this virus. Moreover, various important phytochemical groups, and their potentials for exhibiting human coronaviruses are discussed in details (Fig. 1).

2.1. Several natural products block ACE2

The infiltration of the SARS-CoV-2 genome into the host cells happens because of the SARS-CoV-2 spike protein authoritative to have receptors [32]. [33] exhibited that the ACE2 receptor is utilized by SARS-CoV-2 to enter human cells. Study report that, 25 Chinese natural families were found to fundamentally restrain the communication SARS-CoV – ACE2. Among them, Polygonaceae, Labiatae, Magnoliaceae, and Nelumbonaceae displayed the main inhibitory impacts. These inhibitory impacts were credited to emodin (1,3,8-trihydroxy-6 methylanthraquinone) delivered in significant levels in variety Rheum and Polygonum. Emodin hindered the communication SARS-CoV S protein and ACE2 in a portion subordinate way with an IC50 of 200 μM [34] (Table 1; Fig. 2).

2.2. Natural products targeting the transmembrane proteinase Serine 2 (TMPRSS2)

Recently [33], demonstrated that besides using ACE2 receptor arrive to the host cells, SARS-CoV-2 uses also TMPRSS2 for S protein priming. After the interaction among the S protein (SARS-CoV-2) and the ACE2 (host cell), the complex is cleaved by the TMPRSS2 to facilitate viral entry (Rabi et al., 2020) [55]. found that an significant TMPRSS2

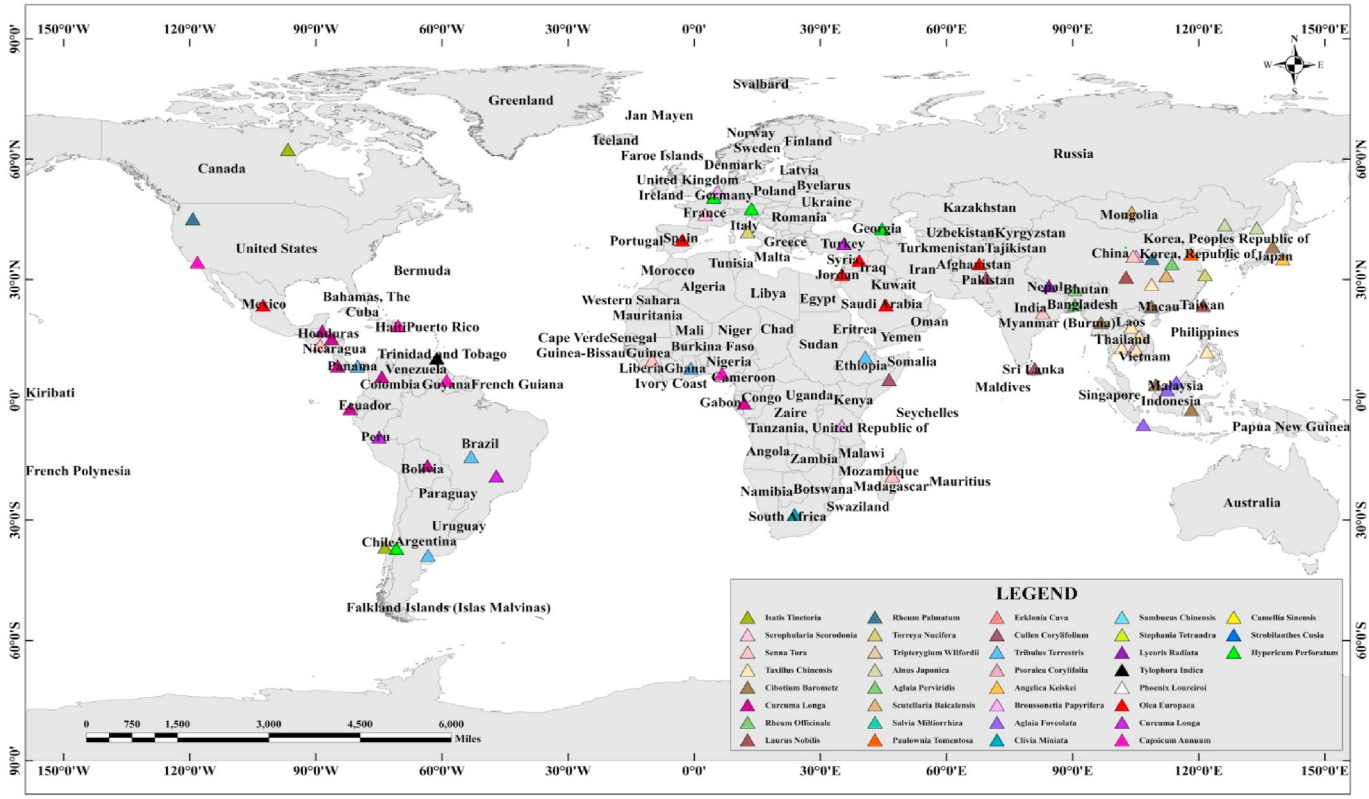

Fig. 1. Widely distribution patterns of medicinal plants used in our study.

Table-1
Activity of Natural medicinal plant products against corona virus.

Medicinal plants	Antiviral compound (s)	Virus	Antiviral effects	References
Hypericum perforatum L.	Hypericin	2019-nCoV NSP 14	C- & N-terminal domains of Covid-19 NSP 14 were found to be bound by Hypericin.	[35]
Strobilanthes cusia (Nees) Kuntze	Tryptanthrin, Indigodole B	HCoV-NL63	Blocking viral RNA genome synthesis and papain-like protease 2 activity	[36]
Camellia sinensis (L.) Kuntze	Theaflavin	SARS-CoV-2	Binding to RNA-dependent RNA polymerase	[37]
Capsicum annuum L., *Curcuma longa* L., *Mentha longifolia* L., *Olea europaea* L., *Phoenix hanceana* Naudin and *Camellia sinensis* (L.) Kuntze	Glucoside, Curcumin, Oleuropein, Luteolin-7, Epicatechin gallate, Catechin, Demethoxycurcumin, glucoside, and Apigenin-7	Coronavirus (CoV)	Covid-19 Mpro protein was inhabited by all these antiviral compounds. However, further investigations are required to confirm their forthcoming applications.	[38]
Tylophora indica (Burm. f.) Merrill	Tylophorine	Coronaviruses	Tylophorine-based biomolecules exhibit broad spectrum potential for inhabiting coronaviruses.	[35]
Lycoris radiata (L'Her.) Herb	Lycorine	Severe acute Respiratory syndrome (SARS)- CoV	Lycorine could be a potential reagent for antiviral drug development.	[39]
Stephania tetrandra S. Moore and related species	Tetrandrine, Fangchinoline, Cepharanthine	HCoV-OC43	Inhibit viral replication and expression of viral S and N protein.	[40]
Sambucus formosana Nakai	Caffeic acid	HCoV-NL63	Inhibits cell docking.	[41]
Clivia miniata (Lindl.) Verschaff.	Lycorine and mycophenolate mofetil	HCoV-OC43, MERS-CoV, HCoV-NL63 and MHV-A59	Lycorine inhabited DNA, RNA, and synthesis protein which effects on cell division. Mycophenolate mofetil exhibited immune suppressing effect on coronaviruses.	[42]
Aglaia foveolata Pannell	Silvestrol	HCoV-229E	Silvestrol exhibited in vitro potential of inhibition of cap-dependent viral mRNA translation.	[43]
Broussonetia papyrifera (L.) Vent.	Kazinol A, Kazinol B, Kazinol F, and Kazinol J	Papain-like and 3-chymo-trypsin like Coronavirus cysteine proteases	Both PL and 3CL CoV proteases were distinctly inhibited by these polyphenols.	[44]
Broussonetia papyrifera (L.) Vent.	Polyphenols: biphenyl propanoid, Broussochalcone A, and Broussochalcone B	CoV cysteine proteases	Different polyphenols from *B. papyrifera* could be promising candidates for developing anticorona viral medications.	[44]
Angelica keiskei (Miq.) Koidz	Xanthoangelol E	SARS-CoV- PLpro SARS-CoV- 3CL (pro)	A dose-dependent inhibition of SARSCoV- PLpro & 3CL (pro) activity.	[14]
Psoralea corylifolia L.	Bavachinin	SARS-CoV	The ethanol extract of these secondary. metabolites demonstrated their high activity Against SARS CoV PLpro.	[45]
Tribulus terrestris L.	Cinnamic acid	SARS-CoV PLpro	Inhibition of SARS-CoV - PLpro in a dosedepenedent Manner.	[46]
Cullen corylifolium (L.) Medik.	Psoralidin	SARS-CoV- PLpro	Inhibition of SARS-CoV PLpro in a dosedepenedent Manner.	[45]
Ecklonia cava Kjellman 1885	Dieckol	Porcine epidemic diarrhea CoV	Dieckol can inhabit viral replication.	[47]
Paulownia tomentosa (Thunb.) Steud.	Tomentin 6-galactoside (Flavonoid)	SARS-CoV	SARS-CoV papain-like proteas was inhabited by granulated flavonoids.	[48]
Salvia miltiorrhiza Bunge	Tanshinone IIA, Tanshinone IIB Methyl tanshinonate, Cryptotanshinone, Dihydrotanshinone I	SARS-CoV PLpro	Non-competitive enzyme isomerization inhibitor of protease (except for rosmariquinone which exhibits simple reversible slow-binding inhibition).	[49]
Scutettaria baicalensis Georg	Myricetin, Scutellarein	SARS-CoV helicase nsP13	Inhibit ATPase activity of SARSCoV helicase nsP13.	[50]
Aglaia perviridis Hiern	Myricetin and Scutellarein	SARS-CoV	Affects ATPase activity that leads to inhibit the SARS-CoV helicase protein.	[50]
Camellia sinensis (L.) Kuntze	Catechin gallate	SARS-CoV	Throughout a screening of different teas, catechins from black tea were found to be the inhibitors of SARS-CoV N protein.	[51]
Alnus japonica (Thunb.) Steud.	Hirsutenone	SARS-CoV	A dose-dependent inhibition of the SARS-CoV-PLpro activity.	[49]
Tripterygium regelii Sprag & Takeda	Celastrol, Tingenone, Iguesterin	SARS-CoV CLpro	Competitive inhibition of CoV protease.	[17]
Torreya nucifera (L.) Siebold and Zucc	Amentoflavone and Apigenin	SARS-CoV	The biflavone and amentoflavone showed most potent 3CL (pro) inhibitory effect.	[17]
Rheum palmatum L.	Possibly anthraquinones	SARS-CoV 3CLpro	Inhibition of 3CLpro.	[52]
Rheum officinale Baill.	Emodin	SARS-CoV S protein	Inhibited binding of S protein to ACE2.	[34]
Curcuma longa L.	Curcumin	SARS-CoV	Curcumin exhibits wide-ranging and distinctive anti-SARS CoV activity.	[53]
Cibotium barometz (L.) J.Sm. *Taxillus chinensis* (DC.) Danser *Cassia tora* L.	Abietane-type diterpenoids, Lignoids	SARS-CoV	Demonstrated strong anti-SARSCoV effects.	[53]
Bupleurum spp. *Heteromorpha* spp. and *Scrophularia scorodonia* L.	Saikosaponin A, Saikosaponin B1, 2, Saikosaponin C, Saikosaponin D	HCoV-229E	Possible interference in early stage of viral replication, e.g. absorption and penetration.	[54]
Isatis indigotica Fortune	Sinigrin, Indigo, β-sitosterol, Aloe-emodin, Hesperetin	SARS-CoV 3CLpro	Inhibition of 3CLpro.	[18]

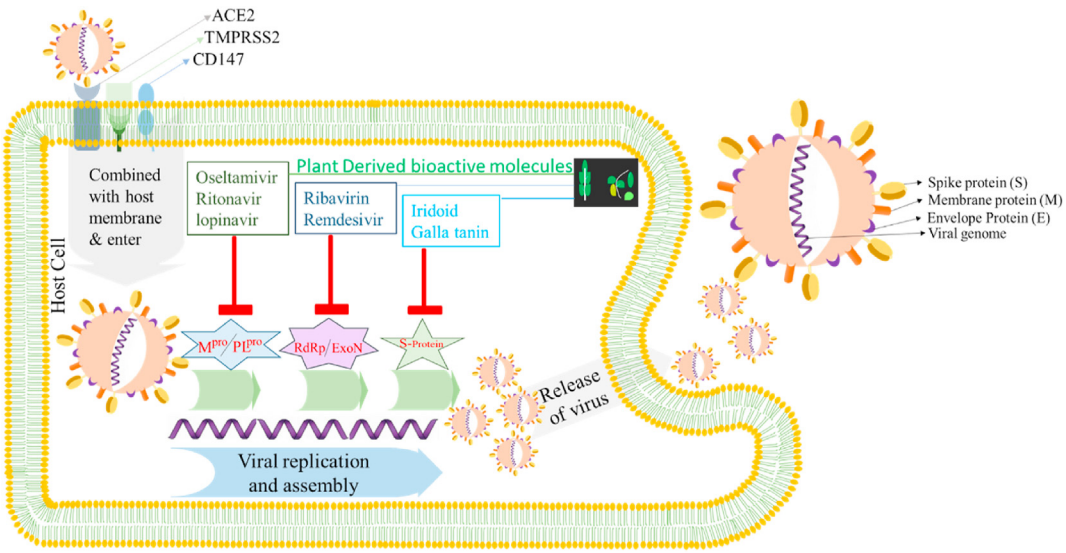

Fig. 2. Structure of Covid-19 and showed the controlling pathway of some Covid-19 viral specific proteins by medicinal plant products.

expression in cells makes them extremely vulnerable to SARS-CoV-2. Several studies have demonstrated that natural products could down regulate or suppress TMPRSS2. It has been shown that kaempferol was able to inactivate TMPRSS2 expression by 49.14 and 79.48% at 5 and 15 mM, respectively [56]. [57] found that a standardized flavonoids formulation including luteolin, quercetin, and kaempferol significantly suppressed TMPRSS2 expression (Table 1; Fig. 2).

2.3. Plant metabolites against main protease (Mpro) protein of Covid-19

Main protease (Mpro) is a homodimer in nature with three structural domains as domain-I, II & III [58]. Also, the M-protease is extremely well-preserved among all the Corona viridae members like as MERS-CoV and SARS-CoV, exhibiting about 40–44% of sequence homology regions [59]. Protease enzymes are actively worked in proteolytic cleaves, where the M-protease generated the non-structural proteins i.e., nsps which actively play an important role in replication of viral genome [60]. The substrate-restricting site is situated in the Cys-His synergist dyad situated in a separated between the domain I and II [61]. Researcher established that, dimerization of these two protomer is significant; notwithstanding, just a single protomer is dynamic at a time. Henceforth, M-protease has developed as the most important potential antiviral objective due to its primary part in self-development and ensuing development of polyproteins [62]. Previous study suggested that phenolic compounds (indigo, indirubin, sinigrin, beta sitosterol and aloeemodin) of *Isatis indigotica* blocks the viral cleavage processing and effects on 3C-like protease of anti-SARS coronavirus [18]. Successfully inhibition of Covid-19 by combination molecular docking of the oseltamivir, ritonavir and lopinavir were supremely active against SARSCoV-2 protease protein [63,64]. Thus, broad in silico contemplates were performed to recognize potential medication competitors, for instance, Bictegravir, Prulifloxacin, Tegobuvi, and Nelfinavir were distinguished as repurposing up-and-comers against Covid-19 by searching for drugs with high restricting limit with SARS-CoV primary protease [26]. Once more, Nelfinavir, a HIV-1 protease inhibitor was likewise anticipated to be an expected inhibitor of Covid-19 fundamental protease by another computational-based investigation [65] (Table 1; Fig. 2).

2.4. Plant metabolites against RdRp of Covid-19

Covid virus are RNA viruses which multiply and replicates in host cells. In the viral genome replication process, RNA-dependent RNA polymerase (RdRp) enzyme plays an important role for synthesis both negative and positive-strand RNA of viral genome [31]. After replication of genomic material, it gone to the maturation phase of virus genome in the host cell using of proteases alike enzyme like as Papain-like protease (PLpro) and 3C-like protease (3CLpro) [4]. Utilizing swine testicular (ST) cells, plant-inferred poisonous substances, as cardenolides (steroid) were applied to watch the movement of hostile to contagious gastroenteritis Covid (TGEV) action [66]. The outcome indicated that ouabain, a significant cardenolide, diminished the amount of TGEV in a given volume of liquid at 0–3000 nM. At the inhibitory centralizations of ouabain (37 nM and 23 nM), the quantity of viral RNA duplicates was likewise decreased to half because of the concealment of viral replication and TGEV action, which at long last lessened viral yield [66]. A few medications are known to have the option to restrain these three cycles, including camostat mesylate as TMPRSS2 inhibitors, arbidol as ACE2 inhibitors, ritonavir and Lopinavir as protease inhibitors, ribavirin and remdesivir as RdRp inhibitors. Previous publication established that, Ritonavir, Chloroquine, Remdesivir, and Lopinavir are an antimicrobial that noticeable has a prospective action in contradiction of Covid-19 [67, 5]. Now, in silico analysis also revealed that polyphenols compounds can inhibit Covid-19 RdRp effectively [68,69] (Table 1; Fig. 2).

2.5. Plant metabolites against spike protein of Covid-19

Covid-19 induces unadorned breathing disorder in humans' beings [[42]]. Major proteins of this viral include nucleocapsid protein (N), matrix protein (M), small envelope protein (E) and spike protein(S) [[70]]. The position of viral add-on to the host cell membrane is within the Spike protein. On average 74 surface spike protein have in coronavirus particle [71]. The Covid-19 S- protein attach to the host cell membrane by a receptor-mediated communication which allows the virous entrance in to the host cell. Researcher established by computationally gritty that, SARS-CoV-2 has alike mechanism like as SARS virus and strongly binds to the angiotensin-converting enzyme-2 (ACE2) receptor [[72,73]]. For attachment, the S protein receptor binding domain (RBD) of SARS coronaviruses in human beings interact with hACE2 receptor binding motif, which existing in the human lungs outer cell membrane [74]. It has proposed that diminishing the degrees of ACE2 on the cell surface or hindering its capacity, helps in forestalling SARS-CoV-2 contamination [[72,75]]. This association will initiation conformational changes of S2 subunit in C-terminal (liable for infection cell film combination) of the S-protein [76]. By restricting the S-protein to the ACE2, the angiotensin 2 is delivered in enormous amounts by the ACE and afterward ties to the AT1R receptor. This cycle prompts fibrosis

and harmful for lung tissues. A potential method of battling the contamination could be the infusion of solvent ACE2 into the circulation system which will have the two-overlay impact; forestalling the connection of the infection to non-tainted cells and renewing ACE2 in contaminated cells. Furthermore, we targeted three different spike protein domains of SARS-CoV-2, where all of these are play crucial roles to manage the viral entry into the host cell [[77]]. Furthermore, docking lessons and MD may likewise be utilized to focus on the Covid S-protein to keep it from entering ACE2 have cells. Cleavage of S-protein of Covid by protease factor Xa is related with viral infectivity [78]. The immunization named mRNA-1273 which contain hereditary material from the S-protein in SARS-CoV-2 and typified with a lipid nanomaterial. In any

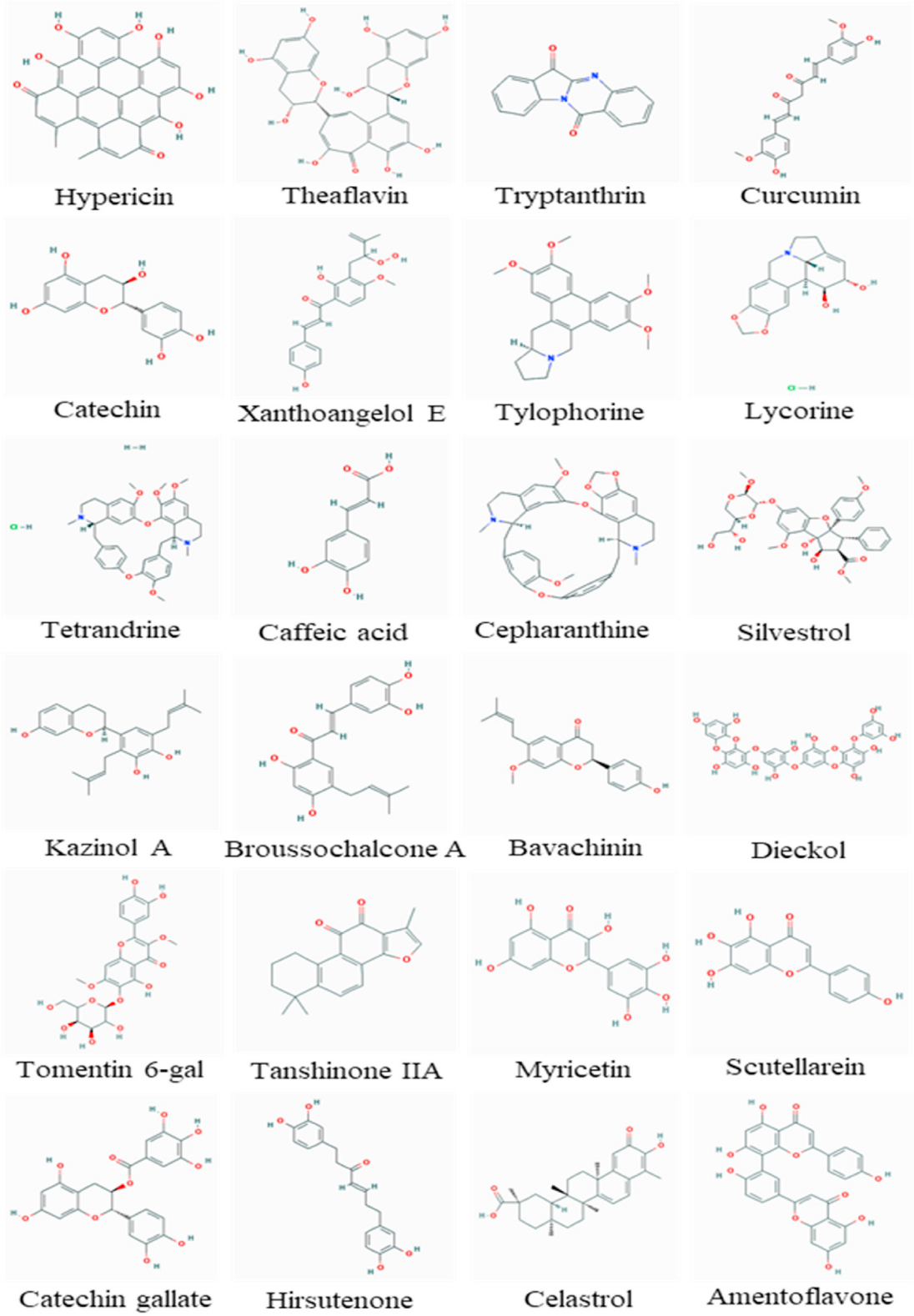

Fig. 3. A: Some phytochemical compound against corona virus.Fig. 3B: Some phytochemical compound against corona virus.

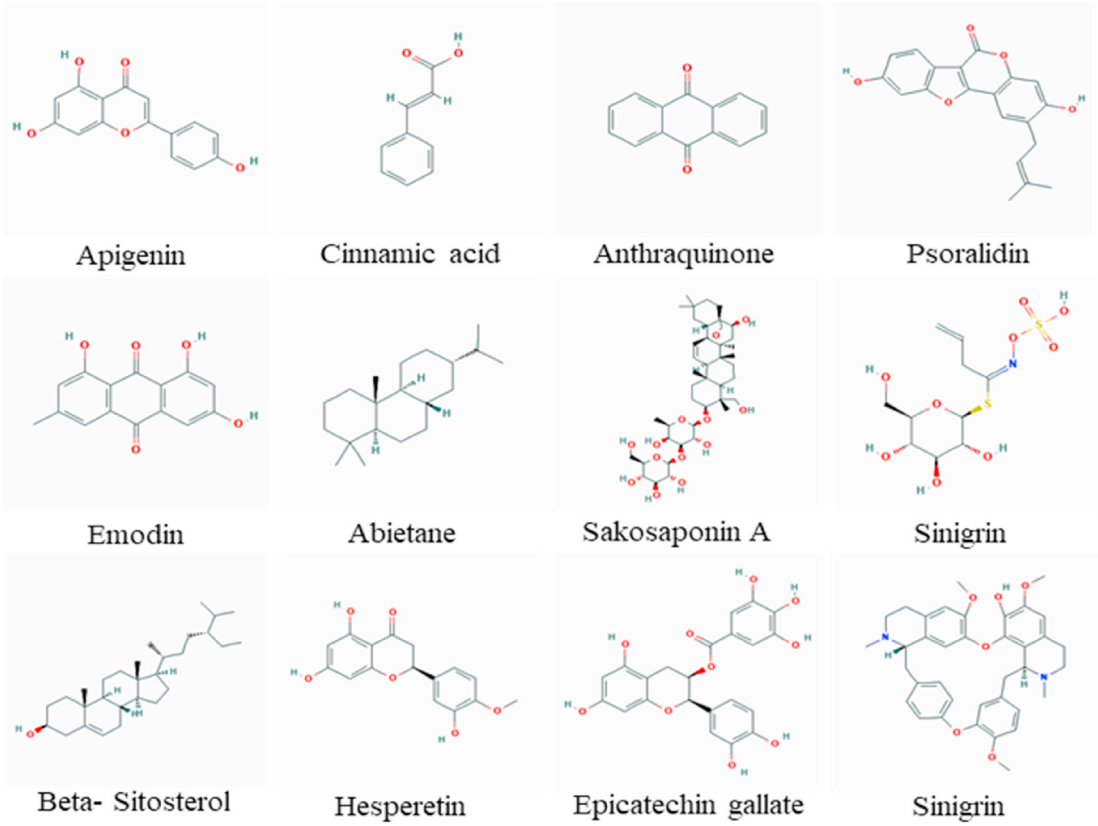

Fig. 3. (*continued*).

case, the investigation of appropriate secure immunization is as of now under assessment and results are yet to be out [79] (Table 1; Fig. 2).

3. Role of different medicinal plants to control the SARS-CoV disease

Researcher established that different protease i.e., papain-like protease (PLpro), main protease (Mpro) and RNA-dependent RNA polymerase (RdRp) are actively work in viral nucleic acid replication and maturation of Covid-19. Therefore, these proteases are play a crucial role for viral multiplication, which cleaves the viral polyproteins such as PP1A and PP1AB into effector proteins [80]. These proteases are blocks by some traditional medicinal plant derived product, here some important medicinal products are listed below (Fig. 3A and B).

3.1. *Cullen corylifolium (L.) Medik & Psoralea corylifolia L*

Previous study supports that Ethanolic extract of some plant species like *Psoralea corylifolia* and *Cullen corylifolium* showed important inhibitory function on PLpro an IC50 of 15 μg/ml. of SARS-CoV. Additionally, some flavonoids compounds present in extract such as Bavachinin, corylifol A, isobavachalcone and psoralidin were inhibit the function of PLpro of SARS-CoV through a dose dependent way with IC50 predictable to be 1.2–38.4 μM. Psoralidin showed highest inhibitory effects (IC50 value 4.2 ± 1.0 μM) and isobavachalcone (IC50 value 7.3 ± 0.8 μM) [45].

3.2. *Paulownia tomentosa (Thunb.)*

Paulownia tomentosa is a high source of miscellaneous secondary metabolites products, mostly prenylated flavonoids compounds. As of today 135, compounds such as flavonoids, glycosides, glycerides, lignans, phenolic quinones, phenolic acids, terpenoids, and other miscellaneous compounds have been isolated from various extracts of this plant. In *P. tomentosa* fruit, five tomentin bioactive compounds such as tomentin A, tomentin B, tomentin C, tomentin D and tomentin E were found till now. An in vitro study to know the efficacy of tomentin bioactive components extracted from P. tomentosa fruit, against SARS-CoVs disease were done by Cho et al. In 2013. These tomentin components has the ability to inhibit SARS-CoV PLpro activity in a dose dependent way with an IC50 value of 5.0–14.4 μM. Tomentin E showed the most elevated inhibitory impact with an IC50 of 5.0 ± 0.06 μM [81].

3.3. *Angelica keiskei (Miq) Koidz*

[14] explored the repressive potential of various alkylated chalcones compounds such as isobavachalcone, xanthoangelol-A, xanthoangelol-B, xanthoangelol-D, xanthoangelol-E, xanthoangelol-F and xantho angelol-G, and four coumarins were extracted from *Angelica keiskei* ethanolic extract. These chalcones can inhibited PLpro of SARS-CoV viral disease in a varied range of significant dose-dependent way, where the IC50 values ranging from 1.2 ± 0.4 to 46.4 ± 7.8 μM.

3.4. *Salvia miltiorrhiza*

Salvia miltiorrhiza ethanolic extract (30 μg/ml) triggered 88% embarrassment of SARS-CoV PLpro gene. Moreover, some bioactive compounds of tanshinones such as rosmariquinone, methyl tanshinonate, tanshinone I, cryptotanshinone, anshinone IIA and IIB) were recognized from the n-hexane element. Fluorometric assay state that these bioactive tanshinones were assessed with esteem to inhibition of PLpro gene of SARS-CoV virus. These molecules exhibited important inhibitory time-dependent activities with IC50 of 0.8–30 μM [49].

3.5. *Alnus japonica (Thunb.) Steud*

[16] utilized movement guided fractionation to distinguish nine

diarylheptanoids (oregonin, platyphyllenone, rubranoside B, hirsutenone, platyphyllone, hirsutanonol, rubranol, platyphyll onol-5-xylopyranoside and rubranoside A) from the ethanol concentrate of Alnus japonica. They assessed their SARS-CoV PLpro inhibitory impact utilizing a consistent fluorometric test. The outcomes demonstrated that hirsutanonol, hirsutenone, oregonin, rubranoside B, rubranol and rubranoside. An applied a critical portion subordinate inhibitory movement towards SARS-CoV PLpro with IC50 going from 3 to 44.5 μM. Hirsutenone had the most intense inhibitory impact with IC50 of 4.1 ± 0.3 μM which was less significant than that of the reference inhibitor curcumin (5.7 μM).

3.6. *Scutettaria baicalensis Georg and Aglaia perviridis Hiern*

64 regular atoms began from 15 restorative species were assessed with respect to their inhibitory action of SARS-CoV helicase. Myricetin and scutellarein altogether hindered 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 repress 90% of the ATPase action of the SARS-CoV helicase. As needs be, Myricetin and scutellarein were recommended to be promising future enemy of SARS drugs.

3.7. *Angelica keiskei (Miq.) Koidz*

Angelica keiskei (Miq.) Koidz. (*Family-Apiaceae*) has usually been used to treat dysgalactia, dysuria, and dyschezia as well as to restore vitality. It was established that nine nine alkylated chalcones, four coumarins, acetylenes, diterpene, various flavonoids, phenolics, sesquiterpene and triterpenes were isolated as the constituents of *A. keiskei*. Inhibitory potential efficacy of nine alkylated chalcones and four coumarins against SARS-CoV protease (3CLpro and PLpro) were determined. Isolated chalcone 6, alkylated chalcones, containing the perhydroxyl group, showed the highly potent SARS-CoV protease (3CLpro and PLpro) inhibitory activity with the IC50 values of 1.2 and 11.4 μM. The activity of these chalkones components ranged from the IC50 11.4 ± 1.4 to 129.8 ± 10.3 μM. Additionally, xanthoangelol E was likewise found to repress SARS-CoV-PLpro [14] it very well may be a promising up-and-comer in the remedial methodology against Covid-19.

3.8. *Ecklonia cava (algae)*

[15] detached nine phlorotannins from the ethanolic concentrate of earthy colored Alga *Ecklonia cava*. These phlorotannins were surveyed with respect to their inhibitory impacts towards SARS-CoV-3C (ace) utilizing a without cell-based test. Some phlorotannins (triphloretol A, 2-phloroeckol, 7-phloroeckol, fucodiphloroethol G, dieckol, and phlorofucofuroeckol A) were demonstrated to be serious inhibitors of SARS-CoV-3CL (expert) in a portion subordinate way. IC50 ranged varied from 2.7 ± 0.6 (dieckol) to 164.7 ± 10.8 μM (triphloretol A).

3.9. *Salvia miltiorrhiza Bunge*

Park O. K. et al. (2012) investigated the inhibitory potential of *Salvia miltiorrhiza* towards SARS-CoV-3CL (pro). They found that *Salvia miltiorrhiza* ethanolic extract (30 μg/ml) resulted in 60% inhibition of SARS-CoV-3CL (pro). Furthermore, they demonstrated that six tanshinones of the plant (lipophilic fraction) exerted marked inhibition of SARS-CoV-3CL (pro) in a dose- but not–time- dependent manner. IC50 was estimated at 14.4–89.1 μM. Dihydrotanshinone I showed the utmost significant repressive outcome with an IC50 of 14.4 ± 0.7 μM.

3.10. *Torreya nucifera (L.) Siebold & Zucc*

Four biflavonoids compounds such as sciadopitysin, ginkgetin, amentoflavone and bilobetin were extracted from the leaves of *Torreya nucifera* also evaluated their inhibitory function on SARS-CoV-3CL (pro) by FRET. All biflavonoids compounds were showed an obvious inhibitory action on SARS-CoV-3CL (pro) gene with IC50 of 8.3–72.3 μM. These repressive actions were showed highly stronger than that of some other eight diterpenoids compounds extracted from the *T. nucifera* (IC50: 49.6–283.5 μM). Amentoflavone applied the main inhibitory action since it had the least IC50 (8.3 ± 1.2 μM). In addition, 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) [17].

3.11. *Isatis indigotica Fortune*

Various plant-based phenolic compounds and isolated 5 major secondary metabolites from root extract of *Isatis indigotica* were acts as potential antiviral against human corona viruses; in which, β-sitosterol, hesperetin, aloe emodin, indigo, & sinigrin were the significant phytochemicals that inhabited the cleavage activity of SARS 3CLpro enzyme with IC50 values of 1210, 365, 8.3, 752, and 217 μM, respectively [18].

3.12. *Lycoris radiata (L'Her.) herb*

According to Ref. [19] ethanol/chloroform extracts of Chinese medicinal herbs produce a single compound (lycorine) from one plant species *L. radiata* was earmarked as a potential drug candidate against SARS-CoV. Lycorine showed the quite higher antiviral efficacy, where the EC50 is 15.7 ± 1.2 nM.

4. Conclusion

The ongoing status of covid-19 is a big issue in the world for the human beings. As we know that, there is no antiviral medicines are available in the market which play the important role to cure the covid-19 patient. The only one-way hope for the present situation is to rely on bioactive molecules from natural products as they have antiviral properties against the covid-19. Researchers are trying to discover the highly effective antiviral compounds to combat covid-19. Medicinal plants and natural plant products are still considered promising substitutes to cure and prevent various diseases. In present situation, our study emphasized some plant derived secondary metabolite compounds that showed actively antiviral properties against coronaviruses through impeding the main machinery used in their pathogenesis and replication cycle. But the lessons assessing the anti-Covid-19 effects of traditional medicinal metabolites are still inadequate and comparatively undeveloped so, there is a crucial necessity to recognize and develop active antivirals in contradiction of Covid-19 to fight it. Present review reveals that some natural medicinal products with IC_{50} value ranging from 0.8 to 46.4 μM and above may well be considered as auspicious anti-Covid-19 agents, also these have capability to block some important proteins i.e., papain-like protease (PLpro), main protease (Mpro), cellular receptor ACE2 and RNA-dependent RNA polymerase (RdRp). Some interventional studies are still required to prevent, assessed the Covid −19 viral infection with suitable plant metabolites or natural herbal medicinal plant products.

Author's contribution

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Declaration of competing interest

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References

[1] S. Boopathi, A.B. Poma, P. Kolandaivel, Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment, J. Biomol. Struct. Dyn. (2020), https://doi.org/10.1080/07391102.2020.1758788.
[2] P.I. Lee, P.R. Hsueh, Emerging threats from zoonotic coronaviruses-from SARS and MERS to 2019-nCoV, J. Microbiol. Immunol. Infect. 53 (3) (2020 Jun) 365–367, https://doi.org/10.1016/j.jmii.2020.02.001. Epub 2020 Feb 4. PMID: 32035811; PMCID: PMC7102579.
[3] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G.F. Gao, W. Tan, A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (2020) 727–733.
[4] A.D. Elmezayen, A. Al-Obaidi, A.T. Sahin, K. Yelekci, Drug repurposing for coronavirus (COVID-19): in silicoscreening of knowndrugs against coronavirus 3CL hydrolase and protease enzymes, J. Biomol. Struct. Dyn. (2020), https://doi.org/10.1080/07391102.2020.1758791.
[5] C. Wu, Y. Liu, Y. Yang, P. Zhang, W. Zhong, Y. Wang, Q. Wang, Y. Xu, M. Li, X. Li, M. Zheng, L. Chen, H. Li, Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods, Acta Pharm. Sin. B. 20 (2020) 1–44.
[6] J.S. Mackenzie, D.W. Smith, COVID-19: a novel zoonotic disease caused by a coronavirus from China: what we know and what we don't, Microbiology Australia 41 (1) (2020) 45, https://doi.org/10.1071/MA20013.
[7] I. Aanouz, A. Belhassan, K. Khatabi, T. Lakhlifi, M. Idrissi, M. Bouachrine, Moroccan medicinal plants as inhibitors of COVID-19: computational investigations, J. Biomol. Struct. Dyn. (2020) 1758790, https://doi.org/10.1080/07391102.2020.
[8] P.K. Bhatraju, B.J. Ghassemieh, M. Nichols, R. Kim, K.R. Jerome, A.K. Nalla, A.L. Greninger, S. Pipavath, M.M. Wurfel, L. Evans, P.A. Kritek, T.E. West, A. Luks, A. Gerbino, C.R. Dale, J.D. Goldman, S. O'Mahony, C. Mikacenic, Covid-19 in critically ill patients in the seattle region—case series, N. Engl. J. Med. 382 (21) (2020) 2012–2022, https://doi.org/10.1056/NEJMoa2004500.
[9] Y.R. Guo, Q.D. Cao, Z.S. Hong, Y.Y. Tan, S.D. Chen, H.J. Jin, K.S. Tan, D.Y. Wang, Y. Yan, The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status, Mil Med Res 7 (2020) 11.
[10] M.K. Gupta, S. Vemula, R. Donde, G. Gouda, L. Behera, R. Vadde, In-silico approaches to detect inhibitors of the human severe acute respiratory syndrome coronavirus envelope protein ion channel, J. Biomol. Struct. Dyn. (2020), https://doi.org/10.1080/07391102.2020.1751300.
[11] M. Yuan, W. Yin, Z. Tao, W. Tan, Y. Hu, Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China, PloS One 15 (3) (2020), e0230548, https://doi.org/10.1371/journal.pone.0230548.
[12] J.F. Chan, K.H. Kok, Z. Zhu, H. Chu, K.K. To, S. Yuan, et al., Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan, Emerg. Microb. Infect. 9 (1) (2020) 221–236.
[13] A. Hasan, B.A. Paray, A. Hussain, F.A. Qadir, F. Attar, F.M. Aziz, M. Sharifi, H. Derakhshankhah, B. Rasti, M. Mehrabi, K. Shahpasand, A.A. Saboury, M. Falahati, A review on the eavage priming of the spike protein on coronavirus by angiotensin-converting enzyme-2 and furin, J. Biomol. Struct. Dyn. (2020), https://doi.org/10.1080/07391102.2020.1754293.
[14] J.Y. Park, J.A. Ko, D.W. Kim, Y.M. Kim, H.J. Kwon, H.J. Jeong, et al., Chalcones isolated from Angelica keiskei inhibit cysteine proteases of SARSCoV, J. Enzym. Inhib. Med. Chem. 31 (1) (2016) 23–30, https://doi.org/10.3109/14756366.2014.1003215.
[15] J.Y. Park, J.H. Kim, J.M. Kwon, H.J. Kwon, H.J. Jeong, Y.M. Kim, et al., Dieckol, a SARS-CoV 3CLpro inhibitor, isolated from the edible brown algae Ecklonia cava, Bioorg. Med. Chem. 21 (13) (2013) 3730, https://doi.org/10.1016/j.bmc.2013.04.026.
[16] J.Y. Park, H.J. Jeong, J.H. Kim, Y.M. Kim, S.J. Park, D. Kim, et al., Diarylheptanoids from *Alnus japonica* inhibit papain-like protease of severe acute respiratory syndrome coronavirus, Biol. Pharm. Bull. 35 (2012) 2036–2042, https://doi.org/10.1248/bpb.b12-00623.
[17] Y.B. Ryu, H.J. Jeong, J.H. Kim, Y.M. Kim, J.Y. Park, D. Kim, et al., Biflavonoids from *Torreya nucifera* displaying SARS-CoV $3CL^{pro}$ inhibition, Bioorg. Med. Chem. 18 (2010) 7940–7947, https://doi.org/10.1016/j.bmc.2010.09.035.
[18] C.W. Lin, F.J. Tsai, C.H. Tsai, C.C. Lai, L. Wan, T.Y. Ho, C.C. Hsieh, P.D. Chao, Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds, Antivir. Res. 68 (1) (2005) 36–42.
[19] S.Y. Li, C. Chen, H.Q. Zhang, H.Y. Guo, H. Wang, L. Wang, X. Zhang, S.N. Hua, J. Yu, P.G. Xiao, R.S. Li, X. Tan, Identification of natural compounds with antiviral activities against SARS-associated coronavirus, Antivir. Res. 67 (1) (2005) 18–23.
[20] N. Jamshidi, M.M. Cohen, The clinical efficacy and safety of tulsi in humans: a systematic review of the literature, Evidence-Based Complementary and Alternative Medicine, 2017 (2017) 9217567.
[21] L. Kapoor, CRC Handbook of Ayurvedic Medicinal Plants/author, L.D. Kapoor. – Version Details – Trove, CRC Press, Boca Raton, FL, 1990. Retrieved June 24, 2020, from, https://trove.nla.gov.au/work/16589020?q&versionId=19467951.
[22] P. Sharma, J. Parmar, P. Sharma, P. Verma, P.K. Goyal, Radiation-induced Testicular Injury and its Amelioration by Tinospora Cordifolia (An Indian Medicinal Plant) Extract. Evidence Based Complementary and Alternative Medicine, ECAM, 2011, p. 643847.
[23] M.R. Ven Murthy, P.K. Ranjekar, C. Ramassamy, M. Deshpande, Scientific basis for the use of Indian ayurvedic medicinal plants in the treatment of neurodegenerative disorders: Ashwagandha, Cent. Nerv. Syst. Agents Med. Chem. 10 (3) (2010) 238–246, https://doi.org/10.2174/1871524911006030238.
[24] V.K. Vyas, P. Bhandari, R. Patidar, A comprehensive review on Withania somnifera dunal, J. Nat. Remedies 11 (1) (2011) 1–13, https://doi.org/10.18311/JNR/2011/43.
[25] D.U. Hong-Zhi, X.Y. Hou, Y.H. Miao, B.S. Huang, D.H. Liu, Traditional Chinese Medicine: an effective treatment for 2019 novel coronavirus pneumonia (NCP), Chin. J. Nat. Med. 18 (3) (2020) 226–230, https://doi.org/10.1016/S1875-5364(20)30022-4.
[26] Z. Xu, C. Peng, Y. Shi, et al., Nelfinavir was predicted to be a potential inhibitor of 2019-nCov main protease by an integrative approach combining homology modelling, molecular docking and binding free energy calculation, bioRxiv (2020), https://doi.org/10.1101/2020.01.27.921627.
[27] Y.H. Jin, L. Cai, Z.S. Cheng, H. Cheng, T. Deng, Y.P. Fan, et al., A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (COVID-19) infected pneumonia (standard version), Mil. Med. Res. 7 (1) (2020a) 4, https://doi.org/10.1186/s40779-020-0233-6.
[28] V. Thiel, K.A. Ivanov, A. Putics, T. Hertzig, B. Schelle, S. Bayer, B. Weibbrich, E.J. Snijder, H. Rabenau, H.W. Doerr, A.E. Gorbalenya, J. Ziebuhr, Mechanisms and enzymes involved in SARS coronavirus genome expression, J. Gen. Virol. 84 (9) (2003) 2305–2315, https://doi.org/10.1099/vir.0.19424-0.
[29] X. Xue, H. Yu, H. Yang, F. Xue, Z. Wu, W. Shen, J. Li, Z. Zhou, Y. Ding, Q. Zhao, X.C. Zhang, M. Liao, M. Bartlam, Z. Rao, Structures of two coronavirus main proteases: implications for substrate binding and antiviral drug design, J. Virol. 82 (5) (2008) 2515–2527, https://doi.org/10.1128/JVI.02114-07.
[30] Z. Jin, X. Du, Y. Xu, Y. Deng, M. Liu, B. Zhao, et al., Structure of Mpro from COVID-19 virus and discovery of its inhibitors, Nature (2020), https://doi.org/10.1038/s41586-020-2223-y.
[31] Y. Gao, L. Yan, Y. Huang, F. Liu, Y. Zhao, L. Cao, T. Wang, Q. Sun, Z. Ming, L. Zhang, J. Ge, L. Zheng, Y. Zhang, H. Wang, Y. Zhu, C. Zhu, T. Hu, T. Hua, B. Zhang, X. Yang, J. Li, H. Yang, Z. Liu, W. Xu, L.W. Guddat, Q. Wang, Z. Lou, Z. Rao, Structure of the RNA-dependent RNA polymerase from COVID-19 virus, Science 368 (6492) (2020 May 15) 779–782, https://doi.org/10.1126/science.abb7498. Epub 2020 Apr 10. PMID: 32277040; PMCID: PMC7164392.
[32] C.J. Sigrist, A. Bridge, P. Le Mercier, A potential role for integrins in host cell entry by SARS-CoV-2, Antivir. Res. 177 (2020) 104759, https://doi.org/10.1016/j.antiviral.2020.104759.
[33] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2020) 1–10, https://doi.org/10.1016/j.cell.2020.02.052.
[34] T.Y. Ho, S.L. Wu, J.C. Chen, C.C. Li, C.Y. Hsiang, Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction, Antivir. Res. 74 (2007) 92–101, https://doi.org/10.1016/j.antiviral.2006.04.014.
[35] Y. Yang, M.S. Islam, J. Wang, Y. Li, X. Chen, Traditional Chinese medicine in the treatment of patients infected with 2019- new coronavirus (SARS-CoV-2): a review and perspective, Int. J. Biol. Sci. 16 (10) (2020) 1708–1717, https://doi.org/10.7150/ijbs.45538.
[36] Y.C. Tsai, C.L. Lee, H.R. Yen, Y.S. Chang, Y.P. Lin, S.H. Huang, C.W. Lin, Antiviral action of tryptanthrin isolated from Strobilanthes cusia leaf against human coronavirus NL63, Biomol 10 (3) (2020). URL: https://pubchem.ncbi.nlm.nih.gov, https://www.who.int/. URL:.
[37] J. Lung, Y.S. Lin, Y.H. Yang, Y.L. Chou, L.H. Shu, Y.C. Cheng, H.T. Liu, C.Y. Wu, The potential chemical structure of anti-SARS-CoV-2 RNA-dependent RNA polymerase, J. Med. Virol. 92 (6) (2020) 693–697.
[38] S. Khaerunnisa, H. Kurniawan, R. Awaluddin, S. Suhartati, S. Soetjipto, Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study, Preprints 2020 (2020), https://doi.org/10.20944/preprints202003.0226.v1, 2020030226.
[39] L. Suryanarayana, D. Banavath, A Review on identification of antiviral potential medicinal plant compounds against with COVID-19. I, J. Rese. Engi. Sci. Manag. 3 (3) (2020) 675–679.
[40] D.E. Kim, J.S. Min, M.S. Jang, J.Y. Lee, Y.S. Shin, J.H. Song, H.R. Kim, S. Kim, Y.H. Jin, S. Kwon, Natural Bis-Benzylisoquinoline Alkaloids-Tetrandrine, Fangchinoline, and Cepharanthine, inhibit human coronavirus OC43 infection of MRC-5 human lung cells, Biomolecules 9 (11) (2019) 696.
[41] J.R. Weng, C.S. Lin, H.C. Lai, Y.P. Lin, C.Y. Wang, Y.C. Tsai, K.C. Wu, S.H. Huang, C.W. Lin, Antiviral activity of Sambucus formosana Nakai ethanol extract and related phenolic acid constituents against human coronavirus NL63, Virus Res. 273 (2019) 197767.
[42] L. Shen, J. Niu, C. Wang, B. Huang, W. Wang, et al., Highthroughput screening and identification of potent broad spectrum inhibitors of coronaviruses, J. Virol. 93 (12) (2019), https://doi.org/10.1128/JVI.00023-19 e00023-e00019.
[43] C. Muller, F.W. Schulte, K. Lange-Grunweller, W. Obermann, R. Madhugiri, et al., Broad-spectrum antiviral activity of the eIF4A inhibitor silvestrol against corona- and picornaviruses, Antivir. Res. 150 (2018) 123–129, https://doi.org/10.1016/j.antiviral.2017.12.010.
[44] J.Y. Park, H.J. Yuk, H.W. Ryu, S.H. Lim, K.S. Kim, et al., Evaluation of polyphenols from *Broussonetia papyrifera* as coronavirus protease inhibitors, J. Enzym. Inhib.

Med. Chem. 32 (1) (2017) 504–512, https://doi.org/10.1080/14756366.2016.1265519.
[45] D.W. Kim, K.H. Seo, M.J. Curtis-Long, K.Y. Oh, J.W. Oh, J.K. Cho, et al., Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of Psoralea corylifolia, J. Enzym. Inhib. Med. Chem. 29 (2014) 59–63, https://doi.org/10.3109/14756366.2012.753591.
[46] Y.H. Song, D.W. Kim, M.J. Curtis-Long, H.J. Yuk, Y. Wang, N. Zhuang, et al., Papain-like protease (PLpro) inhibitory effects of cinnamic amides from Tribulus terrestris fruits, Biol. Pharm. Bull. 37 (6) (2014) 1021–1028, https://doi.org/10.1248/bpb.b14-00026.
[47] H.J. Kwon, Y.B. Ryu, Y.M. Kim, N. Song, C.Y. Kim, et al., In vitro antiviral activity of phlorotannins isolated from *Ecklonia cava* against porcine epidemic diarrhea coronavirus infection and hemagglutination, Bioorg. Med. Chem. 21 (15) (2013) 4706–4713, https://doi.org/10.1016/j.bmc.2013.04.085.
[48] J.K. Cho, M.J. Curtis-Long, K.H. Lee, D.W. Kim, H.W. Ryu, H.J. Yuk, et al., Geranylated flavonoids displaying SARS-CoV papain-like protease inhibition from the fruits of *Paulownia tomentosa*, Bioorg. Med. Chem. 21 (2013) 3051–3057, https://doi.org/10.1016/j.bmc.2013.03.027.
[49] J.Y. Park, H.J. Jeong, J.H. Kim, Y.M. Kim, S.J. Park, D. Kim, et al., Diarylheptanoids from Alnus japonica inhibit papain-like protease of severe acute respiratory syndrome coronavirus, Bioorg. Med. Chem. 5 (11) (2012) 2036–2042, https://doi.org/10.1248/bpb.b12-00623.
[50] M.S. Yu, J. Lee, J.M. Lee, Y. Kim, Y.W. Chin, et al., Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13, Bioorg. Med. Chem. Lett 22 (12) (2012) 4049–4054, https://doi.org/10.1016/j.bmcl.2012.04.081.
[51] C. Roh, A facile inhibitor screening of SARS coronavirus N protein using nanoparticle-based RNA oligonucleotide, Int. J. Nanomed. 7 (2012) 2173–2179, https://doi.org/10.2147/IJN.S31379.
[52] W. Luo, X. Su, S. Gong, Y. Qin, W. Liu, J. Li, et al., Anti-SARS coronavirus 3C-like protease effects of Rheum palmatum L. extracts, Biosci Trends 3 (2009) 124–126.
[53] C.C. Wen, Y.H. Kuo, J.T. Jan, P.H. Liang, S.Y. Wang, et al., Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus, J. Med. Chem. 50 (17) (2007) 4087–4095, https://doi.org/10.1021/jm070295s.
[54] P.W. Cheng, L.T. Ng, L.C. Chiang, C.C. Lin, Antiviral effects of saikosaponins on human coronavirus 229E in vitro, Clin. Exp. Pharmacol. Physiol. 33 (7) (2006) 612–616.
[55] S. Matsuyama, N. Nao, K. Shirato, M. Kawase, S. Saito, I. Takayama, et al., Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells, Proc. Natl. Acad. Sci. U.S.A. 117 (13) (2020) 7001–7003, https://doi.org/10.1073/pnas.2002589117.
[56] J. Da, M. Xu, Y. Wang, W. Li, M. Lu, Z. Wang, Kaempferol promotes apoptosis while inhibiting cell proliferation via androgen- dependent pathway and suppressing vasculogenic mimicry and invasion in prostate cancer, Anal. Cell Pathol, (Amst) 2019 (2019) 1907698, https://doi.org/10.1155/2019/1907698.
[57] K. Mamouni, S. Zhang, X. Li, Y. Chen, Y. Yang, J. Kim, et al., A novel flavonoid composition targets androgen receptor signaling and inhibits prostate cancer growth in preclinical models, Neoplasia 20 (8) (2018) 789–799, https://doi.org/10.1016/j.neo.2018.06.003.
[58] K. Anand, G.J. Palm, J.R. Mesters, S.G. Siddell, J. Ziebuhr, R. Hilgenfeld, Structure of coronavirus main proteinase reveals combination of a chymotrypsin fold with an extra a-helical domain, EMBO J. 21 (13) (2002) 3213–3224, https://doi.org/10.1093/emboj/cdf327.
[59] H. Yang, M. Yang, Y. Ding, Y. Liu, Z. Lou, Z. Zhou, L. Sun, L. Mo, S. Ye, H. Pang, G.F. Gao, K. Anand, M. Bartlam, R. Hilgenfeld, Z. Rao, The crystal structures of severe acute respiratory syndrome virus main protease and its complex with an inhibitor, Proc. Natl. Acad. Sci. Unit. States Am. 100 (23) (2003) 13190–13195, https://doi.org/10.1073/pnas.1835675100.
[60] Q. Zhao, E. Weber, H. Yang, Recent developments on coronavirus main protease/3C like protease inhibitors, Recent Pat. Anti-Infect. Drug Discov. 8 (2) (2013) 150–156, https://doi.org/10.2174/1574891X113089990017.
[61] J. Shi, Z. Wei, J. Song, Dissection Study on the Severe Acute Respiratory Syndrome 3C-like Protease reveals the critical role of the extra domain in dimerization of the enzyme defining the extra domain as a new target for design of highly specific protease inhibitors, J. Biol. Chem. 279 (23) (2004) 24765–24773, https://doi.org/10.1074/jbc.M311744200.
[62] H. Chen, P. Wei, C. Huang, L. Tan, Y. Liu, L. Lai, Only one protomer is active in the dimer of SARS 3C-like proteinase, J. Biol. Chem. 281 (20) (2006) 13894–13898, https://doi.org/10.1074/jbc.M510745200.
[63] Y. Li, J. Zhang, N. Wang, H. Li, Y. Shi, G. Guo, Q. Zou, Therapeutic drugs targeting 2019-nCoV main protease by highthroughput screening, BioRxiv (2020), https://doi.org/10.1101/2020.01.28.922922.
[64] N. Muralidharan, R. Sakthivel, D. Velmurugan, M.M. Gromiha, Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 protease against COVID-19, J. Biomol. Struct. Dyn. (2020), https://doi.org/10.1080/07391102.2020.1752802.
[65] J.S. Miller, The Global Importance of Plants as Sources of Medicines and the Future Potential of Chinese Plants. InDrug Discovery and Traditional Chinese Medicine 2001, Springer, Boston, MA, 2001, pp. 33–42.
[66] C.W. Yang, H.Y. Chang, Y.Z. Lee, H.Y. Hsu, S.J. Lee, The cardenolide ouabain suppresses coronaviral replication via augmenting a Na+/K+-ATPase-dependent PI3K_PDK1 axis signaling, Toxicol. Appl. Pharmacol. 356 (2018) 90–97, https://doi.org/10.1016/j.taap.2018.07.028.
[67] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, G. Xiao, Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res. 30 (2020) 269–271.
[68] M.I. Abdelmageed, A.H. Abdelmoneim, M.I. Mustafa, N.M. Elfadol, N.S. Murshed, S.W. Shantier, et al., Design of a multiepitope-based peptide vaccine against the E protein of human COVID-19: an immunoinformatics approach, BioMed Res. Int. 2020 (2020) 2683286, https://doi.org/10.1101/2020.02.04.934232.
[69] R. Ghosh, A. Chakraborty, A. Biswas, S. Chowdhuri, Evaluation of green tea polyphenols as novel coronavirus (SARS CoV-2) main protease (Mpro) inhibitors – an in-silico docking and molecular dynamics simulation study, J. Biomol. Struct. Dyn. (2020), https://doi.org/10.1080/07391102.2020.1779818 ([Epub ahead of print]).
[70] B.N. Fields, D.M. Knipe, P.M. Howley, D.E. Griffin, Fields' Virology, Lippincott Williams & Wilkins, Philadelphia, 2001.
[71] B.W. Neuman, G. Kiss, A.H. Kunding, D. Bhella, M.F. Baksh, et al., A structural analysis of M protein in coronavirus assembly and morphology, J. Struct. Biol. 174 (1) (2011) 11–22, https://doi.org/10.1016/j.jsb.2010.11.021.
[72] C. Donald, J.R. Hall, J. Hai-Feng, A search for medications to treat COVID-19 via in silico molecular docking models of the SARS-CoV-2 spike glycoprotein and 3CL protease, Trav. Med. Infect. Dis. 35 (2020) (2020) 101646.
[73] P. Zhou, X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, et al., Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin, BioRxiv 2020 (2020), https://doi.org/10.1038/s41586-020-2012-7.
[74] M. Letko, A. Marzi, V. Munster, Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses, Nature Microbiology 5 (2020) 562–569, https://doi.org/10.1038/s41564-020-0688-y.
[75] R. Yan, Y. Zhang, Y. Li, L. Xia, Y. Guo, Q. Zhou, Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2, Science 27 (6485) (2020) 1444–1448, https://doi.org/10.1126/science.abb2762, 367.
[76] B. Benarba, A. Pandiella, Medicinal plants as sources of active molecules against COVID-19, Front. Pharmacol. 11 (2020) 1189, https://doi.org/10.3389/fphar.2020.01189.
[77] J. Shang, Y. Wan, C. Luo, G. Ye, Q. Geng, A. Auerbach, et al., Cell entry mechanisms of SARS-CoV-2, Proc. Natl. Acad. Sci. Unit. States Am. 117 (21) (2020) 11727–11734.
[78] L. Du, R.Y. Kao, Y. Zhou, Y. He, G. Zhao, C. Wong, S. Jiang, K.Y. Yuen, D.Y. Jin, B.J. Zheng, Cleavage of spike protein of SARS coronavirus by protease factor Xa is associated with viral infectivity, Biochem. Biophys. Res. Commun. 359 (1) (2007) 174–179, https://doi.org/10.1016/j.bbrc.2007.05.092.
[79] Y.D. Singh, B. Jena, R. Ningthoujam, S. Panda, P. Priyadarsini, S. Pattanayak, M.K. Panda, M.C. Singh, K.B. Satapathy, Potential bioactive molecules from natural products to combat against coronavirus, Adv. Tradit. Med. (2020), https://doi.org/10.1007/s13596-020-00496-w.
[80] S. Jiang, C. Hillyer, L. Du, Neutralizing antibodies against SARSCoV-2and other human coronaviruses, Trends Immunol. 41 (5) (2020) 355–359, https://doi.org/10.1016/j.it.2020.04.008.
[81] A.J. Siddiqui, C. Danciu, S.A. Ashraf, A. Moin, R. Singh, M. Alreshidi, M. Patel, S. Jahan, S. Kumar, M.I.M. Alkhinjar, R. Badraoui, M. Snoussi, M. Adnan, Plants-derived biomolecules as potent antiviral phytomedicines: new insights on ethnobotanical evidences against coronaviruses, Plants 2020 9 (2020) 1244, https://doi.org/10.3390/plants9091244.