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Review

Medicinal plants with anti-SARS-CoV activity repurposing for treatment of COVID-19 infection: A systematic review and meta-analysis

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The novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus) has emerged as a significant threat to public health with startling drawbacks in all sectors globally. This study investigates the practicality of some medicinal plants for SARS-CoV-2 therapy using a systematic review and meta-analysis of their reported SARS-CoV-1 inhibitory potencies. Relevant data were systematically gathered from three databases, *viz*., Web of Science, PubMed and Scopus. The information obtained included botanical information, extraction method and extracts concentrations, as well as the proposed mechanisms. Fourteen articles describing 30 different plants met our eligibility criteria. Random effects model and subgroup analysis were applied to investigate heterogeneity. According to subgroup analysis, the substantial heterogeneity of the estimated mean based on the IC_{50} values reporting the most potent anti-SARS-CoV 3C-like protease (3CLpro) inhibitors (10.07 %, $p < 0.0001$), was significantly higher compared to the most active anti-SARS-CoV papain-like protease (PLpro) inhibitors (6.12 %, $p < 0.0001$). More importantly, the literature analysis revealed that fruit extracts of *Rheum palmatum* L. and the compound cryptotanshinone isolated from the root of *Salvia miltiorrhiza* ($IC_{50} = 0.8 \pm 0.2$ μmol L^{-1}) were excellent candidates for anti-SARS-CoV targeting PLpro. Meanwhile, iguesterin ($IC_{50} = 2.6 \pm 0.6$ μmol L^{-1}) isolated from the bark of *Tripterygium regelii* emerged as the most excellent candidate for anti-SARS-CoV targeting 3CLpro. The present systematic review and meta-analysis provide valuable and comprehensive information about potential medicinal plants for SARS-CoV-2 inhibition. The chemotypes identified herein can be adopted as a starting point for developing new drugs to contain the novel virus.

Keywords: COVID-19 main protease, inhibition, medicinal plants, systematic review, meta-analysis

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INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been identified as the causative agent for the novel pneumonia-type coronavirus disease 2019 (COVID-19) (1, 2). The outbreak of this disease remains among public health emergencies of international concern as earlier declared by the World Health Organisation (3). As of August 16th 2021, about 222 countries have been affected by this coronavirus, and there were ~209 million confirmed cases and ~ 4.4 million deaths have been recorded globally. The symptoms of COVID-19 include cough, fever, fatigue, myalgia and dyspnoea, with the less common manifestation of runny nose, headache, nasal congestion, sore throat, and diarrhoea (1, 4). Severe conditions such as pneumonitis, acute respiratory distress syndrome (ARDS), respiratory arrest, inflammatory-induced lung injury, sepsis, and multiple organ failure are associated with critically ill COVID-19 patients, consequently resulting in fatalities (5–7).

Coronaviruses (CoVs) belong to the family Coronaviridae, and all species responsible for severe acute respiratory syndrome (SARS) fall under the genus beta-coronavirus (8), most of which is enzootic, and only a few are known to infect humans directly. Having established an animal-human host transmission, the lethality of CoVs has been demonstrated by past outbreaks of SARS and the Middle East respiratory syndrome (MERS) in the years 2003 and 2012, resp. (9–11).

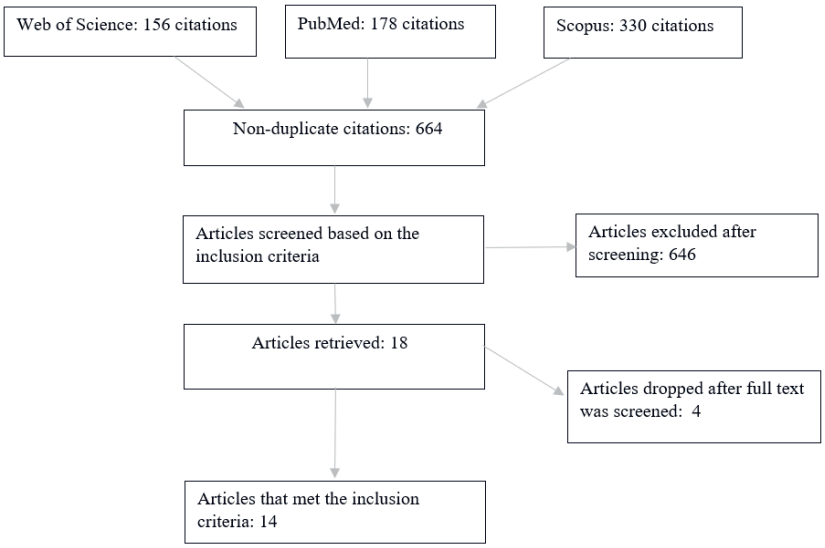
The whole viral genome of the novel SARS-CoV-2 has a 96 % similarity to the bat CoV and 79.6 % sequence identity to SARS-CoV (12). Empirical evidence has shown that although SARS-CoV-2 (reported as 2019-nCoV) is closer to bat-SL-CoVZXC21 and bat-SL--CoVZC45 at the whole-genome level, the receptor-binding domain of SARS-CoV-2 falls within a lineage closer to that of SARS-CoV (13). Genome transcription of beta-coronaviruses yields a polypeptide of approximately 800 kDa, which produces several proteins upon proteolytic cleavage, a process mediated by either the papain-like protease (PLpro) or 3-chymotrypsin-like protease (3CLpro) (14, 15). In addition, SARS-CoV emerged from a zoonotic reservoir and coupled with cytokine, chemokine, and interferon-stimulated gene (ISG) responses in patients, evidence that SARS-CoV pathogenesis is partially controlled by innate immune signaling (16–19). The drug targets among coronaviruses include the main protease (Mpro also called 3CLpro) and papain-like protease(s). The Mpro is liable to block viral replication, meanwhile, papain-like protease (PLpro) is essential for processing the polyproteins translated from the viral RNA (14, 21–23). Thus, 3CLpro and PLpro are validated drug targets for developing antiviral agents against CoVs.

Although the reported cases of previous SARS outbreaks were confined in Asia, the magnitude of the COVID-19 pandemic has presented a more insidious threat to global health and man's livelihood. Nonetheless, the identification of new drugs with high efficacy against CoVs is still elusive. As the search for drugs to combat COVID-19 continues, plant-derived compounds present a catalogue of potential anti-SARS-CoV-2 therapeutics, recording significant inhibitory effects on SARS-associated CoVs (24–26). These natural products provide active pharmaceutical ingredients and structural blueprints for designing their synthetic analogues with improved antiviral activity (27). Therefore, the present review aims to systematically evaluate existing reports on the anti-SARS-CoV activities of medicinal plants and their associated bioactive compounds to identify potential drug candidates for COVID-19 therapy.

METHODOLOGY AND DATA SOURCES

Data curation

The articles subjected to meta-analysis were extracted from the following databases: PubMed, Web of Science and Scopus. These databases were searched within English language papers published between 2005 and 2020, on medicinal plants used in the treatment of SARS-COV infection. The databases were searched using a combination of the following keywords: "coronavirus," "SARS-CoV", "COVID-19", "medicinal plants", "traditional medicine", "Chinese medicine", "plant extract", "cysteine protease", "severe acute respiratory syndrome", "SARS-CoV-1 or SARS-COV-1", "SARS-CoV-2 or SARS-COV-2", "herbs", "SARS-CoV 3CLpro", "SARS-CoV PLpro" and "antiviral agent". A total of 664 published articles between the years 2005 and 2020 were identified; a schematic representation of the selection process for reviewed articles is given in Scheme 1. As a complementary procedure, the relevant studies were checked manually for any citation missed by the electronic database.



Scheme 1

Characteristic evaluation and inclusion barometer

The systematic review was achieved using the PRISMA guidelines protocol (28). Eligibility criteria were set as follows: articles written in English, articles published between years 2005 and 2020, medicinal plants tested against SARS-CoV 3CLpro and PLpro enzymes, and their respective isolated compounds. The exclusion criteria include animal and clinical trial studies. Notably, studies devoid of either mean or standard deviation of inhibitory potencies were also excluded from the meta-analysis to maintain the quality of the findings.

Data synthesis and statistical analysis

The retrieved data were statistically analyzed, and the Stata 15.0 (Stata Corp, College Station, TX, USA) was used for the graphical representation of the pooled data. Statistical heterogeneity was assessed by both a Cochran's chi-squared test (*Q* test) and an *I*-squared test. A fixed-effects model was used when there was no significant statistical heterogeneity ($p > 0.1$ and an I^2 value < 50 %). In other cases, a random effects model statistical approach was employed. In this study, because the extracted articles were from the general population, a random effects meta-analysis was considered to be taken from an inverse-variance model. Effect sizes (ES) were estimated using the forest plot as a prelude for heterogeneity and biases examinations. In this study, the random effects model was applied to estimate and detect sources of statistical heterogeneity that may arise for different reasons. Furthermore, subgroup analysis was conducted to test whether there are subsets of the included studies that capture the pooled ES. The funnel plot and Egger's tests were simultaneously used to assess potential publication biases.

RESEARCH OUTCOMES

Meta-analysis

A forest plot is an orthodox device used to visualize how the estimate of ES of each study is distributed around a zero or pooled effect estimate. The ES estimate of each study is represented in the forest plot as a square box. The area of each box represents the weight of each study contributing to the pooled estimate while the center of a diamond equals the pooled effect estimate. The ends of the diamond indicate the limits of 95 % confidence interval (CI). Hence, the heterogeneity test and *Q* statistics gave significantly large value (chi-square = 5860.22, df = 19, $p < 0.0001$, $I^2 = 99.7$ %), indicating the presence of enormous variation among studies. The residual amount of heterogeneity indicates the extent of variability as compared with the effect size. Besides, the percentage of total variation resulting from heterogeneity across studies is substantial for I2. These findings generally imply that the proportion of total variance among pooled studies (*i.e.*, IC_{50} of the active compounds) can be attributed to the accuracy of evaluation of heterogeneity in the effect sizes. The pooled estimated mean using the fixed effect model showed significant heterogeneity between the studies. Hence, we performed the analyses using the random effects model. Using the random-effects model, the estimated pooled mean of potential anti-SARS-CoV compounds based on the IC_{50} was 6.12 % (95 % CI 6.09-6.16) with significant heterogeneity between studies ($I^2 = 99.7$ %, $p < 0.0001$). The pooled estimated mean of the potential anti-SARS-CoV compounds based on the IC_{50} is presented using a forest plot (Fig. 1).

The main void of the heterogeneity concept is that it provides only global measures without additional information about the sources of heterogeneity. The inherent void demands that subgroup analysis is to be performed to unveil the sources of heterogeneity. Subgroup analysis is the splitting of the participant data into subgroups to establish comparisons between sub-data. The interpretation of subgroup meta-analysis can lead to informative insights into the proper implication that would not be obtained from the non-subgroup analysis. Thus, an analysis of the isolated compounds subgroup was conducted to assess the potential heterogeneity between the studies included in the meta-analysis.

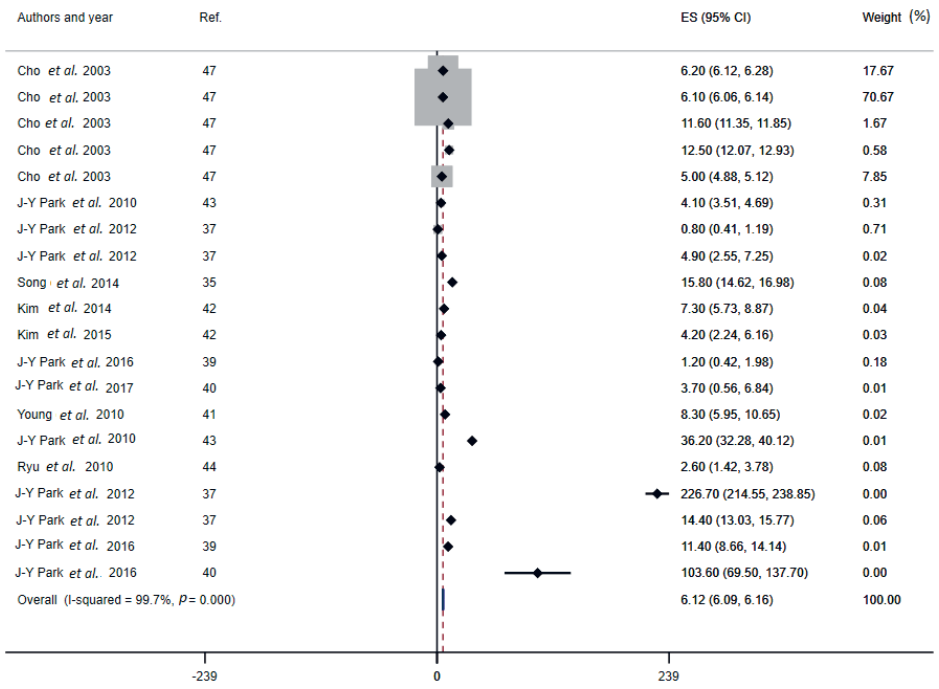


Fig. 1. Overall pooled mean estimate obtained for active chemical constituents (IC_{50}) tested against SARS-CoV proteases.

Further, the subgroup analysis was conducted using 3CLpro and PLpro inhibitors to assess the potential heterogeneity between the studies; the findings established a statistically significant difference ($p < 0.001$) in the subgroup. Of the 20 studies, the highest pooled estimated mean was found in studies reporting 3CLpro inhibitors [10.07 % (95 % CI: 9.29–10.85), I^2 = 99.7 %], followed by the studies conducted with PLpro inhibitors [6.12 % (95 % CI: 6.08–6.15), I^2 = 99.7 %] (Fig. 2). This result suggests that the inhibitory potencies (IC_{50}) against 3CLpro and PLpro were significantly different among the active compounds.

Furthermore, one of the medicinal plants active against SARS-CoV *in vitro* includes *Tribulus terrestris*. The plant belongs to the genus *Tribulus* (Zygophyllaceae), a large, heterogeneous and widely dispersed genus comprising of twenty-seven species (29, 30). *T. terrestris*, the most researched species, is rich in steroids, saponins, flavonoids, sterols, lignan amides and cinnamic acid (30–32). The pharmacological applications of *T. terrestris* such as anticancer, antioxidant, anti-inflammatory, antidiuretic, and antimicrobial have been reported (33, 34). Song *et al*. (35) revealed that the methanolic extracts of *T. terrestris* fruits showed superior inhibitory activity towards SARS-CoV PLpro compared to ethyl acetate, hydroalcoholic and aqueous extracts. Purification of the isolated compounds from the methanolic extracts unveiled cinnamic amide derivatives. All the isolated compounds displayed significant PLpro inhibition with IC_{50} values of 15.8–70.1 μmol L^{-1} (Table I). The highest inhibitory potency was observed for terrestrimine (**1**) and terrestriamide (**2**) with IC_{50} of 15.8 ± 0.6 and 21.5 ± 0.5 μmol L^{-1}, resp. (Fig. 3).

Table I. Plant extracts and isolated compounds with promising SARS-CoV inhibitory potency

Plant (genus/species)	Family	Extraction medium	SARS-CoV-1 protease tested	Plant part studied	Isolated compound(s)	Remark(s)	Ref.
Tribulus terrestris L.	Zygophyllaceae	Ethyl acetate, methanol, aq. ethanol, water	PLpro	Fruits	From methanolic extract: *N-trans*-caffeoyltyramine, *N-trans*-coumaroyl-tyramine, *N-trans*-feruloyl-tyramine, terrestriamide (1), *N-trans*-feruloyl-octopamine, terrestrimine (2)	All extracts (excluding aq. extracts) show good inhibitory potency against PLpro at 300 μg mL^{-1}	35
Isatis indigotica L.	Brassicaceae	Water	3CLpro	Root	Indigo, indirubin, indican, sinigrin (**3**), beta-sitosterol, aloeemodin, hesperetin (**4**), quercetin, naringenin, daidzein, emodin, chrysophanol	50 % inhibitory conc. of aq. extracts: 191.6 ± 8.2 μg mL^{-1} for the cell-based cleavage, 53.8 ± 4.2 μg mL^{-1} for cell-free cleavage assay	36
Salvia miltiorrhiza Bunge	Lamiaceae	Ethanol	3CLpro, PLpro	Root	Tanshinone IIA (**9**), tanshinone IIB (**11**), methyl tanshinonate (**8**), cryptotanshinone (**6**), tanshinone I (**9**), dihydrotanshinone I (**5**), rosmariquinone (**10**)	Ethanolic extracts inhibit 60 and 88 % 3CLpro and PLpro at 30 μg mL^{-1}, resp.	37
Taxus celebica (Warb.) H.L.Li	Taxaceae	Ethanol	3CLpro	Not reported	Not reported	12 %	38
Uvaria macrocarpa (Champ. ex Benth.)	Annonaceae	Ethanol	3CLpro	Not reported	Not reported	21.4 %	38
Rubus suavissimus S. Lee	Rosaceae	Water	3CLpro	Not reported	Not reported	0 %	38
Auricularia auricular (L.) Underw	Auriculariaceae	Water	3CLpro	Not reported	Not reported	0 %	38
Glycyrrhiza uralensis Fisch. ex DC.	Leguminosae	Water	3CLpro	Root	Not reported	13.5 %	38
Mangifera indica L.	Anacardiaceae	Water	3CLpro	Leaves	Not reported	3.5 %	38
Scutellaria baicalensis Georgi	Lamiaceae	Water	3CLpro	Leaves	Not reported	13.6 %	38
Sophora flavescens Aiton	Fabaceae	Ethanol	3CLpro	Radix	Not reported	20.2 %	38

Inhibition rate by the respective extract at 100 μg mL^{-1}

Plant (genus/species)	Family	Extraction medium	SARS-CoV-1 protease tested	Plant part studied	Isolated compound(s)	Remark(s)	Ref.
Cyrtomium fortunei J.Sm.	Dryopteridaceae	Ethanol	3CLpro	Rhizome	Not reported	25.7 %	38
Brucea javanica (L.) Merr.	Simaroubaceae	Ethanol	3CLpro	Fruits	Not reported	5.3 %	38
Rheum palmatum L.	Polygonaceae	Ethanol	3CLpro	Herbs	Extracts/fractions: RH10, RH11, RH12, RH121, RH122, RH124, RH125	Chloroform-methanol extracts markedly inhibit 3C-like protease; RH121 fraction the most active (IC_{50} = 13.76 ± 0.03 μg mL^{-1}), with inhibition rate up to 96 %	38
Angelica keiskei Ito	Apiaceae	Ethanol	3CLpro, PLpro	Leaves	Isobavachalcone (**12**), 4-hydroxyderricin (**13**), xanthoangelol (**14**), xanthoangelol B, D, E, G, F (**15**–**19**), xanthokeistal A (**20**), psoralen (**21**), bergapten (**22**), xanthotoxin (**23**), isopimpinellin (**24**)	The ethanolic extract shows 75 % inhibition of 3CLpro and 88 % inhibition of PLpro at 30 μg mL^{-1}, resp.	39
Broussonetia papyrifera (L.) Vent.	Moraceae	Ethanol	3CLpro, PLpro	Root	Broussochalcone A, B; 4-hydroxy-isolonchocarpin, papyriflavonol A (**25**), 3′-(3-methylbut-2-enyl)-3′,4,7-trihydroxyflavane, kazinol A, B, F, J; broussoflavan A	Papyriflavonol A most potent PLpro inhibitor (IC_{50} = 3.71.6 μmol L^{-1}), but poor inhibitor for 3CLpro (IC_{50} = 103.6 ± 17.4 μmol L^{-1})	40
Torreya nucifera (L.) Siebold and Zucc.	Taxaceae	Ethanol	3CLpro	Leaves	Amentoflavone (**34**), 18-hydroxyferruginol (**26**), hinokiol (**27**), ferruginol (**28**), 18-oxoferruginol, *O*-acetyl-18-hydroxyferruginol (**29**), methyl dehydroabietate (**31**), bilobetin (**35**), ginkgetin (**36**), isopimaric acid (**32**), sciadopitysin (**37**), kayadiol (**33**)	Ethanol extract exhibits good 3CLpro inhibitory activity: 62 % at 100 μg mL^{-1}	41
Psoralea corylifolia L.	Fabaceae	Ethanol	PLpro	Seeds	Bavachinin, neobavaisoflavone, isobavachalcone (**41**), 4′-*O*-methyl-bavachalcone, psoralidin (**42**), corylifol A	Ethanol extract shows 50 % inhibition at 15 μg mL^{-1}	42

Plant (genus/species)	Family	Extraction medium	SARS-CoV-1 protease tested	Plant part studied	Isolated compound(s)	Remark(s)		Ref.
Alnus japonica (Thunb.) Steud.	Betulaceae	Ethanol	3CLpro, PLpro	Stem bark	Platyphyllenone, hirsutenone (**43**), platyphyllone, platyphyllonol-5-xylopyranoside, hirsutanonol, oregonin, rubranol, rubranoside B and rubranoside A	Hirsutenone most potent PLpro inhibitor (IC_{50} = 4.1 μmol L^{-1})		43
Tripterygium regelii (Sprag & Takeda)	Celastraceae	Methanol	PLpro	Bark	Celastrol (**46**), pristimerin (**47**), tingenone (**45**), iguesterin (**44**)	MeOH (95 %) extracts inhibit >70 % 3CLpro activity at 30 μg mL^{-1}		44
Camellia sinensis var. *sinensis*	Theaceae	Water	3CLpro	Green tea	Caffeine, theophylline, catechin (C), epigallocatechin, (–)-epigallocatechin gallate, epicatechin, epicatechin gallate		125 μg mL^{-1}	45
Camellia sinensis (L.) Kuntze var. *assamica*	Theaceae	Water	3CLpro	Black tea	Theaflavin (TF1), mixture of theaflavin-3′-gallate (TF2b) and theaflavin-3-gallate (TF2a), theaflavin-3,3′-digallate (TF3) (**48**), isotheaflavin-3′-gallate (TF2B) (**49**), tannic acid (**50**)	50 % inhibition	70 μg mL^{-1}	45
Camellia sinensis (L.) Kuntze var. *assamica*	Theaceae	Water	3CLpro	Oolong tea, Pu-erh tea	Caffeine, theophylline, catechin (C), epigallocatechin, (-)-epigallocatechin gallate, epicatechin, epicatechin gallate isolated from oolong tea Not reported for Pu-erh tea		125 and 25 μg mL^{-1}, resp.	45
Gentiana scabra Bunge	Gentianaceae	Ethanol, water, methanol, hexane	3CLpro	Rhizome	Not reported		Hexane extracts at > 50 μg mL^{-1}	46
Dioscorea batatas Decne	Dioscoreaceae	Ethanol, water, methanol, hexane	3CLpro	Tuber	Not reported	50 % inhibition by the respective extract	Methanolic extracts at 44 μg mL^{-1}	46
Cassia tora (L.) Roxb	Leguminosae	Ethanol, water, methanol, hexane	3CLpro	Seed	Not reported		Hexane extracts at > 50 μg mL^{-1}	46

Plant (genus/species)	Family	Extraction medium	SARS-CoV-1 protease tested	Plant part studied	Isolated compound(s)	Remark(s)	Ref.
Taxillus chinensis (DC.) Danser	Loranthaceae	Ethanol, water, methanol, hexane	3CLpro	Stem, leaves	Not reported	Hexane extracts at > 50 μg mL^{-1}	46
Cibotium barometz (L.) J.Sm.	Cibotiaceae	Ethanol, water, methanol, hexane	3CLpro	Rhizome	Not reported	Ethanol and methanol extracts at > 50 and 39 μg mL^{-1}, resp.	46
Paulownia tomentosa (Thunb.) Steud.	Paulowniaceae	Methanol	PLpro	Fruit	Tomentin A-E (**51-55**), 3′-*O*-methyldiplacol (**56**), 4′-*O*-methyldiplacol (**60**), 3′-*O*-methyldiplacone (**57**), 4′-*O*-methyldiplacone (**58**), mimulone (**59**), diplacone (**61**), 6-geranyl-4′,5,7-trihydroxy-3′,5′-dimethoxy-flavanone (**62**)	Tomentin A-E show excellent inhibitory activity (IC_{50} from 5 to 13 μmol L^{-1})	47
Chamaecyparis obtuse (Siebol & Zucc) var. *formosana*	Cupressaceae	Ethyl acetate	3CLpro	Heart-wood	Ferruginol (**63**), dehydroabieta-7-one (**64**), sugiol (**66**) 8-hydroxy-abieta-9(11),13-dien-12-one (**67**), 6,7-dehydroroyleanone (**69**), pinusolidic acid (**71**), *R*-cadinol (**74**), hinokinin (**77**), savinin (**78**)	Betulinic acid (not isolated) and savinin competitive inhibitors of SARS-CoV 3CL protease (IC_{50} = 10 and 25 μmol L^{-1}, resp.)	25
Juniperus formosana Hayata	Cupressaceae	Ethyl acetate	3CLpro	Heart-wood	3β,12-diacetoxyabieta-6,8,11,13-tetraene (**70**), cedrane-3a,12-diol (**73**), betulonic acid (**76**), cryptojaponol (**66**)	Betulonic acid inhibits 3CL protease 0.63 μmol L^{-1} at 50 %	25
Cryptomeria japonica (L.f.) D.Don	Cupressaceae	Ethyl acetate	3CLpro	Heart-wood	7β-hydroxydeoxycryptojaponol	7β-hydroxydeoxycryptojaponol inhibits 3CL protease 1.15 μmol L^{-1} at 50 %	25

The roots of *Isatis indigotica*, a member of the family Cruciferae, native to China, are known for their potency against influenza, hepatitis A and Japanese encephalitis (48–50). Lin *et al*. (36) examined the efficacy of five major compounds of *I. indigotica* root, namely, indigo, indirubin, indican, sinigrin and beta-sitosterol, and seven plant-derived phenolic compounds, namely, aloe emodin, hesperetin, quercetin, naringenin, daidzein, emodin and chrysophanol, which were tested for anti-SARS-CoV 3CLpro effects using cell-free and cell-based cleavage assays. Only two phenolic compounds, aloe emodin and hesperetin, isolated from the aqueous extracts of the plant's root, dose-dependently inhibited cleavage activity of the 3CLpro, in which the IC_{50} was 366 μmol L^{-1} for aloe emodin and 8.3 μmol L^{-1} for hesperetin in the cell-based assay (Table I). Sinigrin (**3**) (IC_{50} = 217 μmol L^{-1}) and hesperetin (**4**) (IC_{50} = 8.3 μmol L^{-1}) shown in Fig. 4 emerged as potential leads for developing inhibitors of SARS-CoV 3CLpro. Sinigrin was more efficient in blocking the cleavage processing of 3CLpro than indigo (IC_{50} = 300 μmol L^{-1}). The report from the literature accredited the antiviral effect of sinigrin (**3**) and hesperetin (**4**), including poliovirus, pseudorabies virus, Sindbis virus, herpes simplex virus types 1 and 2, parainfluenza virus and vaccinia virus (51–53). In addition, the most potent compounds, *i.e.*, sinigrin (**3**) and hesperetin (**4**) with CC_{50} of above 2 mmol L^{-1} were considerably less cytotoxic to Vero cells than

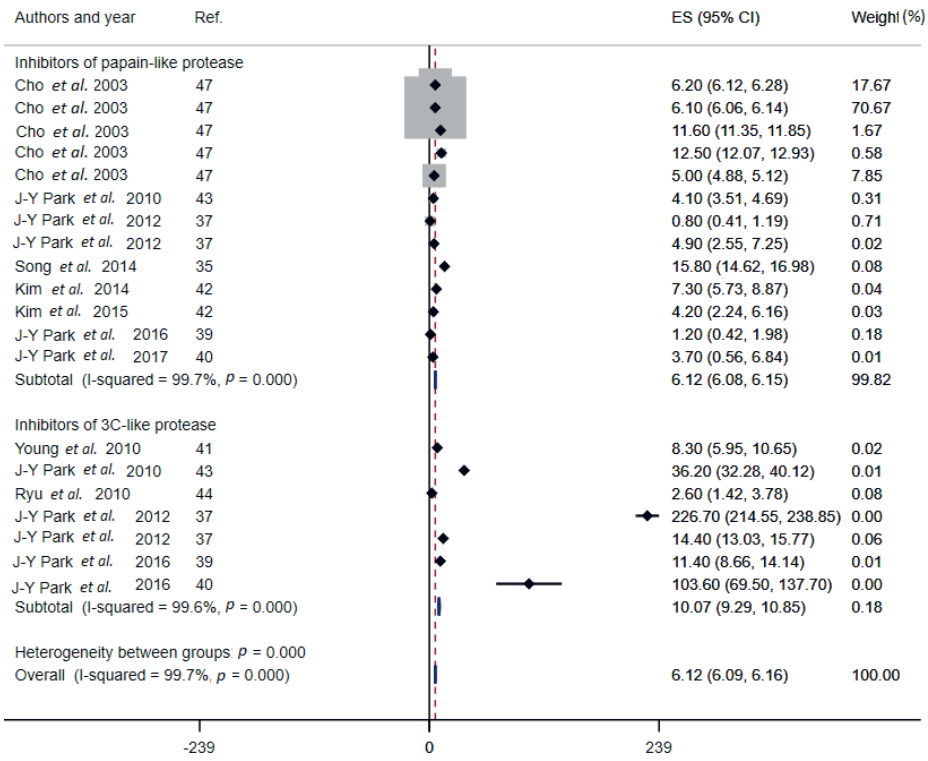


Fig. 2. Sub-group analysis of the active chemical constituents (IC_{50}) tested against 3CLpro and PLpro SARS-CoV.

indigo and beta-sitosterol. Therefore, they may be considered as potential leads in the development of inhibitors of SARS-CoV and SARS-CoV-2 3CLpro.

Similarly, in a quest to find inhibitors of viral replication in SARS-CoV, Ji-Y Park *et al.* (37) focused on the inhibitory action of naturally derived tanshinones against 3CLpro and PLpro of the virus. All the isolates were found in the lipophilic fraction (*n*-hexane) of *S. miltiorrhiza* extracts. The 3CLpro inhibitory potency of the compounds, dihydrotanshinone I (**5**), cryptotanshinone (**6**), tanshinone IIB (**7**), methyl tanshinonate (**8**), tanshinone I (**9**), rosmariquinone (**10**) and tanshinone IIA (**11**), ranged from 14.4 to 226.7 μmol L^{-1}, whereas all the isolated compounds (**5–11**) showed inhibitory activities to both 3CLpro and PLpro. The activity was significantly affected by subtle changes in the structure. Notably, dihydrotanshinone I (**5**) (IC_{50} = 14.4 μmol L^{-1}) showed ~16-fold superior potency compared to cryptotanshinone (**6**) (IC_{50} = 226.7 μmol L^{-1}) (Fig. 5). Cryptotanshinone (**6**) exhibited the lowest inhibitory activity compared to the compounds with furan moiety. The introduction of the hydroxymethyl group on the D-ring of tanshinone IIB (**7**) increased its enzyme inhibitory activity with an IC_{50} value of 24.8 μmol L^{-1} (Fig. 5). The corresponding methyl ester on the D-ring, methyl tanshinonate (**8**), also showed a similar potency enhancement (IC_{50} = 21.1 μmol L^{-1}). In contrast, the dihydrofuran moiety of dihydrotanshinone (IC_{50} = 14.4 μmol L^{-1}) showed higher inhibitory activity against 3CLpro than tanshinone I (**9**) (IC_{50} = 38.7 μmol L^{-1}).

The isolated compounds were also tested against PLpro, and surprisingly, cryptotanshinone (**6**) displayed the most potent inhibitory activity (IC_{50} = 0.8 μmol L^{-1}), whereas tanshinone I (**9**) (IC_{50} = 8.8 μmol L^{-1}) and dihydrotanshinone I (**5**) (IC_{50} = 4.9 μmol L^{-1}) exhibited similar inhibitory potencies possibly due to their identical ring-A structure (Fig. 5).

Interestingly, the structurally related abietane analog, rosmariquinone (**10**), displayed significant activity against both 3CLpro and PLpro with IC_{50} values of 21.1 and 30.0

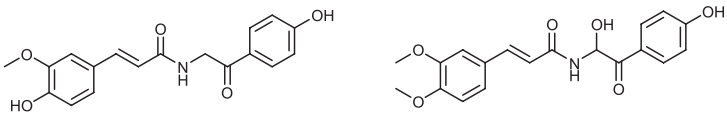


Fig. 3. Chemical structure of terrestriamide and terrestriamine isolated from *T. terrestris* fruits.

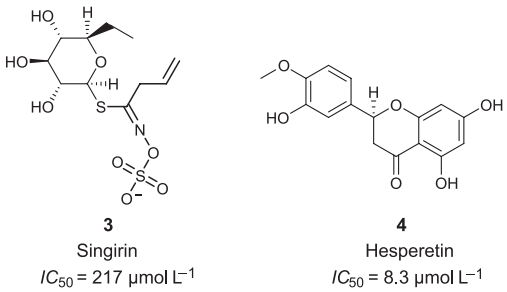
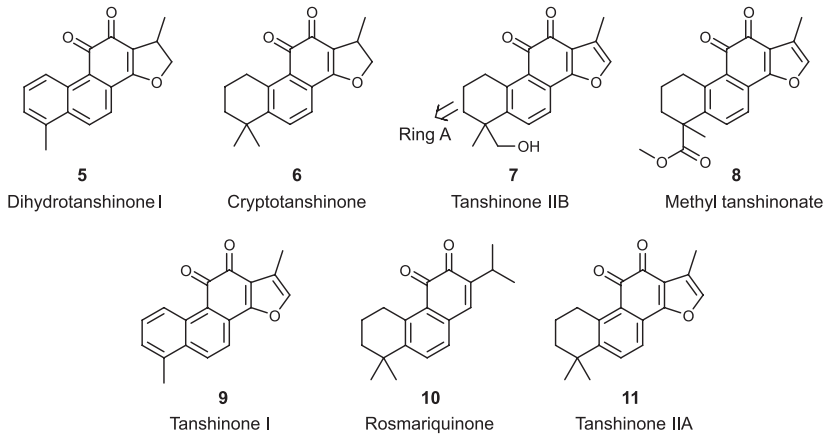


Fig. 4. Chemical structure of sinigirin and hesperetin isolated from *I. indigotica*.

μmol L^{-1}, resp. The introduction of a three-ringed abietane analog, rosmariquinone (**10**), showed simple reversible slow-binding inhibitor and mixed-type inhibition. In addition, tanshinone I (**9**) showed the most potent DUB activity with an IC_{50} value of 0.7 μmol L^{-1}. The results from the isolated compounds merit further examination for their effect on the inhibition of SARS-CoV-2.

Luo *et al*. (38) reported twelve plants as 3CLpro inhibitors (Table I). The extracts/fractions of *Rheum palmatum* L. such as RH10, RH11, RH12, RH121, RH122, RH124 and RH125 significantly inhibited SARS coronavirus 3C-like protease. Fraction RH121 (IC_{50} = 13.76 ± 0.03 μg mL^{-1}) (Fig. 6) emerged as highly potent anti-SARS-CoV therapeutic agent. The ethanolic extracts of rhubarb showed no cytotoxicity at 20 mg mL^{-1}, which partly makes them an excellent tool for anti-coronavirus drug screening. Rhubarb is plentiful in China as traditional medicine for viral diseases.

Ji-Y Park *et al*. (39) showed the significant inhibition of 3CLpro and PLpro by EtOAc-soluble fraction of ethanolic extract of *Angelica keiskei* (75 and 88 % inhibition at 30 mg mL^{-1}, resp.). Nine alkylated chalcones, namely isobavachalcone (**12**), 4-hydroxyderricin



Compd.	IC_{50} (μmol L^{-1})	
	3CLpro	PLpro
Tanshinone IIA	89.1 ± 5.2	1.6 ± 0.5
Tanshinone IIB	24.8 ± 5.2	10.7 ± 1.7
Methyl tanshinonate	21.1 ± 0.8	9.2 ± 2.8
Cryptotanshinone	226.7 ± 6.2	0.8 ± 0.2
Tanshinone I	38.7 ± 8.2	8.8 ± 0.4
Dihydrotanshinone I	14.4 ± 0.7	4.9 ± 1.2
Rosmariquinone	21.1 ± 0.8	30.0 ± 5.5

Fig. 5. Chemical structures and inhibitory effects of isolated compounds from *S. miltiorrhiza*.

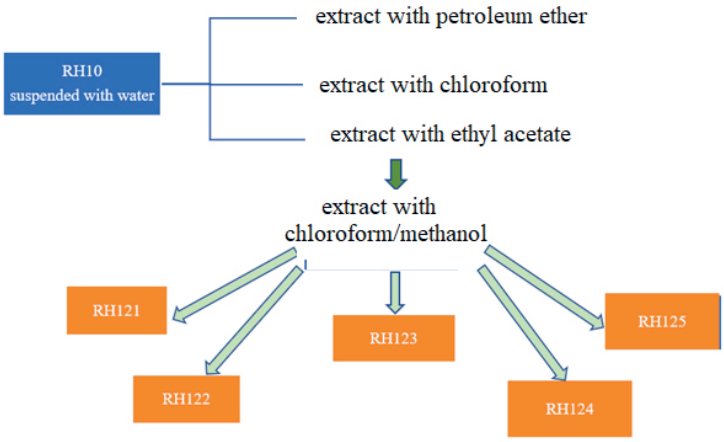


Fig. 6. Flow diagram of separation of various extracts/fractions from *Rheum palmatum* L. using different solvents.

(**13**), xanthoangelol (**14**), xanthoangelol F (**15**), xanthoangelol D (**16**), xanthoangelol E (**17**), xanthoangelol B (**18**), xanthoangelol G (**19**), xanthokeistal A (20), and psoralen (**21**) and four coumarins, bergapten (**22**), xanthotoxin (**23**) and isopimpinellin (**24**) were isolated from *Angelica keiskei*, and the inhibitory activities of these constituents against SARS-CoV 3CL-pro and PLpro were reported. Among the different chalcones, flavanones, and coumarins isolated from the plant (Table I), xanthoangelol E (**12**) containing the perhydroxyl group showed 3CLpro and PLpro inhibitory potencies (IC_{50} = 11.4 and 1.2 μmol L^{-1}) that are 5- to 40-fold superior to other analogs (Fig. 7). The structure-activity relationship analysis showed that the peroxide unit on hemiterpene might influence the polyhydroxylated chain's binding and conformational stability through intramolecular hydrogen bonding. The optimization of this compound in the development of protease inhibitors may yield an effective anti-SARS-CoV-2 agent.

Papyriflavonol A (**24**), a polyphenol, has been reported as the most potent PLpro inhibitor with an IC_{50} value of 3.7 μmol L^{-1} compared to other isolated polyphenols from *Broussonetia papyrifera* (40). All the isolated polyphenols were more potent against PLpro than 3CLpro (Table I). An evaluation of the structure-activity relationship revealed that the prenyl groups' position was beneficial to inhibitory potency of papyriflavonol A (**24**) (Fig. 8). Hence, the significant activity of this compound showed that it can be further developed as an anti-coronavirus agent targeting PLpro and 3CLpro proteases.

Ryu *et al*. (41) reported the SARS-CoV 3CL pro-activity of eight diterpenoids and four bioflavonoids isolated from *Torreya nucifera*. *T. nucifera* is a slow-growing, coniferous tree native to snowy areas near the Sea of Jeju Island in Korea (54). The traditional use of the plant in Asian medicine as a remedy for stomachache, hemorrhoids, and rheumatoid arthritis was reported by Bae *et al*. (55). The pharmacological activity of *T. nucifera* also included antioxidative, antiproliferative, anti-inflammatory, hepatoprotective, and neuroprotective ones (56–58). The isolated diterpenes, namely, 18-hydroxyferruginol (**26**), hinokiol (**27**), ferruginol (**28**), 18-oxoferruginol (**29**), *O*-acetyl-18-hydroxyferruginol (**30**),

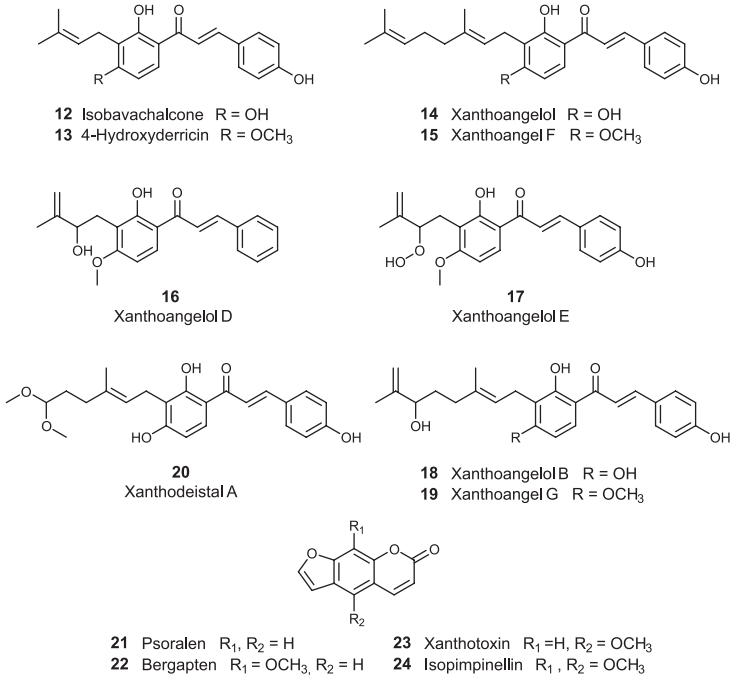


Fig. 7. Chemical structures of chalcones and coumarins isolated from *A. keiskei*.

methyl dehydroabietate (**31**), isopimaric acid (**32**) and kayadiol (**33**), and bioflavonoids amentoflavone (**34**), bilobetin (**35**), ginkgetin (**36**) and sciadopitysin (**37**) from *T. nucifera* (41) were tested in parallel with the standard flavones apigenin (**38**), luteolin (**39**) and quercetin (**40**) (Fig. 9). The latter compounds were included to establish the structure-activity relationship of biflavones and they inhibited 3CLpro activity with IC_{50} values of 280.8, 20.2, and 23.8 μmol L^{-1}, resp.

The eight in-house diterpenoid libraries tested against SARS-CoV 3CLpro showed that ferruginol (**28**) exhibited superior inhibitory activity (IC_{50} = 49.6 μmol L^{-1}) which was approximately four-fold more potent than that of abietic acid (IC_{50} = 189.1 μmol L^{-1}). Intro-

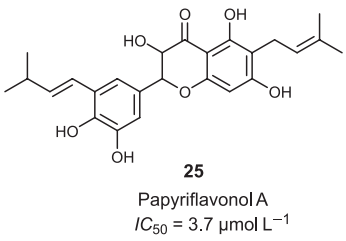


Fig. 8. Chemical structure of papyriflavonol A, the promising anti-SARS-CoV compound, isolated from *B. papyrifera*.

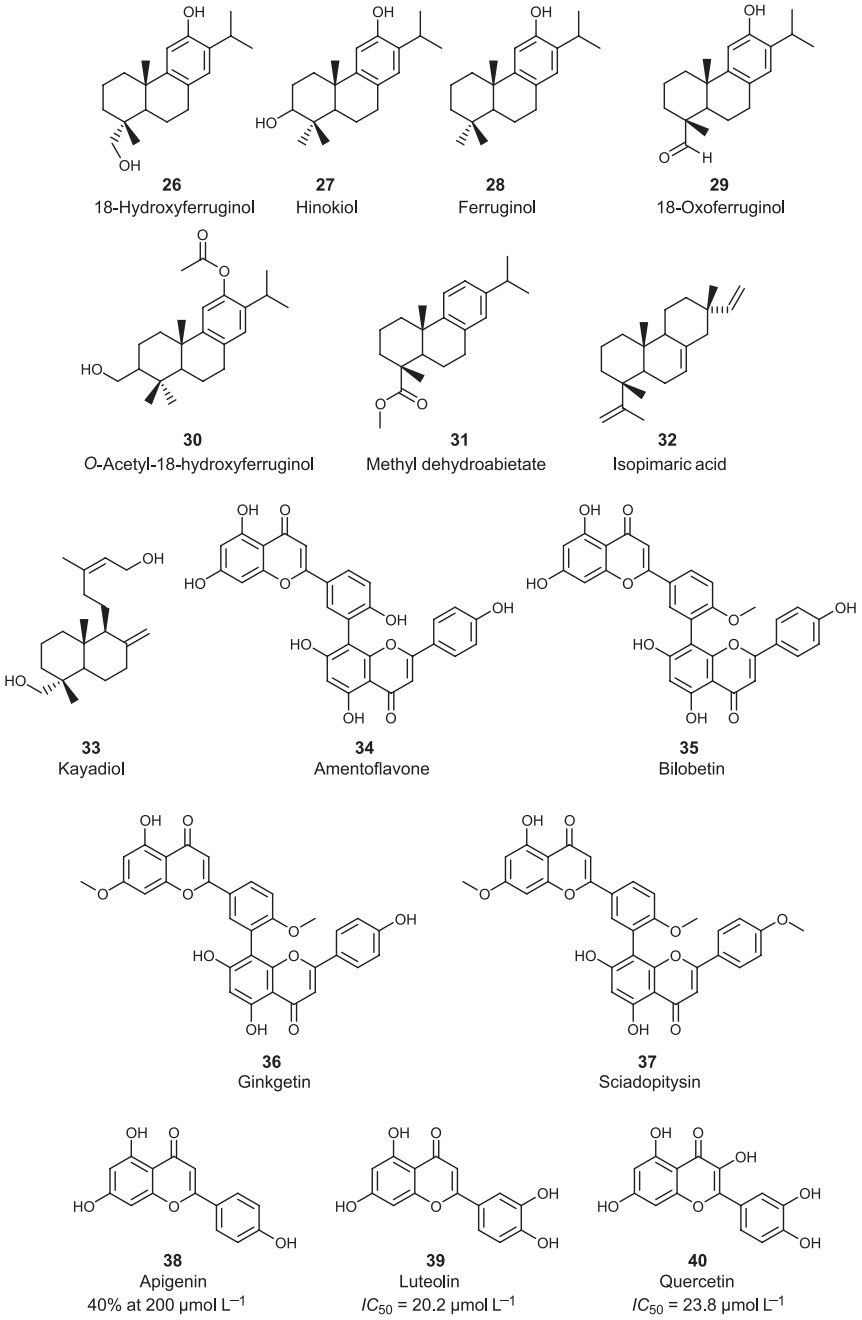
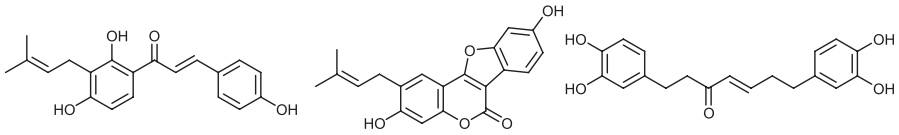


Fig. 9. Chemical structures of compounds isolated from the leaves of *T. nucifera* tested against SARS-CoV 3CLpro.



41
Isobavachalcone
IC_{50} = 7.3 μmol L^{-1}

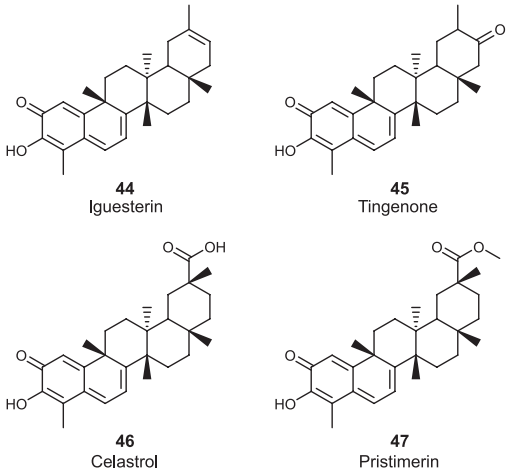
42
Psoralidin
IC_{50} = 4.2 μmol L^{-1}

43
Hirsutenone
IC_{50} = 4.1 μmol L^{-1}

Fig. 10. Chemical structures of some promising compounds (isobavachalcone, psoralidin, hirsutenone) showing anti-SARS-CoV properties, isolated from *Alnus japonica*.

duction of methoxy group to amentoflavone (**34**) moiety to give bilobetin (**35**), ginkgetin (**36**) and sciadopitysin (**37**) bioflavonoids, resulted in the less potent inhibitory activity of these compounds (IC_{50} = 32.0–72.3 μmol L^{-1}). The methoxy group at position C-7 of ginkgetin (**36**) with IC_{50} of 32.0 μmol L^{-1} and sciadopitysin (**37**) with IC_{50} of 38.4 μmol L^{-1} might be responsible for a two-fold increase in the anti-SARS-CoV 3CLpro inhibitory activity compared to bilobetin (**35**), with hydroxyl functional group at position C-7 (IC_{50} = 72.3 μmol L^{-1}). The most potent inhibitor, amentoflavone (**34**) exhibited an IC_{50} value of 8.3 μmol L^{-1} toward SARS-CoV 3CLpro, making this compound about 30-fold more potent than apigenin. Meanwhile, the inhibitory activity of luteolin (**39**) (IC_{50} = 20.2 μmol L^{-1}) was inferior to amentoflavone (**34**) inhibitory activity. The apigenin motif in amentoflavone has possibly played a pivotal role in the SARS-CoV 3CLpro inhibition.

Psoralea corylifolia (Leguminosae) is used as a food additive and is distributed from India to Southeast Asia. The seeds are found to be helpful as a tonic or an aphrodisiac (50, 59). Moreover, the phytochemicals from *Psoralea corylifolia* demonstrate a wide range of biological activities such as antioxidant, antibacterial, anti-inflammatory, antidepressant, and antiviral (60–69). Kim and coworkers (42) have also shown that the ethanolic extracts of *P. corylifolia* seeds exhibit potent inhibitory potency against SARS-CoV PLpro. Fraction



44
Iguesterin

45
Tingenone

46
Celastrol

47
Pristimerin

Fig. 11. Chemical structures of quinone-methide triterpenes isolated from *T. regelii*.

purification yielded phenolic phytochemicals with excellent PLpro inhibitory activities, isobavachalcone (**41**) and psoralidin (**42**) being the most potent inhibitors with IC_{50} values of 7.3 and 4.2 μmol L^{-1}, resp. (Fig. 10). In another study reported by J.-Y. Park and colleagues (43) hirsutenone (**43**), isolated from *Alnus japonica*, a diarylheptanoid, showed the strongest inhibition of PLpro with an IC_{50} value of 4.1 μmol L^{-1}. The presence of catechol and α,β-unsaturated carbonyl moiety was found to be critical for its inhibitory potency (Fig. 10).

Furthermore, among the isolated compounds of *Triterygium regelii* as shown in Table I, iguesterin (**44**) (IC_{50} = 2.6 μmol L^{-1}) was identified as a superior inhibitor of anti-SARS-CoV 3CLpro compared to quinone-methide triterpenes [tingenone (**45**) with IC_{50} = 9.9 μmol

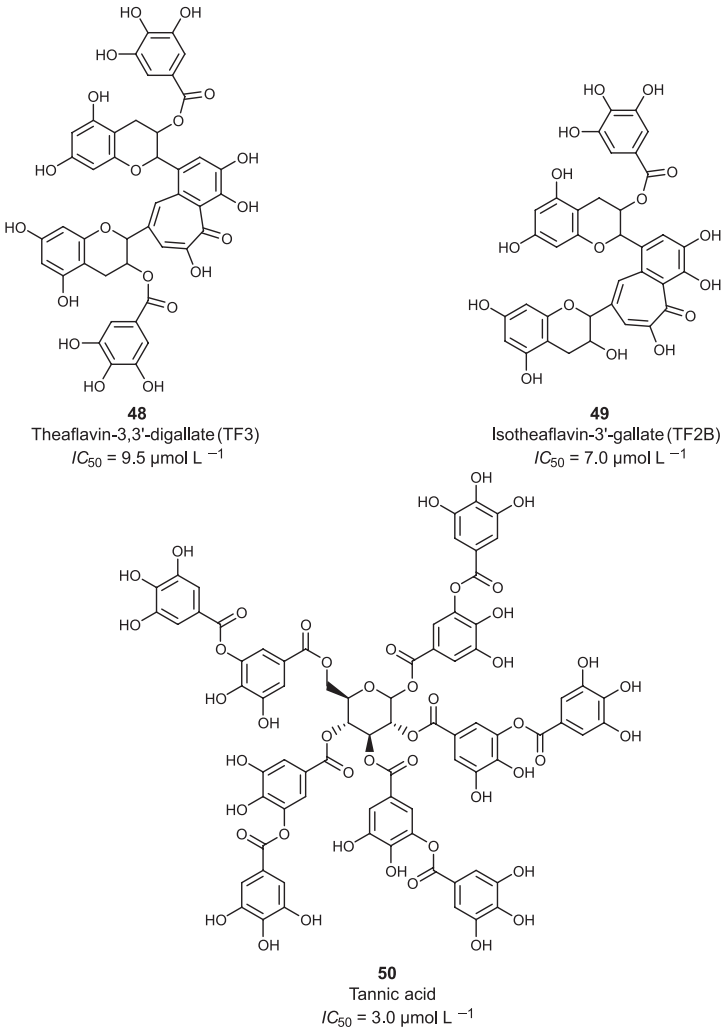


Fig. 12. Chemical structure of TF3, TF2B and tannic acid isolated from black tea extract.

L^{-1} and celasterol (**46**) with IC_{50} = 10.3 μmol L^{-1})] (Fig. 11). Pristimerin (**47**) substituted with methyl ester group inhibited SARS-CoV 3CLpro activity which was two-fold greater in potency (IC_{50} = 5.5 μmol L^{-1}) than celasterol (**46**).

The existing literature has shown that green and black tea constitutes 20 and 78 %, resp., of global tea consumption, whereas, approximately 2 % is consumed as oolong tea (70, 71). Interestingly, these teas are from the same plant species, namely *Camellia sinensis*. These tea types also differ based on the variety of *Camellia sinensis* used in their production. For instance, green teas are made from smaller young leaves and leaf buds (*Camellia sinensis* var. *sinensis*), while black, oolong, and Pu-erh teas are made from broad leaves (*Camellia sinensis* var. *Assamica*). In addition, the crucial factor that affects the production of a particular tea is oxidation, and the process begins from leaf picking to dryness, wilting, rolling, treating and preserving. The polyphenolic content in these varieties confers a broad spectrum of biological activities including antimicrobial, antifungal, antitoxin, antioxidant and antiviral (72–75). Accordingly, Chen *et al*. (45) explored four different varieties of tea, *viz*., green, puer, oolong and black tea, against SARS-CoV 3CLpro. Along with theaflavin (TF1), a mixture of theaflavin-3′-gallate (TF2b) and theaflavin-3-gallate (TF2a), three polyphenol compounds – theaflavin-3,3′-digallate (TF3) (**48**), isotheaflavin-3′-gallate (TF2B) (**49**) and tannic acid (**50**) were abundantly identified in the extract of black tea as effective anti-SARS-CoV inhibitors (IC_{50} = 9.5, 7.0 and 3.0 μmol L^{-1}, resp.) (Fig. 12). Notably,

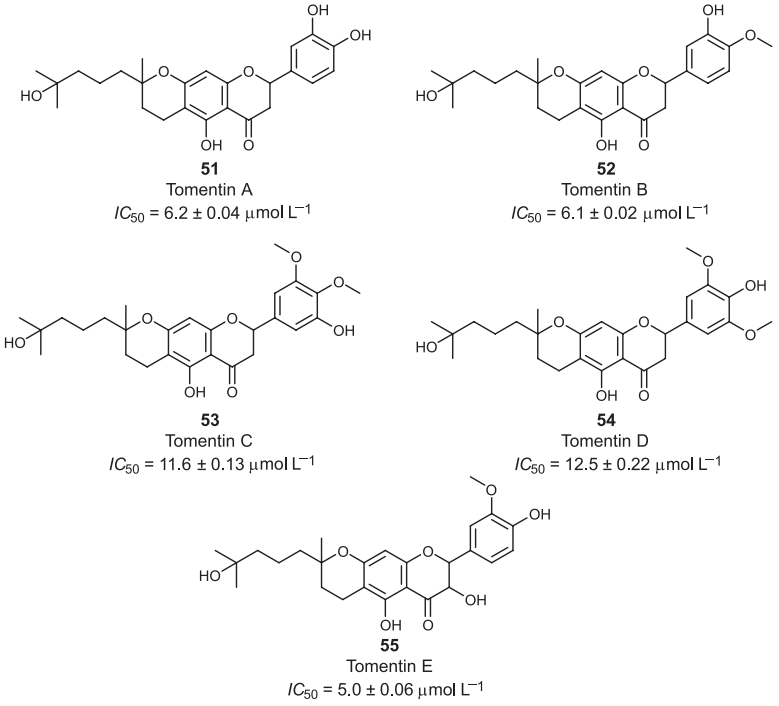


Fig. 13. Chemical structures of isolated flavonoids with anti-SARS-COV activity from the fruits of *Paulownia tomentosa.*

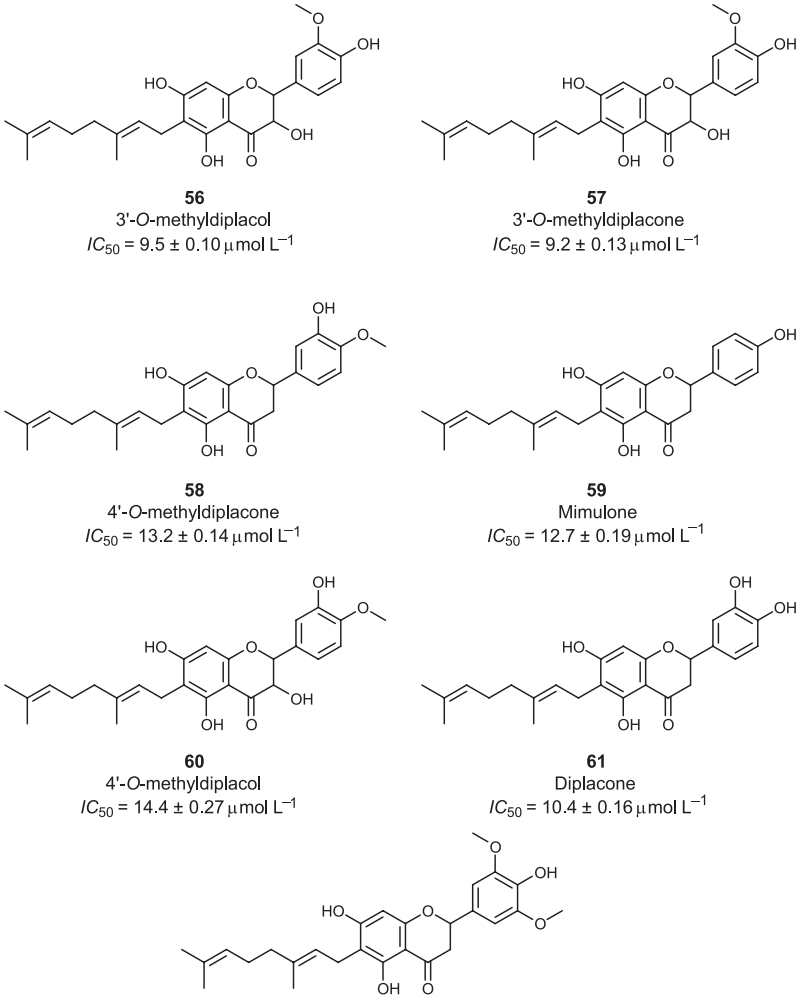


Fig. 13. Continued.

it will be very interesting to explore whether drinking black tea can be used to prevent or treat COVID-19 infection since both SARS-CoV and SARS-CoV-2 are known to dynamically replicate in the gastrointestinal tract.

A similar study evaluated twelve polyhydroxy compounds isolated from *Paulownia tomentosa* against SARS-CoV PLpro (Fig. 13) (47). Notably, compounds with a 3,4-dihydro-2*H*-pyran motif [tomentin A (**51**), tomentin B (**52**) and tomentin E (55)] with IC_{50} values ranging from 5.0–6.3 μmol L^{-1} were more effective PLpro inhibitors than other iso-

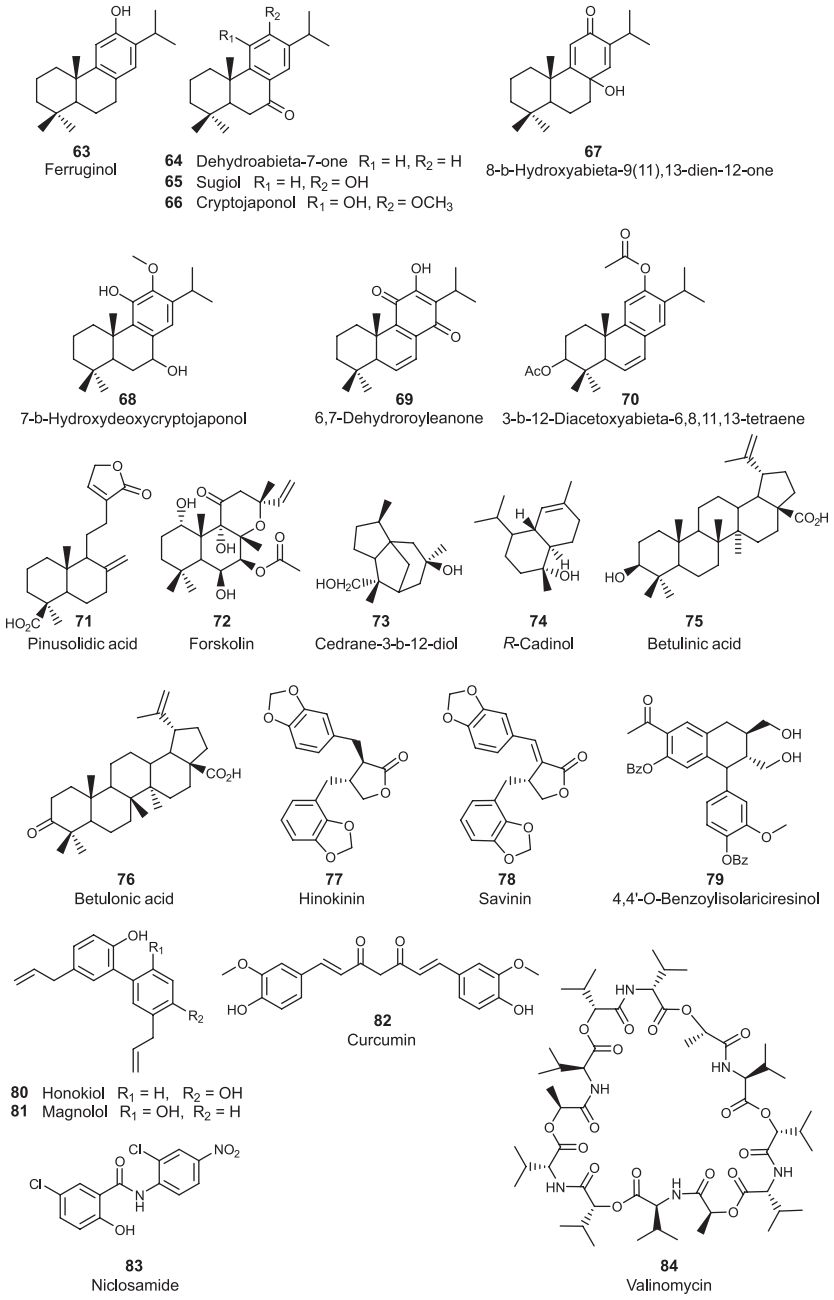


Fig. 14. Chemical structures of diterpenoids **63–72**, sesquiterpenoids **73** and **74**, triterpenoids **75** and **76** lignoids **77–81**, phenolic compound (curcumin, **82**) and two positive controls, niclosamide (**83**) and valinomycin (**84**).

lated compounds, namely, tomentin C (**53**), tomentin D (**54**), 3′-*O*-methyldiplacol (**56**), 3′-*O*-methyldiplacone (**57**), 4′-*O*-methyldiplacone (**58**), mimulone (**59**), diplacone (**61**), and 6-geranyl-4′,5,7-trihydroxy-3′,5′-dimethoxyflavanone (**62**) with IC_{50} values ranging from 9.2–14.4 μmol L^{-1}.

Wen *et al*. (46) reported the efficacy of *Cibotium barometz* and *Dioscorea batatas* extracts against SARS-CoV 3CLpro at concentrations between 25 and 200 μg mL^{-1} (Table I). Methanolic extracts of these plants displayed significant inhibitory potencies with 50 %-inhibitory values of 39 and 44 μg mL^{-1}, resp. Moreover, the anti-SARS-CoV efficacy of *Cibotium barometz* and *Dioscorea batatas* extracts was superior compared to *Isatis indigotica*, *Torreya nucifera* and tea extract with 50 %-inhibitory values of 53.8, 100 and 125 μg mL^{-1}, resp.

Wen and colleagues (46) examined the anti-SAR CoV activities of 221 phytocompounds by exploring cell-based assay to determine the SARS CoV-induced cytopathogenic outcome on Vero E6 cells. As shown in Fig. 14, twenty out of the tested compounds emerged as potent anti-SARS CoV agents at concentrations between 3.3 and 10 μmol L^{-1}, including ten diterpenoids, namely, ferruginol (**63**) dehydroabieta-7-one (**64**), sugiol (**65**), cryptojaponol (**66**), 8-β-hydroxyabieta-9(11),13-dien-12-one (**67**), 7-β-hydroxydeoxycryptojaponol (**68**), 6,7-dehydroroyleanone (**69**), 3-β-12-diacetoxyabieta-6,8,11,13-tetraene (**70**), pinusolidic acid (**71**), forskolin(**72**), two sesquiterpenoids, namely, cedrane-3-β,12-diol (**73**) and *R*-cadinol (**74**), two triterpenoids [betulinic acid (**75**) and betulonic acid (**76**)], five lignoids [hinokinin (**77**), savinin (**78**), 4,4′-*O*-benzoylisolariciresinol (**79**), honokiol (**80**), magnolol (**81**)], phenolic compound, curcumin (**82**), whereas niclosamide (**83**) and valinomycin were used as the reference compounds. Further, the 22 compounds were evaluated in a 3CL protease inhibition assay to identify the probable sites on the virus targeted by the specific anti-SARS CoV compounds using quenched fluorescence energy transfer (FRET) method. The results showed that diterpenoids (**63–72**) lacked SARS-CoV 3CL protease inhibition at concentrations less than 100 μmol L^{-1}. Betulinic acid (**75**), savinin (**78**), curcumin (**82**) and niclosamide (**83**) showed the highest inhibitory activity on 3CL protease with IC_{50} values of 10, 25, 40 and 40 μmol L^{-1}, resp., whereas betulonic acid (**76**) and hinokinin (**77**) [analogues to betulinic acid (**75**) and savinin (**78**)], resp., inhibited 3CL-protease activity with IC_{50} values > 100 μmol L^{-1}. Hence, savinin, a lignoid purified from ethyl acetate extracts of the heartwood of *Chamaecyparis obtuse* var. *formosanal*, and betulinic acid emerged as the most potent anti-SARS-CoV compounds (IC_{50} = 25 and 10 μmol L^{-1}, resp.) (25). The inhibitory potential of savinin for 3CLpro of SARS-CoV-2 is conceived by the presence of benzo[1,3] dioxole moiety.

CONCLUSIONS

The present study unveils plant extracts with potent inhibitory activities against SARS-CoV. More importantly, the literature analysis revealed that the fraction RH121 of *Rheum palmatum* L. with IC_{50} = 13.76 ± 0.03 μg mL^{-1}, along with compounds isolated from other plants, such as terrestrimine isolated from *Tribulus terrestris,* cryptotanshinone, tanshinone IIA and dihydrotanshinone I (*Salvia miltiorrhiza*), xanthoangelol E (*Angelica keiskei*), papyriflavonol A (*Broussonetia papyrifera*), psoralidin (*Psoralea corylifolia*), hirsutenone (*Alnus japonica*), tannic acid (*Camellia sinensis* var. *assamica*) and tomentin E (*Paulownia tomentosa*) with IC_{50} values ranging from 0.6–5 μmol L^{-1} were excellent candidates for

anti-SARS-CoV targeting PLpro. Meanwhile, iguesterin with an IC_{50} value of 2.6 ± 0.6 μmol L^{-1} emerged as the most potent anti-SARS-CoV targeting 3CLpro.

According to all the extracted data, phytotherapy has offered a large and encouraging concept to new, safe and effective anti-SARS-CoV-2 agents. Consequently, the inhibitory potency of these medicinal plants yearns for large-scale research and development to validate their efficacy and safety for combating emerging coronavirus diseases. We also hope these findings will motivate researchers to explore the structural architecture of these compounds for the discovery of new antiviral drugs against SARS-CoVs.

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Abbreviations, acronyms, codes. – ARDS – acute respiratory distress syndrome, 3CLpro – 3C-like protease, COVID-19 – coronavirus disease 2019, ES – effect sizes, IC_{50} – half maximal inhibitory concentration, ISG – interferon stimulated gene, MERS – Middle East respiratory syndrome, PLpro – papain-like cysteine protease, PRISMA – preferred reporting items for systematics reviews and meta-analyses, SARS-CoV – severe acute respiratory syndrome coronavirus, TF2B – isotheaflavin-3′-gallate, TF3 – theaflavin-3,3′-digallate

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