Review

Potential medicinal plants involved in inhibiting 3CL^pro activity: A practical alternate approach to combating COVID-19

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ABSTRACT

At present, a variety of vaccines have been approved, and existing antiviral drugs are being tested to find an effective treatment for coronavirus disease 2019 (COVID-19). However, no standardized treatment has yet been approved by the World Health Organization. The virally encoded chymotrypsin-like protease (3CL^pro) from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which facilitates the replication of SARS-CoV in the host cells, is one potential pharmacological target for the development of anti-SARS drugs. Online search engines, such as Web of Science, Google Scholar, Scopus and PubMed, were used to retrieve data on the traditional uses of medicinal plants and their inhibitory effects against the SARS-CoV 3CL^pro. Various pure compounds, including polyphenols, terpenoids, chalcones, alkaloids, bifla-vonoids, flavanones, anthraquinones and glycosides, have shown potent inhibition of SARS-CoV-2 3CL^pro activity with 50% inhibitory concentration (IC$_{50}$) values ranging from 2–44 μg/mL. Interestingly, most of these active compounds, including xanthoangelol E (isolated from *Angelica keiskei*), dieckol 1 (isolated from *Ecklonia cava*), amentoflavone (isolated from *Torreya nucifera*), celastrol, pristimerin, tingenone and iguesterin (isolated from *Tripterygium regelii*), tannic acid (isolated from *Camellia sinensis*), and theaflavin-3,3′-digallate, 3-isotheaflav1in-3 gallate and dihydrotanshinone I (isolated from *Salvia miltior-rhiza*), had IC$_{50}$ values of less than 15 μg/mL. Kinetic mechanistic studies of several active compounds revealed that their mode of inhibition was dose-dependent and competitive, with K_i values ranging from 2.4–43.8 μmol/L. Given the significance of plant-based compounds and the many promising results obtained, there is still need to explore the phytochemical and mechanistic potentials of plants and their products. These medicinal plants could serve as an effective inexpensive nutraceutical for the general public to help manage COVID-19.

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Contents

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], has been declared a global pandemic. According to the World Health Organization (WHO), globally, more than 500 million cases and more than 6 million deaths are attributed to COVID-19 [2]. The genomic sequencing of SARS-CoV-2 revealed 96.2% similarity with SARS-CoV [3]. However, SARS-CoV-2 is mutating constantly, producing variants, and the WHO has classified them as variants of concern (VOCs) based on their transmission rates, potential for immune evasion, and epidemiological properties [4]: the α lineage (13 mutations in spike proteins) first appeared in the United Kingdom in September 2020 [5]; the β lineage (10 mutations in spike proteins) was first reported in South Africa in August 2020 [6]; the δ lineage (with multiple amino acid substitutions in spike proteins) was first detected in India (Maharashtra) in October 2020 [7]; the omicron variant (37 amino acid substitutions in the spike proteins) was identified in November 2021 in Botswana and South African [8] and declared as a VOC by the WHO in the same month. All these variants of SARS-CoV-2 pose a grave threat to global human health.

Researchers have observed that remdesivir or molnupiravir in combination with brequinar blocked the replication of the virus in lung cells of mice [9]. This combination has been approved by the United States Food and Drug Administration for emergency use but has not yet been clinically tested. Moreover, globally the vaccination rate is still low, especially in poorer countries, and the emerging threat posed by VOCs may evade vaccines and drugs. Therefore, it is imperative to find effective strategies to lessen the impact of this global pandemic, and there is an urgent need for therapeutics to treat COVID-19. The use of medicinal plants is an ancient practice to treat human ailments, including different types of microbial and viral infections, and often is perceived as having fewer side effects than synthetic drugs [10]. Medicinal plants have been a major focus of research due to the presence of bioactive compounds that may provide the foundation for drug design. Traditional medicinal plants, particularly those with antiviral properties, may help to reduce the spread of COVID-19 [11]. The inclusion of medicinal plants in the general medical toolkit for COVID-19 would be beneficial, especially for developing countries, as access to these plants is often more economically viable than access to medicines. Various studies have shown that herbal medicine can help to prevent COVID-19 and minimize its severity [12,13]. Traditional Chinese medicine (TCM) has successfully been used to improve clinical symptoms, reduce mortality, and reduce recurrence rate of COVID-19. The uneven access to COVID-19 vaccines has compelled many Asians to rely on traditional medicinal systems to combat this deadly disease. In China, traditional medicines, such as Yinqiao San and Sangju Yin, are commonly used in the clinical management of COVID-19 to treat high fever and severe cough, respectively [14]. In 2004, WHO also announced that the careful use of TCM alone in the treatment of SARS-CoV is more effective than Western medicine for reducing the mortality rate. Herbal supplements such as black seed, ginger, vitamin C, lemon/orange, honey and costus showed convincing results against COVID-19 [10,15]. Similarly, in India, traditional medicines along with modern medicine and vaccination are used for the effective management of COVID-19. However, most of the herbal medicines being used in developing countries lack data from rigorous trials to confirm the efficacy of these traditional medicines against SARS-CoV-2 infection.

Antiviral drug development, to effectively stop the replication of the virus after it enters the host cell, is the primary challenge. The ideal targets in antiviral drug development are the receptor proteins, the enzymes involved in the replication of viral DNA or RNA, and the proteins responsible for uncoating the virus or releasing its contents. The SARS-CoV-2 genome is composed of two open reading frames (ORFs): ORF1a and ORF1ab that form 16 nonstructural proteins (NSPs) by proteolytical cleavage. These include four structural proteins (spike, envelope, membrane and nucleocapsid) and eight accessory proteins (ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8a, ORF8b and ORF9b) [16]. However, main protease (3CL^{pro}), papain-like protease, spike glycoprotein receptor-binding domain, RNA-dependent RNA polymerase, and angiotensin-converting enzyme 2 [17,18] have also been suggested as potential antiviral drug targets. Accessory proteins are considered to not be necessary for viral replication but appear to play a role in pathogenesis [19].

The 3CL^{pro} enzyme controls SARS-CoV-2 replication and transcription and is crucial for its life cycle. SARS-CoV 3CL^{pro} and SARS-CoV-2 3CL^{pro} have 96% similarity in their genome sequence, with 12-point mutations [20,21]. The main proteinase, or 3CL^{pro}, cuts the polyproteins at 11 distinct sites to form different NSPs essential for viral replication and other functions. It is already well understood that the development of immunity is a crucial element for curing viral diseases, but the NSPs generated by proteases restrict interferon signaling [22,23]. As auto-cleavage is important for the viral replication cycle, 3CL^{pro} is a potential pharmacological target for anti-COVID-19 drug development. A recent study sug-

gested that 3CL^{pro} activity could be further accelerated under cellular oxidative stress. The 3CL^{pro} impairs the antioxidant capacity of cells by regulating the cleavage of glutathione peroxidase 1 at its N-terminus. Consequently, the 3CL^{pro}-proximate oxidative activity is elevated, which facilitates aggregation and activation of 3CL^{pro}, thus resulting in a positive feedback loop. Hence, oxidative stress converts 3CL^{pro} into a detergent-insoluble form with increased capacity for enzyme activation, leading to enhanced viral replication and transcription [24].

Recently, results of a clinical trial revealed that SARS-CoV-2-infected patients, when treated orally with the 3CL^{pro} inhibitor nirmatrelvir (PF-07321332) during the first three days of infection, showed an 89% lower risk of COVID-19-related hospital admission or death [25]. In line with this important result, a group of Japanese scientists reported that patients infected with a SARS-CoV-2 sub-lineage (B.1.1.284) containing the Pro108Ser mutation in 3CL^{pro} required a milder clinical treatment compared to the patients infected with the same sub-lineage of virus without the mutation [26]. Moreover, Abdelnabi et al. [27] also reported that PF-07321332 exerted potent inhibition of 3CL^{pro} activity within different variants of SARS-CoV-2. In 2004, researchers found that metal ions such as Hg^{2+}, Zn^{2+} and Cu^{2+} effectively inhibited the 3CL^{pro} activity and were considered to be noncompetitive inhibitors. However, 1-hydroxypyridine-2-thione zinc showed higher affinity than Zn^{2+}, suggesting that it is a more potent inhibitor of 3CL^{pro} activity [28]. Similarly, recent studies also suggest that metal complexes have distinct mechanisms of action, compared to organic compounds, due to their rich molecular geometries, their ability to endure ligand exchange reactions and accessible redox processes [29,30]. Further efforts are needed to find metal-based inhibitors with enhanced affinity and selectivity that could serve as an alternative to the conventional therapeutic approach to treating SARS-CoV-2.

Although vaccine is crucial to combat COVID-19 and provides prophylactic protection for healthy adults, it may be less effective for people with weak immune system or other underlying medical problems. Moreover, the appearance of different variants of SARS-CoV-2 could also undermine the effectiveness of vaccines, thus it is necessary to find alternate therapeutic strategies and antiviral drugs. Therefore, the purpose of this review is to document medicinal plants that can effectively reduce 3CL^{pro} activity, and identify their bioactive compounds, because inhibition of 3CL^{pro} may stop the infection at the initial stage of replication. The present review not only provides background information about candidate plants for future drug development studies but is also a source of reliable information for the general public about medicinal plants that may be effective treatments for COVID-19.

2. Literature search

Online search engines, such as Web of Science, Google Scholar, Scopus and PubMed, were used to retrieve data on medicinal plants with inhibitory activity against the SARS-CoV 3CL^{pro}. The primary source data for this review were published papers, and the criteria for the inclusion of articles were: (1) research or review papers published in English-language journals; (2) the paper contained information about plant extracts, their chemical constituents, 50% inhibitory concentration (IC$_{50}$) values, and were based upon verified material. Articles containing ambiguous information outside the main scope of this review, for example, those examining plant extracts tested against other proteases of SARS-CoV, were excluded from this discussion. The keywords used for the search and data collection were "medicinal plants used to treat SARS-CoV," "role of medicinal plants in inhibiting SARS-CoV 3CL^{pro}," "phytochemicals with anti-SARS-CoV activities," and "phy-

tochemicals inhibiting SARS-3CL^{pro} activity." Microsoft Excel (2010) was used for data organization and analysis and to prepare summary tables and figures. Online botanical databases, such as "Tropicos" (https://www.tropicos.org) and "The Plant List" (https://www.theplantlist.com) were used for the taxonomic treatment of documented medicinal plants. ChemDraw software (ChemOffice 2004, CambridgeSoft) was used to draw the chemical structures of individual bioactive constituents from documented plant species.

3. Medicinal plants and 3CL^{pro} activity

The present review documents 15 medicinal plants that inhibit SARS-CoV 3CL^{pro} activity, including *Angelica keiskei* (Miq.) Koidz., *Salvia miltiorrhiza* Bunge, *Ecklonia cava* Kjellman, *Torreya nucifera* (L.) Siebold & Zucc., *Tripterygium regelii* Hook. f., *Lycoris radiata* (L'Hér.) Herb., *Isatis indigotica* L., *Chamaecyparis obtusa* (Siebold & Zucc.) Endl. and *Camellia sinensis* (L.) Kuntze, among others (Table 1). Most of the chemical constituents investigated belonged to different chemical classes, such as polyphenols, triterpenes and alkaloids (Figs. 1–3), and have shown dose-dependent competitive inhibition of SARS-CoV 3CL^{pro} activity (Table 1). In Fig. 4 we summarize possible pathways through which plant compounds may affect SARS-CoV 3CL^{pro}.

3.1. A. keiskei

A. keiskei belongs to the family Apiaceae, and its leaves are commonly used in health-promoting foods and folk medicine. *A. keiskei* possesses a variety of secondary metabolites, including coumarins, flavanones and chalcones, with different biological effects, including antioxidant, antihypertensive, anticancer, anti-influenza and antidiabetic activities [31,47–49]. The antiviral activity of this plant was found by Park et al. [32] against influenza virus neuraminidase. Park et al. [32] successfully isolated nine alkylated chalcones and four coumarins from *A. keiskei* and quantified their inhibitory activities against SARS-CoV 3CL^{pro}, using cell-free and cell-based assays. Among the isolated constituents, xanthoangelol E (an alkylated chalcone substituted with a perhydroxyl group) and xanthoangelol B had the strongest inhibitory activity against 3CL^{pro}, with IC$_{50}$ values of 11.4 and 22.2 µmol/L, respectively. The detailed mechanistic analysis revealed that xanthoangelol E and xanthoangelol B act through competitive inhibition of SARS-CoV 3CL^{pro}. Further interaction between these chalcones and 3CL^{pro} was studied using *in silico* docking simulations. The results suggested that these chalcones fit very well into the pocket (substrate-binding) of 3CL^{pro}, as represented by a ball-and-stick model. The inhibitory potential of alkylated chalcones and coumarins was determined using the fluorescence resonance energy transfer technique. Alkylated chalcones, with the exception of coumarins, showed a dose-dependent inhibitory action (IC$_{50}$ = 11.4 to 129.8 µmol/L). The most effective inhibitor was discovered to be xanthoangelol E. As a result, it might be a candidate for a COVID-19 therapy strategy.

3.2. C. sinensis

C. sinensis is a member of the Theaceae family, and its leaves are used to prepare a beverage known as "tea" or "Chai," which is the second most-consumed drink after water, globally. Tea was first used as medicine in ancient China around 2737 B.C. [50]. In ancient Asian folk medicines, tea was considered a potent medicine for treating a variety of ailments. The diversity of compounds in different forms of tea depends on the extent to which the leaves are fermented. Black tea is rich in tannins, whereas green tea contains

Table 1
Bioactivity of plant extracts and their chemical constituents against SARS-CoV-2 3CL protease.

Plant/family	Part	Extract	Bioactive compound	Class	Dose	IC$_{50}$	Inhibition type/K_i	Reference
Angelica keiskei (Miq.) Koidz. (Apiaceae)	Leaves	Ethanol	Xanthoangelol E	Chalcones	0, 12.5, 25 and 50 μmol/L	11.4 μmol/L	Competitive (11.4 μmol/L)	[31,32]
			Xanthoangelol B			22.2 μmol/L	Competitive (22.2 μmol/L)	
Camellia sinensis (L.) Kuntze (Theaceae)	Leaves	Aqueous	Theaflavin-3,3′-digallate	Polyphenol	No data	9.5 μmol/L	No data	[33]
			3-Isotheaflavin-3 gallate			7 μmol/L		
			Tannic acid			3 μmol/L		
Cassia tora L. (Fabaceae)	Seeds	*n*-Hexane	No data	No data	0–10 μg/mL	8.43 μg/mL	No data	[34,35]
Chamaecyparis obtusa (Siebold & Zucc.) Endl. (Cupressaceae)	Heartwood	Ethyl acetate	Savinin	Polyphenol	0.1–10 μmol/L	25 μg/mL	Competitive (9.1 μmol/L)	[36]
Cibotium barometz (L.) J. Sm. (Cibotiaceae)	Rhizome	Methanol Ethanol and methanol	No data	No data	25–200 μg/mL 0–10 μg/mL	39 μg/mL 8.42 μg/mL	No data	[34,35]
Dioscorea batatas Decne. (Dioscoraceae)	Tuber	Methanol	No data	No data	25–200 μg/mL 0–10 μg/mL	44 μg/mL 8.03 μg/mL	No data	[34]
Eckionia cava Kjellman (Laminariaceae)	Whole plant	Ethanol	Dieckols 1 and 2	Polyphenol	0–200 μmol/L	2.7 and 68.1 μmol/L	Competitive (2.4 μmol/L)	[37]
Houttuynia cordata Thunb. (Saururaceae)	Whole plant	Aqueous	No data	No data	200 μg/mL	No data	No data	[38]
Isatis indigotica Fortune ex Lindl. (Brassicaceae)	Roots	Aqueous	Sinigrin Aloeemodin Hesperetin	Glycoside Anthraquinone Flavanone	No data	217 μmol/L 366 μmol/L 8.3 μmol/L	No data	[39]
Litchi chinensis Sonn. (Sapindaceae)	Seeds	No data	No data	Flavonoids	0–100 mg/L	40.35 mg/L	No data	[40]
Lycoris radiata (L'Hér.) Herb. (Amaryllidaceae)	Stem cortex	Ethanol	Lycorine	Alkaloid	886.6 μg/mL	15.7 nmol/L	No data	[41,42]
Rheum palmatum L. (Polygonaceae)	Whole plant	Ethanol	No data	No data	No data	13.76 μg/mL	No data	[43]
Salvia miltiorrhiza Bunge (Lamiaceae)	Roots	*n*-Hexane	Dihydrotanshinone I	Diterpenoid	0–200 μmol/L	14.4 μmol/L	Noncompetitive	[44]
Torreya nucifera (L.) Siebold & Zucc. (Taxaceae)	Leaves	Ethanol	Amentoflavone	Biflavonoid	0–300 μmol/L	8.3 μmol/L	Noncompetitive (13.8 μmol/L)	[45]
			Bilobetin			72.3 μmol/L	Noncompetitive (80.4 μmol/L)	
			Ginkgetin			32.0 μmol/L	Noncompetitive (30.2 μmol/L)	
			Sciadopitysin			38.4 μmol/L	Noncompetitive (35.6 μmol/L)	
Tripterygium regelii Hook. f. (Celastraceae)	Bark	Chloroform	Celastrol	Triterpenes	0–300 μmol/L	10.3 μmol/L	Competitive (4.2 μmol/L)	[46]
			Pristimerin			5.5 μmol/L	Competitive (3.1 μmol/L)	
			Tingenone			9.9 μmol/L	Competitive (4.0 μmol/L)	
			Iguesterin			2.6 μmol/L	Competitive (0.8 μmol/L)	

SARS-CoV-2 3CL: virally encoded chymotrypsin-like protease of severe acute respiratory syndrome coronavirus 2; IC$_{50}$: 50% inhibitory concentration.

mainly catechins [51]. Tea is very useful for treating cardiovascular problems, obesity, cancer and neurological disorders [52,53]. Chen et al. [33] reported that aqueous extracts of different forms of tea showed inhibitory effects on SARS-CoV 3CL^{pro}. Different compounds derived from *C. sinensis* were tested against 3CL^{pro}, but few of them inhibited 3CL^{pro} activity. Among those with 3CL^{pro} inhibitory activity, theaflavin-3,3′-digallate, 3-isotheaflavin-3-gallate and tannic acid had IC$_{50}$ values of 9.5, 7 and 3 μmol/L, respectively. These findings highlight the antiviral potential of *C. sinensis* and suggest that drinking tea could alleviate or prevent SARS-CoV-2 infection. Moreover, the polyphenols (sanguiin, theaflavin digallate, kaempferol, theaflavin gallate, protocatechuic acid and punicalagin) present in this plant can inhibit viral proliferation by targeting SARS-CoV 3CL^{pro}, a crucial enzyme in coronavirus replication and transcription. Black tea consumption boosts resistance to SARS-CoV-2 in the early stages of human infection. The main proteases of SARS-CoV-2, post-fusion core of 2019-nCoV S2 component, prefusion spike glycoproteins, and NSP15 endoribonuclease from SARS-CoV-2 are among the targets of epigallocatechin gallate from this plant. Green tea catechins from *C. sinensis* leaves, especially epigallocatechin-3-gallate, have shown antiviral activity against different viruses, i.e., adenovirus, hepatitis B virus, hepatitis C virus (HCV), human immunodeficiency virus (HIV), herpes simplex virus (HSV), human T cell lymphotrophic virus type 1, dengue virus, Epstein-Barr virus, tick-borne encephalitis virus, Japanese encephalitis virus, Zika virus (ZIKV), chikungunya virus, rotavirus, enteroviruses, influenza virus, Ebola virus, and porcine reproductive and respiratory syndrome virus [54].
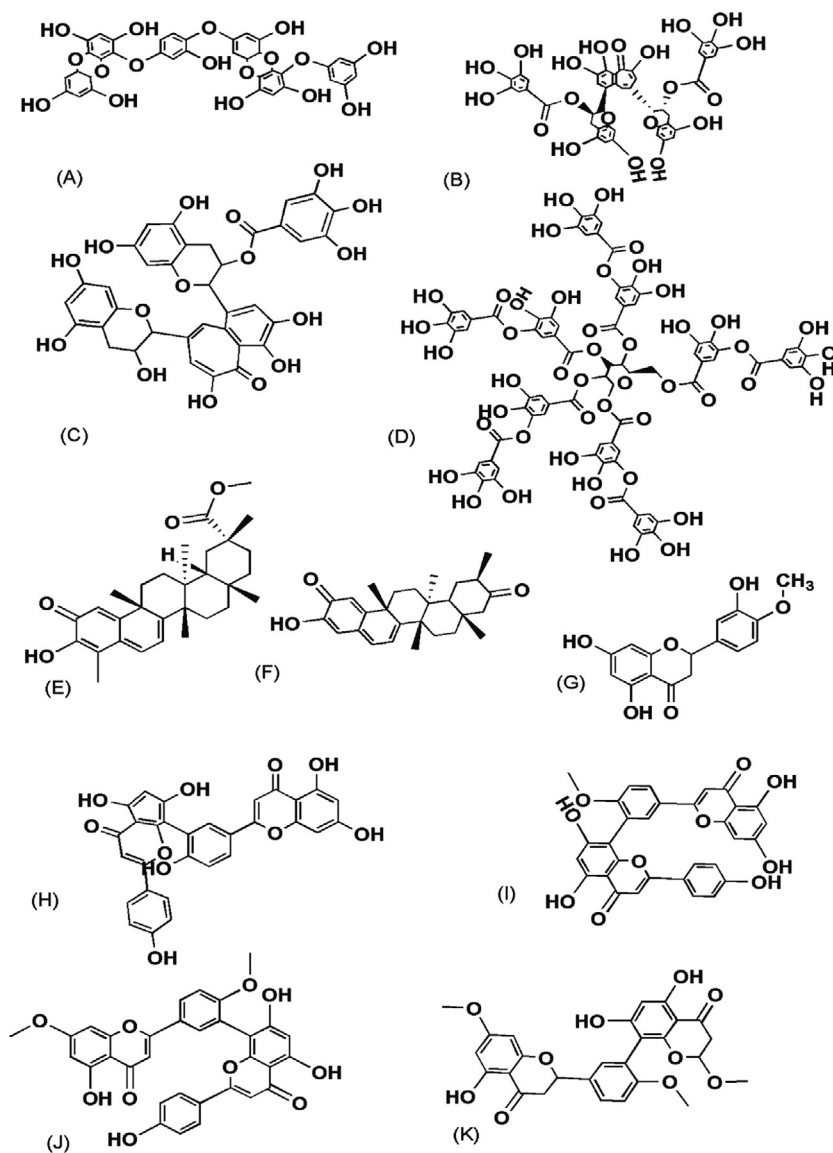
Fig. 1. Chemical structure of polyphenol and flavonoid compounds reported to inhibit 3CL protease. A–D: polyphenols, including dieckol (A), theaflavin-3,3′-digallate (B), 3-isotheaflavin-3 gallate (C) and tannic acid (D). E–K: flavonoids, including xanthoangelol E (E), xanthoangelol B (F), hesperetin (G), amentoflavone (H), bilobetin (I), ginkgetin (J) and sciadopitysin (K).

3.3. C. obtusa

C. obtusa belongs to the Cupressaceae family and is a slow-growing tree with commercial and medicinal importance. The essential oil extracted from the leaves of *C. obtusa* has antimicrobial and antifungal activities, which may result from the presence of a high proportion of longifolene [55,56]. Owing to the biological importance and special fragrance of its essential oil, this plant has commercial uses, including in furniture products [57]. Wen et al. [36] isolated nine compounds from the ethyl acetate extract of *C. obtusa* heartwood and tested them against SARS-CoV using a cell-based assay. Among the tested compounds, only savinin showed significant inhibition of the activity of SARS-CoV 3CL^{pro} with an IC$_{50}$ value of 40 μmol/L. A detailed characterization of the inhibition mechanism revealed that savinin was a potential inhibitor of 3CL^{pro} activity with a K_i value of 9.1 μmol/L. Structural modeling suggested that savinin's inhibition of 3CL^{pro} activity was a result of the development of multiple hydrogen bonds between specific amino acids and the compounds located on the active site of the enzyme. Moreover, yatein from *C. obtusa* inhibits multiplication of HSV-1 in HeLa cells by disrupting early gene expression [58].

3.4. E. cava

E. cava is an alga belonging to the family Laminariaceae and has been used widely as a traditional medicine and as a food source in Asian countries [59]. The extract of *E. cava* was approved by the United States of America Food and Drug Administration as a dietary ingredient in 2008 [60]. Traditionally, *E. cava* has been used to treat urinary infections, hemorrhoids, postpartum problems, goiter, stomach ailments and scrofula [61]. Many types of active compounds have been identified in *E. cava*, including carotenoids, phlorotannins and fucoidan; these compounds possess various biological effects, including antioxidant, immunomodulatory, anti-cancer and antiviral activities [62,63]. Park et al. [37] were the first to confirm the inhibitory activity of phlorotannins from *E. cava* against SARS-CoV 3CL^{pro}. Overall, nine phlorotannins were isolated from the ethanolic extract of *E. cava,* and all of these compounds,
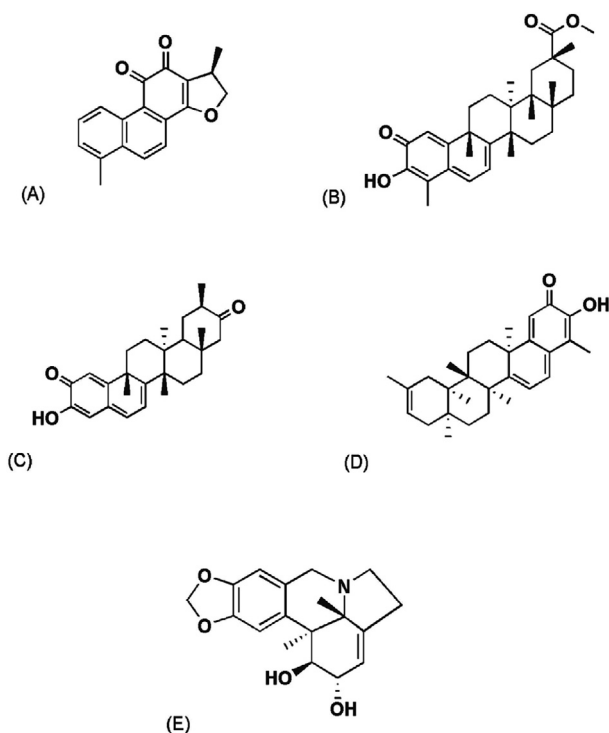
Fig. 2. Chemical structure of triterpene and diterpenoid compounds reported to inhibit 3CL protease. A and B: triterpenes, including dihydrotanshinone I (A) and celastrol (B). C–E: diterpenoids, including tingenone (C), pristimerin (D) and iguesterin (E).
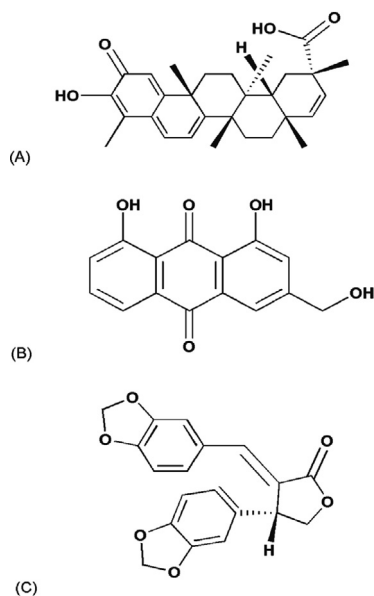

Fig. 3. Chemical structure of alkaloids and anthraquinones reported to inhibit 3CL protease. Lycorine (A) is an alkaloid. Aloe emodin (B) and savinin (C) are anthraquinones.

except phloroglucinol, showed competitive and dose-dependent inhibitory activities against 3CL^pro. Among those eight potent compounds, dieckol, which possesses two eckol groups, showed the most potent trans/cis-cleavage inhibitory activity against SARS-CoV 3CL^pro, with IC$_{50}$ values of 2.7 and 68.1 μmol/L, respectively.

Further analysis revealed that dieckol forms strong hydrogen bonds to the catalytic dyad and has a high affinity for SARS-CoV 3CL^pro. Moreover, identification and characterization of different bioactive compounds, through protein-molecular docking combined with network pharmacology analysis, from the fruits of the brown alga, *Juniperus communis* and *E. cava* are well documented in the literature [64]. However, quercetin isolated from *E. cava* proved effective against respiratory diseases and could be used to help heal the lung damage caused by the SARS-CoV-2 infection.

3.5. H. cordata

H. cordata belongs to the family Saururaceae and has been used for a long time in TCM for the treatment of lung-related problems such as pneumonia, and other infectious diseases. Several studies have provided evidence that *H. cordata* possesses anti-inflammatory, anticancer, antioxidant and antiviral activities [65–67]. *H. cordata* has shown antiviral activities against the herpes and influenza viruses [68]. Lau et al. [38] studied the aqueous extract of *H. cordata* using a fluorogenic protein-based assay and found that it exhibited potent activity against SARS-CoV-2 3CL^pro at a concentration of 200 μg/mL. A higher concentration (1000 μg/mL) decreased the 3CL^pro activity to 50% of the control sample. These findings indicated that *H. cordata* extracts exhibited dose-dependent inhibition of 3CL^pro activity.

3.6. I. indigotica

I. indigotica belongs to the family Brassicaceae and is a native plant species in China. This herb was commonly used in China for the prevention of SARS during the outbreak. *I. indigotica* root possesses antiviral properties against influenza, HIV, hepatitis and Japanese encephalitis. Several phytocompounds have been isolated from the root, including indican, indigo, sitosterols, indirubin and sinigrin [69–71]. Lin et al. [39] assessed the aqueous extract of *I. indigotica* root and root-derived compounds using cell-free and cell-based cleavage assays. Their results demonstrated that the root extract and three compounds (hesperetin, sinigrin and aloee-modin) from *I. indigotica* exerted inhibitory activity against SARS-CoV 3CL^pro. The cell-based cleavage assay revealed that sinigrin, hesperetin and aloeemodin inhibited 3CL^pro activity at IC$_{50}$ concentrations of 217, 8.3 and 366 μmol/L, respectively. Moreover, the results demonstrated that sinigrin and hesperetin were considerably less cytotoxic than Vero cells, with a 50% cytotoxic concentration of over 2 mmol/L.

3.7. L. radiata

L. radiata belongs to the family Amaryllidaceae, is commonly used in horticulture, and is distributed widely throughout Vietnam, Malaysia, Nepal, Korea and South China. It has many uses in traditional medicine: to expel phlegm, as an emetic and antipyretic, for pain relief, and for poliomyelitis, neurodegenerative diseases and a variety of other health conditions [72,73]. *In vitro* studies reveal that *L. radiata* has several biological effects, including anticancer, antimalarial, antiviral and anti-inflammatory activities, which may be due to the abundance of alkaloids [41]. Li et al. [42] found that the ethanol extract of *L. radiata* exhibits potent inhibitory effects against SARS-CoV-induced cytopathy, which may result from its role in the inhibition of 3CL^pro activity. Phytochemical analysis of *L. radiata* extract led to the identification of lycorine, an alkaloid involved in the inhibition of SARS-CoV, with a half maximal effective concentration (EC$_{50}$) value of 15.7 nmol/L
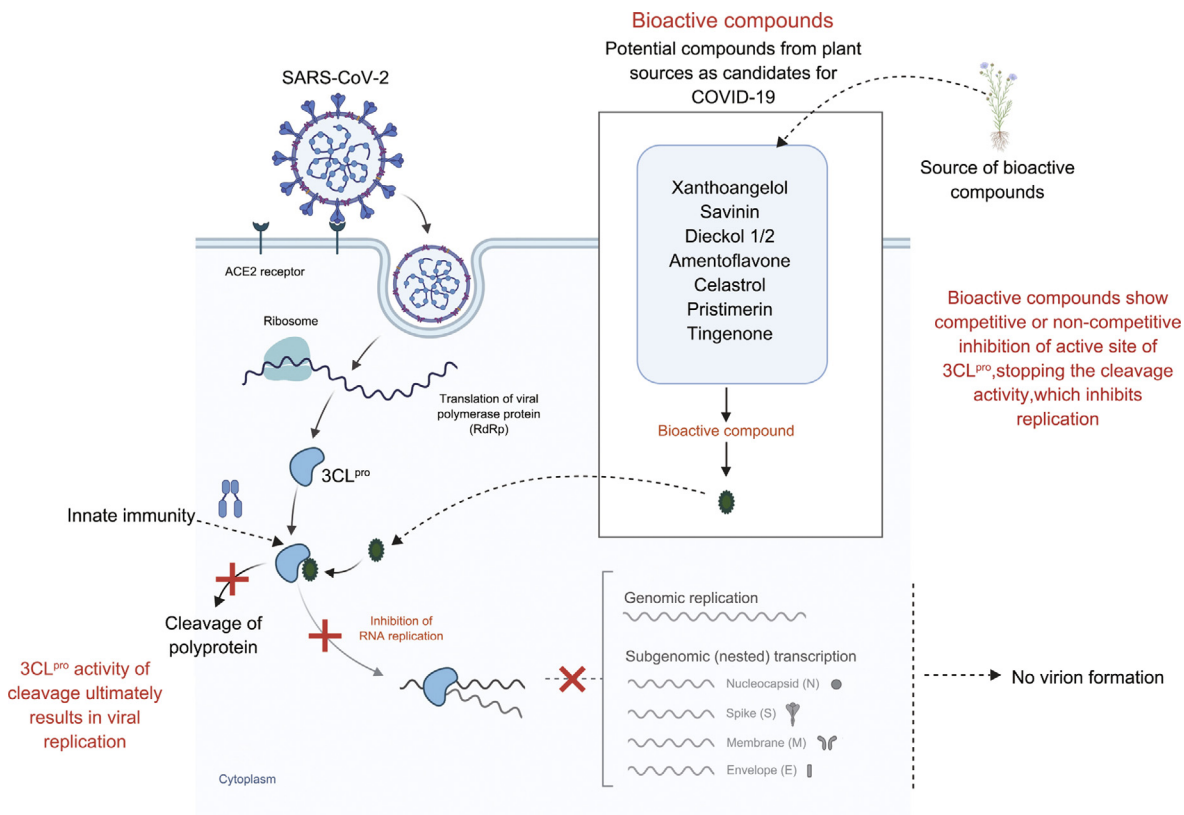
Fig. 4. Possible action pathways of plant compounds against SARS-CoV-2 3CL protease. ACE2: angiotensin-converting enzyme 2; 3CL^{pro}: virally encoded chymotrypsin-like protease; COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

[42]. In fact, this alkaloid has been found to possess antiviral activities against HCV, HIV-1, ZIKV and SARS-CoV [74].

3.8. S. miltiorrhiza

S. miltiorrhiza belongs to the family Lamiaceae and has been used widely in many countries, such as China, Japan, Korea and other Asian countries, to treat heart diseases, particularly myocardial infarction and angina pectoris [44]. There are two major classes of active compounds in *S. miltiorrhiza* (hydrophilic salvinolic acid and lipophilic tanshinones), both of which exhibit antiviral, antioxidant, anti-inflammatory and anti-HIV properties [75–77]. Lee et al. [78] showed that the aqueous extract of this plant had a protective effect in BALB/c mice against influenza virus by upsetting the viral replication or inhibiting the viral infection, leading to an antiviral state in the lungs. Hence, *S. miltiorrhiza* aqueous extract, as an orally active antiviral agent, could be used for prophylactic treatments against influenza. Wu et al. [79] also reported antiviral activity of different extracts obtained from this plant against enterovirus 71. Park et al. [44] confirmed that the ethanolic extract of *S. miltiorrhiza* root inhibited SARS-CoV 3CL^{pro} activity by 60% at a concentration of 14.4 μmol/L. The main active compounds of this plant are tanshinones, including diterpene quinolones and salvianolic acid derivatives. Lipophilic *n*-hexane fractionation yielded seven tanshinones and all the identified tanshinones exhibited remarkably potent inhibition of SARS-CoV 3CL^{pro}; however, dihydrotanshinone I showed extremely high inhibition (IC$_{50}$ = 14.4 μmol/L). Moreover, the kinetic mechanistic assessment showed that all the tanshinones acted as noncompetitive enzyme isomerization inhibitors, except rosmariquinone, which showed mixed-type simple reversible slow-binding inhibition.

3.9. T. nucifera

T. nucifera belongs to the family Taxaceae and is native to South Korea and Japan. This tree has been used in traditional medicine as a remedy against rheumatoid arthritis, hemorrhoids and stomachache in Asian countries. Ryu et al. [45] observed that the ethanolic extract of *T. nucifera* leaves inhibited 62% of 3CL^{pro} activity at a concentration of 100 μg/mL. Eight diterpernoids and four biflavonoids were extracted and tested for 3CL^{pro} inhibition using a fluorescence resonance energy transfer assay. Among the isolated compounds, amentoflavone appeared to be the most potent inhibitor of SARS-CoV 3CL^{pro}, with an IC$_{50}$ value of 8.3 μmol/L. Further mechanistic and molecular docking analyses revealed that amentoflavone showed noncompetitive inhibition characteristics toward 3CL^{pro}, and it fit well into the binding pocket of SARS-CoV 3CL^{pro}.

3.10. T. regelii

T. regelii belongs to the family Celastraceae and is a woody plant native to Japan, Korea, and Southern and Eastern China [80]. Historically, it has been used in TCM to treat cancer, and autoimmune and inflammatory diseases; this may be due to the presence of a variety of diterpenes, triterpenes and sesquiterpenes in the bark of *T. regelii* [81]. Triptofordin C-2 isolated from this plant is an inhibitor of HSV-1 replication at concentrations that are not harmful for the host cells. The compound showed efficacy in the inactivation of virus [82]. Ryu et al. [46] isolated quinone-methide triterpenes (celastrol, pristimerin, tingenone and iguesterin) from *T. regelii* and were the first to test them against SARS-CoV 3CL^{pro}. Their results suggested that all the isolated triterpenes effectively inhibited 3CL^{pro} activity dose-dependently, with IC$_{50}$ values in the range

of 2.6–10.2 μmol/L. Celastrol was found to have an acidic moiety at C-20, which inhibited 3CL^{pro} with an IC$_{50}$ of 10.3 μmol/L. Pristimerin inhibited 3CL^{pro} activity with twofold greater potency (IC$_{50}$ = 5.5 μmol/L) than celastrol, because the C-20 was substituted with a methyl ester group. Tingenone (a ketone-substituted analog at C-21) inhibited 3CL^{pro} activity with an IC$_{50}$ value of 9.9 μmol/L, whereas the double bond present in the E-ring of iguesterin conferred inhibitory activity, with an IC$_{50}$ value of 2.6 μmol/L. Kinetic analysis showed that the mode of inhibition was competitive for all quinone-methide triterpenes.

3.11. Other plants

In addition to the plants discussed above, several other medicinal species are known to inhibit SARS-CoV 3CL^{pro}. Wen et al. [34] studied several extracts of Chinese medicinal herbs and reported that six plant extracts showed potent inhibition of SARS-CoV at concentrations between 25 and 200 μg/mL, but only two plants (*Dioscorea batatas* and *Cibotium barometz*) significantly inhibited SARS-CoV 3CL^{pro} activity, with IC$_{50}$ values of 39 and 44 μg/mL, respectively. The *n*-hexane extract of *Cassia tora* seeds also showed inhibitory activity against SARS-CoV with an EC$_{50}$ value of 8.03 μg/mL, but its IC$_{50}$ value was greater than 50 μg/mL for the inhibition of SARS-CoV 3CL^{pro} activity [35]. Gong et al. [40] reported that flavonoids extracted from the seeds of *Litchi chinensis* showed marked inhibition of SARS-3CL^{pro} activity. Moreover, Luo et al. [43] reported that the ethanol extract of *Rheum palmatum* had very potent activity against SARS-CoV 3CL^{pro}, with an inhibition rate of 96% and an IC$_{50}$ value of 13.76 μmol/L, accompanied by no cytotoxicity at a dose of 20 mg/mL. While most of the extracts of these plants were proven effective against SARS-3CL^{pro}, there is a lack of detailed understanding of the mechanism of inhibition and the phytochemicals involved.

4. Conclusions

Although some vaccines for COVID-19 have been approved by WHO, the vaccination of the global population has been very slow, especially in poor countries, and scientists throughout the world are still struggling to combat SARS-CoV-2. Medicinal plants may offer an easy and safe resource from which to derive new antiviral drugs for use in the current pandemic. Most of the plants documented in this review have been used in traditional medicine since ancient times and have been reported to be active against SARS-CoV infections due to their role in the inhibition of 3CL^{pro} activity. Various active compounds have been isolated from a large number of documented plants and tested against SARS-CoV 3CL^{pro}, with promising results. Medicinal plants documented in this review are traditionally used to prevent or alleviate SARS-CoV infection, and the compounds reported here may be considered as potential leads for the development of anti-SARS drugs. However, there is still a lack of detailed mechanistic understanding (kinetic and molecular docking) of several plants that are reported to be active inhibitors of SARS-CoV 3CL^{pro}. Several researchers have tested plant extracts against SARS-CoV without any phytochemical analysis or isolation of the active compounds responsible for inhibition. These potential scientific gaps should be seriously considered in future studies and will help to open new avenues and assist the global community to alleviate the threat of SARS-CoV.

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Authors' contributions

FY, XJ and AT carried out the study design and manuscript draft. FY, XJ, SS and AT collected and analyzed the data. FY, XJ, AT and SS wrote the original manuscript. All authors participated in data interpretation and manuscript review and revision. FJ and XJ contributed equally to this manuscript.

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Declaration of competing interest

The authors have none to declare.

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