future pharmacology

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Review

Insights for Future Pharmacology: Exploring Phytochemicals as Potential Inhibitors Targeting SARS-CoV-2 Papain-like Protease

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Abstract: (1) Background: The SARS-CoV-2 papain-like protease (PLpro) remains an underexplored antiviral target so far. The reduced efficacy of approved treatments against novel variants highlights the importance of developing new agents. This review aims to provide a comprehensive understanding of phytochemicals as inhibitors of PLpro, identify gaps, and propose novel insights for future reference. (2) Methods: A thorough literature search was conducted using Google Scholar, ScienceDirect, and PubMed. Out of 150 articles reviewed, 57 met inclusion criteria, focusing on SARS-CoV-2 PLpro inhibitors, excluding studies on other coronaviruses or solely herbal extracts. Data were presented class-wise, and phytochemicals were grouped into virtual, weak, modest, and potential inhibitors. (3) Results: Approximately 100 phytochemicals are reported in the literature as PLpro inhibitors. We classified them as virtual inhibitors (70), weak inhibitors (13), modest inhibitors (11), and potential inhibitors (6). Flavonoids, terpenoids, and their glycosides predominated. Notably, six phytochemicals, including schaftoside, tanshinones, hypericin, and methyl 3,4-dihydroxybenzoate, emerged as potent PLpro inhibitors with favorable selectivity indices and disease-mitigation potential; (4) Conclusions: PLpro stands as a promising therapeutic target against SARS-CoV-2. The phytochemicals reported in the literature possess valuable drug potential; however, certain experimental and clinical gaps need to be filled to meet the therapeutic needs.

Keywords: phytochemicals; COVID-19; SARS-CoV-2; anti-viral; papain-like protease (PLpro)

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1. Introduction

The first case of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China, in December 2019. The virus rapidly spread far and wide across the globe, infecting billions of people and leading to millions of deaths worldwide [1]. The virus leads to a severe type of pneumonia, characterized by prevalent symptoms such as fever, cough, fatigue, and a diminished sense of taste or smell [2], while chest discomfort and respiratory distress syndrome may be present in severe cases [3]. By 9 December 2022, it had affected around 237 countries, infected over 643,875,406 people, and tragically claimed the lives of over 6.6 million [4].

The SARS-CoV-2 is a novel beta-coronavirus belonging to Coronaviridae, a family of viruses known to cause disease in several species of animals and humans. Over the course of the last twenty years, two novel coronaviruses from the same family emerged, resulting in respiratory-related illnesses known as severe acute respiratory syndrome (SARS) and Middle-Eastern Respiratory Syndrome (MERS). Like these viruses, SARS-CoV-2 is also thought to have originated from zoonotic transmission [5]. The human coronaviruses discovered have all been single-stranded RNA viruses. These viruses contain two major types of proteins: structural and non-structural proteins with enzyme-like functions. The structural proteins include the Spike (S), Envelope (E), Matrix (M), and Nucleocapsid

(N) proteins. The non-structural proteins include Papain-like protease (PLP/PLpro), 3-Chymotrypsin-like protease (3CLpro), Helicase, and RNA-dependent RNA polymerase (RdRp) [6]. The spike proteins are vital for viral cell entry, while the non-structural proteins modulate the viral replication and life cycle. Hence, these five proteins have been focused on previously and targeted in the treatments of SARS (severe acute respiratory syndrome) and MERS (Middle Eastern Respiratory Syndrome) [7].

PLpro is a cysteine protease, and like all proteases, it cuts down proteins into smaller constituents by targeting the peptide linkages [8]. In SARS-CoV-2, it recognizes the 'LXGG↓XX' sequence at three sites and cleaves the viral polyprotein into functional proteins to form a replication complex [9–11]. The LXGG motif is also found in ubiquitin and interferon-stimulated gene 15 (ISG15) proteins. PLpro also recognizes this motif, and its cleavage results in deubiquitinating and deISG15ylating activities [12]. This results in the inhibition of chemokines and cytokines, which activate the host immune system against SARS-CoV-2. Therefore, PLpro plays a significant role not only in the cleavage of viral polyproteins but also in the suppression of the host's innate immune response [11,13,14].

Despite their great disease-mitigating potential, PLpro-targeting drugs did not materialize into therapeutic products. Instead, the focus largely remained on other targets such as spike protein, Mpro, and RdRp. By December 2022, there were three FDA (Food and Drug Administration)--approved COVID-19 treatments, i.e., remdesivir (Veklury), baricitinib (Olumiant), and tocilizumab (Actemra) [15]. These drugs target RdRp [16] and immune modulation, respectively [17,18]. However, the FDA initially approved some emergency-use authorized treatments as well. These were anakinra (Kineret), bebtelovimab, molnupiravir (Lagevrio), nirmatrelvir with ritonavir (Paxlovid), tixagevimab with cilgavimab (Evusheld), tocilizumab, sotrovimab, bamlanivimab with etesevimab, casirivimab with imdevimab (REGEN-COV), and baricitinib [19]. Of these, two drugs were later approved by the FDA, whereas five of them, viz., REGEN-COV, sotrovimab, bamlanivimab with etesevimab, bebtelovimab, and Evusheld, were suspended due to their diminished efficacy against new SARS-CoV-2. All five of these drugs were focused on targeting the spike protein. This highlights how the treatments became ineffective owing to the genetic variations in the virus and the need to explore other reliable targets against the coronaviruses to load sufficient ammunition against any unanticipated future outbreaks. In this view, PLpro inhibitors offer a unique prospect in the therapeutics against SARS-CoV-2 to prevent any unfortunate health outcomes in the future.

Phytochemicals—nature's arsenal of bioactive compounds, present an enticing prospect in the quest for potent PLpro inhibitors. Historically, these compounds have been revered for their therapeutic potential and cost-effectiveness [20]. The word 'phyto' is from Greek, meaning 'plant'. These are non-nutritive elements present in plant-based products that exert protective or disease-preventing effects [21]. The unmatched potential of phytochemicals is evident through their key contributions to therapeutics, such as digoxin in congestive heart failure, paclitaxel in chemotherapy, and artemisinin for malarial infections. Moreover, the chemical scaffolds of phytochemicals have served as the basis for deriving more efficacious therapeutic products such as semisynthetic penicillins, opioids, taxanes, and ergot alkaloids. These contributions have had monumental effects on disease therapeutics in the areas of cardiology, oncology, infectious diseases, and pain management.

Recent clinical evidence has shown that phytochemicals can be promising candidates in the therapeutics against COVID-19 individually and in combination with other complementary medicines or approved treatments [22–26]. For example, a clinical trial demonstrated the synergistic effect of Quercetin Phytosome® in improving COVID-19 symptoms alongside standard therapies [25]. Similarly, a formulation containing a natural flavonoid luteolin (NeuroProtek® by Algonot™, Sarasota, Florida, United States) was described to mitigate the Long-COVID syndrome-associated brain fog and chemofog in affected patients [22]. In addition, a combination of luteolin with palmitoylethanolamide (PEA-LUT) showed improved $GABA_B$-ergic transmission in patients suffering from cognitive difficulties and fatigue after mild COVID-19 [26]. Likewise, hesperidin, primarily

an S-protein receptor blocker, has been shown to alleviate COVID-19 symptoms in a double-blinded, randomized controlled trial [27]. Some other phytochemicals with clinical evidence against COVID-19 include curcumin [28,29], resveratrol [30], berberine [31,32], colchicine [33], and many others [34].

Notably, the phytochemicals tried so far in clinical studies target SARS-CoV-2 through mechanisms other than prime inhibition of PLpro (e.g., targeting S-protein, Mpro, or RdRp) or playing a supportive role by reducing inflammation and improving symptoms [34]. Therefore, this review aims to leverage nature's pharmacopeia to unveil novel phytochemicals capable of robustly inhibiting PLpro, thereby introducing a new era in antiviral therapeutics. This review will bring to light valuable research on natural compounds in terms of PLpro inhibition to help readers gain a comprehensive understanding of the subject area, analyze existing trends to identify gaps, and assist researchers, practitioners, and policymakers in making informed decisions for future investigations.

2. Methodology

2.1. Data Retrieval

Figure 1 provides a detailed map of the review process. The published literature was thoroughly reviewed using online databases such as Google Scholar, ScienceDirect, and PubMed. More than 150 articles were consulted. Of them, 57 were shortlisted based on the inclusion criteria to generate this review. Keywords such as 'papain-like protease', 'PLpro inhibitors', 'SARS-CoV-2', 'phytochemicals against SARS-CoV-2', 'natural products against COVID-19', and 'potential targets against COVID-19' were used to explore the data.

2.2. Inclusion and Exclusion Criteria

The in silico, in vitro, ex vivo, and in vivo studies reporting plant-based phytochemicals as inhibitors of SARS-CoV-2 PLpro were included. At the same time, articles in languages other than English, those reporting synthetic compounds, and those related to SARS-CoV and MERS-CoV PLpro inhibitors were excluded from the review. Articles solely reporting data on herbal extracts without reporting the activity of individual phytochemicals were also excluded.

2.3. Data Presentation

The data were summarized and expressed in tables to enhance understanding and perception. Based on the nature of the data (in silico, in vitro, and key findings), phytochemicals were grouped into the following tables: (1) those reported with in silico data only (virtual inhibitors), (2) those reported with in vitro data but IC_{50} of >20 μM for PLpro (weak inhibitors) (3) those with IC_{50} < 10–20 μM but the selectivity index (SI) was compromising (modest inhibitors), and (4) those with IC_{50} < 10 μM, good SI, and disease-mitigation potential (good inhibitors, lead compounds).

2.4. Supporting Data

The chemical classes of phytochemicals were obtained from online natural product databases COCONUT (https://coconut.naturalproducts.net/ (accessed on 12 August 2024)) and LOTUS (https://lotus.naturalproducts.net/ (accessed on 12 August 2024)) [35] if not mentioned in the relevant studies. Chemical structures and figures were drawn using ChemDraw Professional 16 in ACS 1996 format.

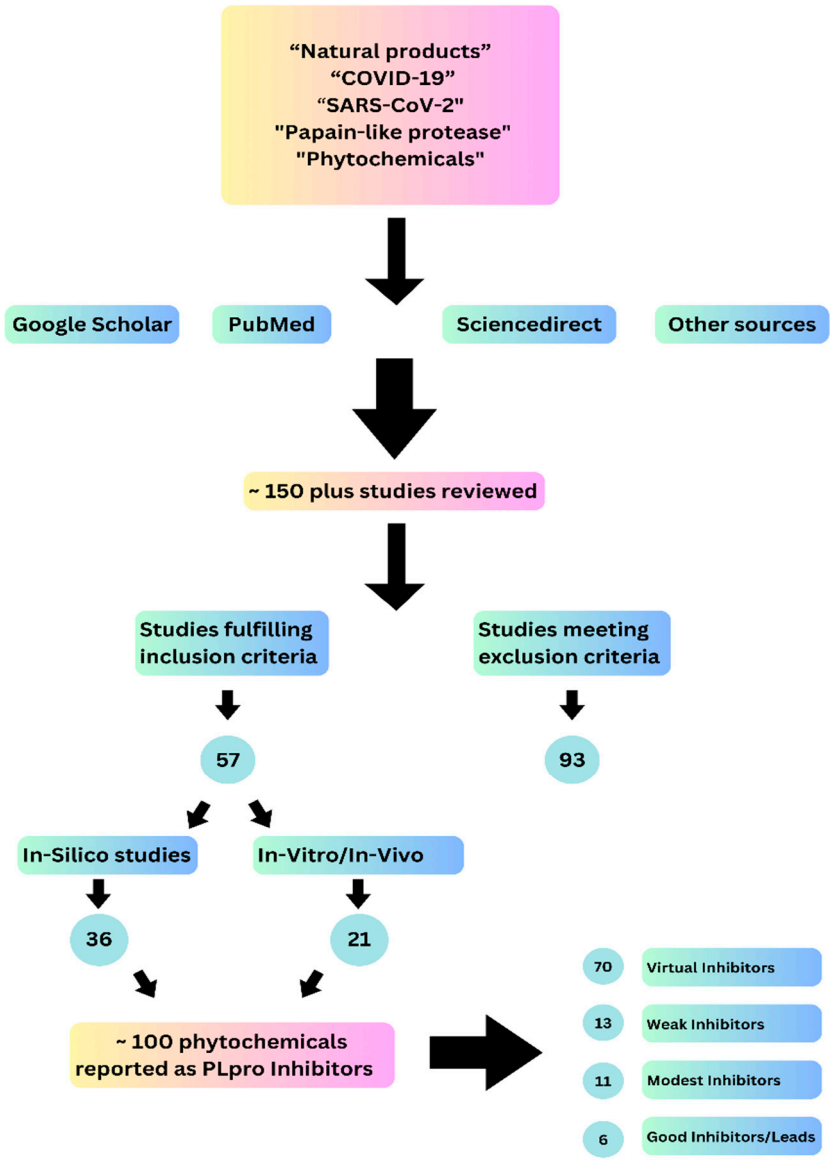

Figure 1. Review methodology.

3. Results and Discussion

3.1. Potential Phytochemicals against SARS-CoV-2 PLpro

An overview of the phytochemicals reported in the literature on PLpro inhibitors can be obtained from Figure 2. Their detailed properties have been discussed in the following sections and Tables 1–4.

3.2. Flavonoids

Flavonoids and their derivatives have been documented to exhibit inhibitory effects on several proteins of SARS-CoV-2 [36]. The antiviral properties of flavonoids are attributed to their ability to act as antioxidants, enzyme inhibitors, disruptors of cell membranes, preventers of virus entry and binding to cells, and inducers of host defense mechanisms [37]. According to a recent literature review conducted by Verma et al. (2020), flavonoids were identified as the most prominent class of compounds with potential antiviral activity against coronaviruses [38]. Therefore, a wide interest has been shown in this class of phytochemicals to find potential agents against several targets of SARS-CoV-2, including PLpro.

Among the various classes of flavonoids, flavones have garnered significant attention as they have been extensively investigated for their antiviral properties [39,40]. Li et al.

(2022) reported a panel of nine biflavones as potential PLpro inhibitors supported by docking analysis, anti-proteolytic, and anti-PLpro-mediated deISGylation activities [41]. These biflavones include amentoflavone, podocarpusflavone A, ginkgetin, isoginkgetin, sciadopitysin, morelloflavone, hinokiflavone, cryptomerin B, and 4′-*O*-methylochnaflavone. Hinokiflavone, amentoflavone, and 4′-*O*-methylochnaflavone were the potential lead compounds among all. Hinokiflavone and 4′-*O*-methylochnaflavone have C-O-C connections in their biflavone structures, whereas amentoflavone carries C-C connections. Biflavones with C-O-C connections showed pronounced effects in anti-proteolytic and deISGylation assays. Interestingly, 4′-*O*-methylochnaflavone showed exceptional performance in the deISGylation inhibition assay. It showed near complete inhibition at 20 μM, 98% at 10 μM, and exceptionally 50% at 5 μM concentrations. Derived from *Lonicera japonica* Thunb., a plant commonly referred to as 'honeysuckle', 4′-*O*-methylochnaflavone is a naturally occurring biflavone. *L. japonica* is widely used in traditional Chinese medicine and has shown clinical evidence of alleviating SARS-CoV-2 infection. 'Lianhua Qingwen capsule' and 'Jinhua Qingan granules' are two Traditional Chinese Medicine (TCM) formulations that feature 4′-*O*-methylochnaflavone as a key component. These formulations have been included as recommended medicines for the treatment of COVID-19 in the 'Diagnosis and Treatment Scheme for Novel Coronavirus Pneumonia' [42–44]. Given the best deISGylation scores of 4′-O-methylochnaflavone, it might play a major role in the antiviral properties of *L. japonica* formulations. Hence, it would be valuable to conduct further research on this phytochemical's in vivo antiviral activity and pharmacokinetics.

Recently, a study comprising various computational methods such as docking, ADMET (absorption, distribution, metabolism, excretion, and toxicity), and DFT (density functional theory) studies reported a flavone metabolite from licorice (*Glycyrrhiza glabra* L.) as a potential inhibitor of SARS-CoV-2 Plpro [45]. The compound glycyrrhizoflavone exhibited binding free energy of −51.63 kcal/mol into the PLpro active site and made four hydrogen bonds with key amino acid residues (Tyr265, Thr302, Tyr274, and Gln270). Moreover, the aromatic systems were included in many hydrophobic interactions with Asp165, Pro249, Tyr265, Gly164, Leu163, and Tyr269. Although the results of in silico ADMET and toxicity studies were favorable, further in vitro and in vivo experiments are needed to establish the efficacy of this flavone.

A prenylated flavonol, papyriflavonol from *Broussonetia papyrifera* (L.) Vent., showed good docking scores in an in silico study reported by Hossain et al. (2022). In a screening of 25 natural phytochemicals against various SARS-CoV-2 proteins, papyriflavonol demonstrated the highest binding affinity, specifically with PLpro, recording a value of −8.3 kcal/mol. Hossain et al. (2022) also reported broussoflavan A, another member of *B. papyrifera* with an excellent binding affinity (−8.5 kcal/mol) with Plpro [46].

Some other phytochemicals from the flavonoids class reported as SARS-CoV-2 PLpro inhibitors include Albanol B from *Morus alba* L., Morin from *Maclura pomifera* (Raf.) C.K.Schneid., Caesalpiniaphenol A from *Caesalpinia sappan* (L.) Tod., Wighteone from *Erythrina suberosa* Roxb., Quercetin and Kaempferol from *Phyllanthus amarus* Schumach. & Thonn., 7-*O*-galloylquercetin, and myricetin. Their relevant details can be obtained from Tables 1–3.

Table 1. Phytochemicals targeting SARS-CoV-2 PLpro categorized as 'virtual inhibitors'.

Phytochemicals Reported against SARS-CoV-2 PLpro	PubChem CID	Pharmacognostic Class	Plant Scientific Name	Plant Family	Docking Score (Kcal/mol)	Control	Reference
10-Gingerol	168115	Phenolic Compound	*Zingiber officinale* Roscoe	Zingiberaceae	−42	Chloroquine −27 kJ/mol	[47]
14-deoxy 11,12-didehydro andrographolide	5708351	Diterpenoid	*A. paniculata*	Acanthaceae	−6.7	-	[48]
2′,4′-Dihydroxy-4-methoxychalcone	5711223	Chalcone	*Astragalus laxmannii* Jacq.	Fabaceae	−14.1	Cocrystallized ligand TTT −9.30 kcal/mol	[45]
6-Gingerol	442793	Phenolic Compound	*Z. officinale*	Zingiberaceae	−39	Chloroquine −27 kJ/mol	[47]
8-Gingerol	168114	Phenolic Compound	*Z. officinale*	Zingiberaceae	−43	Chloroquine −27 kJ/mol	[47]
Afzelin	5316673	Flavonoid glycoside	*S. androgynus*	Phyllanthaceae	−190.23	Chloroquine −231 kcal/mol	[49]
Albanol B	480819	Arylbenzofuran Flavonoid	*M. alba*	Moraceae	−9.3	-	[50]
Alpha-spinasterol	5281331	Phytosterol	*Nigella Sativa* L.	Ranunculaceae	−9.6	Ivermectin −9.8 kcal/mol	[51]
Andrographolide (AGP)	5318517	Diterpenoid	*A. paniculata*	Acanthaceae	−6.5	-	[48]
Astragalin	5282102	Flavonoid glycoside	*P. amarus*	Phyllanthaceae	−9.7	Remdesivir −9.50 kcal/mol	[52]
Baccharin	117587576	Resins	Propolis (*Apis mellifera* L.)	Apidae	−8.2	Darunavir −3.8 kcal/mol Favipiravir −4.0 kcal/mol	[53]
Broussoflavan A	44257178	Flavandiol	*B. papyrifera*	Moraceae	−8.5	Lopinavir −6.8 kcal/mol GRL0617 −6.5 kcal/mol	[46]
Caesalpiniaphenol A	71454364	Isoflavonoid	*C. sappan*	Fabaceae	−9.2	GRL0617 −6.9 kcal/mol	[54]
Calonysterone	101281312	Steroid	*Senna obtusifolia* (L.) H.S.Irwin & Barneby	Fabaceae	−6.9	GRL0617 −6.5 kcal/mol	[55]

Table 1. *Cont.*

Phytochemicals Reported against SARS-CoV-2 PLpro	PubChem CID	Pharmacognostic Class	Plant Scientific Name	Plant Family	Docking Score (Kcal/mol)	Control	Reference
Campesterol	173183	Phytosterol	*N. Sativa*	Ranunculaceae	−9.8	Ivermectin −9.8 kcal/mol	[51]
Cannabichromanon	25105340	Terpene phenolic compound	*C. sativa*	Cannabaceae	−28.3	Y97 Ligand −4.08 kcal/mol	[56]
Cannabicyclolic acid	71437560	Salicylic acid	*C. sativa*	Cannabaceae	−19.8	Y97 Ligand −4.08 kcal/mol	[56]
Cannabinolic acid	3081990	Meroterpenoids	*C. sativa*	Cannabaceae	−22.8	Y97 Ligand −4.08 kcal/mol	[56]
Canthin-6-one 9-O-beta-glucopyranoside	637482	Alkaloidal glycoside	*Eurycoma harmandiana* Pierre	Simaroubaceae	−9.4	Remdesivir −8.3 kcal/mol	[57]
Cassigarol G	10005549	Piceatannol dimers	*Cocos nucifera* L.	Arecaceae	−10.5	Reference Inhibitor −8.2 kcal/mol	[58]
Cepharanthin	10206	Biscoclaurine alkaloid	*E. lathyris*	Euphorbiaceae	−8.1	GRL0617 −6.5 kcal/mol Lopinavir −6.8 kcal/mol	[46]
Costunolide	5281437	Steroid	*Costus speciosus* (J.Koenig) Sm.	Zingiberaceae	−8.2	Disulfiram −3.11 kcal/mol	[59]
Curcumin	969516	Diarylheptanoid	*Curcuma longa* L.	Zingiberaceae	−8.0	-	[60]
Cycloeucalenol	101690	Phytosterol	*N. Sativa*	Ranunculaceae	−9.8	Ivermectin −9.8 kcal/mol	[51]
Dihydrotanshinone	5316743	Terpenoids	*G. pensilis*	Cupressaceae	−7.3	Remdesivir −6.8 kcal/mol	[61]
Demethyloleuropein	6450302	Olive secoiridoid	*Olea europaea* L.	Oleaceae	−94.54	-	[62]
Emetine	10219	Alkaloid	*Carapichea ipecacuanha* (Brot.) L.Andersson	Rubiaceae	−9.0	-	[63]
Epigallocatechin gallate (EGCG)	65064	Gallic acid esters	*C. sinensis*	Theaceae	−8.6	GRL0617 −6.5 kcal/mol	[64]
Ferulic acid	445858	Phenolic acid	*Sesamum indicum* L.	Pedaliaceae	−4.8	VER 250 (Co-Crystallized Ligand) −7.2 kcal/mol	[65]

Table 1. *Cont.*

Phytochemicals Reported against SARS-CoV-2 PLpro	PubChem CID	Pharmacognostic Class	Plant Scientific Name	Plant Family	Docking Score (Kcal/mol)	Control	Reference
Fortunellin	5317385	Flavonoid glycoside	*Citrus japonica Thunb.*	Rutaceae	−28.1	-	[66]
Gallocatechin gallate (GCG)	199472	Gallic acid esters	*C. sinensis*	Theaceae	–8.8	-	[67]
Glycobismine F	12111778	Acridone alkaloids	*G. pentaphylla*	Rutaceae	−9.6	-	[50]
Glycyrrhizoflavone	5317764	Flavone	*G. glabra*	Fabaceae	−51.63	-	[45]
Hesperidin	10621	Flavanone glycoside	*Citrus aurantium* L.	Rutaceae	−10.6	-	[68]
Hinokinin	442879	Lignan	*P. amarus*	Phyllanthaceae	−9.8	Remdesivir −9.50 kcal/mol	[52]
Hippacine	10015025	Quinoline alkaloid	*Ammocharis coranica* Herb.	Amaryllidaceae	−13.22	Cocrystallized ligand TTT −9.30 kcal/mol	[69]
Hydroxymatairesinol	10948757	Furanoid lignans	*S. indicum*	Pedaliaceae	−7.2	VER250-Ligand −7.2 kcal/mol	[65]
I-Asarinin	11869417	Furofuranoid lignans	*Piper longum* L.	Piperaceae	−10.8	-	[70]
Ilimaquinone	72291	Diterpenoid	*Hippospongia metachromia de Laubenfels*	Spongiidae	−8.1	Remdesivir −9.9 kcal/mol	[71]
Isocodonocarpine	-	Spermidine Alkaloid	*Capparis decidua* Edgew.	Capparaceae	−7.0	GRL0617 −6.5 kcal/mol	[55]
Isovitexin	162350	Flavonoid glycoside	*V. negundo*	Lamiaceae	−9.3	-	
Jezonofol	46226510	Piceatannol dimers	*C. nucifera*	Arecaceae	−10.4	Reference Inhibitor −8.2 kcal/mol	[58]
Juglanin	5318717	Flavonoid glycoside	*Polygonum aviculare* L.	Polygonaceae	−7.8	Lopinavir −6.8 kcal/mol GRL0617 −6.5 kcal/mol	[46]
Kaempferol	5280863	Flavonol	*P. amarus*	Phyllanthaceae	−9.6	Remdesivir −9.50 kcal/mol	[52]
Maackin A	56666152	Piceatannol dimers	*C. nucifera*	Arecaceae	−9.3	Reference Inhibitor −8.2 kcal/mol	[58]

Table 1. *Cont.*

Phytochemicals Reported against SARS-CoV-2 PLpro	PubChem CID	Pharmacognostic Class	Plant Scientific Name	Plant Family	Docking Score (Kcal/mol)	Control	Reference
Mahuangnin A	5319217	-	*Murraya microphylla* (Merr. & Chun) Swingle	Rutaceae	−9.3	-	[50]
Morin	5281670	Flavonoid	*M. pomifera*.	Moraceae	−6.8	-	[72]
Myricetin	5281672	Flavonoid	*Ficus auriculata* Lour.	Moraceae	−7.3	-	[73]
Neoandrographolide	9848024	Terpene glycoside	*A. paniculata*	Acanthaceae	−7.3	Remdesivir −7.5 kcal/mol	[74]
Oleanolic acid	10494	Terpenoid	*V. negundo*	Lamiaceae	−10	-	[75]
Papyriflavonol A	10343070	Prenylated Flavonol	*B. papyrifera*	Moraceae	−8.6	Lopinavir −6.8 kcal/mol GRL0617 −6.5 kcal/mol	[46]
Pinoresinol	73399	Furanoid lignans	*S. indicum*	Pedaliaceae	−6.51	VER250-Ligand −7.2 kcal/mol	[65]
Podophyllotoxin	10607	Lignan	*P. peltatum*	Berberidaceae	−8.1	-	[76]
Quercetin	5280343	Flavonol	*P. amarus*	Phyllanthaceae	−4.6	-	[77]
Quercetin-3-O-glucoside	5280804	Flavonoid glycoside	*P. amarus*	Phyllanthaceae	−10.3	Remdesivir −9.50 kcal/mol	[52]
Quercetin-3-O-arabinoside 7-O-rhamnoside	-	Flavonoid glycoside	*P. amarus*	Phyllanthaceae	−8.2	Remdesivir −5.8 kcal/mol	[78]
Rheidin B	5320958	Dianthrone	*Rheum palmatum* L.	Polygonaceae	−9.3	-	[50]
Schizanthine y	-	Tropane alkaloids	*S. porrigens*	Asteraceae	−7.1	Lopinavir −7.0 kcal/mol	[79]
Schizanthine z	-	Tropane alkaloids	*S. porrigens*	Asteraceae	−7.5	Lopinavir −7.0 kcal/mol	[79]
Scirpusin A	5458896	Piceatannol dimers	*C. nucifera*	Arecaceae	−10.5	Reference Inhibitor −8.2 kcal/mol	[58]
Sesamin	72307	Furofuranoid lignans	*S. indicum*	Pedaliaceae	−6.5	VER250-Ligand −7.2 kcal/mol	[65]

Table 1. *Cont.*

Phytochemicals Reported against SARS-CoV-2 PLpro	PubChem CID	Pharmacognostic Class	Plant Scientific Name	Plant Family	Docking Score (Kcal/mol)	Control	Reference
Sesamolin	101746	Furofuranoid lignans	*S. indicum*	Pedaliaceae	−6.4	VER250-Ligand −7.2 kcal/mol	[65]
Spicatolignan	72729358	Lignan	*S. indicum*	Pedaliaceae	−6.6	VER250-Ligand −7.2 kcal/mol	[65]
Tanshinone A	114917	Terpenoids	*G. pensilis*	Cupressaceae	−7.2 s	Remdesivir −6.8 kcal/mol	[61]
Tanshinone C	160254	Terpenoids	*G. pensilis*	Cupressaceae	−7.1	Remdesivir −6.8 kcal/mol	[61]
Ursolic acid	64945	Triterpenoid	*V. negundo*	Lamiaceae	−9.7	-	[75]
Vanilic acid	8468	Phenolic acid	*S indicum*	Pedaliaceae	−4.8	VER250-Ligand −7.2 kcal/mol	[65]
Wighteone	5281814	Isoflavonoid	*E. suberosa*	Fabaceae	−16.52	Cocrystallized ligand TTT −9.30 kcal/mol	[69]
Withanolide A	11294368	Steroid	*Datura innoxia* Mill. *Withania somnifera* (L.) Dunal	Solanaceae	−7.4	GRL0617 −6.5 kcal/mol	[55]
Withanolides B	14236711	Steroid	*W. somnifera*	Solanaceae	−10.3	Procainamide −5.03 kcal/mol	[80]

3.3. Terpenoids

The efficacy of terpenoids in inhibiting the effects of SARS-CoV has been established through experimental studies [81,82]. Consequently, there is a growing support for exploring terpenoids as potential agents against SARS-CoV-2. Here, we highlight phytochemicals from the terpenoids class reported as potential candidate inhibitors against SARS-CoV-2 PLpro. The properties of these phytochemicals are mentioned in detail in Tables 1–4.

The root of *Salvia miltiorrhiza* Bunge (red sage or Danshen) is a common herb in TCM used in the treatment of several chronic diseases, including cardiovascular diseases, liver cirrhosis, and chronic renal failure [83]. The phytochemicals from this plant are known as tanshinones, which belong to the class of lipophilic abietane diterpenes. These include tanshinone I (TI), tanshinone IIA (TIIA), cryptotanshinone (CT), dihydrotanshinone I (DH-TI), isotanshinone, tanshilactones, etc. [84]. Tanshinones, particularly TI and DH-TI, have been found to be promising against the cysteine proteases, particularly PLpro, in many studies [61,85–88]. Park et al. (2012) described the tanshinones as time-dependent inhibitors of SARS-CoV PLpro, the IC_{50} values being 8.8 and 4.9 μM for TI and DH-TI, respectively [88]. Lim et al. (2021) reported IC_{50} of 0.59 μM for DH-TI, which inhibited both K48-linked Ub3 and pro-ISG15 cleavage by PLpro at concentrations of 10 μM and suppressed viral proliferation at an EC_{50} of 8 μM. Moreover, Zhao et al. (2021) tested CT and TI, where the IC_{50s} were 5.63 and 2.21 μmol/L, respectively. Both of these terpenoids showed strong antiviral effects in qRT-PCR analysis (real-time quantitative reverse transcription polymerase chain reaction), and the EC_{50s} were 0.70 μmol/L and 2.26 μmol/L, respectively, in a plaque-reduction assay [89]. Most recently, in a docking study, 5 abietane-type diterpenes were isolated from the branches of *Glyptostrobus pensilis* (Staunton ex. D.Don) K.Koch and, upon structural elucidation, were found to be tanshinones. Among these, DH-TI, tanshinone C, and tanshinone A showed good affinity with SARS-CoV-2 PLpro [61]. Particularly, all three of the molecules interacted with the Ser180 and Lys126 residues of PLpro through H-bond and HI. Tanshinone IIA sulphonate sodium (TIISS) is another member of this terpenoid group reported as a PLpro inhibitor [11]. The IC_{50} is 1.65 ± 0.13 μM, with greater than an 80% inhibitory effect against PLpro in a protease activity assay and fluorogenic assay. TIISS also showed dose-dependent inhibition of the deISGylation activity of PLpro [11]. Therefore, tanshinones seem to have profound in vitro effects on SARS-CoV-2 PLpro.

A detailed discussion on the structural relation of tanshinones to their SARS-CoV-2 PLpro-inhibitory activity is limited. However, Park et al. (2012) provided comprehensive insights into the structure–activity relationship of tanshinones with respect to SARS-CoV PLpro [88]. Their study argued that the presence of dimethyl tetrahydronaphthalene moiety (tanshinone IIA and cryptotanshinone) showed a more potent inhibitory response than the naphthalene chemotype (tanshinone I and dihydrotanshinone I). Moreover, their study revealed that the presence of furan moiety on ring A among tanshinone II derivatives (tanshinone IIA, tanshinone IIB, and tanshinone I) did not show improved inhibition with PLpro. Instead, the dihydrofuran moiety (cryptotanshinone and dihydrotanshinone) showed better results.

As we present tanshinones as inhibitors of SARS-CoV-2 PLpro and Mpro, it is noteworthy to mention a recent study by Ma and Wang (2022). This study revealed the lack of PLpro-inhibitory activity for several compounds, including cryptotanshinone, tanshinone I, dihydrotanshinone I, tanshinone IIA, YM155, SJB2-043, 6-thioguanine, and 6-mercaptopurine [90]. The IC_{50} values from this study were found to be 52.24, 18.58, 33.01, and 15.30 μM for cryptotanshinone, tanshinone I, dihydrotanshinone I, and tanshinone IIA, respectively, which are ∼10-fold higher than the previously reported values [87,89]. Overall, their study suggested that tanshinone I, cryptotanshinone, dihydrotanshinone I, and tanshinone IIA were not specific PLpro inhibitors [90].

Pentacyclic triterpenoids, oleanolic acid and ursolic acid, and other phytocompounds (isovitexin and 3β-acetoxyolean-12-en-27-oic acid) from *Vitex negundo* L. formed stable interactions with the binding site of Plpro [75]. The docking scores were −10, −9.7, −9.3, and −9.5 kcal/mol, respectively, and key interactions were made through H-bonds. In the case of ursolic acid, it exhibited hydrogen bonding with ASP108 and engaged in interac-

tions with PRO248, ALA107, and TYR264 through Alkyl and Pi-Alkyl interactions. On the other hand, oleanolic acid formed hydrogen bonds with LEU162 in chain A and ASN109 in chain B, thereby stabilizing its complex with Plpro [75]. Based on molecular docking, another study on triterpenoids and limonoids suggested that the combination of seven phytochemicals, i.e., ursolic acid, glycyrrhizic acid, obacunone, 7-deacetyl-7-benzoylgedunin, corosolic acid, limonin, and masilinic acid, was sufficient to formulate an appropriate therapeutic approach to fight against SARS-CoV-2 [91]. Of these seven phytochemicals, obacunone, glycyrrhizic acid, ursolic acid, and 7-deacetylgedunin were shown to exert their potential by blocking the catalytic triad of the PLpro [91]. The antiviral spectrum of triterpenoid compounds [92], primarily oleanolic acid [93], has been well-reported in the literature. Oleanolic acid and ursolic acid have been shown to significantly affect SARS-CoV-2 Mpro [94–96]. Also, these two triterpenes exhibited suitable ADME parameters, followed by the fulfillment of Lipinski's rule of five [96]. Therefore, triterpenoids can be thought of as an excellent prospect.

Recently, Fuzo et al. (2022) reported a pentacyclic triterpene isolated from *Tripterygium wilfordii* Hook.f. possessing inhibitory effects on SARS-CoV-2 cysteine proteases [97]. The compound, celastrol, favorably interacted with catalytic sites of PLpro (−7.4 kcal/mol) in silico and inhibited viral propagation and IL-6 (Interleukin-16) secretion in vitro without cytopathic effects. Limitations, however, remain to its use owing to low solubility and poor bioavailability, with evaluation needed for its toxicity and adverse effects profile [97].

Terpenoids still keep adding active constituents against COVID-19. *Andrographis paniculata* (Burm.f.) Nees, commonly known as the 'King of bitters', has been extensively utilized in Asia's traditional medicine to address conditions such as fever, diarrhea, and the common cold. Its active constituents, andrographolides (AGP) from the class of diterpenoids, and derivatives have shown different activities, including antiviral activities. Murugan et al. (2020) studied the potency of four phytochemicals, namely, andrographolide (AGP1), 14-deoxy 11,12-didehydro andrographolide (AGP2), neoandrographolide (AGP3), and 14-deoxy andrographolide (AGP4) from *A. paniculata*, and suggested that AGP3, a diterpene glycoside, could be a potential PLpro inhibitor [74]. The result was attributed to the larger molecular surface and presence of many hydroxyl functional groups in AGP3 as they, respectively, increased the magnitude of both van der Waals and electrostatic interactions. Strengthening this, Khanal et al. (2021) independently studied the activity of *A. paniculata* with AGP1 and AGP2 and suggested that by modifying andrographolide, its drug-likeness properties could be improved [48]. The interest in andrographolides continues, and recently, another group of researchers, Veerasamy and Karunakaran (2022), performed in silico molecular docking analysis on 17 semisynthetic AGP derivatives with 5 SARS-CoV-2 enzymes, including PLpro, and revealed that all the derivatives showed promising results with least toxicities [98].

Adding on this, Ilimaquinone (marine sponge metabolite) belonging to the class of terpenoids was assessed and showed binding energy with PLpro (−8.1 kcal/mol). Ilimaquinone was involved in interactions with PLpro in the following order: conventional hydrogen bond: Met208, Lys232, Alkyl/pi–alkyl: Met208, Leu162, and Tyr268 Pi–anion: Glu161 [71].

Parthenolide, a germacrane sesquiterpene lactone from *Tanacetum parthenium* (L.) Sch.Bip., has been shown to exhibit inhibitory activity against the PLpro enzyme of SARS-CoV-2 [99]. The compound is a deISGylation inhibitor with a relatively higher IC_{50} of 132.5 μM. Interestingly, it targets the Cys-191 or Cys-194 instead of Cys-111 at the PLpro catalytic site, indicating a potential allosteric site for inhibiting PLpro activity [99]. Another study reported different sesquiterpene lactones (STLs) from chicory extract (*Cichorium intybus* L.) as SARS-CoV-2 protease inhibitors [100]. This study showed that the STLs interacted with TYR264, TYR268, and ASN267 residues of the PLpro through hydrophobic interaction, interaction with the α-methylene-γ-lactone (aMyL) ring, and a hydrogen bond, respectively. Particularly, lactucin at a concentration of 174 μM showed inhibitory potential against the PLpro in an enzyme-inhibition assay, which is still a relatively higher concentration when compared to other inhibitors reported in this study [100]. Given this discussion, terpenoids are the second phytochemical class rich in PLpro inhibitors (n = 18).

Table 2. Phytochemicals targeting SARS-CoV-2 PLpro categorized as 'weak inhibitors'.

Phytochemicals Reported against SARS-CoV-2 PLpro	PubChem CID	Pharmacognostic Class	Plant Scientific Name	Plant Family	Docking Score (Kcal/mol)	In Vitro/Ex Vivo/In Vivo Data on PLpro Inhibition		Control	Reference
						Assay	Result		
4′-*O*-methylochnaflavone	5384799	Biflavone	*L. japonica*	Caprifoliaceae	−105.2	FBA	IC_{50} = 22.8 µM	Psoralidin IC_{50} = 27.8 µM Plpro + pro-ISG15 95% proteolysis	[41]
						PICA	~100% at 20 µM		
Baicalin	64982	Flavonoid glycoside	*Scutellaria baicalensis* Georgi	Lamiaceae	−10.8	IEIA	IC_{50} = 178 µM	HY-17542 IC_{50} = 1.73 µM	[68,101]
Cryptomerin B	5316145	Biflavone	*Platycladus orientalis* (L.) Franco	Cupressaceae	−87.9	FBA	IC_{50} = 26.3 µM	Psoralidin IC_{50} = 27.8 µM Plpro + pro-ISG15 95% proteolysis	[41]
						PICA	74.8% at 20 µM		
Cyanidin-3-O-glucoside	12303220	Anthocyanin glycoside	*M. alba*	Moraceae	−7.3	DUA	42% at 100 µM	GRL0617 DUA 90% at 100 µM	[102]
Epicatechin-3-Gallate (ECG)	65056	Gallic acid esters	*C. sinensis*	Theaceae	−8.5	IEIA	IC_{50} = 11.62 µg mL^{-1} (37.73 µM)	ECG fraction IC_{50} 0.13 ± 0.001 µg mL^{-1} (0.42 µM)	[64,103]
Ginkgetin	5271805	Biflavone	*Ginkgo. biloba* L.	Ginkgoaceae	−117.2	FBA	IC_{50} = 29.8 µM	Psoralidin IC_{50} = 27.8 µM Plpro + pro-ISG15 95% proteolysis	[41]
						PICA	~100% at 20 µM		
Isoginkgetin	5318569	Biflavone	*G. biloba*	Ginkgoaceae	−123.5	FBA	IC_{50} = 31.2 µM	Psoralidin IC_{50} = 27.8 µM Plpro + pro-ISG15 95% proteolysis	[41]
						PICA	~100% at 20 µM		
Lactucin	442266	Sesquiterpenoids	*Cichorium intybus* L.	Asteraceae	−8.5	IEIA	IC_{50} = 174 µM	GRL0617 DS = −7.5 kcal/mol	[100]
Morelloflavone	5464454	Biflavone	*Garcinia lateriflora* Blume	Clusiaceae	−81.6	FBA	IC_{50} = 36.4 µM	Psoralidin IC_{50} = 27.8 µM Plpro + pro-ISG15 95% proteolysis	[41]
						PICA	34.1% at 20 µM		
Parthenolide	7251185	Sesquiterpene lactones	*Tanacetum parthenium* (L.) Sch.Bip.	Asteraceae	−7.5	ICA	IC_{50} = 132.5 µM	-	[99]
Podocarpusflavone A	5320644	Biflavone	*Podocarpus nakaii* Hayata	Podocarpaceae	−66.2	FBA	IC_{50} = 43.2 µM	Psoralidin IC_{50} = 27.8 µM Plpro + pro-ISG15 95% proteolysis	[41]
						PICA	64.9% at 20 µM		

Table 2. *Cont.*

Phytochemicals Reported against SARS-CoV-2 PLpro	PubChem CID	Pharmacognostic Class	Plant Scientific Name	Plant Family	Docking Score (Kcal/mol)	In Vitro/Ex Vivo/In Vivo Data on PLpro Inhibition		Control	Reference
						Assay	Result		
Rutin	5280805	Flavonoid glycoside	*Azadirachta indica* A.Juss.	Meliaceae	−8.8	DUA	50% at 100 μM	GRL0617 DUA 90% at 100 μM	[102]
Sciadopitysin	5281696	Biflavone	*G. biloba*	Ginkgoaceae	−113.4	FBA	IC_{50} = 34.8 μM	Psoralidin IC_{50} = 27.8 μM Plpro + pro-ISG15 95% proteolysis	[41]
						PICA	32.3% at 20 μM		

Key: ICA, ISG15 cleavage assay; IEIA, In Vitro Enzyme-Inhibition Analysis; DUA, deubiquitinase activity; FBA, fluorescence-based assay; PICA; Pro-ISG15 cleavage assay; IC_{50}, Half-Maximal Inhibitory Concentration; dS, docking score.

3.4. Alkaloids

Alkaloids are a distinct category of nitrogenous organic compounds that are commonly found in plants and possess well-defined pharmacological properties [104]. They represent a vast and diverse group of natural products originating from various sources, including microorganisms, plants, and animals. Alkaloids can be found in numerous plant families, including but not limited to Papaveraceae, Fabaceae, Rutaceae, Asteraceae, and Rubiaceae [105]. The indoles and isoquinolines constitute the two major classes of alkaloids. Additionally, there are several other significant classes of alkaloids, such as tropane, pyrrolizidine, pyridine, and steroidal alkaloids. These diverse classes of alkaloids contribute to the extensive range of natural products found in plants.

Besides their use in various areas of human medicine, such as metabolic and neurological problems, cancer, and infectious diseases, alkaloids have attracted significant research attention due to their wide-ranging antiviral properties against diverse DNA and RNA viruses. Their antiviral spectrum includes influenza virus (IAV), herpes simplex virus-I and II (HSV-I and II), dengue virus (DENV), Chikungunya virus (CHIKV), Ebola virus (EBOV), human cytomegalovirus (HCMV), and Zika virus (ZIKV) [104]. Alkaloids have also shown activity against a number of SARS-CoV-2 targets. These include viral inhibition [106,107], in silico Nsp-15 repression [108], and also a good in silico interaction with Mpro and RdRp [109]. Here, we highlight alkaloidal phytochemicals listed in Tables 1–4, which can be potential PLpro inhibitors and contribute to viral suppression.

Various studies have been conducted on emetine, an iso-quinoline alkaloid, to find out its antiviral potential against a number of viral infections. Multiple research groups have reported the potential in vitro antiviral effectiveness of emetine against both RNA and DNA viruses. In a recent study by Kumar et al. in 2021, it was demonstrated that emetine can disrupt the binding between SARS-CoV-2 RNA and eIF4E (eukaryotic translation initiation factor 4E), leading to the inhibition of viral protein synthesis [110]. Snoussi et al. (2022) demonstrated in an in silico study that emetine exhibited inhibitory effects on multiple important components of SARS-CoV-2, including NSPs (non-structural proteins), proteases, and the spike protein [63]. The affinities ranged from −10.8 to −8.5 kcal/mol, with a particularly notable affinity of −9.0 kcal/mol for the PLpro enzyme. With PLpro, emetine established two conventional hydrogen bonds (Gln134, Lys127), two van der Waals interactions (Glu135, Val126), one Pi-Pi stacked (Tyr138), and three alkyl/Pi-Alkyl interactions with active site residues [63]. These findings suggest that emetine holds significant potential for research on COVID-19 eradication, provided its proven efficacy in vitro and in vivo [63,110].

Schizanthus porrigens Graham, a herbaceous plant native to Chile and Argentina, provided two tropane alkaloids, schizanthine Z and schizanthine Y, as potential inhibitors of Plpro [79]. In a molecular docking study by Alfaro et al. (2020), schizanthine Z formed the most stable complex, with a binding affinity of −7.5 kcal/mol, followed by schizanthine Y. Based on molecular docking scores, hydrogen bridge interactions, and Lipinski's rule of five, the study suggested that these alkaloids possess the potential to inhibit SARS-CoV-2 PLpro, which is essential for virus maturation and host immunosuppression [79].

Another in silico study reported Glycobismine F, a dimeric acridone alkaloid from *Glycosmis pentaphylla* (Retz.) DC., as a potential inhibitor of SARS-CoV-2 Plpro [50]. Glycobismine F fit the substrate binding pocket of PLpro and showed a docking score of −9.6 kcal/mol involving Tyr384 and Gln385 residues from the substrate-binding loop (BL2) of PLpro. The complex was stabilized by H-bonds and π–π and van der Waals interactions [50].

Hossain et al. (2022) performed an in silico study of 25 natural phytochemicals acting against SARS-CoV-2. Among these screened compounds, cepharanthin, a quinoline alkaloid isolated from *Euphorbia lathyrism* L., showed a good binding affinity of −8.1 kcal/mol with Plpro [46]. Alamri et al. (2020) revealed a spermidine alkaloid, named isocodonocarpine, as a potential inhibitor of SARS-CoV-2 PLpro through computational screening and molecular docking mechanisms. Scoring a binding affinity of −7.0 kcal/mol, isocodoncarpine interacted with Tyr264 and Tyr268 residues via hydrophobic attractions and with Tyr264 by π-π stacking.

It did not show any hydrogen bonds in molecular docking, but an average of three H-bonds were observed in molecular dynamic simulations [55].

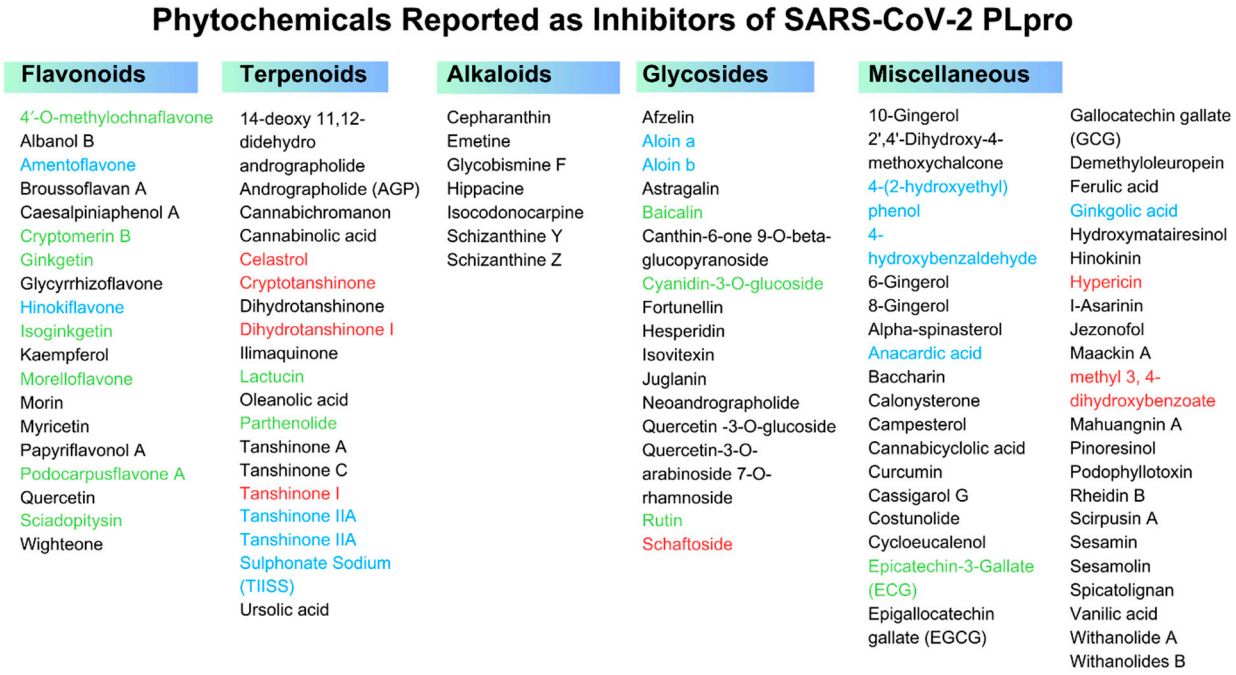

Figure 2. List of phytochemicals reported as SARS-CoV-2 PLpro inhibitors.

Table 3. Phytochemicals targeting SARS-CoV-2 PLpro categorized as 'modest inhibitors'.

Phytochemicals	PubChem CID	Pharmacognostic Class	Plant Scientific Name	Plant Family	Docking Score (Kcal/mol)	In Vitro/Ex Vivo/In Vivo Data on PLpro Inhibition		Control	Cellular Toxicity/Selectivity Index	Reference
						Assay	Outcome			
4-(2-hydroxyethyl)phenol (YRL)	10393	Phenolic Compound	*Lawsonia alba* Lam.	Lythraceae	−7.17	ICA	70% Inhibition IC_{50} = 6.68 μM	GRL0617 IC_{50} = 0.82 μM	No cellular toxicity at 100 μM SI = not studied	[111]
						qRT-PCR	IC_{50} = 1 μM			
4-hydroxybenzaldehyde (HBA)	126	Phenolic Compound	*Acalypha torta* hort. ex-Pax & K.Hoffm.	Euphorbiaceae	−6.97	ICA	73% Inhibition IC_{50} = 3.99 μM	GRL0617 IC_{50} = 0.82 μM	~80% cell viability at 100 μM SI = not studied	[111]
						CCAA	-			
Aloin a	12305761	Anthraquinone Glycoside	*Aloe barbadensis* Mill.	Asphodelaceae	-	IEIA	IC_{50} = 13.16μM	-	No significant cytotoxicity after 48 h at 50 μM and 100 μM SI = not studied	[112]
						DUA	IC_{50} = 15.68 μM			
Aloin b	14989	Anthraquinone Glycoside	*A. barbadensis Mill.*	Asphodelaceae	-	IEIA	IC_{50} = 16.08μM	-	No significant cytotoxicity after 48 h at 50 μM and 100 μM SI = not studied	[112]
						DUA	IC_{50} = 17.51μM			
Amentoflavone	5281600	Biflavone	*G. biloba*	Ginkgoaceae	−129.6	FBA	IC_{50} = 13.0 μM	Psoralidin IC_{50} = 27.8 μM PLpro + pro-ISG15 95% proteolysis	CC_{50} > 200 μM EC_{50} 46.79 μM SI > 4.27	[41,113]
						ICA	48.1% at 20 μM			
Anacardic acid	167551	Phenolic acid	*Anacardium occidentale* L.	Anacardiaceae	-	IEIA	IC_{50} = 17.08 ± 1.30 μM	-	SI = 2.83	[114]
						CA	CC_{50} = 25.48 ± 0.69 μM			
						PRA	13% at 7.5 μM EC_{50} = 9.0 ± 2.5 μM			
Celastrol	122724	Triterpenoid	*T. wilfordii*	Celastraceae	−7.4	FBA	IC_{50} = 8.9 ± 0.8 μM	-	CC_{50} > 1000 nM SI > 4.52	[97]
						CCAA	EC_{50} = 221 nM			
Ginkgolic acid	5281858	Phenolic acid	*A. occidentale*	Anacardiaceae	−4.9	IEIA	IC_{50} = 16.30 ± 0.64 μM	-	CC_{50} = 27.88 ± 0.77 μM SI = 3.35	[114]
						PRA	42% at 7.5 μM EC_{50} = 8.3 ± 0.03 μM			
Hinokiflavone	5281627	Biflavone	*P. orientalis*	Cupressaceae	−119.1	FBA	IC_{50} = 9.5 μM	Psoralidin IC_{50} = 27.8 μM PLpro + pro-ISG15 95% proteolysis	-	[41]
						PICA	~100% at 20 μM			
Tanshinone IIA	164676	Terpenoids	*S. miltiorrhiza*	Lamiaceae	-	FBA	IC_{50} = 1.57 μM	GRL-0617 IC_{50} = 1.789 μM EC_{50} = 32.6 μM	CC_{50} > 300 μM SI = 1.5	[87]
						CCAA	EC_{50} > 200 μM			
Tanshinone IIA Sulphonate Sodium (TIISS)	40580588	Terpenoids	*S. miltiorrhiza*	Lamiaceae	−8.6	PAA	IC_{50} = 1.65 ± 0.13 μM	-	-	[11]

Key: ICA, ISG15 cleavage assay; qRT-PCR, real-time quantitative reverse transcription polymerase chain reaction; SI, selectivity index; CCAA, Cell Culture Antiviral Assay; IEIA, In Vitro Enzyme-Inhibition Analysis; DUA, deubiquitinase activity; FBA, fluorescence-based assay; CA, cytotoxic assay; PRA, plaque-reduction assay; PICA; Pro-ISG15 cleavage assay; PAA, Protease Activity-based Assay; IC_{50}, Half-Maximal Inhibitory Concentration; EC_{50}, 50% effective concentration; CC_{50}, 50% cytotoxicity concentration.

3.5. Glycosides

According to a recent report, the antiviral activity of steroid glycosides was tested and found to be effective against SARS-CoV [85]. Thus, glycoside derivatives need detailed investigation as drug candidates for minimizing the current pandemic scenario [115]. Regarding the SARS-CoV-2 PLpro enzyme, glycoside phytochemicals have demonstrated promising potential in both in vitro and in silico studies for inhibiting this essential protease.

Two flavonoid glycosides, viz. baicalin, and hesperidin, have been characterized as potential inhibitors of Plpro [68]. The binding site is the same as of GRL0617, and π-π interactions with Tyr268 resulted in definite inhibition of PL^{pro} activity. In addition, baicalin inhibits the enzymatic activity of PLpro in vitro (IC_{50} = 178 μM) and manipulates inflammatory pathways in COVID-19 [101]. Hesperidin, on the other hand, does not directly reduce the activities of viral proteases, such as PLpro and Mpro (main protease of SARS-CoV-2), in the enzyme activity assays. However, it has been shown to effectively suppress viral replication [116], particularly during the early stages of infection. Additionally, hesperidin has been shown to reduce the protein expression of ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 (transmembrane serine protease 2) in lung cells, which are important factors involved in viral entry and infection [117]. Two clinical trials have included hesperidin for the treatment of COVID-19 [118,119].

Fortunellin, a flavonoid glycoside, has been identified as a powerful inhibitor of crucial protein targets associated with SARS-CoV-2, including Plpro [66]. Through molecular docking and simulation analysis, it was found that fortunellin forms stable interactions with PLpro, facilitated by three to four hydrogen bonds involving the Gln250 and Gly266 backbone, along with non-polar and polar interactions. Additionally, fortunellin interacts with His272, a catalytic site residue, indicating its inhibitory potential. With a binding free energy of −28.1 kcal/mol, fortunellin shows promise as a potential oral antiviral agent, capable of targeting multiple aspects of SARS-CoV-2, exhibiting immunomodulatory properties, and demonstrating oral bioavailability and safety [66].

Molecular docking of ethanol extract of Katuk leaves (*Sauropus androgynus* (L.) Chakrab. & N.P.Balakr.) demonstrated that the phytoconstituents in the Katuk leaves showed inhibitory activity for many components of SARS-CoV-2, including PLpro. The compounds were afzelin, trifolin, and kaempferol, out of which afzelin had the highest bond energy (−190.23 Kcal/mol) with PLpro. So, it should be further evaluated as an herbal candidate for the treatment of COVID-19 [49].

Two more flavonoid glycosides, namely, quercetin-3-*O*-arabinoside-7-*O*-rhamnoside and quercetin-3-*O*-glucoside, have been reported as promising PLpro inhibitors in independent studies by Bhattacharya et al. (2022) and Hiremath et al. (2021) [52,78]. These are the glycoside derivatives of quercetin, a natural flavonoid. Quercetin itself demonstrated a weak interaction (binding energy of −4.62 kcal/mol) with PLpro in a docking study by Di Pierro et al. (2021) [77]. However, the glycoside derivatives showed modest binding affinities towards PLpro with docking scores of −8.2 kcal/mol and −10.30 kcal/mol, respectively. Quercetin-3-*O*-arabinoside-7-*O*-rhamnoside formed 9 H-bonds with papain-like protease with other interactions, as well as involved major amino acids of the binding site, whereas quercetin-3-*O*-glucoside interacted with the HIS74, ARG83, TYR155, ASN157, and HIS176 amino acid residues at the PLpro binding site.

Schaftoside, another flavonoid glycoside isolated from liquorice (*Glycyrrhiza uralensis* Fisch.), inhibited SARS-CoV-2 PLpro in vitro [120]. The IC_{50} and EC_{50} values were 3.91 ± 0.19 μmol/L and 11.83 ± 3.23 μmol/L, respectively. It showed good safety and pharmacokinetic properties and regulated the immune response of the host cells [120]. At the molecular level, schaftoside interacted with A246 and E167 of PLpro through the C6-glucosyl moiety via hydrogen bonding. It formed another H-bond with K157 via the C8-arabinosyl moiety. In addition, 7-OH of schaftoside could form two hydrogen bonds with E167 and Y268 [120].

Pitsillou et al. (2020) investigated the potential of some dietary compounds against SARS-CoV-2 PLpro. Rutin, a flavonoid glycoside, returned the second-best results, pre-

ceded by hypericin and followed by cyanidin-3-O-glucoside. It showed a binding affinity of −8.8 kcal/mol and interacted with T301, D164, R166, E167, G271, and Y264 residues at the naphthalene binding site of PLpro. It also formed a H-bond with the Y268 residue at the same site. In the deubiquitinase assay, rutin showed comparable inhibition of PLpro deubiquitinase activity (~ 50%) at 100 μM [102]. The inhibition is relatively mild compared to other phytocompounds presented in this review. However, it can be potentially valuable. Some additional flavonoid glycosides that have been reported as promising PLpro ligands include astragalin (−9.7 kcal/mol), juglanin (−7.8 kcal/mol), kaempferitrin (−7.5 kcal/mol), and myricitrin (−7.3 kcal/mol) [46,52,73].

Aloin A and B, isomeric anthraquinone glycosides, are active ingredients in many mouthwashes. Studies have shown that Aloin A and Aloin B selectively inhibit the proteolytic and deubiquitinating activity of PLpro. In vitro assays by Lewis et al. (2022) confirmed these activities, revealing IC_{50} values of 13.16 and 16.08 μM for proteolytic activity and 15.68 and 17.51 μM for deubiquitinating activity for aloin A and B, respectively. With a hydrogen bond to Tyr268, a strong interaction with Glu167, and cytotoxic concentrations above 120 μM, aloin A and B show potential as drug candidates to inhibit SARS-CoV-2 replication and regulate cytokine storms in COVID-19 patients [112].

Alkaloidal glycosides isolated from the roots of *Eurycoma harmandiana* Pierre have been used as anti-viral agents [121]. Two important phytocompounds include canthin-6-one 9-O-beta-glucopyranoside and 7-hydroxy-β-carboline 1-propionic acid. Of them, canthin-6-one 9-O-beta-glucopyranoside was found effective against dengue virus in a docking study performed by ul Qamar et al. (2019). Further insights were provided by Verma et al. (2021) through in silico analysis to explore the inhibitory potential of canthin-6-one-9-O-beta-gluco-pyranoside against SARS-CoV-2's 3CLpro and PLpro proteases [57]. The compound exhibited a binding affinity of −9.4 kcal/mol to the PLpro active site, interacting with GLU161 (pi-anion), LEU162, GLY160, and ASN109 (conventional hydrogen bonds), and LEU162 (Pi-donor hydrogen bond). These findings suggest canthin-6-one-9-O-beta-gluco-pyranoside as a promising lead molecule for inhibiting both proteases of SARS-CoV-2 [57,122].

3.6. Miscellaneous

In addition to the reporting of phytochemicals from some major classes like flavonoids, glycosides, alkaloids, and terpenoids, various other phytochemicals from different classes were also found to be effective against SARS-CoV-2 PLpro. They include phytochemicals from the class of phenolic acids such as ferulic acid and vanillic acid [65]; phytophenols such as 6-Gingerol, 8-Gingerol, and 10-Gingerol with binding affinities in the order of nM [47]; Mahuangnin A [50]; diarylheptanoid such as curcumin [60]; dianthrone such as rheidin B [50]; phytosterols, viz., campesterol (BE (binding energy) = −9.7 kcal/mol, Kd (dissociation constant) = 76.87 nM), alpha-spinasterol (BE = −9.54 kcal/mol, Kd = 101.42 nM), calonysterone (BA = −6.9 kcal/mol), and withanolide A (BE = −7.4 kcal/mol) [51,55]. The details of their reported activities are outlined in Tables 1–4.

Two aromatic polyketides, viz., ginkgolic acid and anacardic acid, were analyzed using an in vitro enzyme-inhibition assay, and both of them showed IC_{50} values of 16.30 ± 0.64 and 17.08 ± 1.30 μM, respectively [114]. Chen et al. (2021) further evaluated the antiviral potency of two hit inhibitors through a cytotoxicity assay using Vero E6 cells and a plaque-reduction assay. Recently, Yan et al. (2022) also reported anacardic acid as a potential PLpro inhibitor by employing a sandwich-like fluorescence polarization (FP) screening assay. The IC_{50} reported was, however, 24.26 ± 0.4 μM [123]. Hence, ginkgolic acid and anacardic acid are two novel potential natural products with SARS-CoV-2 PLpro-inhibitory properties.

Furofuranoid lignans, including I-Asarinin, sesamin, sesamolin, pinoresinol, hydroxymatairesinol, and spicatolignan, were isolated. Among them, hydroxymatairesinol emerged as the top lead, with a docking score of −7.20 kcal/mol. Hydroxymatairesinol formed hydrogen bonds with Met 208 and Asp 164 as hydrogen donors, while it interacted with Arg166 as a hydrogen acceptor. ADME prediction indicated favourable properties and

adherence to Lipinski's Rules for hydroxymatairesinol [65,70]. Moreover, in a comprehensive review by Xu et al. (2022), tetrahydrofuranoid and tetrahydrofurofuranoid-lignans were reported to have activities against HIV (human immunodeficiency virus) and EBV (Epstein–Barr virus), strengthening their antiviral potential [124]. In addition to furofuranoid lignans, a nonalkaloid toxin lignan, Podophyllotoxin, from *Podophyllum peltatum* L., also returned good results (−8.1 kcal/mol binding affinity) against PLpro in an in silico screening study [76].

Piceatannol dimers, viz., Jezonofol, Scirpusin A, Cassigarol G, and Maackin A, with the binding energies of −10.4 kcal/mol, −10.5 kcal/mol, −10.5 kcal/mol, and −9.3 kcal/mol, respectively, were promising candidates against SARS-CoV-2 PLpro and open the door to future in vitro and in vivo studies of this important group against SARS-CoV-2 [58].

Thangevel and Albratty (2022) reported demethyloleuropein, a secoiridoid from dietary olive, as a potent non-covalent inhibitor of PLpro [62], therefore highlighting the beneficial role of olive diets in the defense against COVID-19. Three phenol phytochemicals were reported as promising compounds to be developed into specific PLpro inhibitors by Srinivasan et al. (2022) [111]. The compounds methyl 3, 4-dihydroxybenzoate), (4-(2-hydroxyethyl) phenol, and 4-hydroxybenzaldehyde showed binding to an unidentified allosteric site of PLpro (ISG15/Ubiquitin-S2). In vitro IC_{50} values obtained ranged from 3.76 μM to 6.68 μM, and the compounds were noncytotoxic in cellular cytotoxic assays. Moreover, given the positive results in deISGylation activity assays, these phytochemicals can provide interesting scaffolds for future PLpro inhibitors [111].

Catechins, particularly their gallic acid esters, are also reported as inhibitors of SARS-CoV-2 PLpro. These are found abundantly in tea, cocoa, and berries [125]. *Camellia sinensis* (L.) Kuntze, commonly known as green tea, is recognized for its abundant content of catechins, including epicatechin (EC), epigallocatechin (EGC), epigallocatechin-3-gallate (EGCG), and epicatechin-3-gallate (ECG) [103]. Chourasia et al. (2021) performed docking of various catechins with PLpro and determined the molecular mechanisms of PLpro inhibition. They found that EGCG and ECG had greater binding affinities, −8.601 and −8.566 kcal/mol, respectively, towards PLpro than other catechins. Both these catechins showed H-bonds with L162 and G163 residues of PLpro and hydrophobic interactions with M208, P247, P248, Y264, and Y273 residues [64]. ECG was also found to exhibit in vitro inhibition of PLpro in a study performed by Montone et al. (2021). Various fractions of green tea (*C. sinensis*) extract were prepared and evaluated in vitro. The F5 fraction, with forty-five flavonoids in it, was the most active fraction among the five others and showed an IC_{50} of 0.13 ± 0.001 μg mL^{-1}. ECG was the main constituent of this fraction. Interestingly, ECG alone showed an IC_{50} of 11.62 ± 0.47 μg mL^{-1}, which is 10 times less than the IC_{50} of the whole of the F5 fraction. This emphasizes the additive effect of various components of an extract rather than the effects of an isolated component of the same fraction [103].

Pitsillou et al. (2020) reported hypericin, an anthraquinone derivative from *Hypericum perforatum* L., as a PLpro inhibitor in docking analysis and in vitro enzyme assay of PLpro deubiquitinase activity. The key interaction was made with the Y268 residue of the PLpro through pi–pi interaction. In addition, several other residues also interacted with the compound, including Y264, Q269, G271, L162, Y273, G163, and D164. At concentrations exceeding 50 μM, hypericin demonstrated significant inhibition of protease activity, comparable to that of GRL-0617, with an inhibition level of approximately 90% [102]. The interaction of hypericin with some other SARS-CoV-2 targets has also been reported, such as the spike protein, Mpro, and RdRp [126,127]. Moreover, Matos et al. (2022) have shown that, at non-cytotoxic concentrations, hypericin reduces the replication of SARS-CoV-2 in vitro [126]. Some other experiments are also underway to determine IC_{50} of hypericin in human cellular models and determine the mode of action of hypericin against SARS-CoV-2, which will further put confidence in the efficacy of this anthraquinone derivative [126].

3.7. Flavonoids and Terpenoids Possess a Rich Reservoir of SARS-CoV-2 PLpro Inhibitors among Other Phytochemical Classes

Approximately 100 phytochemicals are found in the literature as potential PLpro inhibitors, of which 19 are flavonoids, 18 are terpenoids, 7 are alkaloids, and 16 are glycosides, whereas 40 phytochemicals belong to miscellaneous origin (phenolic compounds, lignans, steroids, and tannols, etc.). Based on this data, flavonoids (19%) and terpenoids (18%) appear to be the richest class in terms of promising natural SARS-CoV-2 PLpro inhibitors, followed by glycosides and alkaloids to date. The finding is consistent with recent literature reviews, which highlighted a greater extent of flavonoids as potential inhibitors targeting coronaviruses [38]. Figure 3 shows a graphical illustration of PLpro inhibitors distributed among various classes of natural compounds.

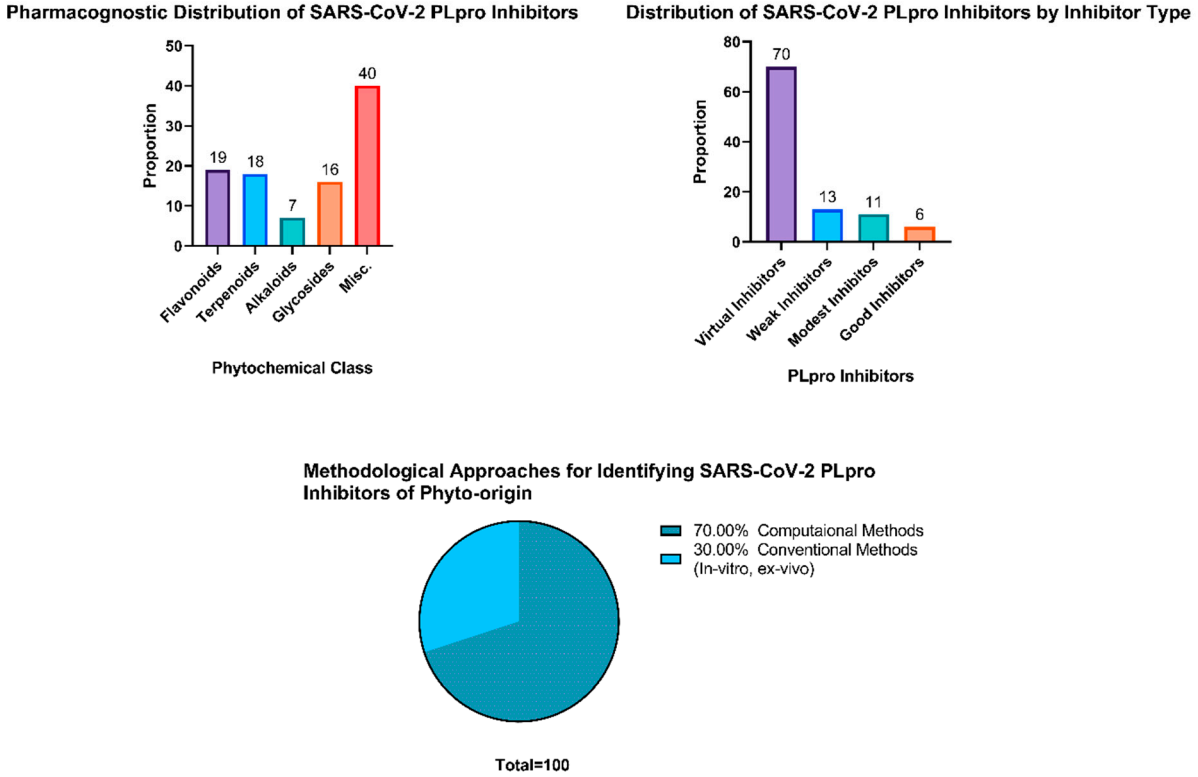

Figure 3. Proportionate view of SARS-CoV-2 phytochemical inhibitors: segmented by pharmacognostic classification, inhibitor nature, and the techniques employed in PLpro inhibitor research.

3.8. Promising Natural Candidates as Inhibitors of SARS-CoV-2 PLpro

The literature on drug discovery suggests the use of the selectivity index (SI) to establish the role of new drug candidates as therapeutic agents. The SI represents a ratio of CC_{50} (50% cytotoxic concentration) to EC_{50} (50% effective concentration). The CC_{50} is the concentration of the agent that kills 50% of the viable (host) cells, whereas the EC_{50} represents the concentration of the active agent that is needed to inhibit 50% of viral replication determined by cell-based assays or by IC_{50} assays, where the viral enzymes, such as proteases (e.g., PLpro) and polymerases, are targeted. From a bird's-eye view, the SI ensures that the lead compound is effective at preventing viral infection without causing harm to the host cells. The higher the SI, the better. There are no guidelines or cut-off values for an acceptable or appropriate SI value. However, generally, an SI value of greater than 10 should be considered a good candidate. Those with lesser values can undergo improvements in their pharmacokinetic and delivery profiles to alleviate the associated toxicities [38].

Based on this, we have categorized the phytochemicals into four distinct groups, considering their IC_{50} values and selectivity indices. These are virtual inhibitors (in silico studies

only), weak inhibitors (IC_{50} > 20 μM), modest inhibitors (IC_{50} < 10–20 μM but SI < 10), and good inhibitors or lead compounds (IC_{50} < 10 μM and SI equal to or greater than 10). Our analysis revealed the following distribution among these categories: 70 virtual inhibitors, 13 weak inhibitors, 11 modest inhibitors, and 6 good inhibitors/lead compounds (refer to Figures 2 and 3; Tables 1–4). Notably, computational methods dominate 70% of the phytochemical drug discovery literature, while wet labs account for the remaining 30%. However, for a candidate to thrive in the market, it is imperative to demonstrate promising results both in vitro and in vivo.

Further exploration is required for the weak and modest inhibitors. Specifically, their PLpro-inhibition mechanisms and cytotoxicity profiles need to be refined. While other mechanisms might underscore their efficacy, their performance concerning PLpro seems suboptimal.

Conversely, six phytochemicals—schaftoside, dihydrotanshinone I, tanshinone I, cryptotanshinone, hypericin, and 4-(2-hydroxyethyl) phenol—stand out as promising candidates (Table 4, Figure 4). These compounds not only exhibit potential in inhibiting PLpro but also target multiple pathological pathways associated with COVID-19. A detailed assessment of their drug potential is provided below.

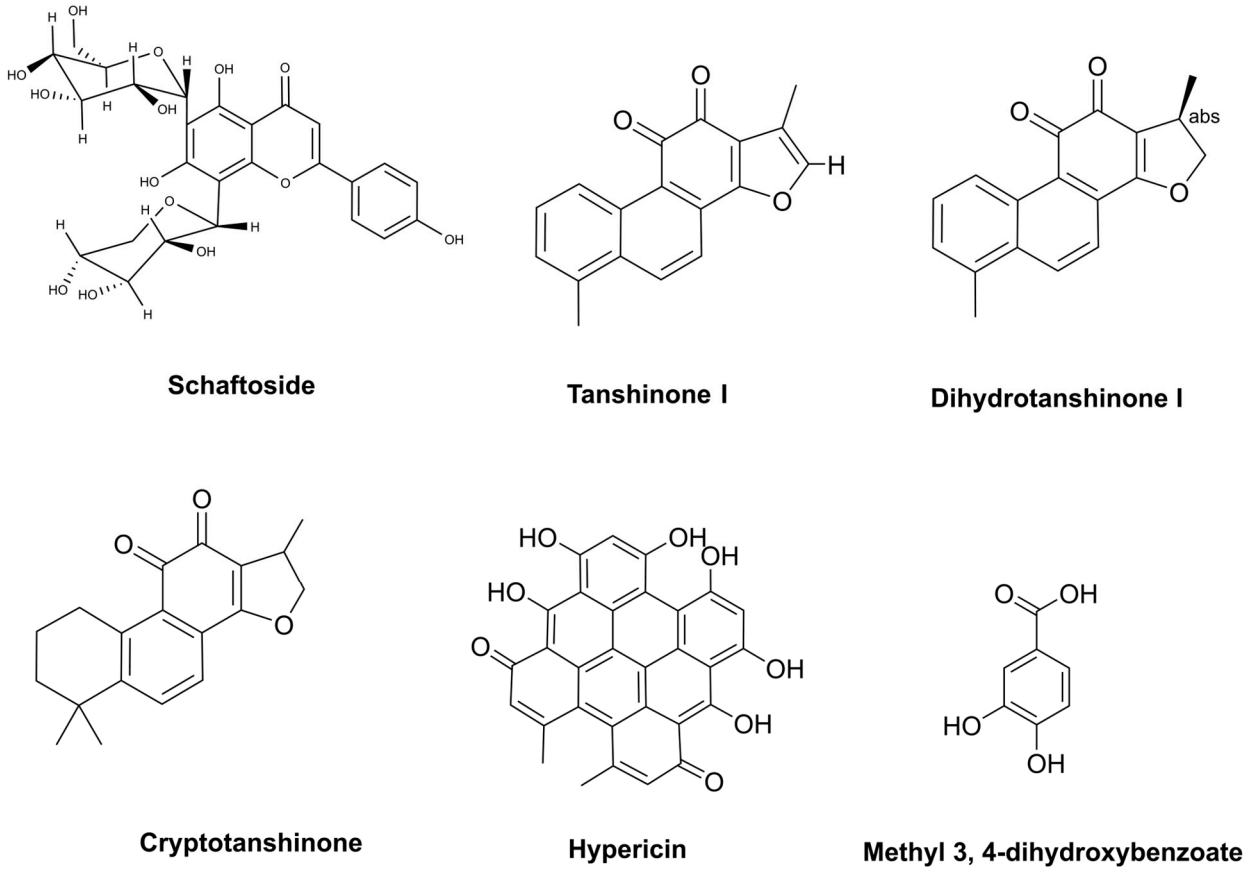

Figure 4. Chemical structures of six lead phytocompounds. Abs, absolute configuration.

Table 4. Phytochemicals targeting SARS-CoV-2 PLpro categorized as 'good inhibitors/lead compounds'.

Phytochemicals	PubChem CID	Pharmacognostic Class	Plant Scientific Name	Plant Family	Docking Score (Kcal/mol)	Assay	Outcome	Control	Cellular Toxicity/Selectivity Index	Reference
Schaftoside	442658	Flavonoid glycoside	*G. uralensis*	Fabaceae	−8.5	IEIA	60% at 8 µmol/L IC_{50} = 3.91 µmol/L	GRL0617 84.75% at 8 µmol/L IC_{50} = 0.34 µmol/L	CC_{50} > 200 µmol/L SI > 16.90	[120]
						CCAA	EC_{50} = 11.83 µmol/L			
Dihydrotanshinone I	11425923	Terpenoid	*S. miltiorrhiza*	Lamiaceae	-	FBA	IC_{50} = 0.59 µM	GRL0617 IC_{50} = 1.789 µM EC_{50} = 32.6 µM	CC_{50} > 300 µmol/L SI > 37.5	[87]
						CCAA	EC_{50} = 8 µM			
Tanshinone I	114917	Terpenoid	*S. miltiorrhiza*	Lamiaceae	-	FBA	IC_{50} = 2.21 µmol/L	GRL0617 IC_{50} = 1.39 µmol/L EC_{50} = 3.18	CC_{50} > 300 µmol/L SI > 132	[89]
						PRA	EC_{50} = 2.26 µmol/L			
Cryptotanshinone	160254	Diterpenoid	*S. miltiorrhiza*	Lamiaceae	-	FBA	IC_{50} = 5.63 µmol/L	GRL0617 IC_{50} = 1.39 µmol/L EC_{50} = 3.18	CC_{50} > 300 µmol/L SI > 428.5	[89]
						PRA	EC_{50} = 0.70 µM			
Hypericin	3663	Anthraquinone derivative	*H. perforatum*	Hypericaceae	−6.5	DUA	90% at 100 µM	GRL0617 90% inhibition of deubiquitinase activity at 100 µM	CC_{50} > 100 µg/mL SI = >178,858.88	[102,128]
						ICA	IC_{50} = 559.1 pg/mL			
methyl 3, 4-dihydroxybenzoate (HE9)	287064	Phenolic Compound	*Tagetes patula* L.	Asteraceae	−6.15	ICA	55% Inhibition IC_{50} = 3.76 µM	GRL0617 IC_{50} = 0.82 µM	CC_{50} > 100 µM SI > 9.64	[111]
						qRT-PCR	IC_{50} = 0.13 µM			
						CPE	IC_{50} = 10.37 µM			

Key: SI, selectivity index; FBA, fluorescence-based assay; ICA, ISG15 cleavage assay; IEIA, In vitro Enzyme-Inhibition Analysis; CCAA, Cell Culture Antiviral Assay; DUA, deubiquitinase activity; PRA, plaque-reduction assay; qRT-PCR, real-time quantitative reverse transcription polymerase chain reaction; CA, cytotoxic assay; CPE, Cytopathic Effect Assay; IC_{50}, Half-Maximal Inhibitory Concentration; EC_{50}, Median Effective Concentration; CC_{50}, 50% cytotoxicity concentration.

Schaftoside (SI 16.9), a flavonoid glycoside, is present in more than 184 species and 39 families of higher plants [129]. It has shown remarkable promise as a candidate towards COVID-19. The antiviral mechanism is mainly related to the inhibition of SARS-CoV-2 proteases, i.e., PLpro (IC_{50} 3.91 ± 0.19 μmol/L) and CLpro (1.73 ± 0.22 μmol/L). The phytocandidate not only reduces the viral infection in vitro (11.83 ± 3.23 μmol/L) but also exerts inhibitory effects on host inflammatory mechanisms. It enhances neutrophil-mediated immunity and downregulates leukocyte-mediated inflammation. The pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) are remarkably reduced (both in vivo and in vitro) upon treatment with schaftoside, which is useful for preventing cytokine storm in COVID-19 [120,130]. The toxicity and pharmacokinetic profile of the compound also favor its promise as a drug candidate for COVID-19.

A detailed discussion about tanshinones has been provided in the terpenoids section. Their potential as inhibitors of PLpro and SARS-CoV-2 is well-established [87–89]. It is noteworthy that the inhibition is specific towards PLpro compared to CLpro. Another advantage of these compounds is the favorable toxicity profile, which is shown by the half-cellular cytotoxicity concentration (CC_{50}) values above 300 μM. Tanshinones are derived from the lipophilic fraction of *S. miltiorrhiza*, which has a long history in traditional Chinese medicine [131]. The China FDA approved it for treating cardiovascular diseases [132] and has been included in Chinese clinical guidelines for COVID-19 pneumonia under the patent 'Xuebijing' [133]. In addition to these approved indications, pharmacological studies indicate that tanshinones have anti-oxidant, anti-inflammatory, anti-HIV, anti-bacterial, and neuroprotective activities [134]. Given these aspects, tanshinones may prove to be useful herbal remedies in the fight against infectious, particularly antiviral, diseases subject to comprehensive in vivo safety and efficacy evaluation.

Hypericin is an anthraquinone derivative from *H. perforatum* commonly known as St. John's wort (available in the market readily). Its anti-COVID potential has been explained by Pitsillou et al. (2020) and Matos et al. (2022) [102,126]. Hypericin inhibits PLpro in a manner comparable to GRL-0617 (>90% inhibition of deubiquitinase activity at >50 μM). It also has significant interaction with SARS-CoV-2 RdRp and can inhibit SARS-CoV-2 Mpro in a concentration-dependent manner (IC_{50} 63.6 ± 5.7 μM). Hypericin has a profound effect on SARS-CoV-2 replication, resulting in an 84–96% reduction in viral RNA at non-toxic concentrations. Previously, hypericin has also shown potential against some viruses such as influenza A, human immunodeficiency virus (HIV), hepatitis C virus, and avian coronavirus [135–137]. Therefore, hypericin is a potential herbal candidate to be tried in the fight against COVID-19.

Finally, the phenolic compound methyl 3,4-dihydroxybenzoate (HE9) has been selected as a potent PLpro inhibitor (IC_{50} 6.68 μM) [111]. Of note, the compound does not inhibit the SARS-CoV-2 Mpro under the same conditions tested for PLpro, implying that the inhibition is enzyme-specific. Further, the phytochemical inhibits the viral RNA replication in vitro without cytotoxicity and is also effective in ameliorating the cytopathic effect of SARS-CoV-2 in human cell lines (Table 4) [111]. On the molecular side, the dihydroxyphenol edge of the compound formed a hydrogen bond with the side chain of Glu 70. In addition, the benzene core of HE9 made hydrophobic interactions with Phe69. The antiviral promise is encouraging, yet the mechanism needs to be further evaluated in terms of disease-specific pathological linkages.

4. Conclusions and Perspective

Phytochemicals possess a rich reservoir of SARS-CoV-2 PLpro inhibitors. This review has highlighted ~100 phytochemicals reported as inhibitors of SARS-CoV-2 PLpro and classified them as 'virtual', 'weak', 'modest', and 'good' inhibitors. The 'flavonoids' class, followed by terpenoids, contained most of the phytochemicals reported in this study. Out of the phytochemicals studied, several have exhibited remarkable potential as drug candidates, exhibiting not only inhibitory effects against PLpro but also addressing various pathological pathways associated with COVID-19. Noteworthy candidates such as schafto-

side, tanshinones, hypericin, and methyl 3,4-dihydroxybenzoate (HE9) present exciting prospects, showcasing potent PLpro inhibitory efficacy, low cytotoxicity, and sound disease-mitigating potential. However, while substantial strides have been made, the journey to harnessing these phytochemicals as viable therapeutic agents needs further exploration in terms of pre-clinical and clinical aspects.

Currently, there are very few studies that have evaluated the in vivo efficacy of these phytochemicals. Such studies have heavily relied upon the computational power to estimate the molecular mechanisms of inhibition, few conducted in vitro enzyme-inhibition assays, and still fewer conducted cell culture-based assays to determine the efficacy in the cellular environment. While the in vitro studies are invaluable for advancing our understanding of potential therapeutic options, there are several limitations associated with them, such as non-physiological environment, off-target effects, and concentration differences. Therefore, there is a need to establish repeatable in vivo pre-clinical experimental models to evaluate the efficacy of these drugs in physiological environments and pave the way for clinical studies.

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