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REVIEW

Curative Potential of High-Value Phytochemicals on COVID-19 Infection

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Abstract—Medicinal plants and their therapeutically promising chemical compounds belonging to the valued category of 'traditional medicine' are potential remedies for various health problems. Due to their complex structure and enormous health benefits, the high-value plant-derived metabolites collectively termed as 'phytochemicals' have emerged as a crucial source for novel drug discovery and development. Indeed, several medicinal plants from diverse habitats are still in the 'underexplored' category in terms of their bioactive principles and therapeutic potential. COVID-19, infection caused by the SARS-CoV-2, first reported in November 2019, resulted in the alarming number of deaths (6.61 million), was further declared 'pandemic', and spread of the disease has continued till today. Even though the well-established scientific world has successfully implemented vaccines against COVID-19 within the short period of time, the focus on alternative remedies for long-term symptom management and immunity boosting have been increased. At this point, interventions based on traditional medicine, which include medicinal plants, their bioactive metabolites, extracts and formulations, attracted a lot of attention as alternative solutions for COVID-19 management. Here, we reviewed the recent research findings related to the effectiveness of phytochemicals in treatment or prevention of COVID-19. Furthermore, the literature regarding the mechanisms behind the preventive or therapeutic effects of these natural phytochemicals were also discussed. In conclusion, we suggest that the active plant-derived components could be used alone or in combination as an alternative solution for the management of SARS-CoV-2 infection. Moreover, the structure of these natural productomes may lead to the emergence of new prophylactic strategies for SARS-CoV-2-caused infection.

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Keywords: natural products, high-value phytochemicals, terpenoids, alkaloids, phenolics, medicinal plants, COVID-19

INTRODUCTION

Since the first case of respiratory infection caused by the severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) were detected in November 2019, the disease (later called COrona VIrus Disease of 2019, COVID-19) spread worldwide as pandemic and continues till today. As the newly developed vaccines have been implemented successfully and broadly, the treatment strategies have been established globally, the confusions and concerns at the early stage of this pandemic have been settled. However, this infection is still affecting many people with different waves and the latest one is caused by the Omicron sub-variants BA.2 and BA.2.38

Abbreviations: 3CLpro, chymotrypsin-like protease; HSPA5, Shock Protein A5; PLpro, papain-like protease; RdRp, RdRp RNA-dependent RNA polymerase; SARS-CoV-2, severe acute respiratory syndrome-related coronavirus 2.

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in India, while the BA.4 and BA.5 sub variants are also rising. Indeed, how long this infection will be there still seeming unpredictable and unclear. Moreover, insufficient medical resources in certain undeveloped countries could prohibit them from using the internationally accepted treatment strategies [1]. Therefore, in addition to the existing treatment strategies, there is a need in long-term symptom management and immunity boosting strategies to prevent infection. In this context, the herbal medicine interventions could be implemented as an alternative solution for COVID-19 treatment considering the level of medical support of each country. Approximately 80% of the world's population still depends on traditional remedies for their health issues [2]. The herbs are proven to be able to support immunity of the body [3]. Chemical composition of medicinal plants is extremely complex and this mystery is being resolved by isolation, identification, and characterization of its high-value phytochemicals. Importance of herbal medicine even during the initial days of COVID-19 pandemic was recognized in China and 90% of the treated patients were recovered. Preventive capacity of certain traditional medicines for healthy persons from SARS-CoV-2-caused infection has been also reported [4, 5]. Lianhuaqingwen and Shufeng Jiedu, the traditional medicines from China, have been also recommended for treatment of COVID-19, considering their efficacy against H1N1 or SARS-CoV-1 [6]. The use of herbal formulations and medicinal plants was recommended as a preventive measure and also for the treatment of COVID-19 [7]. Guidelines on the use of traditional and herbal medicines for the symptom management and prevention of COVID-19 have already been issued in China, India, and South Korea [3].

As the highly active phytochemicals are contributors to the effectiveness of the aforementioned herbal medicine interventions, this review attempts to explore potential of these phytochemical natural products for COVID-19 infection. By discussing the previous studies and their experimental data, we attract attention to the high-value phytochemicals as a powerful source for managing COVID-19 both in terms of prevention and treatment.

METHODS

This study is a systematic overview of the current status of research works on efficiency of phytochemicals against COVID-19. The literature survey for this review article was conducted using PubMed Central, Google Scholar, ScienceDirect, and Google search. The key words used: COVID-19; Corona virus review; phytochemicals and COVID-19; natural products against COVID-19; medicinal plants and COVID-19; traditional medicine and COVID-19; herbal medicine and COVID-19. Article search was conducted between January and June 2022 and the collected articles were screened. Articles, which satisfied the aim of this review, were further screened and systematically summarized. The phytochemical structures were drawn using ChemSketch software.

POTENTIAL VALUE OF PHYTOCHEMICALS IN COVID-19 INFECTION

Several phytochemicals, mainly secondary metabolites, were considered as COVID-19 preventives and also exhibiting SARS-CoV-2 inhibitory potential. The reported high-value phytoconstituents against COVID-19 infection have been discussed in the following sections under three important classes of plant secondary metabolites *viz.*, terpenoids, alkaloids, and phenolics (Fig. 1).

TERPENES (TERPENOIDS)

Terpenes are the largest class of plant secondary metabolites and they are isoprene (C_5H_8) derivatives. Acetyl-CoA is precursor for the synthesis of terpenes through the mevalonate or isoprenoid pathway. There are several types of terpenes recognized (hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, sesterterpenes, triterpenes, tetraterpenes, and polyterpenes) based on the number of isoprene units. Terpenoids have great commercial significance and therapeutic importance [8]. The following subsections explain the studies that emerged on the effectiveness of terpenoid phytochemicals for COVID-19.

Diterpenoids. Inhibitory effect of eight diterpenoid compounds (hinokiol, 18-hydroxyferruginol, ferruginol, 18-oxoferruginol, methyl dehydroabietate, kayadiol, O-acetyl-18-hydroxyferruginol and isopimaric acid) isolated from the medicinally valued *Torreya nucifera* was tested against SARS-CoV-3CLpro. It was found that, these compounds are effective inhibitors exhibiting IC_{50} values ranged from 49.6 to 283.5 μM. Ferruginol was

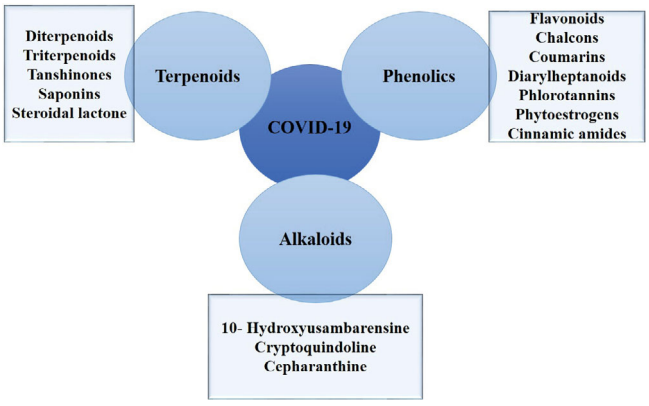

Fig. 1. Potential phytochemical classes and secondary metabolites discussed for COVID-19 infection.

found to be the most potent inhibitor among those tested (IC_{50} 49.6 μM) [9]. With the help of *in silico* approach, the terpenoid compounds 22-hydroxyhopan-3-one and 6-oxoisoiguesterin isolated from the African plants along with two alkaloids (10-hydroxyusambarensine, cryptoquindoline) were identified as powerful inhibitors of the 3CLpro protein of SARS-CoV-2 [10].

3CLpro (chymotrypsin-like protease) and PLpro (papain-like protease) are non-structural proteins encoded in the SARS-CoV-2-genome and vital for its replication; this fact attracted attention of the researchers to these proteins as useful drug targets for SARS-CoV-2-caused infection [11]. Proteins related to life-cycle of SARS-CoV-2 could be potential targets for anti-viral drugs. Hence, the compounds with inhibitory action against these proteins might be effective against SARS-CoV-2 infection [12].

Tanshinones. Tanshinones are diterpenes and inhibitory effects of seven tanshinones (methyl tanshinonate, cryptotanshinone, rosmariquinone, dihydrotanshinone I, tanshinone I, IIA, and IIB) isolated from the n-hexane fraction of *Salvia miltiorrhiza* against SARS-CoV-PLpro and 3CLpro was investigated using a fluorometric assay and it was revealed that the identified tanshinones are good inhibitors of both PLpro and 3CLpro. They showed a time-dependent inhibitory activity (IC_{50} 0.8 to 30 μM) against PLpro and a dose- but not time-dependent effect against 3CLpro (IC_{50} 14.4-89.1 μM). Among these, cryptotanshinone and dihydrotanshinone I were identified as having the most potent inhibitory capacity for PLpro (IC_{50} 0.8 ± 0.2 μM) and 3CLpro (IC_{50} 14.4 ± 0.7 μM), respectively. Kinetic investigations disclosed that rosmariquinone exhibited a mixed-type reversible inhibition and other tanshinones showed non-competitive inhibition of the SARS-CoV-PLpro protein whereas, all tanshinones were non-competitive inhibitors of the SARS-CoV-3CLpro protein [13].

Saponins. Acute inflammation and release of the pro-inflammatory cytokines are always associated with infection caused by SARS-CoV. Hence, natural compounds that exhibit an anti-inflammatory effect could be considered as potential drugs to treat these viral infections [11]. Anti-inflammatory and anti-SARS-CoV effects of escins, the triterpenoid saponin mixtures from *Aesculus turbinata* seed that has been used as herbal medicine, have been studied (EC_{50} 6.0 μM) [11, 14]. However, severe cytotoxic effects of escins reported in human lung-derived cells diminished its potential to be considered as a prophylactic medicine. However, a safer and more powerful drug can be developed from the original natural productome that shows the desired activity [11]. By this way, escin derivatives without tigloyl or angeloyl groups (that are crucial for the cytotoxic effects of escins) and with modified glycosidic bonds have been designed and synthesized. These escin derivatives showed lower cytotoxicity [15].

Withanone. TMPRSS2-the transmembrane protease serine 2, is the host enzyme that facilitates the viral particle entry into the host cells and its inhibition is actually a potential target to inhibit both the virus entry and further infection [11]. The ability of withanone, a steroidal lactone from *Withania somnifera* (Ashwagandha), to bind and stably interact with the TMPRSS2 catalytic site has been revealed through molecular docking and molecular dynamics simulations studies [16]. They have further investigated the effect of withanone on the expression of TMPRSS2 in MCF7 cells and found that the compound greatly downregulated the TMPRSS2 mRNA in the treated cells, which showed the dual action of withanone compound blocking the entry of SARS-CoV-2 into the host cells.

Structures of the aforementioned terpenoid compounds potentially effective against COVID-19 are presented in Fig. 2.

ALKALOIDS

Alkaloids are physiologically active, heterogeneous, and heterocyclic secondary metabolites. They include phytochemicals with therapeutic, nutritional, toxicological, and cosmetic potential [8]. Efficiency of different alkaloids against COVID-19 has been also studied. Cepharanthine is a tetrandrine alkaloid isolated from the plant *Stephania tetrandra* and already reported to have anti-oxidant and anti-inflammatory activities [17]. The homologous models for virtual screening were also established by researchers and through that, the ability of cepharanthine binding to the interface active pockets of the SARS-CoV-2 NSP12-NSP8 has been revealed [18]. The alkaloids 10-hydroxyusambarensine and cryptoquindoline from the African plants were identified as highly active inhibitors of SARS-CoV-2-3CLpro through *in silico* approaches [10]. Figure 3 shows the structures of alkaloid compounds potential for COVID-19.

PHENOLICS

Phenolics, a ubiquitous plant secondary metabolite class, comprise more than 8000 biologically active phytochemicals, and they exist as free phenols or their glycosides. Phenolics are phenylalanine derivatives and synthesized through the phenylpropanoid pathway. They include simple phenols, phenolic acids, hydroxycinnamic acids, phenylacetic acids, phenylpropenes, quinones, coumarins, stilbenes, lignans, xanthones, neolignans, tannins, melanins, and flavonoids [8]. The following sections discuss the phenolic constituents studied for their effectiveness to protect from COVID-19. Figure 4 represents the potential phenolic compounds reported to be effective against COVID-19.

RdRp (RNA-dependent RNA polymerase) is an important viral replicase that essentially catalyzes synthesis of the complementary RNA strands using the virus RNA template [11]. The RdRp molecular structure was reported in May 2020 [19], which suggested a new strategy for developing prophylactics for SARS-CoV-2 infection. Potentiality of eight phenolic compounds (gallic acid, quercetin, benzoic acid, resveratrol, naringenin, oleuropein, caffeine and ellagic acid) were studied as SARS-CoV-2 RdRp inhibitors using molecular docking technique [20]. These compounds formed hydrogen bonds with amino acids of the NTP (nucleotide triphosphate) entry channel in RdRp (except oleuropein and caffeine). Quercetin and gallic acid showed high RdRp binding affinity and exhibited good pharmacokinetic properties and drug likeness. Hence, they might be considered as potential drug candidates for COVID-19 treatment. A library containing 720 natural compounds were tested with HPLC and fluorogenic substrate peptide assay for their ability to inhibit SARS-CoV-3CLPro [21]. They have identified two effective polyphenolic compounds of black tea, *viz.*, tannic acid and theaflavin-3,3'-digallate, with IC_{50} values of 3 μM and 7 μM, respectively.

Flavonoids. Inhibitory effects of six flavonoids (bavachinin, neobavaisoflavone, isobavachalcone, 40'-O-methylbavachalcone, psoralidin, and corylifol A) isolated from the ethanolic extract of *Psoralea corylifolia* seeds on SARS-CoV-PLpro were reported. These flavonoids revealed a promising, dose-dependent inhibitory effect on PLpro, and among these, the highest effect was shown by psoralidin and isobavachalcone with an IC_{50} values of 4.2 ± 1.0 μM and 7.3 ± 0.8 μM, respectively [22]. Further, five geranylated flavonoids (tomentin A to E) were isolated and purified from *Paulownia tomentosa* fruits and their inhibitory effect on SARS-CoV-PLpro was explored. Even though all of the five compounds showed a dose-dependent inhibitory effect (IC_{50} 5.0-14.4 μM), Tomentin E was shown to be remarkably effective inhibitor with a very low IC_{50} value of 5.0 ± 0.06 μM [23].

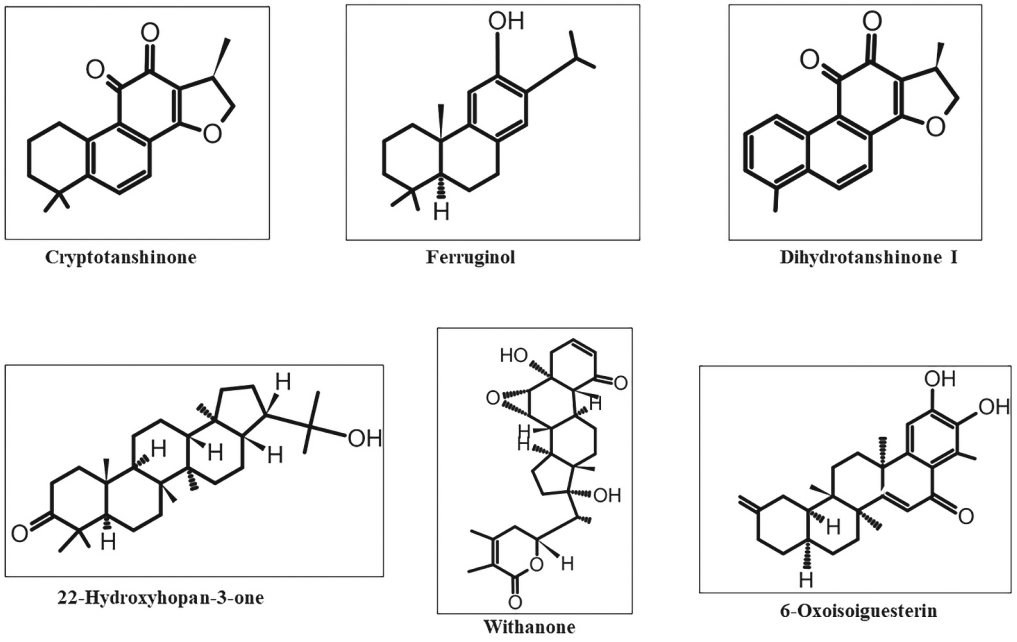

Fig. 2. Structures of potential terpenoid compounds effective against COVID-19.

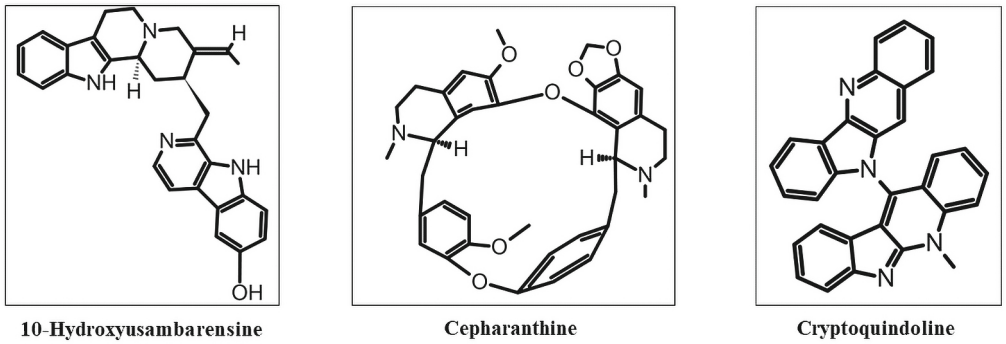

Fig. 3. Structures of alkaloids potential for COVID-19.

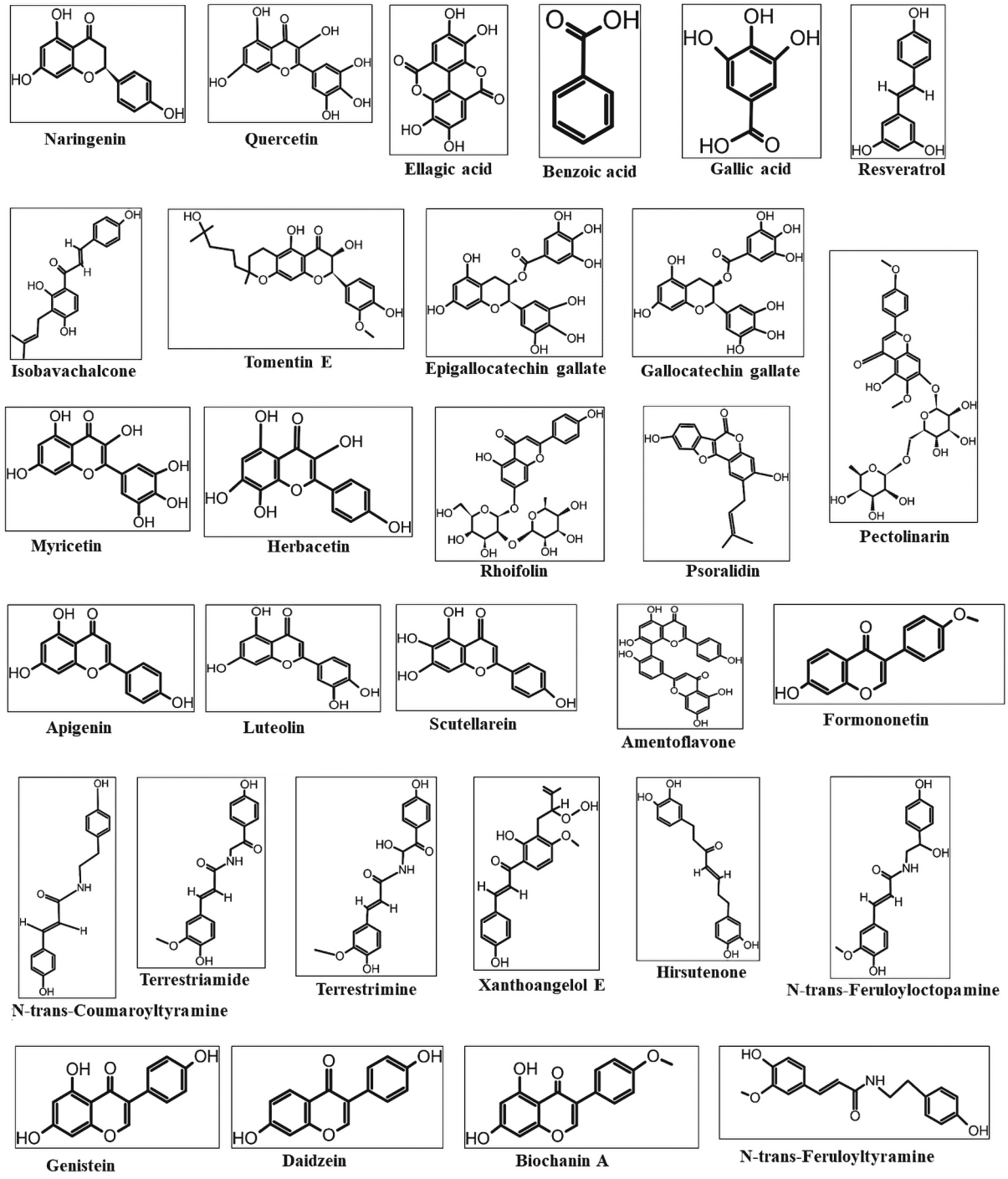

Fig. 4. Structures of phenolic phytochemicals potential for COVID-19.

The effects of seven flavonoids (puerarin, quercetin, daidzein, epigallocatechin gallate, gallocatechin gallate, ampelopsin, and epigallocatechin) were tested against 3CLpro. The purified 3CLpro expressed in *P. pastoris* was used for the study. Among the flavonoids, epigallocatechin gallate, gallocatechin gallate, and quercetin showed good anti-3CLpro activity (IC_{50} 73, 47, and 73 μM, respectively) [24]. Since 3CLpro has a crucial role in the replication process of SARS-CoV-2, it can be considered as a potential therapeutic target for the development of drugs effective in COVID-19 treatment [12]. Efficiency of SARS-CoV-3CLpro inhibition by different flavonoids was evaluated using the FRET method. Among these, they identified rhoifolin (flavone), herbacetin (flavonol), and pectolinarin (flavone) as demonstrating higher inhibitory effects (IC_{50} 27.45, 33.17, and 37.78 μM, respectively). Further molecular docking studies also revealed that these flavonoids showed binding affinity for

SARS-CoV-3CLpro [25]. While evaluating 64 molecules originated from 15 medicinal plant species for their inhibitory effect on the SARS-CoV helicase, it was observed that, two flavonoid compounds, myricetin and scutellarein, significantly inhibited the SARS-CoV helicase activity. At 10 μM concentration, myricetin (IC_{50} 2.71 ± 0.19 μM) and scutellarein (IC_{50} 0.86 ± 0.48 μM) were able to inhibit the SARS-CoV helicase [26]. Considering that helicase is a key protein for replication of the SARS-CoV-genome, this enzyme could be a target of novel anti-viral drugs. Accordingly, scutellarein and myricetin were suggested as promising anti-SARS drugs for the future [12].

The anti-SARS-CoV effect in terms of inhibition of the cysteine protease 3CLpro by four biflavonoids (bilobetin, amentoflavone, sciadopitysin, and ginkgetin) from *Torreya nucifera* leaves was tested with the FRET method [9]. Even though all the biflavonoids showed a significant inhibitory effect on the 3CLpro (IC_{50} 8.3-72.3 μM), amentoflavone exerted the highest inhibitory effect with the lowest IC_{50} value (8.3 ± 1.2 μM). Further, molecular docking revealed that amentoflavone had good affinity to the SARS-CoV-3CLpro and formed strong hydrogen bonds. The authors have also reported inhibitory activity of the flavones luteolin, apigenin, and quercetin against SARS-CoV-3CLpro with IC_{50} values of 20.2, 280.8, and 23.8 μM, respectively, and compared their effect with amentoflavone and found that amentoflavone is the superior inhibitor of SARS-CoV-3CLpro.

Chalcones and coumarins. Nine alkylated chalcones (4-hydroxyderricin, isobavachalcone, xanthoangelol, xanthokeistal A, xanthoangelol D, F, E, G, and B) and four coumarins from *Angelica keiskei* were investigated for their inhibition of SARS-CoV-PLpro and 3CLpro [27]. Even though the tested coumarins were not effective, the alkylated chalcones exhibited strong dose-dependent effect against these proteases (IC_{50} 1.2 ± 0.4-46.4 ± 7.8 μM for PLpro and 11.4 ± 1.4-129.8 ± 10.3 μM for 3CLpro). Among these, xanthoangelol E was most active against both proteases with very low IC_{50} values (1.2 ± 0.4 μM for PLpro and 11.4 ± 1.4 for 3CLpro) and, hence, this natural compound could be a promising drug candidate for treatment of COVID-19.

Diarylheptanoids. Inhibitory effects of nine diarylheptanoids (hirsutenone, platyphyllenone, platyphyllone, hirsutanonol, platyphyllonol-5-xylopyranoside, rubranol, oregonin, rubranoside A and B), which were purified and identified from the ethanolic extract of *Alnus japonica*, against SARS-CoV-PLpro was evaluated. Among these isolated compounds, hirsutenone exhibited most profound inhibitory effect (IC_{50} 4.1 ± 0.3 μM) and its effect was found to be comparable with that of the known viral protease inhibitor curcumin (IC_{50} 5.7 ± 0.3 μM) [28].

Phlorotannins. Inhibitory effect of nine phlorotannins (triphloretol A, phloroglucinol, eckol, 2-phloroeckol, dioxinodehydroeckol, dieckol, fucodiphloroethol G, 7-phloroeckol and phlorofucofuroeckol A) extracted and isolated from the brown alga *Ecklonia cava* against SARS-CoV-3CLpro was tested using the cell-free assay. All the phlorotannins except phloroglucinol inhibited SARS-CoV-3CLpro dose-dependently and in a competitive manner (IC_{50} 2.7 ± 0.6-164.7 ± 10.8 μM) and dieckol was the most potent inhibitor of 3CLpro [29].

Phytoestrogens. HSPA5, heat shock protein A5, is the host cell receptor recognized by the virus S protein. During infection, upregulation of expression and translocation of HSPA5 to the cell membrane occurs. The SARS-CoV-2 spike protein recognize HSPA5 on the membrane and that facilitates further progression of the infection process [11]. Through molecular docking and molecular dynamics simulations, the effect of natural compounds against HSPA5 substrate binding domain β have been studied [30]. The result revealed that the isoflavone phytoestrogens *viz*., genistein, daidzein, biochanin A, and formononetin exhibited the highest binding affinities with HSPA5. Hence, these compounds might interfere with the SARS-CoV-2 attachment to the stressed cells and, therefore, could be effective prophylactics for COVID-19 for those with high risk of cell stress.

Cinnamic amides. Several compounds of natural origin were identified with promising inhibitory capability of PLpro proteins [12]. Cinnamic amides are among such compounds and six cinnamic amides (*N-trans*-coumaroyltyramine, *N-trans*-feruloyloctopamine, *N-trans*-caffeoyltyramine, terrestrimine, *N-trans*-feruloyltyramine and terrestriamide) from the fruits of *Tribulus terrestris* were tested and showed promising dose-dependent inhibitory effect on PLpro protein (IC_{50} 15.8-70.1 μM). Terrestrimine [(E)-N-(1-hydroxy-2-(4-hydroxyphenyl)-2-oxoethyl)-3-(4-hydroxy-3-methoxypheny) acrylamide] exhibited the highest inhibitory effect on SARS-CoV-PLpro with IC_{50} of 15.8 ± 0.6 μM [31].

The list of compounds among the aforementioned terpenoids, alkaloids, and phenolics potentially effective in COVID-19 is presented in Fig. 5.

CONCLUSIONS

Medicinal plants and their high-value phytometabolites are considered as promising alternative drug candidates for treatment or prevention of various diseases, and now the attention is on COVID-19. This review, which covered a different dimension of COVID-19 infection in terms of medicinal plants and phytochemicals, could help to find a solution for long-term symptom management and immunity boosting in the fight against COVID-19. We emphasize importance of exploring phytochemical natural products as a potential source of prophylactics and/or therapeutics against COVID-19. Further experimental research is suggested to prove efficacy and druggability of these phytoconstituents against COVID-19.

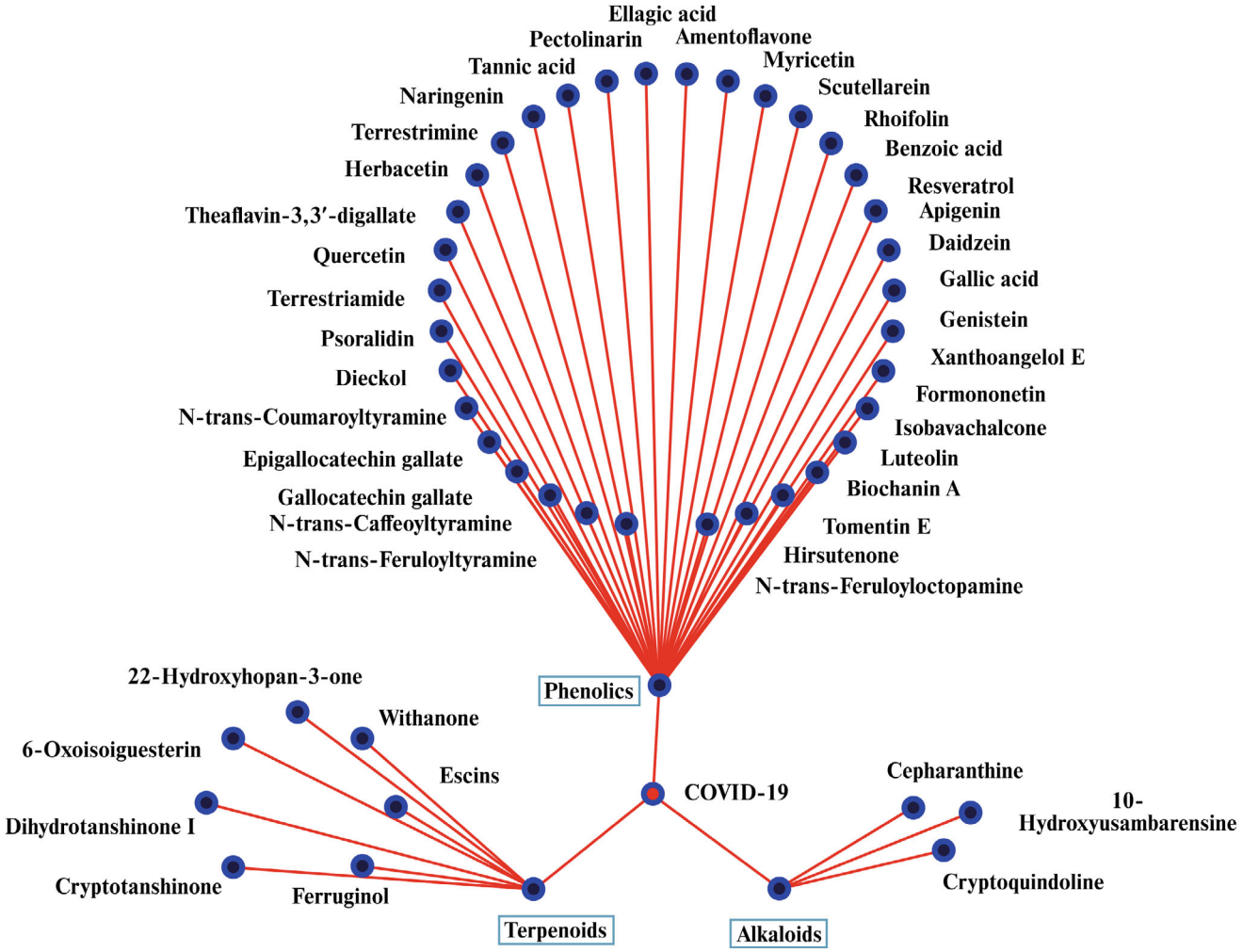

Fig. 5. Overview of potential high-value phytochemicals effective for COVID-19.

Contributions. DS: Conceptualization, data curation, methodology, writing, reviewing, and editing original draft; MD: Structure drawing, reference formatting, reviewing, and editing original draft; HCYR and RP: Reviewing and editing original draft; SPD: Structure drawing, reviewing, and editing original draft; CJ: Supervision.

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Ethics declarations. The authors declare no conflict of interest in financial or any other sphere. This article does not contain any studies with human participants or animals performed by any of the authors.

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