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REVIEW ARTICLE

Phytovid19: a compilation of phytochemicals research in coronavirus

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Abstract

The COVID-19 pandemic has immensely impacted global health causing colossal damage. The recent outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has increased the quest to explore phytochemicals as treatment options. We summarize phytochemicals with activity against various coronaviruses including SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). We compiled 705 phytochemical compounds through text mining of 893 PubMed articles. The physicochemical properties including molecular weight, lipophilicity, and the number of hydrogen bond donors and acceptors were determined from the structures of these compounds. A structure-based evaluation of these properties with respect to drug likeness showed that most compounds have a positive score of drug likeness. QSAR analysis showed that 5 descriptors, namely polar surface area, relative polar surface area, number of hydrogen bond donors, solubility, and lipophilicity, are significantly related to IC50. We envisage that these phytochemicals could be further explored for developing new potential therapeutic molecules for COVID-19.

Keywords COVID-19 · Phytochemicals · Text mining · Cheminformatics · Physicochemical properties

Introduction

The COVID-19 pandemic caused by novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has caused colossal damage worldwide [1]. Coronaviruses consist of a large diverse family of viruses, namely, Alpha-, Beta-, Gamma-, and Delta coronaviruses. The SARS-CoV-2 belongs to the beta subfamily, which also includes the SARS-CoV and bat CoV ZXC21. CoV ZXC21 and CoV ZC45 are closest to SARS-CoV-2. SARS-CoV-2 shares 76.04% amino acid sequence identity in the Spike (S)-protein sequence with that of SARS-CoV, 80.32% with bat CoV ZXC21 Spike protein, and 81.00% identity to the sequences of Spike proteins of bat-derived SARS-like coronaviruses bat-SL-CoVZC45 and 35.10% identity to the sequence of the Spike protein of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [2]. SARS-CoV-2 is a single-stranded RNA virus with at least ten open reading frames (ORFs) [3]. The first set of ORFs (ORF1a/b) code for polyproteins and the remaining encode for four main structural proteins of the virus. These structural proteins are, namely, spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins [4, 5]. The Spike glycoprotein mediates the invasion of coronaviruses into human cells by interacting with the ACE2 receptors [6]. The Spike glycoprotein has a large ectodomain, a single-pass transmembrane anchor, and a short C-terminal tail. The ectodomain contains a receptor-binding unit S1 that binds to cell surface receptors. The S2 unit of the ectodomain fuses with the host cell and viral membranes thereby enabling the entry of viral genomes into host cells [7].

SARS-CoV-2 causes infections mainly in the respiratory tract and lungs [8]. Virus excretions from gastrointestinal tracts have also been observed. The ongoing COVID-19 pandemic has caused over 575,887,049 infections and over 6,398,412 deaths (data as of 02 Aug 2022, 9:34 pm CEST) worldwide and the numbers are still rising [9]. Several different strains have emerged in different countries since the beginning of the pandemic causing a huge disease burden on

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global health and the economy. Despite significant efforts, there are no specific anti-COVID-19 therapies available [10]. Patients with associated comorbidities, namely, chronic respiratory disease, cardiovascular disease, cancer, or diabetes, tend to be susceptible to infection. In one study, Guan et al. (2020) reported that 25.1% of Chinese patients have at least one associated comorbidity, and 8.2% of patients had two or more comorbidities. The major comorbidities were hypertension (16.9%), diabetes (8.2%), cardiovascular diseases (3.7%), and chronic kidney diseases (1.3%) [11]. Meta-analysis of various comorbidities suggested that leukemia, psoriasis, and non-alcoholic fatty liver (NFLD) patients are at higher risk [12]. Therefore, there is a pressing demand for effective therapeutic solutions for the treatment of COVID-19 [13].

Human civilization has looked high and low into nature for healing strategies ever since ancient times [14]. Several time-honoured drugs were prepared from plant parts and are in use even today. Due to their potentially high therapeutic qualities and acceptance by patients with diverse health issues, herbal medications play a significant role in treating a variety of disorders. The use of a plant's complete body, a specific isolated phytoconstituent, or a portion of the plant are all part of the practice of herbal medicine. The discovery of herbal medicines from various natural resources rekindled interest in the scientific era's hunt for novel pharmaceuticals [15]. Examples of drugs include morphine, antibiotics such as penicillin, erythromycin, cardiac stimulant digoxin, salicylic acid (aspirin), reserpine (antipsychotic and antihypertensive), quinine (antimalarial), and lovastatin (lipid reducing) [16–18]. Many therapeutics under development for cancer are using natural products. Paclitaxel is a widely known anticancer compound from natural plant sources. Several anticancer therapeutics have been developed through combinatorial chemistry from the original natural source [19]. The use of natural plant compounds over many years has been noted to be well tolerated, more affordable, and accessible. Not surprisingly, the discovery of therapeutics against SARS progressed rapidly and significantly by searching the natural plant source compounds. Various phytochemicals have been reported to have prophylactic activity against MERS and SARS coronaviruses. For example, leptodactylone extracted from *Boenninghausenia sessilicarpa* was reported to have 60% of anti-SARS-CoV activity at 100 µg/ml concentration [20].

Recently, some phytochemicals were studied in COVID patients as complementary treatment options, for example, ginger, traditional Chinese medicine Bufei Huoxue capsules etc. [21, 22]. The traditional Chinese herbal medicine therapy, recommended by Chinese herbalists, includes a combination of herbs, based on the distinction of the patient's syndrome. Traditional Chinese herbal medicine therapies were said to have effectively prevented and cured SARS during the outbreaks. It was used extensively for the treatment of SARS in 2002 and was administered to 58.3% of confirmed patients [23]. For example, the Traditional Chinese Medicine (TCM) Ma xing shi gan decoction (MXSG) is made up of four herbs namely, *Ephedra sinensis*, *Semen armeniacae amarum, Glycyrrhiza,* and *Gypsum fibrosum*. The major therapeutic role of this herbal medicine is to treat asthma, lung heat, and cough. This TCM can be used for early coronavirus infections [24].

In this paper, we examine how different types of herbs responded to the SARS virus pandemic during its early phases and we evaluate major results on how early warning systems created during earlier epidemics responded to limit the virus. We have used themes of coronavirus, and herbs in data mining of scientific literature records from the NCBI PubMed database [25]. The CRAN package pubmed.mineR [26] was used for text mining. The records were individually examined, and the results are contrasted with records covering all of the Covid-19 study themes. From the positively curated literature dataset, herbal compounds with anti-coronavirus activity were shortlisted to facilitate therapeutic development against these highly health and economy-disrupting diseases. A compound dataset was prepared from text mining. The quantitative descriptors of selected compounds such as molecular weight, polar surface area, number of hydrogen bond donors and acceptors, lipophilicity, drug likeness along with reported activity, i.e., 50% inhibitory concentration (IC50) were examined. Following that, a quantitative structure–activity relationship (QSAR) was drawn out using statistical techniques between activity and physiological descriptors that were significantly related to the activity.

Methodology

Text mining PubMed (https://pubmed.ncbi.nlm.nih.gov/) database [25] was searched using specific keywords, "COVID-19 OR SARS-CoV-2 OR Severe acute respiratory syndrome coronavirus-2 OR Coronavirus) AND Herbal". Abstracts were retrieved on 16.02.2022. All text mining work was carried out using the R package pubmed.mineR version 1.0.19 [26]. The abstract set was first to read using *readabsnew()* function. To extract species and chemical entities, the *pubtator_function* was used. The extracted data were manually examined to include those mentioning phytochemicals or natural compounds and plant species.

Inclusion and exclusion criteria Specific criteria chosen for text mining were as follows:

- *In silico* studies were excluded.
- Only articles with accessible full text were included.

- *In vivo*, *in vitro*, and random clinical trials were included.
- Reviews were included.
- Phytochemicals with reported activity against SARS and MERS were included.

Through manual curation, studies focussing on SARS and MERS viruses were shortlisted. We examined for phytochemicals and herbal compounds and their reported activities, namely, inhibitory concentration (IC50) if any. For example, the review article by Silveira et al., 2020 described different herbal medicines as adjuvants for Covid-19 [27]. This article was categorized as "positive" in manual curation and names of different herbal medicines extracted from this review were included in the final compound dataset. On the other hand, Gani et al., 2021 carried out a computational screening of biologically active metabolites from Indonesian plants [28]. This study was classified as "negative" as it was performed *in silico*.

Structure retrieval The PubChem database (https://pubchem.ncbi.nlm.nih.gov/) was referred for retrieval of chemical structures. The 3D (most preferably) or 2D (when 3D was unavailable) structures were downloaded [29]. The compound dataset was prepared by assigning a unique ID to each compound. Redundant compounds from multiple PMIDs were removed.

Analysis of physicochemical properties Various physicochemical properties were analyzed using DataWarrior software [30]. DataWarrior is open-source software for structure-based data analysis and visualization. The structures of herbal compounds extracted through text-mining were first loaded into DataWarrior. The physicochemical properties calculated from structures include Lipinski's properties, solubility, polar surface area, and drug likeness. Further, the distribution of these properties across the compounds of the dataset was plotted.

Quantitative structure–activity relationship Quantitative structure–activity relationship (QSAR) is used for quantifying the effect of physicochemical properties on the biological activity of compounds [31]. Different descriptors may contribute to and affect the activity of compounds, and hence the highly correlated features among different descriptors were identified. This analysis was performed using *cor* function in R. The descriptors were, namely, molecular weight (MW), lipophilicity (cLogP), solubility (cLogS), number of hydrogen bond acceptors (HA) and donors (HD), total surface area (TSA), polar surface area (PSA), druglikeness (DL), relative polar surface area (RPSA), molecular shape index (SI), molecular flexibility (MF), molecular complexity (MC), and reported IC50. Linear regression-based statistical modelling was used with IC50 as the dependent variable. The compounds dataset used here is a subset of literature retrieved compounds with reported IC50 values. These compounds have different targets such as SARS-CoV S protein-ACE2 interaction, 3CLpro, PLpro, helicase, viroporin 3a, ACE receptor, and compounds targeting endocytic machinery [32] and reported with a role in increasing intracellular Zn^{2+} concentration [33]. Further, to fit the linear models, *lm* function in R was used. Only the significant descriptors with a p-value ≤ 0.05 were considered. The estimated regression equation was derived as $Y = mX + c$, where Y is IC50 and X is the selected descriptor.

Result and discussion

Text mining From the PubMed database, 893 abstracts were retrieved with the given keywords. This abstract set was further used as a primary dataset for text mining and data collection. This dataset contains original research articles, reviews, meta-analysis studies, trials, comment articles, case reports, multicentre studies, observational studies, and letters to editors. Using the pubtator_function of pubmed.mineR package, 222 abstracts were screened from the whole abstract set. This selection was based on the exclusion and inclusion criteria mentioned in the methodology section. Word atomization shows that the frequency of specific terms, namely, "medicine," "Chinese," "treatment," "herbal," and "traditional" are prominent in these abstracts. This highlights the importance of natural product-based treatments regarding Covid-19. A graphical representation of the same is shown as a word cloud in Fig. 1a.

Phytochemicals for Covid-19 Phytochemicals and natural products have been abundantly explored for Covid-19. Yearwise inspection of the 893 retrieved abstracts shows that there is a drastic increase in herbal product-related studies after the COVID-19 pandemic began. The abstract set contains only 5 abstracts from the year 2011, which increased to 393 in 2020 and 494 in 2021 (Fig. 1b). Our extensive literature review collects phytochemicals belonging to classes such as phenolic acids, terpenes, and coumarins.

- Phenolic acids: Phenolic acids are secondary plant metabolites, majorly present in cereals and berries [34, 35]. These are derivatives of cinnamic and benzoic acids [36]. Kim et al. 2014 identified polyphenolic compounds from *Psoralea corylifolia* seeds having inhibitory activity against papain-like protease (PLpro) of SARS-CoV [37]. The herbal medicine *Ocimum gratissimum* contains phenolic compounds and their derivatives like quercetin, luteolin, cafeic acid [38, 39] and can be used for relieving early COVID-19 symptoms [27]. Other examples of antiviral phenolic acids include caffeic acid, gallic acid, and caffeoylquinic

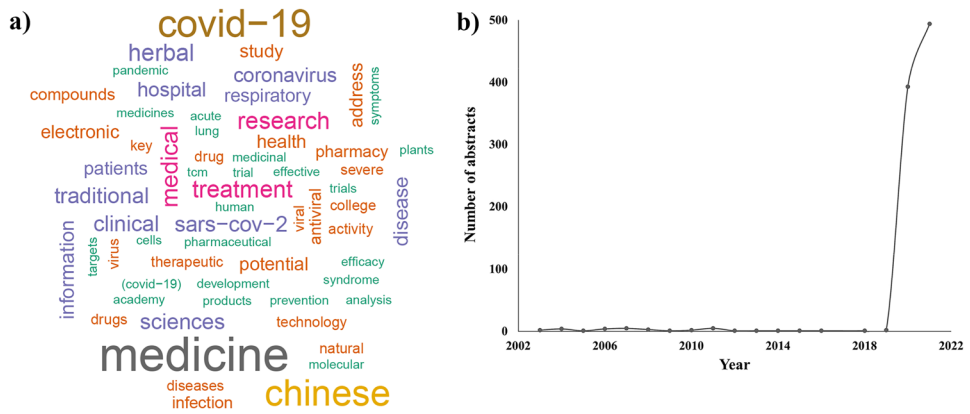

Fig. 1 **a** Wordcloud showing prominent terms in retrieved abstracts. **b** Yearwise distribution of abstracts

acids. Chlorogenic acid is a caffeic acid derivative extracted from *Echinacea purpurea* with IC50 0.1 µM against ACE inhibitory activity [40]. Xing et al. 2014 reported that gallic acid isolated from *Tamarix hohenackeri* Bunge had ACE-inhibitory activity with 20 mg/ml of EC50 [41].

Flavonoids are classes of polyphenolic compounds, abundant in fruits and vegetables. They possess anti-inflammatory, anti-oxidative, anti-carcinogenic, and anti-mutagenic properties [42]. Several reports have suggested the antiviral activity of different flavonoids against viruses including respiratory syncytial virus, human immunodeficiency virus (HIV), and herpes simplex virus (HSV). For example, the flavonoid baicalin inhibits infection and replication of HIV-1 [43, 44]. Numerous studies have reported the activity of flavonoid compounds against respiratory viruses belonging to the SARS family. The roots and leaves of *Althaea officinalis L* contain different flavonoids namely, Isoscutellarein, hypolaetin, kaempferol, and luteolin [45]. The extracts from this plant can suppress cough and are therefore reported as potential use in COVID-19 [27]. Yi et al. 2004 had reported that Luteolin and quercetin can inhibit SARS-CoV spike protein (S) through interaction with ACE2 receptors [46].

Among the flavonoids, chalcones are aromatic ketones and enones [47]. Chalcones like broussochalcone A and B were reported to have activity against coronavirus -chymotrypsin-like protease ($3CL^{pro}$) [48]. Park et al. 2016 studied alkylated chalcones from *Angelica keiske*. These include various Xanthoangelol compounds with IC50 ranging between 1.2 and 13 µM against 3CLpro and PLpro of SARS-CoV [49]. Prenylated flavonoids like Tomentin (A-E) extracted from the fruits of *Paulownia tomentosa* were reported as competitive inhibitors of SARS-CoV papain-like protease (PLpro) with IC50 ≤ 12.5µM [50]. Other categories of flavonoids like glycosides were mentioned to have an antiviral activity such as Juglanine inhibits ion channel activity of SARS-CoV 3a protein with IC50 of 2.3 µM [51]. Further, Carlinoside from *Desmodium styracifolium* inhibits ACE activity with IC50 of 33.6 µM [52].

Additionally, tannins are phenolic bioactive molecules [53]. The antiviral activity is based on adsorption to the viral cell membrane leading to inhibition of the virus that reduces the ability to attack human cells [54]. Polyphenols, specifically tannins from black tea (*Camellia sinensis*) namely, Theaflavin-3,3′ digallate, Tannic acid, 3-Isotheaflavin-3 gallate were reported to have activity against SARS- 3CLPro enzyme with IC50 9.5 µM, 3 µM, and 7 µM respectively [55]. Tetra-O-galloyl-β-d-glucose (TGG) is a component of *Galla chinensis* reported to inhibit the SARS-CoV S protein-ACE2 interaction with IC50 of 10.6 µM [46].

- Terpenes: Essential oils abundantly contain terpenes [56]. These are hydrocarbons having isoprene ($CH_2C(CH_3)CHCH_2$) units. They are classified into 5 categories based on the number of isoprene units, namely, Monoterpenes, Sesquiterpenes, Diterpenes, Triterpenes, and Tetraterpenes [57]. Triterpenes extracted from *Triterygium regelii* namely, celastrol, iguesterin, tingenone, and pristimerin showed activity against 3CLpro of SARS-CoV with IC50 ranging from 2.6 to 10.3 µM [58]. Another pentacyclinc triperpene Betulinic acid was reported to have activity against the same enzyme with IC50 10uM [59]. Andrographoside is a diterpenoid extracted from the traditional Chinese medicinal plant *Andrographis paniculata* having activity against SARS-CoV-2 [60]. *Commiphora molmol* (Engl.) has sesquiterpenes such as furanoeudesma1,3-diene and lindestrene as major chemical components [61] that was reported to relieve respiratory syndromes since ancient times [62].
- Coumarins: Coumarins are composed of benzene and α-pyrone rings. These are abundant in seeds, roots, leaves, flowers, and fruits of plants, and are reported to have anti-inflammatory roles. Coumarin and associated derivatives possess inhibitory activity against a wide range of viruses including HIV, influenza, Enterovirus 71 (EV71), coxsackievirus A16 (CVA16), chikungunya, and dengue

virus [63]. As Coumarin derivatives were earlier studied in respiratory diseases, therefore such compounds can be of great importance as an anti-Covid-19 agent. Several herbal medicines for respiratory diseases contain coumarins including roots and leaves of *Althaea officinalis,* roots of *Glycyrrhiza glabra* and *Justicia pectoralis* [27]. In a recent study, extracts from *Angelica decursiva* were reported to have anti-ACE activity with IC50 of 20 µM [64]. Coumarins including Decursidin extracted from *Angelica decursiva* plant showed IC50 ranging between 4.68 and 20.04 µM [64].

The recent surge in COVID-19 infection has increased the investigation of traditional medicines as part of modern medicine. An overwhelming 705 compounds (Supplementary Table S1) were compiled through this literature survey. These provide a better understanding of phytochemicals that can be explored further against SARS-CoV-2. As evident from the literature survey, many randomized control trials have been conducted to study the effect of herbal formulations on alleviating COVID-19 symptoms [65]. A few phytochemicals are also being evaluated in clinical trials as a potential therapy for COVID-19 [65] as per data on ClinicalTrials.gov. We have enlisted 11 completed (Supplementary Table S2) clinical trials using herbal products as interventions for the treatment of COVID-19. This list includes clinical trials using natural products such as Colchicine, curcumin, Plitidepsin, Essential Oil, *Nigella Sativa* oil, Xagrotin, and Vitamin C. The consolidated list is shown in Supplementary Table S2.

Compounds dataset The structure of 705 literature retrieved compounds with possible antiviral activity against different coronaviruses was extracted from PubChem and a compound dataset was prepared. Evaluation of functional groups revealed that these compounds contain amine nitrogen including imides and sulfonamides, amines, alkyl-amines, aromatic and basic nitrogen atoms, and acidic oxygen atom count. Literature studies confirm the antiviral property of these compounds with these functional groups [66–70].

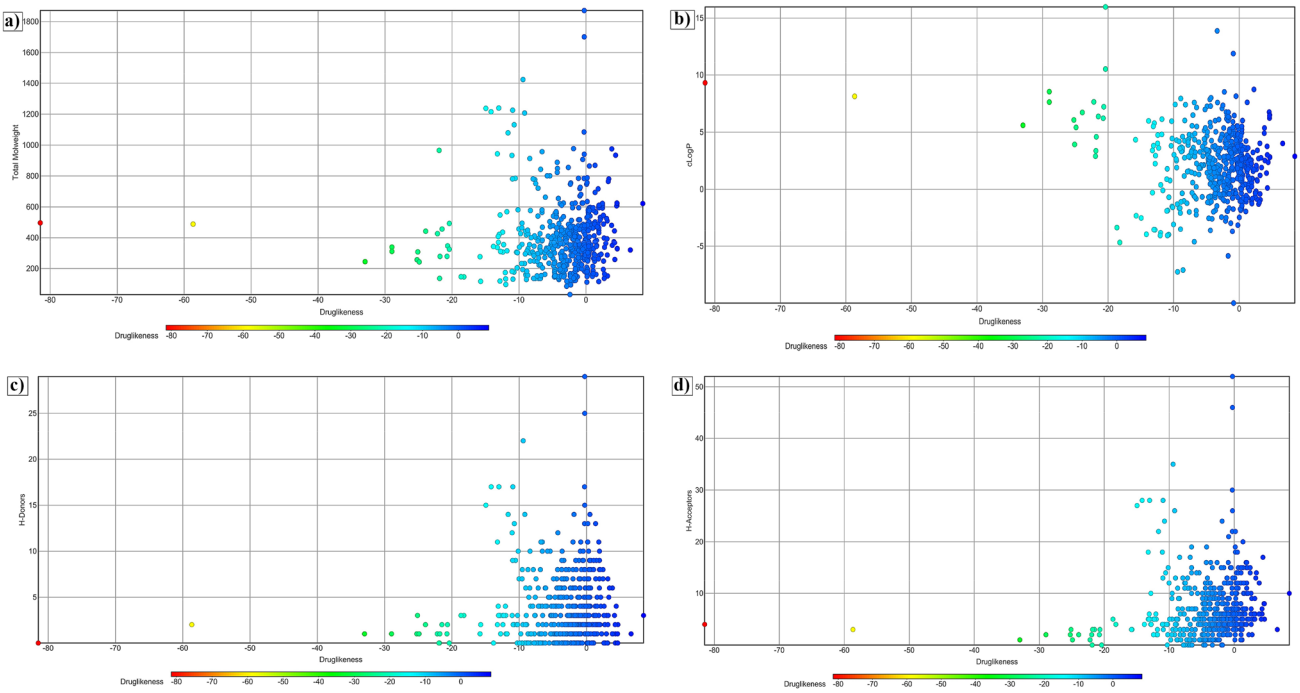

Fig. 2 Distribution of physicochemical properties. **a** Molecular weight, **b** cLogP, **c** number of hydrogen bond donors, and **d** number of hydrogen bond acceptors, with respect to drug likeness

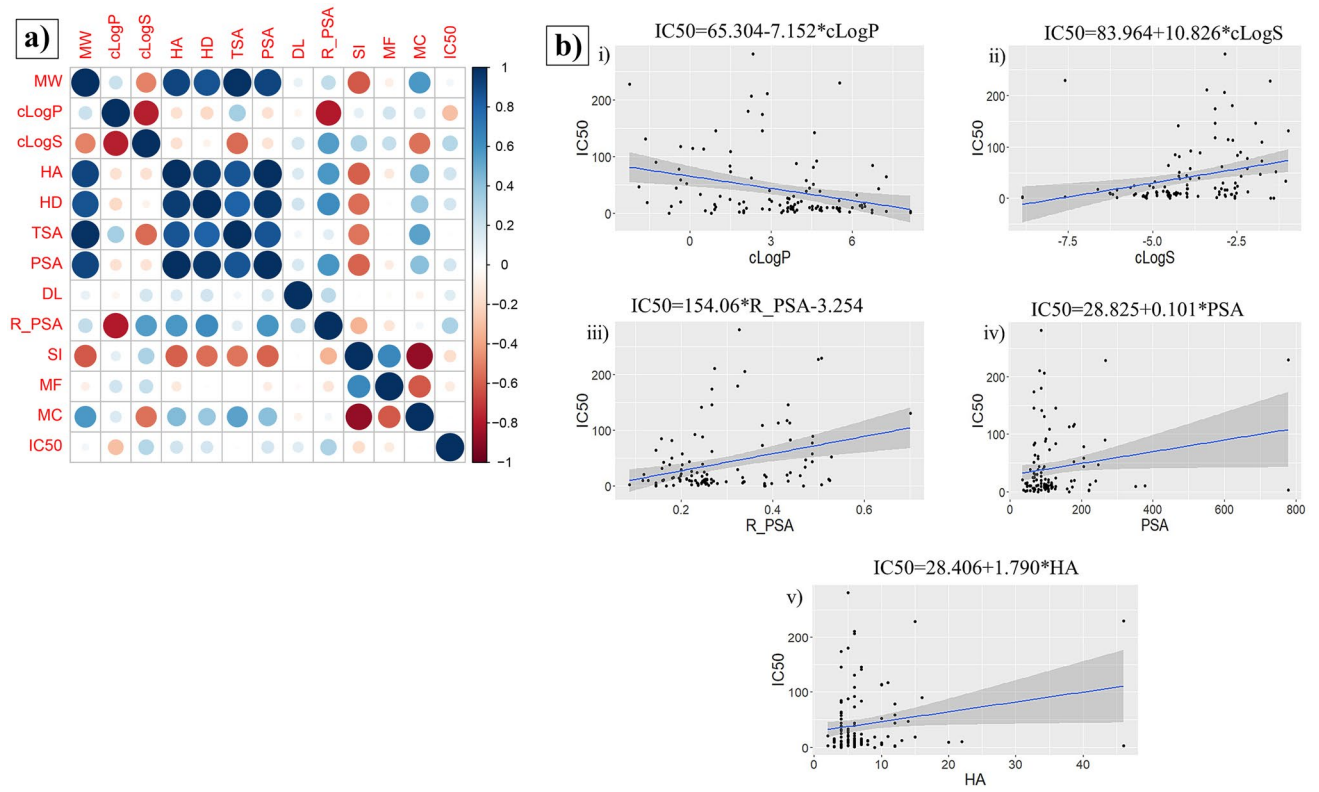

Fig. 3 **a** Correlation plot showing the relationship among different descriptors. The correlation values scale bar is shown on the right. **b** Regression fit showing descriptors with significant linear relationship with IC50. MW molecular weight, cLogP lipophilicity, cLogS solubility, HA number of hydrogen bond donors, HD number of hydrogen bond acceptors, R_PSA relative polar surface area, PSA polar surface area, TSA total surface area, MF molecular flexibility, SI molecular shape index, DL druglikeness, and MC molecular complexity

Further, physicochemical properties and drug likeness of each compound were also calculated using DataWarrior. The drug likeness is a quantitative measure of how various physicochemical properties can affect the drug ability of any compound. The higher the score, the more the drug likeness of any compound. The distribution of molecular weight, lipophilicity, and the number of hydrogen bond donors and acceptors with respect to drug likeness is shown in Fig. 2. It is apparent that most compounds lie in the positive range of drug likeness score.

QSAR analysis For QSAR analysis, 109 compounds with reported IC50 were selected. As it can be observed from the correlation plot in Fig. 3a, 6 descriptors, cLogS, HD, HA, PSA, RPSA, and DL, are positively correlated with IC50 whereas cLogP, SI, and MF are negatively correlated with IC50. Further, linear regression analysis was carried out using descriptors correlated with IC50. Of these selected descriptors, 5 were found to be significant ($p < 0.05$) namely cLogP, cLogS, PSA, RPSA, and HA (Supplementary Table S3) and the other 4 descriptors such as DL, MF, MC, and HD were not found to be significant. After model fitting, 5 different lines of the equation were derived (Table 1). HA, PSA, RPSA, and cLogS followed a positive linear relationship with IC50, whereas cLogP followed a negative linear relationship (Fig. 3b).

Table 1 Quantitative structure activity relationship of IC50 with descriptors

Descriptors	*p*-value	Linear equation
Lipophilicity (cLogP)	0.00164	IC50 = 65.304- 7.152*cLogP
Solubility (cLogS)	0.001949	IC50 = 83.964 + 10.826*cLogS
Number of hydrogen bond acceptor (HA)	0.03764	IC50 = 28.406 + 1.790*HA
Topological polar surface area (PSA)	0.04359	IC50 = 28.825 + 0.101*PSA
Relative polar surface area (R_PSA)	0.000554	IC50 = 154.06*RPSA—3.254

Conclusion

The current COVID-19 pandemic has impacted global health severely. Along with modern medicine, traditional remedies are rapidly emerging as potent therapies. In this compilation, we have carried out extensive text mining to obtain insights into various phytochemicals with potent activity against coronaviruses. Comprehensively, 893 abstracts were retrieved from the PubMed database for text mining using specific query terms and a dataset of 705 compounds was prepared. This dataset contains phytochemicals of classes including phenolic acids, flavonoids, terpenes, and coumarins. QSAR study using linear regression predicted that physicochemical properties like PSA, HA, and cLogS follow a positive linear relationship with minimum inhibitory concentration (IC50) whereas, cLogP follows a negative relation. We envision that this comprehensive review will be helpful for obtaining insights into phytochemicals with activity against coronaviruses. Also, a quantitative understanding of various physicochemical properties of the phytochemicals can be informative for future drug development.

We confirm that the manuscript is original and has not been published before.

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Author contribution The study was designed by Anasuya Bhargav, Pratibha Chaurasia, and Srinivasan Ramachandran, data collection was performed by Anasuya Bhargav, Pratibha Chaurasia, and Rohit Kumar, and the manuscript was written by Anasuya Bhargav, Pratibha Chaurasia, Rohit Kumar, and Srinivasan Ramachandran. The manuscript has been read and approved by all authors.

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Data availability The dataset analyzed during the current study is available as supplementary files.

Code availability Not applicable.

Declarations

Competing interests The authors declare no competing interests.

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