An *in silico* pharmacokinetic approach to decipher the antiviral potential of phytoligands against SARS-CoV-2 receptors

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ABSTRACT:

The emergence, rapid spread, and resurgence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as a potentially fatal disease are considered an alarming situation for the worldwide health crises. Treatment is essentially supportive, and the role of antiviral agents is yet to be established. Currently, there are few specific antiviral strategies, but several potent candidates of antivirals and repurposed drugs are under urgent investigation. Nature is bestowed with potential medicinal plants and the possible drug development based on herbal components against the viral receptors is essential for SARS-CoV-2 prevention. In the present investigation, Molecular docking was performed to estimate the spatial affinity of target compounds for the active sites of Spike glycoprotein with S1 receptor-binding domain, angiotension-converting enzyme 2 (ACE2) receptor complexes with spike receptor-binding domain, SARS-coronavirus 2 main protease (Mpro), and non-structural protein (Nsp-16) receptor of SAR CoV-2. In the present investigation based on the literature survey, a total of 1378 phytocompounds of 58 ethnomedicinal plants were screened. The structures of these 1378 chemical compounds were retrieved from PubChem and ChemSpider online servers based on the python web scrapping technique. The retrieved compounds were screened for drug-likeliness, ADMET, pharmacokinetic potentials, antiviral properties, and the best 198 Compounds were obtained. Additionally, the compounds were subjected to pass prediction to screen compounds based on antiviral potential. The top-ranked 52 compounds that have anchored with key residues located at the binding pocket of the protein were subjected to molecular docking employing PyRX. It was observed that all the 52 compounds have aligned to the pharmacophore and have demonstrated a higher binding affinity ranging from -14 to -4 KCal/mol were found to be potent antiviral drug candidates. Compounds such as Nimbidiol, Nimbolide (*Azadirachta indica*), 3R-Claussequinone (*Millettia pendula*), and Zingiberenol (*Zingiber officinale*) exhibited high-affinity binding energy and reported to possess antioxidant

and anti-inflammatory potential indeed. Therefore, these compounds could serve as lead molecules for further optimization and drug development against all the receptors for SARS-CoV-2 and related viral receptors. Thus, the present *in silico* studies regarded as valuable towards the exploration and development of a broad-spectrum natural anti-viral therapy.

Keywords: Sars-Co- V2 receptors, phytoligands, Pharmacokinetic potential, Molecular docking, antiviral compounds.

1. INTRODUCTION:

The Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). The virus has rapidly spread in humans, causing the ongoing Coronavirus pandemic. Recent studies have shown that similarly to SARS-Co-V, SARSCoV-2 utilizes the Spike glycoprotein on the envelope to recognize and bind the human receptor ACE2. This event initiates the fusion of viral and host cell membranes and then the viral entry into the host cell. Despite several ongoing clinical studies, there are currently no approved drugs that specifically target SARS-CoV-2. Computer-aided drug discovery (CADD) is a fundamental shortcut in the drug discovery area. CADD tools help to identify key molecules, predicting the effectiveness, the possible side effect, and also assist in upgrading the drug-likeliness of molecules. (Leelananda SP 2016). From literature, it is known that SARS-CoV-2 is a coronavirus that has glycoprotein spikes arranged like a crown. It infects its host with three stages. The first stage is the virus infects its host by attaching the transmembrane spike glycoprotein to the host through angiotensin-converting enzyme 2 (ACE2) in the host so that a complex is formed between S-glycoprotein with ACE2. (Shahid S.M.A 2018) (Hoffman M 2020). The next stage is the replication stage using RNA-dependent RNA polymerase (RdRp). Coronaviruses are RNA viruses that use host cells to replicate. Coronavirus uses RdRp to make new RNA copies. The last stage is the maturation stage of virus replication in the host cell using proteases such as 3CLpro (3C-like protease) and PLpro (Papain-like protease) (Kong R 2020). Hopefully, this research can contribute to the drug discovery process for COVID-19 disease. The study focuses on proteins Spike (S) glycoprotein the main protease, RNA-dependent RNA-polymerase M Protein (Mpro), and SARS-CoV Helicase (NTPase) because of their importance in the viral life cycle. In this study, we attempted to employ *in silico* virtual screening using molecular docking to screen the phytochemicals from the ethnomedicinal plants which have the inhibitory ability on proteins

of SARS-CoV-2 for identification of antiviral therapeutics. There are lots of drug compounds that do not pass the drug-likeliness analysis. Efficiency and safety of the drug to the human system are the main cause of drug failure which indicates the ADMET properties of molecules plays an essential role in every stage of drug discovery and development. Therefore, it is necessary to find potent molecules with better ADMET properties. (Guan L 2019).

Plants have been exploited over the millennia for human welfare in the promotion of health and as therapeutic drugs. Most of the developing countries such as China, India, Sri Lanka, and a few others endowed with vast resources of medicinal and aromatic plants. Plants being rich sources of secondary metabolites such as alkaloids, terpenoids, triterpenes, flavonoids, tannins, and phenolic compounds, etc. which are responsible for various biological activities have been used as a treatment for various ailments (De Fátima A 2006). Drugs, chemical compounds capable of influencing biological systems, have been used to treat human disease for thousands of years, mainly in the form of plant extracts. The first demonstrable substantiation of plants being used for medicinal purposes developed in Sumeria 5000 years ago and was subsequently codified meticulously, predominantly in India and China (Alavijeh 2005) (Petrovska 2012). As natural product-based drug discovery is associated with some intrinsic difficulties, the pharmaceutical industry has shifted its main focus toward synthetic compound libraries and high throughput screening (HTS) for the discovery of new drug leads (Atanasov 2015). The objective of drug design is to find a chemical compound that can fit a specific cavity on a protein target both geometrically and chemically. After passing the animal tests and human clinical trials, this compound becomes a drug available to patients. The conventional drug design methods include a random screening of chemicals found in nature or synthesized in laboratories. The problems with this method are long design cycle and high cost. Modern approach including structure-based drug design with the help of informatics technologies and computational methods has speeded up the drug discovery process in an efficient manner. Remarkable progress has been made during the past five years in almost all the areas concerned with drug design and discovery. An improved generation of software with easy operation and superior computational tools to generate chemically stable and worthy compounds with refinement capability has been developed. These tools can tap into the information to shorten the cycle of drug discovery, and thus make drug discovery more efficiency, cost-effectiveness, time-saving, and will provide strategies for combination therapy in addition to overcoming toxic side effect (Mandal 2009) (Baldi 2010) (V. I. Sharma 2013). The term pharmacokinetics describes the fate of compound in the organism during therapeutic

purpose. In other words, the pharmacokinetics depend upon absorption, distribution, metabolism, and excretion (ADME) parameters. According to (Hay M 2014), an early measure of ADME in the discovery phase reduced drastically the fraction of pharmacokinetics-related failure in the clinical phases. For drug discovery, ADME is an important parameter. Bioavailability term describes the extent and rate in which the active moiety (drug or metabolite) entered systemic circulation, ultimately accessed the site of action (Le J 1989). An in silico approach, especially computational prediction through ADME software is a suitable method for faster screening, less time consuming, no animal testing, etc. Among several tools, SwissADME online tool is a valid alternative of an experimental drug design from natural products or synthetic compounds (M. O. Daina A 2014) (Z. V. Daina A 2016) (B. M.-C. Daina A 2017) (M. O. Daina A 7 (2017 a)). This tool helps to find a narrow range of compounds for future experimental work on pharmacokinetics; bioavailability, etc. lead to new drug development (Puja Tripathi 2019).

2. METHODS AND IMPLICATIONS

2.1. ACTIVE SITES PREDICTION OF TARGET PROTEINS

Binding and active sites of proteins are often associated with structural pockets and cavities. We have used the CASTp server (Dundas J. 2006) (http://sts.bioe.uic.edu/castp/index.html?2pk9). CASTp server uses the weighted Delaunay triangulation and the alpha complex for shape measurements. It provides identification and measurements of surface accessible pockets as well as interior inaccessible cavities, for proteins and other molecules. It measures analytically the area and volume of each pocket and cavity, both in solvent-accessible surface (SA, Richards' surface) and molecular surface (MS, Connolly's surface). CSA is a database documenting enzyme active sites and catalytic residues of enzymes in the 3D structure (Purohit 2008). We performed this analysis for all the five viral protein structures individually, to find the binding site of each protein. In CASTp analysis, we have chosen the first pocket from the result, based on the area and the volume of the pocket.

2.2. PROSPECTION OF PHARMACOKINETIC POTENTIAL OF SELECTED PHYTOLIGANDS

2.2.1. SELECTION OF PLANTS AND THEIR PHYTOCOMPOUNDS

A total of 1378 phytocompounds present in 58 commonly available ethnomedicinal plants viz., *Acacia pennata* (Aye 2019), *Achyranthus aspera* (A. T. Sharma 2016), *Allium cepa* (M. &. D'auria 2017), *Allium sativum* (Prabodh Satyal 2017), *Allium Vineale* (Prabodh Satyal 2017), *Alternanthera philoxeroides* (A. T. Sharma 2016), *Andrographis echioides* (Aye 2019), *Andrographis paniculate* (Nv 2017), *Avicennia marina* (D. G. Kumar 2016), *Azadirachta indica* (Dineshkumar 2015), *Bacopa monnieri* (Subashri 2014), *Camellia sinensis* (D. &. Gupta 2016), *Canthium coromandelicum* (Mohan 2014), *Carica papaya* (Canini 2007)((Ezekwe 2017), *Carissa edulis* (Fowsiya 2017), *Cassia auriculate* (Aye 2019), *Cinnamomum zeylanicum* (Jayaprakasha 2003), *Croton oblongifolius* (Aye 2019), *Curcuma longa* (Naz 2010), *Dalbergia culrata* (Aye 2019), *Ensete Superbum* (Shivprasad 2018), *Erigeron bonariensis* (A. T. Sharma 2016), *Eriosema chinense* (Aye 2019) (, *Erythrina suberosa* (Aye 2019), *Ficus religiosa* (Poudel 2015), *Glycine max* (Xiao 2011), *Glycomis pentaphylla* (Aye 2019), *Guazuma ulmifolia* (Augusti Boligon 2013), *Hippophae rhamnoides* (Panossian 2013), *illicium verum* (Huang 2010), *Justicia gendarussa* (Aye 2019), *Lantana camara* (A. T. Sharma 2016), *Leucas aspera* (Ramasamy 2012), *Millettia pendula* (Aye 2019) , *Moringa oleifera* (Kadhim 2014), *Musa acuminate* (Mordi 2016), *Ocimum sanctum* (Awasthi 2007), *Oroxylum indicum* (Shivprasad 2018), *Phyllanthus amarus* (Adomi 2017), *Piper nigrum* (Mohammed 2016), *Premna integrifolia* (Aye 2019), *Punica granatum* (Jung 2014), *Rumex dentatus* (A. T. Sharma 2016), *Rumex nepalensis* (Shrestha 2017), *Ruta graveolens* (Azalework 2017), *Sesbania bisp* (A. T. Sharma 2016), *Sesbania grandiflora* (Aye 2019), *Smilax zeylanica* (Shivprasad 2018), *Tadehagi treiquetrum* (Aye 2019), *Terminalia arjuna* (D. &. Gupta 2016), *Terminalia bellerica* (R. S. Gupta 2016), *tinospora cordifolia* (Naik 2014), *Vitex trifolia* (Aye 2019), *Woodfordia fruticose* (Shivprasad 2018), *Xanthium strumarium* (Fan 2019), *Zanthoxylum rhetsa* (Shivprasad 2018), *Zingiber officinale* (Singh 2008). obtained from GC-MS analysis were taken from various authentic research papers and tested for their biological activity and pharmacological activity for use as promising therapeutic compounds. The structures of these chemical compounds were obtained from online servers viz., PubChem (https://pubchem.ncbi.nlm.nih.gov/), and ChemSpider (https://www.chemspider.com/) web scraping technique is used for data retrieval.

2.2.2. WEB SCRAPING USING PYTHON

After compiling the metabolites from potential entheogenic plants, the next step was to find the appropriate canonical smiles for each metabolite. This entire process was automated

through python scripts designed to web scrape from several databases. The Canonical Smiles were scraped from the PubChem database using the PUG Rest Application Programming Interface (API). The script queried the name of the metabolites against the PubChem database and the obtained results were updated in the appropriated document. The criterion used to validate a canonical smile was such that the script will only accept the canonical smile if and only if there are no other dissimilar canonical smiles under the same name. The resulting document after the script was finished contained a number of missing entries. This either meant that the canonical smiles for those metabolites were simply not available in the PubChem database or there were multiple canonical smiles obtained and they differed from each other.

In order to remedy the missing entries, the next database that was scraped was ChEMBL. The web scraper queried the ChEMBL API in two ways: first and foremost, a direct query using the metabolites name; secondly, if the first attempt failed to furnish any results, the script would attempt to find a standard InChI key and use the InChI key to query the database again. Furthermore, the already obtained canonical smiles were used to procure a detailed report of the molecular weight, how many of the criteria of the Lipinski Rules were satisfied, and other necessary information. All of the obtained results were used to update the appropriate documents and saved.

2.2.3. STRUCTURAL RESOURCES

The proteins from SARS-CoV-2 were selected from literature which is the main protease in the apo form [PDB ID: 6M03] (Zhang 2020), The main protease complex with an inhibitor N3 [PDB ID: 6LU7] (Jin Z 2020), Spike glycoprotein with single receptor-binding domain [PDB ID:6VSB] (Wrapp D 2020), SARS protein receptor-binding domain, we have also selected the protein from host human cell which is responsible for the host-virus interaction, angiotensin-converting enzyme 2 (ACE2) receptor complex with spike receptor-binding domain [PDB ID:6LZG] (Wang Q 2020) and SARS spike protein receptor-binding domain [PDB ID:2GHV] (Hwang WC 2006) The crystal structures were retrieved from RCSB PDB. (https://www.rcsb.org). These were used as receptors**.**

2.2.4. PREDICTION DRUG-LIKENESS PROPERTIES

Drug-likeness of a chemical compound is equilibrium amongst the molecular properties of a compound which directly affects biological activity, pharmacodynamics, and

pharmacokinetics of a drug in the human body (Menezes JC 2011). The "drug-likeness" test was carried out using Lipinski's "Rule of Five", ro5 (Lipinski CA 2012). The distributions of the compound molecular weights (MW), calculated lipophilicity (logP), number of hydrogen bond acceptors (HBA), and number of hydrogen bond donors (HBD) were used to assess the "drug-likeness" of Compounds (Ntie-Kang 2013) Depending on these four molecular descriptors, the approach generates a vigilant about apparent absorption trouble; the rule states that most "druglike" molecules must have log P≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, and number of hydrogen bond donors ≤ 5. Molecules violating more than one of these rules may have problems with oral bioavailability (Paramashivam SK 2015). ADMETlab (http://admet.scbdd.com/calcpre/calc_rules/#) drug-likeness analysis module is designed for users to filter those chemical compounds that are not likely to be leads or drugs. The drug-likeness properties of the compounds were predicted using the ADMETlab online server based on the 'rule-of-five' given by Lipinski in these which shows the highest bandwidth has been selected for further analysis (Dong 2018).

2.2.5. ADME PROPERTIES PREDICTION

The predictive study of pharmacokinetics especially ADME, bioavailability, drug-likeness, and medicinal chemistry of ligands were carried out by using the SwissADME (http://www.swissadme.ch/) online tool developed by (B. M.-C. Daina A 2017) (M. O. Daina A 7 (2017 a)). The canonical SMILES string for each chemical was incorporated in this tool for the computational simulation. The tool predicts bioavailability radar as per six physicochemical properties such as lipophilicity, size, polarity, solubility, flexibility, and saturation to detect drug-likeness. The ADME properties viz. passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation as well as substrate or non-substrate of the permeability glycoprotein (P-gp) as detected positive or negative in the BOILED-Egg model within the tool developed by (Z. V. Daina A 2016) and (B. M.-C. Daina A 2017). The estimation of lipophilicity (Log p/w) parameters such as iLOGP was calculated for n-octanol and water on free energies of solvation as per the generalized-born and solvent accessible surface area (GB/SA) model developed by (M. O. Daina A 2014), XLOGP3 is an atomistic method including corrective factors and knowledge-based library developed by (Cheng T. 2007), WLOGP has been implemented for a purely atomistic method based on the fragment system of (Wildman SA 1999), M-LOGP is an archetype of topological method relying on a linear relationship with 13 molecular descriptors implemented as per researchers

(S. H. Moriguchi I 1992) (S. H. Moriguchi I 1994) and SILICOS-IT is an hybrid method, relying on 27 fragments and 7 topological descriptors (M. O. Daina A 7 (2017 a)). The Lipinski (Pfizer) filter is the pioneer rule-of-five has been incorporated in this tool from (Lipinski CA 2012)and this tool has also been inbuilt for the prediction of drug-likeness (M. O. Daina A 7 (2017 a)). The bioavailability radar for oral bioavailability prediction as per different physico-chemical parameters has been developed by SwissADME tool (B. M.-C. Daina A 2017) (M. O. Daina A 7 (2017 a)). The medicinal chemistry techniques prediction has based on the root of structural alert (Brenk R 2008), the pan assay interference compounds or PAINS structural alert (Baell JB 2010) or the Lilly MedChem (Bruns RF 2010) filters applied to cleanse chemical libraries of compounds most likely unstable, reactive, toxic, or prone to interfere with biological assays because unspecific frequent hitters, dyes or aggregators (Irwin JJ 2015). The synthetic accessibility (SA) score has based primarily on the assumption that the frequency of molecular fragments in 'really' obtainable molecules correlates with the ease of synthesis. The developed and validated method has been characterized through the molecule synthetic accessibility score, which observed between 1 and 10 easy and very difficult to make has been described by (S. A. Ertl P 2009).

2.2.6. TOXICITY PREDICTION

The predictive study of toxicity studies carried out by using pkCSM: predicting small-molecule pharmacokinetic properties using graph-based signatures web server (http://biosig.unimelb.edu.au/pkcsm/prediction). pkCSM uses the concept of graph-based structural signatures to study and predict a diverse and complementary range of Toxicity properties for novel chemical entities like AMES toxicity, human maximum tolerated dose, oral rat acute and chronic toxicity, hERG inhibition, hepatotoxicity, and skin sensitization (Pires 2018). Currently, along with a lack of efficacy, toxicity issues are the main reason for drug failure. Similar to how the incorporation of ADME screening into the early drug development pipeline drastically reduced failures (in the 80s and 90s pharmacokinetic failures were a leading cause of drug failures), consideration of toxicity issues early in the drug development process can mitigate these issues. Strong electrophiles, and functional groups that are prone to the formation of strong electrophilic metabolites, are often toxic and/or mutagenic. Chromophores such as quinolines may be phototoxic and lead to skin sensitization. Inhibition of human Ether-a-go-go related gene has been linked to the withdrawal of several drugs that led to cardiac complications and should be avoided (Pires 2018). Toxicity measurements are

important to consider relative to the concentration of a compound needed to exert a therapeutic effect. This is known as the Therapeutic Index/Window-the ratio of the dose that leads to lethality in 50% of the population (Rat LD50 in pkCSM) divided by the minimum effective dose for 50% of the population. Larger therapeutic indices are preferable since a much larger dose of a drug would need to be administered to reach the toxicity threshold than that needed to elicit the therapeutic effect (Pires 2018).

2.2.7. IN SILICO PREDICTION OF ACTIVITY SPECTRA FOR SUBSTANCES (PASS)

The pharmacological activities of the compounds were predicted individually with the help of a computer program, PASS (Predicted Activity Spectrum for Substances) server (http://www.pharmaexpert.ru/passonline/) Software estimates the predicted activity spectrum of a compound as probable activity (Pa) and probable inactivity (Pi). Prediction of this spectrum by PASS was based on structural activity relationship (SAR) analysis of the training set containing more than 205,000 compounds having more than 3750 kinds of biological activities (Goel 2011). The compounds showing higher Pa value than Pi are the only constituents considered as possible for a particular pharmacological activity (Khurana 2011) (Goel 2011) This research majorly concentrated on the antiviral activity.

2.2.8. BIOACTIVITY SCORE PREDICTION

The predictive study of Bioactivity studies carried out by using the Molinspiration web server. Molinspiration supports the internet chemistry community by the calculation of important molecular properties such as logP, polar surface area, a number of hydrogen bond donors and acceptors, and others, as well as prediction of bioactivity score for the most important drug targets like GPCR ligands, kinase inhibitors, ion channel modulators and nuclear receptors (R. B. Ertl P 2000). Bioactivity of the drug, can be checked by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor legend, a kinase inhibitor, protease inhibitor, enzyme inhibitor. All the parameters were checked with the help of the software Molinspiration drug-likeness score online (www.molinspiration.com).

2.3. MOLECULAR DOCKING:

PyRx is open source software and it is written in Python programming language and it can run on nearly any modern computer, from PC (personal computer) to supercomputer. The binary distribution of PyRx version 0.8 for Windows available free from http://pyrx.sourceforge.net. Molecular screening of all the compound libraries was performed using PyRx software by autodock wizard as the engine for docking (S.Dallakyan 2015.), (Pagadala NS 2017). During the docking period, the ligands were considered to be flexible and the protein was considered to be rigid. The configuration file for the grid parameters was generated using the Auto Grid engine in Pyrex. The application was also used to know/predict the amino acids in the active site of the protein that interact with the ligands. The results of less than 1.0Å in positional root-mean-square deviation (RMSD) were considered ideal and clustered together for finding the favorable binding. The highest binding energy (most negative) was considered as the ligand with a maximum binding affinity (Chandel 2020). In this study Autodock vina, the wizard was used in the virtual screening of Molecular screening.

3. RESULTS:

Ethnomedicinal plants have medicinal purposes since ancient times and are known for their antiviral properties and more tolerable side effects. The novel Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, which can infect humans and vertebrate animals. The outbreak of COVID-19 is wreaking havoc worldwide due to inadequate risk assessment regarding the urgency of the situation (Chandel 2020). The infection hampers liver, respiratory, central nervous system, and digestive of humans and animals. It has killed 1,122,953 of people around the globe with an increase in death rate every single day.

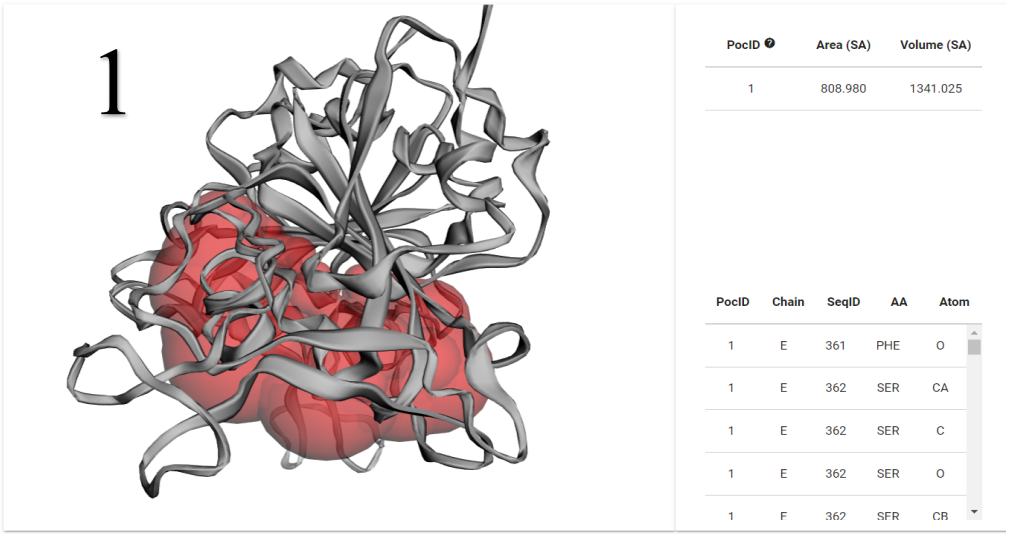
3.1. 1. STRUCTURE RETRIEVAL OF THE TARGET

In our study the three-dimensional protein structures of SARS-CoV-2 were selected. Protein targets from literature are the main protease in apo form [PDB ID: 6M03]. The main protease complex with an inhibitor N3 [PDB ID: 6LU7]. Spike glycoprotein with single receptor-binding domain [PDB ID: 6VSB]. SARS protein receptor-binding domain, we have also selected the protein from host human cell, which is responsible for the host virus interaction, angiotension-converting enzyme 2 (ACE2) receptor complexes with spike receptor-binding domain [PDB ID: 6LZG]. SARS spike protein receptor-binding domain [PDB ID: 2GHV].

The crystal structures were retrieved from RCSB PDB. (https://www.rcsb.org). These were used as receptors**.**

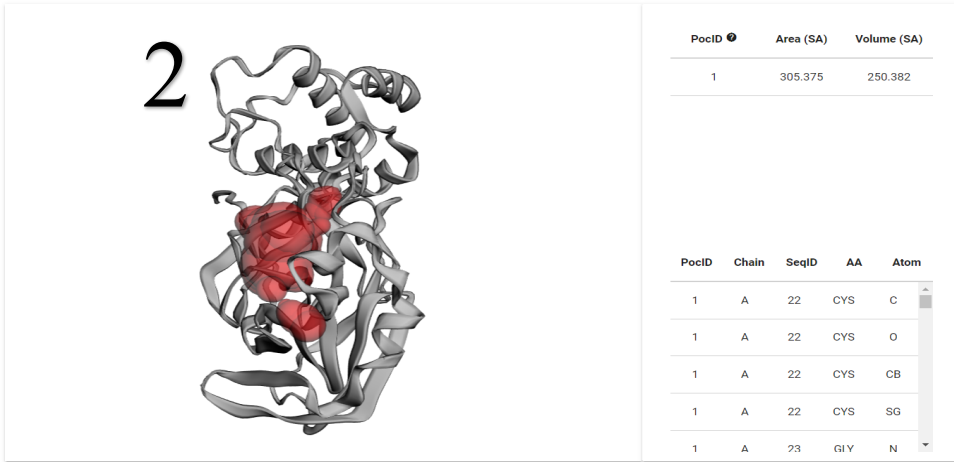
3.1.2. RECEPTOR ACTIVE SITE PREDICTION

Active site, amino acid residues of proteins with PDB IDs: 2GHV, 6M03, 6VSB, 6LZG, and 6LU7 were identified using an online server CASTp tool .The pockets of these five proteins are shown in figure 1.



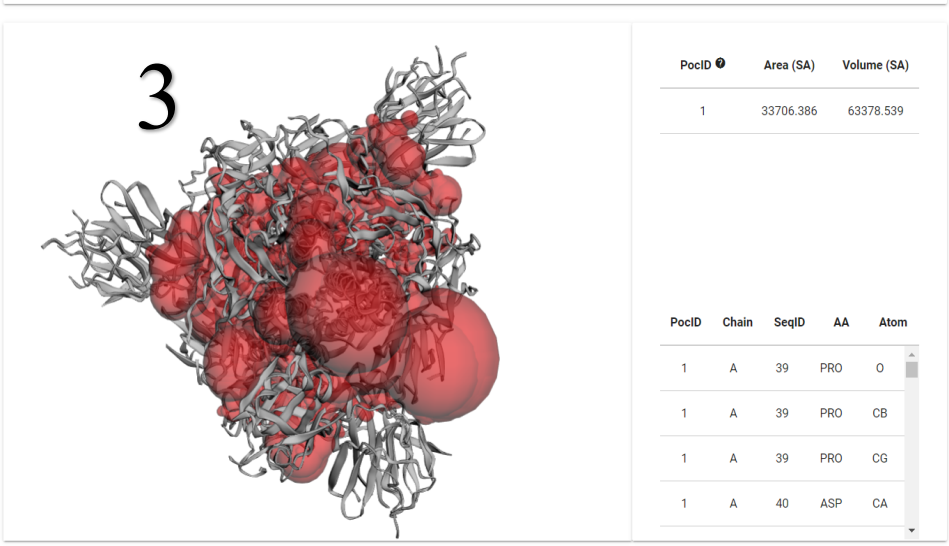
PocID	Area (SA)	Volume (SA)
1	808.980	1341.025

PocID	Chain	SeqID	AA	Atom
1	E	361	PHE	O
1	E	362	SER	CA
1	E	362	SER	C
1	E	362	SER	O
1	E	362	SER	CB



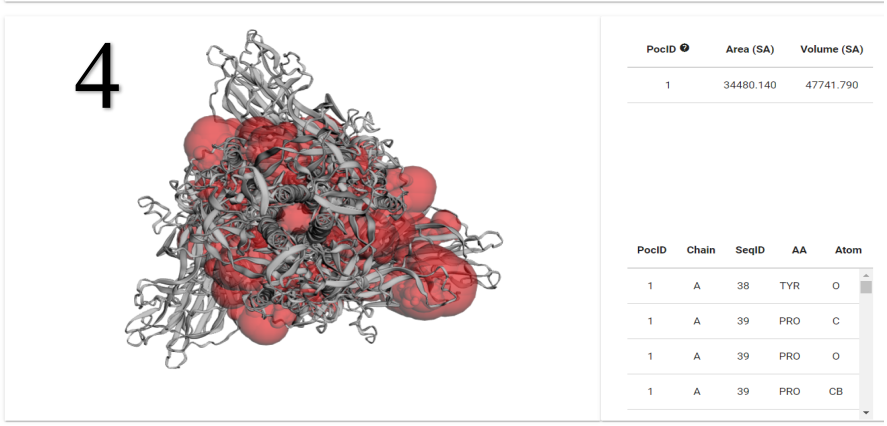
PocID	Area (SA)	Volume (SA)
1	305.375	250.382

PocID	Chain	SeqID	AA	Atom
1	A	22	CYS	C
1	A	22	CYS	O
1	A	22	CYS	CB
1	A	22	CYS	SG
1	A	23	GLY	N



PocID	Area (SA)	Volume (SA)
1	33706.386	63378.539

PocID	Chain	SeqID	AA	Atom
1	A	39	PRO	O
1	A	39	PRO	CB
1	A	39	PRO	CG
1	A	40	ASP	CA



PocID	Area (SA)	Volume (SA)
1	34480.140	47741.790

PocID	Chain	SeqID	AA	Atom
1	A	38	TYR	O
1	A	39	PRO	C
1	A	39	PRO	O
1	A	39	PRO	CB

PocID	Area (SA)	Volume (SA)
1	225.365	182.909

PocID	Chain	SeqID	AA	Atom
1	A	24	THR	C
1	A	24	THR	O
1	A	24	THR	OG1
1	A	25	THR	CA

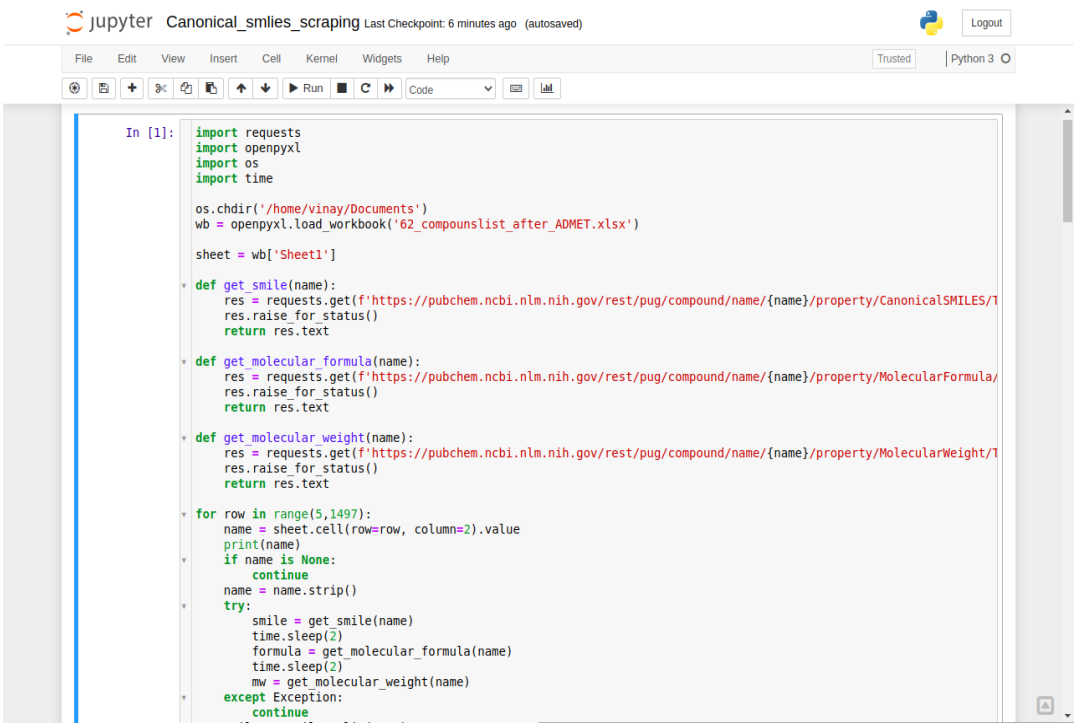
Figure 1: CastP images 1)2GHV, 2)6M03, 3)6VSB, 4)6LZG, 5)6LU7

3.2. ETHANOMEDICINAL PLANTS RETRIEVAL OF GC-MS LIST FROM LITERATURE

From the Literature survey phytochemicals from various ethnomedicinal plants were screened. Around 1378 phytochemical compounds were retrieved based on GC-MS data and used for our study.

3.2.1.WEB SCRAPING TECHNIQUE USING PYTHON FOR RETRIEVAL OF PHYTOCOMPOUNDS STRUCTURE

To retrieve the chemical structure of phytochemicals python web scrapping technique was used. Python scraping code was developed for the retrieval of phytochemical compounds from the database sources like PubChem, Chembl, and ChemSpider. Out of 1378 phytocompounds 698 phytocompounds smile structures, Molecular formula , Molecular weight , ID data were retrieved. All the required data sets retrieved from web scrapping using python and authenticated. The code for python web scraping is depicted in the picture.



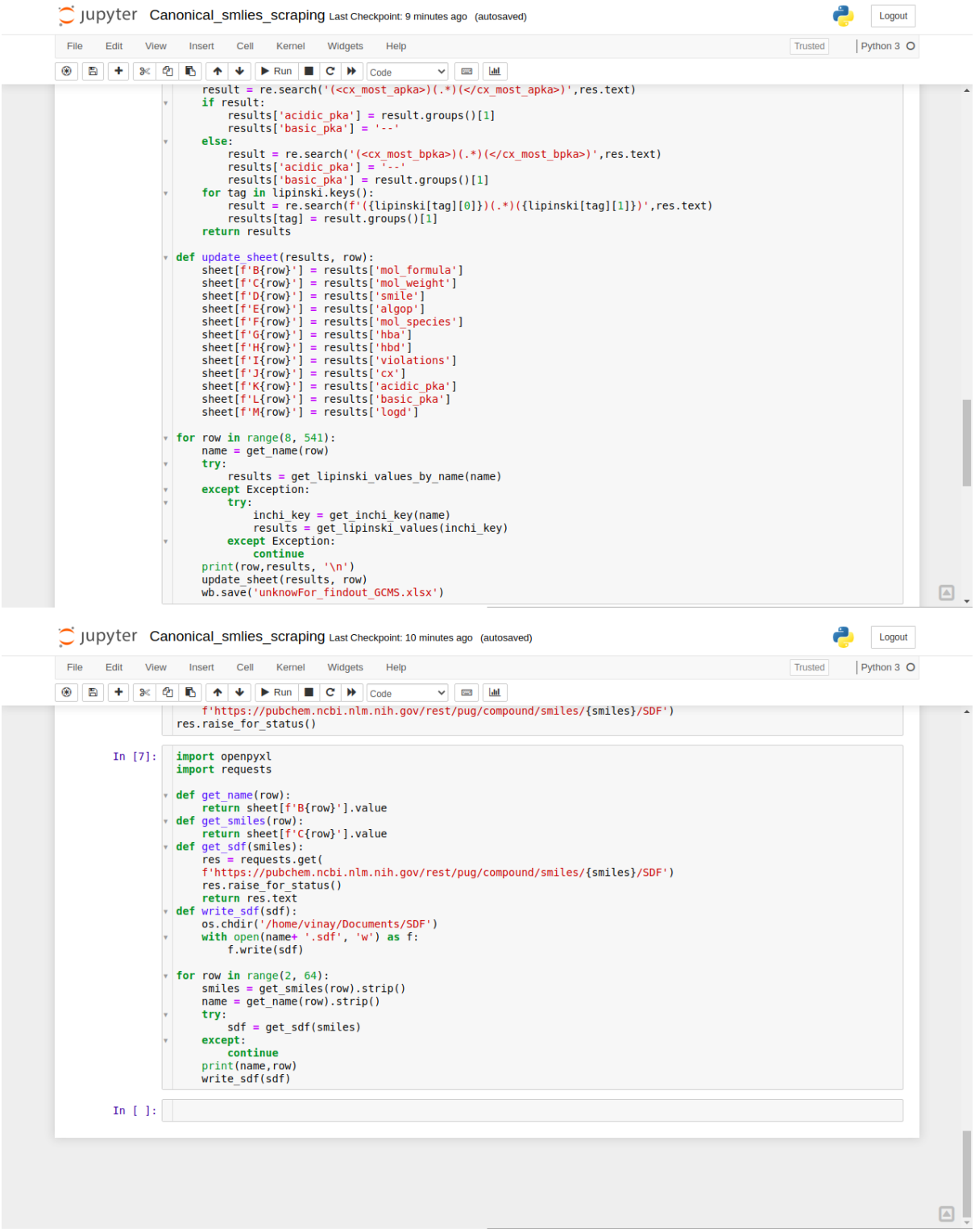


Fig.2. Molecular chemical structure retrieving through the python web scraping method.

3.2.2. DRUGLIKLINESS TEST PREDICTION USING ADMETLAB WEB SERVER

Our study shows 52 phytocompounds passes all Druglikliness, ADMET properties in acceptable ranges were selected. Out of 57 plants, 30 plants have one or the other 52

phytocompounds and the lists of plants for compounds are represented in Table1. Preliminarily screening of all the 649 phytocompounds was subjected to the ADMETlab web server for drug-likeness analysis. Around 410 phytocompounds passed the Lipinski rule of 5 with a 100% width score and no violation of pharmacological property. Based on drug-likeness, 52 phytocompounds could be identified as promising drug lead in the early stage of drug discovery [listed in Table 2].

TABLE 1: LIST OF PHYTOCHEMICAL COMPOUNDS SELECTED BASED ON DRUGLIKLINESS TEST.

Sl.No	Plants name	Phytocompounds lists with respect to plants
1	*Achyranthes aspera*	Patchouli alcohol
2	*Andrographis Paniculata*	1-hexyl-2-nitrocyclohexane
3	*Avicennia marina*	nonanoic acid
4	*Azadirachta indica*	Nimbidiol, Nimbolide
5	*Bacopa monnieri*	2,4-Quinolinediol
6	*Canthium coromandelicum*	Ethyl iso-allocholate
7	*Carica papaya*	Caffeic acid, p-Coumaric acid, Protocatechuic acid
8	*Carissa edulis*	gamma-eudesmol
9	*Cinnamomum zeylanicum*	10-epi-eudesmol, Cadinol, Cubenol, Globulol, Spathulenol
10	*Croton oblongifolius*	Furanocembranoid 3
11	*Erythrina suberosa*	Millettilone A, 3R-Claussequinone
12	*Ficus religiosa*	Cadinol
13	*Glycine max*	nonanoic acid
14	*Guazuma ulmifolia*	Cubenol, Spathulenol, Butylated hydroxytoluene, Globulol
15	*Hippophae rhamnoides*	Caffeic acid, gallic acid
16	*Lantana camara*	Glaucyl alcohol
17	*Leucas aspera*	(E,E)-farnesol, nerolidol, nonanoic acid, decanoic acid
18	*Millettia pendula*	3R-Claussequinone, Millettilone A, Pendulone
19	*Moringa oleifera*	Methyl 2,4,6-trihydroxybenzoate
20	*Ocimum sanctum*	Cadinol, cis-Sesquisabinene hydrate, nerolidol
21	*Piper nigrum*	2-Pinen-4-ol, Cedr-8-en-13-ol, Cedr-8-en-15-ol, exo-2-Hydroxycineole acetate, Santalol, Spathulenol
22	*Rumex nepalensis*	7-hydroxy-2,5-dimethyl 4H-1-Benzopyran-4-one

Sl.No	Plants name	Phytocompounds lists with respect to plants
23	*Ruta graveolens*	Acetic acid, dec-2-yl ester:, Ficusin,Isopsoralen
24	*Sesbania bispinosa*	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester: Glaucic acid,
25	*Sesbania grandiflora*	nonanoic acid
26	*Tadehagi treiquetrum*	Dihydroechioidinin
27	*Terminalia arjuna*	Cadinol, Globulol, 2,4-ditert-butylphenol
28	*Tinospora cordifolia*	Berberine
29	*Xanthium strumarium*	(-)-simulanol, Caffeic acid, Protocatechuic acid, scopoletin, sibirolide A, sibirolide B, caffeic acid ethyl ester, formononetin, inusoniolide
30	*Zingiber officinale*	nerolidol, Zingiberenol, Beta-eudesmol, Guaiol

TABLE 2: ADMETLAB PROPERTY OF SCEEREND PHYTOCHEMICAL

Sl.no	COMPOUNDS	MW	HBA	HBD	logP	RB	Tpsa	Score%
1	(-)-simulanol	388.416	7	3	2.633	7	97.61	width:100.0%;
2	(E,E)-farnesol	222.372	1	1	4.398	7	20.23	width:100.0%;
3	10-epi-eudesmol	222.372	1	1	3.92	1	20.23	width:100.0%;
4	1-hexyl-2-nitrocyclohexane	213.321	2	0	3.792	6	43.14	width:100.0%;
5	2,4-ditert-butylphenol	206.329	1	1	3.987	2	20.23	width:100.0%;
6	2,4-Quinolinediol	161.16	2	2	1.234	0	53.09	width:100.0%;
7	2-Pinen-4-ol	152.237	1	1	1.97	0	20.23	width:100.0%;
8	3R-Claussequinone	286.283	5	1	1.552	2	72.83	width:100.0%;
9	7-hydroxy-2,5-dimethyl 4H-1-Benzopyran-4-one	190.198	3	1	2.115	0	50.44	width:100.0%;
10	Acetic acid, dec-2-yl ester	200.322	2	0	3.689	9	26.3	width:100.0%;

Sl.no	COMPOUNDS	MW	HBA	HBD	logP	RB	Tpsa	Score%
11	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester	292.419	3	1	4.093	6	46.53	width:100.0%;
12	Berberine	336.367	4	0	3.096	2	40.8	width:100.0%;
13	Beta-eudesmol	222.372	1	1	3.92	1	20.23	width:100.0%;
14	Butylated hydroxytoluene	220.356	1	1	4.296	2	20.23	width:100.0%;
15	Cadinol	222.372	1	1	3.776	1	20.23	width:100.0%;
16	Caffeic acid	180.159	3	3	1.196	2	77.76	width:100.0%;
17	caffeic acid ethyl ester	208.213	4	2	1.674	4	66.76	width:100.0%;
18	Cedr-8-en-13-ol	220.356	1	1	3.387	1	20.23	width:100.0%;
19	Cedr-8-en-15-ol	220.356	1	1	3.387	1	20.23	width:100.0%;
20	cis-Sesquisabinene hydrate	222.372	1	1	3.92	4	20.23	width:100.0%;
21	Cubenol	222.372	1	1	3.776	1	20.23	width:100.0%;
22	decanoic acid	172.268	1	1	3.212	8	37.3	width:100.0%;
23	Dihydroechioidinin	286.283	5	2	2.813	2	75.99	width:100.0%;
24	Ethyl iso-allocholate	436.633	5	3	3.927	6	86.99	width:100.0%;
25	exo-2-Hydroxycineole acetate	212.289	3	0	2.286	2	35.53	width:100.0%;
26	Ficusin	186.166	3	0	2.539	0	43.35	width:100.0%;
27	formononetin	268.268	4	1	3.174	2	59.67	width:100.0%;
28	Furanocembranoid 3	336.472	4	3	3.24	1	73.83	width:100.0%;
29	gallic acid	170.12	4	4	0.502	1	97.99	width:100.0%;
30	gamma-eudesmol	222.372	1	1	4.064	1	20.23	width:100.0%;
31	Glaucic acid	234.339	1	1	3.79	2	37.3	width:100.0%;

Sl.no	COMPOUNDS	MW	HBA	HBD	logP	RB	Tpsa	Score%
32	Glaucyl alcohol	220.356	1	1	3.698	2	20.23	width:100.0%;
33	Globulol	222.372	1	1	3.466	0	20.23	width:100.0%;
34	Guaiol	222.372	1	1	3.92	1	20.23	width:100.0%;
35	inusoniolide	250.338	3	0	2.89	4	43.37	width:100.0%;
36	Isopsoralen	186.166	3	0	2.539	0	43.35	width:100.0%;
37	Methyl 2,4,6-trihydroxybenzoate	184.147	5	3	0.59	2	86.99	width:100.0%;
38	Millettilone A	316.309	6	1	1.697	3	82.06	width:100.0%;
39	nerolidol	222.372	1	1	4.396	7	20.23	width:100.0%;
40	Nimbidiol	274.36	3	2	3.768	0	57.53	width:100.0%;
41	Nimbolide	466.53	7	0	3.743	4	92.04	width:100.0%;
42	nonanoic acid	158.241	1	1	2.822	7	37.3	width:100.0%;
43	Patchouli alcohol	222.372	1	1	3.61	0	20.23	width:100.0%;
44	p-Coumaric acid	164.16	2	2	1.49	2	57.53	width:100.0%;
45	Pendulone	316.309	6	1	1.526	3	82.06	width:100.0%;
46	Protocatechuic acid	154.121	3	3	0.796	1	77.76	width:100.0%;
47	Santalol	220.356	1	1	3.698	4	20.23	width:100.0%;
48	scopoletin	192.17	4	1	1.507	1	59.67	width:100.0%;
49	sibirolide A	244.29	3	0	2.029	0	43.37	width:100.0%;
50	sibirolide B	244.29	3	1	1.946	0	46.53	width:100.0%;
51	Spathulenol	220.356	1	1	3.386	0	20.23	width:100.0%;
52	Zingiberenol	222.372	1	1	4.086	4	20.23	width:100.0%;

3.2.4. ADME TEST PREDICTION USING SWISS ADME WEB SERVER

The ADME test was carried out in the SWISS ADME web server for all the 410 phytocompounds and screened to 198 phytocompounds based on the following criteria. The results on predictive data for pharmacokinetics, bioavailability, drug-likeness, and medicinal chemistry friendliness were established for major 52 phytocompounds listed in Table 3. For pharmacokinetics prediction, the gastrointestinal (GI) absorption rate was obtained and all 52 phytocompounds were showing high absorption. The blood-brain permeability was observed as Yes or No, permeation as well as substrate or non-substrate of the permeability glycoprotein (P-gp) as yes or no. CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitor all the inhibitors are showed as Yes or No. Skin Permeability log Kp (cm/s) more the negative value means the less permeability.

TABLE 3: PHARMACOKINETICS PREDICTION OF PHYTOLIGANDS

Sl. no	COMPOUNDS	GI absorption	BBBpermeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Skin Permiability log Kp (cm/s)
1	(-)-simulanol	High	No	Yes	No	No	No	Yes	No	-7.33
2	(E,E)-farnesol	High	Yes	No	Yes	No	Yes	No	No	-3.81
3	10-epi-eudesmol	High	Yes	No	No	No	No	No	No	-5.17
4	1-hexyl-2-nitrocyclohexane	High	Yes	No	No	No	No	No	No	-4.21
5	2,4-ditert-butylphenol	High	Yes	No	No	No	No	Yes	No	-3.87
6	2,4-Quinolinediol	High	Yes	No	Yes	No	No	No	No	-6.79
7	2-Pinen-4-ol	High	Yes	No	No	No	No	No	No	-4.99
8	3R-Claussequinone	High	No	No	Yes	No	No	No	No	-6.9

Sl. no	COMPOUNDS	GI absorption	BBBpermeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Skin Permiability log Kp (cm/s)
9	7-hydroxy-2,5-dimethyl 4H-1-Benzopyran-4-one	High	Yes	No	Yes	No	No	No	No	-6.09
10	Acetic acid, dec-2-yl ester	High	Yes	No	No	No	No	No	No	-4.32
11	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester	High	Yes	No	No	No	No	Yes	No	-4.66
12	Berberine	High	Yes	Yes	Yes	No	No	Yes	Yes	-5.78
13	Beta-eudesmol	High	Yes	No	No	No	Yes	No	No	-5
14	Butylated hydroxytoluene	High	Yes	No	No	No	No	Yes	No	-4.02
15	Cadinol	High	Yes	No	No	Yes	No	No	No	-5.29
16	Caffeic acid	High	No	No	No	No	No	No	No	-6.58
17	caffeic acid ethyl ester	High	Yes	No	No	No	No	No	No	-5.75
18	Cedr-8-en-13-ol	High	Yes	No	No	No	Yes	No	No	-5.24
19	Cedr-8-en-15-ol	High	Yes	No	No	No	Yes	No	No	-5.25
20	cis-Sesquisabinene hydrate	High	Yes	No	No	Yes	Yes	No	No	-4.76
21	Cubenol	High	Yes	No	No	Yes	Yes	No	No	-5.03
22	decanoic acid	High	Yes	No	No	No	No	No	No	-4.45

Sl. no	COMPOUNDS	GI absorption	BBBpermeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Skin Permiability log Kp (cm/s)
23	Dihydroechioidinin	High	Yes	No	Yes	Yes	No	No	Yes	-5.96
24	Ethyl iso-allocholate	High	No	Yes	No	No	No	No	No	-7.04
25	exo-2-Hydroxycineole acetate	High	Yes	No	No	No	No	No	No	-6.33
26	Ficusin	High	Yes	No	Yes	No	No	No	No	-6.25
27	formononetin	High	Yes	No	Yes	No	No	Yes	Yes	-5.95
28	Furanocembranoid 3	High	Yes	Yes	No	No	No	Yes	No	-6.15
29	gallic acid	High	No	No	No	No	No	No	Yes	-6.84
30	gamma-eudesmol	High	Yes	No	No	No	No	No	No	-5.25
31	Glaucic acid	High	Yes	No	No	No	Yes	No	No	-5.4
32	Glaucyl alcohol	High	Yes	No	No	Yes	Yes	No	No	-5.28
33	Globulol	High	Yes	No	No	Yes	No	No	No	-5
34	Guaiol	High	Yes	No	No	No	No	No	No	-5.48
35	inusonioliide	High	Yes	No	No	No	No	No	No	-6.26
36	Isopsoralen	High	Yes	No	Yes	No	No	No	No	-5.96
37	Methyl 2,4,6-trihydroxybenzoate	High	No	No	No	No	No	No	No	-6.53
38	Millettilone A	High	No	No	No	No	No	No	No	-7.48
39	nerolidol	High	Yes	No	Yes	No	Yes	No	No	-4.23
40	Nimbidiol	High	Yes	Yes	No	No	No	Yes	No	-5.03
41	Nimbolide	High	No	Yes	No	No	No	No	No	-7.61
42	nonanoic acid	High	Yes	No	No	No	No	No	No	-4.84
43	Patchouli alcohol	High	Yes	No	No	No	Yes	No	No	-4.78

Sl. no	COMPOUNDS	GI absorption	BBBpermeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Skin Permiability log Kp (cm/s)
44	p-Coumaric acid	High	Yes	No	No	No	No	No	No	-6.26
45	Pendulone	High	No	No	Yes	No	No	No	No	-6.95
46	Protocatechuic acid	High	No	No	No	No	No	No	Yes	-6.42
47	Santalol	High	Yes	No	No	Yes	Yes	No	No	-4.14
48	scopoletin	High	Yes	No	Yes	No	No	No	No	-6.39
49	sibirolide A	High	Yes	No	No	No	No	No	No	-6.8
50	sibirolide B	High	Yes	No	No	No	No	No	No	-6.97
51	Spathulenol	High	Yes	No	No	Yes	No	No	No	-5.44
52	Zingiberenol	High	Yes	No	No	No	Yes	No	No	-4.63

3.2.5. BIOAVAILABILITY PREDICTION USING SWISS ADME WEB SERVER

The bioavailability predictions of 52 phytocompounds are listed in Table 4: Bioavailability Scores of all 52 phytocompounds in the range of 0.55 to 0.85; which is a good range of score for bioavailability. Water solubility LogS of all 52 phytocompounds are less than -10 and water solubility class are in the range of soluble, moderate soluble, very soluble were selected. The lipophilicity of all the 52 phytocompounds; iLOGP, XLOGP3, WLOGP, MLOGP, Silicos-IT LogP should be less than 5 to qualify the prediction. It was observed that the G-Protein Coupled Receptor activity ranges from -1.11 to -0.344; Kinase inhibitor activity ranges from -84 to 0.05; Protease inhibitor activity ranges from -1.25 to -0.23, and the enzyme inhibitors activity are from -0.37 to 0.82 for the designed compounds was obtained. The bioactivity score based on the Molinspiration study for all the 52 compounds were between 0.00 and -0.50. Nearly 98% of the molecule were presumed to have bioactivity scores between -0.50 to 0.00 are expected to be moderately active, 2% of compounds exhibit good bioactive potential.

TABLE 4: BIOAVAILABILITY PREDICTION OF PHYTOLIGANDS COMPARED TO SYNTHETIC LIGANDS

Sl. no	COMPOUNDS	Bioavailability Score	Water solubility LogS	water solubility Class	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT LogP
1	(-)-simulanol	0.55	-3.29	Soluble	3.09	1.88	2.2	0.78	3.23
2	(E,E)-farnesol	0.55	-4.17	Moderately soluble	3.71	5.42	4.4	3.86	4.21
3	10-epi-eudesmol	0.55	-3.36	Soluble	3.18	3.5	3.92	3.67	3.35
4	1-hexyl-2-nitrocyclohexane	0.55	-3.77	Soluble	2.79	4.77	3.79	2.35	1.58
5	2,4-ditert-butylphenol	0.55	-4.55	Moderately soluble	3.08	5.19	3.99	3.87	3.81
6	2,4-Quinolinediol	0.55	-1.9	Very soluble	1.13	0.7	1.23	1.04	2.1
7	2-Pinen-4-ol	0.55	-2.77	Soluble	2.26	3.16	1.97	2.3	1.86
8	3R-Claussequinone	0.85	-2.71	Soluble	1.99	1.62	1.55	0.42	2.4
9	7-hydroxy-2,5-dimethyl 4H-1-Benzopyran-4-one	0.55	-2.76	Soluble	1.91	1.93	2.12	0.82	2.88
10	Acetic acid, dec-2-yl ester	0.55	-3.33	Soluble	3.51	4.51	3.69	3.15	3.48
11	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester	0.55	-4.5	Moderately soluble	3.75	4.82	4.09	3.77	4.69
12	Berberine	0.55	-4.55	Moderately soluble	0	3.62	3.1	2.19	3.74
13	Beta-eudesmol	0.55	-3.51	Soluble	3.11	3.74	3.92	3.67	3.64

Sl. no	COMPOUNDS	Bioavailability Score	Water solubility LogS	water solubility Class	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT LogP
14	Butylated hydroxytoluene	0.55	-4.56	Moderately soluble	3.33	5.1	4.3	4.12	4.34
15	Cadinol	0.55	-3.26	Soluble	3.15	3.34	3.78	3.67	3.22
16	Caffeic acid	0.56	-1.89	Very soluble	0.97	1.15	1.09	0.7	0.75
17	caffeic acid ethyl ester	0.55	-2.78	Soluble	2.04	2.56	1.57	1.3	1.64
18	Cedr-8-en-13-ol	0.55	-3.28	Soluble	2.94	3.39	3.39	3.67	3.27
19	Cedr-8-en-15-ol	0.55	-3.26	Soluble	2.9	3.37	3.39	3.67	3.27
20	cis-Sesquisabinene hydrate	0.55	-3.53	Soluble	3.37	4.08	3.92	3.67	4.01
21	Cubenol	0.55	-3.48	Soluble	3.24	3.7	3.78	3.67	3.22
22	decanoic acid	0.85	-2.96	Soluble	2.5	4.09	3.21	2.58	2.63
23	Dihydroechioidinin	0.55	-3.76	Soluble	2.35	2.94	2.49	0.96	2.57
24	Ethyl iso-allocholate	0.55	-3.86	Soluble	4.03	2.71	3.93	3.46	3.49
25	exo-2-Hydroxycineole acetate	0.55	-2.15	Soluble	2.82	1.78	2.29	1.88	2.32
26	Ficusin	0.55	-2.73	Soluble	2.01	1.67	2.54	1.48	2.91
27	formononetin	0.55	-3.73	Soluble	2.49	2.8	3.17	1.33	3.52
28	Furanocembranoid 3	0.55	-3.97	Soluble	2.98	3.1	3.24	1.95	2.88
29	gallic acid	0.56	-1.64	Very soluble	0.21	0.7	0.5	-0.16	-0.2
30	gamma-eudesmol	0.55	-3.29	Soluble	3.12	3.39	4.06	3.67	3.75
31	Glaucic acid	0.85	-3.23	Soluble	2.68	3.28	3.79	3.35	3.05
32	Glaucyl alcohol	0.55	-3.17	Soluble	3.11	3.33	3.7	3.56	3.51
33	Globulol	0.55	-3.57	Soluble	3.08	3.74	3.47	3.81	3

Sl. no	COMPOUNDS	Bioavailability Score	Water solubility LogS	water solubility Class	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT LogP
34	Guaiol	0.55	-3.09	Soluble	3.29	3.07	3.92	3.67	3.35
35	inusoniolide	0.55	-2.52	Soluble	2.51	2.21	2.89	2.47	3.14
36	Isopsoralen	0.55	-2.99	Soluble	2.03	2.08	2.54	1.48	2.91
37	Methyl 2,4,6-trihydroxybenzoate	0.55	-1.99	Very soluble	1.19	1.26	0.59	0.18	0.28
38	Millettilone A	0.56	-2.46	Soluble	2.25	1.05	1.37	-0.15	2.02
39	nerolidol	0.55	-3.8	Soluble	3.64	4.83	4.4	3.86	4.21
40	Nimbidiol	0.55	-4.37	Moderately soluble	2.14	4.14	3.77	2.59	3.59
41	Nimbolide	0.55	-3.94	Soluble	3.51	2.17	3.74	2.28	3.83
42	nonanoic acid	0.85	-2.51	Soluble	2.3	3.42	2.82	2.28	2.2
43	Patchouli alcohol	0.55	-3.77	Soluble	2.96	4.05	3.61	3.81	3.4
44	p-Coumaric acid	0.85	-2.02	Soluble	0.95	1.46	1.38	1.28	1.22
45	Pendulone	0.56	-2.93	Soluble	2.4	1.8	1.53	-0.15	2.42
46	Protocatechuic acid	0.56	-1.86	Very soluble	0.66	1.15	0.8	0.4	0.26
47	Santalol	0.55	-4.05	Moderately soluble	3.15	4.94	3.7	3.56	3.95
48	scopoletin	0.55	-2.46	Soluble	1.86	1.53	1.51	0.76	1.94
49	sibirolide A	0.55	-2.24	Soluble	2.34	1.4	2.03	2.38	2.91
50	sibirolide B	0.55	-2.09	Soluble	2.58	1.16	1.95	2.38	2.31
51	Spathulenol	0.55	-3.17	Soluble	2.88	3.11	3.39	3.67	3.27
52	Zingiberenol	0.55	-3.64	Soluble	3.39	4.26	4.09	3.56	3.61

3.2.6. MEDICINAL CHEMISTRY PREDICTION USING SWISS ADME WEB SERVER

Medicinal chemistry predictions of all the 52 phytocompounds are in Table 5. The pan assay interference compounds, or PAINS most likely unstable, reactive, toxic alerts and BRENK filter which is based on root structural alert were checked. Leadlikliness violation alert also predicted more the violation less Leadlikliness. Molecule synthetic accessibility score, which observed between 1, is easy and 10 is very difficult.

TABLE 5: MEDICINAL CHEMISTRY PREDICTION OF PHYTOLIGANDS COMPARED TO SYNTHETIC LIGANDS

Sl.no	COMPOUNDS	PAINS #alerts	Brenk #alerts	Leadlikeness #violations	Synthetic Accessibility
1	(-)-simulanol	0	0	1	4.25
2	(E,E)-farnesol	0	1	2	3.17
3	10-epi-eudesmol	0	1	1	4.08
4	1-hexyl-2-nitrocyclohexane	0	2	2	3.39
5	2,4-ditert-butylphenol	0	0	2	1.43
6	2,4-Quinolinediol	0	0	1	1.51
7	2-Pinen-4-ol	0	1	1	4.47
8	3R-Claussequinone	1	1	0	3.51
9	7-hydroxy-2,5-dimethyl 4H-1-Benzopyran-4-one	0	0	1	2.64
10	Acetic acid, dec-2-yl ester	0	0	3	2.48
11	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester	0	0	1	2.13
12	Berberine	0	1	1	3.14
13	Beta-eudesmol	0	1	2	3.38
14	Butylated hydroxytoluene	0	0	2	1.48
15	Cadinol	0	1	1	4.29
16	Caffeic acid	1	2	1	1.81
17	caffeic acid ethyl ester	1	2	1	2.2
18	Cedr-8-en-13-ol	0	1	1	5.44
19	Cedr-8-en-15-ol	0	1	1	5.32
20	cis-Sesquisabinene hydrate	0	1	2	3.82
21	Cubenol	0	1	2	4.34
22	decanoic acid	0	0	3	1.67
23	Dihydroechioidinin	0	0	0	3.14

Sl.no	COMPOUNDS	PAINS #alerts	Brenk #alerts	Leadlikeness #violations	Synthetic Accessibility
24	Ethyl iso-allocholate	0	0	1	5.39
25	exo-2-Hydroxycineole acetate	0	0	1	4.28
26	Ficusin	0	1	1	3.06
27	formononetin	0	0	0	2.81
28	Furanocembranoid 3	0	1	0	6.27
29	gallic acid	1	1	1	1.22
30	gamma-eudesmol	0	1	1	3.88
31	Glaucic acid	0	2	1	4.28
32	Glaucyl alcohol	0	1	1	4.48
33	Globulol	0	0	2	3.58
34	Guaiol	0	1	1	4.48
35	inusoniolide	0	2	0	4.21
36	Isopsoralen	0	1	1	3.07
37	Methyl 2,4,6-trihydroxybenzoate	0	0	1	1.4
38	Millettilone A	1	1	0	3.9
39	nerolidol	0	1	2	3.53
40	Nimbidiol	1	1	1	3.13
41	Nimbolide	0	2	1	6.07
42	nonanoic acid	0	0	1	1.57
43	Patchouli alcohol	0	0	2	3.73
44	p-Coumaric acid	0	1	1	1.61
45	Pendulone	1	1	0	3.67
46	Protocatechuic acid	1	1	1	1.07
47	Santalol	0	1	2	4.52
48	scopoletin	0	1	1	2.62
49	sibirolide A	0	1	1	4.37
50	sibirolide B	0	1	1	4.78
51	Spathulenol	0	1	1	3.78
52	Zingiberenol	0	1	2	4.15

3.2.7. TOXICITY TEST USING PKCSM WEB SERVER

Meanwhile, the toxicity of 198 phytocompounds is tested using pkCSM: predicting small-molecule pharmacokinetic properties using graph-based signatures web server. Similarly, 52 phytocompounds were predicted as good compounds out of 198 phytocompounds and listed in Table 6: AMES /Toxicity in 52 phytocompounds shows non-mutagenic. Max. tolerated dose (human) less than or equal to 0.477 log(mg/kg/day) is considered to be low and high if

greater than 0.477 log(mg/kg/day) in these all 52 phytocompounds comes in the lower range. To determine whether hERG I inhibitor and hERG II inhibitor present or not, and in these 52 phytocoumpounds hERG I and hERG II inhibitor is absent. Oral Rat Acute Toxicity (LD50) the lethal dosage values (LD50) are a standard measurement of acute toxicity used to assess the relative toxicity in mol/kg. Oral Rat Chronic Toxicity (LOAEL) results need to be interpreted relative to the bioactive concentrations and were predicted. Hepatotoxicity, it predicts whether a given compound is likely to be associated with the disrupted normal function of the liver. Skin Sensitisation of some phytocompounds is likely to be associated with skin sensitisation. T.Pyriformis toxicity > -0.5 log µg/L. Minnow toxicity a logLC50 predicted LC50 values below 0.5 mM if (log LC50 < - 0.3) are regarded as high acute toxicity. This toxicity analysis makes a good selection of drugs-based suitability for further study of drug discovery.

TABLE 3.2.7 : TOXICITY ANALYSIS OF THE SCREENED COMPOUNDS

Sl No	Compound	AMES toxicity	Max. tolerated dose (human)	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity (LD50)	Oral Rat Chronic Toxicity (LOAEL)	Hepatotoxicity	Skin Sensitisation	T.Pyriformis toxicity	Minnow toxicity
1	(-)-simulanol	No	0.196	No	No	2.222	1.779	No	No	0.464	1.034
2	(E,E)-farnesol	No	0.096	No	No	1.558	1.208	No	Yes	2.328	0.1
3	10-epi-eudesmol	No	0.131	No	No	1.68	1.231	No	Yes	1.522	0.819
4	1-hexyl-2-nitrocyclohexane	No	0.079	No	No	2.326	1.09	No	Yes	2.045	0.199
5	2,4-ditert-butylphenol	No	0.11	No	No	2.321	1.414	No	Yes	0.969	-0.571
6	2,4-Quinolinediol	No	0.308	No	No	2.115	1.794	No	No	0.456	1.278
7	2-Pinen-4-ol	No	0.325	No	No	2.11	1.844	No	Yes	0.359	1.629

Sl No	Compound	AMES toxicity	Max. tolerated dose (human)	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity (LD50)	Oral Rat Chronic Toxicity (LOAEL)	Hepatotoxicity	Skin Sensitisation	T.Pyriformis toxicity	Minnow toxicity
8	3R-Claussequinone	No	-0.125	No	No	2	1.288	No	No	0.408	1.44
9	7-hydroxy-2,5-dimethyl 4H-1-Benzopyran-4-one	No	0.285	No	No	2.154	2.41	No	No	0.662	1.257
10	Acetic acid, dec-2-yl ester	No	0.417	No	No	1.727	2.493	No	Yes	1.496	0.19
11	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester	No	-0.412	No	No	2.315	1.912	No	No	0.704	-1.812
12	Berberine	No	-0.132	No	No	3.313	1.275	No	No	0.288	-0.869
13	Beta-eudesmol	No	-0.371	No	No	1.697	1.271	No	Yes	1.79	0.59
14	Butylated hydroxytoluene	No	0.256	No	No	2.586	1.387	No	Yes	1.017	-0.381
15	Cadinol	No	0.164	No	No	1.963	1.409	No	Yes	1.36	0.917
16	Caffeic acid	No	-0.106	No	No	2.422	1.646	No	No	0.023	2.22
17	caffeic acid ethyl ester	No	-0.172	No	No	2.069	1.574	No	No	0.511	1.507
18	Cedr-8-en-13-ol	No	0.021	No	No	1.726	1.198	No	Yes	1.476	0.724
19	Cedr-8-en-15-ol	No	-0.054	No	No	1.683	1.206	No	Yes	1.474	0.726
20	cis-Sesquisabinene hydrate	No	0.055	No	No	1.627	1.203	No	Yes	1.769	0.531
21	Cubenol	No	0.354	No	No	2.084	1.472	No	Yes	1.301	0.741

Sl No	Compound	AMES toxicity	Max. tolerated dose (human)	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity (LD50)	Oral Rat Chronic Toxicity (LOAEL)	Hepatotoxicity	Skin Sensitisation	T.Pyriformis toxicity	Minnow toxicity
22	decanoic acid	No	-0.059	No	No	1.533	2.75	No	Yes	0.701	0.48
23	Dihydroechioidinin	No	-0.294	No	No	2.332	1.647	No	No	0.365	1.893
24	Ethyl iso-allocholate	No	-1.461	No	No	3.033	0.105	No	No	0.337	0.417
25	exo-2-Hydroxycineole acetate	No	0.418	No	No	2.202	1.69	No	Yes	-0.009	1.934
26	Ficusin	No	-0.543	No	No	1.806	1.05	No	No	0.63	0.823
27	formononetin	No	0.008	No	No	1.946	1.17	No	No	0.637	0.041
28	Furanocembranoid 3	No	0.451	No	No	2.469	1.562	No	No	0.578	1.519
29	gallic acid	No	-0.335	No	No	2.087	2.372	No	No	-0.107	2.842
30	gamma-eudesmol	No	0.055	No	No	1.681	1.249	No	Yes	1.524	0.842
31	Glaucic acid	No	0.047	No	No	1.965	2.219	No	Yes	0.297	0.721
32	Glaucyl alcohol	No	0.351	No	No	1.714	1.213	No	Yes	1.395	0.877
33	Globulol	No	-0.193	No	No	1.615	1.187	No	Yes	1.369	1.063
34	Guaiol	No	0.445	No	No	1.789	1.212	No	Yes	1.254	0.906
35	inusoniolide	No	0.193	No	No	1.76	1.841	No	Yes	0.918	0.833
36	Isopsoralen	No	-0.448	No	No	2.616	1.061	No	No	0.673	0.978
37	Methyl 2,4,6-trihydroxybenzoate	No	0.072	No	No	1.679	2.665	No	No	0.237	2.065
38	Millettilone A	No	-0.278	No	No	2.275	1.953	No	No	0.471	2.638
39	nerolidol	No	0.245	No	No	1.597	1.178	No	Yes	2.285	0.185

Sl No	Compound	AMES toxicity	Max. tolerated dose (human)	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity (LD50)	Oral Rat Chronic Toxicity (LOAEL)	Hepatotoxicity	Skin Sensitisation	T.Pyriformis toxicity	Minnow toxicity
40	Nimbidiol	No	-0.639	No	No	2.433	1.864	No	No	1.729	0.469
41	Nimbolide	No	-0.178	No	No	2.787	1.96	No	No	0.292	0.544
42	nonanoic acid	No	0.1	No	No	1.54	2.68	No	Yes	0.499	0.762
43	Patchouli alcohol	No	0.014	No	No	1.747	1.229	No	Yes	1.058	0.851
44	p-Coumaric acid	No	0.446	No	No	2.402	1.847	No	No	0.183	1.963
45	Pendulone	No	-0.032	No	No	2.175	1.269	No	No	0.348	0.992
46	Protocatechuic acid	No	-0.025	No	No	2.122	2.005	No	No	-0.258	2.358
47	Santalol	No	-0.025	No	No	2.122	2.005	No	No	-0.258	2.358
48	scopoletin	No	-0.051	No	No	1.636	1.281	No	Yes	2.015	0.147
49	sibirolide A	No	0.292	No	No	2.012	1.424	No	No	0.453	1.604
50	sibirolide B	No	0.017	No	No	1.648	2.32	No	No	0.634	1.252
51	Spathulenol	No	-0.538	No	No	2.042	2.435	No	No	0.775	1.399
52	Zingiberenol	No	0.055	No	No	1.627	1.203	No	Yes	1.769	0.531

3.2.8.PREDICTION OF PHARMACOLOGICAL POTENTIAL USING PASS SERVER

The pharmacological effects and Antiviral activities of 52 phytocompounds were analyzed through PASS (Prediction of activity spectra for substances) online server; the values of Pa and Pi vary between 0.000 and 1.000. Only activities with Pa > Pi are considered as possible for a particular compound. If Pa > 0.7, the probability of experimental pharmacological action is high and if 0.5 < Pa < 0.7, probability of experimental pharmacological action is less. The tested phytocompounds shows many pharmacological activities and Antiviral activities. All

the 52 phytocompounds show good activities and the criteria considered as Pa > 0.6 and a few of those potential compounds were listed in Table 7.

TABLE 7: PASS PREDICTION ALL 52 COMPOUNDS HAVE ANTIVIRAL PROPERTY FILTERED TABLE WERE PA > 0.6

Sl.no	Compound name	Pa	Pi	Activity
1	(E,E)-farnesol	0,766	0,001	Antiviral (Rhinovirus)
2	nerolidol	0,765	0,001	Antiviral (Rhinovirus)
3	Ethyl iso-allocholate	0,747	0,004	Antiviral (Influenza)
4	Nimbidiol	0,694	0,006	Antiviral (Influenza)
5	decanoic acid	0,671	0,008	Antiviral (Picornavirus)
6	nonanoic acid	0,671	0,008	Antiviral (Picornavirus)
7	Patchouli alcohol	0,668	0,008	Antiviral (Influenza)
8	Acetic acid, dec-2-yl ester	0,658	0,004	Antiviral (Rhinovirus)
9	1-hexyl-2-nitrocyclohexane	0,656	0,010	Antiviral (Picornavirus)
10	gallic acid	0,654	0,009	Antiviral (Influenza)
11	Zingiberenol	0,651	0,004	Antiviral (Rhinovirus)
12	cis-Sesquisabinene hydrate	0,626	0,005	Antiviral (Rhinovirus)
13	Protocatechuic acid	0,610	0,012	Antiviral (Influenza)
14	Dihydroechioidinin	0,607	0,013	Antiviral (Influenza)

3.2.9. PREDICTION OF BIOACTIVITY SCORE

The bioactivity scores were predicted using molinspiration tool (www.molinspiration.com) for the most important drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes, and nuclear receptors) and the Drug likeliness property of 52 phytocompounds against these targets was depicted in Table 8. The compound having a bioactivity score of more than 0.00 is likely to possess considerable biological activities, values -0.50 to 0.00 are expected to be moderately active and if the score is less than -0.50, it is presumed to be inactive (Paramashivam SK 2015). Hence from the evaluated scores, one can say that all the 52 phytocompounds having bioactivity scores in acceptable ranges.

TABLE 8: BIOACTIVITY SCORES OF PHYTOCOMPOUNDS PREDICTED BY MOLINSPIRATION.

Sl No	Compound	GPCR LIGAND	ION CHANNEL MODULATOR	KINASE INHIBITOR	NUCLEAR RECEPTOR LIGAND	PROTEASE INHIBITOR	ENZYME INHIBITOR
1	(-)-simulanol	0.34	-0.04	-0.12	0.11	-0.18	0.47
2	(E,E)-farnesol	-0.13	0.22	-0.6	0.2	-0.43	0.42
3	10-epi-eudesmol	0.03	0.37	-0.63	0.55	-0.11	0.5
4	1-hexyl-2-nitrocyclohexane	-0.48	0.09	-0.78	-0.56	-0.49	-0.08
5	2,4-ditert-butylphenol	-0.37	0.05	-0.51	-0.07	-0.64	-0.07
6	2,4-Quinolinediol	-0.72	-0.18	-0.46	-0.87	-1.17	-0.08
7	2-Pinen-4-ol	-0.18	0.03	-1.42	-0.17	-0.54	0.02
8	3R-Claussequinone	-0.48	-0.19	0.05	-0.07	-0.38	0.28
9	7-hydroxy-2,5-dimethyl 4H-1-Benzopyran-4-one	-1.11	-0.79	-1.16	-0.56	-1.25	-0.32
10	Acetic acid, dec-2-yl ester	-0.53	-0.13	-0.85	-0.39	-0.51	-0.08
11	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester	0.07	0.09	-0.22	0.35	-0.04	0.15
12	Berberine	-0.11	0.71	-0.27	-0.78	-0.35	0.82
13	Beta-eudesmol	-0.02	0.43	-0.62	0.6	-0.1	0.48

Sl No	Compound	GPCR LIGAND	ION CHANNEL MODULATOR	KINASE INHIBITOR	NUCLEAR RECEPTOR LIGAND	PROTEASE INHIBITOR	ENZYME INHIBITOR
14	Butylated hydroxytoluene	-0.34	0	-0.48	-0.08	-0.57	-0.07
15	Cadinol	-0.09	0.05	-0.87	0.39	-0.63	0.4
16	Caffeic acid	-0.48	-0.23	-0.81	-0.1	-0.79	-0.09
17	caffeic acid ethyl ester	-0.59	-0.29	-0.78	-0.18	-0.71	-0.22
18	Cedr-8-en-13-ol	-0.18	-0.01	-0.7	0.34	-0.48	0.55
19	Cedr-8-en-15-ol	-0.12	-0.07	-0.65	0.12	-0.54	0.54
20	cis-Sesquisabinene hydrate	-0.12	0.12	-0.63	0.31	-0.04	0.22
21	Cubenol	-0.17	0.41	-0.69	0.11	-0.48	0.27
22	decanoic acid	-0.46	-0.14	-1.03	-0.45	-0.56	-0.07
23	Dihydroechioidinin	0.01	-0.27	-0.3	0.31	-0.13	0.15
24	Ethyl iso-allocholate	0.17	0.21	-0.38	0.65	0.18	0.58
25	exo-2-Hydroxycineole acetate	-0.39	0.45	-0.94	-0.24	-0.29	0.48
26	Ficusin	-0.89	-0.38	-1.1	-1.13	-1.19	-0.37
27	formononetin	-0.3	-0.69	-0.19	0.05	-0.8	-0.02
28	Furanocembranoid 3	0.27	0.06	-0.24	0.58	0.23	0.31
29	gallic acid	-0.77	-0.26	-0.88	-0.52	-0.94	-0.17
30	gamma-eudesmol	-0.29	0.2	-0.81	0.53	-0.32	0.4
31	Glaucic acid	-0.16	-0.2	-0.95	0.29	-0.22	0.12
32	Glaucyl alcohol	-0.31	-0.4	-84	0.09	-0.38	0.05
33	Globulol	-0.5	-0.29	-0.82	-0.22	-0.48	-0.13
34	Guaiol	-0.21	-0.13	-0.89	0.17	-0.17	0.07
35	inusoniolide	0.06	-0.12	-0.68	0.44	0.06	0.33

Sl No	Compound	GPCR LIGAND	ION CHANNEL MODULATOR	KINASE INHIBITOR	NUCLEAR RECEPTOR LIGAND	PROTEASE INHIBITOR	ENZYME INHIBITOR
36	Isopsoralen	-0.87	-0.48	-0.88	-0.93	-1.15	-0.28
37	Methyl 2,4,6-trihydroxybenzoate	-0.85	-0.46	-0.96	-0.71	-1.03	-0.34
38	Millettilone A	-0.48	-0.3	0.02	-0.24	-0.34	0.24
39	nerolidol	-0.17	0.21	-0.64	0.42	-0.43	0.39
40	Nimbidiol	0.31	0.26	-0.22	0.6	-0.28	0.42
41	Nimbolide	0.22	0.2	-0.36	0.32	0.04	0.36
42	nonanoic acid	-0.57	-0.21	-1.2	-0.57	-0.67	-0.14
43	Patchouli alcohol	-0.12	0.37	-0.88	0.55	-0.32	0.4
44	p-Coumaric acid	-0.56	-0.26	-0.91	-0.12	-0.87	-0.15
45	Pendulone	-0.16	-0.13	0.03	0.21	-0.27	0.31
46	Protocatechuic acid	-0.88	-0.35	-1.1	-0.58	-1.09	-0.34
47	Santalol	-0.09	-0.04	-0.65	0.23	-0.42	0.39
48	scopoletin	-1	-0.65	-0.95	-0.81	-1.16	-0.24
49	sibirolide A	-0.3	-0.12	-1.09	-0.2	-0.28	0.12
50	sibirolide B	-0.42	-0.37	-0.59	0.13	-0.19	0.41
51	Spathulenol	-0.42	-0.28	-0.68	0.28	-0.36	0.06
52	Zingiberenol	-0.04	0.02	-0.66	0.5	-0.29	0.38

3.3. PHYTOCOMPOUNDS SCREENING USING PYRX SOFTWARE

Molecular screenings of all the 52 phytocompounds were performed using PyRx software by Autodock vina wizard as the engine for docking. During the docking period, the ligands were considered to be flexible and the protein was considered to be rigid. The configuration file for the grid parameters was generated using Auto Grid engine in Pyrx. The application was also used to know/predict the amino acids in the active site of the protein that interact with the ligands. The results less than 1.0Å in positional root-mean-square deviation (RMSD) were considered ideal and clustered together for finding favorable binding. The highest binding

energy (most negative) was considered as the ligand with maximum binding affinity. In our study, 52 phytocompounds respective to the receptor-ligand interactions; binding affinity scores shows negative for all the phytocompounds listed in Table 9 : The top 6 phytocompounds are listed with binding affinity score here, they are Nimbolide (2ghv -12.6, 6LU7 -10.1,6LZG -14.1, 6m03-12.3, 6vsb -14), gamma-eudesmol (2ghv -9.4, 6LU7-6.4,6LZG-9.6,6m03-8.4, 6vsb -9), Beta-eudesmol (2ghv -9.4, 6LU7-6.4, 6LZG -11.2, 6m03-8.4, 6vsb -9), 10-epi-eudesmol (2ghv -9.4, 6LU7-6.4, 6LZG -11.5, 6m03-8.4, 6vsb -9.3) Nimbidiol (2ghv -8,6LU7-6, 6LZG -8.9, 6m03-7.9, 6vsb -9.3-8.2). The other interactions of phytoligands are depicted in Table 9.

TABLE 9: BINDING AFFINITY SCORES FROM PYRX AUTODOCK VINA

Sl.no	Ligand(IUPAC)	2ghv	6LU7	6LZG	6m03	6vsb
1	Nimbolide(methyl 2-[6-(furan-3-yl)-7,9,11,15-tetramethyl-12,16-dioxo-3,17-dioxapentacyclo[9.6.1.02,9.04,8.015,18]octadeca-7,13-dien-10-yl]acetate)	-12.6	-10.1	-14.1	-12.3	-14
2	gamma-eudesmol(2-(4a,8-dimethyl-2,3,4,5,6,7-hexahydro-1H-naphthalen-2-yl)propan-2-ol)	-9.4	-6.4	-9.6	-8.4	-9
3	Beta-eudesmol(2-(4a-methyl-8-methylidene-1,2,3,4,5,6,7,8a-octahydronaphthalen-2-yl)propan-2-ol)	-9.4	-6.4	-11.2	-8.4	-9
4	10-epi-eudesmol(2-(4a,8-dimethyl-2,3,4,5,6,8a-hexahydro-1H-naphthalen-2-yl)propan-2-ol)	-9.4	-6.4	-11.5	-8.4	-9.3
5	Nimbidiol(6,7-dihydroxy-1,1,4a-trimethyl-3,4,10,10a-tetrahydro-2H-phenanthren-9-one)	-8	-6	-8.9	-7.9	-8.2
6	sibirolide A((1R,2R,9R,10R,12S)-5,9-dimethyl-13-methylidene-3-oxatetracyclo[7.4.0.02,6.010,12]tridec-5-ene-4,7-dione)	-7.9	-5.6	-8.2	-7.2	-7.4
7	Berberine(16,17-dimethoxy-5,7-dioxa-13-azoniapentacyclo[11.8.0.02,10.04,8.015,20]henicosa-1(13),2,4(8),9,14,16,18,20-octaene)	-7.6	-5.9	-7.8	-7.2	-8.2
8	Glaucic acid(2-(3,8-dimethyl-1,2,3,4,5,6,7,8-octahydroazulen-5-yl)prop-2-enoic acid)	-7.6	-5.6	-8.3	-7.2	-7
9	sibirolide B((2S,9R,10R,12S)-2-hydroxy-4,9-dimethyl-13-methylidene-6-	-7.6	-5.5	-8.5	-7.9	-7.3

Sl.no	Ligand(IUPAC)	2ghv	6LU7	6LZG	6m03	6vsb
	oxatetracyclo[7.4.0.03,7.010,12]trideca-3,7-dien-5-one)					
10	Furanocembranoid 3((4S,5E,7S,10R,11S)-7,11-dimethyl-4-propan-2-yl-14-oxabicyclo[11.2.1]hexadeca-1(15),5,13(16)-triene-7,10,11-trio)	-7.4	-5.5	-7.6	-7.2	-7.9
11	Cadinol(1,6-dimethyl-4-propan-2-yl-3,4,4a,7,8,8a-hexahydro-2H-naphthalen-1-ol)	-7.3	-5	-7.1	-6.3	-6.9
12	Cubenol(4,7-dimethyl-1-propan-2-yl-2,3,4,5,6,8a-hexahydro-1H-naphthalen-4a-ol)	-7.3	-4.9	-7.3	-6.1	-7.1
13	Millettilone A(2-(7-hydroxy-4-methoxy-3,4-dihydro-2H-chromen-3-yl)-5-methoxycyclohexa-2,5-diene-1,4-dione)	-7.2	-5.4	-8.3	-7.3	-8
14	formononetin(7-hydroxy-3-(4-methoxyphenyl)chromen-4-one)	-7.2	-5.7	-8	-7.3	-7.5
15	Glaucyl alcohol(2-(3,8-dimethyl-1,2,3,4,5,6,7,8-octahydroazulen-5-yl)prop-2-en-1-ol)	-7.2	-5.5	-7.6	-6.4	-6.6
16	Dihydroechioidinin(5-hydroxy-2-(2-hydroxyphenyl)-7-methoxy-2,3-dihydrochromen-4-one)	-7.2	-5.8	-8.4	-7.4	-7.8
17	3R-Claussequinone(2-(7-hydroxy-3,4-dihydro-2H-chromen-3-yl)-5-methoxycyclohexa-2,5-diene-1,4-dione)	-7.1	-6	-8.2	-7	-8.2
18	Guaiol(2-(3,8-dimethyl-1,2,3,4,5,6,7,8-octahydroazulen-5-yl)propan-2-ol)	-7.1	-5.3	-7.5	-6.7	-6.7
19	Ficusin(furo[3,2-g]chromen-7-one)	-7.1	-5.2	-6.9	-6.3	-7.2
20	Ethyl iso-allocholate(ethyl 4-(3,7,12-trihydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate)	-7	-6	-8.3	-7.5	-8.3
21	Spathulenol(1,1,7-trimethyl-4-methylidene-1a,2,3,4a,5,6,7a,7b-octahydrocyclopropa[h]azulen-7-ol)	-6.9	-4.9	-7.5	-6.3	-7.1
22	cis-Sesquisabinene hydrate(2-methyl-5-(6-methylhept-5-en-2-yl)bicyclo[3.1.0]hexan-2-ol)	-6.8	-4.4	-6.6	-5.8	-6
23	Pendulone(5-(7-hydroxy-3,4-dihydro-2H-chromen-3-yl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione)	-6.8	-5.9	-8.2	-7	-7.5
24	Isopsoralen(furo[2,3-h]chromen-2-one)	-6.7	-5.4	-7.2	-6.1	-7.1
25	(-)-simulanol(4-[(2R,3S)-3-(hydroxymethyl)-5-[(E)-3-hydroxyprop-1-enyl]-7-methoxy-2,3-	-6.7	-5.2	-7.7	-6.8	-7.2

Sl.no	Ligand(IUPAC)	2ghv	6LU7	6LZG	6m03	6vsb
	dihydro-1-benzofuran-2-yl]-2,6-dimethoxyphenol)					
26	inusoniolide(4-[(3aS,6S,8aS)-6-methyl-2-oxo-3,3a,4,5,6,8a-hexahydrocyclohepta[b]furan-7-yl]-2-methylbutanal)	-6.7	-5.5	-7.1	-6.3	-7.2
27	Globulol(1,1,4,7-tetramethyl-2,3,4a,5,6,7,7a,7b-octahydro-1aH-cyclopropa[e]azulen-4-ol)	-6.5	-5.2	-7.8	-6.9	-6.7
28	Zingiberenol(1-methyl-4-(6-methylhept-5-en-2-yl)cyclohex-2-en-1-ol)	-6.5	-4.5	-6.5	-6.4	-5.9
29	nerolidol(3,7,11-trimethyldodeca-1,6,10-trien-3-ol)	-6.5	-4.9	-7.3	-5.2	-5.8
30	(E,E)-farnesol (3,7,11-trimethyldodeca-2,6,10-trien-1-ol)	-6.4	-4.8	-7.9	-5.9	-6
31	Cedr-8-en-13-ol((2,6,8-trimethyl-6-tricyclo[5.3.1.01,5]undec-8-enyl)methanol)	-6.4	-5.2	-7.1	-6.2	-6.8
32	Patchouli alcohol(2,2,6,8-tetramethyltricyclo[5.3.1.03,8]undecan-3-ol)	-6.4	-5.1	-7.7	-6.5	-7
33	Santalol(2-methyl-5-(2-methyl-3-methylidene-2-bicyclo[2.2.1]heptanyl)pent-2-en-1-ol)	-6.4	-4.9	-6.8	-5.9	-6.3
34	2,4-ditert-butylphenol (2,4-ditert-butylphenol)	-6.4	-4.9	-7.1	-6	-6.3
35	Butylated hydroxytoluene(2,6-ditert-butyl-4-methylpheno)	-6.3	-4.7	-6.4	-6	-6.7
36	caffeic acid ethyl ester(ethyl 3-(3,4-dihydroxyphenyl)prop-2-enoate)	-6.3	-5	-6.7	-6	-6.3
37	7-hydroxy-2,5-dimethyl 4H-1-Benzopyran-4-one (7-hydroxy-2,5-dimethylchromen-4-one)	-6.2	-4.9	-7.4	-6.2	-6.8
38	Cedr-8-en-15-ol(2,6,6-trimethyl-8-tricyclo[5.3.1.01,5]undec-8-enyl)methanol)	-6.2	-5.3	-7.1	-6.5	-7
39	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester(methyl 3-(3,5-ditert-butyl-4-hydroxyphenyl)propanoate)	-6.1	-5.5	-6.9	-6	-6.6
40	scopoletin(7-hydroxy-6-methoxychromen-2-one)	-6	-5.2	-6.6	-6.1	-6.5
41	1-hexyl-2-nitrocyclohexane(1-hexyl-2-nitrocyclohexane)	-6	-4.6	-6.2	-5.4	-5.6
42	2,4-Quinolinediol(4-hydroxy-1H-quinolin-2-one)	-5.8	-5	-6.9	-5.8	-6.2
43	Caffeic acid(3-(3,4-dihydroxyphenyl)prop-2-enoic acid)	-5.7	-5.4	-6.9	-5.8	-6.3

Sl.no	Ligand(IUPAC)	2ghv	6LU7	6LZG	6m03	6vsb
44	p-Coumaric acid(3-(4-hydroxyphenyl)prop-2-enoic acid)	-5.7	-5.1	-6.8	-5.7	-5.9
45	gallic acid(3,4,5-trihydroxybenzoic acid)	-5.7	-5.1	-6.4	-5.5	-6.3
46	exo-2-Hydroxycineole acetate((1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-yl) acetate)	-5.6	-5.6	-6.1	-5.7	-6.2
47	Protocatechuic acid(3,4-dihydroxybenzoic acid)	-5.4	-4.8	-6.3	-5.3	-6.2
48	Acetic acid, dec-2-yl ester(decan-2-yl acetate)	-5.3	-3.6	-4.7	-4.7	-4.9
49	Methyl 2,4,6-trihydroxybenzoate (methyl 2,4,6-trihydroxybenzoate)	-5.3	-4.5	-6.2	-5.4	-6.3
50	nonanoic acid(nonanoic acid)	-5.3	-4.1	-6	-4.5	-4.6
51	decanoic acid(decanoic acid)	-5.1	-4.5	-5.1	-4.6	-5.1
52	2-Pinen-4-ol(4,6,6-trimethylbicyclo[3.1.1]hept-3-en-2-o)	-5.1	-4.4	-6.1	-5.5	-5.7

4. DISCUSSION:

The emergence of Novel Coronavirus (SARS CoV2) had caused an unprecedented level of global public health emergency with 40,890,712 Confirmed cases and 1,126,351 Confirmed deaths across 235 Countries, areas, or territories as reported by World Health Organization (WHO 2020) (information updated till 22nd October 2020). Therefore, there is an urgent need for the discovery of a potential treatment to control the COVID-19 pandemic. There are no randomized clinical trials (RCT) that have found an effective drug against COVID-19. However, some preliminary trials using the non-specific SARS-CoV2 drug approach have shown good outcomes such as the use of repurposed corticosteroid drugs (Sanders JM 2020) (Dyall 2014) and convalescent plasma therapy (Sanders JM 2020). Therefore, no clinically available antiviral drugs have been developed for SARS-CoV-2. Traditional Indian medicinal systems offer a strong base for the utilization of many plants in terms of safety and effective leads for different disease management and treatment strategies (Nyika 2007); (Zasławski 2005); (Emanuel 2004). Many plant-derived substances previously studied would possibly serve as potential antiviral agents for the treat severe acute respiratory syndrome (SARS). Hence, molecular docking is the fastest way to explore the mechanism of action of potential ethnomedicinal against protein targets associated with SARS-CoV-2.

4.1. RECEPTOR SELECTION AND ACTIVE SITE PREDICTION:

SARS-CoV-2 has four main structural proteins including spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein, and several accessory proteins (Jiang Shibo 2020). The viral entry into the host cells occurs through the interaction of the SARS-CoV-2 S protein with the angiotensin-converting enzyme 2 (ACE2) receptor (Astuti Indwiani 2020). Because of this, bioinformatics analysis of the proteins encoded by the novel coronavirus genes was systematically retrieved from the Protein data bank. In this present study, Spike glycoprotein with single receptor-binding domain [PDB ID:6VSB], SARS protein receptor-binding with angiotensin-converting enzyme 2 (ACE2) receptor complex with spike receptor-binding domain [PDB ID:6LZG], SARS spike protein receptor-binding domain [PDB ID:2GHV], two forms of main protease one in the apo form [PDB ID: 6M03] and another one complex with an inhibitor N3 [PDB ID: 6LU7] were investigated for high throughput virtual ligand screening.

4.2. PROSPECTION OF PHARMACOKINETICS AND BIOACTIVITY POTENTIAL OF PHYTOLIGANDS:

4.2.1. MOLECULAR STRUCTURE RETRIEVAL OF PHYTOLIGANDS BASED ON PYTHON WEB SCRAPING APPROACH

Furthermore, to search for potential coronavirus therapeutic drugs a total of 1378 phytochemical metabolites of 58 ethnomedicinal plants were screened. The structures of these 1378 chemical compounds were retrieved from PubChem and ChemSpider online servers based on the python web scrapping technique. Python web scrapping is an alternative method of machine learning approaches have recently (re)emerged, some of which may be considered instances of domain-specific AI which have been successfully employed for robust drug discovery and design (Yang 2019).Many individual chemicals have a specific page on the PubChem database that will give information about the use, manufacture, and properties of that chemical. The properties that are displayed off to the side include the relevant chemical identifiers along with alternate names and reaction information. Accordingly, the Canonical Smiles were scraped for 698 out of 1378 phytochemical compounds using automated python

scripts designed to web scrape from the PubChem database using the PUG Rest Application Programming Interface (API) and ChEMBL API.

4.2.3. DRUG-LIKELINESS AND ADMET PROPERTIES

Thus retrieved 1378 phytochemical compounds were validated for its drug-likeliness and ADMET properties. The drug-like property of the designed compounds was carried out, based on Lipinski's rule of five by using the ADMETlab web server for drug-likeness analysis. All the designed compounds showed zero violations. As per Lipinski's Rule of Five, an orally active drug has not more than one violation, it should have not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms), not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms), a molecular weight under 500 g/mol., and a partition coefficient log P less than 5 and Not more than 15 rotatable bonds were considered, the number of hydrogen bond donors (HBD's) ≤ 5 and number of hydrogen bond acceptors (HBAs) ≤ 10.6 (Sumathy 2016) (Ursu 2011). According to the results, the phytochemical ligand exhibiting Molecular weight (152.237 to 466.53 Daltons), log P values of the compounds are ranges from 0.502 to 4.398 and topological polar surface area ranges from 20.23 to 97.99 angstrom were narrow down. Among the screened phytochemicals 52 compounds are within the limit of the Lipinski rules are used for further process. A higher log P value indicates lower hydrophilicity and, thus, poor absorption and permeation. A value indicates solubility; the lesser the value, the higher the solubility which would enhance the absorption. A lower molecular weight would again enhance the absorption rate and thus most of the drugs are tried to be kept at the lowest possible molecular weight (Menting 2014) TPSA or *Topological Polar Surface Area* indicates the surface belonging to polar atoms in the compound. An increased TPSA is associated with diminished membrane permeability and compounds with higher TPSA were better substrates for p-glycoprotein (responsible for drug efflux from a cell). Thus, comparing the compounds, lower TPSA was favorable for the drug-like property. It was also predicted that a molecule with better CNS penetration should have a lower TPSA value (Yang 2019). ADMET properties of a compound deal with its absorption, distribution, metabolism, excretion, and toxicity through the human body. Toxicity is an important factor that often overshadows the ADME behavior. Failure of drugs at the clinical trial stage due to adverse effects generated because of their toxicity proves expensive and detrimental in the drug development process (Menting 2014). ADMET, which constitutes the pharmacokinetic profile of a drug molecule, is very essential in evaluating its

pharmacodynamic activities (Nisha 2016). A high-quality drug candidate should not only have sufficient efficacy against the therapeutic target but also show appropriate ADMET properties at a therapeutic dose which was proved in these findings.

4.2.4. PHARMACOKINETICS AND BIOACTIVITY PREDICTION OF PHYTOLIGANDS

In silico study, especially pharmacokinetics and bioavailability prediction were performed by using the SwissADME online tool to know the lead phytochemical compound for the drug candidate for the prevention of pain and inflammation (Puja Tripathi 2019). In the present investigation, drug likeliness property of five compounds against GPCR ligand, ion channel modulator, a kinase inhibitor, nuclear receptor ligand, protease inhibitor, and enzyme inhibitory activity was studied. It showed that the G-Protein Coupled Receptor activity ranges from -1.11 to -0.344; Kinase inhibitor activity ranges from - 84 to 0.05; Protease inhibitor activity ranges from -1.25 to -0.23, and the enzyme inhibitors activity are from -0.37 to 0.82 for the designed compounds was obtained. The bioactivity score based on the Molinspiration study for all the 52 compounds were between 0.00 and -0.50. Nearly 98% of the molecules were presumed to have bioactivity scores between -0.50 to 0.00 are expected to be moderately active, 2% of compounds exhibit good bioactive potential.

To find out the possible biological activity of selected bioactive constituents was obtained by using the PASS online server. The set of pharmacological effects, mechanisms of action, and specific toxicities, that might be exhibited by a particular compound in its interaction with biological entities, and which is predicted by PASS score (Liao 2013) (Paramashivam SK 2015). The Pa and Pi values vary from 0 to 1, and Pa >Pi since these probabilities are calculated independently. Pa and Pi can be considered to be measures of the compound under study belonging to the classes of active and inactive compounds, respectively. Around 410 compounds pass drug likeliness and then screened for ADMET analysis whereas the binding behaviors were further elucidated for 198 compounds for pharmacokinetic potential (pk CSM score). In the present study, the PASS prediction results denoted that the highest Pa value than Pi value occurred for all the 52 compounds thus showed that all these compounds exhibited antiviral potential.

4.2.5. MOLECULAR DOCKING AND VISUALIZATION

The molecular interaction of the screened phytoligands with antiviral pharmacokinetic potential leading to the surface interaction with the selected protein receptors of SARS-CoV-2 was subjected to PyRx virtual screening software. The results revealed that the maximum of the screened phytoligands exhibited strong affinities towards all the target proteins [viz., PDB ID: 6M03, 6LU7, 6VSB, 6LZG, and 2GHV]. The results of less than 1.0Å in positional root-mean-square deviation (RMSD) were considered ideal and clustered together for finding favorable binding. Binding energy is the primary parameter that is generated as a result of molecular docking. It gives us the idea of the strength and affinity of the interaction between the ligand and the receptor. The greater the binding energy is, the weaker the interaction is and vice versa. Thus, during any docking study, it is intended to look for the ligand which displays the least binding energy, thus the best affinity among the test molecules. The highest binding energy (most negative) was considered as the ligand with a maximum binding affinity (Kumar et al., 2020). In our study, 52 phytocompounds respective to the receptor-ligand interactions; binding affinity scores show negative for all the phytocompounds. The top 6 phytocompounds are listed with binding affinity score here, they are Nimbolide (2ghv -12.6, 6LU7 -10.1,6LZG -14.1, 6m03-12.3, 6vsb -14), gamma-eudesmol (2ghv -9.4, 6LU7-6.4,6LZG-9.6,6m03-8.4, 6vsb -9), Beta-eudesmol (2ghv -9.4, 6LU7-6.4, 6LZG -11.2, 6m03-8.4, 6vsb -9), 10-epi-eudesmol (2ghv -9.4, 6LU7-6.4, 6LZG -11.5, 6m03-8.4, 6vsb -9.3) Nimbidiol (2ghv -8,6LU7-6, 6LZG -8.9, 6m03-7.9, 6vsb -9.3-8.2). Thus the molecular docking studies indicate thus the established antiviral phytochemicals could also be used for the treatment of COVID-19, if found producing desirable inhibitory effect against SARS-CoV-2 viral receptors after under venting *in vivo*/ *in vitro* studies like biochemical activity assay or cell-based assays.

5. CONCLUSION

Thus, the present investigation reveals the potential of antiviral phytochemical ligands binds to the possible targets against the selected SARS-CoV-2 receptors were predicted. Furthermore, these selected phytochemical ligands could serve as an efficacious antiviral agent against multi viral targets will provide a new lead of antiviral compounds and targets that could be experimentally confirmed for further *in vitro* and *in vivo* studies of SARS-CoV-2.

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