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Review Article

Insilico Studies On Herbal Phytoconstituents For The Treatment Of Covid-19: A Review Article

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ABSTRACT

The SARS-CoV2 virus, which triggered the COVID-19 pandemic, has made a major contribution to world health. This article describes the characteristics of the virus, transmission routes, signs and symptoms, and possible treatments. SARS-CoV2, a virus belonging to the Coronaviridae family, was initially identified in Wuhan, China, in December 2019, and it rapidly spread across the globe. People usually transmit it through physical contact with infected people or contaminated surfaces. Symptoms can range from mild respiratory symptoms to fatal organ failure. Through clinging to the human ACE2 (angiotensin-converting enzyme II) receptor, the virus can penetrate the host cell more easily and multiply there. The study shows how important molecular docking studies are for drug development, as they can predict how potential inhibitors and viral proteins would interact. Natural products have been proposed as potential options to inhibit SARS-CoV2 because of the diversity of their structures and lower toxicity. Some substances, such as flavonoids, terpenes, alkaloids, and phenolic compounds, have demonstrated the capacity to block Mpro, the main protease of the virus, along with additional important proteins engaged in the virus's replication. The highest binding energy was found to be -11.89 kcal/mol, opposing the primary protease of SARS-CoV2. Despite the encouraging outcomes, additional clinical trials are required to verify the safety and effectiveness of the components in the COVID-19 treatment.

INTRODUCTION

People of all ages can become infected with COVID-19, an unbearable virus that can result in fatal instances and serious respiratory infections in some situations [1]. A major emergence of the coronavirus illness brought on by the SARS-CoV-2, which started in Wuhan, China, was reported at the end of December 2019 [2]. The coronavirus is a positive sense RNA (ribonucleic acid) from the

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Coronaviridae family that resembles a crown. The mortality rate from the SARS-CoV pandemic was 10%, whereas the mortality rate from the Middle East respiratory syndrome pandemic (MERS-CoV) was 37 in 2002 over the last 20 years [3]. SARS-CoV first infected civets before spreading to humans. While it is uncertain who the intermediary host is in the human transmission chain, it is assumed that SARS-CoV-2 is also a bat virus [4]. Direct contact between infected people exhibiting symptomatic or asymptomatic indications, direct contact with animals harboring the coronavirus, as well as via the environment, e.g., via surfaces polluted by droplets from sick individuals who sneezed and coughed [5]. Frequent clinical manifestations of COVID-19 comprise fever, cough, dry mucus, sore muscles, and exhaustion. Some of those affected also experienced other symptoms of the upper respiratory or digestive tract, such as diarrhea, runny nose, and rhinitis constipation. The most common causes of patient death were coagulation problems, multiple organ failure, septic shock, and acute respiratory distress syndrome [6]. The elderly and children are particularly susceptible to severe respiratory issues because of their compromised immune systems. Nevertheless, the elderly and those with concomitant conditions,, including diabetes, cardiovascular disease, and chronic respiratory diseases are more likely to have the severe symptoms listed above. Other symptoms, including bruises on the feet, blood clots, and strokes, have recently been observed in people who have tested positive for COVID-19 [7]. ACE2 (humanudies revealed that SARS-CoV2 is more able to identify human ACE2 than SARS-CoV, which could control the rate and extent of human-to-human transmission. angiotensin-converting enzyme II) is an effective SARS-CoV receptor. when the virus replicates in host cells either in vivo or in vitro. It has a strong binding affinity to SARS-CoV. Protein studies revealed that SARS-CoV2 is more able to identify human ACE2 than SARS-CoV, which could control the rate and extent of human-to-human transmission. Human cells are infected by SARS-CoV2 when it binds to the ACE2 receptor on the cell membrane. replicating its genome and then translating within the host cells. The translation of the viral RNAs leads to polypeptides, which consist of several proteins. For the viruses to assemble and survive, functioning enzymes are required to break them down into individual polypeptides. According to the CDC report, there are five major COVID-19 variants (VoC) that seriously harm: a) B.1.1.7 (initially found in South Africa, but it had a significant impact on the USA in early 2021); b) B.1.351 (early in 2024, although it was first settled in South Africa, which then affected the USA.); c) P.1 (initially noted among Brazilian tourists who revealed positive reults from Japan's initial Covid-19 screening; The US population was severely harmed bthe sameis variation as well, as in January 2021: d) B.1.427 as well as B.1.429 (They were first discovered in California in February 2021, and in March of same year they were designated as a variation of concern (VoC) [1]. When a ligand—a small molecule that resembles a medicine and binds to a target protein—is properly targeted, it can be shown using molecular docking experiments. Based on their binding energy, it is a bioinformatics-based technique for evaluating the fit, binding, and the ways in which a ligand and a protein interact [7]. A popular method in contemporary drug development for figuring out how a medication interacts with a receptor is molecular docking. Molecular docking is frequently used. to predict the affinity and activity of small molecules as well as the direction of small molecule therapy candidates' binding to their intended target proteins. It also provides valuable information on drug-receptor interactions [8].

NATURAL PRODUCTS FOR INHIBITING SARS-CoV-2:

Natural products are utilized to treat a wide range of diseases and problems in the field of medicine development. Organic chemicals or their derivatives are used to make about 1/3 of the medications that are the best-selling worldwide. Natural chemicals are well-known in the pharmaceutical industry because they offer great structural diversity and are less harmful than synthetically produced drugs [9]. The goal of creating novel medications to fight SARS-CoV-2 is to stop the virus from infecting, multiplying, and transcribing into host cells. When the SARS-CoV-2 genome (GenBank: MN908947.3) was analyzed, it was discovered that four structural proteins—the nucleocapsid (N) protein, the membrane (M) protein, the envelope (E) protein, and the spike (S) protein—as well as four non-structural proteins—the papain-like protease (PLpro), 3-chymotrypsin-like protease (3CLpro or major protease Mpro), helicase, and RNA polymerase—were translated [9,10]. Due to its critical function in controlling the transcription and viral replication" complex, 3CLPRO is a very appealing target for therapeutic development against SARS-CoV2. Abelson homolog 1 of the viral leukemia oncogene (ABL1), calcineurin-activated nuclear T-cell factor (NFAT), human angiotensin-converting enzyme receptor 2 (hACE2R), RdRp (RNA-dependent RNA polymerase), as well as papain-like protease (PLPRO), are additional target proteins [10]. Major protease (Mpro)/chymotrypsin-like protease (3CLpro) inhibitors: Mpro has been identified as a possible target for the creation of medications that combat coronavirus, as it is thought to be a highly conserved molecular target among coronaviruses as well as one of the possible development's goals and look for SARS-CoV2 treatment options that work [9,11]. It is anticipated that the Mpro amino acids Asn119, Thr24, and Thr26 are expected to be involved in drug interactions. Proteases are often used as protein targets in the development of antiviral therapies as they are crucial for the replication of many viruses [12].

1. FLAVONOIDS:

Natural phytochemicals called flavonoids have a variety of biological effects, including inhibition of carbonic anhydrase, cholinesterase, antibacterial, antifungal, antiviral, and anti-inflammatory effects [13]. A 2017 library of flavone analogs was acquired, set up, and digitally examined for compatibility with SARS-CoV2-Major protease. PubChem 88507127 and PubChem 129716607 developed 10 and 9 H-bonds, respectively, using major protease essential amino acid residues. The most remarkable result is that PubChem-129716607 and Pub-88507127 have an estimated binding affinity twice that of rutin, which was used as a reference compound in this study. PubChem-129716607 and PubChem-88507127 demonstrated encouraging binding affinities, as measured by the MM/GBSA binding energy estimates, with a ΔG binding of less than -68.0 kcal·mol−1 [14]. Amentoflavone, a biflavonoid derivative, markedly inhibited SARS-CoV-2 3CLPRO at 8.3 μmol/L. Amentoflavone demonstrated a strong binding affinity for the 3CLPRO and PLPRO proteins, having a -9.7 kcal·mol−1 binding affinity [10]. The extracts of Boesenbergia rotunda contained a total of twenty-three significant active phytochemical compounds, three of which were active flavonoids with high binding affinity to the target receptor of the drug: alpinetin, pinocembrin, and pinostrobin. These chemicals have a binding affinity of -7.51, -7.21, and -7.18 kcal·mol−1, respectively [15]. From the ethanol preparations of Artemisia sublessingiana, seven compounds—six flavonoids as well as 1 sesquiterpene lactone—were found. Among them, 3′,4′-dimethoxyluteolin showed the best binding mode and a maximum binding energy of -6.81 kcal·mol−1 [16]. Coriander is another

name for Coriandrum sativum L. It's been used for ages as a traditional treatment for a number of illnesses, including diabetes, inflammatory disorders, insomnia, anxiety, convulsions, and abnormalities of the digestive, urinary, and respiratory systems. Flavonoids such as quercetin, rutin, chlorogenic acid, and caffeic acid have been discovered to be abundant in coriander seeds. Rutin, the studied chemical with the highest binding affinity (-9.6 kcal/mol) to Mpro, was discovered as a possible component of Coriandrum sativum seeds [17].

2. ALKALOIDS:

Docking experiments with alkaloids from more than 500 medicinal plants and sponges were performed on the SARS-CoV-2 Mpro active pocket. 9 natural alkaloids selected showed encouraging results against SARSCoV-2 Mpro. Among several natural alkaloids, ajmalicin and yohimbine proved to be the most potent inhibitors due to their interactions with active site residues and binding affinity [18]. A plant widely used in West African herbal medicine is Cryptolepis sanguinolenta. Plant extracts from this plant are used to treat diseases such as diarrhea, diabetes, high blood pressure, malaria, and respiratory diseases. A total of thirteen alkaloids isolated from Cryptolepis saguinolenta were compared with Mpro with binding affinities of less than -8.50 kcal·mol−1, and biscryptolepine, cryptoquindoline, cryptomisrin, and cryptospirolepine had the best binding affinities [19]. Seventeen carefully selected alkaloids were bonded to the COVID-19 protein's Mpro (PDB ID: 6LU7). The study concludes that two alkaloids, sophalin D and thalimonine, may be able to block the Mpro. The binding energies of the thalimonine-Mpro complex and the sophalin D-Mpro complex were -8.39 and -8.79 kcal/mol, respectively [20]. With docking values of −8.5 kcal·mol−1 (L1 and L7), fumarostellin and brucine achieved the highest values among the 50 compounds. As enhanced SARS-CoV-2 inhibitory lead compounds, the following substances are suggested: fumarostellin, 2,3-dimethoxy-brucine (L-7), strychnidin-10-1 (L-1), and the alkaloid ND-305B (L-16), following which these outcomes have been compared with the antiviral medication Remdesivir, which has FDA approval [21]. Negro pepper, or X. aethiopica, is a spice that has been shown to have antiviral, antibacterial, analgesic, antioxidant, anticancer, and antimalarial properties. The docking study's findings demonstrated that the natural alkaloids liriodenine, lysicamine, o-methylmoschatoline, oxoglaucine, and andoxophoebin had excellent free energies of binding with Mpro of SARS-CoV2 [22]. The 5 alkaloids had different binding energies to the Mpro of SARS-CoV2, between -7.0 and -7.9 kcal/mol. With a binding energy of -7.9 kcal/mol, liriodenine has a higher value than the other alkaloids studied when it comes to inhibiting SARS-CoV2 Mpro. Among the 6 alkaloids found in Justicia adhatoda, isotine had a greater binding affinity (-7.9 kcal/mol) towards Mpro than did darunavir and lopinavir. Cys145 and His41, the two main catalytic residues of Mpro, reacted with anisole [23].

3. PHENOLIC COMPOUNDS:

Rosmarinic acid has the maximum affinity for binding (- 8.0 kcal/mol) targeting the Mpro viral target protein. Naringenin is another phenolic A compound with a -7.9 kcal·mol−1 docking score against the target protein of the MPro virus [24]. Significant interaction was seen between GLN 127, LYS 5, LYS 137, and ARG 131, as well as TYR 23-glycyrrhizin and the main protease, along with an affinity of −8.9 kcal/mol and five hydrogen bonds in particular [25]. 18 phenolic compounds from Satureja L. underwent a docking assay against the Mpro, the SARS-CoV-2 protease. Three different naturally occurring phenolic compounds: Acid chlorogenic 2, 3,4-dimethoxyphenyl, 5,6-dihydroxy-2-(4-hydroxy-3-

methoxyphenyl)- 7,8-dimethoxy4H-chromen-4-one With a docking score of –7.190, –7.182, and –6.903, -5,6-dihydroxy-7,8-dimethoxy-4Hchromen-4-one formed more hydrophobic interactions with amino acid residues and had potential affinities against the major protease of SARS-CoV-2 [26]. The "CCurcuma longa plant produces the wonderful yellow substance known as curcumin. It is the most important curcuminoid contained in turmeric (Curcuma longa), a plant from the Zingiberaceae family, which belongs to the ginger family. Curcumin belongs to the class of diarylheptanoid compounds. The optimal docked molecule was found to be hexahydrocurcumin and hexahydrocurcuminol. For both compounds, the Autodock score was -6.6 kcal·mol−1 [27]. With "glide G-score values ranging from −6.13 kcal/mol (curcumin) to − 6.77 kcal·mol−1 (cyclocurcumin), the ligands compared favorably with the currently indicated medicines for COVID-19, hydroxychloroquine (G-score −5.47) and nelfinavir (−5.93), according to the results of the molecular docking" research. The cyclocurcumin of turmeric is significantly more active than remdesivir (−6.38) [28]. For the molecular docking, three natural chemicals have been selected from various natural sources. The main component of Mangifera indica is mangiferin. Phlorizin is the glucoside derivative of phloretin that can be found in apple bark and unripe apples. Gallic acid and UDP-glucose are used for the biosynthesis of glucogallin, a member of the gallotannin class. It is mainly found in amla fruits and oak leaves. Phlorizin's binding affinity was -7.9 kcal/mol, while glucogallin's was -7 kcal/mol, while the maximum binding affinity for Mpro was -8.5 kcal/mol for mangiferin [29]. The present study examined the potential of S. lycopersicum L. carotenoids and polyphenols to inhibit human ACE-2 and SARS-CoV2 Mpro. According to in silico molecular modeling studies, cyanidin from polyphenols and β-carotene, among other carotenoids, were found to have binding affinities of –6.75 kcal/mol as well as –7.24 kcal/mol, respectively, making them the most efficient SARS-CoV2 Mpro inhibitors [30].

4. TERPENES:

Terpenes are naturally occurring isoprene-based molecules with a broad spectrum of medicinal effects and great chemical diversity. The discovery of new medical agents has benefited greatly from this class of natural compounds. Terpenoids, or derivatives of terpenoids, are traditional medicines with a variety of therapeutic applications derived from medicinal plants [31]. Triterpenoids, which consist of 30 carbon atoms polymerized into 6 isoprene units, are the most prevalent phytochemical class. They consist of almost 20,000 known chemicals. They are widely scattered in nature. Triterpenes have long been used in Asian countries as hepatoprotective, analgesic, anti-inflammatory, cardiotonic, and sedative drugs. Studying different triterpenoid chemicals obtained from mangroves that could be used to stop the spread of COVID-19 was the goal of the study. The compounds such as beta-amyrin, betulin, germanicol, taraxerol, lupeol, lupane, simiarenol, tiraculallol, ursolic acid, and oleanolic acid have the lowest binding energies and inhibition constants. Compared to the other compounds, the compounds of ursolic acid exhibit greater anisotropy—9.24 kcal/mol is the binding energy of ursolic acid [32]. Compounds from Syzygium aromaticum or cloves have antibacterial, anti-inflammatory, antioxidant, and antiparasitic properties. The active component of clove, crategolic acid, showed the highest binding affinity to this protease among the substances studied; this is probably due to the fact that it has the most hydrogen bonds. Sennoside A, B, C, and D, the active components of Sana Makki, came in second. Crategolic acid has an affinity for binding of -13.5 kcal·mol−1 [33]. The activity of SARS-CoV 3CLpro can be significantly inhibited by

MeOH (95%) extracts from the bark of Tripteryguim regelii (Celastraceae) (>70% inhibition at 30 lg/mL). Four quinone methide triterpenoid derivatives were isolated from the CHCl3 extracts. Based on their spectroscopic analysis, they identified these compounds as celastrol, pristimerin, tingenone, and iguesterin. Celastrol, pristimerin, tingenone, and iguesterin are among the recently discovered bioactive compounds with SARS-CoV 3CLpro inhibitory activity. Their binding affinities are -9.58, -9.87, -9.75, and -9.97 kcal/mol, respectively [34]. It was found that triterpenes and polysaccharides are the main components of Poria cocos. The triterpenes, which have biological immunomodulatory, anti-inflammatory, antitumor, and antioxidant properties, were the most important active compounds. The best Mpro binding activity of Poria cocos was found for sterol triterpenes (ergosterol peroxide) and sterane triterpenes (pachymic acid), according to the results of molecular docking. The findings show that pachymic acid partially inhibits the SARS-CoV2 3CL hydrolysis enzyme. Pachymic acid has a -7.3 kcal·mol−1 binding affinity [35]. Twelve chemicals were extracted from the different parts of Lawsonia inermis: two flavonoids, two naphthoquinone derivatives, β-sitosterol, five triterpenoids, and two long-chain alcohols. The triterpenoids exhibited remarkable binding energies to Mpro, with ΔG values even lower than those of the controlled antiviral drug (Remdesivir) (−6.43 kcal/mol). The most effective chemical was suavissimoside R1, which bound to SARS-CoV Mpro with a binding energy ΔG and IC50 calculated values of −8.19 kcal/mol [36]. In total 20 different compounds, the compounds of Allium sativum were selected. Out of all the compounds, squalene, trans-13-octadecenoic acid, methyl 11-hexadecenoate, 1,2,3-propanetriyl ester, as well as 1,4-dihydro-2,3-benzoxathiin-3-oxide, are the five that had the highest binding affinity to 3CL-Pro. Squalene, a triterpene, has the maximum affinity for binding (-7 kcal/mol) [37].

5. ISO FLAVONOIDS:

An isoflavone isolated from Psorothamnus arborescens, 5,7,3’,4’-tetrahydroxy-2’-(3,3-dimethylallyl)-isoflavone, generated strong H-bonds and had the highest docking score (S = -16.35) and binding affinity (-29.57) [38].

6. COUMARIN DERIVATIVES:

Psoralen, Bergapten, Imperatorin, Heraclenin, Heraclenol, Saxalin, Oxepeucedanin, Angelicin, Toddacoumaquinone, as well as Aesculetin, are the most strongly advised compounds; they could serve as potent COVID-19 primary protease inhibitors. These compounds are derived from medicinal plants. Using a binding energy of −7.8 kcal/mol, toddacoumaquinone, a natural coumarin derivative, has shown a remarkable capacity to inhibit other molecules, according to molecular docking experiments. Toddalia asiatica (Rutaceae) was the source of the isolated toddacoumaquinone [39].Mesuol, glycycoumarin, Inophyllum pylori, oxypeucedanin hydrateas well as mesuol showed the best binding affinities and negative energy scores among the 50 coumarin phytochemicals that were isolated from plants. Through hydrophilic and hydrophobic interaction, these compounds interacted with either or both of the catalytic residues (Cys145 and His41) of 3CLpro. Regarding the components of Inophyllum and P, oxypeucedanin hydrate, glycycoumarin, and mesuol, the best docking scores were found to be -11.89, -11.43, -11.76, and -11.17 kcal/mol, respectively [40].

7. OTHER HERBAL PHYTOCONSTITUENTS:

3 significant native Indian medicinal herbs are Tinospora cordifolia (Giloy), Phyllanthus niruri Linn. (Bhumi amla), and Emblica officinalis (Amla) that are widely used in ayurvedic formulations to treat a range of diseases. 96 bioactive compounds comprising giloy, amla, and

bhumi amla were isolated from recent literature. For the docking analysis in this work, 32 bioactive candidates from Giloy were selected. Of the 32 bioactives found in giloy, apigen-6-C-glucosyl7-O-glucoside (−6.4 kcal/mol) and amritoside (−7.2 kcal/mol) exhibited the highest binding affinity. Pectolinarin (− 5.8 kcal/mol) and astragalin (−5.8 kcal/mol) of the 35 bioactives from bhumi amla showed the maximum affinity for binding to the COVID-19 Mpro target. Of the thirty amla bioactives, it was found that 7-ketositosterol (− 5.5 kcal/mol) and quercetin (− 6.9 kcal/mol) fit the Mpro substate binding cleft [41]. Ayurvedic concoction made up of 26 active ingredients derived from four different plants: Piper nigrum (black pepper), Ocimum basilicum (sweet basil), Glycyrrhizaglabra (liquorice), and Zingiber officinale (ginger). Five active compounds were identified after screening 26 compounds, primarily focusing on those with antiviral and anti-inflammatory properties: moupinamide, coumaperine, curcumin, and 6-Dehydrogingerdione. With a docking score of -4.997 kcal/mol, moupinamide, which is found in Piper nigrum, is the most suitable because it binds both Mpro and SpikBeing e protein firmly [42]. It was discovered that the stilbenolignans employed in this study belonged to three distinct plant families. It is possible to identify Lehmbachol D, Gnetifolin F, and Gnetofuran A from Gnetum cleistostachyum (Gnetaceae). Maackia amurensis (Fabaceae) is the source of maackolin, while Aiphanes aculeata (Arecaceae) is the source of aiphanol. Following Gnetifolin F's molecular interaction investigations, the binding affinity with Glu166 residues was determined to be − 8.5 (kcal/mol), indicating the possibility of Gnetifolin F being a strong inhibitor candidate. Furthermore, the SARS-CoV-2 Mpro-Maackolin analogue complex, measuring − 103.61 kJ·mol−1, exhibited the largest negative binding free energy value, according to estimations of binding free energy. The SARS-CoV-2 Mpro-Gnetifolin F analogue complex, with a value of − 99.59 kJ·mol−1, came after this [43]. The in silico study's outcomes demonstrated that numerous chemical components from the ginger and black pepper families may be effective against COVID-19. The chemical components of ginger, such as 8- and 10-gingerol, and black pepper, such as piperdardiine and piperanine, are highly potent against COVID-19. The above-mentioned compounds have glide scores of -5.95, -5.88, -5.72, and -5.52 kcal/mol [44]. In addition to their documented immunomodulatory action in host cells, bioactive components of the traditional ayurvedic medicine Tulsi exhibit a strong binding affinity to COVID-19 Main protease (Mpro), suggesting that they may be able to regulate viral proliferation. Vicenin has demonstrated the highest binding affinity (-7.02) and ability to make hydrogen bonds with amino acid residues, such as Thr26, Phe140, His163, Glu166, and Thr190, making it the most effective chemical among the other compounds under consideration [45]. Through docking scores of − 9.7 and − 9.2 kcal/mol, respectively, molecular docking calculations presented the strong binding affinities of the curcumin, extracted from Curcuma longa, and salvianolic acid A, obtained from Salvia officinalis (Sage), towards Mpro [46]. Eight eucalyptus chemicals were chosen to be used against the main protease target. Each of the eight drugs exhibited substantial binding affinities to the binding pocket, as determined by molecular docking studies. Three compounds (allo-aromadendrene, aromadendrene, and α-gurjunene) having the least inhibitory Reliable readings were selected for additional examination. The docking scores of aromadendrene and α-gurjunene are -7.23 and -7.34 kcal·mol−1, respectively. The binding affinity of allo-aromadendrene was -7.17 kcal·mol−1 [47].

TABLE 1 : List of phytochemical constituents with their biological source and binding affinity towards Mpro target protein

PHYTOCHEMICAL CONSTITUENT	BIOLOGICAL SOURCE	BINDING AFFINITY (KCAL/MOL)
FLAVONOIDS:		
PubChem 885-071-27	-	-9.5
PubChem 129-716-607	-	-10.7
Amentoflavone	Gingko biloba Hypericum perforatum	-9.7
Alpinetin	Boesenbergia rotunda	-7.51
Pinocembrin	Boesenbergia rotunda	-7.21
Pinostrobin	Boesenbergia rotunda	-7.18
3',4'-dimethoxy luteolin	Artemisia sublessingiana	-6.81
Rutin	Coriandrum sativum L.	-9.6
ALKALOIDS:		
Ajmalicine	Catharanthus roseus	-8.28
Yohimbine	Pausinystalia johimbe	-8.68
Biscryptolepine	Cryptolepis saguinolenta	-8.80
Cryptoquindoline	Cryptolepis saguinolenta	-9.50
Cryptomisrine	Cryptolepis saguinolenta	-10.6
Cryptospirolepine	Cryptolepis saguinolenta	-10.0
Sophaline D	-	-8.79
Thalimonine	Thalictrum simplex	-8.39
Strychnidin-10-one	Strychonus nux-vomica	-8.5
2,3-dimethoxy brucin	Strychonus nux-vomica	-8.5
Liriodenine	Xylopia aethiopica	-7.9
Anisotine	Justicia adhatoda	-7.9
PHENOLIC COMPOUNDS:		
Glycyrrhizin	Glycyrrhiza glabra	-8.9
Rosmarinic acid	Rosmarinus officinalis	-8.0
Naringenin	Citrus fruits	-7.9
Chlorogenic acid	Satureja L.	-7.19
Hexahydrocurcumin	Curcuma longa	-6.6
Hexahydrocurcuminol	Curcuma longa	-6.6
Cyclocurcumin	Curcuma longa	-6.77
Glucogallin	Amla fruit, oak leaves	-7
phlorizin	Apple bark	-7.9
Mangiferin	Mangifera indica	-8.5
Cyanidin	Solanum lycopersicum	-7.24
β-carotene	Solanum lycopersicum	-6.75
TERPENES:		
Ursolic acid	Bruguiera gymnorhiza	-9.24
Crategolic acid	Syzygium aromaticum	-13.5
Celastrol	Tripterygium regelii	-9.58
Pristrimerin	Tripterygium regelii	-9.87
Tingenone	Tripterygium regelii	-9.75
Iguesterin	Tripterygium regelii	-9.97
Pachymic acid	Poria cocos	-7.3
Suavissimoside R1	Lawsonia inermis	-8.19
Squalene	Allium sativum	-7

ISO FLAVONOID:		
5,7,3',4'-tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone	Psorothamnus arborescens	-29.57
COUMARIN DERIVATIVES:		
Toddacoumaquinone	Toddalia asiatica	-7.8
Glucycoumarin	Glycyrrhiza uralensis	-11.89
Inophyllum P	Calophyllum inophyllum	-11.43
Oxypeucedanin hydrate	Angelica japonica	-11.76
Mesuol	Mesua ferrea	-11.17
OTHERS:		
Moupinamide	Piper nigrum	-4.997
Gnetifolin F	Gnetum cleistostachyum	-8.5
8-gingerol	Zingiber officinale	-5.95
10-gingerol	Zingiber officinale	-5.88
Piperdardine	Piper nigrum	-5.72
Piperanine	Piper nigrum	-5.52
vicenin	Ocimum tenuiflorum	-7.02
Salvianolic acid A	Salvia officinalis	-9.2
Curcumin	Curcuma longa	-9.7
Aromadendrene	Eucalyptus globulus	-7.23
α-gurjunene	Eucalyptus globulus	-7.34
Allo-aromadendrene	Eucalyptus globulus	-7.17
Stigmasta-5,22-dien-3-ol	Cyperus rotundus linn	-45.12 (CDOCKER score)
β-amyrin	Cyperus rotundus linn	-48.36 (CDOCKER score)

CONCLUSION:

By the end of 2019, the SARS-CoV2 virus had given rise to COVID-19, which had spread quickly all over the world. The spread of the disease has been significantly contained thanks to public health initiatives such as vaccinations, mask wearing, and social distancing. Scientific progress has advanced rapidly due to the pandemic, particularly in the areas of vaccine development and antiviral therapies. As antiviral medications stop the SARS-CoV2 virus from proliferating and spreading, they have proven to be extremely important in the fight against COVID-19. Among the earliest antiviral medications approved for the COVID-19 emergency was Remdesivir, which had previously been developed for the Ebola virus. Several target proteins in SARS-CoV2 are essential to the life cycle of the virus as well as the subject of ongoing research for vaccines and treatments: spike (S) protein, major protease (Mpro or 3CLpro), nucleocapsid (N) protein, papain-like protease (PLpro), as well as RNA-dependent RNA polymerase (RdRp). Several target proteins are essential for the virus's lifecycle and are the subject of ongoing research into vaccines and treatments, which are as follows: Spike (S) Protein, Main Protease (Mpro or 3CLpro), Papain-like Protease (PLpro), RNA-dependent RNA Polymerase (RdRp), Nucleocapsid (N) Protein. Targets for treatment include 2 proteases, 3CLpro and PLpro, as well as the RNA-dependent RNA polymerase (RdRp), which are crucial for viral replication. Herbal medications have been looked into for COVID-19 treatment because of their possible antiviral, anti-inflammatory, and immune-stimulating qualities. Numerous herbs have been studied, including those used in Indian Ayurvedic therapy, traditional Chinese medicine formulations, and other plant-based therapies. Combining herbal remedies with

medical therapies may provide an additional strategy for managing the illness. Among many phytochemicals, we have reviewed the effects of flavonoids, alkaloids, phenolic compounds, terpenes, iso flavonoids, coumarin derivatives, and other phytochemical constituents identified from herbs. From the above-mentioned phytochemicals, there are compounds that showed the highest binding affinity towards Mpro target protein; they are as follows: In flavonoids PubChem 129-716-607 (-10.7 kcal/mol), cryptomisrine (-10.6 kcal/mol) in alkaloids, glycyrrhizin (-8.9 kcal/mol) in phenolic compounds, iguesterin (-9.97 kcal/mol) in terpenes, glycycoumarin (-11.89 kcal/mol) in coumarin derivatives, and curcumin also showed highest binding affinity (-9.7 kcal/mol), which was isolated from curcuma longa, one of the most important herbs used for the management of various illnesses. Although some have shown promising results, thorough clinical trials are necessary to verify their security and efficiency in treating COVID-19.

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