International Journal of Innovative Technology and Exploring Engineering (IJITEE)
ISSN: 2278-3075 (Online), Volume-11 Issue-9, August 2022

Exploring the Potential of Natural Compounds Against Pro-Inflammatory Cytokine Proteins Involved in Worsening COVID-19 and Against COVID-19 Proteins: An in Silico Approach

Aayushka P. Nashte, Sneha T. Patnawar, Guruprasad N. Kulkarni, Pallavi S. Patil

Abstract: ***Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a causative agent for global pandemic disease nCOVID'19, has directed the attention of the scientific community towards the development of effective vaccines and drugs. Attempts are being made for repurposing existing drugs known for their antiviral activities, and test the traditional herbal medicines, natural compounds, nutraceuticals known for their health benefiting and immune-boosting activity against SARS-CoV-2. Multidimensional approach is employed to find effective drugs against SARS-CoV2. In this study, 108 natural compounds were examined in inhibiting human protein targets which are responsible for worsening the condition of COVID-19 through a virtual screening approach. This study has screened the natural compounds 3-Hydroxydecanedioic acid, Cucurbitacin S, Diosgenin which may exhibit inhibitory activity against IL-1 receptor,IL-6 receptor respectively. It has also revealed that Dihydro-beta-ergocryptine and cucurbitacin S may exhibit inhibitory activity against TNF-alpha receptor. Further it concluded that exfoliazone shows better inhibitory activity against P38-MAPK and NF-κB pathway inhibitory proteins. These natural compounds could lead the way for future drug discovery, design and development. This will help researchers to scout new drugs in drug discovery(in-vitro and in-vivo studies).***

Keywords: Docking Studies, Insilico Analysis, Covid-19, Cytokine Storm, Natural Compounds.

I. INTRODUCTION

Novel coronavirus disease (nCOVID-19) is caused by SARS-CoV-2 Wuhan in China witnessed a spur in unknown respiratory tract infection cases in late 2019. Covid-19 has accounted for high levels of mortality rate. Globally, as of 6:25 pm CEST, 1 July 2022, there have been 545,226,550 confirmed cases of COVID-19, including 6,334,728 deaths, reported to WHO until now worldwide [1].

Manuscript received on 20 July 2022 | Revised Manuscript received on 13 August 2022 | Manuscript Accepted on 15 August 2022 | Manuscript published on 30 August 2022.

*Correspondence Author

Aayushka Nashte, Student, Department of Biotechnology Engineering, Kolhapur Institute of Technology's (Autonomous), College of Engineering Kolhapur (Maharashtra), India.

Sneha T. Patnawar*, Assistant Professor, Department of Biotechnology Engineering, Kolhapur Institute of Technology's (Autonomous), College of Engineering Kolhapur (Maharashtra), India.

Guruprasad Kulkarni, Student, Department of Biotechnology Engineering, Kolhapur Institute of Technology's (Autonomous), College of Engineering Kolhapur (Maharashtra), India.

Dr. Pallavi S. Patil, Associate Professor & Head, Department of Biotechnology Engineering, Kolhapur Institute of Technology's (Autonomous), College of Engineering Kolhapur (Maharashtra), India.

It has a unique genetic setup which has made it unresponsive to the existing medical treatments and accelerated search of novel targets for vaccine development and drugs for prevention and treatment against nCOVID'19 [20].

The symptoms of COVID-19 range from asymptomatic upper respiratory tract infection to critical illness and pneumonia associated with acute respiratory distress syndrome (ARDS) causing severe inflammatory response. Excessive inflammation is considered as a risk factor for ARDS [45]. Majority of people develop mild to moderate symptoms and only few require hospitalisation, especially people with previous illnesses like cardiovascular disease, diabetes, chronic respiratory disease, cancer etc. People above 60 have a greater risk of developing acute respiratory distress syndrome (ARDS)[6]. Severe Immune manifestations are found in 20 to 30 percent of the patients hospitalised with COVID-19 and even develop cytokine storms in the later stages[7]. Patients showing critical illness characteristics have few phenomena in common for e.g., patients who have died due to COVID showed lower counts of lymphocyte, cytokine storm and also exaggerated release of pro-inflammatory cytokines (IL-6 and IL-1, TNF-alpha) have been noted which expand the clinical course by causing tissue damage which eventually causes multi organ failure and death [6], [48][49][50].

Firstly, the approach employed was to target proinflammatory cytokines to reduce the effect of COVID-19 attack. Pro-inflammatory cytokines promotes T cell expansion, B-cell differentiation leading to cytokine storm (a condition also seen in severe patients) inflammation, oxidative distress and hyper inflammatory response resulting in the recruitment of macrophages, T and B cells in the lung alveolar cells[52], [53], [6]. The uncontrolled and dysregulated secretion of inflammatory and pro-inflammatory cytokines increases the severity of the viral infection and mortality rate[47], [54].This torrent of events may lead to multiple organ failure, acute respiratory distress, or pneumonia[51].Pro-inflammatory cytokines released in higher amounts also cause oxidative distress to a greater extent. Oxidative distress participates in the amplification and perpetuation of the cytokine storm, coagulopathy, and cell hypoxia [8], [44].

Another approach employed was to target the viral proteins. Viral proteases 3CLpro and PL pro on attacking alveolar cells cleave polyproteins(pp1a and pp1ab) of COVID-19 which are employed in the process of replication, leading to the development of new viruses that further attack other alveolar cells[6]. Many drugs such as Molnupiravir, Paxlovid, Tocilizumab, Remdesivir are approved by FDA to treat COVID-19[2], [3], [4], [5]. Studies have shown that the drugs like Remdesivir and Molnupiravir have severe side effects like organ dysfunction, respiratory failure and diarrhoea, nausea, dizziness [42][43], [51]. Paxlovid comprises of nirmatrelvir and ritonavir, it cannot be used in patients taking CYP3A4 or 2D6 substrate medication as a CYP3A4 enzyme inducer reduces the concentration of nirmatrelvir and ritonavir [46]. Phytocomounds, nutraceuticals and other naturally occurring compounds show very less side effects [10], [9] and hence to minimise the risk of the side effects of drugs, there is a need to explore the therapeutic nature of phytochemicals, natural products and nutraceuticals to combat Covid-19.

Studies till now have employed a limited number of ligands and have narrow exploration of viral proteins and cytokine pathways, which is an obstacle in the discovery of the best suited therapeutic against Covid-19 with minimum or no side effects. In the current study, targeting receptors of proinflammatory cytokines such as IL-6, IL-1,TNF-alpha also the pathways viz. p38-MAPK, NF-κB with potential phytocompounds, nutraceuticals and natural compounds which may have minimum or no side effects as ligand molecules. The current study has employed the screening of 108 ligands through *in Silico* molecular docking, drug likeliness and ADMET analysis. Analysis of protein-ligand interactions has helped in shortlisting the potential phytocompounds, nutraceuticals and natural compounds for drug development. The future scope of this study is to perform molecular simulation, validating the potential inhibitors through laboratory and clinical trials.

II. MATERIALS AND METHODS

A. Retrieval of Data

Protein Targets

The X-ray crystal structures of most of the proteins in the human receptor have facilitated the search of virtual screening for potential inhibitors [20]. Protein targets were retrieved from the Protein Data Bank (PDB),[52] in the PDB format. Five proteins were selected as targets which played a role in worsening the COVID-19 condition. Human receptor proteins included Crystal Structure of the extracellular domains of Human Interleukin-6 Receptor alpha chain (PDB-ID-1N26),Extracellular domain of the 55 KDA Tumour Necrosis Factor Receptor Crystallised at PH3.7 in P 21 21 21(PDB ID-1EXT), Crystal structure of an Interleukin-1 receptor complex (PDB ID-3O4O) were used to target the release of IL-6,IL-1 and TNF-alpha which are pro-inflammatory cytokines. The proteins targeted to inhibit the MAPK and NF-κB pathways are Human p38 MAP kinase in complex with BIRB796 (PDB ID-1KV2),NF-κB P50 HOMODIMER BOUND TO DNA(PDB ID-1SVC).

Ligand Dataset Preparation

The structures of the phytocompounds were obtained from the PubChem database in SDF format for docking studies from PubChem[21]. The compounds were converted to .pdb with the help of Open Babel software[18].

108 natural compounds were targeted against Extracellular domain of the 55 KDA Tumour Necrosis Factor Receptor Crystallised at PH3.7 in P 21 21 21(PDB ID-1EXT),Human receptor proteins included Crystal Structure of the extracellular domains of Human Interleukin-6 Receptor alpha chain (PDB-ID-1N26),Human p38 MAP kinase in complex with BIRB796(PDB ID-1KV2),NFKB P50 HOMODIMER BOUND TO DNA(PDB ID-1SVC) and Crystal structure of an Interleukin-1 receptor complex (PDB ID-3O4O).

Energy minimization of the phytocompounds was performed to get the structure with lowest free energy using universal force field with a conjugate gradient optimization algorithm at 200 steps which was done through Open Babel in PyRx[14][16].The models were later converted into pdbqt format for molecular docking.

Protein Structure Preparation

Biovia Discovery Studio Visualizer software was used for protein preparation. The proteins were converted into the pdbqt format using the Autodockvina module PyRx software tool[22]. The additional configuration parameters were set to their default values. The ligand binding sites were recognized with the help of Biovia Discovery Studio and accordingly the grid parameters were set for docking.

B. Setting grid parameters

Active binding sites of a macromolecule are the surface areas where a substrate or a ligand binds and leads to chemical and structural changes. Thus, the protein interfaces serve as generic binding sites to ligands. Protein cavities were detected on the protein surface and their centre x, y and z coordinates were noted from Biovia Discovery studio application [53]. The grid box was set as per co-ordinates in PyRx.

C. Acquiring binding site residues

Binding site residues were acquired with the help of pymol. Residues at a distance of 5 Å from the ligand were considered as not only the interacting residues but all in the vicinity should be understood. Hydrogen bonds approximately have a bond length between 2.8 Å to 3.4 Å, compared to this ionic interaction are a little shorter. Vander waals interactions have comparatively longer bond lengths between 3.8 Å to 4.2 Å. With the consideration of all these aspects and bond length, the distance of 5 Å was set.

D. Standard drugs and Standard natural compounds

Standard drugs and standard natural compounds were used to compare the binding affinity, binding site interactions, structure and ADMET. The structures of standard natural compounds and standard clinical drugs were retrieved from PubChem [23].

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They were retrieved in .sdf format and were converted into .pdb format through Open Babel software [24]. Table displays standard natural compounds and table II displays standard clinically approved drugs.

Table I: Details of Standard Natural Compounds

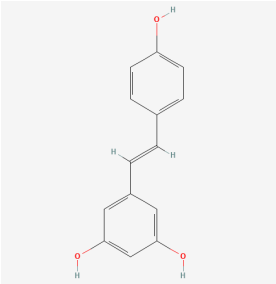
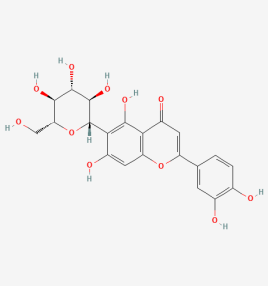
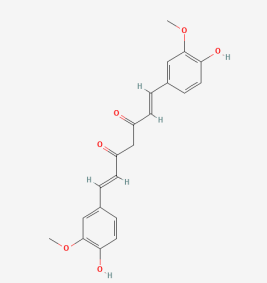
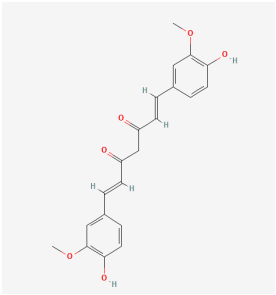
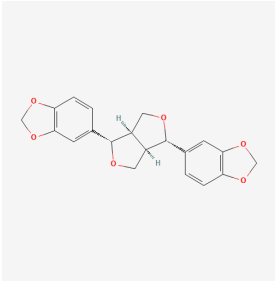
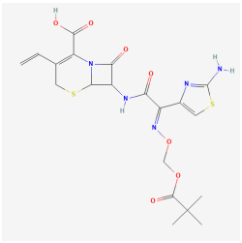
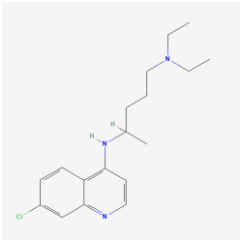
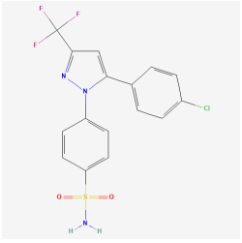
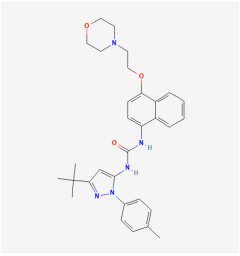
Sr. No.	Protein	Ligand	PubChem ID	Chemical Structure
1.	3o4o (IL-1inhibitor)	Resveratrol	445154	
2.	IL-6 receptor	Isoorientin	114776	
3.	TNF-alpha receptor	Curcumin	969516	
4.	1svc (NF-κB)	Curcumin	969516	
5.	1kv2 (p-38MAP)	Sesamin	72307	

Table II: Details of Standard Clinically Approved Drugs

Sr. No.	Protein	Ligand	PubChem ID	Chemical structure
1.	3o4o (IL-1inhibitor)	Anakinra	146171046	
2.	TNF-alpha receptor	Chloroquine	2719	
3.	1svc (NF-κB)	SC-236	9865808	
4.	1kv2 (p-38MAP)	Doramapimod	156422	

E. Molecular docking studies

Autodockvina in PyRx software which is an inbuilt algorithm which was employed for docking of 108 natural compounds with protein targets [13]. To get the maximum binding affinity and best conformational pose the grid parameters noted from discovery studio were adjusted accordingly. Site specific and blind docking both were performed on standard natural compounds and clinically approved drugs. Site specific docking was performed for comparison of molecular interactions on that particular site. The assessment of the docked protein-ligand complex was made on the lowest binding energy (kcal/mol) values and was considered for comparison with the selected natural compounds. BIOVIA discovery studio was used for the analysis of 2D and 3D interactions [17].

F. ADMET analysis

Towards the end of the drug discovery process ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties were predicted. ADMET analysis helps in the elimination of Drug molecules failure and narrows our focus on potential drug candidates. Early prediction of these properties helps in the reduction of research costs. It also aims at replacement of traditional in vitro and in vivo experiments [141].

The Swiss ADME tool was used to study the ADME parameters (http://www.swissadme.ch). By using parameters like, bond acceptors, bond donors, Log s (esol), Log s (ali), bioavailability, GI absorption, BBB permeate, Lipinsky violations, Pains alerts, LD 50 in rats etc. Analysis was done for CYP inhibition. First the ligands with highest binding affinity were tested. The tests were continued in ascending order of binding affinity until a compound was spotted which satisfied most of the parameters.

G. Drug Likeness Prediction Studies

A good drug candidate is absorbed properly in a given time frame and gets evenly distributed throughout the system for its effective action and output [12], [15][29]. Toxicity plays a very important role in determining side-effects and overall effectiveness of drugs [11]. Failure of drugs at the stage of clinical trials amounts to huge amounts of loss and detrimental in the drug development process.

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Insilico drug-likeness prediction along with other ADME/Tox tools helps in accelerating the drug discovery process with minimum loss and greater assurance and ultimately leading to compounds with predicted biological activity.

OSIRIS Property Explorer was used to study the drug likeness properties[19]. The parameters considered were clog p, solubility log s,molecular weight, TPSA and drug score. First the ligands with high binding affinity were tested. The tests were continued in descending order of binding affinity until a compound was spotted which satisfied most of the parameters.

III. RESULT AND DISCUSSION

A. Dataset Retrieval

The selected protein targets and the ligands for the study are listed in the Table III (pdbid, name, structure) and Table IV respectively.

Table III: Details of protein targets

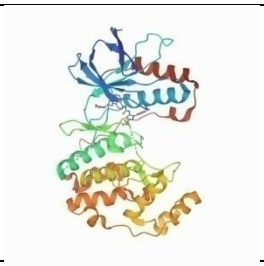
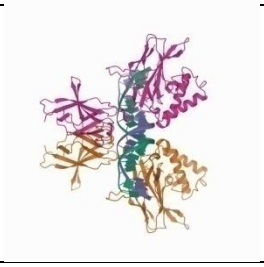
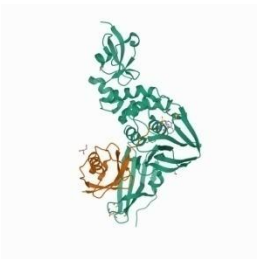
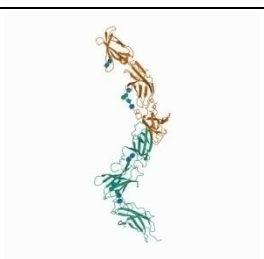
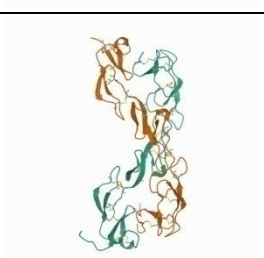
Sr. No.	Protein name	PDB ID	Structure
1.	Human p-38 MAP kinase in complex with BIRB796 (p-38 MAP)	1KV2	
2.	NFKB P50 Homodimer bound to DNA (NF-κB)	1SVC	
3.	Crystal structure of an interlukin-1 receptor complex (IL-1 receptor)	3O4O	
4.	Crystal structure of the extra-cellular domains of human Interlukin-6 receptor alpha chain (IL-6 receptor)	1N26	
5.	Extracellular domain of the 55KDA Tumor Necrosis Factor receptor crystallized at pH 3.7 (TNFR1)	1EXT	

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Table IV: List of Natural Compounds Used in This Study and Their Distribution and Medicinal Uses

Sr. No.	Phytochemical names	Pubchem ID	source/origin	Plant part	Geographical distribution	Medicinal use	References
1.	1,2 - Dithiolane-4-carboxylic acid	6451512	Asparagus officinalis	Shoot	Eastern mediterranian, Western coasts of Europe	—	[113]
2.	Glucoraphanin	9548634	Brassica oleracea	Flower, leaf, seed, root	Mediterranean region and southwestern Europe	Anti-cancer	[77]
3.	Gluconasturtin	15560248	Armoraciarusticana	Plant	Europe and north America	Anti-cancer	[76]
4.	Glucotropaeolin	656498	Lepidiumsativum	Plant	African region	Anti microbial	[118]
5.	Chavicine	1548912	Piper nigrum	Fruit	Western ghats of Kerala of India	Anti-oxidant, anti-ashmatic, Anti-carcinogenic, Anti-inflammatory, anti-ulcer etc.	[104]
6.	Tetrahydrocorticosterone	65553	Koala (Phascolarctoscinereus)	metabolite	Australia	Anti-inflammatory functions	[121]
7.	[7]-Gingerol / Dihydrocapsiato	11472344	Zingiberofficinale	Rhizome	Tropics of asia, africa, america and australia	Anti-microbial, antioxidant, anti-inflammatory, and antitumor activity	[78]
8.	Nordihydrocapsaicin	168836	Capsicum annuum	Fruit	South-east Asia	Anti-oxidant, anti-bacterial	[57], [126]
9.	Capsaicin	1548943	Capsicum annuum	Fruit, Resin, Exudate, Sap	South-east Asia	Anti-oxidant, anti-bacterial, anti-microbial	[57], [126]
10.	Oleuropein	5281544	Ligustrumjaponicum	Leaf	Japan, South Korea, California	Antioxidant,anti-inflammatory, anti-atherogenic, anti-cancer activities, antimicrobial activity, antiviral activity	[75]
11.	3 - Hydroxyflavone	11349	Astragalusmicrocephalus,Acaciaholosericea, Acacia implexa	Leaf	Western Asia	Anti-cancer	[63]
12.	Kermesic acid (Carminic acid)	11727234	Occurs naturally incochineal, Armenian cochineal, and Polish cochineal.	—	-	Anti-cancer and anti-viral	[140]
13.	Scutellarin	185617	Scutellariabaicalensis	Plant, root	Northern hemisphere	Anti-oxidant, anti-inflammation, vascular relaxation, anti-platelet, anti-coagulation, and myocardial protection	[128]
14.	Exfoliazone	131529	Streptomyces exfoliatus	—	—	Anti-cancer	[137]
15.	Procyanidin β-1	11250133	Aesculushippocastanum	Fruit and leaf	Europe	Anti-inflammatory	[133]
16.	1,2,6 - Trigalloylglucose	440308	Terminaliachebula	Fruit	Sub-himalayan region of Nepal, northern India to srilanaka, Myanmar, Thailand, southern china	Anticancer, antidiabetic, antimutagenic, antibacterial, antifungal, and antiviral effects	[129]
17.	1,3,4, 5- tetra - O -galloylquinic acid	124020	Guierasenegalensis	Leaves	Tropical Africa (Senegal to Sudan)	Akt-dependent NF-κbactivation is required for bile acids to rescue colon cancer cells from stress-induced apoptosis	[124]

18.	Punicalagin	44584733	Punicagranatum, Terminaliacatappa	Leaf, pericarp, steam bark,fruit, root bark	Iran to northern India, Asia, Australia	Anti-oxidant	[72]
19.	Casuarictin	73644	Syzygiumaromaticum	Leaf	Indonesia, Sri lanka, Parts of caribbean	Anti-inflammatory	[55]
20.	Castalin	99973	Castanea sativa	Plant	North-western Africa, north western Europe, western Asia	—	—
21.	Phytoene	5280784	Crocus sativus	Silk Stigma Style	Western Asia, northern India and China	Anti-tumor,Anti-cancer	[99]
22.	(-) - Epicatechingallate	107905	Camellia sinensis	Leaf	South eastern asia - china, Tibet and northern India	Anti-allergic, anti-oxidant, anthelmintics, anti-cancer, anti-mutagenic	[101], [107], [120]
23.	Theaflavin - 3 - gallate	71307578	Camellia sinensis	Leaf	South eastern asia - china, Tibet and northern India	Anti-proliferative and cytoctoxic	[62]
24.	Castalagin	168165	Terminaliaarjuna	Bark	Indian Subcontinent	Anti-viral	[127]
25.	Flavylium	145858	Tradescantiapallida	Fruits, flowers, leaves	Forests, roadsides, coastal forests	Anti-cancer and anti-inflammatory	[74]
26.	Dillapiole	10231	Anethumgraveolens	Leaf, seed, fruit	Mediterranean region and south and southwestern Europe	Anti-inflammatory	[112]
27.	Carnosol	442009	Salvia mellifera	Shoot	Coast ranges of California	Anti-cancer and anti-inflammatory	[88]
28.	Apiole	10659	Anethumgraveolens	Root, seed	Mediterranean region and south and southwestern Europe	Anti-tumor	[130]
29.	Tocopherols	14986	Moringaoleifera	Leaf	Northern India and Pakistan	Anti-oxidant	[82]
30.	Campesterol	173183	Aloe vera	Leaf	Africa, India and arid areas	Anti-inflammatory	[110]
31.	Rubixanthin	5281252	Rosa canina	Fruit	Western and central asia, Europe, north-western africa	—	—
32.	Canthaxanthin	5281227	Brassica	Leaves	Mediterranean region and southwestern Europe	Anti-cancer	—
33.	Neurosporene	5280789	Daucuscarota	Root	Europe, western Asia, northern and tropical africa	Cancer Prevention	[123]
34.	Brassica NapusNon-FlurescentChlorophyllcatabolite 3	100917761	Brassica Napus	Leaves	Western Europe, Canada, China, India	—	—
35.	Arctiin	100528	Forsythia suspensa	Fruit	China	Antiinflammatory, antioxidative, antiproliferativeand antitumor	[60]
36.	Indirubin	10177	Isatistinctoria	Leaves	Central Asia	Anti-inflammatory and antiviral	[106]
37.	Thymoquinone	10281	Monardafistulosa	Essential oil	Quebec to the Northwest Territories and British Columbia, south to Georgia, Texas, Arizona, Idaho, and northeastern Washington.	Anti-oxidant, anti-inflammatory,immuno modulatory, anti-histaminic, anti-microbial and anti-tumor	[71]
38.	Ascochlorin	11258227	Acremoniumegyptiacum (Fungi)	—	Asia (India), Europe	Treat diabetes, high blood pressure, high cholesterol, asthma, seizures, cancer and depression	[105]

39.	Cucurbitacin S	119287	Cucumissativus	Fruits and root	Western Asia (including China and spread to Europe)	Anti-inflammatory, Antitumor, Anti-artherosclerotic, Antidiabetic	[91]
40.	Celastrol	122724	Tripterygiumwilfordii	Plant	Eastern and southern China, Taiwan, Korea, and Japan	Anti-cancer, anti-inflammation, anti-obesity, and anti-diabetic	[68]
41.	Nimbolide	12313376	Azadirachtaindica	Leaf	Northern Australia, tropical Asia, Africa, Fiji, Mauritius, Puerto Rico, the Caribbean and many countries in South and Central America.	Anticancer, Antidiabetic, Antimicrobial	[56]
42.	Myrcenyl acetate	14235	Origanumonites	Shoot	Mediterranean region	Anti-inflammatoryand anti-oxidant	[139]
43.	Bavachin	14236566	Psoraleacorylifolia	Seed	Central India	LPS-induced inflammatory response	[84]
44.	Cryptotanshinone	160254	Salvia miltiorrhiza	Root	China and Japan	Anti-cancer, anti-inflammation, anti-obesity, and anti-diabetic	[132]
45.	Caryophyllene	5281515	Elsholtziacristata	Shoot	Asia to Peninsula Malaysia	Anti-cancer and chemotherapy	[97]
46.	Dihydro-artemisinin	3000518	Artemisia annua L	Leaves and Flower	Himalayan ranges	Anti-malaria	[92]
47.	Brassinin	3035211	Brassica oleracea	Leaf	Mediterranean region, south-western Europe, and southern England	Anticancer	[69]
48.	Dihydro-Beta-Ergocryptine	3084313	Ergot	Rye	Oregon	Treatment of idiopathic decline in mental capacity	[138]
49.	Silibinin	31553	Silybummarianum	Seeds	Southern Europe, the Mediterranean and Northern Africa	Anti-Inflammatory	[61]
50.	Emodin	3220	Aloe vera	Leaf, plant	Africa, India and areas.	Anticancer, antiinflammatory, antioxidant and antimicrobial	[73]
51.	Evodiamine	442088	Euodiarutaecarpa	Leaf	China and Korea	Anti-inflammatory	[142]
52.	Resveratrol	445154	Vitisvinifera	Fruit, shoot, leaf	Mediterranean region, Central Europe, and southwestern Asia	Anti-inflammatory effects	[135]
53.	Formononetin	5280378	Cicerarietinum	Seed	Asia, Europe, Africa	antimicrobial activity towards Giardia lamblia	[89]
54.	Apigenin	5280443	Cryptomeria japonica	Plant	South of Japan to north of Japan	Anti-oxidant and intiinflammatory	[134]
55.	Butein	5281222	Viciafaba	Fruit	Western Asia	Anti-inflammatory, anticancer, antioxidant, and anti-angiogenic	[125]
56.	Capillarisin	5281342	Artemisia capillaris	Plant	Pakistan, western Himalayas	Anti-oxidant , anti-inflammatory	[95]
57.	Garcinol	5281560	Garciniacambogia	Bark, Latex Exudate	Maharashtra, Goa, Karnataka, Kerala and Tamilnadu	Antitumor, antimicrobial	[122]
58.	Wedelolactone	5281813	Hypericumerectum	Essential oil	Europe, Western Asia and North Africa	Hepatitis, snake venom treatment, septic shock	—
59.	Gamma-Tocotrienol	5282349	Foeniculumvulgare	Seed, fruit	Southern Europe and Asia Minor	Anti-cancer	[85]

60.	Casticin	5315263	Vitexagnuscastus	Seed, shoot, leaf, fruit	Mediterranean region	Anti-cancer	[114]
61.	Andrographolide	5318517	Andrographispaniculata	Plant	Tropical Asian countries	cancer, diabetes, high blood pressure, ulcer, leprosy	[109]
62.	Oridonin	5321010	Isodonrugosus	Aerial parts	Western Himalayas	Anticancer, anti-inflammatory, cardioprotective	[98]
63.	Ergosterol peroxide	5351516	Ananascomosus	Leaf, plant	Tropics and subtropics	Anti-tumor and Anti-angiogenic	[67]
64.	Cardamonin	641785	Vitextripinnata	From cardamom spice	Tropical and subtropical regions of Australia, Asia	Anti-cancer and anti-inflammatory	[114]
65.	(z)-Guggulsterone	6450278	Commiphorawightii	Resin	Australia, Pacific Island, and Saudi Arabia	selective antagonist of farnesoid X receptor	[70]
66.	Ursolic acid	64945	Uncariatomentosa	Plant	South American countries	Anticancer	[79]
67.	Betulinic acid	64971	Arbutus unedo	Leaf	Eurosiberian region	Anti-cancer	[80]
68.	(-)-Epigallocatechin Gallate	65064	Camellia sinensis	Leaf	Southeastern Asia – China, Tibet, and northern India	Exerts potent anti-inflammatory effects by inhibiting signaling events and gene expression	[58]
69.	Caffeic acid	689043	Salvia nemorosa	Seed	Europe to W. Siberia and Afghanistan	Antioxidant, anti-inflammatory and anticarcinogenic	[108]
70.	Honokiol	72303	Magnolia obovata	Bark	Japan	Anti-inflammatory, anti-angiogenic, antioxidative and anti-cancer	[59]
71.	Parthenolide	7251185	Tanacetumvulgare	Plant	Eastern and Central Europe	Exceptional anti-cancer and anti-inflammatory properties	[103]
72.	Isoalantolactone	73285	Inulahelenium	Plant, rhizome, shoot, root	Eurasia, western China	Anti-inflammatory agent	[94]
73.	Brusatol	73432	Bruceamollis	Root	KarbiAnglong District of Assam, India	Treatment for amebiasis	[65]
74.	Curcumin	969516	Curcuma longa	Plant	South Asia, India to Malaysia	Cancer, diabetes, cardiovascular diseases, arthritis, Alzheimer's disease, psoriasis	[111]
75.	DIOSGENIN	99474	Solanumdulcamara	Plant	Eurasia and temperate northern Africa	Cancers, hyperlipidemia, inflammation, and infections.	[64]
76.	Piceatannol	667639	Rheum officinale,Euphorbialagascae	Plant	Seed of Euphorbia lagascae	Antiproliferative, antioxidant, antiinflammatory effects	[93]
77.	Pinoresinol	73399	Sesamumindicum	Seed	East African to Indies	Cancer treatment	[67]
78.	Secoisolariciresinol	65373	Viciafaba	Seed	Western Asia	Type 2 Diabetes	[90]
79.	Matairesinol	119205	Arctiumlappa	Plant, fruit, seed	Europe, Asia, and North America	Cancers, diabetes and AIDS	[131]
80.	Petunidin	441774	Vacciniumcorymbosum	Fruit	Eastern USA and Canada	Antioxidant and antiinflammatory activity,	[119]
81.	Malvidin	159287	Catharanthusroseus	Plant	Tropical and sub-tropical parts of India	Reduces TNF-α-induced inflammatory responses in endothelial cells	[83]

82.	Eriodictyol	440735	Ocimumbasilicum	Leaf	Tropics of Asia and Africa	Antioxidativeandanti-inflammatory activity.	[136]
83.	Isorhamnetin	5281654	Opuntiaficus-indica	Flower	Australia, southern Europe, Africa, La, southern Asia, southern USA and some oceanic islands	Reduces proinflammatory cytokine levels	[66]
84.	Fisetin	5281614	Acacia Catechu	Plant	India	Anticancer	[86]
85.	Kaempferol	5280863	Acacia Catechu	Plant	India	Inflammatory diseases	[115]
86.	Carvacrol	10364	Thymus vulgaris	Plant, Essential oil	European part of the Mediterranean	Antibacterial	[102]
87.	Stigmasterol	5280794	Panax ginseng	Root	Mountainous regions of Russian East, Northeast China, and Korean Peninsula.	Ayurvedicmedicine to treat arthritis	[81]
88.	Cafestol	108052	Coffeaarabica	Seed	Ethiopia and robusta	Anti-inflammation, anti-cancer, anti-diabetic, and anti-osteoclastogenesis	[116]
89.	Moronic acid	489941	Rhuschinensis	Leaves, stem	India, Indonesia, Japan, Korea, Laos, Malaysia, Singapore, Thailand	Anti-inflammatory ,Anti-AIDS Agents	[87]
90.	B - Cryptoxanthin	5281235	Cucurbitapepo	Fruit	Eastern United States and Mexico	Anti-inflammation	[100]
91.	L - Kynurenine	161166	A Saccharomyces cerevisiae metabolite ,mouse metabolite and human metabolite	—	—	Biomarker for assessing cancer risk.	[96]
92.	Lignan	261166	Schisandrachinensis	Petiole, hull husk, seed	Saschalin and Kurili islands	lowered risk of heart disease, menopausal symptoms, osteoporosis and breast cancer	[117]

B. Identification of Binding site residues and getting Grid Parameters

The grid parameters of protein cavities are listed in Table V The binding site residues of protein are listed in Table VI.

Table V: Grid parameters of protein cavity

Sr. No.	Protein	Site No.	X co-ordinate	Y co-ordinate	Z co-ordinate
1.	3o4o (IL-1 inhibitor)	1	-17.966000	-9.393000	-36.187000
		2	-37.216000	-28.893000	-7.937000
		3	1.784000	5.357000	8.063000
		4	0.534000	1.107000	-12.187000
		6	-26.216000	2.857000	-20.687000
2.	IL-6 receptor	1	13.244000	46.055000	94.859000
		2	20.994000	52.305000	65.109000
		3	56.805000	56.805000	43.109000
		4	27.805000	27.805000	108.359000
3.	TNF-alpha receptor	1	4.133000	29.158000	-4.620000
		2	-11.117000	46.658000	-24.620000
		3	18.133000	7.158000	11.630000
		4	-1.367000	43.408000	-5.870000
		5	21.383000	32.658000	2.130000
		6	7.383000	5.408000	9.130000
		8	-35.117000	52.408000	-14.370000
		9	-2.117000	33.408000	-19.370000
		11	-20.867000	53.158000	-21.370000
		12	23.883000	14.908000	7.630000
		13	12.133000	39.658000	-0.620000
		14	-15.367000	44.408000	-2.120000
4.	1svc (NF-κB)	1	53.233000	19.538000	44.513000
		2	24.483000	4.288000	28.513000
		4	40.233000	28.788000	44.263000
		6	58.733000	17.288000	44.763000
5.	1kv2 (p-38MAP)	1	13.210000	33.106000	18.432000
		2	43.460000	30.356000	9.432000
		3	47.210000	40.106000	17.932000
		4	36.960000	32.606000	21.682000
		5	27.710000	42.606000	6.682000

Table VI: Binding site residues of protein target

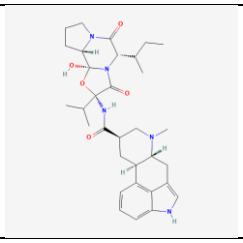
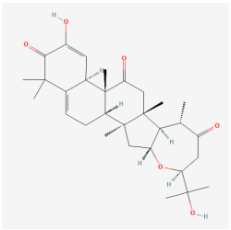
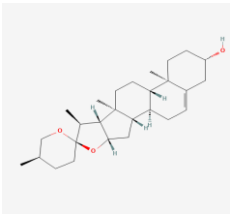
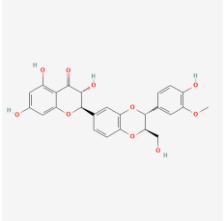
Protein name	Binding site residues
IL-1 receptor	127 GLN, 128 ILE, 129 LEU, 135 GLY, 136 VAL, 137 LEU, 138 VAL, 139 CYS, 156 TRP, 157 TYR, 158 LYS, 161 LEU, 162 LEU, 163 LEU, 170 PHE, 171 LEU, 172 SER, 177 THR, 178 HIS, 179 LEU, 180 LEU, 181 VAL, 184 VAL, 185 ALA, 188 ASP, 190 GLY, 192 TYR, 193 ARG, 211 ILE, 212 GLY, 213 LEU, 214 ARG, 215 ILE
IL-6 receptor	199 PRO, 200 PRO 201 ALA, 203 ILE, 204 THR, 205 VAL, 206 THR, 214 TRP, 216 SER, 215 LEU, 217 VAL, 218 THR, 219 TRP, 220 GLN, 221 ASP, 232 LEU, 233 ARG, 234 PHE, 235 GLU, 236 LEU, 237 ARG, 238 TYR, 239 ARG, 247 THR, 248 THR, 251 VAL, 255 GLN, 256 HIS, 257 HIS, 258 CYS, 259 VAL, 260 ILE, 261 HIS, 262 ASP, 263 ALA, 269 HIS, 270 VAL, 271 VAL, 272 GLN, 273 LEU, 274 ARG, 275 ALA, 291 ALA, 292 MET, 293 GLY, 294 THR, 295 PRO
TNFR1	20 TYR, 21 ILE, 22 HIS, 23 PRO, 24 GLN, 25 ASN, 28 ILE, 29 CYS, 30 CYS, 31 THR, 32 LYS, 33 CYS, 37 THR, 39 LEU, 40 TYR, 41 ASN, 42 ASP, 43 CYS, 44 PRO, 45 GLY, 50 THR, 51 ASP, 52 CYS, 60 PHE, 61 THR, 62 ALA, 63 SER, 64 GLU, 65 ASN, 66 HIS, 67 LEU, 68 ARG, 69 HIS, 70 CYS, 71 LEU, 72 SER, 75 LYS, 76 CYS, 77 ARG, 78 LYS, 79 GLU, 80 MET, 81 GLY, 91 ASP, 92 ARG, 93 ASP, 105 HIS, 106 TYR, 107 TRP, 108 SER, 111 LEU, 112 PHE, 113 GLN, 114 CYS, 115 PHE, 116 ASN

NF-κB	43 PRO, 44 TYR, 45 LEU, 46 GLN, 47 ILE, 84 GLN, 85 VAL, 86 LYS, 87 ILE, 88 CYS, 90 TYR, 91 VAL, 92 GLY, 93 PRO, 94 ALA, 95 LYS, 96 VAL, 97 ILE, 126 VAL, 127 THR, 128 ALA, 133 MET, 134 VAL, 135 VAL, 136 GLY, 137 PHE, 215 LEU 216 MET, 217 PHE, 218 THR, 219 ALA, 220 PHE, 221 LEU, 230 ARG, 231 ARG, 232 LEU, 234 PRO, 235 VAL, 236 VAL, 237 SER
p-38 MAP	9 TYR, 16 THR, 17 ILE, 18 TRP, 19 GLU, 20 VAL, 21 PRO, 23 ARG, 24 TYR, 25 GLN, 26 ASN, 27 LEU, 28 SER, 35 TYR, 36 GLY, 37 SER, 38 VAL, 39 CYS, 40 ALA, 41 ALA, 42 PHE, 43ASP, 44 THR, 45 LYS, 46 THR, 47 GLY, 48 LEU, 49 ARG, 50 VAL, 51 ALA, 52 VAL, 53 LYS, 54 LYS, 55 LEU, 56 SER, 57 ARG, 58 PRO, 59 PHE, 64 HIS, 65 ALA, 67 ARG, 68 THR, 69 TYR, 72 LEU, 87 LEU, 88 ASP, 89 VAL, 90 PHE, 91 THR, 92 PRO, 99 PHE, 100 ASN, 102 VAL, 103 TYR, 104 LEU, 105 VAL, 106 THR, 107 HIS, 337 TRP, 338 LYS, 339 SER, 341 THR, 342 TYR, 344 GLU, 345 VAL

C. Molecular Docking studies

The selected proteins were targeted by 108 natural compounds (Listed in Table IV).The free binding energy and the hydrogen bonding were focused on analysing the results of docking. The compounds with binding energy values between -7 to -14 for IL-1 receptor, IL-6 receptor, TNF-alpha receptor, NF-κB pathway protein target, MAPK pathway protein target are listed in table VII. Dihydro-beta-Ergocryptine displayed highest affinity of -11.4 at site 4 of IL-1 receptor protein which is a derivative of beta ergocryptine. Castalagin exhibited the highest binding affinity of -11.5 extracted from terminaliaarjuna at site 2 of protein responsible for the inhibition of p-38 MAPK pathway. Diosgenin extracted from solanumdulcamara showed highest binding affinity of -10.8 at site 4 and site-1 of IL-6 alpha receptor protein. Dihydro-beta-ergocryptine derivative of beta-ergocryptine displayed highest binding affinity of -7.8 at site 3 and site 12.Silibinin extracted from silybummarianum also exhibited binding affinity of -7.8 at site 4 of TNF-alpha receptor protein. Punicalagin extracted from terminaliacatappa displayed the highest binding affinity of -14.3 with NF-κB protein transcription factor.

Table VII: Molecular docking analysis of natural compounds showing binding affinities between -7.00 kcal/mol and -14.00 kcal/mol for proteins

Sr. No.	Protein	Ligand	Pubchem ID	Chemical structure	Binding affinity kcal/mol	Plant name/source
1.	3o4o (IL-1 inhibitor) (Site 4)	Dihydro-Beta-Ergocryptine	3084313		-11.4	Derivative of beta ergocryptine
2.	3o4o (IL-1 inhibitor) (Site 6)	Cucurbitacin	119287		-10.3	Cucumissativus
3.	IL-6 receptor (site 1) IL-6 receptor (site 4)	Diosgenin	99474		-10.8	Solanumdulcamara
4.	TNF-alpha receptor (site-3)	Dihydro-Beta-Ergocryptine	3084313	Mentioned above	-7.8	Derivative of beta ergocryptine
5.	TNF-alpha receptor (site-4)	Silibinin	31553		-7.8	Silybummarianum

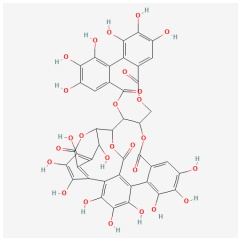
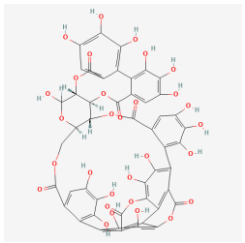
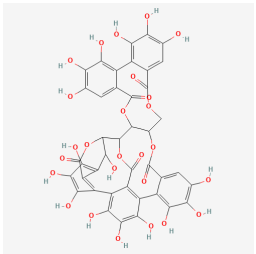
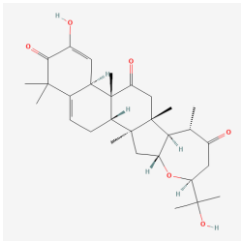
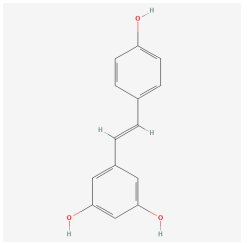
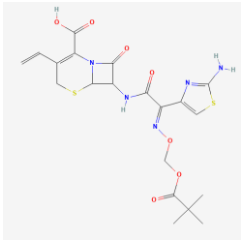
6.	TNF-alpha receptor (site-12)	Dihydro-Beta-Ergocryptine	3084313	Mentioned above	-7.8	Derivative of beta ergocryptine
7.	1svc (NF-κB) (site-1)	Castalagin	168165		-12	Terminaliaarjuna
8.	1svc (NF-κB) (site-2)	Punicalagin	44584733		-14.3	Terminaliacatappa
9.	1kv2 (p-38MAP) (site-2)	Castalagin	168165		-11.5	Terminaliaarjuna
	1kv2 (p-38MAP) (site-4)				-11	

Table VIII: Comparative Analysis of Binding Affinities

Sr. No.	Protein	Type	Ligand	Pubchem ID	Chemical structure	Binding affinity kcal/mol	Source/Information
1.	3o4o (IL-1inhibitor)	Selected phytocompound	Cucurbitacin S	119287		-10.3	Cucumissativus
		Standard natural compound	Resveratrol	445154		-6	vitisvinifera
		Standard clinically approved drug	Anakinra	146171046, DB00026		-7.3	FDA approved for rheumatoid arthritis

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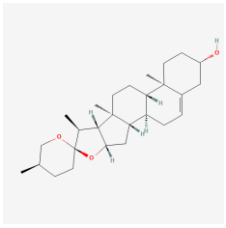
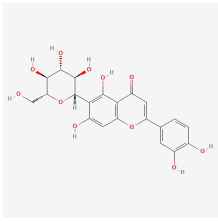
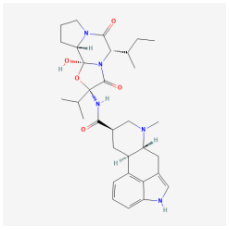
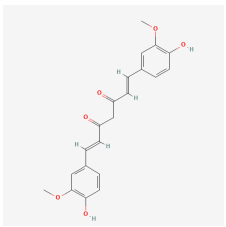
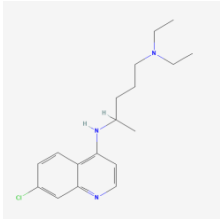
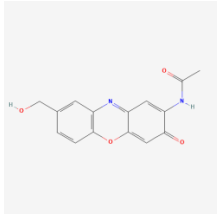
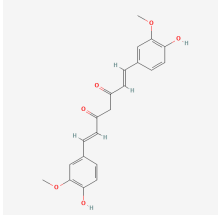
2.	IL-6 receptor	Selected phytocompound	Diosgenin	99474		-10.8	Solanumdulcamara
		Standard natural compound	Isoorientin	114776		-8.7	Vitexnegundo
		Standard clinically approved drug	—	—	—	—	—
3.	TNF-alpha receptor	Selected phytocompound	Dihydro-beta ergocryptine	3084313		-7.8	Derivative of beta ergocryptine
		Standard natural compound	Curcumin	969516		-7.4	Curcuma longa
		Standard clinically approved drug	Chloroquine	2719		-4.4	Cinchona officinalis
4.	1svc (NF-κB)	Selected natural compound	Exfoliazone	131529		-7	Streptomyces exfoliatus
		Standard natural compound	Curcumin	969516		-7.4	Curcuma longa

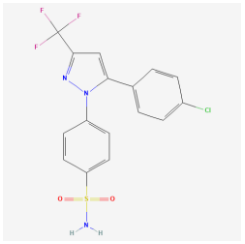
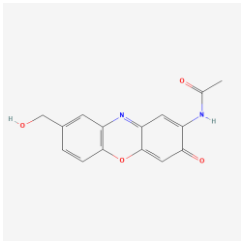
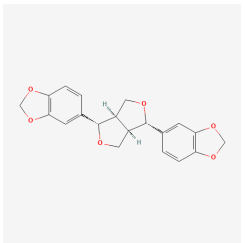
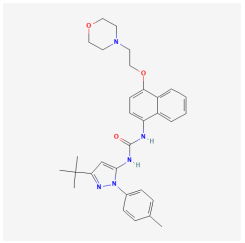
		Standard clinically approved drug	SC-236	9865808, DB14059		-8.1	FDA approved drug
5.	1kv2 (p-38MAP)	Selected natural compound	Exfoliazone	131529		-7	Streptomyces exfoliates
		Standard natural compound	Sesamin	72307		-8.2	Sesamumindicum
		Standard clinically approved drug	Doramapimod	156422, DB03044		-8.6	FDA approved drug

Table IX: Comparative analysis of ADMET properties

Sr. No.	Protein	Type	Ligand	Molecular Weight	Bond Acceptors	Bond Donors	Bioavailability	Log p	Log s (esol)	Log s (ali)	Gi absorbtion	BBB Permeate	Lipinski (violations)	Pains (alerts)	Toxicity	LD50 in rat
1	3o4o (IL-1inhibitor)	Selected phytocompound	Cucurbitacin S	498	8	3	0.55	3.52	-4.56	-5.26	Low	No	1	0	No	2.364
		Standard natural compound	Resveratrol	228	3	3	0.55	1.71	-3.62	-4.07	high	yes	0	0	Yes	2.529
		Standard clinically approved drug	Anakinra	509	9	3	0.11	2.39	-3.09	-5.48	low	No	2	0	No	2.04
2	IL-6 receptor	Selected phytocompound	Diosgenin	414	3	1	0.55	4.45	-5.98	-6.25	High	Yes	1	0	No	1.921
		Standard natural compound	Isoorientin	448	11	8	0.17	2.12	-2.7	-3.62	low	no	2	1	No	2.55

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		Standard clinically approved drug	—	—	—	—	—	—	—	—	—	—	—	—	—	—
3	TNF-alpha receptor	Selected phytocompound	Dihydro-beta ergocryptine	577	6	3	0.55	3.44	-5.12	-5.22	High	No	1	0	No	3.144
		Standard natural compound	Curcumin	368	6	2	0.55	3.27	-3.94	-4.83	High	No	0	0	No	1.833
		Standard clinically approved drug	Chloroquine	319	2	1	0.55	3.95	-4.55	-4.95	high	yes	0	0	Yes	2.85
4	1svc (NF-κB)	Selected natural compound	Exfoliazone	284	5	2	0.55	2.15	-1.89	-1.47	high	no	0	0	No	2.34
		Standard natural compound	Curcumin	368	6	2	0.55	3.27	-3.94	-4.83	High	No	0	0	No	1.833
		Standard clinically approved drug	SC-236	401	7	1	0.55	2.11	-4.86	-5.17	High	no	0	0	No	2.049
5	1kv2 (p-38MAP)	Selected natural compound	Exfoliazone	284	5	2	0.55	2.15	-1.89	-1.47	high	no	0	0	No	2.34
		Standard natural compound	Sesamin	364	6	0	0.55	3.46	-3.93	-3.5	high	yes	0	0	Yes	2.883
		Standard clinically approved drug	Doramapimod	527	5	2	0.55	4.99	-6.47	-7.2	high	no	1	0	No	2.369

Table X: Comparative analysis based on CYP inhibition

Sr. No.	Protein	Type	Ligand	Molecular Weight	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
1.	3o4o (IL-1inhibitor)	Selected phytocompound	Cucurbitacin S	498.0	No	No	No	No	Yes
		Standard natural compound	Resveratrol	228.0	Yes	No	Yes	No	Yes
		Standard clinically approved drug	Anakinra	509.0	No	No	No	No	No
2.	IL-6 receptor	Selected phytocompound	Diosgenin	414.0	No	No	No	No	No
		Standard natural compound	Isoorientin	448.0	No	No	No	No	No
		Standard clinically approved drug	—	—	—	—	—	—	—
3.	TNF-alpha receptor	Selected phytocompound	Dihydro-beta ergocryptine	577.0	No	No	No	Yes	Yes

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		Standard natural compound	Curcumin	368.0	No	No	Yes	No	Yes
		Standard clinically approved drug	Chloroquine	319.0	Yes	No	No	Yes	Yes
4.	1svc (NF-κB)	Selected natural compound	Exfoliazone	284.0	Yes	No	No	No	Yes
		Standard natural compound	Curcumin	368.0	No	No	Yes	No	Yes
		Standard clinically approved drug	SC-236	401.0	Yes	Yes	Yes	No	No
5.	1kv2 (p-38MAP)	Selected natural compound	Exfoliazone	284.0	Yes	No	No	No	Yes
		Standard natural compound	Sesamin	364.0	No	Yes	No	Yes	Yes
		Standard clinically approved drug	Doramapimod	527.0	No	Yes	Yes	Yes	Yes

Table XI: Comparative analysis of drug likeliness

Sr. No.	Protein	Type	Ligand	c log P	Solubility log S	Molecular Weight	TPSA
1.	3o4o (IL-1inhibitor)	Selected phytocompound	Cucurbitacin S	3.66	-5.04	498.0	100.9
		Standard natural compound	Resveratrol	2.83	-2.86	228.0	60.69
		Standard clinically approved drug	Anakinra	1.43	-4.1	509.0	227.0
2.	IL-6 receptor	Selected phytocompound	Diosgenin	4.88	-5.58	414.0	38.69
		Standard natural compound	Isoorientin	-0.42	-1.97	448.0	197.3
		Standard clinically approved drug	—	—	—	—	—
3.	TNF-alpha receptor	Selected phytocompound	Dihydro-beta ergocryptine	3.71	-3.85	577.0	118.2
		Standard natural compound	Curcumin	3.58	-3.67	368.0	96.22
		Standard clinically approved drug	Chloroquine	4.01	-4.06	319.0	28.16
4.	1svc (NF-κB)	Selected natural compound	Exfoliazone	0.3	-2.61	284.0	87.99
		Standard natural compound	Curcumin	3.58	-3.67	368.0	96.22
		Standard clinically approved drug	SC-236	2.85	-4.57	401.0	86.36
5.	1kv2 (p-38MAP)	Selected natural compound	Exfoliazone	0.3	-2.61	284.0	87.99
		Standard natural compound	Sesamin	3.22	-4.39	364.0	55.38
		Standard clinically approved drug	Doramapimod	5.09	-6.55	527.0	80.65

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Table XII: Comparative analysis based on molecular interactions of binding site residues

Sr. No.	Protein	Type	Ligand	Site No.	Interacting residues	Category	Type of interactions
1.	3o4o (IL-1inhibitor)	Selected phytocompound	Cucurbitacin S	6	GLN C:127	H-bond	Conventional
					TRP C:156	H-bond	Conventional
		Standard natural compound	Resveratrol		PRO A:78	Hydrophobic	pi-sigma
					CYS A:71	H-bond	Carbon
					VAL A:100	Hydrophobic	Amide-pi stacked
		Standard clinically approved drug	Anakinra		SER B:178	H-bond	Conventional
					THR B:139	H-bond	Conventional
					LEU B:209	H-bond	Conventional
					ARG B:207	H-bond	Carbon
					CYS B:192	H-bond	Conventional
2.	IL-6 receptor	Selected phytocompound	Diosgenin	1	GLY A:293 (2)	H-bond	Conventional
					ARG A:274	H-bond	Carbon
		Standard natural compound	Isoorientin		VAL A:271	H-bond	Carbon
					ARG A:237	H-bond	Conventional
					GLN A:272	H-bond	Conventional
					GLN A:255	H-bond	Conventional
					LEU A:232	H-bond	Conventional/Carbon
		Standard clinically approved drug	—		—	—	—
3.	TNF-alpha receptor	Selected phytocompound	Dihydro-beta ergocryptine	12	PRO B:23	Unfavorable	Donar-donar
					LYS B:32	H-bond	Carbon
					THR B:31	H-bond	Carbon
					ASP B:42 (2)	H-bond	Carbon
			Cucurbitacin S		ASP B:42	H-bond	Conventional
					HIS B:66	H-bond	Conventional
					LEU B:67	H-bond	Conventional
					ASN B:65	H-bond	Carbon
					GLU A:79	H-bond	Carbon
					ASP B:93	H-bond	Conventional
		Standard natural compound	Curcumin		LEU A:160	H-bond	Carbon
					LYS A:157	H-bond	Conventional
					SER A:159	Hydrophobic	Amide-pi stacked
					PRO B:16	H-bond	Conventional
					GLU A:149	H-bond	Conventional
					ARG A:146	H-bond	Conventional
					PHE A:144	H-bond	Conventional
		Standard clinically approved drug	Chloroquine		HIS B:66	H-bond	Carbon
					CYS B:43	Unfavorable	Donar-donar
4.	1svc (NF-κB)	Selected natural compound	Exfoliazone	6	ALA P:219	Hydrophobic	Amide-pi stacked
					ILE P:87	H-bond	Carbon
					VAL P:135	H-bond	Conventional
					VAL P:96	H-bond	Carbon
					ARG P:230	H-bond	Conventional
		Selected natural compound	Curcumin		ILE P:87	Hydrophobic	pi-sigma
					VAL P:96	H-bond	Conventional
					VAL P:135	H-bond	Conventional
					ALA P:219	H-bond	Conventional
					PHE P:217	H-bond	Conventional
					GLU P:233	H-bond	Conventional
		Standard clinically approved drug	SC-236		GLY P:92	H-bond	Conventional
					VAL P:135	Hydrophobic	Halogen (F)
					VAL P:126 (2)	Hydrophobic	Halogen (F)
					THR P:127	Hydrophobic	Halogen (F)
					VAL P:96	Hydrophobic	Halogen (F)
					VAL P:96	Hydrophobic	pi-sigma
5.	1kv2 (p-38MAP)	Selected natural compound	Exfoliazone	3	ALA A:51	H-bond	Conventional
					GLU A:19 (2)	H-bond	Conventional
		Standard natural compound	Sesamin		ALA A:51	Hydrophobic	Amide-pi stacked
					ASP A:88	Hydrophobic	Amide-pi stacked
					VAL A:89	Hydrophobic	pi-sigma
					LEU A:72	H-bond	Carbon
					TYR A:69	H-bond	Conventional
					TRP A:337	H-bond	Carbon
					THR A:341	Hydrophobic	Amide-pi stacked

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		Standard clinically approved drug	Doramapimod		VAL A:52	H-bond	Conventional
					SER A:37	H-bond	Conventional
					VAL A:52	Hydrophobic	Amide-pi stacked

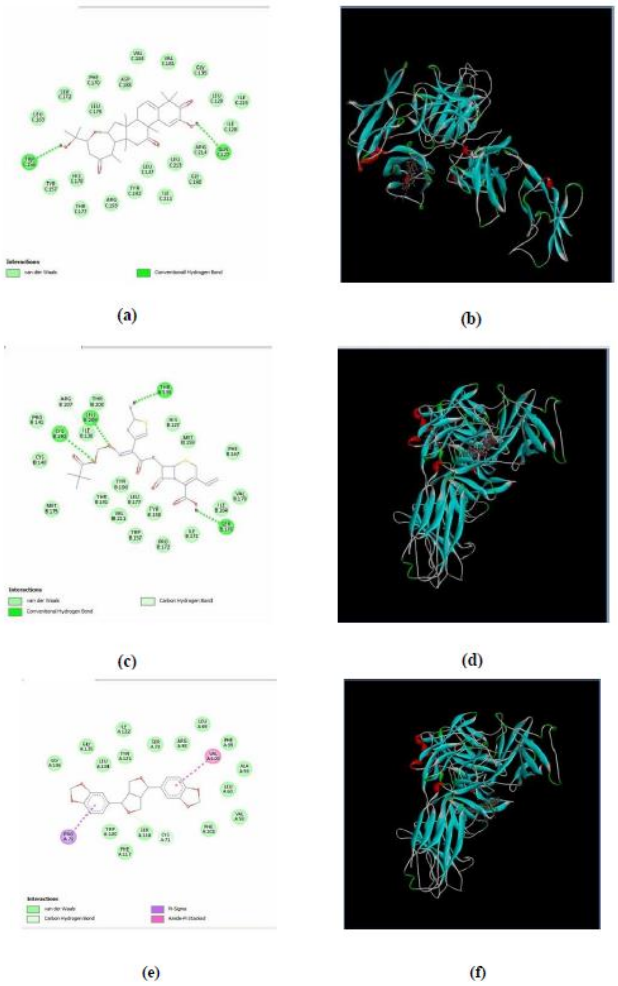


Fig.1 Docked complex 2D structure of 3o4o (IL-1inhibitor) with (a) Cucurbitacin S, (c) Anakinra, (e) Resveratrol, Docked complex 3D structure of 3o4o (IL-1inhibitor) with (b) Cucurbitacin S, (d) Anakinra, (f) Resveratrol

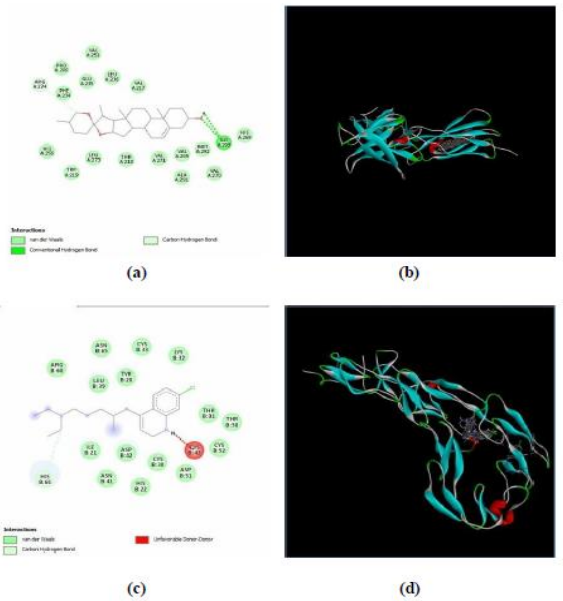


Fig.2 Docked complex 2D structure of IL-6 receptor with (a) Diosgenin, (c) Isoorientin
Docked complex 3D structure of IL-6 receptor with (b) Diosgenin, (d) Isoorientin

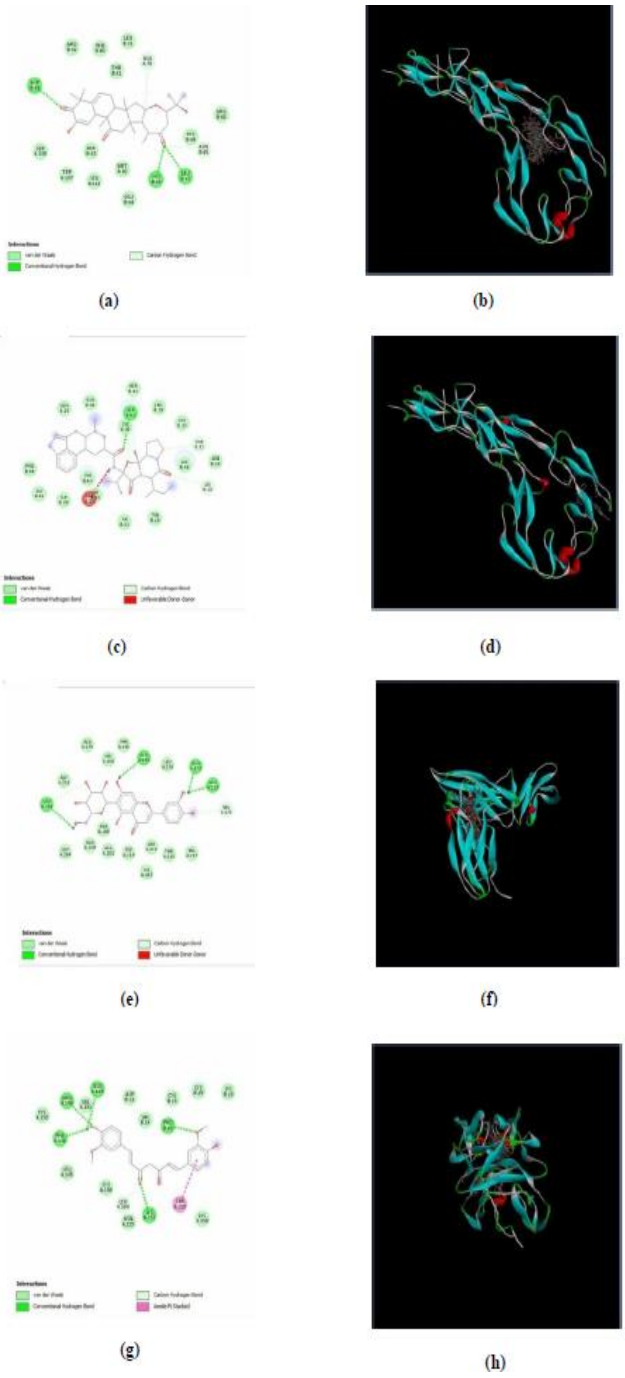


Fig.3 Docked complex 2D structure of TNF-alpha receptor with (a) Dihydro-beta ergocryptine, (c) Cucurbitacin S, (e) Chloroquine, (g) Curcumin
Docked complex 3D structure of TNF-alpha receptor with (b) Dihydro-beta ergocryptine, (d) Cucurbitacin S, (f) Chloroquine, (h) Curcumin

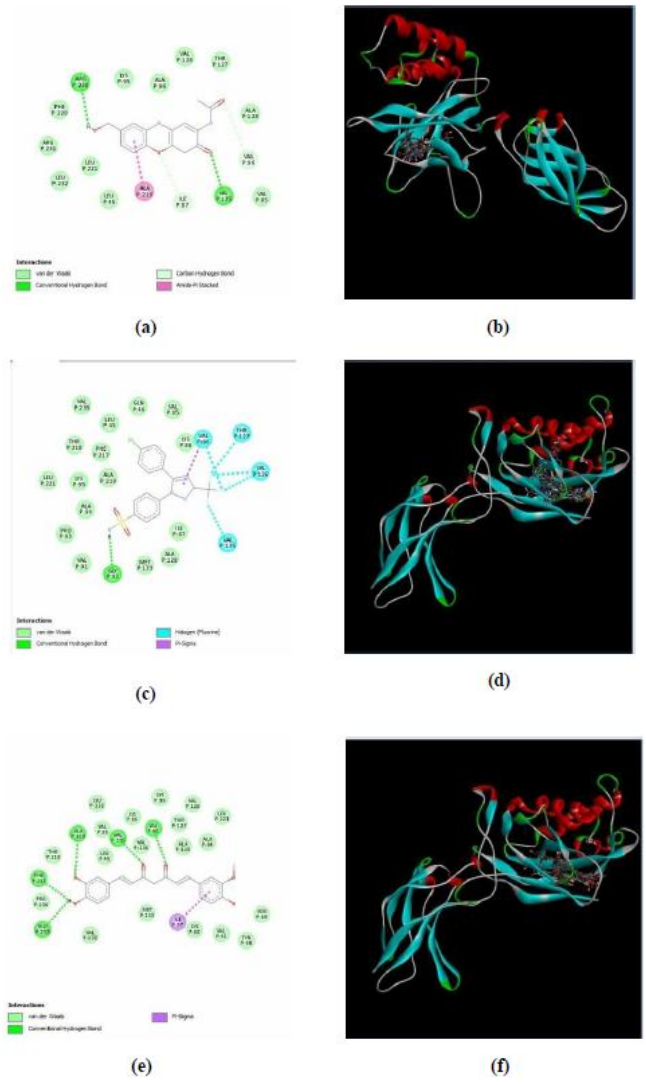
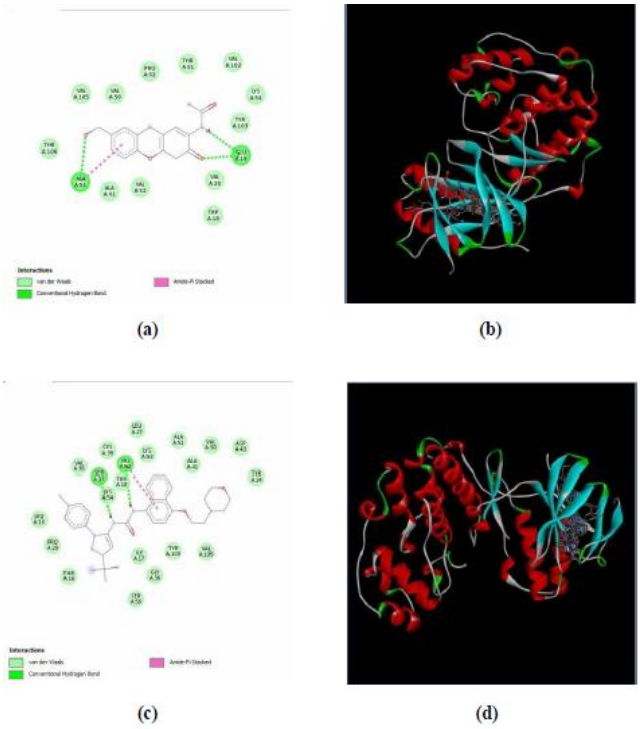


Fig. 4 Docked complex 2D structure of 1svc (NF-κB) with (a) Exfoliazone, (c) SC-236, (e) Curcumin Docked complex 3D structure of 1svc (NF-κB) with (b) Exfoliazone, (d) SC-236, (f) Curcumin



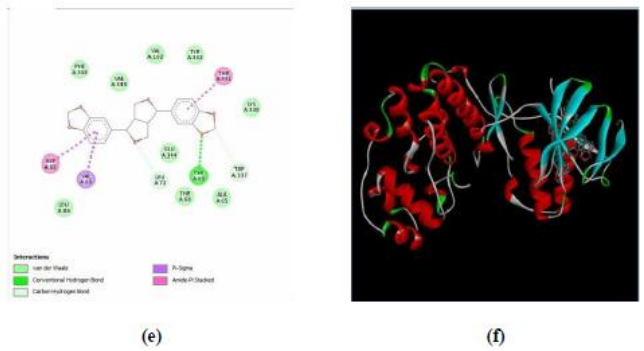


Fig. 5 Docked complex 2D structure of 1kv2 (p-38MAP) with (a) Exfoliazone, (c) Doramapimod, (e) Sesamin Docked complex 3D structure of 1kv2 (p-38MAP) with (b) Exfoliazone, (d) Doramapimod, (f) Sesamin

D. ADMET analysis

Lipinsky's rule states an ideal drug must be one with a molecular mass less than 500 Da, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and an octanol–water partition coefficient log P not greater than 5. For oral and intestinal absorption the idea value for coefficient log P is 1.35–1.8.c log P value measures how much of a solute dissolves in the water portion versus an organic portion [35].

The natural compounds which showed highest binding affinity were considered for ADMET analysis. The ligands with binding affinity values -7.00 kcal/mol being the least and above till -14 were taken for ADMET analysis for all the 5 protein targets. Most of the ligands violated the Lipinsky's rule and other parameters as shown in the supplementary tables, were further not considered for comparative studies with clinically approved drugs and standard natural compounds.

E. Drug Likeness prediction studies

In speeding up the process of drug discovery, in silico drug likeness studies play a role in reducing the expensive process involved in the drug development process. The properties of Drug likeness was predicted using OSIRIS Property Explorer. The OSIRIS tool assists in measuring the clog P(logarithm of compound's partition coefficient between n-octanol and water) which measures the compound's hydrophilicity value, log S value, TPSA and also the molecular weight. The ligands for all the 5 protein targets were chosen based on these parameters and were considered for comparative studies [38].

F. Comparative Studies

The clinically approved drugs and standard natural compounds which are in use against COVID-19 were used as standard drug molecules for the comparative studies. Comparison was based on binding affinities, ADMET properties, drug likeness, active site residue binding. Table VIII depicts the comparison based on binding affinities. Table IX displays the comparison based on ADMET properties. Table X shows the comparison based on CYP inhibition. Table XI depicts the comparison based on drug likeliness.

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Table XII displays the comparative analysis based on molecular interactions of binding site residues.

MAP-38

Human p38 MAP kinase in complex with BIRB796(PDB ID: 1kv2) was selected for performing virtual screening. Exfoliazone shows significantly lower log p values as compared to clinically approved drug doramapimod and standard natural compound sesamin which indicates exfoliazone exhibits better absorption and permeability. Log s(esol) and log s(ali) values are a bit higher for exfoliazone when compared to doramapimod and sesamin and hence satisfied good absorption range. Gi absorption and bioavailability were same for all the three drugs. One lipinski's violation was observed for doramapimod and no violations were seen for exfoliazone and sesamin .The lowest LD50 value was observed for exfoliazone which means it is the least toxic. Doramapimod was the standard clinical drug considered and sesamin was the standard natural compound considered. Doramapimod showed higher binding affinity as compared to sesamin. No adverse side effects were seen for Doramapimod [26], [33] but for sesamin some side-effects have been reported like when consumed in excessive amounts it might cause blood glucose levels to drop below normal, drop blood pressure to dangerously low levels. Fibre from sesame seeds can form a layer over the appendix, causing bloating and pain [26], [33], [37]. Hence even if it displays high binding affinity, exfoliazone proves to be a better alternative.

Interleukin-1 receptor

Crystal structure of an Interleukin-1 receptor complex (PDB ID:3O4O)was selected for performing virtual screening. Log p and clog p value for Cucurbitachin S was higher as compared to standard natural compound resveratrol and standard clinically approved drug Anakinra but was still in the range of Lipinski's rule [54]. Log S(esol) and Log S(ali) values were seen to be low as compared to the standards but Gi absorption was low for Cucurbitachin S. Cucurbitachin S showed one Lipinski's violation due to 8 hydrogen bond donors but was still less to the hydrogen bond donors of standard drug Anakinra. LD50 value of Cucurbitachin S was slightly lower than resveratrol but slightly higher than Anakinra Bioavailability of Cucurbitachin S was higher than Anakinra. Other Cucurbitacins especially cucurbitacin B and cucurbitacin E have been studied earlier for their anti-inflammatory, antioxidant and immunomodulatory mechanisms [32], [34]. Resveratrol(PubChem CID: 445154) shows some side effects like nausea, vomiting, diarrhoea, liver dysfunction etc. when taking a dose which is more than 2.5g per day [32], [34], [41]. Anakinra(Drug bank accession no: DB00026) also shows some side effects like flu symptoms, joint pain etc. Side -effects specifically for Cucurbitacin S have not yet been studied. Both Anakinra and Resveratrol showed less binding affinity as compared to CucurbitacinS.

Interleukin-6 receptor

Crystal Structure of the extracellular domains of Human Interleukin-6 Receptor(PDB ID:1N26) was selected for performing virtual screening. Bioavailability of diosgenin is higher as compared to Isoorientin. Log p and clog p value for diosgenin is higher but satisfies the lipinski's range. Log S(esol) and Log S(ali) values were less for Diosgenin and even the Gi absorption was higher. LD50 value for Diosgenin was also seen to be low. TPSA score for selected natural compounds as well as standard followed Lipinski's range. Diosgenin(PUBCHEM ID:99474) has earlier been used to treat cancer, diabetes mellitus, metabolic syndrome, natural alternative for estrogen replacement therapy [25], [28], [36]. Standard drug for IL-6 is trastuzumab used to treat rheumatoid arthritis [31] whose structure isn't available due to commercial reasons. Standard Phytocompound considered was isoorientin extracted from P. edulisflowermostly found in southern Brazil, Paraguay and northern Argentina. No significant side effects have been reported for both Diosgenin and isoorientin.The binding affinity for Diosgenin was greater with respect to isoorientin.

TNF alpha receptor

Extracellular domain of the 55 KDA Tumour Necrosis Factor Receptor Crystallised at PH3.7 in P 21 21 21(PDB ID:1EXT) was selected for performing virtual screening .Curcumin extracted from plant Curcuma longa mainly found in South Asia was used as a standard phytocompound [30], [31]and Chloroquine was used as a standard clinically approved drug[39]. Dihydro-beta-ergocryptine and cucurbitacin S both were considered as potential drugs to inhibit TNF alpha receptors after ADMET and Drug likeliness analysis. Dihydro-beta-ergocryptine is beta-Ergocryptine in which a single bond replaces the double bond between positions 9 and 10. It derives from a beta-ergocryptine(www.PubChem.com).Dihydro-beta-ergocryptine showed slightly high log P values when compared with the standards .Chloroquine showed highest clog p value followed by dihydro-beta-ergocryptine and curcumin. Log S(esol) and Log S(ali) were low as compared to curcumin and chloroquine and even the Gi absorption was observed to be high. It has one lipinski's violation due to slightly higher molecular weight than 500.

There are some FDA approved drugs which have molecular weight higher than 500 and violate lipinski's rule [39], [40]. The LD50 value is greater for Dihydro-beta-ergocryptine but still is non-toxic. Lipinski's range limit was followed by all except chloroquine which has a TPSA score slightly lower than 30. Curcumin showed high log p values as compared to the standards. The clog p values of curcumin and cucurbitacin S were similar but the value of chloroquine was slightly highe. Cucurbitacin S showed higher log S(esol) value when studied against curcumin but showed similar log S(ali) against chloroquine. The LD50 value for cucurbitacin S is slightly higher when compared to curcumin but lower against chloroquine. Some side-effects were also seen in the case of Chloroquine like headache, nausea, diarrhoea, rash, itching etc. [27], [39]. Side-effects recorded for curcumin were mild digestive issues such as bloating, acid reflux, flatulence, and diarrhoea at daily doses exceeding 1,000 mg.

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Doses of 450 mg or higher may cause headache and nausea, skin rash but it is generally safe to use [39]. Side-effects for dihydro-beta-ergocryptine and cucurbitacin S have not yet been noted.

NF-κB

NF-κB P50 homodimer bound to DNA(PDB ID:1SVC) was selected for performing virtual screening. Exfoliazone (PUBCHEM ID:131529) extracted from Streptomyces exfoliatus. Exfoliazone and standard clinically approved drug SC-236 showed similar log P values but were slightly lower as compared to curcumin. cLog P value for exfoliazone was exceptionally lower as compared to the standards. Log S(esol) and Log S(ali) values were highest for exfoliazone. Gi absorption was seen to be high for all three and the bioavailability score was also similar. The LD50 value was higher for exfoliazone but was categorised as non-toxic All the compounds followed the TPSA lipinski's range limit. Exfoliazone is an antibiotic which displays binding affinity of -7.5. Curcumin (PuBchem ID:969516) was used as a standard phytocompound which showed approximately same binding affinity and is generally safe to use with some mild side-effects when taken in high amounts.SC-236 (DrugBank Accession Number:DB14059) is a potent, selective, orally active inhibitor of nuclear factor NF-kappa-b complex[15]that has been studied in cancer therapy , lower back pain and inflammation. It is currently under clinical trials but it causes severe side-effects when used with other drugs like abacavir, abciximab(www.drugbank.com).

IV. CONCLUSION

Thus in this study,108 natural compounds were examined in inhibiting human protein targets which are responsible for worsening the condition of COVID-19 through a virtual screening approach. This study has screened the natural compounds 3-Hydroxydecanedioic acid, Cucurbitacin S, Diosgenin which may exhibit inhibitory activity against IL-1 receptor, IL-6 receptor respectively. It has also revealed that Dihydro-beta-ergocryptine and cucurbitacin S may exhibit inhibitory activity against TNF-alpha receptor. Further it concluded that exfoliazone shows better inhibitory activity against P38-MAPK and NF-κB pathway inhibitory proteins. These natural compounds could lead the way for future drug discovery, design and development. This will help researchers to scout new drugs in drug discovery (in-vitro and in-vivo studies).

ACKNOWLEDGMENT

We would like to acknowledge the Department of Biotechnology, KIT's college of engineering (Autonomous), Kolhapur for their support throughout the research.

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AUTHOR PROFILE

Aayushka. P. Nashte is currently a final year Biotechnology engineering student at KIT's College of Engineering Kolhapur. Consistently striving to learn and research further in the field of biotechnology, bioinformatics, microbiology and informatics under the guidance of eminent and distinguished faculty members at KIT's College of Engineering Kolhapur. Focused on multidisciplinary use of technology to find effective solutions for problems related to healthcare, fermentation process optimization, food technology and drug discovery. She has worked on several projects which uses neural networks and other machine learning approaches for optimizing various processes. Her strengths include discipline, patience and dedication, curiousness, confidence and persistence.

Sneha Patnawar has pursued her Bachelor degree in B.E Biotechnology and Post-graduation in Biotechnology at RVCE, Bangalore. She has an industry experience of 1 year, teaching and research experience of 5 and 1 year respectively. Her research areas include molecular biology, bioinformatics, Environmental Biotechnology, etc. She has worked on various research projects including immunology, Insilco drug designing, etc. She is passionate towards teaching and optimistic. Her strengths include determination, hard work, discipline.

Mr. Guruprasad Kulkarni, He is presently studying in the final year of my B.Tech degree in Biotechnology at KIT's College of Engineering (Autonomous), Kolhapur. He has got a CGPA of 9.64 at third year level along with qualifying GATE 2022 with AIR 1007. He has completed my junior college from The New College, Kolhapur with 3rd rank in 12th standard. Also, he stood first at school level in the SSC exam. His field of interest is research in biotechnology; specifically genetic engineering. Besides this, he has worked as an NSS volunteer for two years and currently working as brand ambassador for Mayura AICTE IDEA LAB at college level.

Dr. Pallavi S. Patil She is an Associate Professor and currently working as Head of Biotechnology Engineering Department at KIT's College of Engineering, Kolhapur. She has pursued her Ph.D from VTU, Belgaum. She has had teaching and research experience of around 22 years. Her research interests include Fermentation Technology, Fluid Mechanics, etc. She has worked on several projects including food technology, wine fermentation, Bioremediation, Bioinformatics, etc. Her strengths include determination, very good administration, hardworking and confident.

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Blue Eyes Intelligence Engineering and Sciences Publication (BEIESP)