Research Article

iMedPub Journals
http://www.imedpub.com

American Journal of Pharmacology and Pharmacotherapeutics

2021
Vol. 8 No. 4: 17

Screening of Therapeutic Pathways of Herbal Drug Ligands and Proteogenomic Analysis

Lalit Raj Singh*and Rupam Singh

Department of Medicinal Plants Sciences, Dev Sanskriti University, Gayatrikunj-Shantikunj, Haridwar Uttarakhand 249411, India

Corresponding author:
Lalit Raj Singh, Department of Medicinal Plants Sciences, Dev Sanskriti University, Gayatrikunj-Shantikunj, Haridwar Uttarakhand 249411, India,

lalitrajsingh@gmail.com

Citation: Singh LR, Singh R (2021) Screening of Therapeutic Pathways of Herbal Drug Ligands and Proteogenomic Analysis. Am J Pharmacol Pharmacother Vol.8 No.4:17.

Abstract

The search for safer and more therapeutically effective drugs is accelerating, giving medicinal plants an advantage as lead structure sources. The plant is *Cynodon dactylon* (L.) Pers., according to the current study, and it belongs to the Poaceae family. The current research focuses on comparing one major bioactive principle to a newly designed small drug-like molecule *in silico* (scaffold analogue). The goal of the study was to figure out how ligands/scaffold analogues work by looking at genetic links, cellular signalling, and the top ten diseases/disorders they were associated to. When compared to a naturally occurring ingredient, the scaffold analogue exhibited promising drug-like potential. These studies could help herbal medicines reach more people, propose new formulations for existing diseases or disorders, and pave the way for drug repurposing.

Keywords: Taxonomy; Poaceae; Scaffold; Cheminformatics; Proteogenomic

Received: December 01, 2021; **Accepted:** December 15, 2021; **Published:** December 22, 2021

Introduction

Herbal plants have been recommended by practitioners for healing purposes in many treatment systems (Ayurveda, Unani, Homeopathy, and Siddha) since ancient times, and have been described as essential sources of medicine even in the present period [1]. Several ailments/diseases are treated by Bahama grass (*Cynodon dactylon* (L.) Pers.), including obesity, remittent fever, menstrual abnormalities, urinary tract infection, hydrocele, diabetes, hysteroepilepsy, bowel disorders, irritable bowel syndrome, piles, coronary artery disease, and other neuromuscular concerns [2,3]. The major therapeutic agents are found in the whole part of the herb. A plethora of bioactive constituents is found in it including 2-methyl-4-vinyl phenol, catechin, beta-carotene, lutein, rutin, myricetin, quercetin, which represents different classes of secondary metabolites such as alkaloids, phenols, tannins, saponins, steroids, coumarins, flavonoids, carotenoids, and vitamins (A and C) [4]. *In silico* techniques can be used to develop herbal drug-derived ligands and personalized treatment approaches [5]. By keeping a curative space for drug discovery, drug redevelopment, advancement, and creative outcomes, the ligands (bioactive component, scaffold analogue) of *Cynodon dactylon* (L.) Pers. was assessed to identify its molecular activities at different target sites [6]. The topological polar surface area (TPSA) of a molecule is defined as the surface sum of all polar atoms or molecules including oxygen, nitrogen, and their attached hydrogen atoms. Log P is the logarithm of the partition coefficient (P) when one of the solvents is water and other is a non-polar solvent. For the optimal results, the log P value is 0<LogP<3, LogP<0-poor lipid bilayer permeability, and LogP>3-poor aqueous solubility. It is a measure of the lipophilicity or hydrophilicity of the compound. XLogP3 predicts the octanol/water partition coefficient of an organic compound. Water solubility (LogS) is represented from insoluble to highly soluble; insoluble<-10<poorly<-6<moderately<-4<soluble<-2 very<0<highly soluble. The pharmacokinetic parameters include the absorption (gastrointestinal absorption and p-glycoprotein substrate), distribution (blood-brain-barrier), metabolism (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 inhibitor), elimination (half time ($T^{1/2}$)-3 hr<$T^{1/2}$<8; clearance(cl)-5 ml/min/kg<cl<15 ml/min/kg; toxicity (human Ether-a-go-go-Related Gene (hERG)-category 0: non-blocker and category 1: blocker; human hepatotoxicity (H-HT)-category 0: negative and category 1: positive; Ames mutagenicity-category 0: negative and category 1: positive; skin sensitization-category 0: non sensitizer and category 1: sensitizer; drug-induced liver injuries (DILI)-category 0: negative and category 1: positive) and FDA maximum recommended daily dose (FDAMDD)-category 0:

negative and category 1: positive [7]. The bioactivity scores of the ligands on different target sites such as GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor, and enzyme inhibitor activities are covered under pharmacodynamics. The bioactivity of screened molecules may then be calculated as a sum of activity contributions of fragments in these molecules. This provides a molecule activity score (between-3 and 3). Molecules with the highest activity score have the highest probability to be active. These efforts include an *in silico* approach to cheminformatics, and proteogenomic analysis including drug similarities, scaffolding analogue, target predictions, pharmacology modelling, molecular anchoring, identification of genes interactions, and their biological insights through representative overexpression analysis (ORA) and Network Topology-based Analysis (NTA) [8-10]. The drug-likeness properties were evaluated by the application of '*Lipinski rule of five', 'Ghose's rule', 'Veber's rule', 'Egan rule', and 'Muegge rule'* [11]. To detect toxicity, pan-assay interference structure (PAINS) analysis is used on substances with favourable physicochemical features. Because of the existence of some group components that disrupt biological processes by interfering with DNA or protein, the test is also known as toxicophore. This results in catastrophic situations like as carcinogenicity and hepatotoxicity. Brenk analysis provides information on structural alert, such as chirality and steric hindrances. The lead-likeness comprises the ligands having $250 \leq MW \leq 350$, $XLogP \leq 3.5$, and no. of rotatable bonds ≤ 7. The synthetic accessibility score from 1(very easy) to 10 (very difficult) [12,13].

Materials and Methods

Details of the plant

Hindi Name: Doob

Common Name: Bahama grass

Latin Name: *Cynodon dactylon* (L.) Pers.

Family: Poaceae

General procedure

One major bioactive phytoconstituent was selected from the experimental plant material based on their availability (in percentage) and a scaffold analogue was drawn by ChemBioDraw [14]. The cheminformatic attributes (MW: Molecular weight, HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor, Lipophilicity: LogP and XLogP3, Water solubility: LogS, TPSA: Total polar surface area) of the ligands were studied with the assistance of Swiss ADME, ADMET lab and Molinspiration Cheminformatics Software [15-18]. The pharmacokinetic studies that are facilitated by SwissADME and ADMET lab include absorption, distribution, metabolism, elimination, and toxicity investigations. Molinspiration Cheminformatics Software was used to help in the pharmacodynamic analyses of the ligands, which included bioactivity scores at target sites. Swiss ADME and ADMET labs deciphered the ligands' drug-likeness and medicinal chemistry profiles [18]. Swiss Target Prediction was used to forecast the ligands' targets based on probability [19]. The molecular docking was upheld by Swiss DOCKING an open-access web server by feeding the PDB file of the target site and .mol2 file of ligand molecules [20,21]. The mol, mol2, and PDB files were reviewed by PyMOL and Jsmol respectively [22,23]. The docking results were obtained in the form of chimerax format which was further observed by UCSF Chimera [24,25]. The cellular signalling pathways and gene-gene interactions were also studied for a comprehensive view of the prospective mode of action of ligand molecules at the genomic level through the WebGestalt 2019 (WEB-based Gene Set Analysis Toolkit) **Figures 1** [26,27].

Results and Discussion

Cheminformatics (Physicochemical, pharmacokinetics, pharmacodynamics, drug-likeness, and medicinal chemistry) of the ligands

The cheminformatics of the bioactive constituent (2-methoxy-4-Vinyl phenol) and a Scaffold analogue are given in **Table 1.** The IUPAC nomenclatures were used for the generation of smile notations, and .mol2 files for further exploration. A scaffold analogue (SA) with the best cheminformatics parameters was designed. **Table 1** shows the ligands' IUPAC names, smile notation, and two-dimensional structure. The molecular weight, hydrogen bond acceptor (HBA), hydrogen bond donors (HBD), lipophilicity (LogP, XLogP3), water solubility (Log S), and topological surface area (TPSA) are enumerated in **Table 2**.

The cheminformatics data provides important information about the ligands, which has been frequently used to identify potential compounds with desirable properties. The exploration of paths for curated drug formulations and prospective drug repurposing chemicals has been assisted by the evaluation of ligand architecture for drug-like attributes. **Table 3** shows the ligands' pharmacokinetics including absorption (GI absorption, P-glycoprotein substrate), distribution (blood-brain barrier), metabolism, elimination ($T^{1/2}$, clearance), and toxicity profiles. The scaffold analogue shows good results (high absorption and impermeable to BBB) within the acceptable range of all the stated parameters as compared with 2-methoxy-4-vinyl phenol.

The pharmacodynamics (bioactivity score at different targets), drug-likeness, and medicinal chemistry attributes of the ligands are given in **Table 4**. The naturally found active constituent of the herbs i.e. 2-methoxy-4-vinyl phenol showed Ghose (01 violation), Muegge (01 violation), lead-likeness (01 violations), bioavailability score of 0.55, and very easy synthetic accessibility (1.45), while promising novel scaffold analogue (SA) showed no drug-likeness violations, PAINS (1 alert), Brenk (1 alert), lead-likeness (01 violation) and easy to synthesize (2.52). 2-methoxy-4-vinyl phenol showed the highest bioactivity on the ion channel modulator (-0.28) while scaffolding analogue (SA) highest bioactivity on the enzyme inhibitor target site (0.17). With no violations and two alarms (Catechol A), the scaffold analogue deduced the most promising features, indicating that there is a significant probability of developing new drug-like compounds from bioactive parts of other medicinal plants in the future.

Table 1: Representing ligand name, IUPAC name, and 2-D structure.

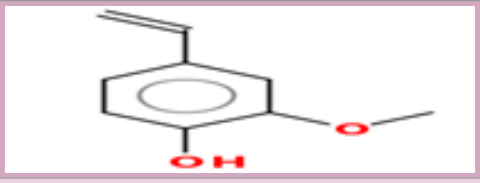
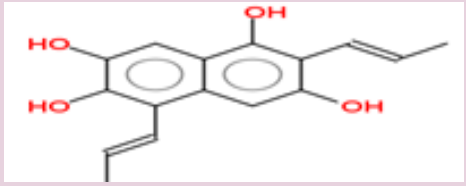
S. No.	Ligand name	IUPAC name	Smile notation	Structure
1	2-methoxy-4-Vinyl phenol	4-ethenyl-2-methoxyphenol	COC1=C(C=CC(=C1)C=C)O	
2	Scaffold analogue(SA)	2,5-bis(prop-1-enyl) naphthalene-1,3,6,7-tetrol	CC=Cc2c(O)cc1c(C=CC)c(O)c(O)cc1c2O	

Table 2: Showing comparative physicochemical properties of 2-methoxy-4-vinyl phenol and Scaffold analogue (SA).

S. No.	Name	M.W.	HBA	HBD	Lipophilicity (log P, X log P3)	Water solubility (log S)	TPSA
1	2-methoxy-4-Vinyl phenol	150.18 g/mol	2	1	2.14, 2.81	-2.81(soluble)	29.46A^2
2	Scaffold analogue	272.30 g/mol	4	4	2.58, 3.77	-4.14 (moderately soluble)	80.91A^2

Table 3: Pharmacokinetic profiles of the ligands (2-methoxy-4-vinyl phenol and Scaffold analogue).

S. No.	Name	Absorption	Distribution	Metabolism	Elimination		Toxicity (Probability, category)
					$T^{1/2}$	Clearance	
1	2-methoxy-4-Vinyl phenol	GI absorption (High) P-gp substrate (No)	BBB permanent (Yes)	CYP1A2 inhibitor (Yes) CYP2C19 inhibitor (No) CYP2C9 inhibitor (No) CYP2D6 inhibitor (No) CYP3A4 inhibitor (No)	0.874 hr	13.581 ml/min/kg	hERG (0.024,0) (0.024,0) H-HT (0.172,0) Ames (0.1,0) Skin Sen (0.207,0) DILI (0.496,0) FDAMDD (0.196,0)
2	Scaffold analogue	GI absorption (High) P-gp substrate (No)	BBB permanent (No)	CYP1A2 inhibitor (Yes) CYP2C19 inhibitor (No) CYP2C9 inhibitor (Yes) CYP2D6 inhibitor (Yes) CYP3A4 inhibitor (Yes)	0.742 hr	10.813 ml/min/kg	hERG (0.032,0) H-HT (0.375,0) Ames (0.572,1) Skin Sen (0.974,1) DILI (0.789,1) FDAMDD (0.94,1)

Table 4: Pharmacodynamics, Drug-Likeness, and Medicinal chemistry profiles of the ligands.

S. No.	Name	Pharmacodynamics (Bioactivity score)	Drug-likeness	Medicinal chemistry
1.	2-methoxy-4-vinyl phenol	GPCR ligand (-0.96) Ion channel modulator (-0.28) Kinase inhibitor (-1.00) Nuclear receptor ligand(-0.77) Protease inhibitor (-1.34) Enzyme inhibitor (-0.46)	Lipinski (Yes) Ghose (No; 1 violation: MW<160) Veber (Yes) Egan (Yes) Muegge (No; 1 violation: MW<200) Bioavailability score (0.55)	PAINS (0 alert) Brenk (0 alert) Lead-Likeness (No; 1 violation: MW<250) Synthetic accessibility (1.45, very easy)
2.	Scaffold analogue	GPCR ligand (-0.17) Ion channel modulator (-0.13) Kinase inhibitor (-0.14) Nuclear receptor ligand (0.05) Protease inhibitor (-0.34) Enzyme inhibitor (0.17)	Lipinski (Yes) Ghose (Yes) Veber (Yes) Egan (Yes) Muegge (Yes) Bioavailability score (0.55)	PAINS (1 alerts: Catechol A) Brenk (1 alerts: Catechol A) Lead-Likeness (No; 1 violation: XLogP3>3.5) Synthetic accessibility (2.52, easy)

Drug targets and molecular docking

The Scaffold analogue, a novel and innovative product, demonstrated promising physicochemical, pharmacokinetics, pharmacodynamics, drug-likeness, and medicinal chemistry profiles when compared to 2-methoxy-4-vinyl phenol, a major bioactive ingredient of *Cynodon dactylon* (L.) Pers. SWISS Target Prediction Software assessed both ligands (2-methoxy-4-vinyl phenol and SA) and projected target sites based on probability as shown in the **Figures 2** and **3** respectively.

The mol and mol2 files of the SA were not available on any database because it was a newly drawn small molecule. The mol2 file was created and then verified, viewed, and standardized by UCSF Chimera. The mol files of 2-methoxy-4-vinyl phenol were available on Zinc 15 and PubChem databases, which were further converted to mol2 files through Open Babel or CORINA Software [28-30]. The results of Swiss target prediction, bioactivity scores at specific target sites, and ligand compatibility with PDB were used to determine target sites, classes, and PDB ids. For further study, PDB data and ligands were standardised and chosen. All missing parameters, including as atoms, missing loops, side chains, and residues, were validated and added into the PDB files. Structure optimization and energy minimization utilising chimera and the Chiron energy minimization and refinement tool were used to remove erroneous chirality, steric conflicts, water molecules, and non-protein residues. The ligand's structure was meticulously examined to ensure that the molecule's topology, protonation state, and tautomeric form were all proper **(Table 5)**.

Molecular Docking: The molecular docking was executed to ascertain the binding conformations **(Figures 4)** (3W12 and 2-methoxy-4-vinyl phenol) and **(Figures 5)** (5TT7 and SA) of the protein-ligand complex using Swiss docking.

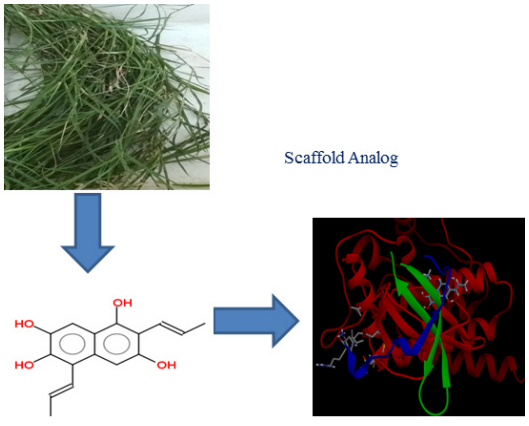


Figure 1 Scaffold Analogue.

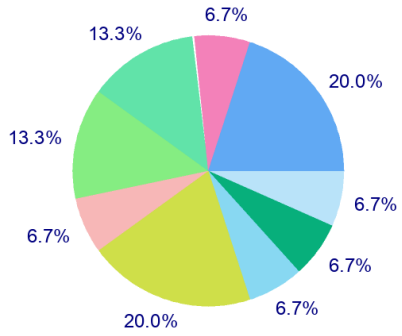


Figure 2 Showing target sites of 2-methoxy-4-vinyl phenol. **Note:** (■) Cytochrome P450; (■) Enzyme; (■) Stutural protin(■) Protease(■) Isomerase(■) Primary active Transporter(■) Transcription factor(■)Lyase (■) Family AG protein-couples receptor

Table 5: Showing Promising targets of the ligands (Cyperene and SA) and their PDB Ids.

S. No.	Name	Target	Class	Common name	PDB Id
1	2-methoxy-4-vinyl phenol	Cytochrome P450 1A2	Cytochrome P450	CYP1A2	3WI2
2	Scaffold analogue	Tyrosine-proteinkinase SYK	Kinase	SYK	5TT7

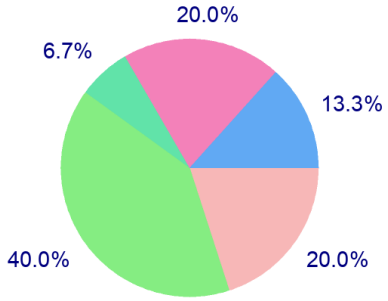


Figure 3 Showing target sites of Scaffold analog (SA).**Note:** (■) Kinase (■) Oxidoreductase (■) Electrochemical transporter (■) Lyase,(■) Cytochrome P450

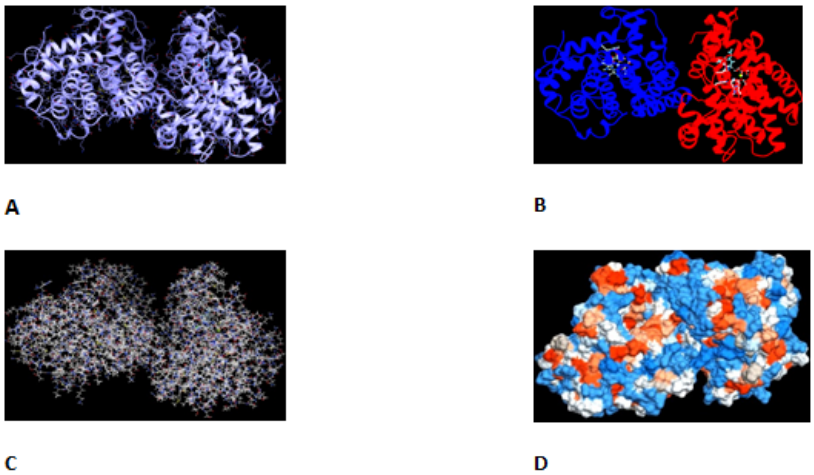


Figure 4 Showing UCSF Chimera view of molecular docking of 3W12 and 2-methoxy-4-vinyl phenol complex. A: Composite view; B: Interactive ribbons; C: All interactive atoms and D: Hydrophobicity surface.

The binding conformation serves in revealing the ligands' binding energy to target locations. The dynamic aspects of molecular simulation docking and its use in structural biology are demonstrated through the viewing of biomolecules. Docking enabled us to understand ligand-protein interactions at the atomic level, helping us to characterise the activity of ligands while interacting with target proteins.

The binding free energy (ΔG_{bind}) comprises Vander Waals energy (ΔG_{vdw}), the sum of electrostatic energy (ΔG_{elect}), the sum of hydrogen bond and desolvation energy (ΔG_{Hbond}), the sum of final total internal energy ($\Delta G_{conform}$), the sum of torsional free energy (ΔG_{tor}), and the sum of unbound system energy (ΔG_{solv}). The energies of 2-methoxy-4-vinyl phenol and scaffold analogue (SA) are shown in **Table 6.**

Table 6: Showing energies of the 2-methoxy-4-vinyl phenol and Scaffold analogue (SA).

S.No.	Energy	2-methoxy-4-vinyl phenol (Kcal/mol)	Scaffold analog (Kcal/mol)
1	Simple Fitness	12.34354	17.3973
2	Full Fitness	-3084.9133	-1545.128
3	Inter Full	-24.5976	-43.6341
4	Intra Full	32.813	56.576
5	Solv Full	-3741.74	-1782.16
6	Surf Full	328.572	224.09
7	Extra Full	0	0
8	Delta Gcompsolvpol	-3741.74	-1782.16
9	DeltaGcompsolnonpol	328.572	224.09
10	Delta Gprotsolvpol	-3641.95	-1791.35
11	DeltaGprotsolvnonpol	330.138	226.489
12	Delta Gligsolvpol	-3.91566	-9.97057
13	Delta Gligsolvnonpol	9.9623	6.68164
14	Delta Gvdw	-24.5976	-43.6341
15	Delta Gelec	0	0
16	Delta G	-6.84599	-7.804192

The Swiss Docking is based on an algorithm that consists of several steps such as a large number of bonding modes (BMs) are generated, either in the user-defined box (local docking) or near to the target cavities of the whole protein surface (blind docking). Concurrently, their CHARMM energies are evaluated. Then BMs with the most favourable energies are ranked, taking into consideration the solvation model. The results of binding free energies (ΔG_{bind}) and compatibility of 3-D crystalline protein structures with ligands are quite important for better elucidating the biochemical pathways. However, the present research discerns the ligand based approach wherein the ligand/scaffold analogue showed activities on multiple targets. The purpose of molecular docking herein is just to establish the binding energy of scaffold analogue irrespective of binding affinity. That generated the primitive idea about binding activity. After Swiss target prediction, 2-methoxy-4 vinyl phenol was docked to cytochrome P450 1A2 (CYP1A2) a target site of Cytochrome P450 receptor but it could not be materialized in the case of scaffold analogue (SA) due to non-compatibility. The molecular docking of SA was done on tyrosine protein kinase SYK, a target site of kinase inhibitor which shows a bioactivity score of -0.14. Hence, it became crucial to conduct proteogenomic analysis to have better insights into the genomic interactions and molecular mechanism of action of the ligands.

Proteogenomic analysis

Proteogenomic analysis: For a deeper understanding and knowledge of ligand behaviour at the genome level, researchers used Over-representation analysis (ORA) and Network topology analysis (NTA). Owing to the unavailability of 3D structures within most proteins in Protein databases (PDB) and their compatibility, executing docking studies of ligands and their all expected target sites was quite difficult. Furthermore, collecting all proteins' crystalline 3D structures in order to analyse ligand-target interactions in detail proved extremely difficult. As a result, ORA and NTA were used to undertake Proteogenomic analysis. We identified 29 and 35 target genes based on probability as predicted by Swiss Target Prediction, open source software, to better understand the genomic interactions of 2-methoxy-4-vinyl phenol and Scaffold ligands.

(i) Network topology analysis (NTA) was performed by following the sequential pathways is given as under:-

Homosapiens>NTA>Network>PPI bio grid>Gene symbol>Gene feeding>Submit>Result

The integration grid of 2-methoxy-4-vinyl phenol and scaffold analogue are shown in Figures 6-9 respectively.

(ii) Over-representation analysis is also a sequential pathway that is performed to find out the cellular signalling pathways (Figure 7): 2-methoxy-4-vinyl phenol and (Figure 10) scaffold analogue and top ten diseases/disorders controlled by these interactive genes specific to the ligands are shown in Figure 8: 2-methoxy-4-vinyl phenol and (Figures 10 and 11): scaffold analogue.

The sequential pathways for analysing the cellular signalling is given as under:-

ORA>Pathway>Reactome>Genesymbol>Genome>Submit>Result

The sequential pathways for analysing interactive genes and their associated diseases/disorders:-

ORA>Disease>Disgenet>genome>Submit>Result

2-methoxy-4-vinyl phenol interaction grid (NTA), cellular signalling and regulated diseases/disorders(ORA): CA2-Carbonic anhydrase2, CA9-Carbonic anhydrase9, CA12-Carbonic anhydrase12, CA1-Carbonic anhydrase1, C5A-Carbonic anhydrase5A, MPI-Mannose phosphate isomerase, MIF-Macrophage migration inhibitory factor, NFE2L2-Nuclear factor erythroid 2-related factor 2, HSPB2-Heat shock protein family B member 2, CYP1B1-Cytochrome P450 family 1 subfamily B member 1, CYP1A1-Cytochrome P450 family 1 subfamily A member 1, VEGFA-Vascular endothelial growth factor A, SAE1-SUMO1 activating enzyme subunit1,ACTBL2-Actin Beta like 2, MAPK6-Mitogen-activated protein kinase 6, SRD5A1-Steroid 5 alpha-reductase 1, ELAVL1-ELAV Like RNA Binding Protein 1, TRIM25-Tripartite motif-containing 25, PARP1-Poly(ADP-Ribose) Polymerase 1, AHR-Aryl hydrocarbon receptor, RELA-RELA Proto-Oncogene, TUBB1-Tubulin beta 1 class VI, TUBB3-Tubulin beta 3

class III, LMNA-Lamin A/C protein-coding gene, CERS6-Ceramide synthase 6, LMBR1-Limb development membrane protein 1, METAP2-Methionyl aminopeptidase 2, GPR84-G Protein-Coupled Receptor 84, MAPT-Microtubule Associated Protein Tau, SRC-Proto-Oncogene tyrosine-protein kinase SRC, EGLN1-EGL-9 family hypoxia-inducible factor 1, REEP5-Receptor accessory protein 5 **(Figure 6)**.

Reversible hydration of carbon dioxide, Synthesis of epoxy(EET) and dihydroxyeicosatrienoic acid, Synthesis of (16-20)-hydroxyeicosatetraenoic acid, Xenobiotics, Arachidonic acid metabolism, Cytochrome P450-arranged by substrate type, Phase-1 functionalization of compounds, Regulation of hypoxia-inducible factor(HIF) by oxygen, Cellular response to hypoxia, Biological oxidation **(Figure 7)**.

Lung injury, Memory disorders, Depressive symptoms, Colitis, Diabetic Nephropathy, Neoplasm experimental, Contact dermatitis, mammary neoplasm, Prostatic neoplasm, Liver cirrhosis experimental **(Figure 8)**.

2-methoxy-4-vinyl phenol may prove as a potential remedy for lung injury, memory disorders, depressive symptoms, colitis, diabetic nephropathy, neoplasm experimental, contact dermatitis, mammary neoplasm, prostatic neoplasm, and liver cirrhosis experimental.

Scaffold analogue interaction grid (NTA), Cellular signalling and regulated diseases/disorders (ORA): ALOX5-Arachidonate 5-Lipoxygenase, CA9-Carbonic anhydrase 9, CA2-Carbonic anhydrase 2, CA12-Carbonic anhydrase 12, CA5B-Carbonic anhydrase 5B, CA1-Carbonic anhydrase 1, CA3-Carbonic anhydrase 3, CYP3A4-Cytochrome P450 family 3 subfamily A member 4, CYP1A2-Cytochrome P450 family 1 subfamily A member 2, CYP2C9-Cytochrome P450 family 2 subfamily C member 9, CYP2C19-Cytochrome P450 family 2 subfamily C member 19, CYP1A1-Cytochrome P450 family 1 subfamily A member 1, POR-Cytochrome P450 Oxido reductase, MAPK6-Mitogen-activated protein kinase 6, NXF1-Nuclear RNA Export Factor 1, NQO2-NAD(P)H dehydrogenase quinone 2, MAOA-Monoamine oxidase A, NOX4-NADPH Oxidase 4, ACTBL2-Actin Beta like 2, PTGS1-Prostaglandin-Endoperoxide Synthase 1, PTGS2-Prostaglandin-Endoperoxide Synthase 2, BAG3-BAG Cochaperone3, CYLD-CYLD Lysine 63 Deubiquitinase, ELAVL1-ELAV Like RNA Binding Protein 1, PIK3CB-Phosphatidylinositol-4,5-Bisphosphate3-Kinase, ALOX5-Arachidonate 5-Lipoxygenase, RELA-RELA Proto-Oncogene, ESR1-Estrogen receptor1, EGFR-Epidermal growth factor receptor, PIK3CA-PIK3CA subunit alpha, AHR-Aryl hydrocarbon receptor, APP-Amyloid beta precursor protein, PTGS1-Prostaglandin-Endoperoxide Synthase 1, SRC-Proto-Oncogene tyrosine-protein kinase SRC,HNRNPL-Heterogeneous nuclear ribonucleoprotein L, TYMS-Thymidylate Synthetase, CHEK1-Checkpoint kinase 1, SYK-Spleen associated tyrosine kinase, IMPDH1-Inosine monophosphate dehydrogenase 1, LCK-Lymphocyte-Specific protein tyrosine kinase, PIK3CG-Phosphatidylinositol-4,5-Biphosphate 3-Kinase, SLC6A2-Solute carrier family 6 member 2, SNCA-Alpha-synuclein **(Figure 9)**.

Reversible hydration of carbon dioxide, Synthesis of epoxy(EET) and dihydroxyeicosatrienoic acid, Biosynthesis of maresins, Biosynthesis of DHA-derived SPMs, Biosynthesis of specialized pro-resolving mediators(SPMs), Xenobiotics, Arachidonic acid metabolism, Cytochrome P450-arranged by substrate type, Phase-1 functionalization of compounds, Biological oxidation **(Figure 10)**

Kidney failure chronic, Colitis, Neoplasm recurrence local, Atherosclerosis, Oesophageal neoplasms, Adenocarcinoma, Reperfusion injury, Colonic neoplasms, Liver carcinoma, Mammary neoplasms **(Figure 11)**.

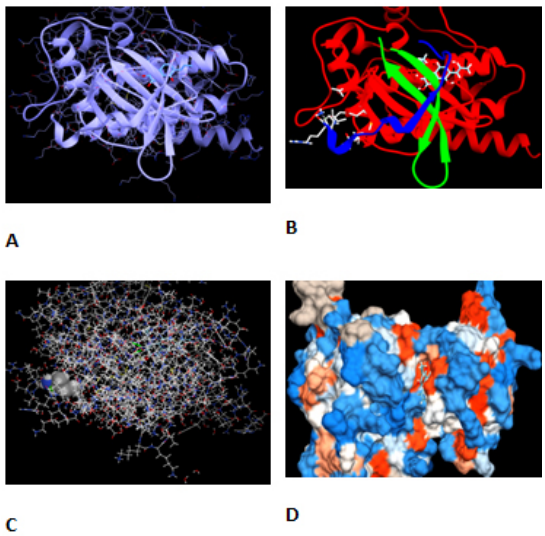


Figure 5 Showing UCSF Chimera view of molecular docking of 5TT7 and Scaffold Analog complex. A: Composite view; B: Interactive ribbons; C: All interactive atoms and D: Hydrophobicity surface.

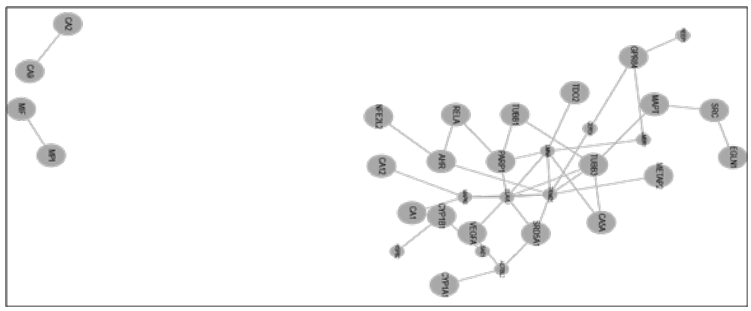


Figure 6 Showing interaction grid of targeted genes of 2-methoxy-4-vinyl phenol.

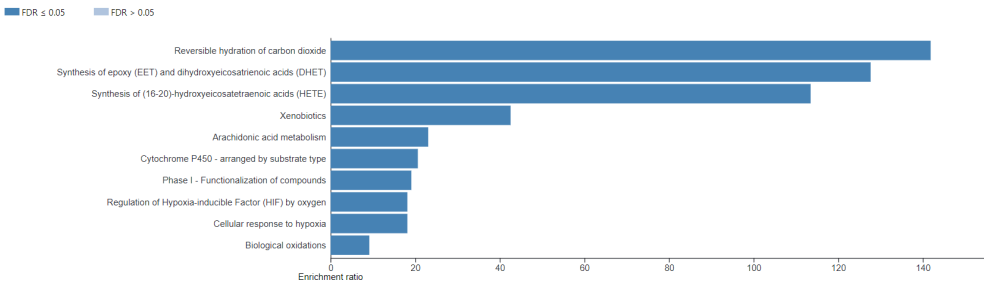


Figure 7 Showing cellular signaling pathways of targeted genes of 2-methoxy-4-vinyl phenol.

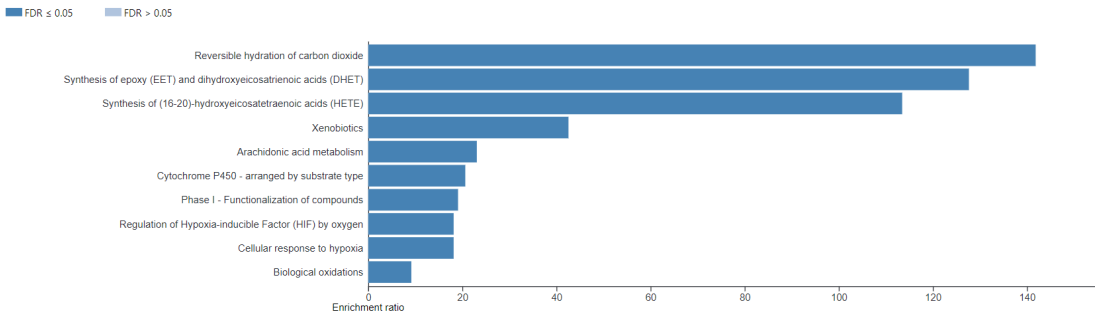


Figure 8 Showing top ten diseases/disorders controlled by the grid of targeted genes of 2-methoxy-4-vinyl phenol.

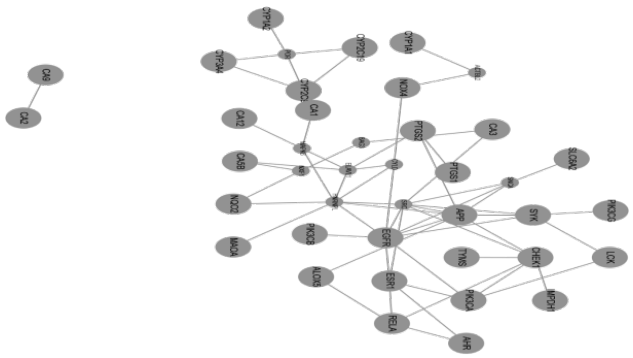


Figure 9 Showing interaction grid of targeted genes of Scaffold Analog.

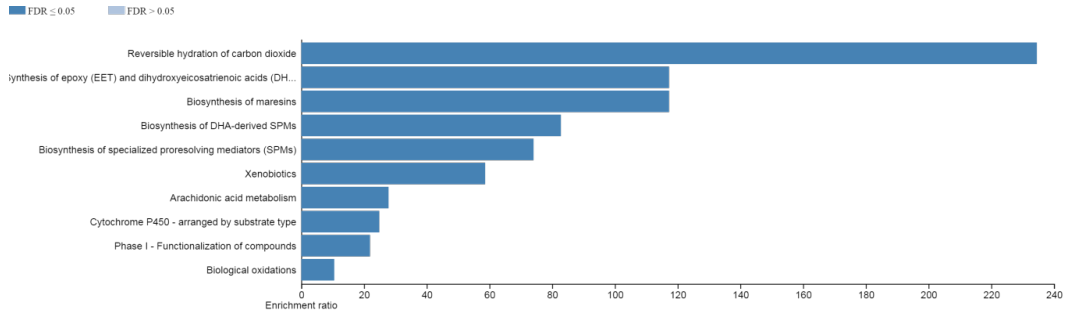


Figure 10 Showing cellular signaling pathways of targeted genes.

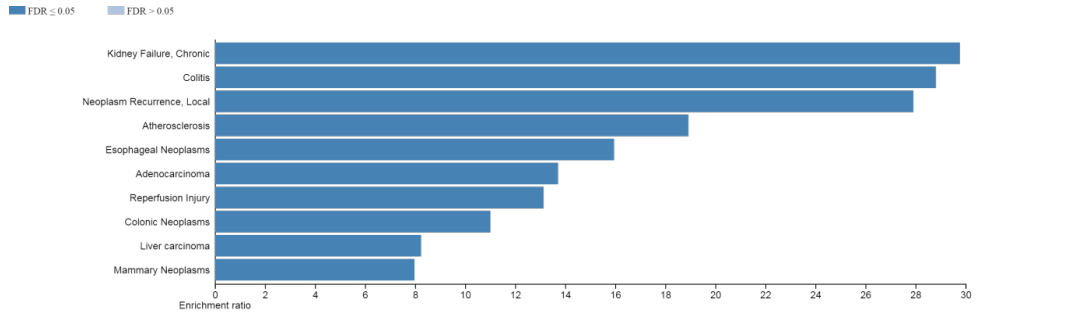


Figure 11 Showing top ten diseases/disorders controlled by the grid of targeted genes of Scaffold Analog.

The novel scaffold analogue may prove as a remedy for kidney failure chronic, colitis, neoplasm recurrence local, atherosclerosis, oesophageal neoplasms, adenocarcinoma, reperfusion injury, colonic neoplasms, liver carcinoma, and mammary neoplasms.

Herbals are ostensibly influential among food culture as well as in holistic health systems embraced by society [31]. The global demand for potential lead compounds is increasing, and active drug particles have been diverted to expedite health problem resolution using *in silico* techniques [32]. There will always be a quest for safer and more effective therapeutic substances, which can be met by doing Cheminformatics and Proteogenomic research on indigenous herbal medicine associations. The current work used a ligand-based strategy to investigate pathways, interactions of genes engaged in certain cellular pathways, and disease and disorder control. The combination of conventional and complementary and alternative medicine (CAM) is a promising cancer-fighting technique. Newly discovered phytochemicals or analogue are in high demand for preclinical and epidemiological investigations to determine their molecular fingerprints [33]. Through the use of an *in silico* technique, it is possible to identify more potent herbal analogue for the treatment of arthritis, diabetes, and cancer [34]. Although a myriad of literature is available on target-based approach and specific target sites were investigated for the different ligands which did not pave the way for exploring new ligands and their scope for drug repurposing is left behind. Hence, the present investigation worked on a ligand-based method (chemical similarity criteria), which does not guarantee similar bioactivity. The bioactivity scores of the ligands at various target locations are evaluated for this purpose, and their binding energy is quantified using Swiss docking. The goal of docking was not to achieve extra precision, but rather to assess the binding energy for a certain receptor class as predicted by Swiss target prediction software. On this front, medicinal plants are the least explored, and the potential for developing novel drugs from their active chemical ingredients via curative and synthetic methods has yet to be realised. The current study finds that this is one of the least researched and studied parts of *in silico* drug design, which involves creating drug-like tiny molecules in novel and curative ways. This approach can also be used to calculate forces, energies, and binding affinity using specific molecular docking studies such as interaction analysis (protein-ligand), replica exchange molecular dynamics (REMD), MM-GBSA, and APBS electro statistics, which are validated by Ramachandran torsion plots [35]. After pathways are disclosed at the genome level, these scientific efforts will not only increase the biological efficacy of the current drug, but will also provide a roadmap for innovative drug creation or a fair possibility for drug reuse [36]. Furthermore, it may be assumed that there is a wide scope for investigation of other members of the Poaceae family including *Digitaria sanguinalis* (L.) *Scop, Saccharum officinarum* L and *Hordeum vulgare* L, etc., for the development of herbal medicines [3,37].

Conclusion

Cynodon dactylon (L) Pers., a Poaceae family member, was

studied using an *in-silico* approach. Given the wide availability in nature and long-term use in a number of ailments, researchers have pursued a thorough understanding of the herbal therapeutic agent's mechanism of action in order to establish its potential as a drug for drug reuse and design successor. The curatively built scaffold analogue was investigated with 2-methoxy-4-vinyl phenol, a key bioactive constituent of the medicinal herb. Proteogenomic network research helped researchers truly understand cell signalling, regulation, and protein-protein interaction pathways. The researchers unveiled where ligands can target, how genes connect, how signalling pathways work, and how these things relate to the top ten diseases and disorders. The scaffold analogue has better drug similarity and safety characteristics than the originals. In general, the current research looked into a variety of ligand-target locations as well as their probable modes of action. Scaffold analogue has been identified as a promising chemical for future phytomedicines based on considerable investigation. More medication development and prospective drug repurposing chemicals might be conceivable as a result of this. These findings can subsequently be corroborated by determining the resilience and electrostatic stability of target-specific ligands using molecular mechanics generalised born surface area continuum solvation (MM-GBSA). This, however, is outside the scope of the current research. According to the findings, the main potential of indigenous medications remains untapped, which may be scientifically researched to meet the global demand for pharmaceuticals? Based on this extensive research, it can be deduced that the scaffold analogue and the bioactive components, either together or separately, could be promising effective molecules for herbal medicines in additional disorders, as mentioned in the pharmacological interaction analysis.

Conflict of Interest

The authors report no conflicts of interest. The authors are responsible for the content, and writing of this article.

Author Contributions

Both authors collaborated on conceptualization, data collection, formal analysis, investigation, methodology, software, validation, visualisation, writing-original manuscript, writing-review, and editing. The published version of the manuscript has been read and approved by both authors.

Funding

The present research is self-sponsored and no external funding agency was approached for the purpose.

Ethical Statement

This study does not involve any human or animal testing.

Acknowledgements

Thanks to honourable Dr.Chinmay Pandav (Pro-Vice-Chancellor, Dev Sanskriti Vishwavidyalaya) for his kind unflinching and unwavering motivation. Further, we are obliged to the experts of Medicinal Plants (Professor KS), Drug Design Scientists (M K), and renowned Academicians for assisting the work successfully.

References

1. Singh LR, Singh K (2021) Organic agri-practices and pharmacognostic evaluation of off- seasoned cultivated madhulika: A wonder herb. Int J Pharma Bio Sci 11:19-23.
2. Das MC, Shilpi S, Chandra S (2013) Overview of Cynodon dactylon (Doob Grass) in Modern Medicine as Anti-diabetic Herb. J Drug Deliv Ther 3(6).
3. Raj Singh L (2019) Dev SV. Pharmacognostic studies of organically cultivated panacea herb Cynodon dactylon (L.) Pers. Int J Ayurveda Pharma Res 7:65-8.
4. Cynodon dactylon (L.) Pers: An updated review of its phytochemistry and pharmacology. J Med Plants Res (2013).
5. Yi F, Li L, Xu L Jia, Meng H, Dong Y mao, et al. (2018) In silico approach in reveal traditional medicine plants pharmacological material basis. Chin Med 13(1).
6. Brunak S, Bjerre Collin C, Eva O Cathaoir K, Golebiewski M, Kirschner M, et al. (2020) Towards standardization guidelines for in silico approaches in personalized medicine. J Integr Bioinform 17(2,3).
7. Xu J, Hagler A (2002) Chemoinformatics and drug discovery. Molecules 7(8): 566-600.
8. Menschheit G, Fenyo D (2017) Proteogenomics from a bioinformatics angle: A growing field. Mass Spectrom Rev 36(5): 584-599.
9. Fabregat A, Sidiropoulos K, Viteri G, Forner O, Marin-Garcia P, et al. (2017) Reactome pathway analysis: A high-performance in-memory approach. BMC Bioinformatics 18(1).
10. Dai J, Yao Z, Zhang G, Liu G, Dai R, et al. (2019) Graph computing-based real-time network topology analysis for power systems. IEEE Power Energy Soc Gen Meet.
11. Mignani S, Rodrigues J, Tomas H, Jalal R, Singh PP, et al. (2018). Present drug-likeness filters in medicinal chemistry during the hit and lead optimization process: How far can they be simplified? Drug Discov Today 23(3): 605-615.
12. Tian S, Wang J, Li Y, Li D, Xu L, et al. (2015) The application of in silico drug-likeness predictions in pharmaceutical research. Adv Drug Deliv Rev 86:2-10.
13. Calkins K (2002) Drug-Likeness Rules. Bio Century.
14. Khajehzadeh M, Sadeghi N (2018) Molecular structure, X-ray crystallography, spectroscopic characterization, solvent effect, NLO, NBO, FMO analysis of [Cu(bpabza)] complexes. J Mol Liq 249: 281-293.
15. Daina A, Michielin O, Zoete V (2017) Swiss ADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 7:42717.

16. Kar S, Leszczynski J (2020) Open access in silico tools to predict the ADMET profiling of drug candidates. Expert Opin Drug Discov 15(12): 1473-1487.

17. Fang Y, Offenhaeusser A (2004) ADMET biosensors: Up-to-date issues and strategies. Med Sci Monit.

18. Molinspiration cheminformatics. Choice Rev Online (2006).

19. Gondokesumo ME, Sumitro SB, Handono K, Pardjianto B, Widowati W, et al. (2020) A computational study to predict wound healing agents from the peel of the mangosteen (garcinia mangostana l.) extract. Int J Bioautomation 24(3):265-276.

20. Jackie B, Sagar S, Alamgir H, Razowanul Md F, Sumaiya F et al. (2018) In silico molecular docking and adme/t analysis of some selected isolated compounds of phyllanthus emblica against type 2 diabetics. Am J Ethnomed 5(2).

21. Chakraborty S, Phu M, de Morais TP, Nascimento R, Goulart LR, et al. (2015) The PDB database is a rich source of alpha-helical anti-microbial peptides to combat disease-causing pathogens. F1000 Res 3: 295.

22. Delano WL (2020) The PyMOL Molecular Graphics System, Version 2.3. Schrödinger LLC.

23. Bendl J, Stourac J, Sebestova E, Vavra O, Musil M, et al. (2016) HotSpot Wizard 2.0: automated design of site-specific mutations and smart libraries in protein engineering. Nucleic Acid Res 44(W1): 479-487.

24. Rodríguez-Guerra Pedregal J, Maréchal JD (2018) PyChimera: Use UCSF Chimera modules in any Python 2.7 project. Bioinformatics 34(10): 1784-1785.

25. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, et al. (2004) UCSF Chimera. J Comput Chem 25(13): 1605-1612.

26. Guan L, Yang H, Cai Y, Sun L, Di P, et al. (2019) ADMET-score-a comprehensive scoring function for evaluation of chemical drug-likeness. Medchemcomm 10(1): 148-157.

27. Liao Y, Wang J, Jaehnig EJ, Shi Z, Zhang B (2019) WebGestalt 2019: Gene set analysis toolkit with revamped UIs and APIs. Nucleic Acid Res 47: 199–205.

28. Rajan K, Zielesny A, Steinbeck C (2021) STOUT: SMILES to IUPAC names using neural machine translation. J Cheminform.

29. Wester MJ, Pollock SN, Coutsias EA, Allu TK, Muresan S (2008) Scaffold topologies. 2. Analysis of chemical databases. J Chem Inf Model 39(43).

30. Yongye AB, Waddell J, Medina-Franco JL (2012) Molecular scaffold analysis of natural products databases in the public domain. Chem Biol Drug Des 80(5): 717-724.

31. Velkoborsky J, Hoksza D (2016) Scaffold analysis of PubChem database as background for hierarchical scaffold-based visualization. J Cheminform 8(1).

32. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, (2011) Open Babel: An open chemical toolbox. J Cheminform 3(1).

33. Tetko I V, Gasteiger J, Todeschini R, Mauri A, Livingstone D, et al. (2005) Virtual computational chemistry laboratory - design and description. J Comput Aided Mol Des 19(6): 453-463.

34. Crisman TJ, Sisay MT, Bajorath J (2008) Ligand-target interaction-based weighting of substructures for virtual screening. J Chem Inf Model 48(10): 1955-1964.

35. Montes-Grajales D, Puerta-Guardo H, Espinosa DA, Harris E, Caicedo-Torres W, et al. (2020) In silico drug repurposing for the identification of potential candidate molecules against arboviruses infection. Antiviral Res 173: 104668.

36. Chetta M, Tarsitano M, Vicari L, Saracino A, Bukvic N (2021) In silico analysis of possible interaction between host genomic transcription factors (TFs) and zika virus (ZikaSPH2015) strain with combinatorial gene regulation; virus versus host—the game reloaded. Pathogens 10(1): 69.

37. Djokovic N, Ruzic D, Djikic T, Cvijic S, Ignjatovic J, et al. (2020) An integrative in silico drug repurposing approach for identification of potential inhibitors of SARS-CoV-2 main protease. ChemRxiv.