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Prospective and Comparative Screening of Bioactive Principle and Scaffold Analogue of Herbal Drug Via Cheminformatics and Proteogenomic Analysis

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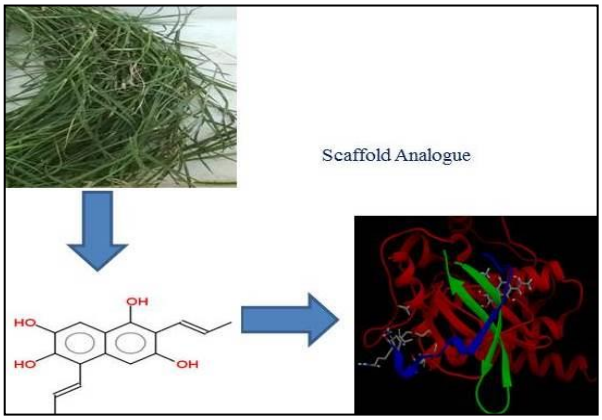
ABSTRACT



***Background**: The global demand for safer and therapeutically effective medications is surging and medicinal plants are optimum indicators of lead particles.*
***Objective**: To figure out how herbal medicine ligands (one major bioactive principle and prospective scaffold) work at a molecular level.*
***Materials and Methods:** The present study confirmed that the plant belongs to the Poaceae family, and taxonomically identified as Cynodon dactylon (L.) Pers.. Current research focuses on an in-silico comparison of ligands having drug-like properties through the application Cheminformatics and Proteogenomics.*
***Results and Conclusion:** The study emboldened the basic mechanism of action of ligands and interactions pathways at the molecular level. It is concluded that scaffold analogue possesses better drug-like qualities than natural bioactive principle of Cynodon dactylon (L.) Pers. These studies may further the scope of innovative herbal formulations for the existing diseases or disorders.*

***Keywords:** Drug-likeness; Clearance; Docking; Toxicity; Proteogenomic*

INTRODUCTION

Herbal plants have been recommended by practitioners for healing purposes in many treatment systems including Ayurveda, Unani, Homeopathy, and Siddha since ancient times, and have also been described as essential sources of medicine even in the present period(1). Obesity, remittent fever, menstrual irregularities, urinary tract infection, hydrocele, diabetes, hysteroepilepsy, bowel disorders, irritable bowel syndrome, piles, coronary artery disease, and other neuromuscular related issues are ameliorated by Bahama grass (*Cynodon dactylon* (L.) Pers.)(2,3).

The major therapeutic agents are found in the whole parts of the herb. A plethora of bioactive constituents is found in it including 2-methyl-4-vinyl phenol, catechin, beta-carotene, lutein, rutin, myricetin, and quercetin; which represents different classes of secondary metabolites-alkaloids, phenols, tannins, saponins, steroids, coumarins, flavonoids, carotenoids, and vitamins-a and vitamin-c(4). In the field of therapeutic development using herbal drug-

derived ligands, in silico approaches are gaining traction to identify lead structures(5). This is particularly true in the case of *Cynodon dactylon* (L.) Pers., where molecular activities of ligands are evaluated at various target sites, in order to enhance drug discovery, redevelopment, and innovation(6). Various techniques such as cheminformatics(7), and proteogenomic analysis(8), including drug similarities, target predictions, pharmacology modelling, molecular anchoring, gene identification, overexpression analysis (ORA)(9), and Network Topology-based Analysis (NTA)(10) are employed to derive biological insights. Additionally, the drug-likeness of these molecules is evaluated using a range of parameters such as the Lipinski Rule of Five, Ghose's Rule, Oprea's Rule, Veber's Rule, Verma's Rule, and Egan Rule(11–13).

MATERIALS AND METHODS

Details of the Plant

Hindi Name: Doob
Common Name: Bahama grass
Latin Name: *Cynodon dactylon* (L.) Pers.
Family: Poaceae

General Procedure

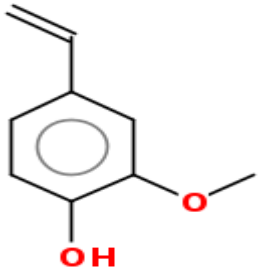
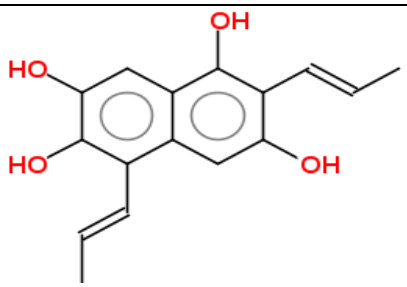
One major bioactive phytoconstituent was selected from the experimental plant material based on their activities and an optimum scaffold analogue was drawn by ChemBioDraw(14). It was comparatively evaluated for their drug-likeness properties via SwissADME(15), ADMET lab(16,17), and Molinspiration Cheminformatics Software(18). The targets of the ligands were predicted based on probability by using Swiss Target Prediction(19). The molecular docking was assisted by Swiss DOCKING-an open-access web server(20) by feeding the PDB file of the target(21) and .mol2 file of ligand molecules. The .mol, .mol2, and PDB files were reviewed by PyMOL(22), and Jsmol(23) respectively. The docking results were obtained in the form of .chimerax file format which was further observed by UCSF Chimera(24,25). The bioactive properties, half-life (T1/2), clearance time, and toxicity profiles of both ligands were undertaken with the assistance of the ADMET lab(26). 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 (WEB-based Gene Set Analysis Toolkit), 2019(27).

RESULTS AND DISCUSSION

Drug-likeness (ADMET) profile of the ligands

The cheminformatics of the bioactive constituent (2-methoxy-4-vinylphenol) and, a Scaffold analogue is given in Table 1. The IUPAC nomenclatures were used for the generation of smile notations and .mol2 files(28) for further exploration. A scaffold analogue (SA) was drawn by taking into consideration of optimum drug-likeness properties, bioactivity scores, half-life (t1/2), clearance time, and toxicity profile. The toxicity profile comprises hERG blocker, human hepatotoxicity, Ames mutagenicity, skin sensitization, drug-induced liver injury, and FDA maximum recommended daily doses(16). The virtual library includes more than 60,000 homogeneous aromatic scaffolds, which indicates a possibility of generating innovative lead molecules from plants as well if suitable target sites are identified and explored through pharmacological network analysis. It is possible to discover the lead structure by selectively planning the scaffold using the primary bioactive component of the plant while ensuring a strong and compatible binding at the target sites(29,30).

Table 1 Enlisting Ligand Name, IUPAC Name, and 2-D Structure

S.N.	Ligand Name	IUPAC Name	Structure
1.	2-methoxy-4-Vinyl phenol	4-ethenyl-2-methoxyphenol	
2.	Scaffold analogue	2,5-bis(prop-1-enyl)naphthalene-1,3,6,7-tetrol	

The drug-likeness characteristics are given in Table 2 and Table 3; enumerating the combined parameters of the 'Lipinski', 'Ghose's Rule', 'Oprea's Rule', 'Veber's Rule', 'Verma's Rule', and 'Egans' rules.

Table 2 Showing comparative drug-likeness profiles of bioactive constituents and Scaffold analogue

S.N.	Name	Smile notation	M.W.	HBA	HBD	LogP	miLogP	TPSA
1.	2-methoxy-4-Vinyl phenol	COC1=C(C=CC(=C1)C=C)O	150.18 g/mol	2	1	2.14	2.13	29.46
2.	Scaffold analogue	CC=Cc2c(O)cc1c(C=CC)c(O)c(O)cc1c2O	272.30 g/mol	4	4	2.58	3.76	80.91

The data generated by cheminformatics provides essential information about the ligands used in screening for potential compounds with specific properties. Ligand structure is characterized to explore pathways for drug formulations and potential repurposing candidates(31). Table 3 shows key information on bioactivity score, t1/2, clearance time, and toxicity profiles of ligands.

Table 3 Showing the Bioactivity score, t1/2, clearance time, and toxicity profiles of the ligands

S.N.	Name	Bioactivity Score		T1/2	Clearance	Toxicity (Probability, Category)
1.	2-methoxy-4-Vinyl phenol	GPCR ligand Ion channel modulator Kinase inhibitor Nuclear receptor ligand Protease inhibitor Enzyme inhibitor	-0.96 -0.28 -1.00 -0.77 -1.34 -0.46	0.874h	13.581 ml/min/kg	hERG (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	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	0.742h	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)

Based on these observations, the decision was made to conduct molecular docking studies. In order to achieve its goal, the process of optimal target prediction was utilized for both ligands and their corresponding 3-D protein structures.

Drug Targets and Molecular Docking

The Scaffold analogue (SA) a unique and curatively drawn compound showed promising bioactivity score, and drug-likeness characteristics when compared with a major bioactive compound of *Cynodon dactylon* (L.) Pers.. The scaffold analogue was evaluated by Molinspiration Cheminformatic Software, ADMET lab, and SWISS Target Prediction Software which predicted the target sites based on probability.

The .mol and .mol2 file of the SA was not available on any database because it was a newly drawn small molecule. The. mol2 file was created, verified, and then, viewed in UCSF Chimera. Although, the .mol files of 2-methoxy-4-vinyl phenol was available on Zinc 15 and PubChem databases, which was further converted to .mol2 files through CORINA Software(33). The target proteins, their classes and their respective ligands are shown in Table 4.

Table 4 Showing Promising Targets of the Ligands and their Classes

S.N.	Name	Target	Class	Common Name	Protein
1.	2-methoxy-4-Vinyl phenol	Cytochrome P450 1A2	Cytochrome P450	CYP1A2	3Wl2
2.	Scaffold analogue	Tyrosine-protein kinase SYK	Kinase	SYK	5TT7

Molecular Docking: The docking helped us to know the interaction of ligands and proteins at the atomic level to significantly and precisely characterise the behaviour of the ligands while interacting with target proteins. Understanding the binding free energies (ΔG) and the compatibility between ligands and 3-D crystalline protein structures is a significant aspect in comprehending biochemical pathways. Table 5 reveals the free energies of both ligands and is divided into two clusters - 0 and 1. Fig. 1-4 and Fig. 5-8 are showing UCSF chimera view of 3-D docking structures of 2-methoxy-4-Vinyl phenol and SA respectively.

Table 5. Showing the free energies of the ligands

S.N.	Name	Free energy (ΔG)	
		Cluster 0 (Kcal/mol)	Cluster 1(Kcal/mol)
1.	2-methoxy-4-Vinyl phenol	-6.17	-6.24
2.	Scaffold analogue (SA)	-7.29	-5.44

3D-Docking Structures of 2-methoxy-4-vinyl phenol

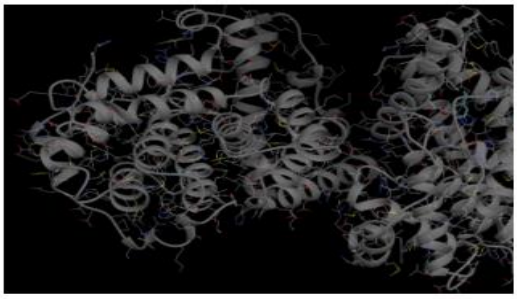


Figure 1Composite view

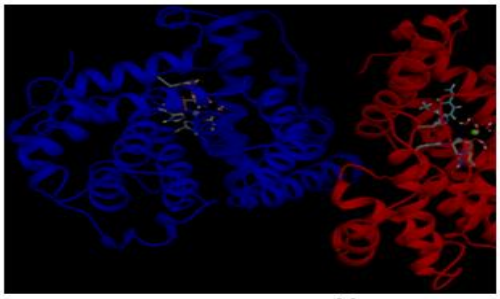


Figure 2 Interactive ribbons

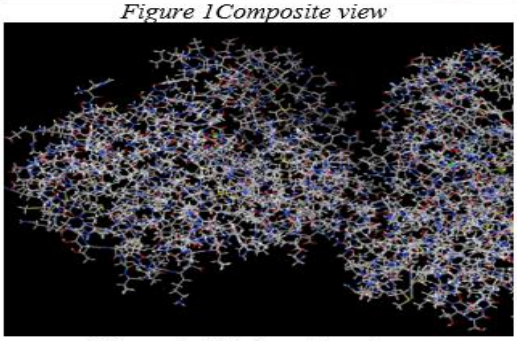


Figure 3 All interactive atoms

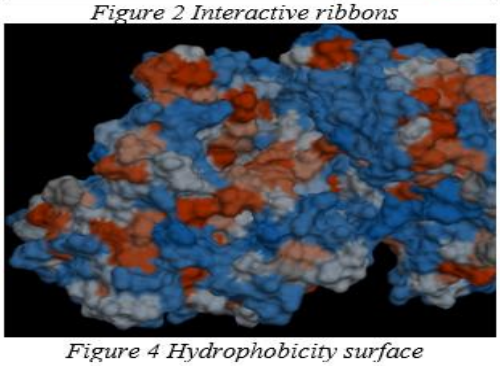


Figure 4 Hydrophobicity surface

Fig. (1-4) Showing UCSF Chimera view of molecular docking of 2-methoxy-4-vinyl phenol

3D-Docking Structures of Scaffold Analogue (SA)

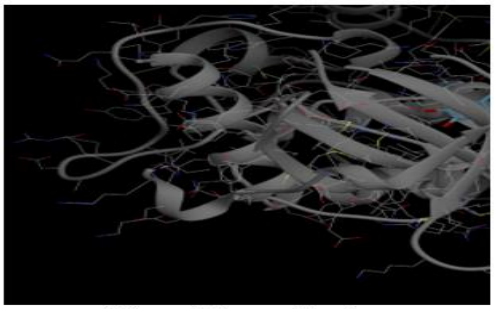


Figure 5 Composite view

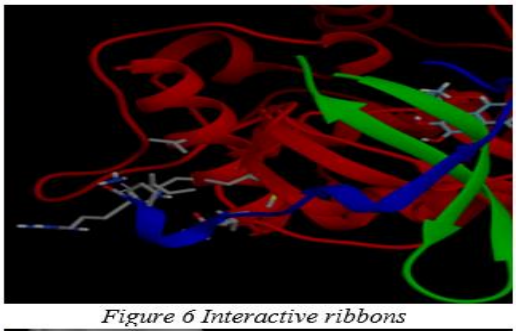


Figure 6 Interactive ribbons

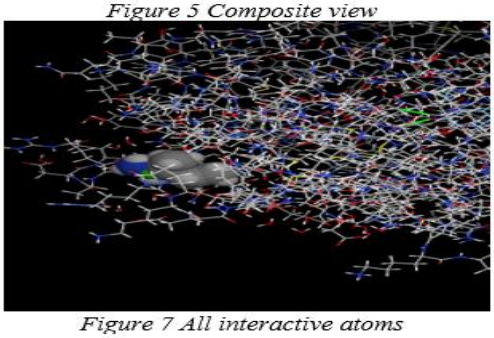


Figure 7 All interactive atoms

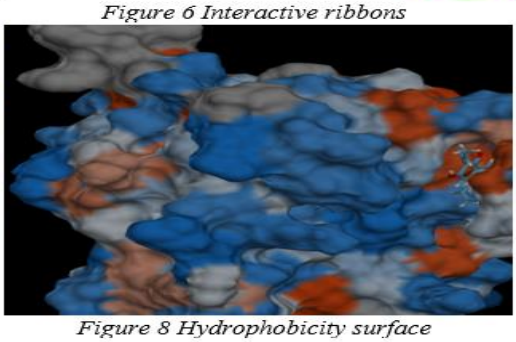


Figure 8 Hydrophobicity surface

Fig. (5-8) Showing UCSF Chimera view of molecular docking of Scaffold Analogue

The goal of molecular docking here is to generate only the binding energy of the scaffold analogue and bioactive principle, regardless of binding affinity. This provided a primitive idea of the specific target site binding activity needed to exert potential therapeutic effects. Performing docking studies of the ligands and all of their predicted target regions has been challenging due to the lack of 3D structures and the incompatibility of most proteins in

protein databases (PDBs) with small ligands. Moreover, it was extremely difficult to obtain 3D crystal structures of all proteins to study ligand-target interactions in detail. Therefore, it has become very important to perform proteogenomic analyses on ORA and NTA.

Proteogenomic Analysis

The analysis was performed through Over-representation analysis (ORA) and Network topology analysis (NTA) for understanding and unravelling the behaviour of genomic interactions and their regulated pathways. We selected 36, and 46 target genes to understand the genomic interactions of 2-methoxy-4-vinyl phenol, and Scaffold analogue respectively.
Network topology analysis (NTA) was performed by following the sequential pathways as given under: -

Homosapiens>NTA>Network>PPI biogrid>Gene symbol>Gene feeding>Submit>Result

The integration grid of 2-methoxy-4-vinyl phenol and scaffold analogue are shown in **fig.** 09 and 11 respectively.

Over-representation analysis is performed to find out the cellular signaling pathways. The sequential pathways for analysing the cellular signalling are given as under: -

ORA>Pathway>Reactome>Gene symbol>Genome>Submit>Result

Fig.10 and 12 are showing cellular signalling pathways of 2-methoxy-4-vinyl phenol and scaffold analogue respectively.

Interaction grid (NTA) and cellular signalling (ORA)of 2-methoxy-4-vinyl phenol

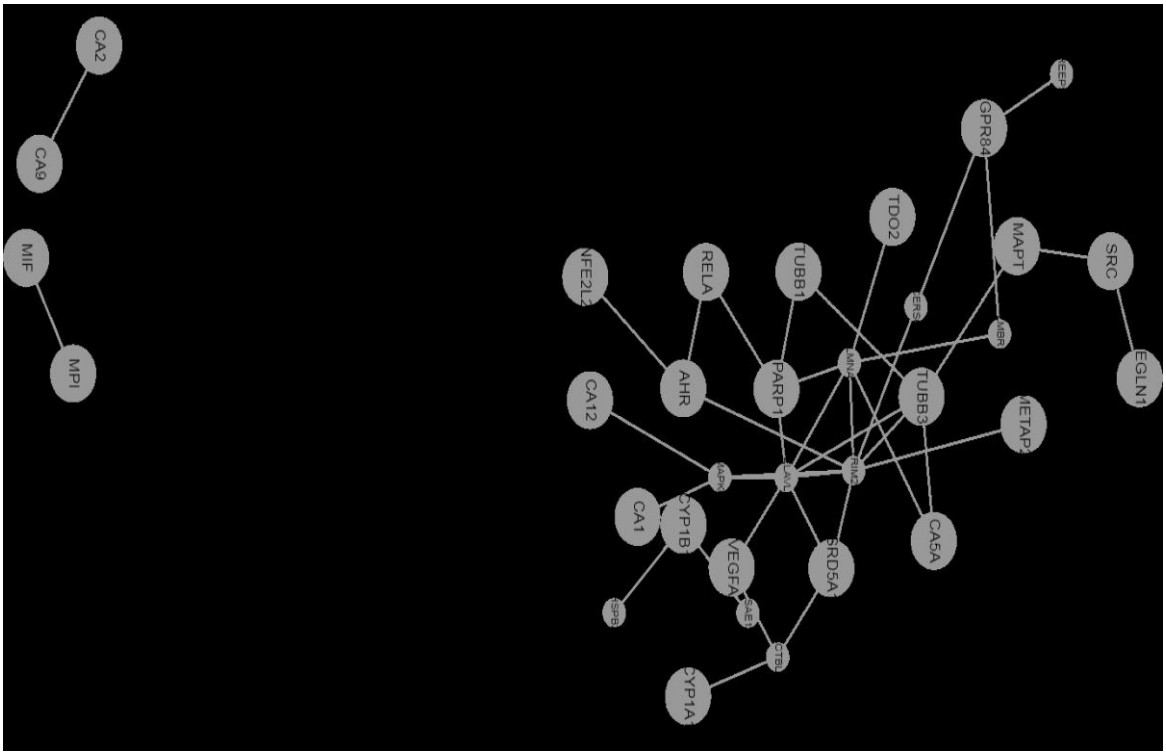


Figure 9. Showing interaction grid of targeted genes (2-methoxy-4-vinyl phenol). CA2-Carbonic anhydrase2, CA9-Carbonic anhydrase9, CA12-Carbonic anhydrase12, CA1-

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.

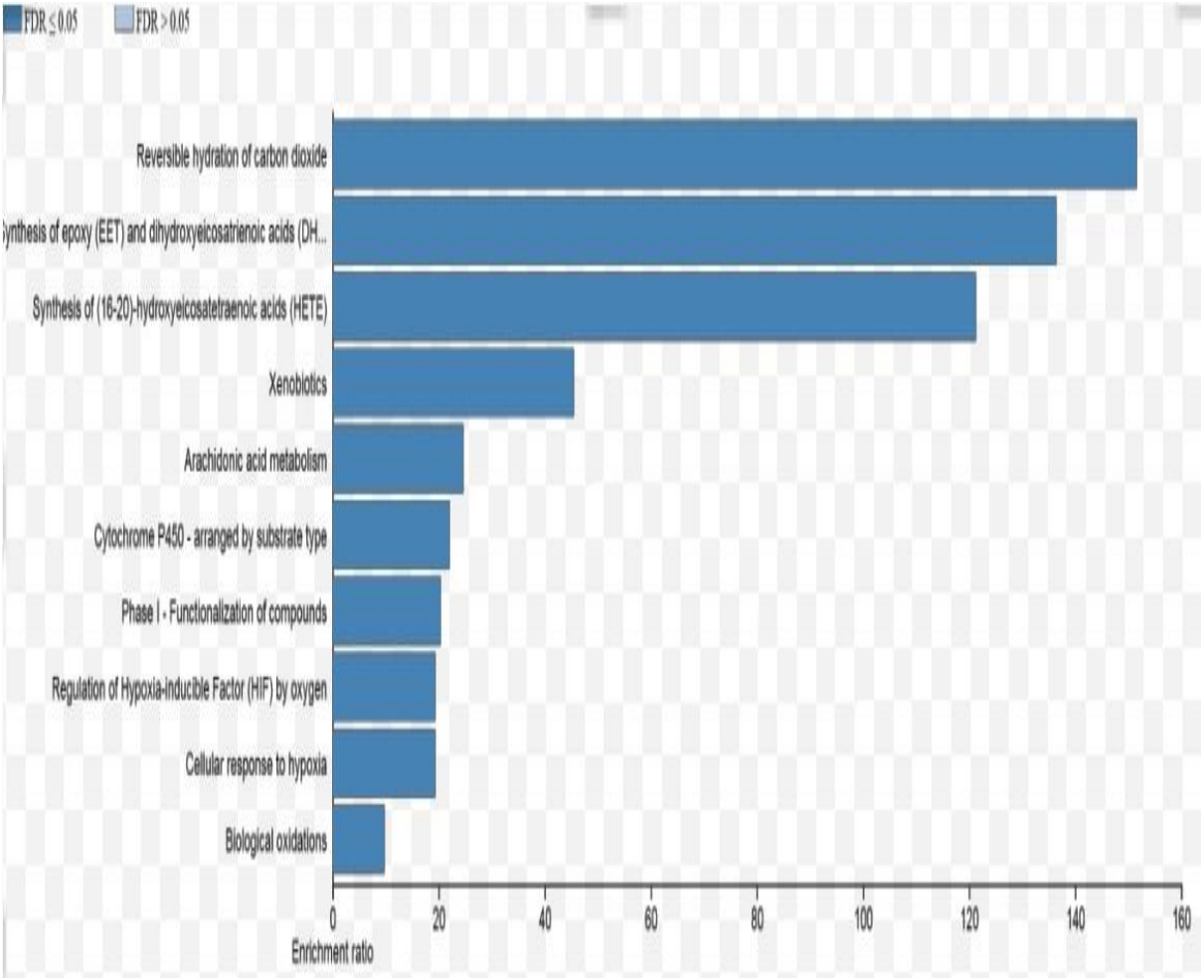


Figure 10 Showing cellular signalling pathways of targeted genes (2-methoxy-4-vinyl phenol). Reversible hydration of carbo dioxide, synthesis of epoxy (EET) and dihydroxyeicosatrienoic acid, synthesis of (16-20)-hydroxyeicosatetraenoic acid, xenobiotics, arachidonic acid metabolism, cytochrome P450-arranged by substrate type, Phase I-Functionalization of compounds, regulation of hypoxia-inducible factor(HIF) by oxygen, cellular response to hypoxia, biological oxidations.

Interaction grid (NTA) and cellular signalling (ORA) Scaffold Analogue (SA)

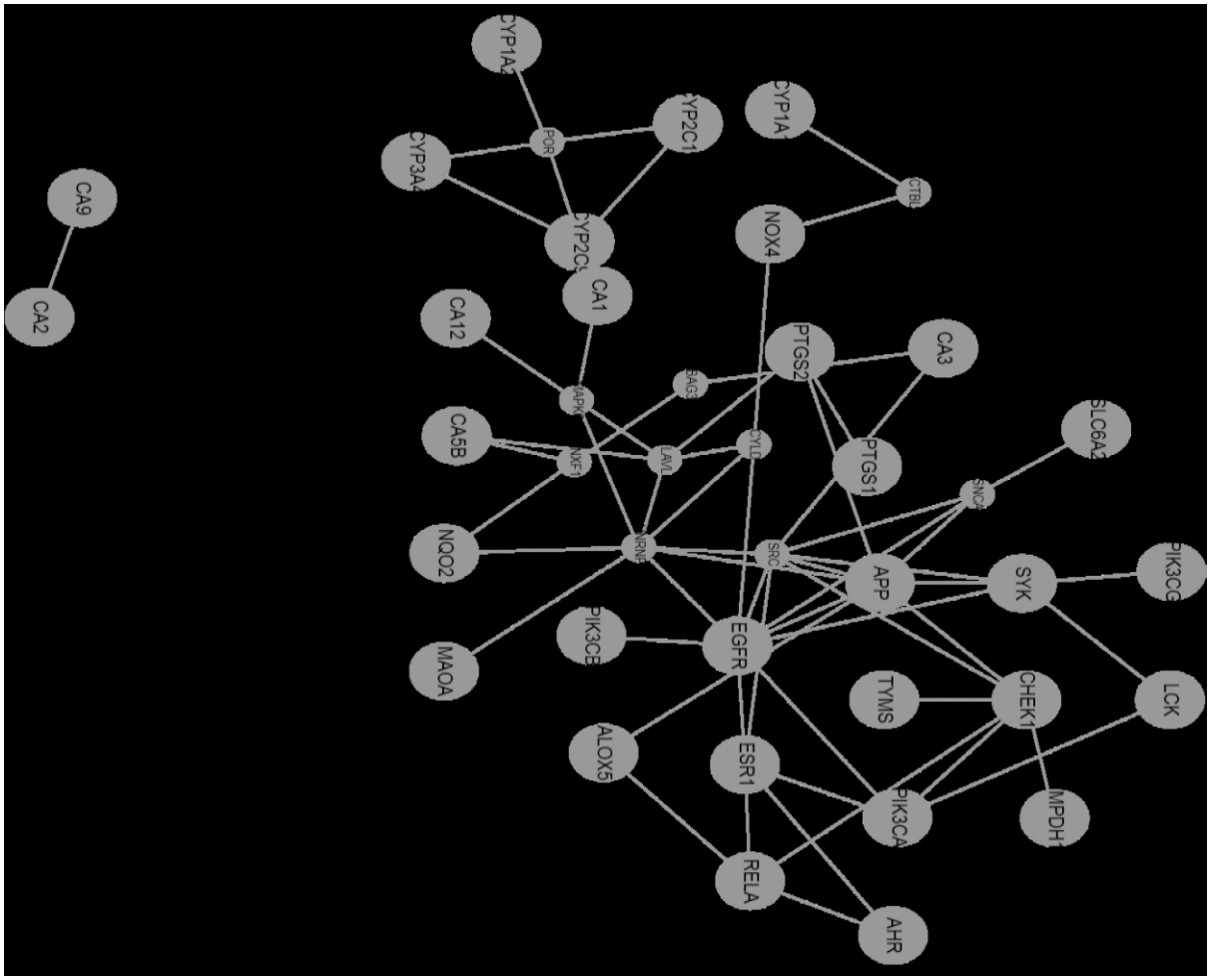


Figure 11. Showing interaction grid of targeted genes (Scaffold Analogue). ALOX5-Arachidonate 5-Lipoxygenase, CA9- Carbonic anhydrase 9, CA2-Carbonic anhydrase 2, CA12-Carbonic anhydrase 12, CA5B-Carbonic anhydrase 5B, CA1-Carbonic anhydrase 1, CA3-Carbonic anhydrase 3, CYP3A4- Cytochrome P450 family 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 Oxidoreductase, 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.

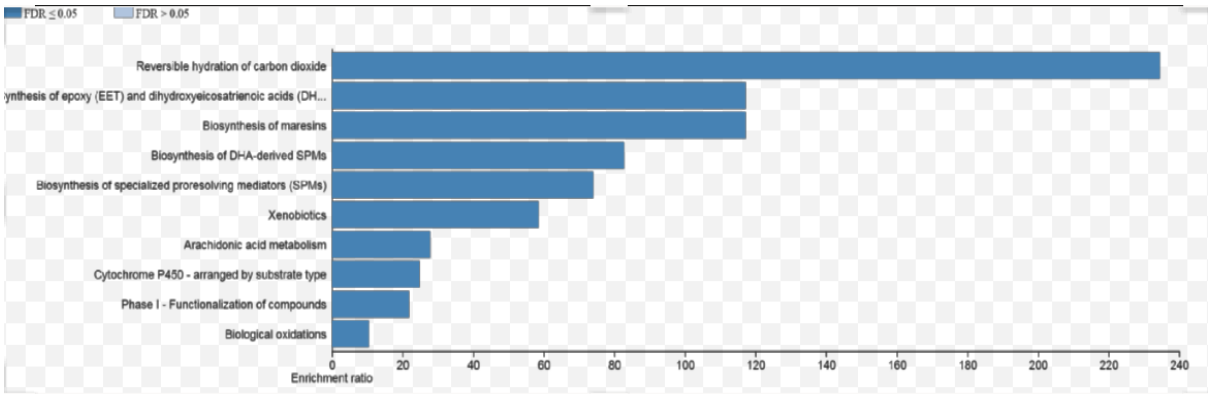


Figure 12. Showing cellular signalling pathways of targeted genes (Scaffold analogue). Reversible hydration of carbon dioxide, synthesis of epoxy and dihydroxyeicosatrienoic acids, biosynthesis of maresins, biosynthesis of DHA derived SPMs, biosynthesis of specialized processing mediators, xenobiotics, arachidonic acid metabolism, cytochrome P450-arranged by substrate type, Phase I-functionalization of compounds, biological oxidants.

Global demand for potential lead molecules is increasing, and active drug particles have been redirected using in silico techniques to rapidly address health issues(35). There continues to be a need for safer and more potent therapeutic compounds, which can be addressed by screening the therapeutic pathways of plant-based drug ligands and rationally applying proteogenomic analysis(36). Other members of the Poaceae family, such as *Digitaria sanguinalis* (L.) Scop., *Saccharum officinarum* L., and *Hordeum vulgare* L., offer a wide range of potential research topics for the creation of herbal medicines.

CONCLUSIONS

The current study pursued ligand-based strategy to identify prospective potential of curatively designed small drug-like molecule (SA) and compared with 2-methoxy-4-vinyl phenol, a naturally found major bioactive principle of *Cynodon dactylon* (L.) Pers. The plant is used for therapeutic purpose since ancient times and described in classical and modern literatures including Indian, Ayurvedic, Unani, and Homoeopathic Pharmacopoeias. An effort for comparative bioactive principle and SA was made via cheminformatics and proteogenomics analysis for unravelling the interaction pathways and cellular signaling of these ligands. The binding energy of these ligands was also worked out by Swiss docking. The curatively-designed SA showed promising results in these silico studies and there is a fair possibility that SA would show prospective results if animal studies are performed in future. It can be concluded that the scaffold analogue and the bioactive components together or individually can be promising potent molecules for phytomedicine. This will open the door to further drug development and potential drug reuse compounds. Overall, current research has led to the investigation of many ligand target sites and their possible modes of action. These results can then be confirmed by testing the activity of target-specific ligands using molecular mechanics generalized continuous Borne surface resolution (MM-GBSA) to determine their resilience and electrostatic stability.

DECLARATION OF INTEREST

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

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