



Research Article

PHARMACOINFORMATICS APPROACH OF IDENTIFIED BIOLOGICAL COMPOUNDS FROM SELECTED *PLECTRANTHUS* (L.) SPECIES IN TAMIL NADU, INDIA: AN *IN-SILICO* APPROACH

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ABSTRACT

Aim: *Plectranthus* (Linn) is a typical genus of the Indian flora. It had been used in the folk medicines for its several medicinal properties. In this study, there are twenty-five major biological compounds were selected from *Plectranthus forskohlii*, *Plectranthus coleoides*, *Plectranthus rotundifolius* and *Plectranthus vittiveroides* for molecular docking analysis and find out the active compounds against Diabetic, Cancer and Tuberculosis diseases. **Materials and methods:** Biological compounds of *Plectranthus* Species were identifying and investigated by GC-MS and the biological activities of these compounds were studied with virtual screening, ADMET analysis, Protein ligand interaction through molecular docking analysis. **Results:** Twenty-five major biological compounds were selected for virtual screening analysis to find out the drug likeness activity. Out of these twenty-five compounds nine compounds are drug likeness in nature. Based on the ADMET analysis, Thymol beta D-Glucoside showed the low toxicity level and it represent Lipinski rule of five. The molecular docking results of Thymol beta D-Glucoside interact with different target proteins used in the study showed the maximum docking energy was obtained against tuberculosis protein -10.1846kcal/mol followed by diabetic protein -10.8736kcal/mol and cancer protein -11.4109kcal/mol. **Conclusion:** *Plectranthus amboinicus* leaves showed significant anti-diabetic, anti-cancer, anti-tuberculosis activity when compared to other studied species such as *Plectranthus forskohlii*, *Plectranthus coleoides*, *Plectranthus rotundifolius* and *Plectranthus vittiveroides*.

Key words: Molecular docking, *Plectranthus*; Virtual screening; ADMET, *In-silico*.

INTRODUCTION

Natural products from medicinal plants, either as pure compounds or as standardized extracts, provide unlimited opportunities for new drug leads because of the unmatched availability of chemical diversity. Due to an increasing demand for chemical diversity in screening programs, seeking therapeutic drugs from natural products, interest particularly in edible plants has grown throughout the world. Medicinal and Aromatic plants (MAPs) utilization and conservation have attracted global attention¹, several of these MAP's have high amounts of polysaccharides, polyphenols, tannins, hydrocolloids (Sugars & Carragenans) and other secondary metabolites such as alkaloids, flavonoids, phenols, terpenes and quinines which would interfere with the DNA isolation procedures.

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex.² Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions. In the context of molecular modeling, docking means predicting the bioactive conformation of a molecule in the binding site of a target structure³.

In essence, this is equivalent to finding the global free energy minimum of the system consisting of the ligand and the target⁴. Docking is used as a tool in structure-based drug design as well as in Structure Based Virtual Screening. Although many of the described synthetic biology tools have emerged only in recent years, several of these techniques have been already used for the production of valuable secondary metabolites. Drug discovery is a highly complex and costly process, which demands integrated efforts in several relevant aspects involving innovation, knowledge, information, technologies, expertise, R&D investments and management skills⁵.

Pharmacokinetics and toxicity issues are responsible for more than half of all failure in the clinical trials. Hence the first part of the virtual screening evaluates drug-likeness of small molecules, drug like molecules exhibit favorable absorption, distribution, metabolism, excretion, toxicological (ADMET) parameters⁶. Database collections of known drugs are typically used to extract knowledge about structure properties of potential drug molecules. Molecular weight, lipophilicity, charges is profiled to extract simple counting rules for an ever-relevant description of ADMET related parameter. Pharmacokinetics has emerged as an integral part of drug development, especially when identifying a drug's biological properties. Understanding of pharmacokinetic and

metabolism characteristic of the drug compounds is needed in designing appropriate human clinical trials⁷.

However, very little is known about the chemical, biological and genomic studies of *Plectranthus* species which are growing in Tamil Nadu and belonging to the family Lamiaceae. This study is mainly focus on to compare the divergence of biological compounds identification investigated by GC-MS and the biological activities of these compounds were studied with virtual screening, ADMET analysis, Protein ligand interaction through molecular docking analysis.

MATERIALS & METHODS

Structure Preparation of Identified Compounds

GC-MS study of identified biological compounds from selected *Plectranthus* species such as *P.amboinicus* (AUBOT0294), *P.forskohlii* (AUBOT0295), *P.coleoides* (AUBOT0296), *P.rotundifolius* (AUBOT0297) and *P.vettiveroides* (AUBOT0305)⁸, totally twenty five major bioactive compounds structure were retrieved from Pubchem online server both of these compounds were under investigation of ChemSketch (Chemically intelligent drawing interface free ware developed by Advance Chemistry Development, Inc. (<http://www.acdlabs.com>)) was used to construct the structure of the ligands (Table 1). The ligand molecules were generated, and the three-dimensional optimizations were done and then saved. SDF file format (a file format for holding information about the atoms, bonds, connectivity and coordinates of a molecule).

High throughput Virtual Screening

Based on the literature reviews, the structural coordinates of plant derived compounds were retrieved in .SDF format of the PubChem chemical database. Prior to the screening, the compounds were filtered based on Lipinski Rule of Five⁹ for Drug likeness. PyRx is a virtual screening tool that uses the built-in Auto Dock and Auto Dock Vina program for screening the best compound. PyRx uses OpenBabel program for visualizing the protein and the ligands. The ligands and the protein target were energy minimized initially, then given charges and converted to pdbqt format in order to support docking using Auto Dock Vina.¹⁰

In-Silico pharmacokinetics

The pharmacokinetic properties such as Absorption, Distribution, Metabolism and Excretion (ADME) toxicity for the compound were calculated using the ADMET under calculate molecular properties in BIOVIA Accelrys Discovery Studio v4.5 2017. The undesired pharmacokinetics properties can lead to failures of most drugs in the later pipeline during the drug development process. Addressing these issues beforehand at the early stages can be advantageous in the drug discovery process.¹¹

Discovery Studio v4.5 Visualizer

The results were visualized using BIOVIA Accelrys Discovery Studio v4.5 2016 Visualizer. The discovery studio visualizer is also a free viewer that is designed to offer an interactive environment for viewing and editing molecular structures, sequences, X-ray reflection data, script and other data. Discovery Studio is designed for use in the Life Sciences, with focus on the study of biologically relevant structures. These ranges from small molecules such as drugs and inhibitors to larger molecules such as proteins and nucleic acid biopolymers to form typically determine function of molecular systems.

RESULTS AND DISCUSSION

High throughput virtual screening

The high throughput virtual screening techniques can be applied by PyRx virtual screening software for computationally screening. The twenty-five (25) major active compounds were identified and selected for this computational screening analysis. The 2D structures of major compounds were retrieved from the PubChem online tool (Figs 1 to 5). The principle of virtual screening was based upon the Lipinski's rule of drug-likeness receptor and for dividing into structural based screening and screening by using the major active compounds were as templates for ligand based virtual screening.

Based on the results of high throughput virtual screening, the species *P.amboinicus* had a drug likeness nature in three compounds, *P.forskohlii* had with two compounds, *P.coleoides* showed the nature of drug likeness in two compounds, *P.rotundifolius* showed the drug likeness activity in two compounds and *P.vettiveroides* showed the activity of drug likeness in two compounds. Totally eleven biological compounds showed and had a drug likeness activity. The compounds are 2-methoxy 4-methyl phenol, n-hexa decanoic acid, Thymol-beta-D-Glucoside, Decanal dimethyl acetal, E,E,Z-1,3,12 Nonadecatriene, phenol 2 methoxy, Squalene, Stigmasta-5,22 dien ol, n hexa decanoic acid, spathulenol and stigmasterol. The binding affinity was also observed from virtual screening such as -6.3, -6.3, -6.7, -5.9, -5.9, -5.8, -5.7, -5.7, -6.3, -5.6 and -5.7 of respective compounds (Table 2).

Screening of compounds through pharmacokinetics properties

The pharmacokinetics and metabolism characteristic of the drug of compounds is needed in designing of new drug for the appropriate human diseases. The totally eleven compounds were filtered with total number of twenty-five major compounds through high throughput virtual screening method. These eleven compounds were tested with ADMET properties of pharmacokinetics approach. The computational virtual screening techniques such as ADMET predictions, molecular dynamics studies to design and analyse eleven potential biological compounds were identified and studied the ADMET properties.

Based on ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties were analyzed by pkCSM online tool (<http://biosig.unimelb.edu.au/pkcsml>). The results indicate out of these eleven compounds, the compound Thymol-beta-D-Glucoside showed the Log P value is -0.4 and it was contained very low toxicity level and represent Lipinski rule of five. So the compound Thymol-beta-D-Glucoside (Fig 6), which one is identified from *P.amboinicus* selected for further *in-silico* studies by using different target proteins.

Molecular docking analysis

The compound interacted with diabetic protein (Fig 7) showed the corresponding amino acids such as arginine, glycine, Pi sulfur methionine, cysteine, alkyl isoleucine and leucine. The docking energy was observed in -10.8736kcal/mol (Figs 8 to 11). The *in-silico* docking results of cancer protein showed (Fig 12), glutamic acid, leucine, alanine, valine and tyrosine amino acids were involved in docking analysis and the observed docking energy in -11.4109kcal/mol (Figs 13 to 16). The compound docked with tuberculosis protein (Fig 17) showed docking energy was -10.1846kcal/mol and was interacted with amino acids tyrosine,

serine, aspartic acid and valine in molecular docking analysis of tuberculosis protein molecule (Figs 18 to 21).

The molecular docking results of Thymol beta D-glucoside interact with different target proteins used in the results showed

the maximum docking energy was obtained against tuberculosis protein -10.1846kcal/mol followed by diabetic protein -10.8736kcal/mol and cancer protein -11.4109kcal/mol (Table 3).

Table 1: Structure of physical and chemical properties of selected ligand molecules for pharmacokinetics analysis

Sp	S.No	Compound name	Pubchem ID	Hydrogen		Canonical Smiles
				Donor	Acceptor	
PA	1	2-Methoxy-4-ethyl-6-methylphenol	71368172	2	4	<chem>CCC(C1=CC(=C(C=C1)O)OC)C(=CC2=CC(=C(C=C2)O)OC)C</chem>
	2	Oleic acid	445639	1	2	<chem>CCCCCCCCC=CCCCCCCCC(=O)O</chem>
	3	n-Hexadecanoic acid	985	1	2	<chem>CCCCCCCCCCCCCCCC(=O)O</chem>
	4	Octadecanoic acid	151734	1	2	<chem>CCCCC=CCCCCCCCCCCCC(=O)O</chem>
	5	Thymol Beta-D-Glucoside	95629	4	8	<chem>CC(=O)OC1C2COC(O2)C(C1OC(=O)C)OC(=O)C</chem>
PF	1	Coleonol	47936	3	7	<chem>CC(=O)OC1C(C2C(CCC(C2C3(C1OC(CC3=O)(C)C=C(C)O)C)O)(C)C)O</chem>
	2	Decanal dimethyl acetal	24513	0	2	<chem>CCCCCCCCC(OC)OC</chem>
	3	Spiro[furan-2(5H),2'(1'H)-naphtho[2,1-b]furan]-5-one, 3'a,4',5	109415	0	1	<chem>C1CC2C(C1)C3CC2CC34CCCCO4</chem>
	4	E,E,Z-1,3,12-Nonadecatriene-5,14-diol	5366546	0	3	<chem>CC(C)OC(=O)C=C(C)C=CCC(C)CCCC(C)(C)OC</chem>
	5	Spiro[4.5]decan-7-one, 1,8-dimethyl-8,9-epoxy-4-isopropyl	270628	0	3	<chem>CC1CC2(CCC1=O)OCCO2</chem>
PC	1	Octadec-9-enoic acid	151734	1	2	<chem>CCCCC=CCCCCCCCCCCCC(=O)O</chem>
	2	Phenol, 2-methyl-5-(1-methylethyl)-	996	1	1	<chem>C1=CC=C(C(C=C1)O)C</chem>
	3	l-(+)-Ascorbic acid 2,6-dihexadecanoate	54676536	4	6	<chem>C(C(C1C(=C(C(=O)O1)O)O)O)O</chem>
	4	Squalene	638072	0	0	<chem>CC(=CCCC(=CCCC(=CCCC(C(C)CCC=C(C)CCC=C(C)C)C)C)C</chem>
	5	1,2,3-Propanetriol	753	3	3	<chem>C(C(CO)O)O</chem>
PR	1	Cis-Vaccenic acid	5282761	1	2	<chem>CCCCCCC=CCCCCCCCCCC(=O)O</chem>
	2	Ergost-5-en-3-ol	5283637	1	1	<chem>CC(C)C(C)CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C</chem>
	3	Stigmasta-5,22-dien-3-ol	5280794	1	1	<chem>CCC(C=CC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C</chem>
	4	Hexadecanoic acid	985	1	2	<chem>CCCCCCCCCCCCCCCC(=O)O</chem>
	5	9-octadecenoic acid (z)-, methyl ester	445639	1	2	<chem>CCCCCCCCC=CCCCCCCCC(=O)O</chem>
PV	1	Spathulenol	92231	1	1	<chem>CC1(C2C1C3C(CCC3(C)O)C(=C)CC2)C</chem>
	2	Stigmasterol	5280794	1	1	<chem>CCC(C=CC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C(C)C</chem>
	3	Stigmast-5-en-3-ol, (3.beta.)-	222284	1	1	<chem>CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C(C)C</chem>
	4	9-isopropyl-1-methyl-2-methylene-5-oxa-tr	70678757	4	6	<chem>CCCCCCC(C)C1C(C(=O)NC(=C)C=CC(=O)NC(C(=O)NC(C=O)O1)C(C)C)CCO</chem>
	5	Ergost-5-en-3-ol, (3.beta.,24r)-	5283637	1	1	<chem>CC(C)C(C)CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C</chem>

Table 2: Virtual screening results of selected *Plectranthus* species derived compounds

Species Name	Compound Name	Binding Affinity
PA	2-Methoxy-4-methylphenol	-6.3
	n-Hexadecanoic acid	-6.3
	Thymol beta-D-Glucoside	-6.7
PF	Coleonol	-5.9
	Decanal dimethyl acetal	-5.9
PC	Phenol, 2-methyl-5 (1-methylethyl)-	-5.8
	Squalene	-5.7
PR	Stigmasta-5,22-dien-3-ol	-5.7
	n-Hexadecanoic acid	-6.3
PV	Spathulenol	-5.6
	Stigmasterol	-5.7

Table 3: Molecular docking results of Thymol beta D-Glucoside (Ligand Molecule) interact with different proteins

Diseases / Proteins	PDB ID	Docking energy (kcal/mol)	Interactions	Amino acid	Amino acid binding site
Diabetics	5DV3	-10.8736	Conventional hydrogen bond	Arginine	288
			Carbon Hydrogen Bond	Glycine	284
			Pi-Sulfur	Methionine	348
				Cysteine	285
			Alkyl	Isoleucine	262, 281
			Pi-Alkyl	Isoleucine	341
Cancer	2ITO	-11.4109		Leucine	330
			Conventional hydrogen bond	Glutamine	697
				Leucine	861
			Carbon Hydrogen Bond	Alanine	698
			Pi-cation	Arginine	831
			Alkyl	Leucine	833
Tuberculosis	4W4L	-10.1846		Valine	769
			Pi-Alkyl	Valine	756
				Tyrosine	764
			Unfavorable bump	Tyrosine	29
			Conventional hydrogen bond	Serine	28
			Pi-Anion	Asparagine	29
			Pi-Pi stacked	Tyrosine	62
			Alkyl	Valine	32
			Pi-Alkyl	Alanine	59

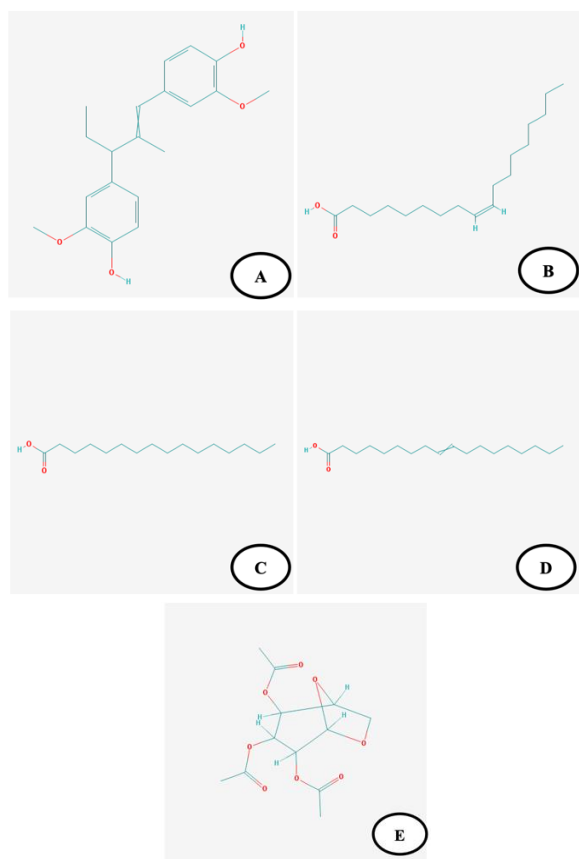


Fig 1: 2D Structure of major identified compounds from *P.amboinicus* species
 (A) 2-Methoxy-4-ethyl-6-methylphenol; (B) Oleic acid; (C) n-Hexadecanoic acid; (D) Octadecanoic acid; (E) Thymol beta D-Glucoside

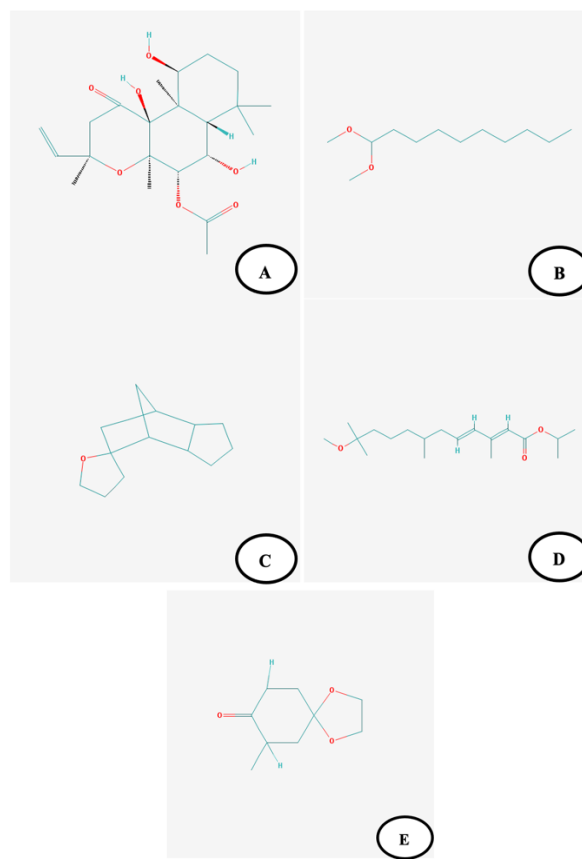


Fig 2: 2D Structure of major identified compounds from *P.forskohlii* species
 (A) Coleonol; (B) Decanal dimethyl acetal; (C) Spiro[furan-2(5H),2'(1'H)-naphtho[2,1-b]furan]-5-one, 3'a,4',5'; (D) E,E,Z-1,3,12-Nonadecatriene-5,14-diol; (E) Spiro[4.5]decan-7-one, 1,8-dimethyl-8,9-epoxy-4-isopropyl

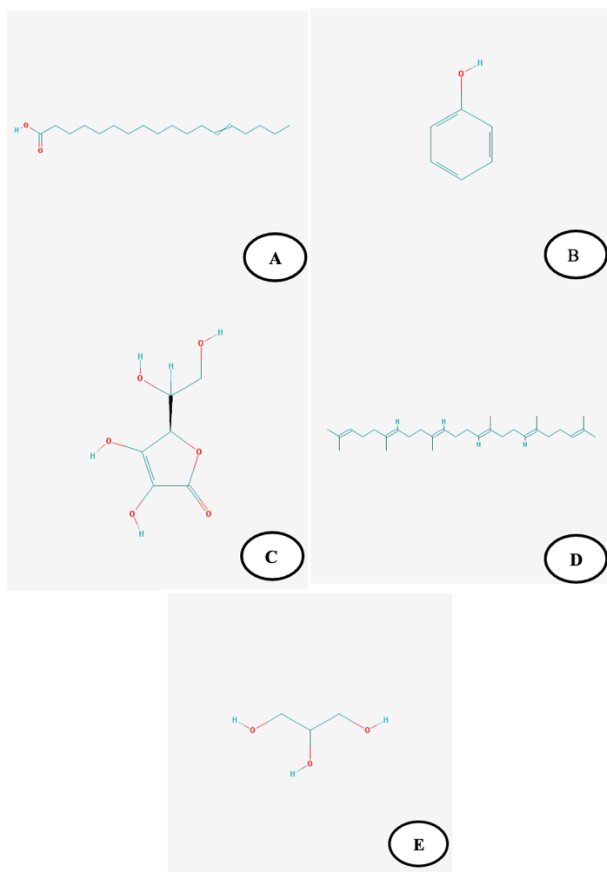


Fig 3: 2D Structure of major identified compounds from *P. coleoides* species

(A) Octadec-9-enoic acid; (B) Phenol; (C) Ascorbic acid; (D) Squalene; (E) 1,2,3-Propanetriol

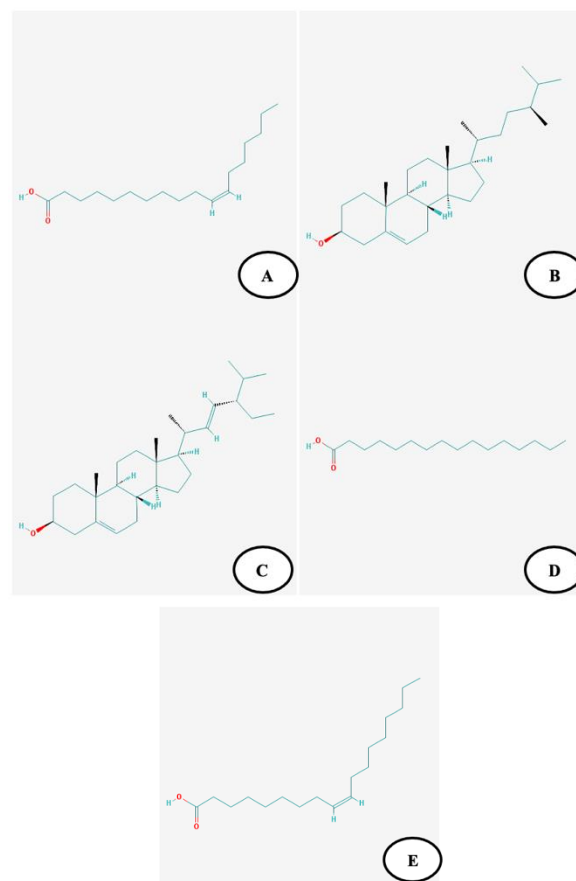
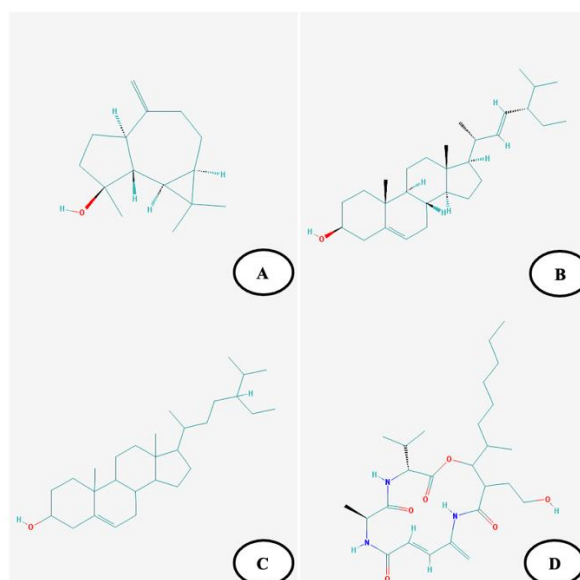


Fig 4: 2D Structure of major identified compounds from *P. rotundifolius* species

(A) Cis-Vaccenic acid; (B) Ergost-5-en-3-ol; (C) Stigmasta-5,22-dien-3-ol; (D) Hexadecanoic acid; (E) 9-octadecenoic acid



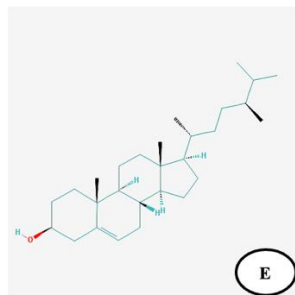


Fig 5: 2D Structure of major identified compounds from *P.vettiveroides* species
(A) Spathulenol; (B) Stigmasterol; (C) Stigmast-5-en-3-ol; (D) 9-isopropyl-1-methyl-2-methylene; (E) Ergost-5-en-3-ol

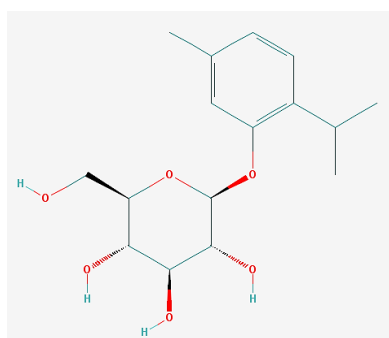


Fig 6: 2D Structure of Ligand molecule (Thymol beta-D-Glucoside)

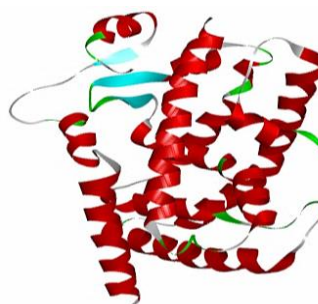


Fig 7: 3D Structure of diabetic protein (ID:5DV3)

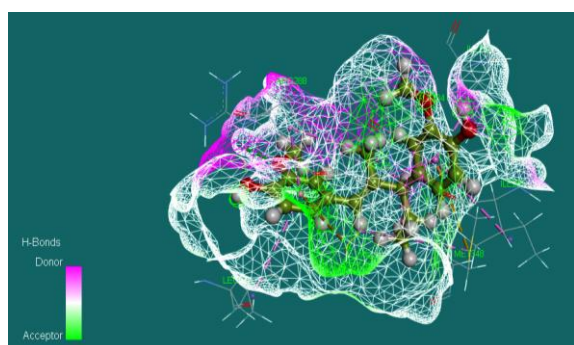


Fig 8: Structure of Hydrogen interaction of ligand molecule bind with target protein molecule (Diabetic)

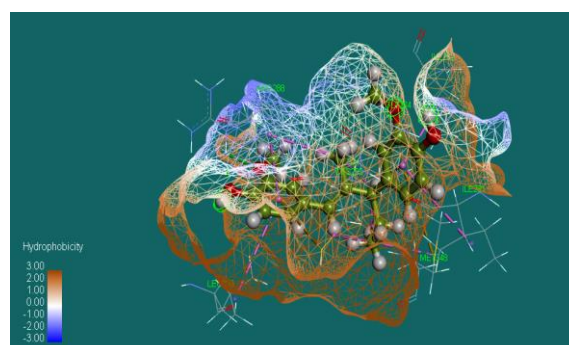


Fig 9: Structure of Hydrophobic interaction of ligand molecule bind with target protein (Diabetic)

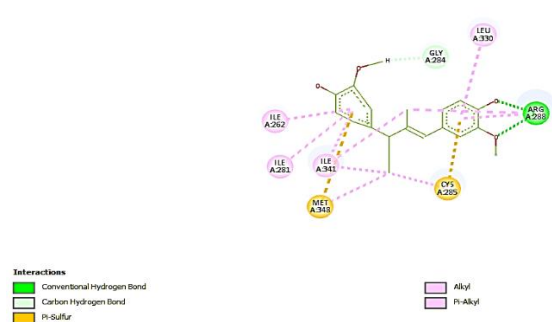


Fig 10: Structure of 2D interaction of ligand molecule bind with target protein (Diabetic)

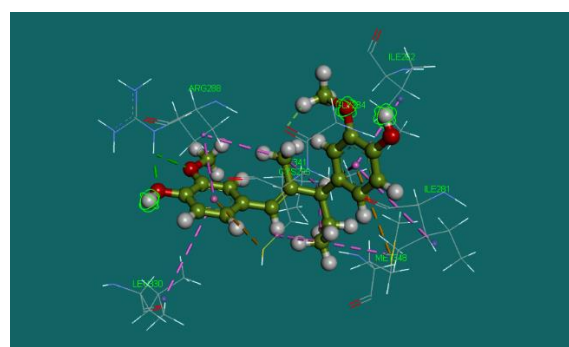


Fig 11: Structure of 3D interaction of ligand molecule bind with target protein (Diabetic)

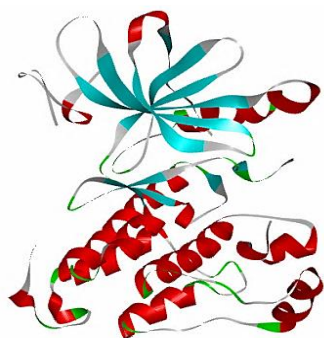


Fig 12: 3D Structure of cancer protein (ID:2ITO)

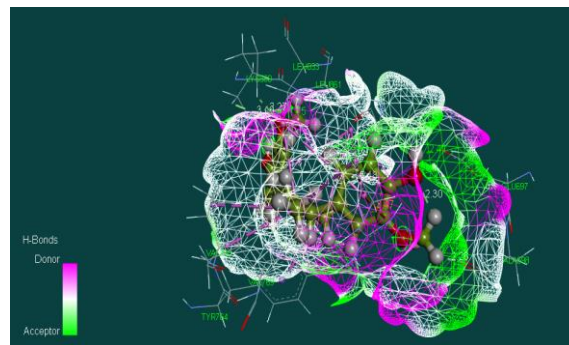


Fig 13: Structure of Hydrogen interaction of ligand molecule with target protein (cancer)

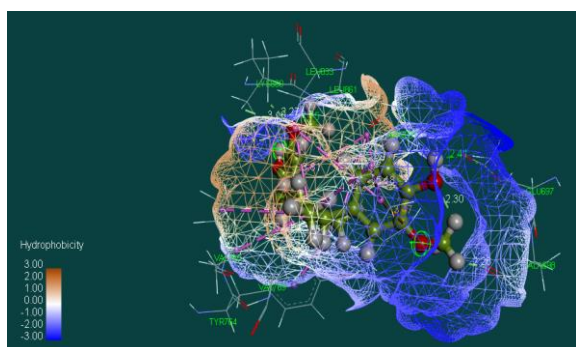


Fig 14: Structure of Hydrophobic interaction of ligand molecule bind with target protein (cancer)

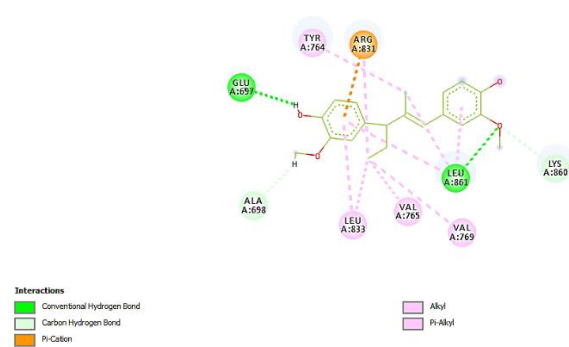


Fig 15: 2D structure of ligand molecule with cancer protein interaction

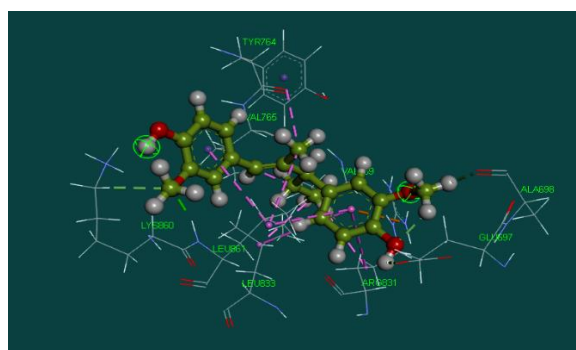


Fig 16: 3D structure of ligand molecule binds with target protein (cancer)

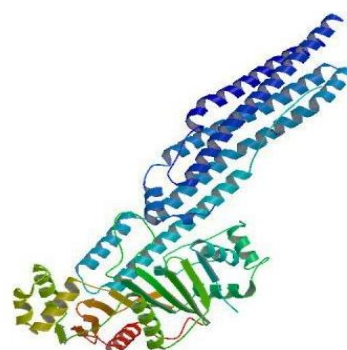


Fig 17: 3D structure of tuberculosis protein (ID:4W4L)

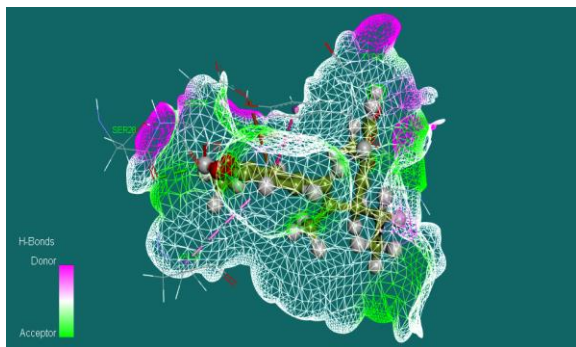


Fig 18: Structure of Hydrogen interaction of ligand molecule with target protein (Tuberculosis)

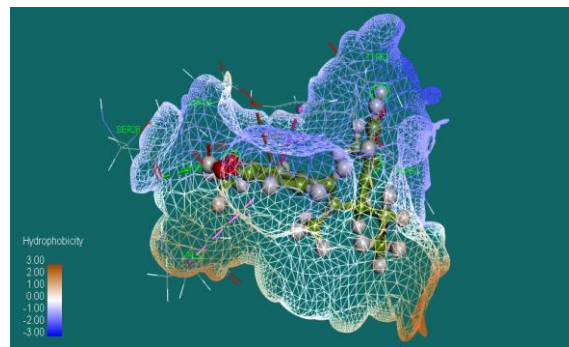


Fig 19: Structure of Hydrophobic interaction of ligand molecule with target protein (Tuberculosis)

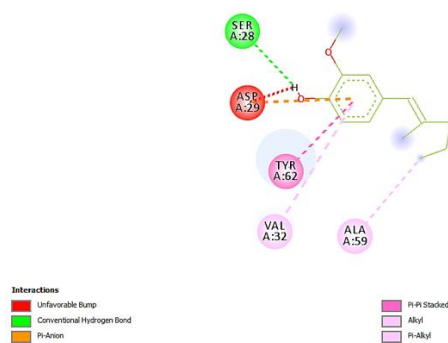


Fig 20: Structure of 2D interaction of ligand molecule bind with target protein (Tuberculosis)

CONCLUSION

The present information demonstrated that based on high throughput virtual screening, twenty-five major compounds were selected, and among them eleven compounds showed binding affinity. The high amount of binding affinity was observed in Thymol beta D-Glucoside compound. The ADMET properties were studied for eleven compounds and Thymol beta D-Glucoside was identified as toxic free/less compound based on its absorption, distribution, metabolism, excretion and logP values properties. Thymol beta D-Glucoside act as ligand molecule to interact with anti-diabetic, anti-cancer and anti-tuberculosis induced proteins through docking analysis. Based on docking energy of Thymol beta D-Glucoside molecule with different proteins, it showed the activity against diabetic, cancer and tuberculosis responsible proteins. The results were concluded that *Plectranthus amboinicus* leaves derived compounds showed significant anti-diabetic, anti-cancer, anti-tuberculosis activity when compared to other studied species such as *Plectranthus forskohlii*, *Plectranthus coleoides*, *Plectranthus rotundifolius* and *Plectranthus vettiveroides*. Finally, the Molecular docking studies on the selected species of *Plectranthus* provide valuable inputs to develop the active components into potential drug in the field of drug development in future.

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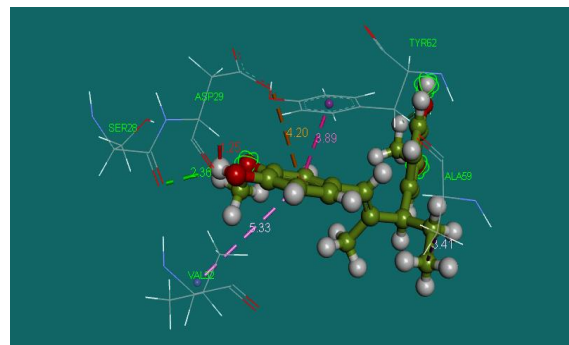


Fig 21: Structure of 3D interaction of ligand molecule bind with target protein (Tuberculosis)

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