In-Silico Pharmacological Studies and RMSD Comparison of FDA Drugs with Bioactive compounds in Musa Paradisica for Ligand Promotion

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ABSTRACT

This study includes Bio-Pharmaceutical research for atomic demonstrating techniques, inside an assortment of medication revelation programs, to examine complex organic and compound frameworks. Comprehensively utilized in a present-day drug plan, Pre docking Pharmacological Investigations of the Drug- Likeness with in coupling of macromolecular targets. Phytochemicals considered from *Musa spp.* for Insilco comparison with FDA approved drugs have more Similarity of Structure with Predicted RMSD values which were revealed by few molecular descriptors with the utilization of bioinformatics online server tools like Chemspider, SwissADME. A Linear Regression Plot of Similarity Percentage versus the Root Mean Square Deviation between the FDA approved Drugs and Bioactive Compounds from *Musa spp.* Reveled the Significant Value of R^2 = 0.0131 (y = -0.7202x + 80.805) upon which approximately 6 Ligand molecules fall near on the regression line which signifies the Potency of becoming a promising drug candidate for future in vivo testing.

Keywords: *ChemSpider, SwissADME, Computer Aided Drug Discovery, Molecular Refractivity, Drug- Likeness.*

INTRODUCTION:

Drug research has effectively taken on the atomic demonstrating techniques for drug disclosure cycle and projects. It is utilized to concentrate on the intricacy of synthetic and natural mixtures. These trial procedures and computational strategies helps for improvement and recognizable proof of novel mixtures. In present day drug planning measure this computational techniques are

extensively utilized. Sub-atomic docking strategy assists with understanding the steady ligand compliances between one particle to the next along the dynamic restricting locales of target proteins.[3]

Musa is one of the a few genera in the family Musaceae. It incorporates bananas and plantains. Plantains allude in India to a coarse banana. Musa has been cultivated for quite 4000 years, the first varieties are increased to 300. Around 70 types of Musa are known, with a wide assortment of application. *Musa* is a plant species in which we can see both female and male organs in the same individual. This plant has large, broad green leaves, bears flowers and fruits, and grows up to 40 feet in height. These leaves grow through a hollow stem. This gathering of plants are ordinarily developed in all the tropical territories and generally found in nations like India, Burma, Australia, tropical Africa and America. [1, 2]

Musa species are well known for several common Human health biological beneficial activities. One of the conventional source form usually done from ancient medication. The various components of the plant are used for the treatment of many disorders. This technique is citied and restricted to Egypt, Florida, South Brazil, and Southern Japan. For the treatment of respiratory disease and for cough issues its leaves are used. And its roots for the treatment of hemoptysis arrest and used as an Anthelmintic.[3] Its fruits reduce the chance of urinary organ cancer and additionally increase the urinary organ activities within the body. This can be additionally effective in reducing the consequences of free radicals if antioxidants are present in it. It can likewise be utilized as a counteracting for consumes, tuberculosis, fever, asthma, gout, syphilis, snake bite, and warts. These plant components can even be used for the immune system strengthening, to boost muscular activity, lack of appetence, to scale back the mental shock and stomach ulcers, and to own robust bone health. [5]

To be a good drug, the molecule ought to reach the target web site within the body and stay there for a extended time in its bioactive kind, and it ought to be in sufficient concentration. Once it reaches the location it ought be able to perform the biological events to cure or cut back the matter within the body. In early medication disclosure and improvement technique the appraisal of ADEM are concerned. [21, 22]

SMILES signify Simplified Molecular Input Line Entry System. It's illustration of a molecule or a matter within the variety of line notation. SMILES strings are vital for the molecule editors for the conversion of these line notations into 2-D drawings or to 3-D models of the molecules. And molecular graph may be illustration of structural formulas of the chemical compounds in terms of graph theory.

Using these chemical structures the various molecular descriptors has been developed by Cheminformaticians. Molecular fingerprint (FP) may be a one in all the favored. Consists of sequence bits that spot the absence and presence or changes in chemical structure of the molecules by United States of American Standard. The FP2 method9 is one in all the trail based mostly FP, it considers the complete bond present within the molecular structure to get range of bonds. And therefore the physicochemical descriptors facilitate United States of America to get the common properties like mass (MW), and specific atom sorts and their total counts. [22, 23]

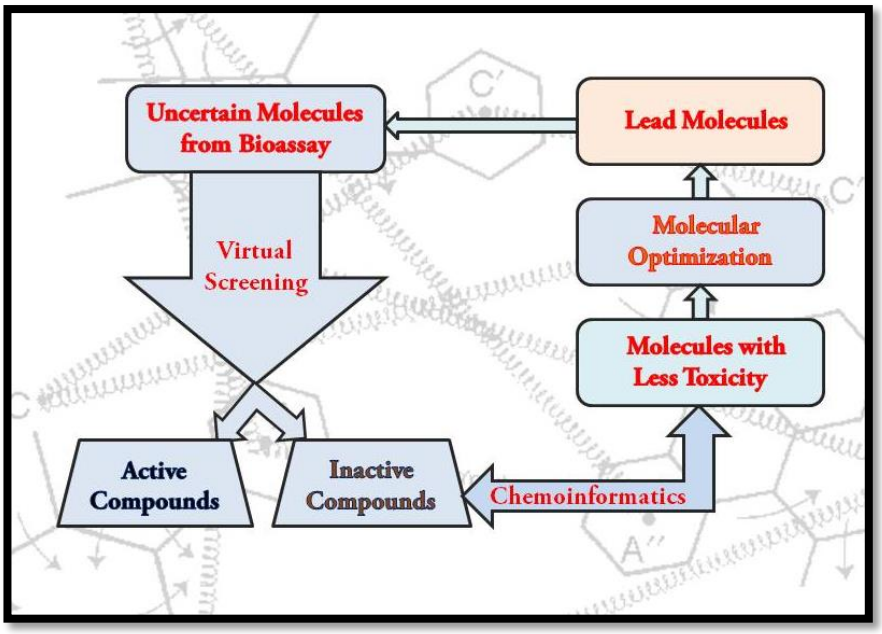


Figure 1: Virtual Screening of Bioactive Compounds via Chemoinformatics approach [21]

"Drug-likeness" is employed to understand the probabilities of a molecule to become a lead molecule within the formulation of oral drug with regard to bioavailability. Bioavailability measures the rate at which a drug reaches a web site of action. Drug-likeness is studied to understand the thoughts that compounds have the flexibility to be a oral drug-candidate. And this

finished the inspections of structural and physicochemical properties of developed compounds, provided that all the parameters like TPSA, Molar refractivity, LOGP values, LOGS, Solubility category, Bioavailability score, Lead likeness, Lipinski's rule and Synthetic accessibility are satisfied and the compound can be considered as a lead molecule for the event of the oral drug. This routine is employed to filter the chemical libraries to get rid of the molecules that are incompatible or not within the appropriate pharmacological medicine profile. [8, 19, 20]

OBJECTIVES:

1. To identify the compounds present in the Musa species for Analog search.
2. Analysis and Prediction of different Pharmological Properties of Bioactive Compounds
3. Identification of Similar kind of FDA Approved Drugs and Biological Target Prediction
4. Evaluation of Predicted Bioactive compound via Computer Aided Drug Discover (CADD)

MATERIALS AND METHODS:

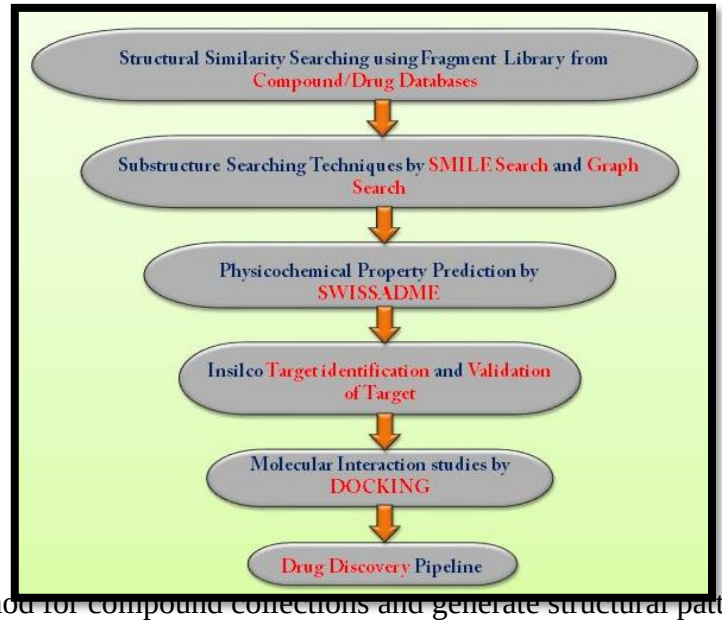


Figure 2: Method for compound collections and generate structural pattern which is used in active compounds selection and validation of those through Structure Based Drug Design (SBDD)

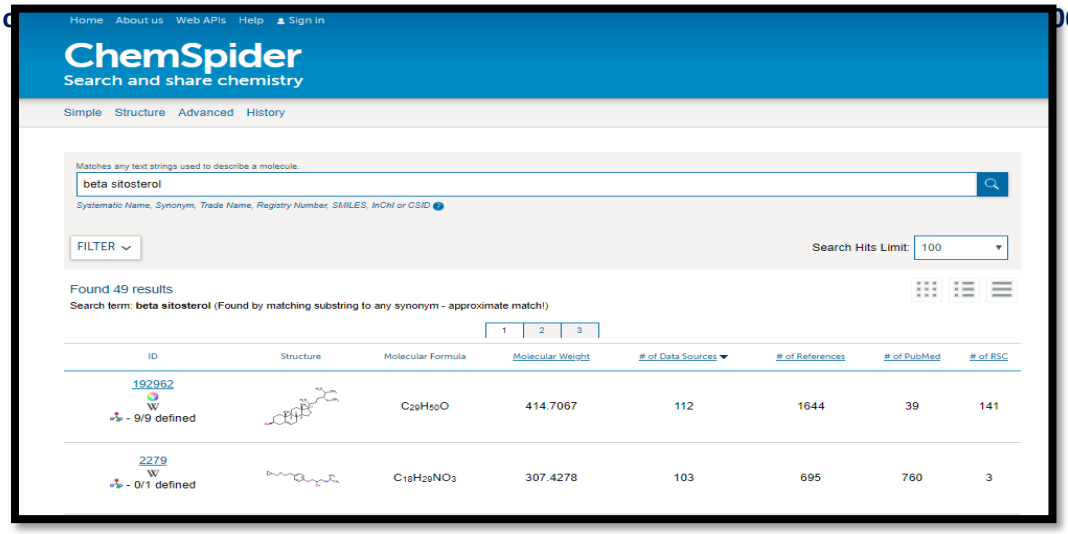


Figure 3: **ChemSpider** a tool used for similarity searching and the analogs are chosen for their further studies. (Structural Similarity Searching using Fragment Library from Compound/Drug Databases)

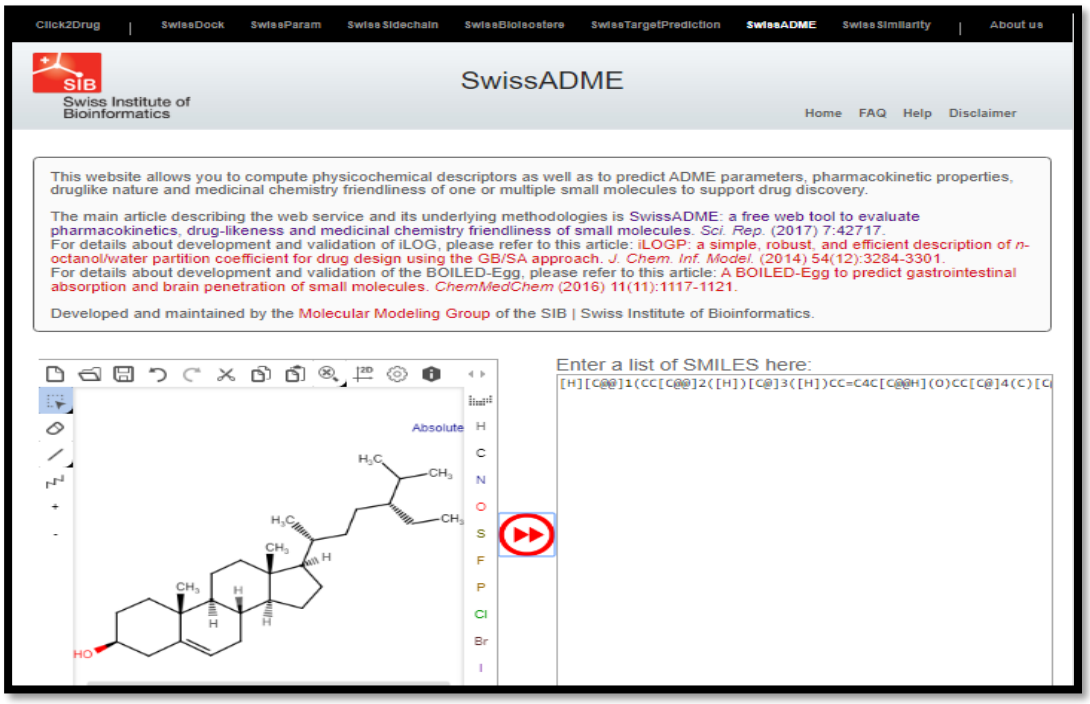


Figure 4: **SwissADME** a tool used for finding SMILES of a compound by Uploading a 3D structure of the required compound. (Substructure Searching Techniques by SMILE Search and Graph Search)

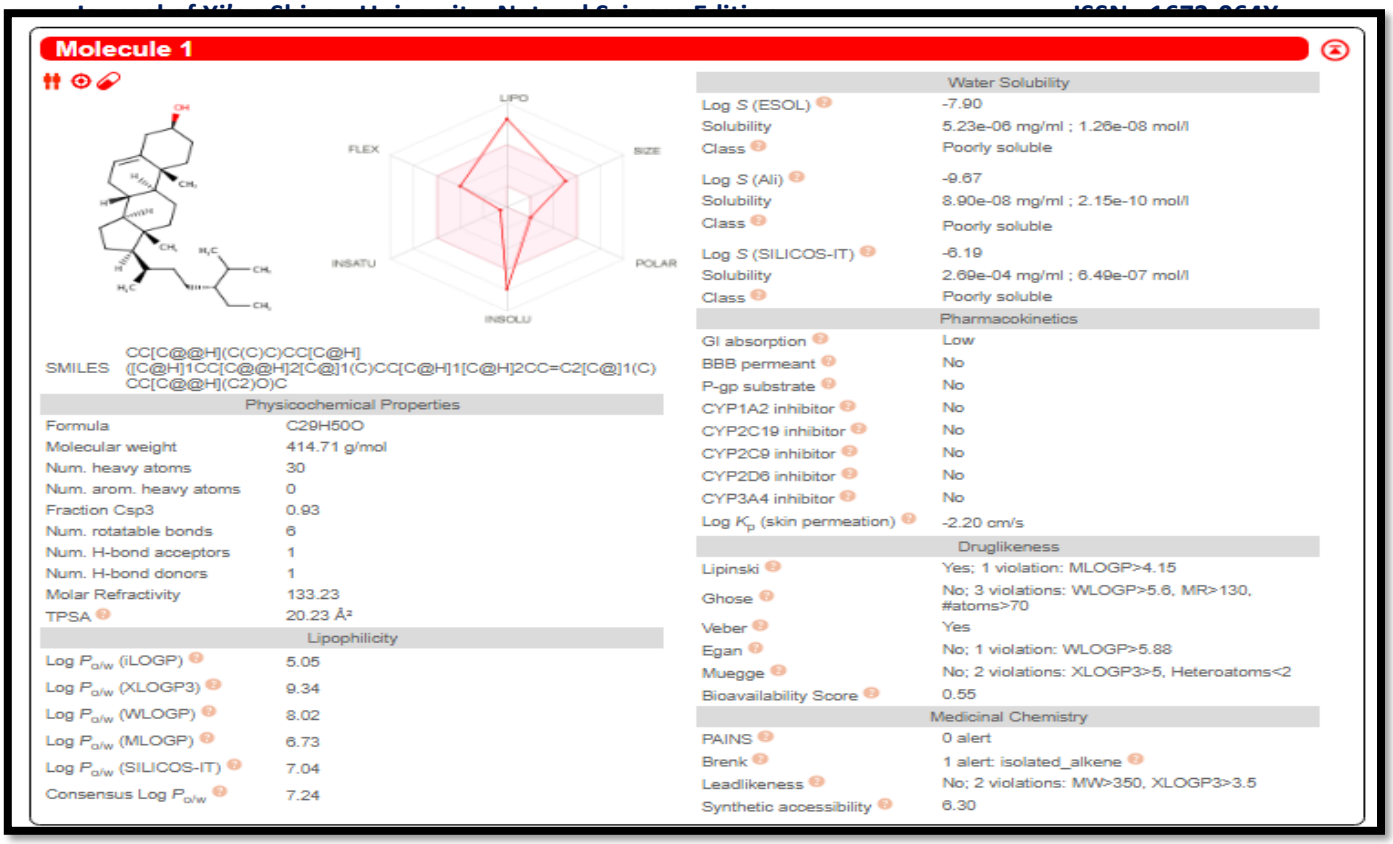


Figure 5: **Physicochemical Property Prediction by SWISSADME** (Essential properties incorporate SMILES, Molecular formula and weight, Number of Rotatable Bonds, Number of hydrogen Bond acceptors and donors, Topological Polar Surface Area along with Secondary properties like Solubility, Leadlikeness, Lipinski property, Bioavailability score.)

Sl. No.	Assigned Molecular-ID	Compounds
1.	1A1.1	Sitosterol
2.	2A1.2	Daucosterol
3.	3A1.3	Fucostanol
4.	4A1.4	β-Sitosterol acetate
5.	5A1.5	clionasterol
6.	6A2.1	(2R,3S,4S)-leucocyanidin
7.	7A2.2	Leucocianidol
8.	8A3.1	Syringin
9.	9A4.1	Quercetin
10.	10A5.1	DL-Tryptophan

11.	11A5.2	L-5-hydroxy-Tryptophan
12.	12A5.3	DL-N-Acetyltryptophan
13.	13A6.1	Serotonin
14.	14A6.2	Bufotenine
15.	15A7.1	Isochroman
16.	16A7.2	1,2,3,3a-Tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one
17.	17A7.3	7-Hydroxy-5-methoxy-2-phenyl-chromen-; 4-one
18.	18A7.4	5-(4-Chloro-benzylidene)-3-ethyl-2-thioxo-thiazolidin-4-one
19.	19A7.5	4-oxo-nonenal

Table 1.List of Bioactive Compound from Musa and their assigned Molecular-ID

RESULTS AND DISCUSSION:

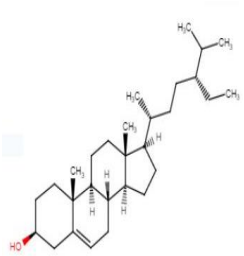
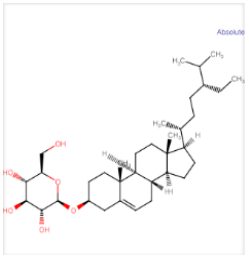
Compounds	Properties	
 **sitosterol**	**Formula:**	$C_{29}H_{50}O$
	SMILES:	[H][C@@]1(CC[C@@]2([H])[C@]3([H])CC=C4C[C@@H](O)CC[C@]4(C)[C@@]3([H])CC[C@]12C)[C@H](C)CC[C@@H](CC)C(C)C
	Mol.Wt:	414.71g/mol
	No. Rotatable bond:	6
	No. of H-bond acceptors:	1
	No. of H-bond donors:	1
	Molar Refractivity:	133.23
	TPSA:	20.23 A^0
	Log Pa/w (iLOGP):	5.05
	Log P a/w(XLOGP3):	9.34
	Log Pa/w(MLOGP):	6.73
	Log S (ESOL):	-7.90
	Solubility class:	Poorly soluble
	Lipinski:	Yes; 1 violation : MLOGP> 4.15
	Bioavailability score:	0.55
	Leadlikeness:	No; 2 violations; MW > 350, XLOGP3 > 3.5
	Synthetic accessibility:	6.30
Daucosterol 	**Formula:**	$C_{23}H_{60}O_6$
	SMILES:	CC[C@@H](C(C)C)CC[C@H]([C@H1CC[C@@H]2[C@]1(C)CC[C@H]1[C@H]2CC=C2[C@]1(C)([C@H]1O)O)O)C
	Mol.Wt:	576.85 g/mol
	No. Rotatable bond:	9
	No. of H-bond acceptors:	6
	No. of H-bond donors:	4
	Molar Refractivity:	165.61
	TPSA:	99.38A^0
	Log Pa/w (iLOGP):	5.17
	Log P a/w(XLOGP3):	7.74
	Log Pa/w(MLOGP):	3.96
	Log S (ESOL):	-7.70
	Solubility class:	Poorly soluble
	Lipinski:	Yes; 1 violation : MW > 500
	Bioavailability score:	0.55
	Leadlikeness:	No; 3 violations: MW> 350, Rotors >7, XLOGP3>5
	Synthetic accessibility:	8.02

Table 2. Example of Natural Compound ***sitosterol*** along with anolog ***Daucosterol*** with different Molecular Descriptors and Pharmacological Properties

Model Protein-ID	Template PDB-ID	% Similarity	Protein Class/Significance
P05023	4xe5.1.A	97.45	Sodium/potassium-transporting ATPase subunit alpha-1
P06401	1sqn.2.A	100	progesterone receptor
P10275	1e3g.1.A	100	ANDROGEN RECEPTOR
Q7Z2W7	6o77.1.A	82.66	Transient receptor potential cation channel subfamily M member 8
P35610	6bug.1.B	12	D-alanyl transfer protein DltB
P35611	3ocr.1.A	44	Class II aldolase/adducin domain protein
P44469	6g9p.1.A	59	Peptidoglycan D,D-transpeptidase MrdA
P11712	5x24.1.A	99	Cytochrome P450 2C9
Q9RVD6	2a4m.1.B	100	Tryptophanyl-tRNA synthetase II
Q9UGM6	5ekd.1.A	100	Tryptophan--tRNA ligase, mitochondrial
P48039	6me2.1.A	95	chimera protein of Melatonin receptor type 1A and GlgA glycogen synthase
P48040	6me8.1.A	62	Soluble cytochrome b562,Melatonin receptor type 1B,Rubredoxin
P10613	5v5z.1.A	100	Lanosterol 14-alpha demethylase
P22303	6o5s.1.A	100	Acetylcholinesterase
Q9Y5Y9	6j8e.1.B	62	Sodium channel protein type 2 subunit alpha
Q12791	6j8e.1.B	62	Sodium channel protein type 2 subunit alpha

Table 3 List of Modeled Protein-ID with Targets Template PDB-ID along with Percentage(%) of Similarity and their Class/Significance

Assigned Mol-ID	Name of the compound	Similar Approved DRUG	% Similarity	Targets UniProt ID for FDA Approved Drug
1A1.1	Sitosterol	Allylestrenol	91.2	P06401
2A1.2	Daucosterol	Ouabain	59.8	P05023
3A1.3	Fucostanol	Menthol	92.9	Q7Z2W7
4A1.4	β-Sitosterol acetate	Nandrolone decanoate	71.4	P10275
5A1.5	Clionasterol	Allylestrenol	91.2	P06401
6A2.1	(2R,3S,4S)-leucocyanidin	Hesperetin	72.4	P35610
7A2.2	Leucocianidol	Hesperetin	72.4	P35611
8A3.1	Syringin	Cefixime	81.2	P44469
9A4.1	Quercetin	Niclosamide	70.8	P11712
10A5.1	DL-Tryptophan	L-Tryptophan	100	Q9UGM6
11A5.2	L-5-hydroxy-Tryptophan	Oxitriptan	100	Q9RVD6
12A5.3	DL-N-Acetyltryptophan	L-Tryptophan	80	Q9UGM6
13A6.1	Serotonin	Melatonin	75.9	P48039
14A6.2	Bufotenine	Melatonin	81.9	P48040
15A7.1	Isochroman	Tioconazole	74.1	P10613
16A7.2	1,2,3,3a-Tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one	Mepivacaine	61.5	Q9Y5Y9
17A7.3	7-Hydroxy-5-methoxy-2-phenyl-chromen-; 4-one	Cromoglicic acid	57.9	Q12791
18A7.4	5-(4-Chloro-benzylidene)-3-ethyl-2-thioxo-thiazolidin-4-one	Pyridostigmine	84.3	P22303
19A7.5	4-oxo-nonenal	Progesterone	72.2	P06401

Table 4: List of Bioactive Compounds from Musa their Percentage of Similarity with FDA approved Drugs and Drug Targets

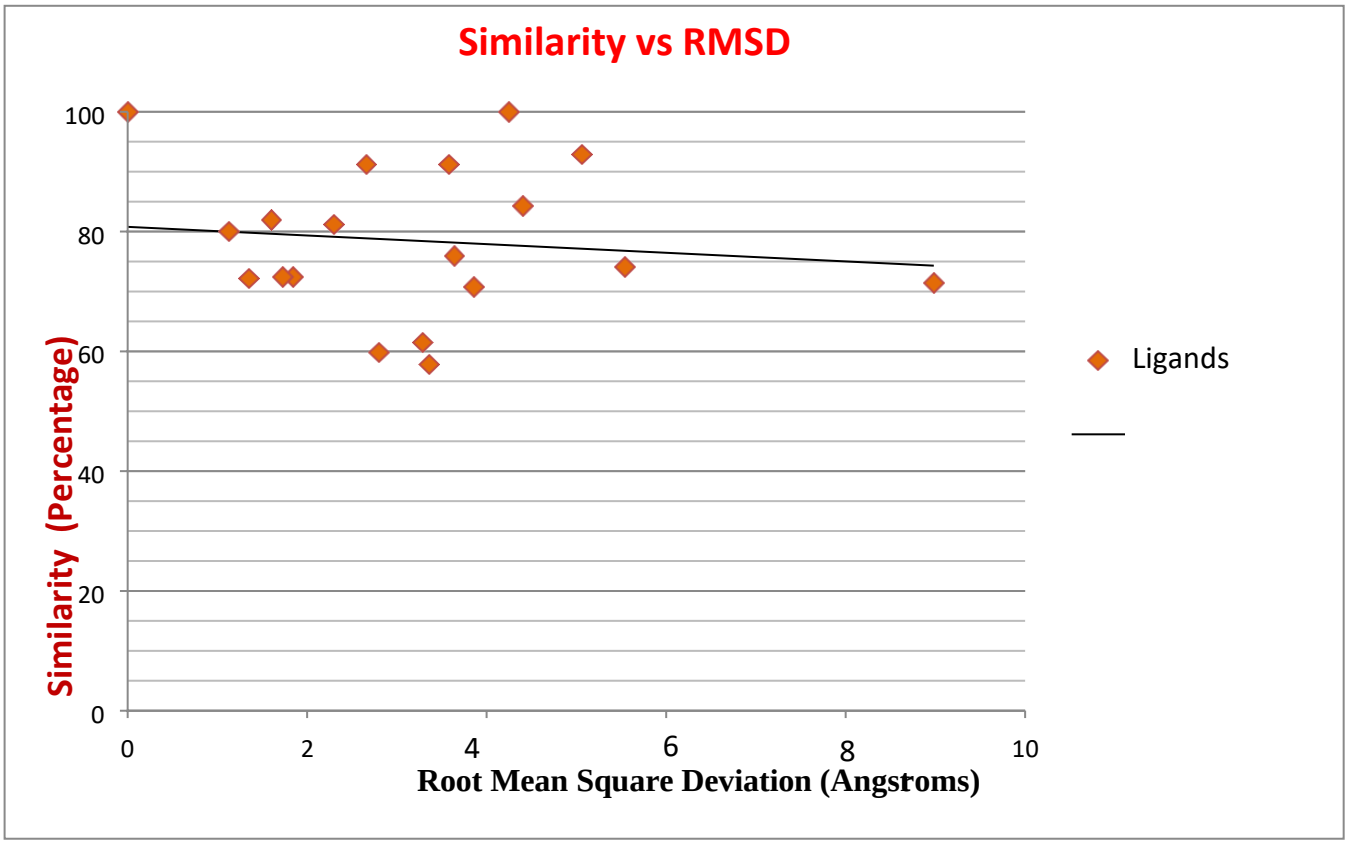


Figure 6: A Linear Regression Plot of Similarity Percentage versus the Root Mean Square Deviation between the FDA approved Drugs and Bioactive Compounds from *Musa spp.*

As per the Table 2 content the compounds in the Musa species and their analogs obtained from the combinational libraries with their 3D modeling. The 3D model, when transferred to the SWISSADME instrument certain physicochemical properties, are viewed as, for example, Sub-atomic Formula close by its Biomolecular weight, Simplified Molecular Input Line Entry System gives a line documentation for encoding sub-atomic structures and explicit examples, Topological Polar Surface Area which giving the surface total over all the polar iotas or particles essentially oxygen and nitrogen including their joined hydrogen ions (TPSA between 20 and 130 $Å^2$), **Molecular Refractivity** is the proportion of absolute polarizability of a mole of a substance and is subject to temperature, file of refraction and weight. **Log S(ESOL)** for predicting the intrinsic water solubility by using log *S* scale: insoluble<−10 <poorly <−6 <moderately <−4 <soluble <−2

<very <0 <highly. **Lipophilicity** is the partition coefficient between *n*-octanol and water (log $P_{o/w}$) which is the classical descriptor**. Lipinski's rule** is a thumb rule to evaluate drug likeness or to determine if the chemical compound having pharmacological activity has chemical or physical properties that would make it a likely orally active drug in humans. The parameters to be followed in Lipinski's rule are MW<=500, MLOGP<=4.15, N or O<=10, NH or OH<=5. **Drug- Likeness** evaluates qualitatively a chance for a molecule to become an oral drug with respect to its bioavailability and helps in the filtering of chemical libraries to eliminate the molecules which are most probably incompatible with an acceptable pharmacokinetic profile. **Bioavailability Score** is for the rapid appraisal of drug-likeness, the score is 0.11 for anions for which TPSA is >150 Å 2, 0.56 if TPSA is between 75 and 150 Å 2, and 0.85 if TPSA is <75 Å 2. **Lead likeness** is considered as it helps to obtain the compound which has the desired properties to be a lead molecule in the development of drug, the parameters considered are (250<=MW<=350, XLOGP<=3.5, rotatable bonds<=7). **Synthetic Accessibility (SA) Score** is based on view of the recurrence of sub-atomic parts in truly realistic particles that relates without any difficulty of union. The fragmental commitment of SA is required to be ideal for successive substance moieties and troublesome for uncommon moieties. [15, 16]

In Table 3 the compounds selected are then searched in the Protein Data Bank to obtain the protein ID, template PDB-ID, % similarity and protein class. The obtained template of the protein is further used to obtain the target protein for the molecular docking studies and this in turn helps us to obtain the % similarity of the protein and the compound and also provides the protein class and significance of the protein.

Further in Table 4 the obtained template protein is then searched in the FDA approved drugs list to obtain the approved drug which is similar to that of our Bioactive compound which gives the % similarity between the compound along with the calculation of Root Mean Square Deviation Value between Bioactive compounds and the FDA approved drug showed some significant RMSD Values. A Linear Regression Plot of Similarity Percentage versus the Root Mean Square Deviation between the FDA approved Drugs and Bioactive Compounds from Musa spp. Reveled the Significant Value of $\mathbf{R^2 = 0.0131}$ **(y = -0.7202x + 80.805)** upon which approximately 6 Ligand molecules fall near on the regression line. The compound with more than 75% similarity and less RMSD values are considered for the further process of drug design; since they are very

similar to the approved FDA drug they are most likely to show the ability to be a good lead molecule in the drug development and production. [16, 17, 18]

CONCLUSION:

The compounds present within the plant are identified and analogs are identified for the further drug development process. The obtained analogs are then studied to understand the physicochemical properties like relative molecular mass, number of atoms, rotatable bonds count, molar refractivity, TPSA, and lipophilicity value, water solubility rate and sophistication, pharmacokinetics properties of the compound, drug-likeness properties like Lipinski, Ghose, Veber and Bioavailability score is additionally studied. And in medicinal chemistry lead-likeness and artificial accessibility is studied to understand whether the compound is eligible to become a lead molecule in drug formulation and to be an oral drug candidate. [9, 10, 12, 14]

After the study of physicochemical properties the compounds which are valid to be lead molecule are considered for next step to spot the target protein. Therefore the compounds are searched within the FDA approved drug data bank to get the compounds almost like the chosen compound then their target protein is identified to conduct the molecular docking studies to obtain the stable complex of molecule and protein binding. [6, 12, 13, 19]

Molecular docking evaluation administered with different compounds which are a part of Phytoconstituents of Musa species which have shown to fulfill the Pharmacological parameters considered under the studies will provide a robust information for in-vivo studies of those evaluated Phytoconstituents and guide them to be LEAD molecules which are growing LIGAND for a possible DRUG molecules from MUSA species. [5, 14]

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