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Screening of phytochemicals from *Couroupita guianensis* as drug candidates against lethal diseases using insilico analysis

Hardika H. Chauhan, Mayuri D. Chavan, Rinku R. Choudhary, Heena M. Madkaikar, Tushar S. Dalvi, Nisha J. Shah *

Department of Life Sciences, University of Mumbai, Mumbai, India

* For correspondence: nisha.shah@lifesciences.mu.ac.in

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ABSTRACT

Couroupita guianensis is a deciduous, huge, versatile tree flourishing with brown, green, pink, white colours and also with phytochemicals like alkaloids, flavonoids, Terpenoids, Saponins, tannins, carbohydrates that are ready to serve to the plant as well as humans. This huge plant also is seen to have some pharmacological activities like antimicrobial, antifungal, antioxidant, anti-diabetic, anti-inflammatory and anticancer. With the passing time, there is a greater demand for effective natural medication. Physicochemical characteristics, drug similarity, toxicity, and efficacy of phytochemicals against numerous targets may now be evaluated using online tools, thanks to a wide database and technical advancements. The insilico method is efficient since it saves time and money. Clinical trials could benefit from such a strategy to increase medication development and market acceptance. Natural sources can provide a pool of molecules for any disease target when they are evaluated for potential therapeutic candidates. Some of the software utilized in the study to evaluate phytochemicals from a plant source included SwissADME and SwissDock. Due to their superior ADME qualities, reduced toxicity, and docking, four of the six phytochemicals studied from these plants are potential therapeutic candidates against diverse targets.

Keywords: *Couroupita guianensis*, Cancer, Diabetes, insilico ADMET, Docking

1. INTRODUCTION

Medicinal plants found around world have some useful activities helping in curing of various diseases. Plant's parts like stem, leaves, barks, flowers are used in ailments of diseases due to their phytochemicals present. Wide range of plants show pharmacological activities like antibacterial, antifungal, antimicrobial, antiviral, anthelminthic, anti-diabetic, anticancer and many more in number [1]. Around 270,000 plants are known to been investigated for medicinal activity globally. Even herbal medicine knowledge is retrieved from local indigenous communities.

Couroupita guianensis is a huge plant which is seen to be used since ancient times and still glow with its different abilities. This plant can be used in treatments of various diseases as well as for decoration purposes [2].

Couroupita guianensis, is an evergreen tree which is inherent to tropical northern South America and Southern Caribbean. These trees is accounted as a sacred tree in Hindu and are grown widely in surroundings of Shiva Temples as the flower lookalike the hood of sacred snake Naga, that protects Shiva Lingam [3]. It is also planted in tropical and subtropical gardens as decorative tree [4-6].

As plants have medicinal properties, their parts are loaded with natural compounds called phytochemicals due to which they show pharmacological activities. With these phytochemicals, different drugs can be designed by studying the molecules by *In-silico* drug designing method. Drug development is a tough, time-consuming, and multidisciplinary process. The use of *in silico* chemistry and molecular dynamics for computer-aided drug creation has generated a lot of interest [7]. The main benefit of in silico drug design is that it reduces the amount of money spent on drug research and development is reduced by using in silico drug design.

Molecular modeling is the main objective of the study for molecular interactions.

2. MATERIALS AND METHODS

2.1. Sample

Couroupita guianensis is a huge tree with fruits and is reservoir of many pharmacological activities. The pharmacological properties need to be studied and researched in depth in order to find some therapeutics with help of the In-silico analysis.

2.2. Chosen Phytochemicals

The selected phytochemicals under this study were stigmasterols, quercetin, p-coumaric acid, o-coumaric acid. Stigmasterol phytochemical was selected because it has anti stiffness factor, anti-mutagenic properties and also anti-inflammatory activity. The p-coumaric acid was selected as isolated phytochemical due to its anticancer activity against MCF-7 breast cancer cell line and anti-diabetic activity [8-9]. Quercetin was selected as it has anti-inflammatory and anti-carcinogenic properties [10].

2.3. Protein Targets

IPF1/ PDX1 insulin promoter factor 1 PDB Code (1EXT) was selected for study. It plays a role in the regulation of key beta cell genes as well as the production of somatostatin. It is also involved in development of pancreas and islet cell ontogeny. The PDX-1 mutation appears to contribute to Type 2 diabetes by adversely impacting compensatory mechanisms that increase beta-cell neogenesis to meet the increased insulin secretory requirement [11].

The BRCA1: breast cancer type 1 susceptibility protein PDB Code (3PXD). The BRCA1 gene is responsible for producing a tumour suppressor protein. An inherited mutation in the BRCA1 or BRCA2 gene is the most common cause of hereditary breast cancer. These genes aid in the production of proteins that repair damaged DNA in normal cells [12].

2.4. Software

UCSF Chimera software visualizes and analyses molecular structures in real time. It can also be used to examine data pertaining to the docking outcomes and their trajectories. SwissDock's predictions can be visualized using Chimera.

The Protein Data Bank (PDB) is a three-dimensional structural data database for large biological molecules including proteins and nucleic acids. The data, which is usually obtained by X-ray crystallography, NMR spectroscopy, or, increasingly, cryo-electron microscopy are analyzed here. The 3D structures of all the phytochemicals are taken from Protein Data Bank [13].

PubChem is a database of chemical molecules and their biological assay activities. It helps in finding details on chemical and physical properties, biological activities, protection and toxicity, patents, and literature citations, among other things [14].

SwissDock automatically prepare the structure of target protein, as well as of the ligand. The seamless visualization significantly aids the analysis of docking findings and their incorporation into existing research pipelines [15]. In the UCSF Chimera molecular viewer, this can be launched directly from the web browser. Users are given several sample files that can be directly imported into the form by clicking on a connection [16].

2.5. Docking

The required phytochemical were searched and retrieved from Pubmed, the canonical SMILE identities of the phytochemicals chosen under study. The 3D conformer in SDF format of the phytochemicals was chosen. The canonical SMILE identities of the phytochemicals retrieved was pasted in SwissADME. The SwissADME analysis includes the Physicochemical, Lipophilicity, Water Solubility, Pharmacokinetic, Drug-likeness and Bioavailability score and Medicinal chemistry Properties of the phytochemicals as a drug are demonstrated.

The abstracted pathway was chosen from KEGG pathway and analyzed for the selection of enzymes. The enzymes such as IPF1/PDX1 and BRCA1 were chosen from the two pathways Type 2 Diabetes Mellitus pathway and Breast Cancer pathway respectively. The relevant enzyme's PDB structure was retrieved from PDB database.

The downloaded 3D conformer in SDF format of the phytochemicals chosen under the study is converted into Mol.2 format using UCSF chimera. The ligands are uploaded for insilico docking analysis on SwissDock. The drug capability of the phytochemicals under study was assessed based on their Absorption Digestion Metabolism Excretion (ADME) properties, docking studies with enzymes, and toxicity predictions.

3. RESULTS AND DISCUSSION

The estimation of drug absorption, distribution, metabolism, and excretion (ADME) is encouraged by computer-assisted drug development; they complement experimental procedures by quickly generating reliable and predictive data. The ADME properties of the potent phytochemicals using the Swiss ADME web tool were evaluated in the current study.

Table 1. General properties of Phytochemicals

Sr. No.	Small Molecule	Molecular formula	Canonical smiles	Molecular weight (g/mol or Da)
1.	Stigmasterols	$C_{29}H_{48}O$	CCC(C=CC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C	412.7
2.	Quercetin	$C_{15}H_{10}O_7$	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O	302.23
3.	p-coumaric acid	$C_9H_8O_3$	C1=CC(=CC=C1C=CC(=O)O)O	164.16
4.	o-coumaric acid	$C_9H_8O_3$	C1=CC=C(C(=C1)C=CC(=O)O)O	164.16

Table 2. Physicochemical properties of Phytochemicals

Sr. No.	Small Molecule	Num. heavy atoms	Num. arom. heavy atoms	Fraction Csp3	Num. Rotatable bonds	Num. H Bond acceptors	Num. H-bond donors	Molar refractivity	TPSA ($^0A^2$)
1.	Stigmasterols	30	0	0.86	5	1	1	132.75	20.23
2.	Quercetin	22	16	0.00	1	7	5	78.03	131.36
3.	p-coumaric acid	12	6	0.00	2	3	2	45.13	57.53
4.	o-coumaric acid	12	6	0.00	2	3	2	45.13	57.53

Table 3. Lipophilicity properties of Phytochemicals

Sr. No.	Small Molecule	Num. heavy atoms	Num. arom. heavy atoms	Fraction Csp3	Num. Rotatable bonds	Num. H Bond acceptors	Num. H-bond donors	Molar refractivity	TPSA ($^0A^2$)
1.	Stigmasterols	30	0	0.86	5	1	1	132.75	20.23
2.	Quercetin	22	16	0.00	1	7	5	78.03	131.36
3.	p-coumaric acid	12	6	0.00	2	3	2	45.13	57.53
4.	o-coumaric acid	12	6	0.00	2	3	2	45.13	57.53

Table 4. Water solubility properties of Phytochemicals

Sr. No.	Small Molecule	ESOL				Ali				SILICOS-IT			
		Log S (ESOL)	Solubility		Class	Log S (ESOL)	Solubility		Class	Log S (ESOL)	Solubility		Class
			mg/mL	mol/L			mg/mL	mol/L			mg/mL	mol/L	
1.	Stigmasterol	-7.46	1.43e-05 mg/ml	3.46e-08 mol/l	Poorly soluble	-8.86	5.71e-07 mg/ml	1.38e-09 mol/l	Poorly soluble	-5.47	1.40e-03 mg/ml	3.39e-06 mol/l	Moderately soluble
2.	Quercetin	-3.16	2.11e-01 mg/ml	6.98e-04 mol/l	Soluble	-3.91	3.74e-02 mg/ml	1.24e-04 mol/l	Soluble	-3.84	1.73e-01 mg/ml	5.73e-04 mol/l	Soluble
3.	p-coumaric acid	-2.02	1.58e+00 mg/ml	9.65e-03 mol/l	Soluble	-2.27	8.73e-01 mg/ml	5.32e-03 mol/l	Soluble	-1.28	8.67e+00 mg/ml	5.28e-02 mol/l	Soluble
4.	o-coumaric acid	-2.37	6.93e-01 mg/ml	4.22e-03 mol/l	Soluble	-2.87	2.24e-01 mg/ml	1.36e-03 mol/l	Soluble	-1.28	8.67e+00 mg/ml	5.28e-02 mol/l	Soluble

From the Cannonball plant, 4 potent phytoconstituents namely Stigmasterols, Quercetin, p-coumaric acid and o-coumaric acid were analyzed using Swiss ADME web tool were evaluated for their general properties such as molecular formula, molecular weight, etc (table 1), physicochemical properties (table 2) such as number of rotatable bonds, hydrogen donor, acceptor, TPSA, heavy atoms. All of the compounds had a molecular weight less than 500 Da.

As a result, phytochemicals studied in this study have the required physicochemical properties and can be considered potential medication candidates. The phytoconstituents of Ipomoea mauritiana revealed all compounds with a molecular weight less than 500 Da, which is a keyfeature that can be referred to as small molecule drug similarity.

The lipophilicity (table 3) of the compound plays a significant role in molecular discovery activities across a wide range of fields. Lipophilicity is estimated as consensus Log P, which is the average value of all Log P evaluated with various lipophilicity criteria. Consensus Log P value is highest (6.97) for stigmasterol and lowest (1.23) for quercetin. Such high lipophilic nature of stigmasterol is suggestive of its enhanced efficacy as a

transdermal drug. Whereas, Quercetin would not show much effect as an oral drug as its ability to cross cell membrane is significantly low.

Solubility (table 4) of the molecules is an important factor as it ensures its minimum concentration to be present in the circulatory system implying a better absorption in the body. SwissADME uses two methods (topological and fragmental) of predicting solubility (log S) where the value of -10 & below is considered insoluble and -4 and above is considered soluble.

The phytochemicals are soluble and moderately soluble except for stigmasterol (-8.86) which is poorly soluble and p-coumaric acid and o-coumaric acid (-1.28) showing the highest solubility.

Pharmacokinetic properties (table 5) such as GI

Table 5. Pharmacokinetic properties of Phytochemicals

Small Molecule	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (cm/s)
Stigmasterol	Low	No	No	No	No	Yes	No	No	-2.74
Quercetin	High	No	No	Yes	No	No	Yes	Yes	-7.05
p-coumaric acid	High	Yes	No	No	No	No	No	No	-6.26
o-coumaric acid	High	Yes	No	No	No	No	No	No	-5.86

Table 6. Phytochemicals Drug-likeness and Bioavailability score

Sr. No.	Small molecules	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
1.	Stigmasterol	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	Yes	No; 1 violation: WLOGP>5.88	No; 2 violations: XLOGP3>5, Heteroatoms<2	0.55
2.	Quercetin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
3.	p-coumaric acid	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.85
4.	o-coumaric acid	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.85

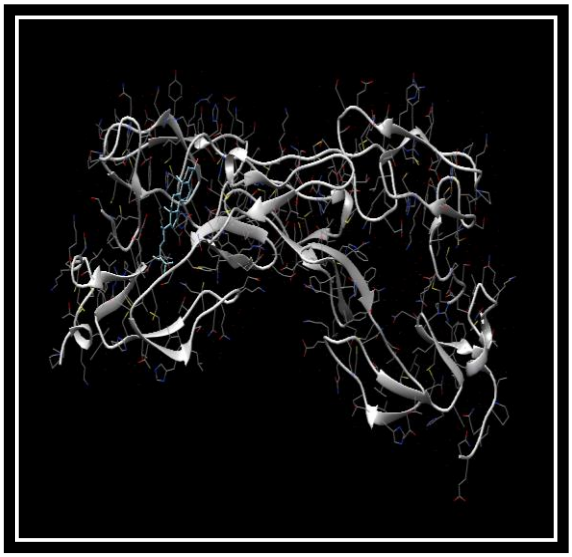
Table 7. Phytochemicals Medicinal Chemistry

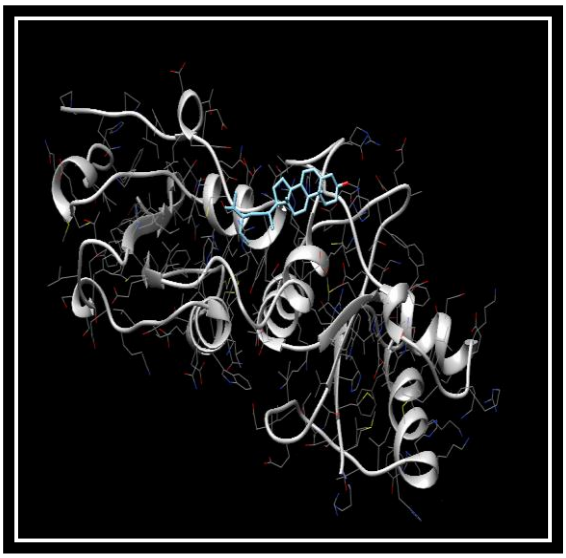
Sr. No.	Small molecules	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
1.	Stigmasterol	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	Yes	No; 1 violation: WLOGP>5.88	No; 2 violations: XLOGP3>5, Heteroatoms<2	0.55
2.	Quercetin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
3.	p-coumaric acid	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.85
4.	o-coumaric acid	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.85

Table 8. Phytochemical Molecular Docking against Target Proteins using SwissDock

Sr. No.	Small Molecule	1EXT ΔG (kJ/mol)	3PXD ΔG (kJ/mol)
1.	Stigmasterol	-7.33	-7.23
2.	Quercetin	-6.57	-7.04
3.	p-coumaric acid	-6.08	-6.30
4.	o-coumaric acid	-5.80	-6.50

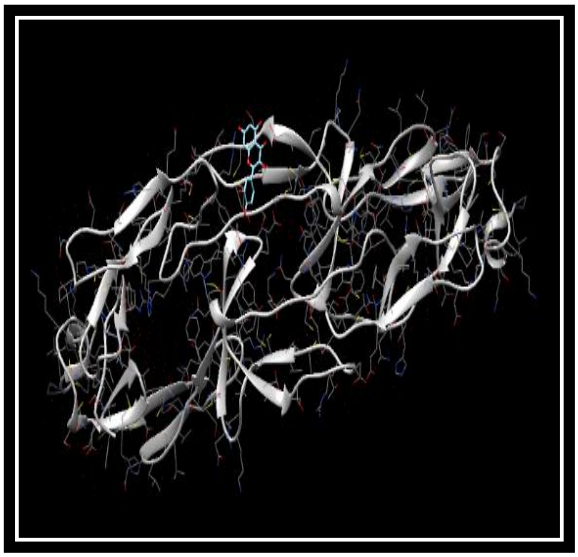
absorption, BBB permeability, PGP substrate and inhibitor of Cytochrome P450 isozymes as well as skin permeation as Log Kp value have been tabulated for each phytochemical. The pharmacokinetics and drug likeness performed using SwissADME showed a high level of GI absorption for quercetin, p-coumaric acid and o-coumaric acid, except stigmasterol with low GI absorption. Yes BBB permeant for p-coumaric acid and o-coumaric acid and No BBB permeant for stigmasterol and quercetin. None of the chemicals are P-gp substrates. The pharmacokinetics and drug likeness performed using SwissADME showed a high level of GI absorption with scopoletin, chloroacetic acid, tetradecanal, dodecanoic acid, tetradecanoic acid, octadecan 1 ol, octadecanoic acid, hexanoic acid and high BBB permeant with scopoletin, dodecanoic acid, tetradecanal, tetradecanoic acid and hexanoic acid respectively, except for a few molecules, none of the chemicals found in I. mauritiana are P-gp substrates. Amongst the phytochemicals under present considered, all of them can be used to easily target specific enzymes for their therapeutic effect without P-gp binding. While p-coumaric acid and o-coumaric acid can be used to target the nervous system. The Swiss ADME model returns "Yes" or "No" if the compound under examination is an inhibitor or non-inhibitor of Cytochrome P 450 isoenzymes. CYP1A2 was Yes (inhibitor) for quercetin from the above mentioned phytochemicals except stigmasterol, p-coumaric acid and o-coumaric acid. CYP2C19 was indicated as No (non-inhibitor) for all the above mentioned phytochemicals. CYP2C9 was indicated as No (non-inhibitor) for all the above mentioned phytochemicals except for stigmasterol. CYP2D6 was indicated as No (non-inhibitor) for all the above mentioned phytochemicals except for quercetin. CYP3A4 was indicated as No (non-inhibitor) for all the above mentioned phytochemicals except for quercetin. Almost all of the small molecules of Ipomoea Mauritian are turned as non-inhibitorsof CYP isoenzymes except for scopoletin, tetradecanal, tetradecanoic acid, octadecan 1 ol, octadecanoic acid and tetracosane for CYP1A2. Except stigmasterol and quercetin all other phytochemicals can inhibit most CYPs (at least 2 out of 4 considered here) which reduces the clearance of xenobiotics from the system and hence increasing the chances of drug-drug interactions (DDI). Adverse drug reactions are a result of DDI. The skin permeability coefficient (Log Kp), a multiple linear regression, indicates how permeant a molecule is to the skin. The lower the log Kp (with Kp in cm/s), the less permeant the molecule is to the skin. Quercetin (-7.05 cm/s) is the least permeant compound among the phytoconstituents, whereas stigmasterol (-2.74cm/s) is the most permeant. Among the phytoconstituents of the Ipomoea mauritiana chloroacetic acid (-6.72) is the least permeant compound and nonacosane (2.08) is highly permeant respectively. Compounds showing high skin permeability are good candidates for transdermal drugs and cosmetics rather than being oral drug candidates. Hence, stigmasterol is better suited as a constituent of transdermal drugs.

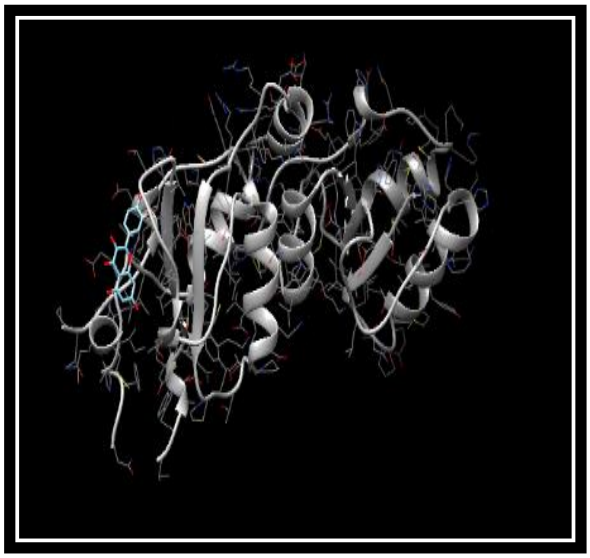




(A) 1EXT **(B) 3PXD**

Figure 1. Molecular Docking of Stigmasterol with (A) 1EXT (B) 3PXD



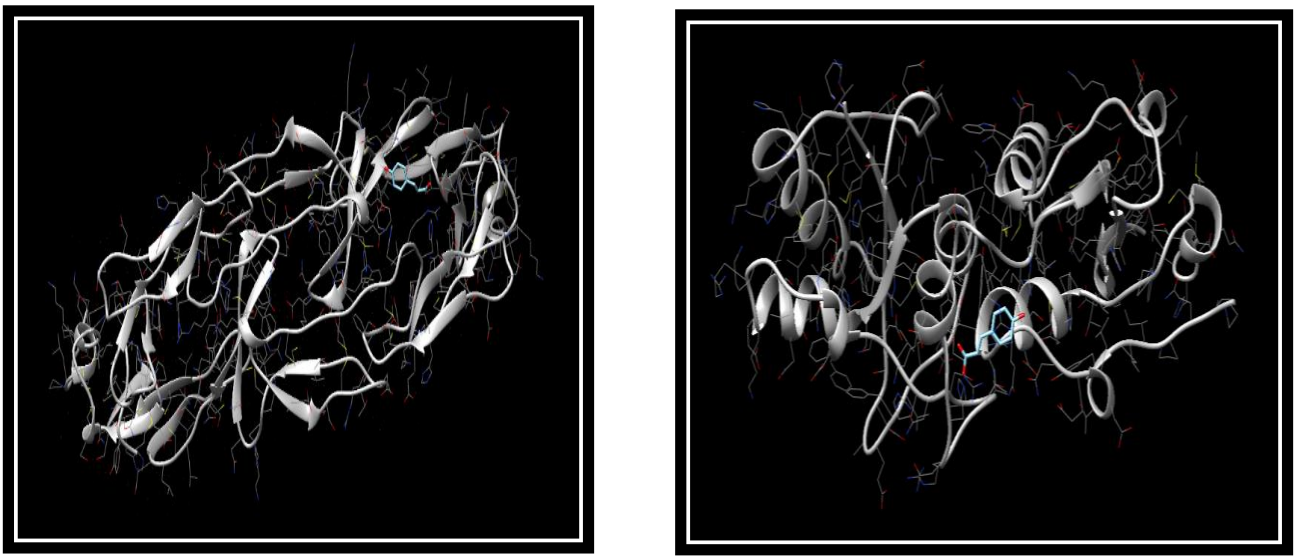


(A) 1EXT **(B) 3PXD**

Figure 2: Molecular Docking of Quercetin with (A) 1EXT (B) 3PXD

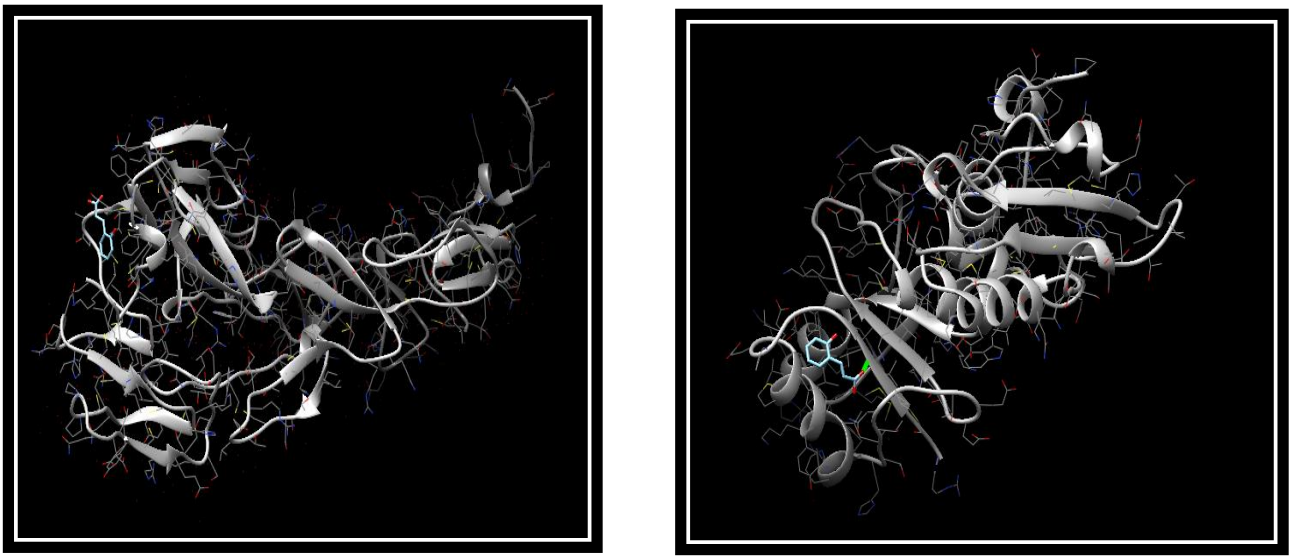
Drug likeness based on different parameter set by various pharmaceuticals and bioavailability score (table 6) as well as medicinal chemistry (table 7) indicating alerts for structures in the molecule that can be responsible for false positive results (PAINS) or toxicity (Brenk) and the synthetic accessibility for each phytochemicals have been obtained using SwissADME.

This area of SwissADME provides access to five alternative rule-based filters, each with a different set of properties within which the molecule is classified as drug-like (table 6). With the Ghose (Amgen), Egan (Pharmacia) filter showing Yes for all the above mentioned phytochemicals except stigmasterol, whereas for Veber (GSK) and Lipinski (Pfizer) filter Yes for all the



(A) 1EXT **(B) 3PXD**

Figure 3. Molecular Docking of p-coumaric acid with (A) 1EXT (B) 3PXD



(A) 1EXT **(B) 3PXD**

Figure 4: Molecular Docking of o-coumaric acid with (A) 1EXT (B) 3PXD

above mentioned phytochemicals, Muegge (Bayer) filter showing No for all the above mentioned phytochemicals except quercetin was the first rule-of-five implementation. Multiple estimates allow for consensus views or the selection of methodologies that best suit the end user's needs in terms of chemical space or project-related demands.

The bioavailability scores for all the above mentioned phytochemicals was 0.55 except for p-coumaric acid and o-coumaric acid with 0.85. None of the compounds in the SwissADME interpretation have a PAINS signal except quercetin with 1 alert. All the compounds of I. mauritiana expressed and followed the filtered rule invoked in the SwissADME, the violations shown by the molecules are

minimal and the SwissADME interpretation did not post any PAINS alert of any of the molecules. All the compounds in the SwissADME interpretation did have a Brenk signal with 1 alert each. The phytochemical quercetin showed leadlikeliness except stigmasterol, p-coumaric acid and o-coumaric acid.

Table 8 shows the docking scores of these plant compounds with various proteins of interest from breast cancer and type II diabetes mellitus pathways. The phytochemicals such as stigmasterol, quercetin, p-coumaric acid and o-coumaric acid from cannonball were docked with signalling molecule and protein related to cancer pathway such as BRCA1 breast cancer type 1 susceptibility protein (3PXD) as well as IPF1/PDX1 insulin promoter factor 1 (1EXT) (Fig.1-4) from type II diabetes mellitus pathways using SwissDock to explore their potential to be used as drugs for these diseases. Although stigmasterol has shown greater affinity with most of these proteins nonetheless, quercetin, p-coumaric acid and o-coumaric acid have also shown moderate binding with the proteins at their catalytic sites and hence can be considered as suitable drug candidates.

Prabhu and Ravi, (2016) has isolated a number of phytoconstituents from flowers of *Couroupita guianensis* flowers [17]. They exposed the flowers to sequential extraction using petroleum ether, chloroform, ethyl acetate and methanol solvents. They isolated new compounds named I Cycloart-24-en-3-ol-4-exomethylene heptadeconate along with stigmasterol II, p-coumaric acid III, o-coumaric acid IV, caeffic acid V and quercetin VI were isolated via column chromatography method and were characterized using IR, H and C NMR and MS spectral data. Compounds I, III, IV and V were reported by them for the first time [18]. The isolated flavonoids by use of high performance liquid chromatography from various parts of cannonball tree and have also tested its antibacterial activity [19].

To summarize, in silico ADMET evaluation along with molecular docking with various targets gives an exemplary estimation of the efficacy and prospect for drug development through natural sources. However, they all show above average binding affinity with some of the critical protein targets considered under this study.

4. CONCLUSION

As this beautiful tree is been seen to have many benefits with respect to human concern and was also used during ancient times, it can be also used in our futures. The phytochemicals or the secondary metabolites that are present is being used by the tree as defense against hosts and can also be useful to mankind. Its pharmacological activities of being antimicrobial, antifungal, anticancer, anti-inflammatory, anti-diabetic can be a boon for modern medicine. *Couroupita guianensis* is a tree which has to be studied much deeper and it can be implemented in cure of various diseases. The rise in the instances of cancer as well as type 2 diabetes mellitus today is destructive. Extensive research in the area of cancer is carried out all around the globe. Computational HTS is a great development in the field as it provides quicker analysis with moderate precision which is comparatively beneficial to the conventional methods. For the growing need of drug development, computational methods are part of the solution. With this software, various plant compounds were evaluated for their ADMET properties using SwissADME and their binding affinity using SwissDock with various proteins involved in crucial steps of cancer and type 2 diabetes mellitus. Only four out of six phytochemicals were studied under this review since no relevant data was found on pubchem for the other two phytochemicals. Most of the compounds under review have given constructive inputs where a range of parameters such as physicochemical properties, drug likeness, medicinal

chemistry, etc., set by various pharmaceutical industries were obeyed. The important ADME interpretations are highlighted under bioavailability radar which reports the overall chances of the molecule for further consideration based on its size, lipophilicity, solubility, in saturation, flexibility and polarity.

5. ACKNOWLEDGEMENT

NA

6. CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

7. SOURCE/S OF FUNDING

NA

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