IN SILICO ANALYSIS OF PHYTOCHEMICALS FROM VARIOUS PLANT SOURCES AS DRUG CANDIDATES AGAINST LIFE-THREATENING DISEASES

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ABSTRACT

Epigenetic changes and glycation play a significant role in the progression of life-threatening diseases like diabetes, cancer, cardiovascular diseases (CVDs), neurodegenarative diseases (ND) and others. Exploring natural sources for overall therapeutic effect can be a beneficial approach for treating these life threatening diseases. The phytocemicals apigenin, aegeline, marmelosin, kaempferol, pyrrolemarumine 4"-*O*-alpha-L-rhamnopyranoside and garcinol from Durva, Bael, Custard apple, Moringa and Kokum were evaluated for their therapeutic value using *in silico* techniques. These phytochemicals and target structures (molecules from diseases pathologies from KEGG database), were obtained from PubChem and PDB, respectively. The docking studies, pharmaceutical parameters and toxicity studies were done using Swiss Dock, Swiss ADME for and Pro Tox II. The above phytochemicals have shown optimal lipophilicity, insaturation, flexibility and solubility. Molecular weight was less than 500 Da and LD_{50} values for each of these was above 400 mg kg^{-1}. Amongst all phytochemicals, garcinol was found to be ideal for dermal drugs.

Keywords: Ayurveda, Glycation, Epigenetics, *in silico*, ADMET, Docking

INTRODUCTION

Herbalism, based on the use of plants and plant extracts, is a common herbal or folk medicinal practice. India has about 45,000 plant species of which 1500 plants have been mentioned in the traditional text and 800 plants have been used in the traditional medicine practices (Henkel & Agarwal, 2020). Phytochemicals found in plants have gained popularity due to their antiviral, antimicrobial and antioxidant activity[1-2].

Epigenetics may be considered to influence gene expression and cellular phenotypes other than the sequence of DNA. The various epigenetic mechanisms involve methylation, acetylation, ubiquitination, sumoylation and phosphorylation. The topic has been of immense interest, particularly in case of complex disorders related to cancer, autoimmune diseases and addiction. Epigenetic mechanisms contribute to the expression of certain specific genes or may result in gene silencing[3]. Glycation is a non-enzymatic reaction between a sugar moiety and protein/lipids generating a range of toxic compounds known as AGEs that accumulate in the body. Reduced detoxification and other contributing factors for AGE accumulation can cause generation of ROS, oxidative stress, various metabolic syndromes, neurodegenerative diseases as well as certain kinds of cancer. Latest studies have shown the beneficial effects of bioactive compounds in medicinal plants such as kokum, moringa and ashwagandha and so on, against the pathogenesis induced by AGEs using experimental diabetic animal models[4]. The anti-cancer, anti-inflammatory, and antioxidant properties of kokum, custard apple and bael have been well proven[5]. Extracts from moringa and durva have a substantial hypoglycemic impact in diabetic patients[6].

Bioinformatics can be defined as "the application of computational tools to organize, analyze, understand, visualize and store information associated with biological macromolecules"[7-8]. *In silico* disease models help in deeper understanding of disease pathophysiology, propose new therapeutic methods, and provide insight into the design of experimental and clinical trials[9]. Various softwares like Swiss ADME, Swiss dock, etc., have been used

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in this study to predict the druggable properties of the phytochemicals and to expand the drug development avenues to natural sources for the ever increasing need for safer and effective drugs against various life threatening diseases.

MATERIALS AND METHODS

Materials

Plants under study: Kokum (*Garcinia indica*), Moringa (*Moringa oleifera*), Durva (*Cynodondactylon*), Custard apple (*Annona squamosa*), and Bael (*Aegle marmelos)* were among the plants employed to investigate the pharmacological properties of natural phytochemicals.

Selected phytochemicals and protein targets: Apigenin, aegeline, marmelosin, kaempferol, Pyrrolemarumine 4"-O-alpha-L-rhamnopyranoside and garcinol were chosen to examine among all other phytochemicals contained in these plants. CDK4: Cyclin-dependent kinase 4 (2W96), PKC alpha: Protein kinase C Alpha (4DNL), TERT: Telomerase reverse transcriptase (5UFW), CDK2: Cyclin-dependent kinase 2 (1B39), PTP1B: Protein tyrosine phosphatase 1B (1A5Y), and APP: Amyloid-beta precursor protein (2FMA) were among the enzymes studied for their interactions with phytochemicals.

Softwares used: SwissADME, SwissDock, Chimera, Pro-tox 2, PubChem, ZINC, and KEGG PATHWAY database were the softwares used to analyse, recruit and evaluate phytochemicals, enzymes, and research interactions.

Method

PubChem: The canonical SMILE identities of the phytochemicals chosen under study were retrieved from PubChem.

SwissADME: The structural and chemical characteristics of the phytochemicals as a drug were demonstrated using SwissADME.

KEGG PATHWAY Database: The pathways, namely the AGE-RAGE signalling pathway in diabetes complications, Alzheimer's disease, FOXO signalling pathway, insulin resistance pathway, gastric cancer and cell cycle pathway were abstracted from the KEGG PATHWAY database.

PDB: The enzymes such as CDK4, PKC alpha, TERT, CDK2, PTP1B and APP were chosen based on reactions taking place in various pathways mentioned above.

SwissDock and UCSF Chimera: Each phytochemical was docked with every enzyme to study the bonding capacity and other characteristics of the bonding using SwissDock. The docking results were viewed using the software UCSF Chimera.

ProTox-II: The toxicity for the various phytochemicals were predicted using Pro-Tox 2 software and the oral, organ, gastrointestinal, etc. toxicity levels of the phytochemicals under study were analysed.

Based on the Absorption Digestion Metabolism Excretion (ADME) properties, docking analysis with enzymes and toxicity predictions of the various phytochemicals, drug capacity of the phytochemicals under study were evaluated.

RESULTS AND DISCUSSION

Currently, computer-assisted drug development encourages the estimation of drug absorption, distribution, metabolism, and excretion (ADME); they generate predictive and reliable data fast and complement experimental procedures[10-11]. In the present study, we evaluated the ADME properties of the potent, phytochemicals using the Swiss ADME web tool, and easy analysis of results, also for non- experts in CADD[12].

A total of 6 potent phytoconstituents from 5 different plants were analyzed using Swiss ADME web tool, apigenin obtained from durva, garcinol from kokum, aegelin and marmelosin from bael, kaempferol from custard apple and pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside from moringa were evaluated for their general properties such as molecular formula, molecular weight, etc (Table I), physicochemical properties (Table II) such as number of heavy atoms, rotatable bonds, hydrogen donor, acceptor and TPSA. All of the compounds had a molecular weight less than 500 Da except garcinol from kokum with 602.80 g mol^{-1}. The phytoconstituents of *Ipomoea mauritiana* revealed all compounds with a molecular weight less than 500 Da, which is a key feature that can be referred to as small molecule drug similarity[13]. Hence, phytochemicals under present study are in the range of the required physicochemical properties and can be considered as ideal drug candidate except for garcinol which has a higher molecular weight.

The lipophilicity (Table III) 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[12]. Consensus Log P value is highest (7.35) for garcinol and lowest (0.8)

Table I: General properties of the phytochemicals

Sl. No.	Small molecule	ZINC AC	Molecular formula	Canonical SMILES	Molecular weight (g mol^{-1} or Da)
1	Apigenin	ZINC387156	$C_{15}H_{10}O_5$	C1=CC(=CC=C1C2=CC(=O) C3=C(C=C(C=C3O2)O)O)O	270.24
2	Aegeline	ZINC311595	$C_{18}H_{19}O_3$	COC1=CC=C(C=C1)C(CNC(=O) C=CC2=CC=CC=C2)O	297.3
3	Marmelosin		$C_{16}H_{14}O_4$	CC(=CCOC1=C2C (=CC3=C1OC=C3)C=CC(=O)O2)	270.28
4	Kaempferol	ZINC28569588	$C_{15}H_{10}O_6$	C1=CC(=CC=C1C2=C(C(=O) C3=C(C=C(C=C3O2)O)O)O)O	286.24
5	Pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside		$C_{19}H_{23}NO_7$	CC1C(C(C(C(O1) OC2=CC=C(C=C2) CN3C(=CC=C3 C=O)CO)O)O)O	377.39
6	Garcinol	ZINC4098424	$C_{38}H_{50}O_6$	CC(=CCC1CC2(C(=O) C(=C(C3=CC(=C(C=C3)O)O)O) C(=O)C(C2=O)(C1(C)C)CC=C(C) C)CC(CC=C(C)C)C(=C)C)C	602.80

Table II: Physicochemical properties of the phytochemicals

Sl. No	Small molecule	Num. heavy atoms	Num. arom. heavy atoms	Fraction Csp3	Num. Rotatable bonds	Num. H Bond acceptors	Num. H-bond donors	Molar refracti-vity	TPSA ($^0A^2$)
1	Apigenin	20	16	0.00	1	5	3	73.99	90.90
2	Aegeline	22	12	0.17	7	3	2	86.10	58.56
3	Marmelosin	20	13	0.19	3	4	0	77.50	52.58
4	Kaempferol	21	6	0.00	1	6	4	76.01	111,13
5	Pyrrolemarumine 4''-O-alpha-L-rhamnopyranoside	27	11	0.42	6	7	4	94.68	121.38
6	Garcinol	44	6	0.50	10	6	3	180.06	111.90

for Pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside. Such high lipophilic nature of garcinol is suggestive of its enhanced efficacy as a transdermal drug. On the other hand, pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside would not show much effect as an oral drug as its ability to cross cell membrane is significantly low.

Solubility (Table IV) 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 and below is considered insoluble and -4 and above is considered soluble. The phytochemicals have shown moderate solubility except for garcinol (-9.50) which is insoluble and pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside(-1.80) showing the highest solubility.

Pharmacokinetic properties (Table V) such as GI 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

Table III: Lipophilicity of the phytochemicals

Sl. No.	Small molecule	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log $P_{o/w}$
1	Apigenin	1.89	3.02	2.58	0.52	2.52	2.11
2	Aegeline	2.54	2.44	2.12	2.18	3.17	2.49
3	Marmelosin	3.05	3.50	3.88	2.14	3.99	3.31
4	Kaempferol	1.70	1.90	2,28	-0,03	2.03	1.58
5	Pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside	1.61	-0.46	-0.10	-1.09	0.42	0.08
6	Garcinol	4.76	10.29	8.76	3.78	9.15	7.35

high level of GI absorption for marmelosin, aegeline, apigenin, kaempferol, pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside, except garcinol with low GI absorption. Yes BBB permeant for marmelosin, aegeline and No BBB permeant for apigenin, kaempferol, pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside and garcinol was determined. Except for garcinol, 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[13]. Amongst the phytochemicals under present consideration, all of them can be used to easily target specific enzymes for their therapeutic effect without P-gp binding except garcinol, which requires a P-gp for its absorption in the body. Marmelosin and aegeline 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 all the above mentioned phytochemicals except garcinol, CYP2C9 and CYP2C19 was indicated as No (non-inhibitor) for all the above mentioned phytochemicals except marmelosin, CYP2D6 was Yes (inhibitor) for apigenin, aegeline and kaempferol and No (non-inhibitor) for marmelosin, garcinol and pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside and CYP3A4 was Yes for apigenin, aegeline, kaempferol and garcinol and No for marmelosin and pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside. Almost all of the small molecules of *Ipomoea mauritiana* returned as non-inhibitorsof CYP isoenzymes except for scopoletin,tetradecanal, tetradecanoic acid, octadecan 1 ol, octadecanoic acid and tetracosane for CYP1A2[13]. Except garcinol, all other phytochemicals can inhibit most CYPs (at least 3 out of 5 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, the less permeant the molecule is to the skin[14]. Pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside (-8.93) is the least permeant compound among the phytoconstituents, whereas garcinol (-2.67) 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[13]. Compounds showing high skin permeability are good candidates for transdermal drugs and cosmetics rather than being oral drug candidates. Hence, garcinol is better suited as a constituent of transdermal drugs[15].

Drug likeness based on different parameters set by various pharmaceuticals and bioavailability score (Table VI) as well as medicinal chemistry (Table VII) 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 phytochemical has been obtained using SwissADME.

Table IV: Water solubility of the phytochemicals

Sl. No.	Small molecule	ESOL				Ali				SILICOS- IT			
		Log *S* (ESOL)	Solubility		Class	Log S (Ali)	Solubility		Class	Log S SILICOS-IT	Solubility		Class
			mg mL^{-1}	mol L^{-1}			mg mL^{-1}	mol L^{-1}			mg mL^{-1}	Mol L^{-1}	
1	Apigenin	-3.94	3.07e-02	1.14e-04	S	-4.59	6.88e-03	2.55e-05	MS	-4.40	1.07e-02	3.94e-05	MS
2	Aegeline	-3.36	2.05e-01	6.88e-04	S	-3.31	1.45e-01	4.86e-04	S	-5.00	2.97e-03	9.98e-06	MS
3	Marmelosin	-4.00	2.68e-0.2	9.91e-05	MS	-4.29	1.39e-02	5.16e-05	MS	-5.51	8.33e-0408	3.08e-06	MS
4	Kaempferol	-3.31	1.40	4.90	soluble	-3.86	3.98	1.39	soluble	-3.82	4.29	1.50	soluble
5	Pyrrolemarumine 4''-*O*-alpha-L-rhamno-pyranoside	-1.80	6.04e+00	1.60e02	VS	-1.62	8.99e+00	2.38e02	VS	-1.80	5.95e+0 0	1.58e02	S
6	Garcinol	-9.50	1.90e-07	3.16e-10	PS	-12.58	1.59e-10	2.64e-13	IS	-8.16	4.13e-06	6.85e-09	PS

Table V: Pharmacokinetic properties of the phytochemicals

Sl. No.	Small molecule	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K_p (Skin Permeation) (cm s^{-1})
1	Apigenin	High	No	No	Yes	No	No	Yes	Yes	-5.80
2	Aegeline	High	Yes	No	Yes	No	No	Yes	Yes	-6.38
3	Marmelosin	High	Yes	No	Yes	Yes	Yes	No	No	-5.46
4	Kaempferol	high	no	no	yes	no	no	yes	yes	-6.70
5	Pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside	High	No	No	Yes	No	No	No	No	-8.93
6	Garcinol	Low	No	Yes	No	No	No	No	Yes	-2.67

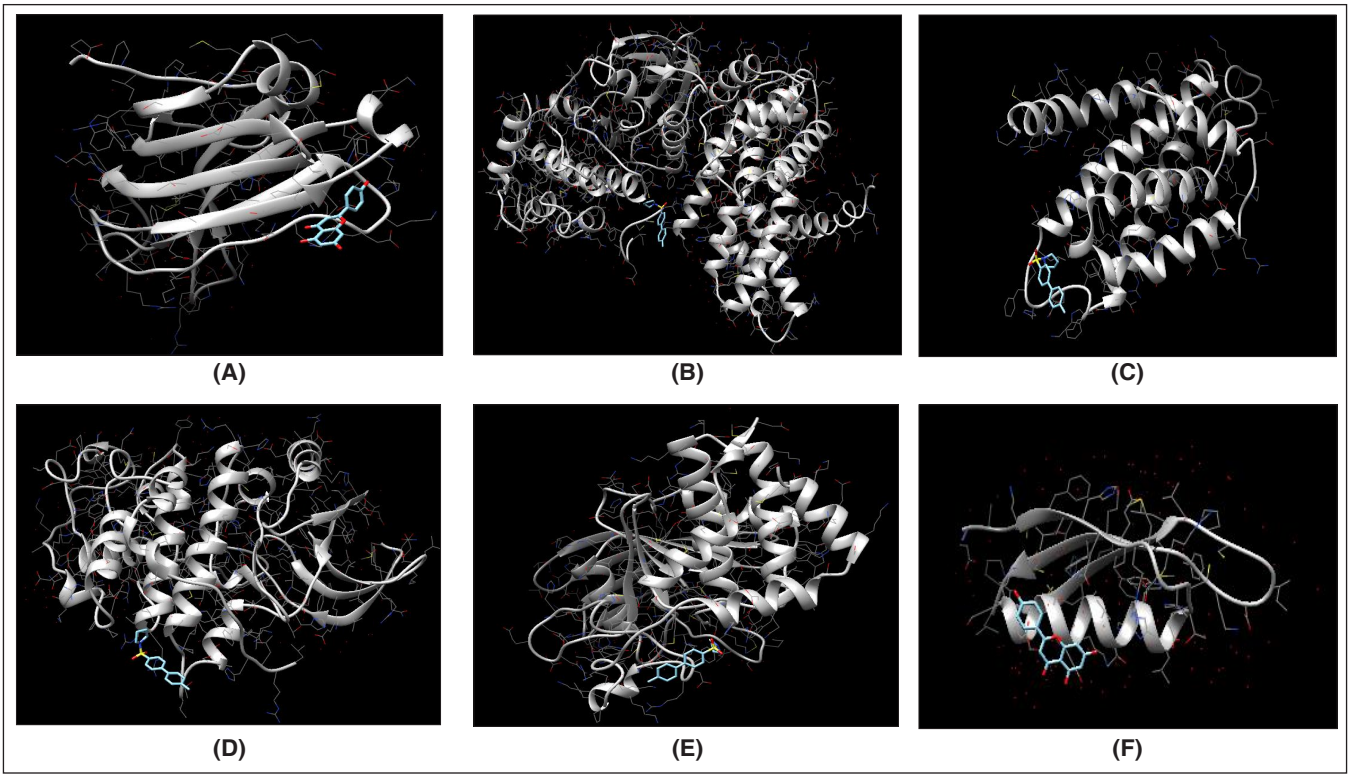

Fig. 1: Molecular docking of apigenin with (A) 4DNL (B)2W96 (C)5UGW (D)1B39 (E)1A5Y (F) 2FMA

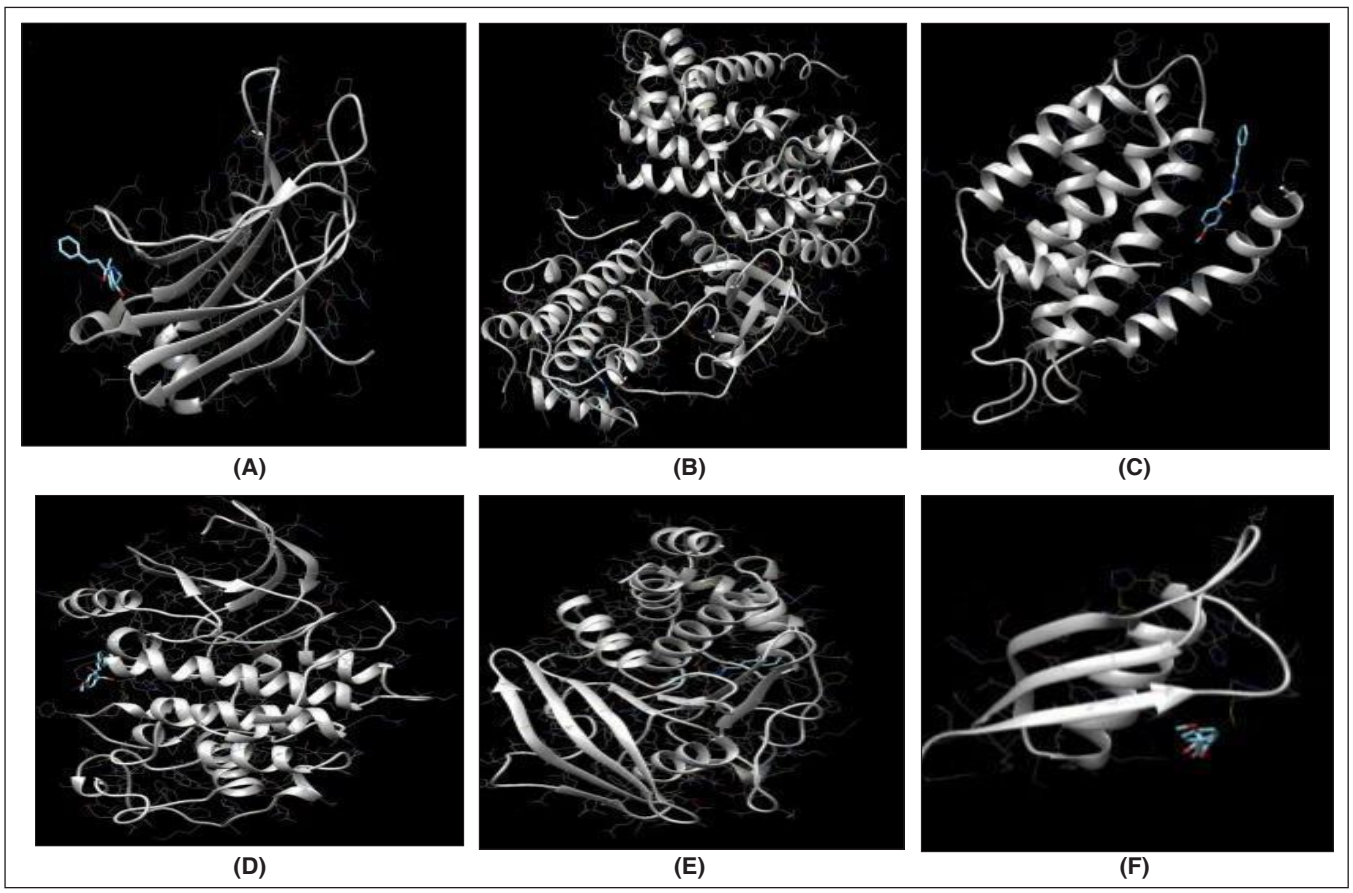

Fig. 2: Molecular docking of aegelin with (A) 4DNL (B)2W96 (C)5UGW (D)1B39 (E)1A5Y (F) 2FMA

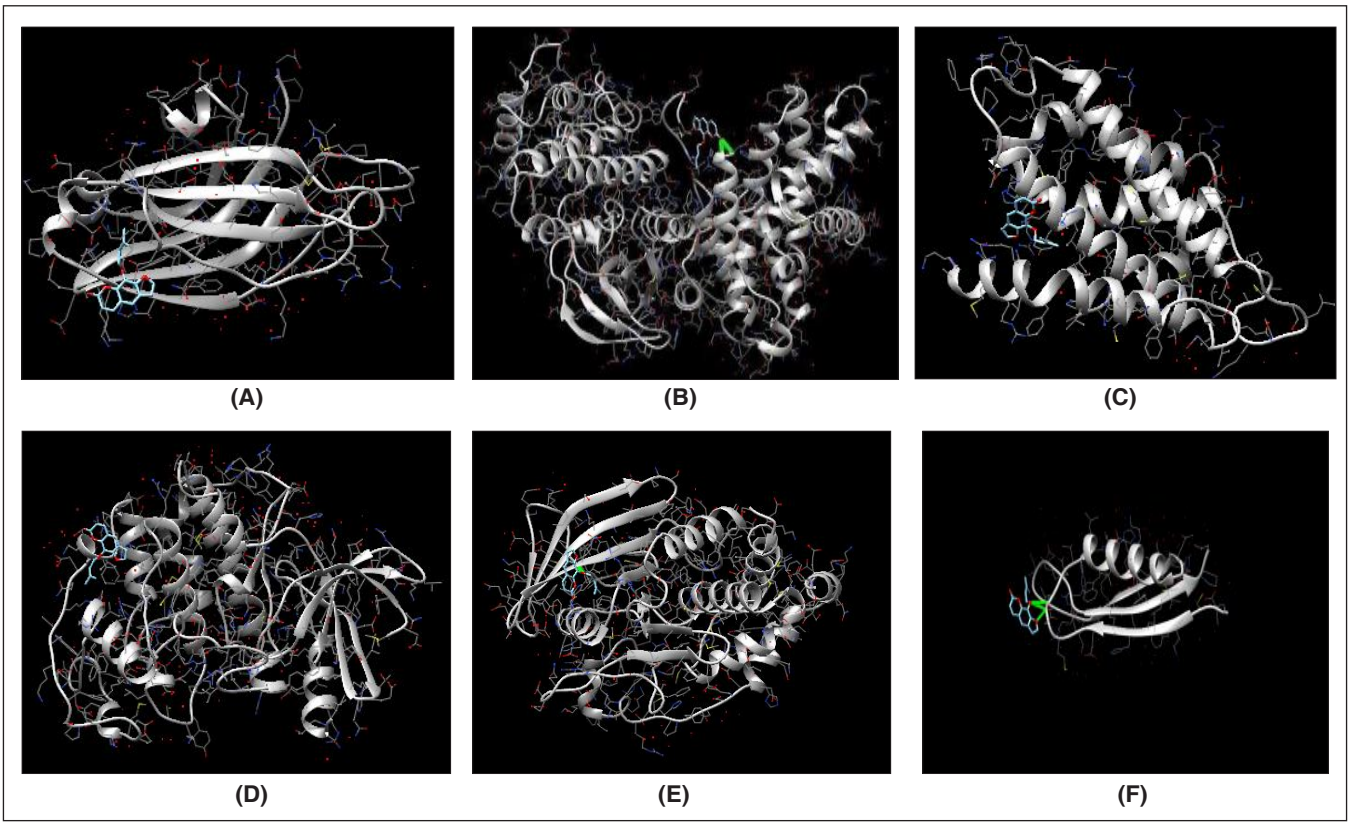

Fig. 3: Molecular docking of marmelosin with (A) 4DNL (B)2W96 (C)5UGW (D)1B39 (E)1A5Y (F) 2FMA

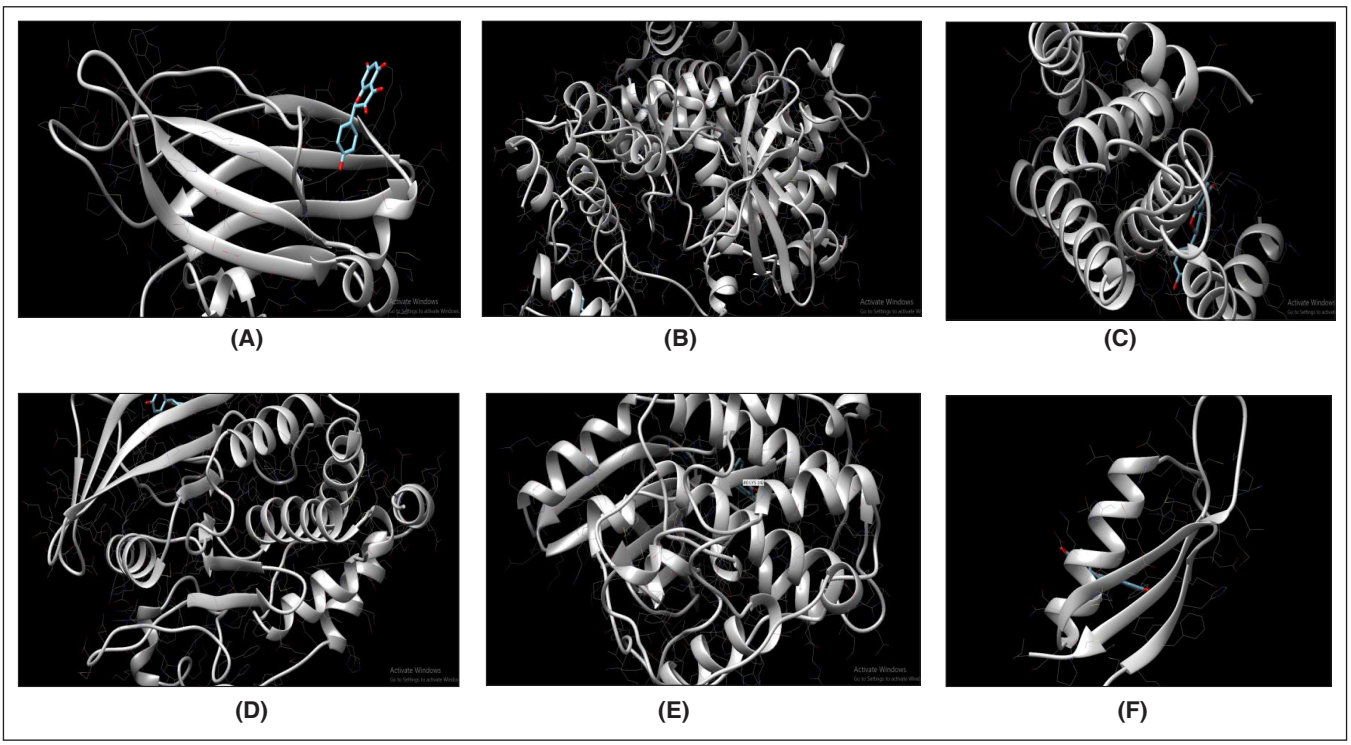

Fig. 4: Molecular docking of kaempferol With (A) 4DNL (B)2W96 (C)5UGW (D)1B39 (E)1A5Y (F) 2FMA

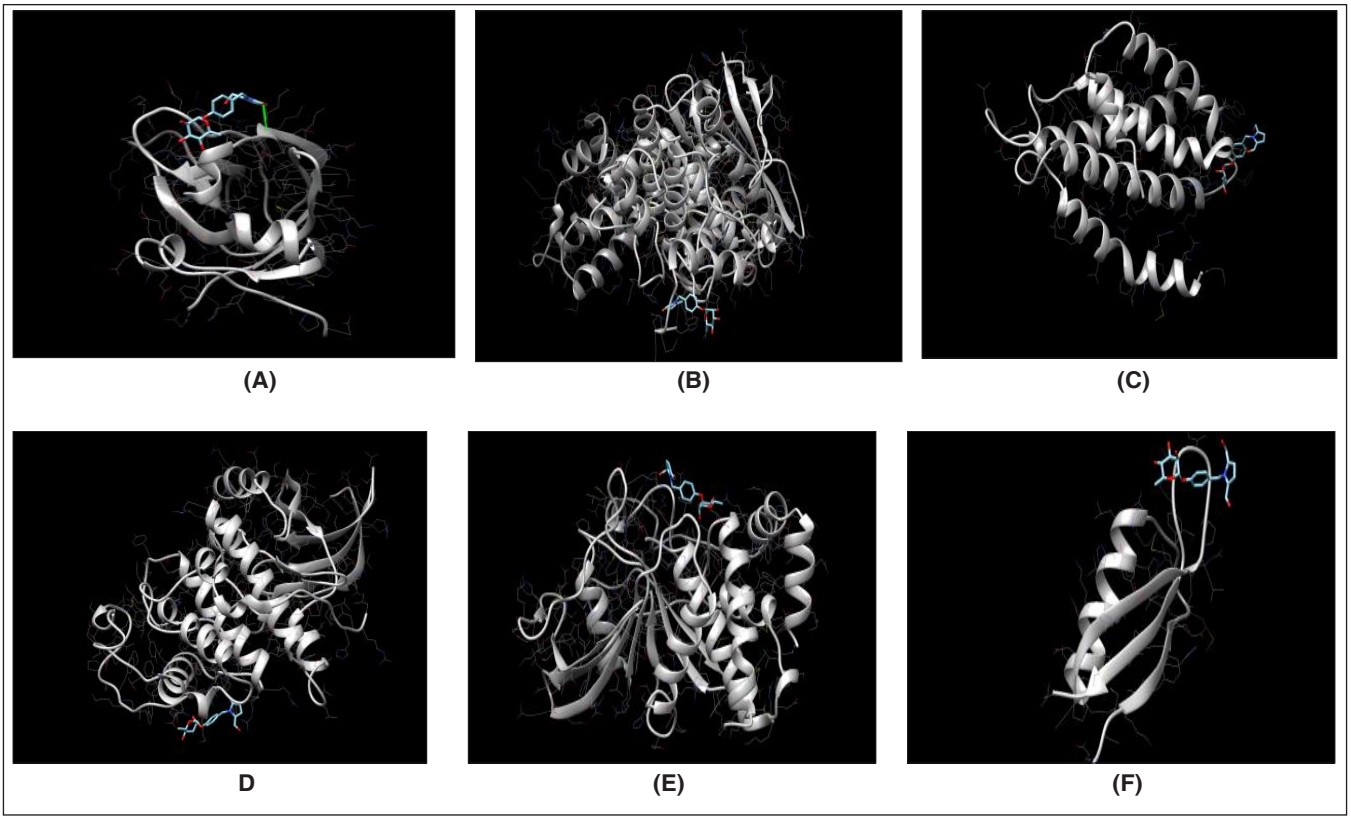

Fig. 5: Molecular docking of pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside with (A) 4DNL (B)2W96 (C)5UGW (D)1B39 (E)1A5Y (F) 2FMA

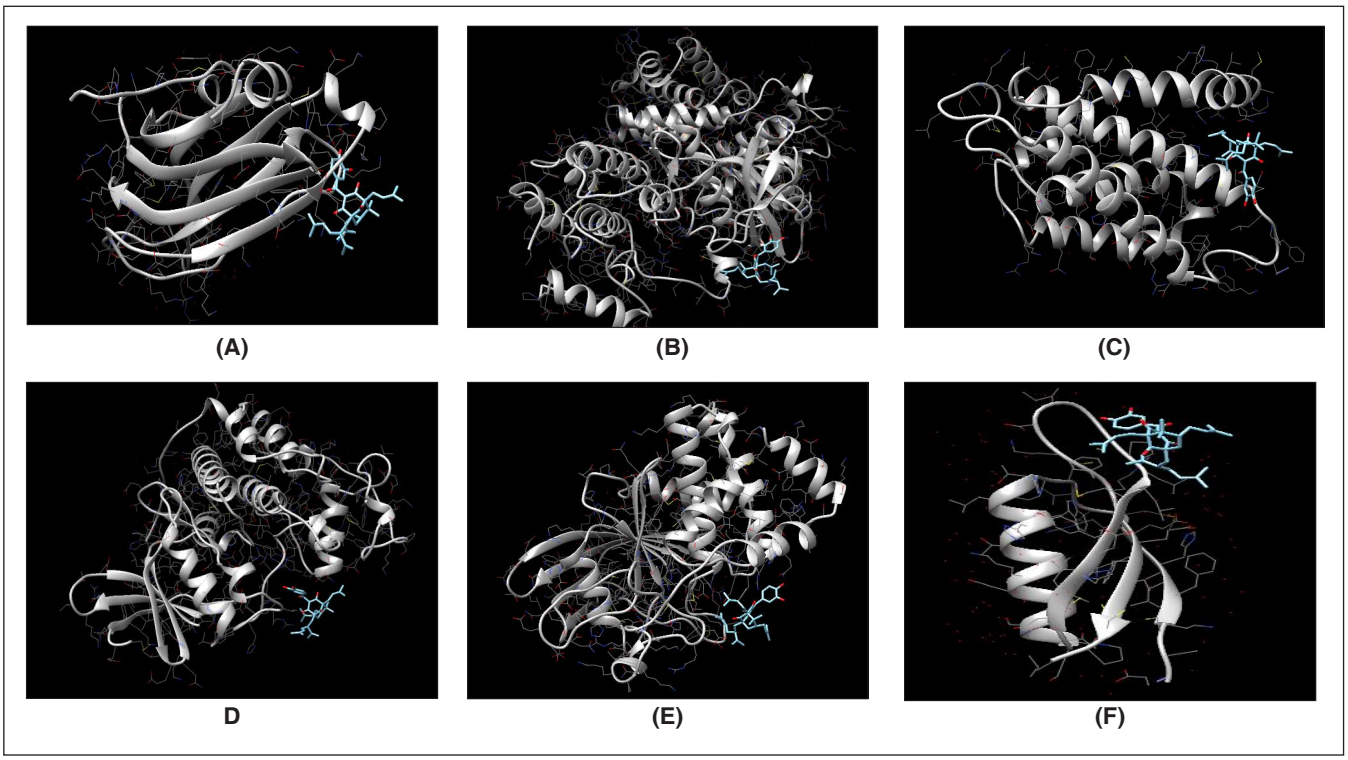

Fig. 6: Molecular docking of garcinol with (A) 4DNL (B) 2W96 (C) 5UGW (D) 1B39 (E) 1A5Y (F) 2FMA

Table VI: Drug-likeness and bioavailability score of the phytochemicals

Sl. No.	Small molecule	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
1	Apigenin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
2	Aegeline	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
3	Marmelosin	Yes	Yes	Yes	Yes	Yes	0.55
4	Kaempferol	Yes, 0 violation	yes	yes	yes	yes	0.55
5	Pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
6	Garcinol	Yes;1 violation: MW>500,	No; 4 violations: MW>480, WLOGP<-0.4, MR>130, #atoms>70	Yes	No; 1 violation: WLOGP> 5.88	No; 2 violations: MW>600, XLOGP3>5	0.56

Table VII: Medicinal chemistry of the phytochemicals

Sl No	Small molecule	PAINS	Brenk	Lead Likeness	Synthetic accessibility
1	Apigenin	0 alert	0 alert	Yes	2.96
2	Aegeline	0 alerts	1 alert: Michale_receptor_1	Yes	2.85
3	Marmelosin	0 alert	2 alerts: cumarine, isolated _alkene	Yes	3.22
4	Kaempferol	0	0	yes	3.14
5	Pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside	1 alert: pyrrole_N	1 alert: aldehyde	No; 1 violation: MW>350	4.34
6	Garcinol	1 alert: catechol_A	6 alerts:acyclic-C=C-O,beta_ keto_anhydride,catechol, isolated_alkene, michael_ acceptor 1 & 4	No; 3 violation: MW>350, Rotors>7, XLOGP3>3.5	6.88

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 VI). With the Ghose (Amgen), Egan (Pharmacia) and Muegge (Bayer) filter showing Yes for all the mentioned phytochemicals except garcinol, whereas for Veber (GSK) and Lipinski (Pfizer) filter Yes for all the phytochemicals, 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 phytochemicals were 0.55 except for garcinol with 0.56. None of the compounds in the SwissADME

interpretation have a PAINS signal except garcinol and pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside with 1 alert each. All the compounds in the SwissADME interpretation did have a Brenk signal except apigenin. The phytochemicals such as apigenin, aegeline, marmelosin and kaempferol showed lead likeness except pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside with 1 violation and garcinol with 3 violations. 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[13]. As these phytochemicals except garcinol and 4''-*O*-alpha-L-rhamnopyranoside show no violations, they do not need major structural modifications to prevent unwanted reactions.

Table VIII: Oral toxicity prediction of phytochemicals using Pro tox II

Small molecules	LD50 (mg Kg^{-1})	Predicted Toxicity Class
Apigenin	2500	5
Aegeline	450	4
Marmelosin	480	4
Kaempferol	3919	5
Pyrrolemarumine 4''-O-alpha-L-rhamnopyranoside	4000	5
Garcinol	2300	5

The toxicity parameters such as oral toxicity (Table VII), organ toxicity and other toxic endpoints (Table IX) as well as Tox21 evaluation for various receptors and signalling molecules in nuclear receptor signalling pathway (Table X) and stress response pathway (Table XI) were also predicted using Pro Tox II. The HTS for toxicity measures median lethal dosage (LD_{50}) and accordingly categorises them in 5 classes[16]. Except for aegeline and marmelosin, all the phytochemicals belong to class V (least toxic) with an LD_{50} value above 2000 mg kg^{-1}. Other toxicity parameters such as hepatotoxicity, one of the leading causes of Drug Induced Liver Injury (DILI), is also predicted with great precision and was found to be inactive for all the plant metabolites[17]. Besides hepatotoxicity, other toxicity endpoints such as carcinogenicity, immunotoxicity, mutagenicity and cytotoxicity were also evaluated by the software which were inactive for all the compounds except pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside and garcinol, which had immunotoxic activity. Two more toxicity parameters are considered: tox21 for nuclear receptor signalling and stress response pathways wherein the toxic activity against various factors and receptors in the aforementioned pathways against these compounds are predicted and it was found to be active for apigenin and kaempferol for most of the receptors in nuclear receptor signalling pathway whereas only apigenin was found most active with receptors from stress response

Table IX: Organ toxicity and toxicity endpoint prediction of phytochemicals using Pro tox II

Classification	Toxicity	Apigenin	Aegeline	Marmelosin	Kaempferol	Pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside	Garcinol
Hepatotoxicity	Prediction Probability	Inactive 0.68	Inactive 0.78	Inactive 0.75	Inactive 0.68	Inactive 0.84	Inactive 0.69
Carcinogenicity	Prediction Probability	Inactive 0.62	Inactive 0.72	Inactive 0.54	Inactive 0.72	Inactive 0.60	Inactive 0.57
Immunotoxicity	Prediction Probability	Inactive 0.99	Inactive 0.75	Active 0.71	Inactive 0.96	Active 0.95	Active 0.65
Mutagenicity	Prediction Probability	Inactive 0.57	Inactive 0.74	Active 0.81	Inactive 0.52	Inactive 0.66	Inactive 0.72
Cytotoxicity	Prediction Probability	Inactive 0.87	Inactive 0.85	Inactive 0.81	Inactive 0.96	Inactive 0.72	Inactive 0.62

Table X: Tox21 Nuclear receptor signalling pathways toxicity prediction of phytochemicals using Pro tox II

Classification	Toxicity	Apigenin	Aegeline	Marmelosin	Kaempferol	Pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside	Garcinol
Aryl hydrocarbon Receptor (AhR)	Prediction Probability	Active 1.0	Inactive 0.86	Active 1.0	Active 1.0	Inactive 0.82	Inactive 0.66
Androgen Receptor (AR)	Prediction Probability	Inactive 0.99	Inactive 0.97	Inactive 0.97	Inactive 0.99	Inactive 0.95	Inactive 0.96
Androgen Receptor Ligand Binding Domain (AR-LBD)	Prediction Probability	Inactive 1.0	Inactive 1.0	Inactive 0.99	Inactive 0.99	Inactive 0.97	Inactive 0.63
Aromatase	Prediction Probability	Active 0.61	Inactive 0.90	Inactive 0.86	Active 0.96	Inactive 0.90	Inactive 0.87
Estrogen Receptor Alpha (ER)	Prediction Probability	Active 1.0	Inactive 0.82	Inactive 0.91	Active 1.0	Inactive 0.91	Inactive 0.79
Estrogen Receptor Ligand Binding Domain (ER-LBD)	Prediction Probability	Active 1.0	Inactive 0.98	Inactive 0.99	Active 0.95	Inactive 0.95	Inactive 0.87
Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	Prediction Probability	Active 1.0	Inactive 0.96	Inactive 0.98	Inactive 0.95	Inactive 0.95	Inactive 0.94

Table XI: Tox21 Stress response pathways prediction of phytochemicals using Pro tox II

Classification	Toxicity	Apigenin	Aegeline	Marmelosin	Kaempferol	Pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside	Garcinol
Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ ARE)	Prediction Probability	Inactive 0.99	Inactive 0.94	Inactive 0.91	Inactive 0.99	Inactive 0.94	Inactive 0.75
Heat shock factor response element (HSE)	Prediction Probability	Inactive 0.99	Inactive 0.94	Inactive 0.91	Inactive 0.99	Inactive 0.94	Inactive 0.75
Mitochondrial Membrane Potential (MMP)	Prediction Probability	Active 1.0	Inactive 0.85	Inactive 0.89	Active 1.0	Inactive 0.76	Active 0.69
Phosphoprotein (Tumor Suppressor) p53	Prediction Probability	Active 1.0	Inactive 0.91	Inactive 0.90	Inactive 0.92	Inactive 0.86	Inactive 0.55
ATPase family AAA domain-containing protein 5 (ATAD5)	Prediction Probability	Active 0.96	Inactive 0.94	Inactive 0.97	Inactive 0.92	Inactive 0.98	Inactive 0.89

Table XII: Molecular docking of phytochemical against target proteins using Swiss dock

Sl. No.	Small molecule	4DNL △G (kJ mol^{-1})	2W96 △G (kJ mol^{-1})	5UGW △G (kJ mol^{-1})	1B39 △G (kJ mol^{-1})	1A5Y △G (kJ mol^{-1})	2FMA △G (kJ mol^{-1})
1	Apigenin	**-9.02**	**-8.91**	**-10.65**	-7.57	-7.55	-5.72
2	Aegeline	-7.65	-7.79	-7.05	-6.82	-7.38	-6.56
3	Marmelosin	-6.74	-7.64	-7.08	-6.76	-6.63	-6.22
4	Kaempferol	-8.83	-6.48	-10.41	-7.13	-7.59	-6.22
5	Pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside	-8.197	-8.11	-7.25	-7.41	-7.43	-6.908
6	Garcinol	-8.90	-7.00	-8.84	-9.31	-9.04	-6.61

pathway indicating its possible side effects. Nevertheless, such effects can be well regulated with drug dosage manipulations[18].

Table XII shows the docking scores of these plant compounds with various proteins of interest from cancer and neurodegenerative pathways[19]. The phytochemicals such as marmelosin and aegeline from bael, apigenin from durva, kaempferol from custard apple, pyrrolemarumine 4''-*O*-alpha-L-rhamnopyranoside from moringa and garcinol from kokum were docked with several signalling molecules and proteins related to cancer pathways such as phosphokinase C Alpha, CDK2, CDK4, TERT, PTP as well as APP (Figs. 1-6) from neurodegenerative diseases such as Alzheimer's disease using SwissDock to explore their potential to be used as drugs for these diseases[20]. Although apigenin has shown greater affinity with most of these proteins, nonetheless, aegeline, marmelosin and kaempferol have also shown moderate binding with the proteins at their catalytic sites and hence can be considered as suitable drug candidates[21].

To summarise, *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. The phytochemicals except garcinol and 4''-*O*-alpha-L-rhamnopyranoside under study were within the range of bioavailability radar making them good drug candidates. The LD_{50} values are in the reasonable range except for aegeline and marmelosin. However, they all show above average binding affinity with some of the critical protein targets considered under this study[22].

CONCLUSION

The rise in the instances of cancer as well as neurodegenerative diseases 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 these softwares, various plant compounds were evaluated for their ADMET properties using SwissADME and ProTox II as well as their binding affinity using SwissDock with various proteins involved in crucial steps of cancer and neurodegenerative pathologies. 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, insaturation, flexibility and polarity. Except for insaturation, all other parameters of bioavailability radar were within the range for the phytochemicals excluding garcinol and 4''-*O*-alpha-L-rhamnopyranoside which were out of range for more than 1 parameter. The compounds have shown moderate toxicity values as well as considerable binding affinity with the target proteins.

In conclusion, apigenin, aegeline, marmelosin, kaempferol can be further processed as suitable drug candidates against various cancers as well as other

metabolic targets that play an important role in numerous disease pathologies. However, they need to be thoroughly tested before they can be administered with other drugs as they are strong inhibitors of certain important enzymes belonging to the CYP450 family which can result in adverse drug reactions. Also, garcinol is a better candidate for external administration due to its large size, insolubility and better skin permeability.

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