IJPSR (2024), Volume 15, Issue 3 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 23 July 2023; received in revised form, 19 November 2023; accepted, 30 December 2023; published 01 March 2024

IN-SILICO PHARMACOKINETIC PROPERTIES PREDICTION OF COUMARINS PRESENT IN *AEGLE MARMELOS* L.

S. A. Agrawal *, S. R. Dhamne and P. S. Shinde

Bharati Vidyapeeth's College of Pharmacy, Sector-8, C.B.D., Belapur, Navi Mumbai - 400614, Maharashtra, India.

Keywords:

Aegle marmelos L., Coumarins, *In-silico* predictions, Pharmacokinetic

Correspondence to Author:
Dr. Sneha A. Agrawal

Assistant Professor,
Bharati Vidyapeeth's College of Pharmacy, Sector-8, C.B.D., Belapur, Navi Mumbai - 400614, Maharashtra, India.

E-mail: sneha.agrawal@bvcop.in

ABSTRACT: *Aegle marmelos* L. (Bael Fruit) is rich in bioactive compounds such as coumarins, alkaloids, terpenoids, tannins, flavonoids, and essential oils. This article focused on the pharmacokinetic profiling of coumarins present using an in silico ADME tool called SwissADME which contributes to a better understanding of enhanced drug monitoring and individualization of drug therapy. Log S (ESOL), Log S (Ali), and Log S (SILICOS-IT) values of umbelliferon, scopoletin, scoparone, xanthotoxol, and marmesin show that they are soluble in water which shows they have good absorption and excretion properties. Lipophilicity data shows that all coumarins can penetrate through the blood-brain barrier (BBB) except marmin, while marmesin and marmin have good oral bioavailability. These coumarins can inhibit the CYP1A2, CYP2C19, and CYP2C9 except CYP2D6, and CYP3A4 isoenzymes. This data helps to select leads for further drug discovery and development.

INTRODUCTION: India is the largest producer of fruits and vegetables in the world ranked at second position. In India, about 2500 plant species belonging to more than 1000 genera are being used in the indigenous system of medicine. In terms of both quantity and value of the medicinal plants exported, India ranks second in the world [2, 3]. It is estimated that approximately 10 to 15 percent of roughly 300,000 species of higher plants have a history of use in traditional medicine. Traditional uses of plants or plant parts give an idea regarding the use of plants for specific kinds of diseases.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.15(3).800-07

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.15(3).800-07

Natural coumarins have enormous power as a natural magical remedy for a wide range of diseases, they are present in high concentrations in several dietary plant species like cinnamon, lemon, dill, soy oil, peanut oil, olive oil, *etc*. In the larger category of nutraceuticals, natural coumarins contribute to various activities, and their pharmacotherapeutic aspects have been already published.

A large amount of coumarin intake may have a negative impact on health as the safety profile of coumarins was not thoroughly reviewed to present data. *Aegle marmelos* (A.M.) commonly known as Bael, is a plant of Indian origin that belongs to the Rutaceae family and has been regarded to possess tremendous medicinal properties [4, 5]. It is believed that the bael fruit is the symbol of lord Shiva. The leaf of this sacred tree which is vernacularly known as “Tripatra” or “Shivdame” has been essential in

offerings to Lord Shiva. According to historical records, Bael has been used as a medicine for diarrhea and dysentery treatment since 5000 B. C. [6, 7]. Analyzing and anticipating the pharmacological basis of the therapeutic activity of traditional medicinal plants are decisive for the goal of modernizing their use, considering the complicated and diverse phytoconstituents of the medicinal plants, and defining the specific chemical components in such plants and their major biological function [6, 7]. The earlier detection of PK/PD properties along with drug-likeness and ADME profiling can save both money and time. It also ensures the safety and stability of the candidate drugs or designed drugs. ADME (absorption, distribution, metabolism, and excretion) studies play a vital role in drug discovery and development with the support of technology, software like SwissADME allows the prediction and compilation of ADME parameters i.e., Physiological properties, Lipophilicity, Water solubility, Pharmacokinetics, Drug likeness, Medicinal chemistry. Selective coumarins present in A.M. like umbelliferon, scopoletin, scoparone, xanthotoxol, marmesin, psoralen, imperatorin (also known as Marmelosin or marmelide), alloimperatorin, and marmin [8-13] were taken for *in-silico* ADME screening using SwissADME software.

MATERIALS AND METHODS: The structural features of 11 potent phytoconstituents (Coumarins) include umbelliferon, scopoletin, scoparone, xanthotoxol, marmesin, psoralen, imperatorin, alloimperatorin, and marmin analyzed in the SwissADME free online software (http://www.swissadme.ch).

PubChem: Information on chemical substances was taken from the reputed public repository PubChem freely available at https://pubchem.ncbi.nlm.nih.gov. was accessed on a web server that displays the chemical information of the resource. Canonical Simplified Molecular Input Line Entry System (SMILES) and their biological activities were obtained by entering the chemical names of small molecules reported in A.M.[12].

SwissADME: *In-silico* study by SwissADME software is user-friendly, the Swiss Institute of Bioinformatics (SIB) developed this a web-based tool for predicting various properties and co-relating important parameters of drug discovery and development. It computes physicochemical descriptors as well as predicts ADME parameters, drug-like nature, and medicinal chemistry of one or multiple small molecules (mol. wt. ≥ 1000 Daltons) [12].

Physicochemical Properties: The range of physicochemical descriptors for small molecules, such as molecular weight, partition coefficient (log P) solubility, hydrogen bond donors and acceptors, and many others were calculated by the software. The prediction of physicochemical properties contributes to estimating drug capacity to cross the biological barriers. The widely used molecular descriptor in drug transport properties, TPSA (topological polar surface area) is the summation of the molecular surface area of polar atoms such as nitrogen, oxygen, and their attached hydrogens [12, 13].

Lipophilicity: A drug having sufficient lipophilic character shows good biological activity, by crossing the cell membrane[14]. Evaluation of log P or distribution coefficient (log D) are parameters to calculate lipophilicity. Selected software evaluates the lipophilicity in a compound by five models i.e., XLOGP3 (an atomistic method including corrective factors and knowledge-based library), WLOGP (atomistic method based on the fragmental system of Wildman and Crippen), MLOGP (an archetype of a topological method relying on a linear relationship with 13 molecular descriptors) [15], SILICOS-IT log P (a hybrid method relying on 27 fragments and 7 topological descriptors), log P which is the arithmetic mean of all five predictions of lipophilic character [16].

Solubility: A drug is considered soluble when the dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 to 7.5. A drug should have good aqueous solubility for absorption and oral bioavailability. Water solubility is predicted by three methods Log S (ESOL), Log S (ali), and Log S (SILICOS-IT). Two topological approaches are included in SwissADME to predict water solubility, the first one is the application of the ESOL model20 and the second one is adapted from the Ali model [17].

The third predictor of SwissADME was developed by SILICOS-IT (where the linear coefficient is corrected by molecular weight (R2=0.75). All predicted values of the molar solubility in water (log S) are the decimal logarithm [18].

Pharmacokinetics: GI absorption of drug display delineation on a plot of two computed descriptors: ALOGP versus PSA respectively. The populated elliptical region represents the presence of well-absorbed molecules termed Egan egg [19]. Egan egg model predicts GI passive absorption and brain access by passive diffusion broadly known as BOILED-Egg (Brain or Intestinal Estimated Permeation Predictive Model)' Potts and Guy adapted and validated this model by evaluating multiple linear regression, to predict the skin permeability coefficient (Kp), whereas Kp linearly correlated with molecular size and lipophilicity (R2 = 0.67).

The more negative the log Kp (cm/s), the molecule has less skin permeability. SwissADME applies the support vector machine algorithm (SVM) on meticulously cleansed large datasets of known substrates/non-substrates or inhibitors/non-inhibitors. The "Yes" or "No" format readings are generated in models if the molecule under investigation has a higher probability being substrate or non-substrate of P-gp (respectively inhibitor or non-inhibitor of a given CYP). Inhibition of CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 these isoenzymes is certainly one major cause of pharmacokinetics-related drug-drug interactions leading to toxic or other unwanted adverse effects due to the lower clearance and accumulation of the drug or its metabolites [21].

Drug Likeness [20, 22]: It is a key criterion in screening drug candidates at the earlier phase of drug discovery and development. SwissADME performs filtering of chemical libraries to exclude molecules incompatible with an acceptable pharmacokinetics profile with five disparate ruled-based filters elemental from considerable Pharma companies intended to improve the condition of proprietary chemical collections. The Lipinski filter (Pfizer) is the first of five rules that characterize small molecules based on physicochemical property profiles such as Molecular Weight (MW) less than 500, MLOGP ≤ 4.15, N or O ≤ 10, NH or OH ≤ 5. The Ghose filter (Amgen) describes small molecules stationed on the physicochemical property, existence of functional groups, and substructures. The qualifying range includes molecular weight between 160 and 480 Da, WlogP between -0.4 to 5.6, and molar refractivity (MR) between 40 to 130 for a total number of atoms; the qualifying range is between 20 and 70 atoms in a small molecule [23]. The Veber filter (GSK filter) model symbolizes molecules as a drug if they have ≤ 10 rotatable bonds and a TPSA equal to or less than 140 Å2 with 12 or fewer H-bond donors and acceptors. Compounds with these properties will have good oral bioavailability, reduced TPSA correlates increased permeation rate, and increased rotatable bond counts which have a negative effect on the permeation rate.

Egan filter (Pharmacia filter) anticipates that drug absorption depends on processes involved in the membrane permeability of the small molecule. These models symbolize molecules as a drug if they have WLOGP ≤5.88 and TPSA ≤ 131.6 respectively [8]. Muegge filter (Bayer filter) is a self-reliant Pharmacophore point filter that segregates drug-like and non-drug-like molecules. These models symbolize molecules as a drug if they have a molecular weight between 200 to 600 Da, TPSA ≤ 150, Number of rings ≤ 7, XLOGP between -2 and 5, Number of carbon atoms > 4, number of heteroatoms > 1, number of rotatable bonds ≤ 15, H-bond acceptor ≤ 10, H- bond donor ≤ 5 respectively. Abbott bioavailability score seeks to predict the probability of a compound to have at least 10% oral bioavailability in rats or measurable Caco-2 permeability which predicts the probability of a compound to have F>10% based on the predominant charge at biological pH in a rat model.

Medicinal Chemistry [24]: This section aims to bolster medicinal chemists in their daily drug discovery endeavors. PAINS (Pan Assay Interference Compounds or frequent hitters or promiscuous compounds) are the molecules that show potent responses in assays irrespective of the protein targets, notably such compounds are reported to be active in many different assays, which can be considered as potential starting points for further exploration.

In other models, Brenk considers compounds that are smaller and less hydrophobic and not those defined by "Lipinski's rule of 5" to widen opportunities for lead optimization. This model restricts the ClogP/ClogD to between 0 and 4, the number of hydrogen-bond donors and acceptors to fewer than 4 and 7, respectively, and the number of heavy atoms to between 10 and 27 respectively. Additionally, only compounds with limited complexity defined as fewer than 8 rotatable bonds, fewer than 5 ring systems, and no ring systems with more than 2 fused rings are considered medicinal.

The concept of lead likeness is designed to provide leads with tremendous affinity in high throughput screening (HTS) that allows for the exploitation of additional interactions in the lead optimization phase. Leads are exposed to chemical modifications that will most likely decrease size and increase lipophilicity which is less hydrophobic than drug-like molecules. Lead optimization has been done by a rule-based method consisting of molecules with molecular weight between 100 and 350 Da, ClogP between 1 and 3.0, and is greatly considered as superior to those of drug-like compounds and therefore like.

BOILED-Egg Model [24, 25]: This is used to simultaneously predict two key ADME parameters, i.e., passive GI absorption (HIA) and brain access (BBB). The egg-shaped classification plot consists of the yellow region (i.e., space for BBB permeability) and the white (i.e., the physicochemical space for probable HIA absorption). Certain molecules with properties predicted for low absorption and limited brain penetration are represented by the outside grey region **Fig. 1.**

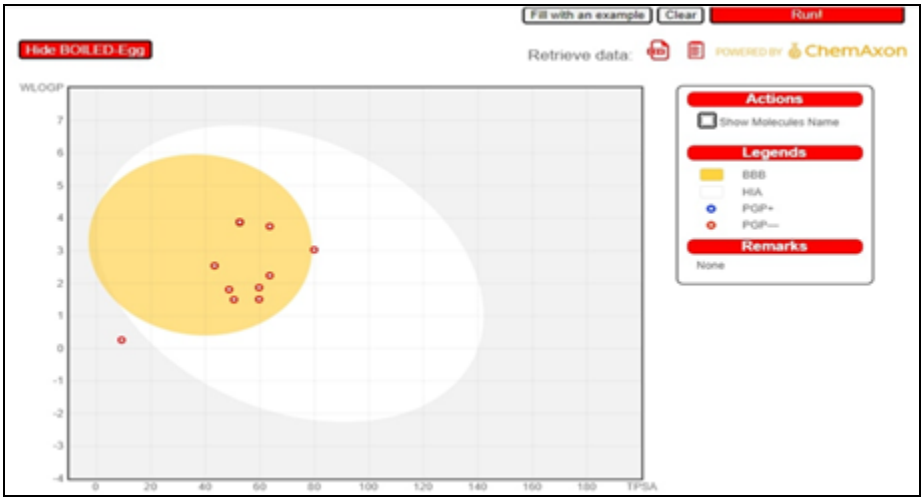

FIG. 1: BOILED-EGG F OR INTUITIVE EVALUATION OF PASSIVE GASTROINTESTINAL ABSORPTION (HIA) AND BRAIN PENETRATION (BBB) IN THE FUNCTION OF THE POSITION OF THE MOLECULES IN THE WLOGP-VERSUS-TPSA REFERENTIAL OF THE COUMARINS OF *AEGLE MARMELOS* L.

RESULT AND DISCUSSION: The most important and most difficult step in drug discovery and development is carrying out DMPK (drug metabolism and pharmacokinetics) studies, often referred to as ADME.A total of 25 potent phytoconstituents of Aegle marmelos were analyzed using the SwissADME web tool i.e., umbelliferon, scopoletin, scoparone, xanthotoxol, marmesin, psoralen, imperatorin, alloimperatorin, marmin to study general characteristics, physiochemical properties, lipophilicity, water solubility, pharmacokinetics parameters, drug-likeness, and medicinal chemistry properties.

TABLE 1: THE PUBCHEM IDS OF EACH SMALL MOLECULE, SPECIFY PHYSIOLOGICAL PROPERTIES

Sr. no.	PubChem Id	Phytoconstituent name	Canonical SMILES	Molecular Weight (g/mol)
1	5281426	Umbelliferon	OC1=CC2=C(C=C1) C=CC(=O) O2	162.14
2	5280460	Scopoletin	COC1=C(O)C=C2OC(=O) C=CC2=C1	192.17
3	8417	Scoparone	COC1=CC2=C(C=CC(=O) O2) C=C1OC	206.19
4	65090	Xanthotoxol	OC1=C2OC(=O) C=CC2=CC2=C1OC=C2	202.16
5	334704	Marmesin	CC(C)(C1CC2=C(O1) C=C3C(=C2) C=CC(=O) O3) O	246.26

6	6199	Psoralen	C1=CC(=O) OC2=CC3=C(C=CO3) C=C21	186.16
7	10212	Imperatorin	CC(=CCOC1=C2C(=CC3=C1OC=C3) C=CC(=O) O2) C	270.28
8	69052	Alloimperatorin	CC(=CCC1C2CCC(=O) OC2C(C2C1CCO2) O) C	270.28
9	6450230	Marmin	CC(=CCOC1=CC2=C(C=C1) C=CC(=O) O2) CCC(C(C)(C) O) O	332.39

The most important and difficult step in drug discovery and development is carrying out DMPK (drug metabolism and pharmacokinetics) studies, often referred to as ADME. In the Lipophilicity property, the rule says, "The larger the log P value greater the lipophilicity".

As shown in **Table 2**, XLOGP3 value of selected coumarin is in the range of -0.7 to + 5.0 size which indicates that they are lipophilic compounds, Log S (ESOL), Log S (Ali), and Log S (SILICOS-IT) values of umbelliferon, scopoletin, scoparone, xanthotoxol, and marmesin shows that they are soluble in water whereas remaining six compounds *viz*. psoralen, imperatorin, marmelosin, alloimperatorin, marmelide, and marmin are moderately soluble in water [6]. All other coumarins show good GI absorption whereas marmin shows no penetration at BBB and the rest of the coumarins show penetration at BBB.

All selected coumarins were within the limit of Lipinski, Veber, and Egan filters which makes them have promising drug-likeness properties. The medicinal chemistry properties of coumarins represent that all compounds are active which can be utilized as a starting point for further exploration in the PAINS model.

TABLE 2: LIPOPHILICITY OF SELECTED COUMARINS

Sr. no.	Phytoconstituent name	Log Po/w (iLOGP)	Log Po/w (XLOGP3)	Log Po/w (WLOGP)	Log Po/w (MLOGP)	Log Po/w (SILICOS-IT)	Consensus Log Po/w
1	Umbelliferone	1.44	1.58	1.5	1.04	1.97	1.51
2	Scopoletin	1.86	1.53	1.51	0.76	1.94	1.52
3	Scoparone	2.23	1.71	1.81	1.05	2.42	1.84
4	Xanthotoxol	1.69	1.67	2.24	0.89	2.4	1.78
5	Marmesin	2.55	1.91	1.87	1.6	2.78	2.14
6	Psoralen	2.01	1.67	2.54	1.48	2.91	2.12
7	Imperatorin	3.05	3.5	3.88	2.14	3.99	3.31
8	Alloimperatorin	2.62	3.88	3.75	2.14	3.97	3.27
9	Marmin	3.09	2.81	3.03	1.91	3.78	2.92

From the boiled egg model **Fig. 1**, it has been found that all selected coumarins found in yellow regions (i.e., regions of high BBB absorption and high GI absorption) except marmin which is located on the boundary of the white and yellow region, so it is high in GI absorption, and it has no BBB permeation property. From selected coumarins, only marmesin and marmin are predicted to be orally bioavailable.

TABLE 3: SOLUBILITY OF SELECTED COUMARINS *S= SOLUBLE AND MS= MODERATELY SOLUBLE

Sr. no.	Phytoconstituent name	Log S (ESOL)	Solubility		Class	Log S (Ali)	Solubility		Class	Log S(Silicos-IT)	Solubility		Class
			mg/ml	mol/l			mg/ml	mol/l			mg/ml	mol/l	
	Umbelliferon	-2.46	5.66e-01	3.49e-03	S*	-2.25	9.12e-01	5.62e-03	S*	-3.03	1.53e-01	9.42e-04	S*
	Scopoletin	-2.46	6.70e-01	3.48e-03		-2.39	7.79e-01	4.06e-03		-3.17	1.31e-01	6.81e-04	
	Scoparone	-2.56	5.72e-01	2.77e-03		-2.35	9.26e-01	4.49e-03		-3.87	2.76e-02	1.34e-04	
	Xanthotoxol	-2.79	2.99e-01	1.63e-03		-2.62	4.86e-01	2.40e-03		-3.93	2.37e-02	1.17e-04	
	Marmesin	-2.92	2.99e-01	1.22e-03		-2.79	4.03e-01	1.64e-03		-3.93	2.92e-02	1.19e-04	
	Psoralen	-2.73	3.44e-01	1.85e-03		-2.19	6.39e-03	1.19e+00		-4.5	5.87e-03	3.16e-05	MS*
	Imperatorin	-4	2.68e-02	9.91e-05	MS*	-4.29	1.39e-02	5.16e-05	MS*	-5.51	8.33e-04	3.08e-06	
	Alloimperatorin	-4.31	1.33e-02	4.91e-05		-4.91	3.30e-03	1.22e-05		-5.2	1.73e-03	6.38e-06	
	Marmin	-3.52	1.01e-01	3.04e-04	S*	-4.15	2.38e-02	7.16e-05		-4.74	6.09e-03	1.83e-05	

While interpretation of pharmacokinetic data, all selected coumarins showed no inhibition of the isoenzymes like CYP2D6, and CYP3A4 as well as they are not good P-gp substrates. The Isoenzyme CYP1A2 was found to be inhibited by all coumarins other than marmin. It is observed that coumarin like imperatorin, marmelosin, alloimperatorin, and marmalide will inhibit the isoenzymes like CYP2C19, and CYP2C9.

TABLE 4: PHARMACOKINETICS OF SELECTED COUMARINS

Sr. no.	Phytoconstituent name	GI Absorption	BBB Permeant	P-gp Substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (cm/s)
1	Umbelliferon	High	Yes	No	Yes	No	No	No	No	-6.17
2	Scopoletin	High	Yes	No	Yes	No	No	No	No	-6.39
3	Scoparone	High	Yes	No	Yes	No	No	No	No	-6.34
4	Xanthotoxol	High	Yes	No	Yes	No	No	No	No	-6.35
5	Marmesin	High	Yes	No	Yes	No	No	No	No	-6.45
6	Psoralen	High	Yes	No	Yes	No	No	No	No	-6.25
7	Imperatorin	High	Yes	No	Yes	Yes	Yes	No	No	-5.46
8	Alloimperatorin	High	Yes	No	Yes	Yes	Yes	No	No	-5.19
9	Marmin	High	No	No	No	No	No	No	No	-6.33

TABLE 5: DRUG LIKENESS PROPERTY

Sr. no.	Phytoconstituent name	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
1	Umbelliferon	Yes	No; 1 violation: #atoms<20	Yes	Yes	No; 1 violation: MW<200	0.55
2	Scopoletin	Yes	Yes	Yes	Yes		0.55
3	Scoparone	Yes	Yes	Yes	Yes	Yes	0.55
4	Xanthotoxol	Yes	Yes	Yes	Yes	Yes	0.55
5	Marmesin	Yes	Yes	Yes	Yes	Yes	0.55
6	Psoralen	Yes	Yes	Yes	Yes	No; 1 violation: MW<200	0.55
7	Imperatorin	Yes	Yes	Yes	Yes	Yes	0.55
8	Alloimperatorin	Yes	Yes	Yes	Yes	Yes	0.55
9	Marmin	Yes	Yes	Yes	Yes	Yes	0.55

In the Brenk model, imperatorin, marmelosin, marmalade and marmin are four compounds found to be good lead compounds according to lead likeness score. Overall synthetic accessibility score shows the ease of compound synthesis on a scale of 1 (very easy) to 10 (very difficult). So, it is found that all selected coumarins have synthetic accessibility scores between 2.56 – 4.02 which indicates they are moderate to synthesize.

TABLE 6: MEDICINAL CHEMISTRY PROPERTIES OF SELECTED COUMARINS

Sr. no.	Phytoconstituent name	Violations		Lead Likeness	Synthetic Accessibility
		PAINS	Brenk		
1	Umbelliferon	0	1 alert: coumarin	No; 1 violation: MW<250	2.56
2	Scopoletin				2.62
3	Scoparone				2.77
4	Xanthotoxol				2.94
5	Marmesin				3.35
6	Psoralen				3.06
7	Imperatorin		2 alerts: coumarin, isolated alkene	Yes	3.22
8	Alloimperatorin			No; 1 violation: XLOGP3>3.5	3.2
9	Marmin			Yes	4.02

Nowadays, due to continuous advancement in computer science, computer-based drug designing has been employed very widely in the prediction of ADMET properties of the drugs which leads to budding stage drug discovery. The rationale behind these *in-silico* approaches is due to the relatively lower cost time factor involved compared to standard ADMET profiling. As an example, it will take a minute in an *in-silico* model to screen 20,000 or more molecules but it will take 20 weeks in the "wet" laboratory to do the same exercise. A host of these theoretical models have been implemented in several software programs currently available for drug discovery protocols. Even though some of the predictions are often disappointing, the software tools currently used to predict the ADMET

properties of potential drug candidates often make use of quantitative structure-activity relationships, QSAR. In the present study, we used SwissADME, a free online software tool for the users to evaluate the ADME properties of individual phytoconstituents present in *Aegle marmelos*.

CONCLUSION: Natural coumarins have enormous power as a natural magical remedy for a wide range of diseases, they are present in high concentrations in several dietary plant species like cinnamon, peanut oil, olive oil, *etc*. The use of computer-based techniques in drug discovery and development is widely appreciated in terms of implementation, time, and money. This data supports conducting pre-clinical and clinical trials of bael fruit-based products such as squash, jelly, candy, *etc*. which will increase their value as food and nutraceutical products by a huge margin. This information can be further used as a primary tool for evaluating the biological and pharmacological properties of the plant.

ACKNOWLEDGMENT: The authors would like to thank Dr. Deepali Jagdale for her constant support in understanding data generated by software. We are thankful to Akshada Kadam, Shrutika Patil, Pratiksha Mulik, and Mayuri Ambawale who helped us to create data of hundreds of phytoconstituents.

CONFLICT OF INTEREST: No conflict of interest between all authors.

REFERENCES:

1. Bhar K, Mondal S and Suresh P: An eye-catching review of *Aegle marmelos* L. (Golden Apple). Pharmacognosy Journal 2019; 11(2): 207–224.
2. Pathirana CK, Madhujith T and Eeswara J: Bael (*Aegle marmelos* L. Corrêa), a medicinal tree with immense economic potential. Advances in Agriculture 2020; 1-13.
3. Swarnkar R, Singh D, Choudhary A, Anand S, Rathore A, and Jediya HK: Pharmacological properties of *Aegle marmelos*: a review. International Journal of Current Microbiology and Applied Sciences 2019; 8(05): 1600–1608.
4. Mahanthesh MT, Ranjith D, Raghavendra Y, Jyothi R, Narappa G and Ravi MV: Swiss ADME prediction of phytochemicals present in *Butea monosperma* (Lam.) Taub Journal Pharmacognosy Phytochemistry 2020; 9(3): 1799–1809.
5. Sarkar T, Salauddin M and Chakraborty R: In-depth pharmacological and nutritional properties of bael (*Aegle marmelos*): a critical review. Journal of Agriculture and Food Research 2020; 2: 100081.
6. Pathirana CK, Madhujith T and Eeswara J: Bael (*Aegle marmelos* L. Corrêa), a medicinal tree with immense economic potential. Advance Agriculture 2020; 1-13.
7. Daina A, Michielin O and Zoete V: SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of small molecules. Science Report 2017; 7(1): 1-13.
8. Helena D, Janse van Rensburg, David D. N'Da and Keisuke Suganuma: *In-vitro* and *In-vivo* Trypanocidal Efficacy of Nitrofuryl- and Nitrothienylazines. ACS Omega 2023; 8(45): 43088-43098.
9. Redka M, Baumgart S, Kupczyk D, Kosmalski T and Studzińska R: Lipophilic Studies and *In-silico* ADME Profiling of Biologically Active 2-Aminothiazol-4(5H)-one Derivatives. International Journal of Molecular Sciences 2023; 24(15): 12230.
10. Tafreshi NK, Kil H, Pandya DN, Tichacek CJ, Doligalski ML, Budzevich MM, Delva NC, Langsen ML, Vallas JA, Boulware DC, Engelman RW, Gage KL, Moros EG, Wadas TJ, McLaughlin ML and Morse DL: Lipophilicity determines routes of uptake and clearance, and toxicity of an alpha-particle-emitting peptide receptor radiotherapy. ACS Pharmacol Transl Sci 2021; 4(2): 953-965.
11. Chi Xu, Zunhui Ke, Chuandong Liu, Zhihao Wang, Denghui Liu, Lei Zhang, Jingning Wang, Wenjun He, Zhimeng Xu, Yanqing Li, Yanan Yang, Zhaowei Huang, Panjing Lv, Xin Wang, Dali Han, Yan Li, Nan Qiao and Bing Liu Systemic: *In-silico* screening in drug discovery for coronavirus disease (covid-19) with an online interactive web server. Journal of Chemical Information and Modeling 2020; 60(12): 5735-5745.
12. Bultum LE, Tolossa GB and Kim G: *In-silico* activity and ADMET profiling of phytochemicals from *Ethiopian indigenous* aloes using pharmacophore models. Sci Rep 2022; 12: 22221.
13. Mahmudul Hasan, Zidan Khan, Mohammed Salahuddin Chowdhury, Md Arif Khan, Mohammad Ali Moni and Md Habibur Rahman: *In-silico* molecular docking and ADME/T analysis of Quercetin compound with its evaluation of broad-spectrum therapeutic potential against particular diseases, Informatics in Medicine Unlocked 2022; 29: 100894.
14. Reiko W, Tsuyoshi E, Rikiya O, Masataka K, Hitoshi K, Hiroshi K, Yayoi N-Kitatani and Kenji M: Development of an *In-silico* prediction model for p-glycoprotein efflux potential in brain capillary endothelial cells toward the prediction of brain penetration. Journal of Medicinal Chemistry 2021; 64(5): 2725-2738
15. Nagamalla S, Saketha P, Noota D, P Mudavath SJ, Pachava A, Neelima K and S Anuradha Bai: Swiss ADME properties screening of the phytochemical compounds present in *Bauhinia acuminata*. Journal of Pharmacognosy and Phytochemistry 2021; 10(4): 411-419.
16. Zafar F, Gupta A, Thangavel K, Khatana K, Sani AA, Ghosal A, Tandon P and Nishat N: Physicochemical and Pharmacokinetic Analysis of Anacardic Acid Derivatives. ACS Omega 2020; 5(11): 6021-6030
17. Daina A, Michielin O and Zoete V: SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 2017; 7: 42717.
18. Mahanthesh MT, Ranjith D, Raghavendra Y, Jyothi R, Narappa G and Ravi MV: Swiss ADME prediction of phytochemicals present in *Butea monosperma* (Lam.) Taub. Journal of Pharmacognosy and Phytochemistry 2020; 9(3): 1799–1809.

19. Sravika N, Priya S, Divya N, Jyotsna PMS, Anusha P, Kudumula N and Bai SA: Swiss ADME properties screening of the phytochemical compounds present in *Bauhinia acuminata*. Journal of Pharmacognosy and Phytochemistry 2021; 10(4): 411–419.
20. Riyadi PH, Romadhon Sari ID, Kurniasih RA, Agustini TW, Swastawati F, Herawati VE and Tanod WA: SwissADME predictions of pharmacokinetics and drug-likeness properties of small molecules present in *Spirulina platensis*. IOP Conference Series: Earth and Environmental Science 2021; 890(1): 012021, 1-13.
21. Yenumala Vamshidhar Reddy: Swiss ADME predictions of phytoconstituents present in *Ocimum sanctum* Linn. J of Pharmacognosy and Phytochemistry 2023; 12(5): 17-26
22. Maliehe TS, Tsilo PH and Shandu JS: Computational Evaluation of ADMET Properties and Bioactive Score of Compounds from *Encephalartos ferox*. Pharmacognosy Journal 2020; 12(6): 1357-1362.
23. NaAllah A, Ayipo YO, Komolafe DI, Solihu S, Bamidele B, Alabi MA, Balogun A, Abdulazeez AT and Mordi MN: Phytochemical screening and *in-silico* pharmacological profiling of ethanolic extract of *Aframomum melegueta* for prostate carcinoma. Journal of Applied Pharmaceutical Science 2021; 11(07): 132–145.
24. Qazi S, Das S and Khuntia BK: *In-silico* molecular docking and molecular dynamic simulation analysis of phytochemicals from Indian foods as potential inhibitors of SARS-CoV-2 RdRp and 3CLpro. Natural Product Communications 2021; 16(9).
25. Ononamadu CJ and Ibrahim A: Molecular docking and prediction of ADME/drug-likeness properties of potentially active antidiabetic compounds isolated from aqueous-methanol extracts of *Gymnema Sylvestre* and *Combretum micranthum*. Bio Technologia (Pozn) 2021; 102(1): 85-99.

How to cite this article:
Agrawal SA, Dhamne SR and Shinde PS: *In-silico* pharmacokinetic properties prediction of coumarins present in *Aegle marmelos* L. Int J Pharm Sci & Res 2024; 15(3): 800-07. doi: 10.13040/IJPSR.0975-8232.15(3). 800-07.