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Swiss ADME predictions of pharmacokinetics and drug-likeness properties of secondary metabolites present in *Trigonella foenum-graecum*

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Abstract
Contemporary pharmaceutical techniques may be complemented by the use of plants, leading to a global increase in the analysis of traditional medicinal plants. With the advancement of computer science, in silico methods such as network analysis and screening have become widely utilized to provide insight into the pharmacological mechanisms of action of these plants. Through the implementation of network pharmacology, insilico screening, and pharmacokinetic screening, the number of active substances among the candidates can be increased, and the therapeutic plant's mode of action can be revealed. The present study focuses on the utilization of the Swiss ADME insilico ADME tool for the pharmacological and pharmacogenetic characterization of secondary metabolites present in *Trigonella foenum-graecum*. The results of these investigations may be utilized by researchers to conduct *in vitro* and *in vivo* studies, thereby uncovering the pharmacological mechanisms of action of traditional medicinal herbs.

Keywords: Medicinal plant, Fenugreek (*Trigonella foenum-graecum*), secondary metabolites, pharmacological properties, Swiss ADME

1. Introduction
Ancient civilizations possessed extensive knowledge regarding the utilization of medicinal plants as herbal remedies. In less developed nations, over 80% of the population relies on traditional medicine, with herbs serving as essential resources for sustenance, shelter, clothing, flavouring, fragrance, and medicinal purposes (Divya and Mini, 2011; Manoj Kumar Mishra, 2016; Gurib-Fakim, 2006; and Brijesh & Madhusudan, 2015) [12, 31, 20, 3]. The exploration of medicinal plants for drug discovery has yielded significant advancements and crucial insights into various pharmacological targets, including the treatment of diseases such as cancer, malaria, cardiovascular diseases, diabetes, and neurological disorders. Ayurveda, an ancient Indian medical system, recommends numerous medicinal plants for the treatment of various ailments. One such plant is *Trigonella foenum-graecum* L., commonly known as fenugreek or methi in Hindi, which has been utilized for its medicinal properties. Fenugreek is a leguminous, herbaceous, semi-arid crop belonging to the Fabaceae family known for its production of complex chemical compounds. Plant secondary metabolites, a diverse group of organic compounds with low molecular weight, are synthesized by plants to facilitate interactions with the biotic environment and serve as defence mechanisms. These secondary metabolites have demonstrated promising therapeutic value and are widely employed in medical practices. The specific uses of *Trigonella foenum-graecum* L have been documented in various studies. These include its antioxidant activity (Dixit P *et al.*, 2005) [13], anti-diabetic activity (Shani J *et al.*,1974) [39], anti-cancer properties (Kaviarasan S, Anuradha CV, 2007) [25], cholesterol-lowering effect (Stark A, Madar Z,1993) [41], anti-bacterial activity (Dash BK *et al.*, 2011) [9], improvement of digestion (Platel K, Srinivasan K, 2000), gastroprotection (Platel K, Srinivasan K, 2000) [37], treatment of obesity (Handa T *et al.*, 2005) [21], anti-inflammatory action (Sharififara F.*et al.*,2009) [40], and anti-hypertensive effect (Talpur N.*et al.*,2005) [42]. Through the establishment of a prompt and expedient pathway for predicting the chemical constituents and conducting *in vivo* and *in vitro* pharmacological experiments for verification, the efficacy of evaluating the chemical activities of medicinal plants can be significantly enhanced (Yi F *et al.*, 2016) [48]. One valuable tool for this purpose is the Swiss ADME website, which facilitates the computation of physicochemical descriptors and the prediction of ADME parameters, pharmacokinetic properties, drug-like nature, and medicinal chemistry friendliness of small molecules. In this investigation, our objective was to employ the Swiss ADME (http://www.swissadme.ch/index.php) to assess individual ADME behaviour and interpret the outcomes.

2. Materials and Methods

2.1 Swiss ADME: The Swiss ADME software, developed by the Swiss Institute of Bioinformatics, was accessed through the website www.swissadme.ch. The web server displayed the Submission page of Swiss ADME on Google, which was utilized to estimate the individual ADME behaviors of the compounds derived from *Trigonella foenum-graecum*. The input list consisted of one molecule per line, with each molecule defined by the simplified molecular input line entry system (SMILES). The results for each molecule were presented in tables, graphs, and an excel spreadsheet, as described by Egan *et al*. (2000) [14].

2.2 Structure and bioavailability radar: The first section presents the two-dimensional chemical structure with canonical SMILES. In order to assess the drug likeness of the molecules of interest, the bioavailability radar takes into consideration six physicochemical properties: lipophilicity (LIPO), size (SIZE), polarity (POLAR), insolubility (INSOLU), insaturation (INSATU), and flexibility (FLEX). The specific criteria for each property are as follows: lipophilicity should have an XLOGP3 value between -0.7 and +5.0, size should have a molecular weight (MW) between 150 and 500 g/mol, polarity should have a topological polar surface area (TPSA) between 20 and 130 0A2, solubility should have a logarithm of the solubility (log S) not exceeding 6, saturation should have a fraction of carbons in sp3 hybridization not less than 0.25, and flexibility should have no more than 9 rotatable bonds. These guidelines were established by Daina *et al*. in 2017 [7].

2.3 Physicochemical properties: This section encompasses the molecular and physicochemical characteristics of the compound, including the molecular formula, molecular weight, number of heavy atoms, number of aromatic heavy atoms, fraction csp3, number of rotatable bonds, number of H-bond acceptors, number of H-bond donors, molar refractivity, and TPSA. These values were calculated using open babel version 2.3.0 (O'Boyle, 2011 & Daina *et al*., 2017) [35, 7].

2.4 Lipophilicity: Lipophilicity is a crucial parameter in drug discovery and design (Leeson & Springthorpe, 2007) [27] because it complements the most informative and successful physicochemical property in medicinal chemistry (Testa *et al*., 2000) [44]. It is experimentally demonstrated as partition coefficients (log P) or as distribution coefficients (log D). Log P represents the partition equilibrium of an un-ionized solute between water and an immiscible organic solvent. Higher log P values correspond to greater lipophilicity (Arnott & Planey, 2012) [1]. To evaluate the lipophilicity of a compound, Swiss ADME provides five freely available models: XLOGP3, WLOGP, MLOGP, SILICOS-IT, and iLOGP. XLOGP3 is an atomistic approach that includes corrective factors and a knowledge-based library (Cheng, 2007) [4]. WLOGP is based on a purely atomistic method using a fragmental system (Wildman and Crippen, 1999) [46]. MLOGP is a topological method based on a linear relationship with 13 implemented molecular descriptors (Moriguchi *et al*., 1992 & Moriguchi *et al*., 1994) [32, 33]. SILICOS-IT is a hybrid method based on 27 fragments and 7 topological descriptors. iLOGP is a physics-based method that relies on the free energies of solvation in n-octanol and water calculated by the generalized-born and solvent accessible surface area (GB/SA) model. Consensus log P o/w is the arithmetic mean of the values predicted by the five proposed methods (Daina *et al*., 2017) [7].

2.5 Solubility: The solubility of a compound is greatly influenced by the solvent used, ambient temperature, and pressure. The extent of solubility is measured as the saturation concentration, which is the point at which adding more solute does not increase its concentration in the solution (Lachman *et al*., 1986 & Savjani *et al*., 2012) [26,]. A drug is considered highly soluble when the highest dose strength can dissolve in 250 mL or less of aqueous media within the pH range of 1 to 7.5. Swiss ADME employs two topological approaches to predict water solubility. The first approach involves the application of the ESOL model, which categorizes solubility into classes based on the logarithmic scale (Insoluble<-10, Poorly soluble<-6, Moderately soluble<-4, Soluble<-2, Very soluble<0). Both approaches differ from the fundamental general solubility equation (Yalkowsky & Valvani, 1980) [47] as they do not consider the melting point parameter. However, there is a strong linear correlation between the predicted and experimental values (R2=0.69 and 0.81 respectively). The third predictor in Swiss ADME was developed by SILICOS-IT, which also categorizes solubility into classes based on the logarithmic scale (Insoluble<-10, Poorly soluble<-6, Moderately soluble<-4, Soluble<-2, Very soluble<0), with the linear coefficient being corrected by molecular weight (R2=0.75). All predicted values are presented as the decimal logarithm of the molar solubility in water (log S). Swiss ADME also provides solubility values in mol/l and mg/ml, along with qualitative solubility classes.

2.6 Pharmacokinetics: The distinction lies within a region of favorable properties for gastrointestinal (GI) absorption on a graph depicting two computed descriptors: ALOGP versus PSA, respectively. The region that is most populated by molecules that are well absorbed is elliptical in shape and has been named the Egan egg. This egg is utilized to evaluate the predictive capability of the model for passive GI absorption and prediction for brain access through passive diffusion, ultimately resulting in the creation of the BOILED-Egg (Brain or Intestina L Estimate D permeation predictive model). The BOILED-Egg model offers a rapid, spontaneous, efficient, yet robust method for forecasting passive GI absorption, which is beneficial for drug discovery and development (Di *et al*., 2012 & Brito-Sanchez *et al*., 2015) [10]. The white region represents the space occupied by molecules with a grater extent of absorption by the GI tract, while the yellow region (yolk) represents the space with the highest probability of permeating to the brain (Daina *et al*., 2017, Daina *et al*., 2016 & Montanari and Ecker, 2015) [7]. Cytochrome p450 (CYP) isoenzymes biotransform more than 50-90% of therapeutic molecules through its five major isoforms (CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6). P-gp is widely distributed in the intestinal epithelium and functions to pump xenobiotics back into the intestinal lumen and from the capillary endothelial cells of the brain back into the capillaries (Ogu & Maxa, 2000 and Ndombera *et al*., 2019) [36, 34]. Swiss ADME employs the support vector machine algorithm (SVM) for datasets consisting of known substrates/non-substrates or inhibitors/non-inhibitors for binary classification. The resulting molecule will be classified as either "Yes" or "No" depending on whether it is expected to be a substrate for both P-gp and CYP, respectively. The SVM model for P-gp substrate was constructed using 1033 molecules in the training set and tested on 415 molecules in the test set, with a

10-fold cross-validation accuracy of 0.72 and an area under the curve (AUC) of 0.77. The external accuracy and AUCAUC=0.94 respectively. The Support Vector Machine (SVM) models for the inhibition of Cytochrome P-450 1A2, 2C19, 2C9, 2D6, and 3A4 molecules were constructed using different training and test sets. For the Cytochrome P-450 1A2 inhibitor molecule, the SVM model was built on a training set of 9145 molecules and tested on 3000 molecules. The 10-fold cross-validation yielded an accuracy (ACC) of 0.83 and an area under the curve (AUC) of 0.90. The external validation resulted in an ACC of 0.84 and an AUC of 0.91. Similarly, for the Cytochrome P-450 2C19 inhibitor molecule, the SVM model was constructed using a training set of 9272 molecules and tested on 3000 molecules. The 10-fold cross-validation showed an ACC of 0.80 and an AUC of 0.86. The external validation exhibited an ACC of 0.80 and an AUC of 0.87. For the Cytochrome P-450 2C9 inhibitor molecule, the SVM model was developed using a training set of 5940 molecules and tested on 2075 molecules. The 10-fold cross-validation yielded an ACC of 0.78 and an AUC of 0.85. The external validation resulted in an ACC of 0.71 and an AUC of 0.81. The SVM model for the Cytochrome P-450 2D6 inhibitor molecule was constructed using a training set of 3664 molecules and tested on 1068 molecules. The 10-fold cross-validation showed an ACC of 0.79 and an AUC of 0.85. The external validation exhibited an ACC of 0.81 and an AUC of 0.87. Lastly, for the Cytochrome P-450 3A4 inhibitor molecule, the SVM model was built on a training set of 7518 molecules and tested on 2579 molecules. The 10-fold cross-validation yielded an ACC of 0.77 and an AUC of 0.85. The external validation resulted in an ACC of 0.78 and an AUC of 0.86.

2.8 Medicinal chemistry: The objective of this section is to support medicinal chemists in their daily efforts to discover new drugs. PAINS (Pan Assay Interference Compounds or frequent hitters or promiscuous compounds) are molecules that exhibit strong responses in assays regardless of the protein targets. These compounds have been found to be active in various assays, making them potential starting points for further investigation. SwissADME issues warnings if such moieties are present in the molecule being evaluated (Baell & Holloway, 2010) [2]. In another approach, Brenk focuses on compounds that are smaller and less hydrophobic, rather than those defined by "Lipinski's rule of 5," in order to expand opportunities for lead optimization. This involves excluding compounds with potentially mutagenic, reactive, and unfavorable groups such as nitro groups, sulfates, phosphates, 2-halopyridines, and thiols. The Brenk model restricts the ClogP/ClogD values to between 0 and 4, the number of hydrogen-bond donors to fewer than 4, the number of hydrogen-bond acceptors to fewer than 7, and the number of heavy atoms to between 10 and 27. Additionally, only compounds with limited complexity, defined as having fewer than 8 rotatable bonds, fewer than 5 ring systems, and no ring systems with more than 2 fused rings, are considered medicinal (Brenk *et al*., 2008). The concept of lead likeness is designed to provide leads with high affinity in high throughput screening (HTS), allowing for the exploration of additional interactions in the lead optimization phase. Leads undergo chemical modifications that are likely to reduce their size and increase their lipophilicity, making them less hydrophobic than drug-like molecules. Lead optimization is typically carried out using a rule-based method, with molecules having a molecular weight between 100 and 350 Da and a ClogP between 1 and 3.0 being considered superior to drug-like compounds and therefore lead-like (Hann & Keseru, 2012 and Teague *et al*., 1999) [22, 43].

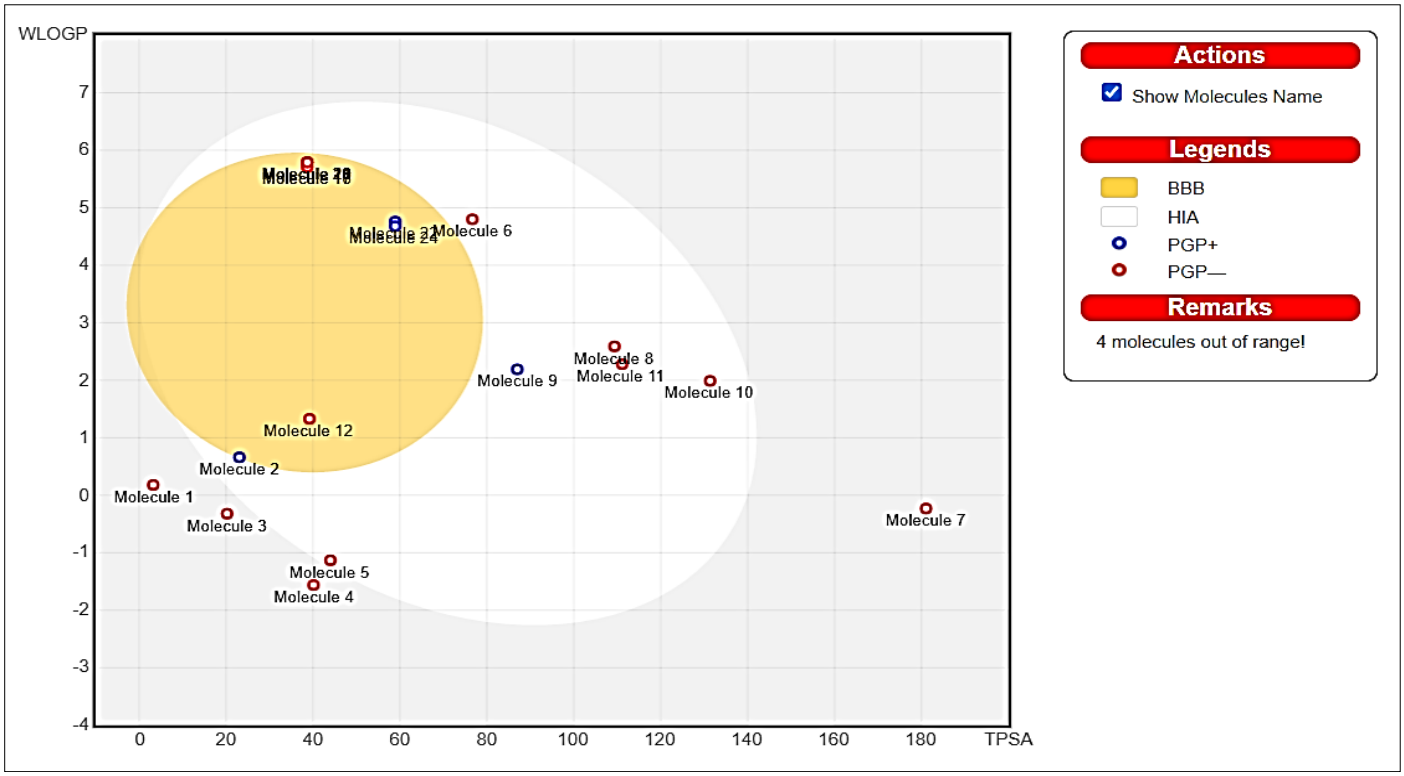

Fig 1: Boiled Egg Model of the Phytoconstituents of *Trigonella foenum-graecum* L

3. Results

Table 1: General Characteristics of Phytoconstituents of *Trigonella foenum-graecum* L. (Fenugreek).

Sr. No	Small molecule	Pub chem ID	Molecular formula	Canonical SMILES	Molecular weight (in g/mol)
1	Trimethylamine	1146	C3H9N	CN(C)C	59.11
2	Neurine	10042	C5H13NO	C[N+](C)(C)C=C.[OH-]	103.16
3	Choline	305	C5H14NO	C[N+](C)(C)CCO	104.17
4	Betaine	247	C5H11NO2	C[N+] (C)(C) CC(=O) [O-]	117.15
5	Trigonelline	5570	C7H7NO2	C[N+]1=CC=CC(=C1)C(=O)[O-]	137.14
6	Carpaine	442630	C28H50N2O4	CC1C2CCC(N1) CCCCCCCC(=O) OC3CCC(CCCCCCCC(=O)O2)NC3C	478.7
7	Vitexin	5280441	C21H20O10	C1=CC(=CC=C1C2=CC(=O) C3=C(O2) C(=C(C=C3O) O)C4C(C(C(C(O4)CO)O)O)O)O)O	432.4
8	Tricin	5281702	C17H14O7	COC1=CC(=CC(=C1O)OC)C2=CC(=O)C3=C(C=C(C=C3O2)O)O	330.29
9	Naringenin	439246	C15H12O5	C1C(OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O	272.25
10	Quercetin	5280343	C15H10O7	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O)O	302.23
11	Luteolin	5280445	C15H10O6	C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O	286.24
12	Gentianine	354616	C10H9NO2	C=CC1=CN=CC2=C1CCOC2=O	175.18
13	Graecunins	156783	C51H82O22	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CC=C6C5(CCC(C6)OC7C(C(C(C(O7)COC8C(C(C(C(O8)C)O)O)OC9C(C(C(C(O9)CO)O C2C(C(C(C(O2)CO)O)O)O)O)O)O)O)O)C)C)C)OC1	1047.2
14	Fenugreekine	444170	C21H27N7O14P2	C1=CC(=NC(=C1)C(=O)N)C2C(C(C(O2)COP(=O)(O)OP(=O)(O)OCC3C(C(C(O3)N4C=NC5=C(N=CN=C54)N)O)O)O)O	663.4
16	Trigofoenosides	10440782	C45H74O18	CC1C2C(CC3C2(CCC4C3CC=C5C4(CCC(C5)OC6C(C(C(C(O6)CO)O)O)OC7C(C(C(C(O7)C)O)O)O)C)C)OC1(CCC(C)COC8C(C(C(C(O8)CO)O)O)O)O)O	903.1
17	Yamogenin	441900	C27H42O3	CC1CCC2(C(C3C(O2) CC4C3(CCC5C4CC=C6C5(CCC(C6) O)C)C)C)OC1	414.6
18	Diosgenin	99474	C27H42O3	CC1CCC2(C(C3C(O2) CC4C3(CCC5C4CC=C6C5(CCC(C6)O)C)C)C)OC1	414.6
19	Smilagenin	91439	C27H44O3	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CCC6C5(CCC(C6)O)C)C)C)OC1	416.6
20	Sarasapogenin	92095	C27H44O3	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CCC6C5(CCC(C6)O)C)C)C)OC1	416.6
21	Trigogenin	99516	C27H44O3	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CCC6C5(CCC(C6)O)C)C)C)OC1	416.6
22	Neotigogenine	12304433	C27H44O3	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CCC6C5(CCC(C6)O)C)C)C)OC1	416.6
23	Gitogenin	441887	C27H44O4	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CCC6C5(CC(C(C6)O)O)C)C)C)OC1	432.6
24	Saponarin	441381	C27H30O15	C1=CC(=CC=C1C2=CC(=O)C3=C(C(=C(C=C3O2)OC4C(C(C(C(O4)CO)O)O)O)C5C(C(C(C(O5)CO)O)O)O)O)O	594.5
25	Yuccagenin	3083608	C27H42O4	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CC=C6C5(CC(C(C6)O)O)C)C)C)OC1	430.6

Table 2: Lipophilicity of the Phytoconstituents of *Trigonella foenum-graecum* L. (Fenugreek).

Sr. No.	Small molecule	Ilogp	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log $P_{0/w}$
1	Trimethylamine	1.56	0.26	0.18	0.29	-0.58	0.34
2	Neurine	-8.01	0.30	0.66	-3.60	-0.10	-2.15
3	Choline	-2.14	-0.40	-0.32	-3.46	-0.57	-1.38
4	Betain	-2.19	-0.13	-1.56	-3.67	-0.91	-01.69
5	Trigonelline	-3.11	0.51	-1.13	0.33	0.36	-0.61
6	Carpain	4.77	6.29	4.80	3.75	3.63	4.65
7	Vitexin	1.38	0.21	-0.23	-2.02	0.33	-0.07
8	Tricin	2.58	3.07	2.59	-0.07	2.59	2.15

9	Naringenin	1.75	2.52	2.19	0.71	2.05	1.84
10	Quercetin	1.63	1.54	1.99	-0.56	1.54	1.23
11	Luteolin	1.86	2.53	2.28	-0.03	2.03	1.73
12	Gentianine	1.65	1.51	1.33	1.20	2.67	1.67
13	Graecunins	3.78	-1.31	-1.96	-3.68	-3.58	-1.35
14	Fenugreekine	0.24	-5.92	-3.01	-5.33	-5.62	-3.93
15	Trigofoenosides	4.66	0.39	-0.83	-2.18	-1.55	0.10
16	Yamogenin	4.41	5.67	5.71	4.94	4.29	5.00
17	Diosgenin	4.41	5.67	5.71	4.94	4.29	5.00
18	Smilagenin	4.40	6.49	5.79	5.08	4.30	5.21
19	Sarasapogenin	4.40	6.49	5.79	5.08	4.30	5.21
20	Tigogenin	4.40	6.49	5.79	5.08	4.40	5.21
21	Neotigogenine	4.40	6.49	5.79	5.08	4.30	5.21
22	Gitogenin	4.19	5.52	4.76	4.23	3.40	4.42
23	Saponarin	1.99	-1.60	-2.76	-4.10	-1.79	-1.65
24	Yuccagenin	3.91	4.70	4.68	4.09	3.39	4.15

Table 3: Water solubility of the phytoconstituents of *Trigonella foenum-graecum L*. (Fenugreek).

Small molecule	ESOL				Ali				SILICOS-IT			
	LogS (ESOL)	Solubility		Class	Log S (ESOL)	Solubility		Class	Log S (ESO)	Solubility		Class
		mg/mL	mol/L			mg/mL	mol/L			mg/mL	mol/L	
Trimethylamine	-0.37	2.52e+01	4.46e-01	Very soluble	0.11	7.63e+01	1.29e+00	Highly soluble	**-0.20**	**3.73e+01**	**6.31e-01**	**Soluble**
Neurine	-0.60	2.58e+01	2.50e-01	Very soluble	-0.35	4.64e+01	4.50e-01	Very soluble	-1.44	3.77e+00	3.66e-02	Soluble
Choline	-0.10	8.24e+01	7.91e-01	Very soluble	0.44	2.86e+02	2.75e+00	Highly soluble	-1.26	5.74e+00	5.51e-02	Soluble
Betain	-0.35	5.20e+01	4.44e-01	Very soluble	-0.26	6.45e+01	5.51e-01	Very soluble	-0.82	1.76e+01	1.50e-01	Soluble
Trigonelline	-1.39	5.59e+00	4.08e-02	Very soluble	-1.00	1.36e+01	9.89e-02	Very soluble	-0.94	1.59e+01	1.16e-01	Soluble
Carpain	-6.77	8.12e-05	1.70e-07	Poorly soluble	-7.69	9.81e-06	2.50e-08	Poorly soluble	-5.71	9.29e-04	1.94e-06	Moderately soluble
Vitexin	-2.84	6.29e-01	1.46e-03	Soluble	-3.57	1.16e-01	2.68e-04	Soluble	-2.38	1.81e+00	4.20e_03	Soluble
Tricin	-4.12	2.52e-02	7.63e-05	Moderately soluble	-5.03	3.06e-03	9.26e-06	Moderately soluble	-4.63	7.71e-03	2.33e-05	Moderately soluble
Naringenin	-3.49	8.74e-02	3.21e-04	Soluble	-3.99	2.77e-02	1.02e-04	Soluble	-3.42	1.04e-01	3.82e-04	Soluble
Quercetin	-3.16	2.11e-02	6.98e-04	Soluble	-3.91	3.74e-02	1.24e-04	Soluble	-3.24	1.73e-01	5.73e-04	Soluble
Luteolin	-3.71	5.63e-02	1.97e-04	Soluble	-4.51	8.84e-03	3.09e-05	Moderately soluble	-3.82	4.29e-02	1.50e-04	Soluble
Gentianine	-2.15	1.23e+00	7.03e-03	Soluble	-1.94	2.01e+00	1.15e-02	Very soluble	-2.93	2.07e-01	1.18e-03	Soluble
Graecunins	-4.78	1.73e-02	1.65e-05	Moderately soluble	-5.23	6.19e-03	5.91e-06	Moderately soluble	2.30	2.10e+05	2.01e+02	Soluble
Fenugreekine	0.25	1.18e+03	1.78e+00	Highly soluble	-0.69	1.35e+02	2.03e-01	Very soluble	1.20	1.05e+04	1.59e+01	Soluble
Trigofoenosides	-4.89	1.16e-02	1.28e-05	Moderately soluble	-5.99	9.33e-04	1.03e-06	Moderately soluble	0.95	8.01e+03	8.87e+06	Soluble
Yamogenin	-5.98	4.31e-04	1.04e-06	Moderately soluble	-6.25	2.35e-04	5.66e-07	Poorly soluble	-4.49	1.34e-02	3.22e-05	Moderately soluble
Diosgenin	-5.98	4.31e-04	1.04e-06	Moderately soluble	-6.25	2.35e-04	5.66e-07	Poorly soluble	-4.49	1.34e-02	3.22e-05	Moderately soluble
Smilagenin	-6.51	1.28e-04	3.08e-07	Poorly soluble	-7.10	3.32e-05	7.97e-08	Poorly soluble	-4.51	1.29e-02	3.10e-05	Moderately soluble
Sarasapogenin	-6.51	1.28e-04	3.08e-07	Poorly soluble	-7.10	3.32e-05	7.97e-08	Poorly soluble	-4.51	1.29e-02	3.10e-05	Moderately soluble
Tigogenin	-6.51	1.28e-04	3.08e-07	Poorly soluble	-7.10	3.32e-05	7.97e-08	Poorly soluble	-4.51	1.29e-02	3.10e-05	Moderately soluble
Neotigogenine	-6.51	1.28e-04	3.08e-07	Poorly soluble	-7.10	3.32e-05	7.97e-08	Poorly soluble	-4.51	1.29e-02	3.10e-05	Moderately soluble
Gitogenin	-6.00	4.33e-04	1.00e-07	Moderately soluble	-6.52	1.32e-04	3.04e-07	Poorly soluble	-3.69	8.87e-02	2.05e-04	soluble
Saponarin	-2.40	2.35 e+00	3.95 e-03	Soluble	-3.36	2.62 e-01	4.41 e-04	Soluble	-0.59	1.54 e+02	2.59 e-01	Soluble
Yuccagenin	-5.47	1.46 e-03	3.38 e-02	Moderately soluble	-5.67	9.30 e-04	2.16 e-06	Moderately soluble	-0.67	9.19 e-02	2.13 e-02	Soluble

Table 4: Pharmacokinetic Parameters of the Phytoconstituents of *Trigonella foenum-graecum* L.

Molecules	GI absorption	BBB permeant	P-Gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (cm/s)
Trimethylamine	Low	No	No	No	No	No	No	No	-6.48cm/s
Neurine	High	Yes	Yes	No	No	No	No	No	-6.72cm/s
Choline	Low	No	No	No	No	No	No	No	-7.22cm/s
Betain	Low	No	No	No	No	No	No	No	-7.11cm/s
Trigonelline	High	No	No	No	No	No	No	No	-6.77cm/s
Carpain	High	No	No	No	No	No	No	No	-4.75cm/s
Vitexin	Low	No	No	No	No	No	No	No	-8.79cm/s
Tricin	High	No	No	Yes	No	Yes	Yes	Yes	-6.14cm/s
Naringenin	High	No	Yes	Yes	No	No	No	Yes	-6.17cm/s
Quercet in	High	No	No	Yes	No	No	Yes	Yes	-7.05cm/s
Luteolin	High	No	No	Yes	No	No	Yes	Yes	-6.25cm/s
Gentianin	High	Yes	No	Yes	No	No	No	No	-6.30cm/s
Greacuni ne	Low	No	Yes	No	No	No	No	No	-13.62cm/s
Fenugreekine	Low	No	No	No	No	No	No	No	-14.55cm/s
Trigpfeonoside	Low	No	Yes	No	No	No	No	No	-11.53cm/s
Yamogenin	High	Yes	No	No	No	No	No	No	-4.80cm/s
Diosgenin	High	Yes	No	No	No	No	No	No	-4.80cm/s
Smilagenin	High	Yes	No	No	No	No	No	No	-4.23cm/s
Sarasapogenin	High	Yes	No	No	No	No	No	No	-4.23cm/s
Tigogenin	High	Yes	No	No	No	No	No	No	-4.23cm/s
NeoTigogenin	High	Yes	No	No	No	No	No	No	-4.23cm/s
Gitogenin	High	Yes	Yes	No	No	No	No	No	-5.02cm/s
Saponarin	Low	No	Yes	No	No	No	No	No	-11.06cm/s
Yaccagenin	High	Yes	Yes	No	No	No	No	No	-5.59cm/s

Table 5: Drug likeness of the Phytoconstituents of *Trigonella foenum-graecum* L

Molecules	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
Trimethylamine	Yes, 0 violation	No; 3violation, MW<160, MR<40, #atoms<20	Yes	Yes	No,3 violation, MW<200, #C<5, heteroatoms<2	0.55
Neurine	Yes, 0 violation	No: 2 violation, MW<160	Yes	Yes	No, 1 violation, MW<200	0.55
Choline	Yes, 0 violation	No:. 2 violation, MW<160, MR<40	Yes	Yes	No, 1 violation, MW<200	0.55
Betain	Yes, 0 violation	No. 4 violation, MW<160, WLOGP<0.4	Yes	Yes	No, 1 violation, MW<200	0.55
Trigonelline	Yes, 0 violation	No. 4 violation, MW<160, WLOGP<0.4	Yes	Yes	No, 1 violation, MW<200	0.55
Carpain	Yes, 0 violation	No, 2 violation MR>130	Yes	Yes	No, 1 violation XLOGP3>5	0.55
Vitexin	Yes, 1 violation	Yes	No, 1 violation: TPSA>140	No, 1 violation: TPSA>131.6	No, 2 violation: TPSA>150	0.55
Tricin	Yes, 0 violation	Yes	Yes	Yes	Yes	0.55
Naringenin	Yes, 0 violation	Yes	Yes	Yes	Yes	0.55
Quercetin	Yes, 0 violation	Yes	Yes	Yes	Yes	0.55
Luteolin	Yes, 0 violation	Yes	Yes	Yes	Yes	0.55
Gentianin	Yes, 0 violation	Yes	Yes	Yes	No, 1 violation MW <200	0.55
Greacunine	No, 3 violation: MW>500	No, 4 violations: MW>480	No, 2 violation, TPSA>140	No, 1 violation, TPSA>131.6	No,5 violation, MW>600, TPSA>150	0.17
Fenugreekine	No, 3 violations: MW>500	No, 4 violations: MW>480, WLOGP<0.4, MR>130	No, 2 violation, TPSA>140	No, 1 violation, TPSA>131.6	No,5 violation, MW>600, XLOGP 3<2, TPSA>150	0.11

Trigpfeonoside	No, 3 violations: MW>500	No, 4 violations: MW>480, WLOGP<0.4, MR>130	No, 2 violation, TPSA>140	No, 1 violation, TPSA>131.6	No,5 violation, MW>600, TPSA>150	0.17
Yamogenin	Yes, 1 violation: MLOGP>4.15	No, 2 violation: WLOGP>5.6	Yes	Yes	No, 1 violation: XLOGP3>5	0.55
Diosgenin	Yes: 1 violation: MLOGP>4.15	No: 2 violations: WLOGP >5.6	Yes	Yes	No: 1 violation XLOGP 3 > 5	0.55
Smilagenin	Yes, 1 violation: MLOGP >4.15	No: 2 violations: WLOGP>5.6	Yes	Yes	No; 1 violation: XLOGP 3>5	0.55
Sarasapogenin	Yes, 1 violation: MLOGP >4.15	No, 2 violation: WLOGP>5.6	Yes	Yes	No, 1 violation, XLOGP3>5	0.55
Tigogenin	Yes:1 violation: MLOGP>4.15	No:2 violation: WLOGP>5.6, #atoms>70	Yes	Yes	No:1 violation: XLOGP3>5	0.55
Neotigogenin	Yes:1 violation: MLOGP>4.15	No:2 violation: WLOGP>5.6, #atoms>70	Yes	Yes	No:1 violation: XLOGP3>5	0.55
Gitogenin	Yes:1 violation: MLOGP>4.15	No: 1 violation: #atoms> 70	Yes	Yes	No:1 violation: XLOGP3>5	0.55
Saponarin	No:3 violation: MW>500, NorO>10, NHorOH>5	No:4 violation: MW>480, WLOGP<-0.4, MR>130, #atoms>70	No,1 violation: TPSA > 140	No:1 violation: TPSA>131.6	No:3 violation: TPSA>150, H-acc>10, H-don>5	0.17
Yaccagenin	Yes:0 violation	No: 1 violation: #atoms> 70	Yes	Yes	Yes	0.55

Table 6: Medicinal Chemistry Properties of Phytoconstituents of *Trigonella foenum-graecum* L.

Molecules	Pains	Brenk	Leadlikeness	Synthetic accessibility
Trimethylamine	0 alert	0 alert	No, 1 violation, MW<250	1.00
Neurine	0 alert	1 alert, quaternary _nitrogen	No, 1 violation, MW<250	1.99
Choline	0 alert	1 alert, quaternary _nitrogen	No, 1 violation, MW<250	1.00
Betain	0 alert	1 alert, quaternary _nitrogen	No, 1 violation, MW<250	1.00
Trigonelline	0 alert	1 alert, quaternary _nitrogen	No, 1 violation, MW<250	1.04
Carpain	0 alert	1 alert: more than 2 esters	No, 2 violation: MW>350, XLOGP3>3.5	6.82
Vitexin	0 alert	0 alert	No, 1 violation; MW>350	5.12
Tricin	0 alert	0 alert	Yes	3.21
Naringenin	0 alert	0 alert	Yes	3.01
Quercetin	1 alert	1 alert	Yes	3.23
Luteolin	1 alert,	1 alert	Yes	3.02
Gentianin	0 alert	0alert	No, 1 violation MW <200	2.24
Greacunine	0 alert	1 alert, isolated_ alkene	No, 2 violations, MW>350	10.00
Fenugreekine	0 alert	1 alert	No, 2 violations, MW >350,	6.00
Trigpfeonoside	0 alert	1 alert, isolated_alkene	No, 2 violations, MW>350	10.00
Yamogenin	0 alert	1 alert, isolated_alkene	No, 2 violation: MW>350, XLOGP3>3.5	6.94
Diosgenin	0 alert	1 alert, isolated _alkene	No, 2 violations: MW>350, XLOGP 3>3.5	6.94
Smilagenin	0alert	0 alert	No, 2 violations, MW >350, XLOGP3>3.5	6.88
Sarasapogenin	0 alert	0 alert	No, 2 violation, MW>350, XLOGP3>3.5	6.88
Tigogenin	0 alert	0 alert	No, 2 violation, MW>350, XLOGP3>3.5	6.88
Neotigogenin	0 alert	0 alert	No, 2 violation, MW>350, XLOGP3>3.5	6.88
Gitogenin	0 alert	0 alert	No, 2 violation, MW>350, XLOGP3>3.5	6.88
Saponarin	0 alert	0 alert	No; 1 violation: MW>350	6.38
Yuccagenin	0 alert	1 alert: isolated alkene	No:2 violation: MW>350, XLOGP3>3.5	7.06

4. Discussion

Ayurveda is one of the earliest system of medicine providing extensive leads to discover the effective and therapeutically useful compounds for drug development from herbs, currently the use of herbal medicine is widespread in both developing and developed countries due to its checked adverse effects and from its natural source (Ekor, 2013) [15]. World Health Organization reports over 30% of all plant species have at one time or another used for medicinal purposes (Schippmann *et al*., 2002) [38]. Currently, due to continuous advancement in computer science, lot of successful findings drugs from natural products using computer aided drug design methods for example the development of Dazamide, Imatinib, Dasatinib and Ponatinib etc. (Ghosh AK, Gemma, 2015) [16]. Computer based drug designing has been employed in the prediction of ADMET properties of the drugs which leads to budding stage drug discovery (Lipinski *et al*. 1997; Lombardo *et al*., 2003; Gleeson *et al*., 2011) [29, 30, 17]. The rationale behind these insilico approaches are due to relatively lower cost time factor involved compared to standard ADMET profiling (DiMasi *et al*. 2003; Darvas *et al*., 2002) [11, 8]. As an example, it takes a minute in an in-silico model to screen 20,000 molecules, but takes 20 weeks in the "wet" laboratory to do the same exercise (Hodgson 2001) [24]. Due to the accumulated ADMET data in the late 1990s, many pharmaceutical companies are now using computational models that, in some cases, are replacing the "wet" screens (Hodgson 2001) [24]. This paradigm shift has therefore spurred up the development of several theoretical methods for the prediction of ADMET parameters. A host of these theoretical models have been implemented in a number of software programs currently available for drug discovery protocols (OCHEM platform 2009; Lhasa 2010; Schrodinger 2011a; Cruciani *et al*., 2000) [28, 6], even though some of the predictions are often disappointing (Tetko *et al*., 2006) [45]. The software tools currently used to predict the ADMET properties of potential drug candidates often make use of quantitative structure-activity relationships, QSAR (Tetko *et al*., 2006; Hansch *et al*., 2004) [45, 23] or knowledge-base methods (Greene *et al*. 1999; Button *et al*. 2003; Cronin 2003) [18, 5]. In the present study we used SwissADME online software tool which is available free for the users to evaluate the ADME properties of *Trigonella foenum-graecum* Lam respectively. The phytoconstituents of the plants were enlisted through the software includes, Alkaloids such as trimethylamine, choline, neurine,carpain trigonelline, and betain, flavonoids such asvitexin, tricin, naringenin, quercetin, and luteolin are some of the phytoconstituents of fenugreek that have been identified. Steroid saponins like gentianine, graecunins, fenugreekine, trigofoenosides and steroidal sapogenins such as yamogenin, diosgenin, smilagenin, sarasapogenin, tigogenin, neotigogenine, gitogenin, saponarin, and yuccagenin. Accordingly the phytoconstituents were analyzed for ADME properties and depicted in respected tables and figures. Further, the values can be used as monographs by researchers and scientists for development of potential semisynthetic and synthetic drugs for multifarious usage.

5. Conclusion

With the exponential growth of biological and chemical data, computer-aided drug design (CADD) has significantly transformed the research and development pathways for identifying drug candidates. The utilization of computational techniques in the drug discovery and development process is widely recognized for its efficiency in terms of implementation, time, and cost. This study presents a web-based tool, SwissADME, which is freely available for evaluating the ADME properties of phytoconstituents found in *Trigonella foenum-graecum* Lam plant. These findings can serve as a primary tool for further assessing the biological and pharmacological properties of the plant. Preliminary in-silico investigations suggest that certain compounds, including gentianine, gitogenin, smilagenin, quercetin, luteolin, and tricin, possess properties that could be further explored and tested as potential drug candidates for various diseases. However, these bioactive substances must be confirmed and subjected to further testing before being considered for clinical trials.

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