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Ranjith D
Assistant Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary and Animal Sciences, Pookode, Wayanad, Kerala, India

Ravikumar C
Associate Professor and Head, Department of Veterinary Pharmacology and Toxicology, Veterinary College, Hassan, Karnataka, India

Corresponding Author
Ranjith D
Assistant Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary and Animal Sciences, Pookode, Wayanad, Kerala, India

SwissADME predictions of pharmacokinetics and drug-likeness properties of small molecules present in *Ipomoea mauritiana* Jacq

Ranjith D and Ravikumar C

Abstract
To bolster in drug discovery, authentic data on pharmacokinetics properties of the molecule must be attainable at the earliest which eventually contributes to the success or failure of the compound. The present study will be the first of its kind reporting the ADME (Absorption, Distribution, Metabolism and Excretion) properties of *Ipomoea mauritiana* Jacq using freely available web tool Swiss ADME. A sum total of 15 potential compounds reported in earlier work from *Ipomoea mauritiana* were screened for ADME properties and the results were analyzed hereafter. Among the compounds screened only 5 molecules showed good brain penetration *viz*. tetradecanal, tetradecanoic acid, dodecanoic acid, hexanoic acid, scopoletin and three with good GIT absorption *viz*. Octadecan-1-ol, octadecanoic acid and Chloroacetic acid. Most of the compounds are non-substrate for both P-gp (P-glycoprotein) and CYP (Cytochrome P-450 isoenzymes). All the compounds passed Lipinski's rule of five to for drug likeness test. SwissADME emerged to be simple, robust and accurate method to understand the ADME properties of the compounds present in *Ipomoea mauritiana*.

Keywords: *Ipomoea mauritiana*, SwissADME, drug discovery, Lipinski's rule of five, P-glycoprotein, cytochrome P-450 isoenzymes

1. Introduction
World health organization (WHO) predicts more than 80% of world population lean on conventional medicaments. India being rich diversity with blooming traditional systems of medical practice, few people of ancient periods have started prospecting plants for their therapeutic attributes and biopharmaceutical segments (Boopathi and Shivakumar, 2011 & Zereena Viji and Paulsamy, 2016) [1, 2]. The family Convolvulaceae is conceded as Morning glory family with more than 2000 species and 58 genera dispersed in tropics and subtropics region (Undirwade, 2015) [3] like West Bengal, Maharashtra, Western Ghats, Goa, Gujarat, Karnataka and Bihar (Deepa Srivastava, 2017) [4]. *Ipomoea mauritiana* Jacq. (Family-Convolvulaceae; syn: *Ipomoea digitata* Linn) is an abundant perennial climber mostly grows in moist areas, monsoon forests and in coastal areas (Mishra and Datta, 1962 & Vidya Dighe and Shreeda Adhyapak, 2011) [5, 6]. It is considered as nutritive, expectorants, diuretics, used for the treatment of fever, bronchitis, as vitalizer, Galactagogue, aphrodisiac, demulcent, Cholagogue with antioxidant and immunomodulatory activity (Iyer, 1962, Chopra *et al*., 1956, Kirtikar and Basu, 1918, Nadkarni and Nadkarni, 1954, Upadhyay, 1997) [7-11].
Ipomoea mauritiana consists of major phytoconstituents *viz* taraxerol, taraxerol acetate, β-sitosterol, scopoletin, and 7-O-β- D-glycopyranosyl scopoletin (Karthik and Padma, 2009, Dharmaratne, 1997) [12, 13]. The GC-MS analysis of tuber of *I mauritiana* give in the presence of 27 major phytochemical constituents with different therapeutic properties *viz*., 6,8 Dioxabicyclo (3,2,1) octan 3a ol-2, 2, 4, 4-D4, 4-acetyl butyric acid, 2-methyl 4, 5 dihydroxy benzaldehyde, thiosulfuric acid, dodecanoic acid, chloroacetic acid, tetradecanal, tetradecanoic acid, E-15- Heptadecenal, Iso propyl myristate, ethyl-3-8-aza-bicycle-oct-2-ene8-carboxylate, hexadecen-1-ol-trans-9, Hexadecanoic acid, 1-octadecene, 9-octadecene-1-ol, 1-octadecanol, 2,2 dideutero octadecanal, 9, 12, octadecadienoic acid, octadecanoic acid, 1-docosanol methyl ether, hexatriacontane, 4, 6 fluro coumarin, n-tetracosanol-1, hahnfett, octacosane, nonacosane, tetratetracontane respectively (Harada *et al*., 2002, Harborne, 1998, Nayana *et al*., 2006 & Ranjith and Viswanath, 2019) [14-17].
Data processing biology and bioinformatics discharges a considerable role in drug design, screening and discovery (Prabhu Srinivasan *et al*., 2018) [18]. *In silico* pragmatic winnowing methodologies are quintessential for radical inquiring assessment of the promising activity of herbs. With *in-silico* studies several thousands of compounds present in a composite mixtures can be appraised contrary to their target swiftly and cost effectively (Chen *et al*., 2018, Dai *et*

al., 2016, Liu *et al*., 2017, Andriea *et al*., 2019) [19-22]. Presently, computer aided reckoning of ADME (Absorption, Distribution, Metabolism and Excretion) of drugs gained consideration to implement anticipative and reliable data compliment to accession of the experiment. These computational models predicts pharmacokinetics, physicochemical and medicinal properties of small molecules and back in development of lead molecules to patient drugs (Sliwoski *et al*., 2014 & Ndombera *et al*., 2019) [23, 24].

SwissADME is one of the most recent and afar-reaching site run by the Swiss Institute for Bioinformatics (SIB) which encourages bioinformatics services and resources for scientists worldwide (Ndombera *et al*., 2019) [24]. It promotes the assessment of ADME parameters of drug candidates and molecules and provides information that acquiesce antecedent uncertainty determination in the drug discovery process, it is the rostrum to determine Lipinski's rule of five (Lipinski *et al*., 2001) [25] for drug likeness of oral bioavailability. Drug likeness is the composite harmony of molecular properties and constitutional appearance which determine whether an unknown molecule is like the known drugs, which include electronic distribution, hydrophobicity, hydrogen bonding characteristics, molecular flexibility and size respectively. One of the extended feature of SwissADME includes BOILED-Egg evaluation (Daina and Zoete, 2016) [26] which predicts gastrointestinal absorption (HIA) and efflux/retention by P-glycoprotein (Pgp). In addition, blood brain barrier (BBB) penetration and Cytochrome P450 (CYP) enzyme substrate inhibition prediction can also been made, here the false positive results frequently encountered in biochemical assays of small molecules is predicted with fair degree of positivity (Matlock *et al*., 2018, Ndombera *et al*., 2019) [27, 24]

The present study was designed to submit the bioactive compounds present in *Ipomoea mauritiana* for insilico ADMET screening using SwissADME website (http://www.swissadme.ch/index.php) to evaluate the individual ADME behaviour like physiochemical properties, Lipophilicity, water solubility, pharmacokinetics, drug likeness and medicinal chemistry properties of the compounds.

2. Materials and Methods

2.1 SwissADME

SwissADME software (www.swissadme.ch) of Swiss institute of bioinformatics (http://www.sib.swiss) was accessed in a web server that displays the Submission page of SwissADME in Google was used to estimate individual ADME behaviors of the compounds from the plant. The input zone itself contains a molecular sketcher based on Chem Axons Marvin JS (http://www.chemaxon.com) that allowed the user to draw and edit 2D chemical structures. The structure are transferred as a list to the right hand side of the submission page, which is the actual input for computation. The list is made to contain one input molecule per line with several inputs, defined by simplified molecular input line entry system (SMILES) and the results are presented for each molecule in tables, graphs and also an excel spreadsheet. The SwissADME output file comprises of one panel per molecule for clear output and export, the panel comprises of all the information's of the molecules (Egan *et al*., 2000) [28].

2.2 Structure and bioavailability radar

The two dimensional chemical structure with canonical SMILES were shown in the first section. The bioavailability radar empowers preliminary glimpse at the drug likeness of the molecules of interest. The pink area exemplifies optimum physicochemical space for each properties predicted to be orally bioavailable. Six physicochemical properties are taken in to account: LIPO (Lipophilicity), SIZE, POLAR (Polarity), INSOLU (Insolubility), INSATU (Insaturation) and FLEX (Flexibility) respectively. Lipophilicity: XLOGP3 between-0.7 and + 5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 $^{0}A^{2}$, solubility: log *S* not higher than 6, saturation: fraction of carbons in the sp^{3} hybridization not less than 0.25 and flexibility: no more than 9 rotatable bonds (Daina *et al*., 2017) [29]

2.3 Physicochemical properties

These section comprises of clean molecular and physicochemical characteristics like 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, TPSA respectively. The values were computed with open babel version 2.3.0 (O'Boyle, 2011 & Daina *et al*., 2017) [30, 29]. A new methodology has been developed for calculating PSA (molecular polar surface area) called TPSA (Topological PSA) by simply calculating the summation of the tabulated surface contributions of polar fragments which is determined by least squares fitting of the fragment based TPSA to the single conformer 3D PSA for a large set of drug like structures. The database was processed by removing molecules with apparent valence errors, molecular weights outside the interval of 100-800 and molecules not having at least one oxygen, nitrogen, sulfur or phosphorus atom (Ertl *et al*., 2000, Daina and Zoete, 2016) [31, 26].

2.4 Lipophilicity

Lipophilicity is a paramount parameter in drug discovery and design (Leeson & Springthorpe, 2007) [32] on the grounds that it complements the single most informational and successful physicochemical property in medicinal chemistry (Testa et al., 2000) [33]. It is experimentally demonstrated as partition coefficients (log P) or as distribution coefficients (log D). Log P portrays partition equilibrium of an un-ionized solute amidst water and an immiscible organic solvent. Larger the log P values corresponds greater lipophilicity (Arnott & Planey, 2012) [34]. For the measurement of lipophilicity two preparatory techniques were characterized *viz*. shake flask method (Sangster, 1997) [35] and potentiometric titration (Avdeef, 1993 & Scherrer and Donovan, 2009) [36, 37]. Potentiometric method analyzes an aqueous pKa to an apparent pKa which is measured in two phase systems (Water-Octanol) by employing difference curve analysis i.e. partition coefficient between n-octanol to water which is designated as log $P_{o/w}$ (Arnott and Planey, 2012) [34].

To evaluate the lipophilicity character in a compound, SwissADME provides five freely available models i.e. XLOGP3, WLOGP, MLOGP, SILICOS-IT and iLOGP respectively. XLOGP3, an atomistic accost including corrective factors and knowledge based library (Cheng, 2007) [38]; WLOGP, application of purely atomistic method stationed on fragmental system (Wildman and Crippen, 1999) [39]; MLOGP, an archetype of topological method suggested on a linear relationship with implemented 13 molecular descriptors (Moriguchi *et al*., 1992 & Moriguchi *et al*., 1994) [40, 41]; SILICOS-IT, an mongrel method entrust on 27 fragments and 7 topological descriptors; iLOGP, a physics based method lean on 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 an arithmetic mean of the values predicted by the five proposed methods (Daina *et al*., 2017) [29].

2.5 Solubility

Solubility of a compound radically confide on the solvent used, ambient temperature and pressure. The breadth of solubility measured as the saturation concentration where upon adding more solute does not increase its concentration in the solution (Lachman *et al*., 1986 & Savjani *et al*., 2012) [42, 43]. A drug is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water (Amidon *et al*., 1995) [44]. All drugs have been divided into four classes: class I-high soluble and high permeable, class II-low soluble and high permeable, class III-low soluble and high permeable and class IV-low soluble and low permeable (Savjani *et al*., 2012) [43]. Two topological approaches included in SwissADME to predict water solubility, the first one is the application of ESOL model (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, moderately<-4 soluble<-2 very<0<highly) and the second one is adapted from Ali et al, 2012 (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, moderately<-4 soluble<-2very<0<highly). Both differ from the fundamental general solubility equation (Yalkowsky & Valvani, 1980) [45] since they avoid the melting point parameter but the linear correlation between predicted and experimental values were strong (R^2=0.69 and 0.81 respectively). The third predictor of SwissADME was developed by SILICOS-IT (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, moderately<-4 soluble<-2 very<0<highly) where the linear coefficient is corrected by molecular weight (R^2=0.75). All predicted values are the decimal logarithm of the molar solubility in water (log S). SwissADME also provides solubility in mol/l and mg/ml along with qualitative solubility classes.

2.6 Pharmacokinetics

The delineation exists in a region of agreeable properties for GI absorption on a plot of two computed descriptors; ALOGP versus PSA respectively. The region most populated by well absorbed molecules is elliptical, it was called Egan egg, which is used to assess the predictive power of the model for GI passive absorption and prediction for brain access by passive diffusion to finally lay the BOILED-Egg (Brain or IntestinaL EstimateD permeation predictive model). The BOILED-Egg model produces a rapid, spontaneous, efficiently imitate yet boisterous method to forecast the passive GI absorption helpful for drug discovery and development (Di *et al*., 2012 & Brito-Sanchez *et al*., 2015) [46, 47]. The white region is the space of the molecules with greater extent of absorption by GI tract, the yellow region (yolk) is the space with highest probability to permeate to the brain (Daina *et al*., 2017, Daina *et al*., 2016 & Montanari and Ecker, 2015) [29, 26, 48]. Cytochrome p450 (CYP) isoenzymes biotransforms more than 50-90% of therapeutic molecules from its five major isoforms (CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6). P-gp is broadly dispersed in intestinal epithelium which pumps xenobiotic back in to the intestinal lumen and from the capillary endothelial cells of the brain back in to the capillaries (Ogu & Maxa, 2000 and Ndombera *et al*., 2019) [49, 24]. Swiss ADME adopts support vector machine algorithm (SVM) for the datasets of known substrates/non- substrates or inhibitors/non-inhibitors for binary classification. The resultant molecule will return "Yes" or "No" if the molecule under investigation expected to be substrate for both P-gp and CYP respectively. The SVM model for P-gp substrate was built on 1033 molecules (training set) and tested on 415 molecules (test set), 10 fold CV: ACC=0.72/AUC=0.77, External: ACC=0.88/AUC=0.94 respectively. The SVM model for Cytochrome P-450 1A2 inhibitor molecule was built on 9145 molecule (training set) and tested on 3000 molecules (test set), 10 fold CV: ACC=0.83/AUC=0.90, External: ACC=0.84/AUC=0.91. The SVM model for Cytochrome P-450 2C19 inhibitor molecule was built on 9272 molecule (training set) and tested on 3000 molecules (test set), 10 fold CV: ACC=0.80/AUC=0.86, External: ACC=0.80/AUC=0.87. The SVM model for Cytochrome P-450 2C9 inhibitor molecule was built on 5940 molecule (training set) and tested on 2075 molecules (test set), 10 fold CV: ACC=0.78/AUC=0.85, External: ACC= 0.71/AUC=0.81. The SVM model for Cytochrome P-450 2D6 inhibitor molecule was built on 3664 molecule (training set) and tested on 1068 molecules (test set), 10 fold CV: ACC=0.79/AUC=0.85, External: ACC=0.81/AUC=0.87. The SVM model for Cytochrome P-450 3A4 inhibitor molecule was built on 7518 molecule (training set) and tested on 2579 molecules (test set), 10 fold CV: ACC=0.77/ AUC=0.85, External: ACC=0.78/AUC=0.86.

Transdermal distribution is an alternative way of oral delivery and hypodermic injection of drugs. The advantages of transdermal delivery includes; avoiding stomach degradation of drugs, supposing steady plasma levels, avoiding first pass metabolism, increasing patient compliance, inexpensive, invasive, ease to use and decreasing side effects (Onyekaba, 2015) [50]. The steady state transport of molecules over biological membrane is characterized as the solubility diffusion process. The permeability coefficient (K_p) relating solute flux to the concentration gradient across the membrane is expressed mathematically (Idson and Behl., 1987) [51]. The more negative the log Kp (with Kp in cm/s), the less skin permeant is the molecule.

$$Kp = Km \times Dm/\delta$$

$$K_p = K_m \times D_m/\delta$$

Where,

K_m = membrane / water partition coefficient of the permeant

D_m = permeant diffusivity within the membrane

δ = diffusion pathlength

2.7 Drug likeness

Drug likeness assesses the chances for a molecule to become an oral drug with respect to bioavailability. It is the property characterized by the red distorted hexagon within pink shade. Swiss ADME performs filtering of chemical libraries to exclude molecules with peculiarities 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 (Daina *et al*., 2017) [29]. The Lipinski filter (Pfizer) is the pioneer rule of five that characterize small molecules based on physicochemical property profiles which includes Molecular Weight (MW) less than 500, MLOGP ≤ 4.15, N or O ≤ 10, NH or OH ≤ 5. Lipinski considers stringently that all nitrogens and oxygen as H-bond acceptor and all nitrogens and oxygens with at least one hydrogen as H-bond donors. Besides, aliphatic fluorines are acceptors and alinine nitrogens

are neither donors nor acceptors (Lipinski *et al*., 2001) [25]. The Ghose filter (Amgen) describes small molecules stationed on physicochemical property, existence of functional groups and substructures. The qualifying range includes of molecular weight is between 160 and 480 Da, WlogP is between -0.4 to 5.6, molar refractivity (MR) is between 40 to 130 for total number of atom; the qualifying range is between 20 and 70 atoms in a small molecule (Ghose *et al*., 1998 & Ghose *et al*., 1999) [52, 53]. Veber filter (GSK filter) model symbolize molecules as drug like 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, increased rotatable bonds counts has a negative effect on the permeation rate (Veber *et al*., 2002) [54]. Egan filter (Pharmacia filter) anticipates drug absorption depend on processes involved in membrane permeability of a small molecule. These model symbolizes molecule as a drug like if they have WLOGP ≤ 5.88 and TPSA ≤ 131.6 respectively. The Egan computational model for human passive intestinal absorption (HIA) of small molecule accounts for active transport and efflux mechanisms and is therefore robust in predicting absorption of drugs (Egan *et al*., 2000) [55]. Muegge filter (Bayer filter) is a self-reliant Pharmacophore point filter that segregates drug like and non-drug like molecules. These model symbolizes molecule as a drug like if they have molecular weight between 200 to 600 Da, XLOGP between -2 and 5, TPSA ≤ 150, Number of rings ≤ 7, Number of carbon atoms > 4, number of heteroatoms > 1, number of rotatable bonds ≤ 15, H-bond acceptor ≤ 10, H-bond donor ≤ 5 respectively (Muegge *et al*., 2001). Abbott bioavailability score seeks to predicts the probability of a compound to have at least 10% oral bioavailability in rat or measurable Caco-2 permeability which predicts probability of a compound to have F>10% based on the predominant charge at biological pH in a rat model. It focusses on fast screening of chemical libraries to select best molecules to be synthesized (Martin, 2005) [56].

2.8 Medicinal chemistry

The aim of these section is to bolster medicinal chemists in their daily drug discovery endeavours. PAINS (Pan Assay INterference compoundS or frequent hitters or promiscuous compounds) are the molecules which shows potent response 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. SwissADME returns warnings if such moieties are found in the molecule under evaluation (Baell & Holloway, 2010) [57]. In other model, 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 was after exclusion of compounds with potentially mutagenic, reactive and unfavorable groups such as nitro groups, sulfates, phosphates, 2-halopyridines and thiols. Brenk 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 (Brenk *et al*., 2008) [58]. The concept of lead likeness designed to provide leads with tremendous affinity in high throughput screening (HTS) that avow for 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 rule based method consisting of molecules with molecular weight in between 100 and 350 Da, ClogP between 1 and 3.0 and are greatly considered as superior to those of drug like compounds and therefore lead like (Hann & Keseru, 2012 and Teague *et al*., 1999) [59, 60].

One of the fundamental aspect of CADD activity is to select the most promising virtual molecules submitting to biological assay. Synthetic accessibility (SA) estimation is based on fingerprint based approach which includes closed source information about fingerprint definition that prevents straight forward implementation open to scientific community. For a molecule to be drug like the SA Score should range from 1 (very easy) to 10 (very difficult) based on 1024 fragmental contributions (FP2) modulated by size and complexity penalties, trained on 12'782'590 molecules and tested on 40 external molecules (r^2 = 0.94) (Ertl & Schuffenhauer, 2009) [61].

3. Results

The structural features of phytoconstituents present in *Ipomoea mauritiana* were entering in SwissADME website (http://www.swissadme.ch) using ChemAxons Marvin JS structure drawing tool. The phytochemicals analyzed includes taraxerol, taraxerol acetate, beta-sitosterol, scopoletin, dodecanoic acid/ lauric acid, chloroacetic acid, tetradecanal/myristaldehyde, tetradecanoic acid/Myristic acid, hexanoic acid/Palmitic acid, octadec-1-ene, octadecan-1-ol, octadecanoic acid/stearic acid, octacosane, nonacosane, tetracosane for their ADME property.

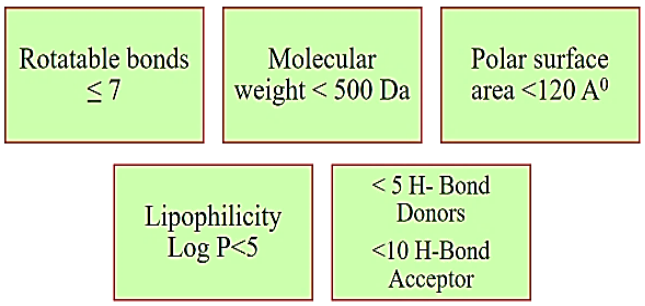

Fig 1: Good *In vivo* Drug absorption and Permeation *Lipinski's Rule of 5*

Table 1: United States Pharmacopeia-2007 and British Pharmacopeia-2009 Solubility Criteria (Savjani *et al*., 2012)

Sl. No.	Descriptive terms	Parts of solvent required per parts of solute
1	Very soluble	Less than 1
2	Freely soluble	From 1 to 10
3	Soluble	From 10 to 30
4	Sparingly soluble	From 30 to 100
5	Slightly soluble	From 100 to 1000
6	Very slightly soluble	From 1000 to 10,000
7	Practically insoluble	10,000 and over

Table 2: General Characteristics of the Phytoconstituents of *Ipomoea mauritiana*

Sl. No	Small molecule	Pubchem ID	Molecular formula	Canonical SMILES	Molecular weight (g/mol or Da)
1	Taraxerol	92097	$C_{30}H_{50}O$	CC1(CCC2(CC=C3C4(CCC5C(C(CCC5(C4CCC3(C2C1)C)C)O)(C)C)C)C)C	426.7
2	Taraxerol acetate	94225	$C_{32}H_{52}O_2$	CC(=O)OC1CCC2(C(C1(C)C)CCC3(C2CCC4(C3=CCC5(C4CC(CC5)(C)C)C)C)C)C	468.8
3	Beta sitosterol	222284	$C_{29}H_{50}O$	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C	414.7
4	Scopoletin	5280460	$C_{10}H_8O_4$	COC1=C(C=C2C(=C1)C=CC(=O)O2)O	192.17
5	Dodecanoic acid/Lauric acid	3893	$C_{12}H_{24}O_2$	CCCCCCCCCCCC(=O)O	200.32
6	Chloroacetic acid	300	$C_2H_3ClO_2$	C(C(=O)O)Cl	94.5
7	Tetradecanal	31291	$C_{14}H_{28}O$	CCCCCCCCCCCCCC=O	212.37
8	Tetradecanoic acid/Myristic acid	11005	$C_{14}H_{28}O_2$	CCCCCCCCCCCCCC(=O)O	228.37
9	Hexanoic acid	8892	$C_6H_{12}O_2$	CCCCCC(=O)O	116.16
10	Octadec-1-ene	8217	$C_{18}H_{36}$	CCCCCCCCCCCCCCCCCC=C	252.5
11	Octadecan-1-ol/Stearyl alcohol	8221	$C_{18}H_{38}O$	CCCCCCCCCCCCCCCCCCO	270.5
12	Octadecanoic acid/Stearic acid	5281	$C_{18}H_{36}O_2$	CCCCCCCCCCCCCCCCCC(=O)O	284.5
13	Octacosoic acid/Montanic acid	10470	$C_{28}H_{56}O_2$	CCCCCCCCCCCCCCCCCCCCCCCCCCCC(=O)O	424.7
14	Nonacosane	12409	$C_{29}H_{60}$	CCCCCCCCCCCCCCCCCCCCCCCCCCCCC	408.8
15	Tetracosane	12592	$C_{24}H_{50}$	CCCCCCCCCCCCCCCCCCCCCCCC	338.7

Table 3: Physicochemical Properties the Phytoconstituents of *Ipomoea mauritiana*:

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 refractivity	TPSA ($^0A^2$)
1	Taraxerol	31	0	0.93	0	1	1	134.88	20.23
2	Taraxerol acetate	34	0	0.91	2	2	0	144.62	26.30
3	Sitosterol beta	30	0	0.93	6	1	1	133.23	20.23
4	Scopoletin	14	10	0.10	1	4	1	51.00	59.67
5	Dodecanoic acid/Lauric acid	14	0	0.92	10	2	1	61.57	37.30
6	Chloroacetic acid	5	0	0.5	1	2	1	18.30	37.30
7	Tetradecanal	15	0	0.93	12	1	0	69.61	17.07
8	Tetradecanoic acid/Myristic acid	16	0	0.93	12	2	1	71.18	37.30
9	Hexanoic acid	8	0	0.83	4	2	1	32.73	37.30
10	Octadec-1-ene	18	0	0.89	15	0	0	88.17	0.00
11	Octadecan-1-ol/Stearyl alcohol	19	0	1	16	1	1	89.90	20.23
12	Octadecanoic acid/Stearic acid	20	0	0.94	16	2	1	90.41	37.30
13	Octacosoic acid/Montanic acid	30	0	0.96	26	2	1	138.48	37.30
14	Nonacosane	29	0	1	26	0	0	141.52	0.00
15	Tetracosane	24	0	1	21	0	0	117.48	0.00

Num.-number, arom.-aromatic, H-bond-hydrogen bond, TPSA-topological polar surface area

Table 4: Lipophilicity characteristics of the Phytoconstituents of *Ipomoea mauritiana*

Sl. No	Small molecule	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log $P_{o/w}$
1	Taraxerol	4.78	9.30	8.17	6.92	6.92	7.22
2	Taraxerol acetate	5.21	9.88	8.74	7.08	7.42	7.67
3	Beta sitosterol	4.79	9.34	8.02	6.73	7.04	7.19
4	Scopoletin	1.86	1.53	1.51	0.76	1.94	1.52
5	Dodecanoic acid/Lauric acid	2.70	4.20	3.99	3.15	3.50	3.51
6	Chloroacetic acid	0.57	0.22	0.31	0.03	0.31	0.29
7	Tetradecanal	3.63	5.97	4.89	3.80	5.08	4.67
8	Tetradecanoic acid/Myristic acid	3.32	6.11	4.77	3.69	4.37	4.45
9	Hexanoic acid	1.57	1.92	1.65	1.27	0.93	1.47
10	Octadec-1-ene	5.05	10.03	7.04	6.77	7.09	7.20
11	Octadecan-1-ol	4.86	8.20	6.24	4.93	6.54	6.15
12	Octadecanoic acid	4.30	8.23	6.33	4.67	6.13	5.93
13	Octacosoic acid/Montanic acid	6.69	13.62	10.23	6.81	10.54	9.58
14	Nonacosane	7.79	15.32	11.56	9.25	11.97	11.18
15	Tetracosane	6.52	12.62	9.61	8.25	9.76	9.35

Table 5: Water Solubility characteristics of the Phytoconstituents of *Ipomoea mauritiana*:

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	mol/L			mg/ml	mol/L			mg/ml	mol/L	
1	Taraxerol	-8.34	1.93e-06	4.52e-09	PS	-9.63	1.01e-07	2.36e-10	PS	-7.16	2.93e-05	6.85e-08	PS
2	Taraxerol acetate	-8.84	6.82-0e-07	1.45e-09	PS	-10.36	207e-08	4.41e-11	I	-7.77	7.89e-06	1.68e-08	PS

3	Sitosterol beta	-7.90	5.23e-06	1.26e-08	PS	-9.67	8.90e-08	2.15e-10	PS	-6.19	2.69e-04	6.49e-07	PS
4	Scopoletin	-2.46	6.70e-01	3.48e-03	S	-2.36	7.79e-01	4.06e-03	S	-3.17	1.31e-01	6.81e-04	S
5	Dodecanoic acid / Lauric acid	-3.07	1.71e-01	8.55e-04	S	-4.69	4.06e-03	2.03e-05	MS	-3.69	4.05e-02	2.02e-04	S
6	Chloroacetic acid	-0.50	3.00e+01	3.17e-01	VS	-0.56	3.00e+01	3.17e-01	VS	-0.18	6.17e+01	6.53e-01	S
7	Tetradecanal	-4.13	1.59e-02	7.49e-05	MS	-6.10	1.67e-04	7.86e-07	PS	-5.08	1.77e-03	8.32e-06	MS
8	Tetradecanoic acid / Myristic acid	-4.31	1.11e-02	4.86e-05	MS	-6.67	4.3e-05	2.11e-07	PS	-4.51	7.12e-03	3.12e-05	MS
9	Hexanoic acid	-1.51	3.62e+00	3.12e-02	VS	-2.33	5.47e-01	4.71e-03	S	-1.21	7.23e+00	6.22e-02	S
10	Octadec-1-ene	-6.73	4.66e-05	1.84e-07	PS	-9.96	2.77e-08	1.10e-10	PS	-6.79	4.09e-05	1.62e-07	PS
11	Octadecan-1-ol	-5.36	6.38e-04	2.36e-06	MS	-8.49	8.85e-07	3.27e-09	PS	-6.57	7.21e-05	2.67e-07	PS
12	Octadecanoic acid	-5.73	5.26e-04	1.85e-06	MS	-8.87	3.80e-07	1.33e-09	PS	-6.11	2.19e-04	7.71e-07	PS
13	Octacosoic acid / Montanic acid	-9.34	1.95e-07	4.59e-10	PS	-14.47	1.45e-12	3.40e-15	I	-10.06	3.66e-08	8.61e-11	I
14	Nonacosane	-10.31	2.00e-08	4.90e-11	I	-15.45	1.45e-13	3.56e-16	I	-11.50	1.30e-09	3.18e-12	I
15	Tetracosane	-8.50	1.06e-06	3.13e-09	PS	-12.65	7.63e-11	2.25e-13	I	-9.53	1.01e-07	2.97e-10	PS

I-Insoluble, PS- Poorly soluble, S- Soluble, MS- Moderately soluble, VS- Very soluble

Table 6: Pharmacokinetics parameters of the phytoconstituents of *Ipomoea mauritiana*

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	Taraxerol	Low	No	No	No	No	No	No	No	-2.30
2	Taraxerol acetate	Low	No	No	No	No	No	No	No	-2.14
3	Sitosterol beta	Low	No	No	No	No	No	No	No	-2.20
4	Scopoletin	High	Yes	No	Yes	No	No	No	No	-6.39
5	Dodecanoic acid/Lauric acid	High	Yes	No	No	No	No	No	No	-4.54
6	Chloroacetic acid	High	No	No	No	No	No	No	No	-6.72
7	Tetradecanal	High	Yes	No	Yes	No	No	No	No	-3.36
8	Tetradecanoic acid/Myristic acid	High	Yes	No	Yes	No	No	No	No	-3.35
9	Hexanoic acid	High	Yes	No	No	No	No	No	No	-5.65
10	Octadec-1-ene	Low	No	No	Yes	No	No	No	No	-0.72
11	Octadecan-1-ol	High	No	No	Yes	No	No	No	No	-2.13
12	Octadecanoic acid	High	No	No	Yes	No	No	No	No	-2.19
13	Octacosoic acid/Montanic acid	Low	No	Yes	No	No	No	No	No	0.78
14	Nonacosane	Low	No	Yes	No	No	No	No	No	2.08
15	Tetracosane	Low	No	Yes	Yes	No	No	No	No	0.59

Table 7: Druglikeness rule and Bioavailability score of the phytoconstituents of *Ipomoea mauritiana:*

Sl No	Small molecule	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
1	Taraxerol	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	Yes	No; 1 violation: WLOGP>5.88	No; 2 violations: XLOGP3>5, Heteroatoms<2	0.55
2	Taraxerol acetate	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	Yes	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.55
3	Sitosterol beta	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	Yes	No; 1 violation: WLOGP>5.88	No; 2 violations: XLOGP3>5, Heteroatoms<2	0.55
4	Scopoletin	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.55
5	Dodecanoic acid/Lauric acid	Yes	Yes	Yes	Yes	Yes	0.56
6	Chloroacetic acid	Yes; 0 violation	No; 3 violations: MW<160, MR<40, #atoms<20	Yes	Yes	No; 2 violations: MW<200, #C<5	0.56
7	Tetradecanal	Yes	Yes	No; 1 violation: Rotors>10	Yes	No; 2 violations: XLOGP3>5, Heteroatoms<2	0.55
8	Tetradecanoic acid/Myristic acid	Yes	Yes	No; 1 violation: Rotors>10	Yes	No; 1 violation: XLOGP3>5	0.56
9	Hexanoic acid	Yes	No; 2 violations: MW<160, MR<40	Yes	Yes	No; 1 violation: MW<200	0.56
10	Octadec-1-ene	Yes; 1 violation: MLOGP>4.15	No; 1 violation: WLOGP>5.6	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 2 violations: XLOGP3>5, Heteroatoms<2	0.55
11	Octadecan-1-ol	Yes; 1 violation: MLOGP>4.15	No; 1 violation: WLOGP>5.6	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 3 violations: XLOGP3>5, Heteroatoms<2, Rotors>15	0.55
12	Octadecanoic acid	Yes; 1 violation: MLOGP>4.15	No; 1 violation: WLOGP>5.6	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 2 violations: XLOGP3>5, Rotors>15	0.56
13	Octacosoic acid/Montanic acid	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 2 violations: XLOGP3>5, Rotors>15	0.56
14	Nonacosane	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 3 violations: XLOGP3>5, Heteroatoms<2, Rotors>15	0.55
15	Tetracosane	Yes; 1 violation: MLOGP>4.15	No; 2 violations: WLOGP>5.6, #atoms>70	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 3 violations: XLOGP3>5, Heteroatoms<2, Rotors>15	0.55

Table 8: Medicinal Chemistry properties of *Ipomoea mautiana*:

Sl No	Small molecule	Pains	Brenk	Leadlikeness	Synthetic accessibility
1	Taraxerol	0	1 alert: isolated alkene	No; 2 violations: MW>350, XLOGP3>3.5	6.04
2	Taraxerol acetate	0	1 alert: isolated alkene	No; 2 violations: MW>350, XLOGP3>3.5	5.98
3	Sitosterol beta	0	1 alert: isolated alkene	No; 2 violations: MW>350, XLOGP3>3.5	6.30
4	Scopoletin	0	1 alert: cumarine	No; 1 violation: MW<250	2.62
5	Dodecanoic acid/Lauric acid	0	0	No; 3 violations: MW<250, Rotors>7, XLOGP3>3.5	1.87
6	Chloroacetic acid	0	1 alert: alkyl halide	No; 1 violation: MW<250	1.33
7	Tetradecanal	0	1 alert: aldehyde	No; 3 violations: MW<250, Rotors>7, XLOGP3>3.5	2.04
8	Tetradecanoic acid / Myristic acid	0	0	No; 3 violations: MW<250, Rotors>7, XLOGP3>3.5	2.09
9	Hexanoic acid	0	0	No; 1 violation: MW<250	1.17
10	Octadec-1-ene	0	1 alert: isolated alkene	No; 2 violations: Rotors>7, XLOGP3>3.5	2.82
11	Octadecan-1-ol/Stearyl alcohol	0	0	No; 2 violations: Rotors>7, XLOGP3>3.5	2.52
12	Octadecanoic acid/Stearic acid	0	0	No; 2 violations: Rotors>7, XLOGP3>3.5	2.54
13	Octacosoic acid/Montanic acid	0	0	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5	3.73
14	Nonacosane	0	0	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5	3.81
15	Tetracosane	0	0	No; 2 violations: Rotors>7, XLOGP3>3.5	3.20

C-Chloroacetic acid, S-Scopoletin, H-Hexanoic acid, D-Dodecanoic acid, TD-Tetradecanal, TDA-Tetradecanoic acid, ODA-Octadecanoic acid, O-1-ol-Octadecan-1-ol, O-1-ene-Octadec-1-ene,

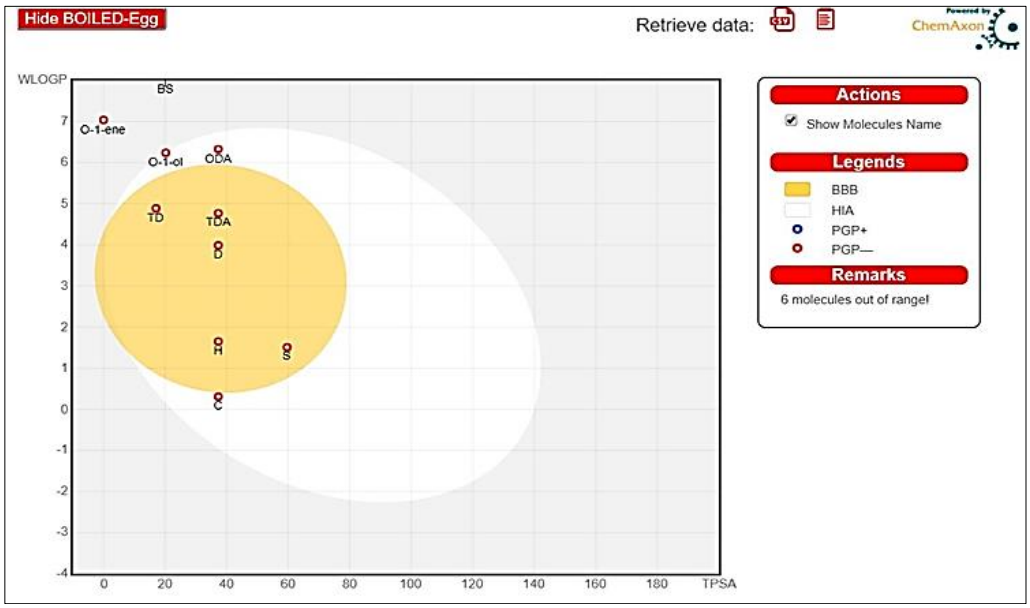

Fig 2: Schematic representation of perceptive evaluation of passive gastrointestinal absorption (HIA) and Brain penetration (BBB) with molecules in the WLOGP-versus-TPSA using BOILED-Egg.

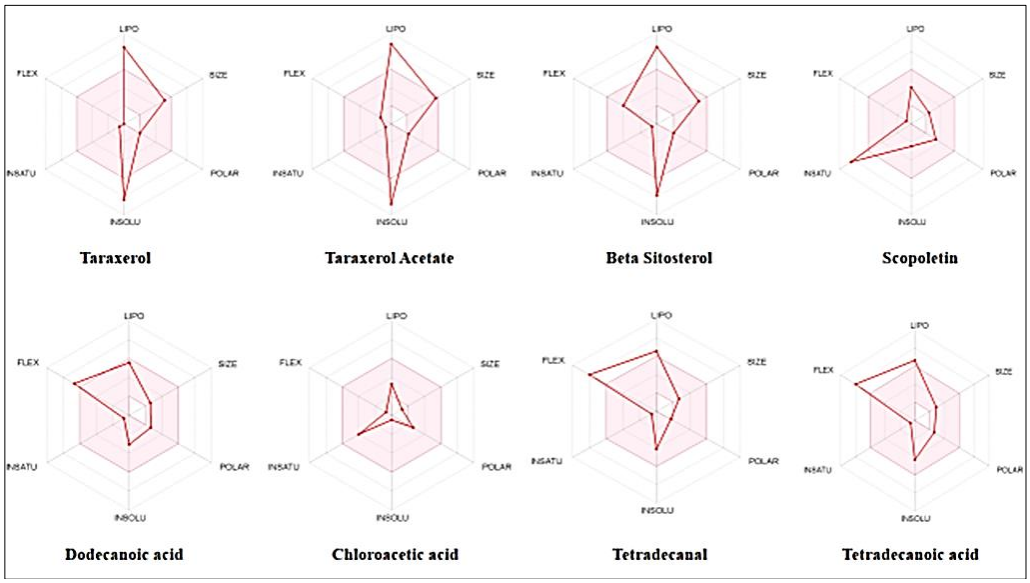

Fig 3: Schematic diagram of Bioavailability Radar for Drug likeness of a molecule (lipophilicity: XLOGP3 between-0.7 and+5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 A2, solubility: log *S* not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds

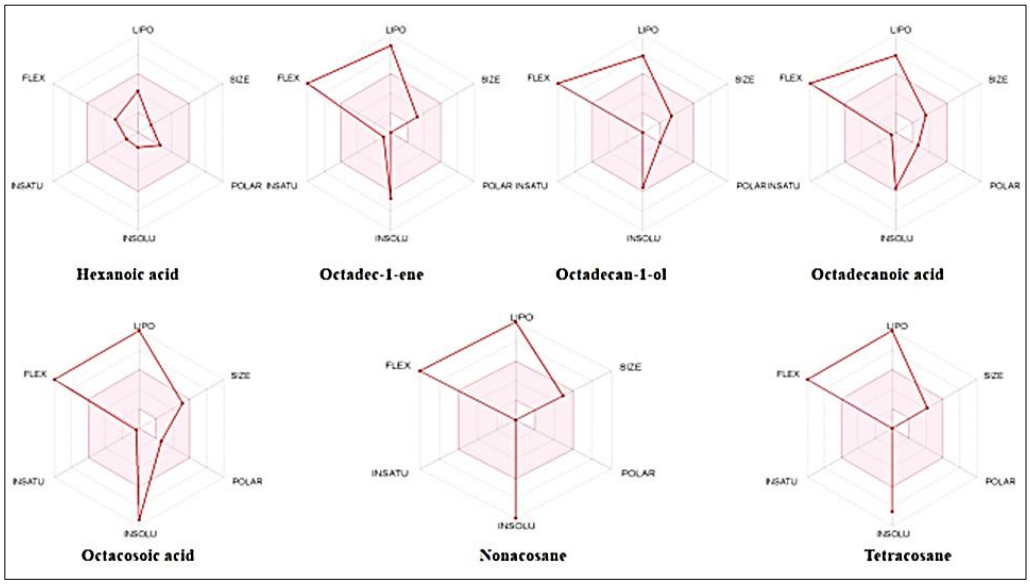

Fig 4: Schematic diagram of Bioavailability Radar for Drug likeness of a molecule (lipophilicity: XLOGP3 between − 0.7 and + 5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 A2, solubility: log *S* not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds)

4. Discussion

Ipomoea mauritiana Jacq. (Convolvulaceae) is a twinning perennial shrub with large tuberous root, widely distributed in the tropical parts of the world. The plants is commonly used to alleviate spinal cord injury, to manage tuberculosis, as aphrodisiac, used in biliary disorders (Jahan *et al*., 2013, Anzumi *et al*., 2014 and Ranjith & Viswanath, 2019) [62, 63, 17]. The reported phytoconstituents of *Ipomoea mauritiana viz*. Taraxerol, Taraxerol acetate, Sitosterol beta, Scopoletin, Dodecanoic acid/Lauric acid, Chloroacetic acid, Tetradecanal, Tetradecanoic acid/Myristic acid, Hexanoic acid, Octadec-1-ene, Octadecan-1-ol/Stearyl alcohol, Octadecanoic acid/ Stearic acid, Octacosoic acid/Montanic acid, Nonacosane and Tetracosane respectively (Aparna *et al*., 2012 and Ranjith & Viswanath, 2019) [64, 17].

Modern drug discovery involves assessment of competence of the dynamic molecules and their strength to reach target site in bioactive form, which involves cellular, animal and human clinical trials which are highly priced and encumbered with risks (Ndombera *et al*., 2019 and Ranjith & Viswanath, 2019) [24, 17]. Presently computer aided drug development encouraged the estimate of absorption, distribution, metabolism and excretion of drugs (ADME), they postulate anticipatory and dependable data very quickly and compliment for experimental approaches (Sliwoski *et al*., 2014 and Ndombera *et al*., 2019) [65, 24]. It has been determined that the initial appraisal of ADME properties in the discovery period diminishes remarkably the fraction of pharmacokinetics related failures in the clinical phase (Ndombera *et al*., 2019 and Hay *et al*., 2014) [24, 66].

In the present study we evaluated the ADME properties of the potent phytochemicals of *Ipomoea mauritiana* using Swiss ADME web tool, which is freely available at http://www.swissadme.ch and easy analysis of results, also for non- expert in CADD (Daina *et al*., 2017) [29]. A total of 15 potent phytoconstituents of *Ipomoea mauritiana* were analyzed using Swiss ADME web tool to study general characteristics (Table 2), Physicochemical properties (Table 3), lipophilicity and water solubility characteristics (Table 4 & 5), pharmacokinetic parameters (Table 6), drug likeness rule and bioavailability score (Table 7) and medicinal chemistry properties (Table 8), BOILED-Egg representation for evaluation of passive gastrointestinal absorption and brain penetration (Figure 2) and bioavailability radar for drug likeness of compounds of Ipomoea mauritiana (Figure 3) respectively.

General characteristics of the phytoconstituents of *Ipomoea mauritiana* revealed all the compounds having molecular weight less than 500 Da, which is a prime property to be called as drug likeness of the small molecules. The lipophilicity property of the compounds portray an important role for molecular discovery activities in multifarious domains (Plika *et al*., 1996) [67]. The quantitative descriptor of the lipophilicity is the partition coefficient P of a given molecule between n-octanol and water system (Daina *et al*., 2014)[68]. Because of its amphiphilic nature, n-octanol is considered a good mimic of phospholipid membrane characteristics (Liu *et al*., 2010) [69]. Multifarious algorithms are accessible to compute log Po/w, which rely on factual methodologies. The classic log P predictors branched in to two division, first ones splits molecular structures in to molecular fragments includes fragmental approach eg. KLOGP (Klopman *et al*., 1994) [70], KOWWNIN (Meylan & Howard, 2000) [71] or atomic approach eg. ALOGP (Ghose & Crippen, 1986 and Ghose *et al*., 1998) [72, 73], XLOGP (Wang *et al*., 1997, Cheng *et al*., 2007) [74, 75]. The second division gathers the topological methods in which, the molecules description is related to its topology being as count or flags for specific atoms, groups or structural properties eg. MLOGP (Moriguchi *et al*., 1992 and Moriguchi *et al*., 1994), the prediction attained by manifold linear regression trained on large molecular data sets. The SILICOS-IT is a hybrid technique which combines both molecular fragments and topological parameters, which confide on 27 fragments and 7 topological descriptors, it was disciplined on 23,455 molecules with experimental n-octanol/water partition values (Daina *et al*., 2014). The version three of the XLOGP atomic model is established on a system of 87 fragments and two corrective factors. If the input structures is similar to a reference compounds, the fragments differentiating them are treated and the corresponding log P contributions added to the reference structure log P value (Cheng *et al*., 2007).

Lipophilicity estimated as consensus Log P, which is the average value of all Log P evaluated with various lipophilicity criteria, determined nonacosane as most lipophilic whereas chloroacetic acid as least lipophilic and water solubility of the small molecules ranged from highly water soluble (chloroacetic acid) to least water soluble or insoluble (nonacosane) respectively.

The pharmacokinetics and drug likeness performed using SwissADME showed a high level of GI absorption with scopoletin, dodecanoic acid, chloroacetic acid, tetradecanal, tetradecanoic acid, hexanoic acid, octadecan 1 ol, octadecanoic acid and high BBB permeant with scopoletin, dodecanoic acid, tetradecanal, tetradecanoic acid and hexanoic acid respectively. Most of the compounds present in Ipomoea mauritiana are not the substrates for P-gp except.

The Swiss ADME model returns "Yes" or "No" if the compound under examination has greater probability to be a substrate or non-substrate of P-gp or inhibitor or non-inhibitor of Cytochrome P 450 isoenzymes (CYP1A2, CYP2c9, CYP2C19, CYP2D6 and CYP3A4). Octacosoic acid, nonacosane and tetracosane returned "Yes" for P-gp substrate and remaining all small molecules as "No" for P-gp substrate (Table 6). Almost all of the small molecules returned as non-inhibitors for inactivation for CYP isoenzymes except for scopoletin, tetradecanal, tetradecanoic acid, octadecan 1 ol, octadecanoic acid and tetracosane for CYP1A2. The skin permeability coefficient (Log K_p), a multiple linear regression (Potts and Guy, 1992), the more negative the log K_p (with K_p in cm/s), the less skin permeant is the molecule. Among the phytoconstituents of the Ipomoea mauritiana chloroacetic acid (-6.72) is the least permeant compound and nonacosane (2.08) is highly permeant respectively.

This SwissADME section gives access to five different rule-based filters, with diverse ranges of properties inside of which the molecule is defined as drug-like. The Lipinski (Pfizer) filter is the pioneer rule-of-five implemented and with the Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer) methods. Multiple estimations allow consensus views or selection of methods best fitting the end-user's specific needs in terms of chemical space or project-related demands. Any violation of any rule described here appears explicitly in the output panel. All the compounds of *Ipomoea mauritiana* expressed and followed the filtered rule invoked in the SwissADME, the violation shown by the molecules are minimal. SwissADME interpretation did not posts any PAINS alert of any of the molecules. Brenk considered compounds that are smaller and less hydrophobic and not those defined by "Lipinski's rule of 5" to widen opportunities for lead optimization This was after exclusion of compounds with potentially mutagenic, reactive and unfavorable groups such as nitro groups, sulfates, phosphates, 2-halopyridines and thiols. (Brenk *et al*., 2008). Among the compounds examined, seven molecules flouted brenks rule, remaining all followed and almost all the compounds failed Leadlikeness criteria respectively.

The boiled egg allows to evaluate passive gastrointestinal absorption (HIA) and brain penetration (BBB), the white region is for high probability for passive absorption by GIT and the yellow region (yolk) is for high probability of brain penetration. In addition the points are coloured in blue, if predicted as actively effluxes by P-gp (PGP^+) and in red if predicted as non-substrate of P-gp (PGP^-). In the present study prediction, nine molecules out of 15 are within the prediction site, among them TD (Tetradecanal), TDA (Tetradecanoic acid), D (Dodecanoic acid), H (Hexanoic acid) and S (Scopoletin) are within yolk (high brain penetration) of the BOILED-Egg and O-1-ol (Octadecan-1-ol), ODA (Octadecanoic acid) and C (Chloroacetic acid) are in white of the BOILED-Egg (high passive absorption of GIT) respectively. All the molecules are depicted as red indicating non-substrate of P-gp. The Bioavailability Radar enables a first glance at the drug-likeness of a molecule. The pink area represents the optimal range for each properties

5. Conclusion

The small molecules originating from plants which impede altered metabolism emerge as potential therapeutic agents in drug discovery and development. In the present study, we used SwissADME web tool to evaluate hit molecule present in *Ipomoea mauritiana* Jacq. From these study the ADME property of the herb is disclosed for researcher, which can be used as appropriate tool for further identification of their *in vitro* and *in vivo* therapeutic potentials.

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