SWISS ADME PROPERTIES SCREENING OF THE PHYTOCHEMICAL COMPOUNDS PRESENT IN *TERMINALIA ARJUNA*

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Abstract
Phytochemical analysis of medicinal plants has become increasingly popular in recent years due to plants' ability to supplement current pharmacological needs. Active compounds among candidates can be augmented using computer mechanics techniques such as in silico screening and pharmacokinetic screening, and mechanisms of action of medicinal plants can be identified using in silico screening and pharmacokinetic screening. The plant is well-known for its anti-tuberculosis activity. It has been shown to have cytotoxicity, antibacterial activity, antioxidant activity, anti-diarrheal activity, and hepatoprotective activity. The current study focuses on using the Swiss ADME in silico ADME tool for pharmacological and pharmacognostic characterization of *Terminalia arjuna.*Researchers can use the findings of these investigations to conduct *in vitro* and *in vivo* studies to discover the pharmacological keystones of phytochemicals.

Keywords: SwissADME, *Teminalia arjuna*, Phytoconstituents

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Introduction

The paleolithic people were well aware of the medicinal plant tradition as herbal medicines. Most of the persons in developing nations rely on traditional medicine, and humans rely on plants for basic needs such as food, clothing, flavour, shelter, scent, and medications. Drug discovery from medicinal plants provides better leads, in addition to a wide range of pharmacological properties such as cytotoxicity, anti-diarrhea, antibacterial, anti-inflammatory, antioxidant, anthelmintic, anti-nociceptive, and hemolytic activity. The plant is widely renowned for its anti-tuberculosis activity. According to Ayurvedic teachings, *Terminalia arjuna* is one of the most essential medicinal herbs for the treatment of illnesses (Biljana Bauer Petrovska, 2012).

Terminalia arjuna (Roxb.) is an evergreen tree commonly known as Arjun in India. It is a tree that grows to a height of 20-30 m and belongs to the Combretaceae family. *T. arjuna* has been cited in ancient Indian literature, Ayurveda, for cardiac disease; it has also been mentioned by Charaka in his treatise Charak Samhita and practised by Ayurvedic practitioners like Chakradatta and Bhava-Mishra. Ayurvedic words characterise the plant's stem bark as acrid, pleasant, cooling, styptic, tonic, antidysenteric, and febrifuge (Kumar and Maulik, 2013). According to the pathophysiological condition, it has been proposed to be used as a powder, decoction, hydroalcoholic extract, bark powder with Ghrita (fat), or bark powder heated in milk (kshirpaak). The study of phytocompound absorption, distribution, metabolism, and excretion (ADME) has increased in recent years. Chemical ADMET characteristics are important in all stages of drug research and development. Pharmacokinetic studies are now being used in medication development.To be effective, a drug molecule must reach its target in sufficient concentration in the body. One of the primary reasons for medication development failure is a failure to address pharmacokinetic parameters.As a result, our primary responsibility is to evaluate the physicochemical and pharmacokinetic properties of the phytochemical elements of *T.arjuna* using Swiss ADME, publicly available online software (Wu *et al*., 2020).

Materials and Methods

Swiss ADME (www.swissadme.ch)

GCMS analysis

According to previous reports, *T. arjuna* has been identified with 20 phytochemicals, and these compounds have been considered to identify the Swiss ADME properties (Mandal *et al*., 2013; Gupta and Kumar, 2017; Subasini Uthirapathy and Javed Ahamad, 2019). Swiss ADME software from the Swiss Institute of Bioinformatics (http://www.sib.swiss) was accessible in a web server that displays the Swiss ADME Submission

page in Google was used to estimate individual ADME behaviors of phytochemicals of *Terminalia arjuna*. The list is constructed with one input per molecule, as defined by a simplified molecular-input line-entry system (SMILES), and the results are presented for each molecule.

Computer-based drug design is currently frequently used in the prediction of ADMET properties of medicines, which leads to early-stage drug discovery. The motivation for these Insilco techniques is due to the lower cost time factor involved when compared to regular ADMET profiling. For example, it takes a minute in an Insilco model to screen 20,000 or more molecules, but it takes 20 weeks in a "wet" laboratory. Because of the accumulating ADME data available with this software in the late 1990s, several pharmaceutical companies are now adopting computer models that, in some situations, are replacing the "wet" screens. As a result of this paradigm shift, various theoretical approaches for predicting ADMET parameters have been developed (Simone*et al*., 2021).

Bio-availability Radar

The bioavailability radar provides a preliminary look at the drug-likeness of compounds of interest by considering six physicochemical properties: LIPO (Lipophilicity), SIZE, POLAR (Polarity), INSOLU (Insolubility), INSATU (Insaturation), and FLEX (Flexibility). Lipophilicity: XLOGP3 between -0.7 and + 5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 0A2, solubility: log S less than 6, saturation: fraction of carbons in the sp3 hybridization less than 0.25, and flexibility: no more than 9 rotatable bonds.

Lipophilicity

Lipophilicity is a critical characteristic in drug discovery and design since it complements the single most informative and successful physicochemical property in medicinal chemistry. It has been experimentally demonstrated as partition coefficients (log P) or distribution coefficients (log D). Log P depicts the partition equilibrium of a unionized solute between water and an immiscible organic solvent. Greater Lipophilicity corresponds to higher log P values. Swiss ADME provides five publicly available models to analyse the Lipophilicity character of a molecule, namely XLOGP3, WLOGP, MLOGP, SILICOS-IT, and iLOGP. XLOGP3, an atomistic accost with corrective elements and a knowledge-based library; WLOGP, a completely atomistic technique based on the fragmental system. MLOGP is an archetype of the topological technique proposed on a linear connection with 13 molecular descriptors incorporated (Morak-Młodawska and Jeleń M, 2022). SILICOS-IT, a hybrid method based on 27 fragments and 7 topological descriptors; iLOGP, a physics-based method based on solvation free energies in n-octanol and water determined by the generalized-born and solvent accessible surface area (GB/SA) model; The arithmetic mean of the values anticipated by the five recommended approaches is the consensus log P o/w (Riyad i*et al*., 2021).

Water Solubility

The solubility of a substance is heavily dependent on the solvent used, as well as the ambient temperature and pressure. The saturation concentration is the point at which adding more solute does not increase its concentration in solution.

A medication is termed very soluble when the highest dose strength is soluble in 250 mL of aqueous media with a pH range of 1 to 7.5. The use of the ESOL model (Solubility class: Log S Scale: Insoluble<10 poorly<6, moderately<4 soluble<2 very<highly) is one of two topological techniques incorporated in Swiss ADME to predict water solubility.

Although they deviate from the fundamental universal solubility equation in that they do not include the melting point parameter, the linear correlation between predicted and experimental values was strong (R2=0.69 and 0.81, respectively). SILICOS-IT produced the third predictor of Swiss ADME (Solubility class: Log S Scale: Insoluble-10 poorly-6, moderately-4 soluble-2 very0highly), where the linear coefficient is corrected by molecular weight (R2=0.75). All anticipated values are the decimal logarithm of the molar solubility in water (log S). Swiss ADME also gives solubility in mol/l and mg/ml units, as well as qualitative solubility classes.

Pharmacokinetics

On a plot of two calculated parameters; ALOGP versus PSA, the delineation exists in a zone with acceptable qualities for GI absorption. The zone most occupied by well-absorbed molecules is elliptical; it was named Egan egg, and it is used to assess the predictive capacity of the model for GI passive absorption and prediction for brain access by passive diffusion to finally lay the BOILED-Egg (Brain or Intestinal Estimate D permeation predictive model).

The BOILED-Egg model generates a quick, spontaneous, efficient, yet raucous technique for forecasting passive GI absorption, which is useful

for drug discovery and development. The white region contains molecules that are more likely to be absorbed by the GI tract, whereas the yellow region (yolk) contains chemicals that are more likely to permeate the brain. Cytochrome p450 (CYP) isoenzymes bio transform more than 50-90% of medicinal compounds from its five primary isoforms. P-gp is widely distributed in intestinal epithelium, where it pumps xenobiotics back into the intestinal lumen and from brain capillary endothelial cells back into the capillaries. Swiss ADME uses the support vector machine (SVM) technique for binary classification of datasets containing known substrates/non-substrates or inhibitors/non-inhibitors. The resulting molecule will return "Yes" or "No" if the molecule under examination is considered to be a substrate for both P-gp and CYP. The P-gp substrate SVM model was constructed on 1033 compounds (training set) and tested on 415 molecules (test set), with 10 fold CV: ACC=0.72/AUC=0.77 and External: ACC=0.88/AUC=0.94 respectively. The SVM model for Cytochrome P-450 1A2 inhibitor molecule was constructed on 9145 molecules (training set) and tested on 3000 molecules (test set), with a 10 fold CV of ACC=0.83/AUC=0.90 and an external ACC=0.84/AUC=0.91.The SVM model for Cytochrome P-450 2C19 inhibitor molecule was trained on 9272 molecules (training set) and tested on 3000 molecules (test set), with 10 fold CV: ACC=0.80/AUC=0.86, and external: ACC=0.80/AUC=0.87. The SVM model for Cytochrome P-450 2C9 inhibitor molecule was trained on 5940 compounds (training set) and tested on 2075 molecules (test set), with 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 constructed on 3664 molecules (training set) and tested on 1068 molecules (test set), with the following 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 trained on 7518 compounds (training set) and tested on 2579 molecules (test set), with 10 fold CV: ACC=0.77/AUC=0.85, and external: ACC=0.78/AUC=0.86.

Drug likeness

Swiss ADME filters chemical libraries to reject compounds with characteristics that are incompatible with an acceptable pharmacokinetic profile, using five distinct ruled-based filters from major pharmaceutical companies in order to improve the quality of proprietary chemical collections. The Lipinski filter (Pfizer) is the first of five pioneer rules for characterising tiny compounds based on their physicochemical property profiles, which include Molecular Weight (MW) less than 500, N or O 10, MLOGP 4.15, NH or OH 5. Lipinski strictly views all nitrogens and oxygens as H-bond acceptors and all nitrogens and oxygens containing at least one hydrogen as H-bond donors.

Furthermore, aliphatic fluorines are acceptors, but alinine nitrogen is neither donor nor acceptor. The Ghose filter (Amgen) defines tiny molecules based on their physicochemical properties, the presence of functional groups, and their substructures. The qualifying range includes molecular weight between 160 and 480 Da, WlogP between -0.4 and 5.6, molar refractivity (MR) between 40 and 130 for a total number of atoms; the qualifying range is between 20 and 70 atoms in a tiny molecule. The Veber filter (GSK filter) model represents compounds as drug-like if they have 10 rotatable bonds and a TPSA equal to or less than 140 2 with 12 or fewer H-bond donors and acceptors.

The Egan filter (Pharmacia filter) predicts the drug absorption is dependent on mechanisms involved in the membrane permeability of the small molecule. These models represent molecules as drugs, such as if they had WLOGP 5.88 and TPSA 131.6, respectively. The Egan computer model for human passive intestinal absorption (HIA) of small compounds allowed for active transport and efflux pathways and will thus be robust in predicting medication absorption (Mahanthesh*et al*., 2020). Muegge filter (Bayer filter) is a self-contained Pharmacophore point filter that separates drug-like and non-drug-like compounds. These models represent molecules as a medication if they have a molecular weight between 200 and 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, and so on. The Abbott bioavailability score aims to estimate the likelihood of a chemical having at least 10% oral bioavailability in rats or observable Caco-2 permeability, which predicts the likelihood of a substance having F>10% based on the predominant charge at biological pH in a rat model. It focuses on rapid screening of chemical libraries in order to pick the best compounds for synthesis (Ranjith and Ravikumar, 2019).

Table1: General characteristics of Phyto-chemicals of *Terminalia arjuna*.

Sl.No	Name of compounds	Drug Likeness – Lipinski Role of 5					Solubility			Pharmacokinetics		Lipinski Violations	Drug Likeness
		MW g/mol	HBD	HBA	HBR	log P	Log S (ESOL)	Log S (Ali)	Log S (SILICO S-IT)	GI absorption	CYP enzymes inhibitors		
1.	Anethole	148.20	0	1	2	2.55	-3.11	-3.17	-2.98	High	No	1	Yes
2.	1,1-Diethoxy-3-methylbutane	160.25 g/mol	0	2	6	2.81	-2.03	-2.55	-2.21	High	No	0	Yes
3.	S)-(+)-2-Amino-3-methyl-1-butanol	239.22 g/mol	6	8	5	1.15	1.90	1.83	-0.09	Low	No	1	Yes
4.	Ethyl pipecolinate	157.21 g/mol	1	3	3	1.79	-1.03	-1.04	-1.56	High	No	0	Yes
5.	Glycerin	92.09 g/mol	3	3	2	0.45	0.83	1.00	1.08	High	No	0	Yes
6.	Pentanoic acid	102.13 g/mol	1	2	3	1.32	-1.15	-1.78	-0.78	High	No	0	Yes
7.	Cyclopropane carboxyli cacid, 1-amino-	177.20 g/mol	2	3	2	0.97	-0.10	0.84	-2.00	High	No	0	Yes
8.	Benzeneacetaldehyde	120.15 g/mol	0	1	2	1.33	-2.07	-1.76	-2.70	High	No	0	Yes
9.	Glycine, N-(2-methyl-1-oxo-2-butenyl)-, methyl ester, (E)-	229.35 g/mol	1	3	6	2.89	-2.18	-2.87	-2.11	High	No	0	Yes
10.	2,4-Dihydroxy-2,5-dimethyl-3(2H)-furan-3-one	144.13 g/mol	2	4	0	1.24	-0.68	-0.87	-0.18	High	No	0	Yes
11.	1-Methoxyhexane	116.20 g/mol	0	1	5	2.56	-1.75	-2.25	-2.36	High	No	0	Yes
12.	9-Oximino 2,7-diethoxyfluorene	283.32 g/mol	1	4	4	-4.34	-4.89	-5.71	-5.71	High	Yes	0	Yes
13.	Heptadecane, 9-hexyl	324.63 g/mol	0	0	19	6.20	-8.40	-12.40	-8.76	Low	Yes	1	Yes
14.	9,10 Secocholesta 5,7,10(19) triene 3,24,25 triol	432.64 g/mol	4	4	7	4.29	-4.56	-5.37	-3.90	High	No	0	Yes
15.	Butanoic acid, 2,3 dihydroxypropyl ester	162.18 g/mol	2	4	6	1.28	-0.34	-0.78	-0.46	High	No	0	Yes
16.	2-Naphthalene methanol	158.20 g/mol	1	1	1	2.08	-2.76	-2.27	-3.89	High	No	0	Yes
17.	9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)	392.57 g/mol	0	4	16	5.77	-5.30	-7.22	-5.45	High	Yes	0	Yes
18.	3-Hydroxyspirost-8-en-11-one	428.60 g/mol	1	4	0	3.94	-5.14	-5.07	-4.82	High	No	0	Yes
19.	Protriptyline	263.38 g/mol	1	1	4	3.26	-4.43	-4.38	-6.70	High	No	0	Yes
20.	Olean-12-ene-3,15,16,21,22,28-hexol,(3α,15α,16α,21α,22α)	506.71 g/mol	6	6	1	2.94	-5.22	-5.90	-3.30	High	No	0	No

Bioavailability Radar

The bioavailability radar assesses a compound's drug-likeness quickly. As shown in Fig.1, the pink area represents the optimal range of each parameter; when considering the parameters of a phytocompound, the radar plot of the compound must fall in the pink area in order to be considered drug-like; thus, the ligands are either predicted to be orally bioavailable or not orally bioavailable via the radar plot (Bojarska *et al*., 2020). Flexibility (FLEX) and polarity (polar) are two important qualities that affect chemical bioavailability. Flexibility is determined by rotatable bonds; compounds with rotatable bonds > 10 are projected to have low oral bioavailability, whereas polarity, as indicated by topological polar surface, predicts that molecules with TPSA > 20 2 130 2 have good oral bioavailability (Veber *et al*., 2002; Daina e tal., 2017s). Fourteen phytochemicals (1,1-Diethoxy-3-methylbutane, (S)-(+)-2-Amino-3- methyl-1- butanol, Ethyl pipecolinate, Glycerin, Pentanoic acid, Glycine, N-(2-methyl-1-oxo-2-butenyl)-, methyl ester, (E)-2,4-Dihydroxy-2, 5-dimethyl-3 (2H)-furan 3- one, 1-Methoxyhexane, 9,10 Secocholesta 5,7,10 (19) triene 3,24,25 triol, Butanoic acid, 2,3 dihydroxypropyl ester, 3-Hydroxyspirost-8-en-11-one, Protriptyline, and Olean-12-ene-3,15,16, 21, 22,28-hexol, (Fig. 1).

Boiled Egg for Prediction of GI Absorption and Brain Penetration

The BOILED-Egg model provides a quick, simple, readily repeatable, and statistically unparalleled robust technique for predicting the passive gastrointestinal absorption and brain access of small compounds relevant for drug discovery and development. Figure 2 depicts the BOILED-EGG (Naveed *et al*., 2023). The user may add the WLOGP and tPSA for up to 100 molecules, and the associated spots are mapped onto the BOILED-Egg. One molecule is anticipated not to be absorbed and not to be BBB permeant since it is beyond of the plot's range (Antoine Daina and Vincent Zoete, 2016).

Figure.1 Bioavailability Radar and its Significance

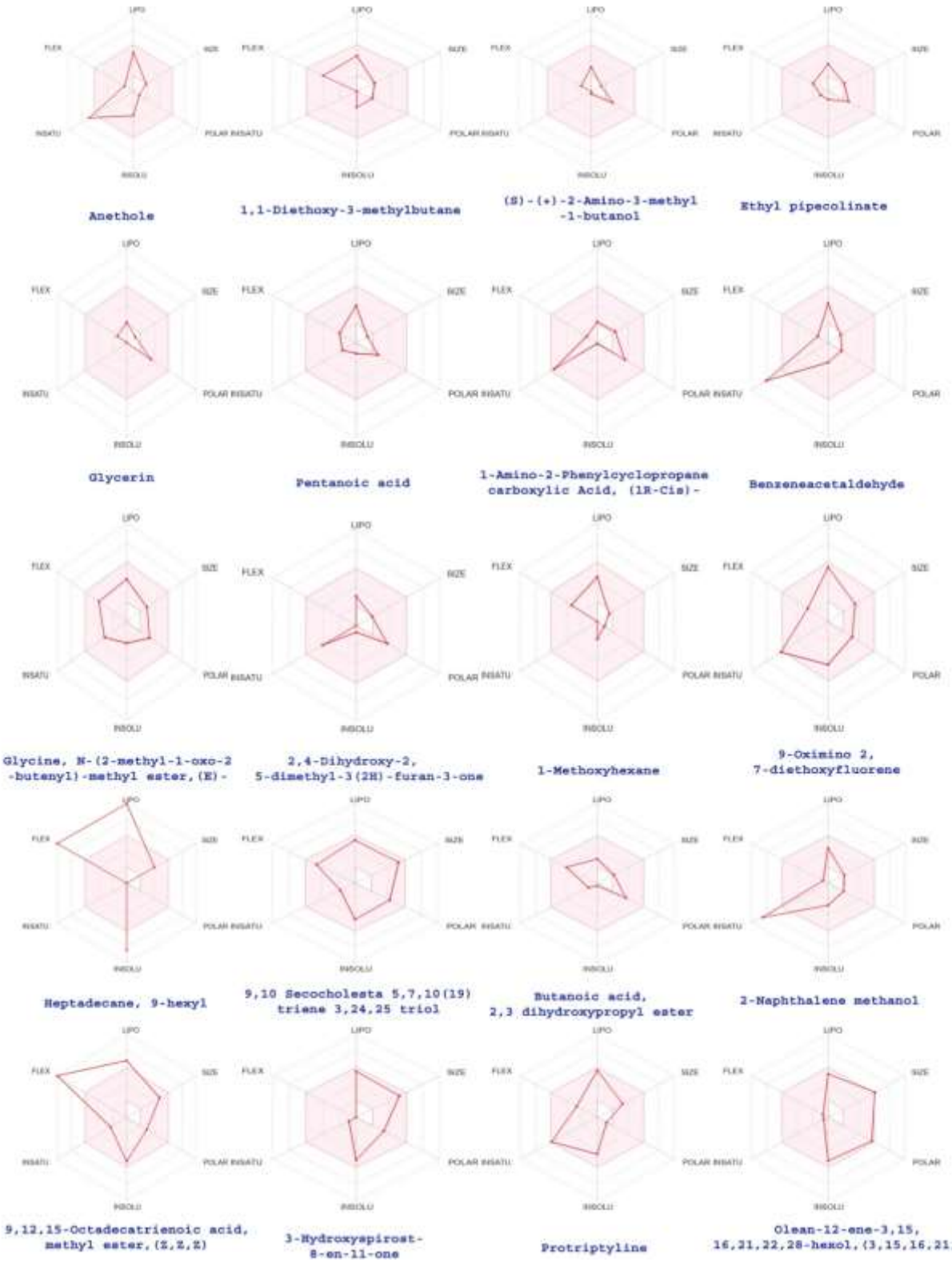

Figure.2. The BOILED egg Model prediction of GI absorption and BBB penetration of the Phyto-constituents of *T.arjuna* by using swissADME

Conclusion

CADD has dramatically reshaped the research and development pathways in drug candidate identification due to the rapid increase in chemical and biological information. Computational techniques are widely used in the drug discovery and development process because they save money and time. This study presents a freely available Swiss ADME, a web-based tool for evaluating the ADME properties of phytoconstituents found in *Terminalia arjuna*. The phyto constituents of the plants were enlisted through the software includes Fourteen phytochemicals (1,1-Diethoxy-3-methylbutane, (S)-(+)-2-Amino -3-methyl-1- butanol, Ethyl pipecolinate, Glycerin, Pentanoic acid, Glycine, N-(2-methyl-1-oxo-2-butenyl)-, methyl ester, (E)-2,4-Dihydroxy-2, 5-dimethyl-3 (2H)-furan3-one, 1-Methoxyhexane, 9,10 Secocholesta5,7,10(19) triene 3,24,25 triol, Butanoic acid, 2,3 dihydroxypropyl ester, 3-Hydroxyspirost-8-en-11-one, Protriptyline, and Olean-12-ene-3,15,16,21,22,28-hexol.As a result, the physicochemical and pharmacokinetic properties of the phytoconstituents were investigated, as shown in the tables and figures. Furthermore, researchers and scientists can use the values as guidelines when developing potential semisynthetic and synthetic drugs for a variety of applications.

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