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Computational Prediction of Pharmacokinetic and Toxicological Properties of Selected Phytochemicals from *Eugenia jambolana* Lam.

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Abstract

Background: *Eugenia jambolana* Lam. is a herb distributed throughout the world and documented to possess many beneficial effects. The plant has been documented for the presence of various phytochemicals including primary and secondary metabolites.

Aim of the Study: In the present investigation an attempt has been made to carry out computational prediction of pharmacokinetic and toxicological properties of selected phytoconstituents from *Eugenia jambolana* Lam.

Methodology: We have selected oleanolic acid, ursolic acid, arjunolic acid, maslinic acid, corosolic acid, asiatic acid, alphitolic acid, betulinic acid. PubChem database was utilized to collect the canonical smiles. Molsoft server was utilized to determine the drug likeness of selected phytochemicals. The admetSAR (Structure Activity Relationship) and Swiss ADME (Absorption, Distribution, Metabolism, and Excretion) server were used for the determination of toxicity and pharmacokinetic properties.

Results: The results of investigation yielded the drug likeness score of selected phytoconstituents along with its pharmacokinetic and toxicity properties. The selected constituents such as Maslinic acid, Arjunolic acid, Oleanolic acid, Ursolic acid, Corosolic acid, Asiatic acid, Alphitolic acid, Betulinic acid were found to be better drug like candidates.

Conclusion: The proposed *In-silico* work concluded that computer aided prediction and server based investigation was important and informative in collecting the data regarding drug like candidates and pharmacokinetic and toxicological properties of bioactive compounds from plant *Eugenia jambolana* Lam.

Keywords: Arjunolic Acid, Computational Prediction, Drug Likeness, Pharmacokinetics, Toxicology

Introduction

Eugenia jambolana Lam. is a herb that is available throughout the world with many beneficial effects and is mainly documented in the family known as Myrtaceae. It is commonly referred as Jamun or black plum and is very beneficial for the management of hyperglycaemia. It has a good integral part in various traditional systems of medicines. The ripened fruits are sweetish with mild sour taste and are used to prepare jellies, drinks, wine and juices. It contains various primary and secondary metabolites such as minerals, carbohydrates and pharmacologically active phytoconstituents like anthocyanins, terpenes and flavonoids. The leaves of *Eugenia jambolana* Lam are known to have constituents like-hepatcosane, n-nonacosane, β-sitosterol, betulinic

acid, mycaminose, n-hentriacontane, noctacosanol, n-triacontanol, n-dotricontanol, quercetin, myricetin, flavonol glycosides, crategolic (maslinic) acid, myricetin, acylated flavonol glycosides, 3-O-(4″-acetyl)-α-L-rhamnopyranosides. Various scientific studies on *Eugenia jambolana* Lam. have documented important pharmacological actions such as antibacterial, antifungal, cardio-protective, anti-inflammatory, anti-allergic, antivirals, anti-genotoxic, anticancer, chemopreventive, radioprotective, antioxidant, hepatoprotective, anti-diarrheal, hypoglycaemic and antidiabetic effects.[1,2]

Lipinski's rule of five, also known as Pfizer's rule of five is used to evaluate the drug ability or to determine if chemical compounds with a specific biological or pharmacological activity have physical or chemical properties that would make it an orally active drug in human beings. The rule of five predicts that poor permeation or absorption is more likely to exist when the molecular weight is greater than 500, more than 5H bond donors, 10H bond acceptor and calculated logP >5. However, Lipinski specifically stated that the rule of five only holds for compounds that are not substrates for active transporter. The admetSAR and SwissADME servers are used for describing the molecular properties that are important in drug pharmacokinetic property in the human body.

Literature search revealed that till date no computational study has been reported on computer based screening on *Eugenia jambolana* Lam. to investigate its drug like properties and prediction of ADME (Absorption, Distribution, Metabolism, and Excretion) and toxicity profile. Hence the present study aimed to study drug likeness properties, ADME and toxicity profile of selected phytochemicals of *Eugenia jambolana* Lam. using computer applications and servers.

Materials and Methods

Server used: PubChem database, Molsoft, admetSAR, SwissADME.

Phytoconstituents used: Alphitolic acid, Betulinic acid Oleanolic acid, Ursolic acid, Arjunolic acid, Maslinic acid, Corosolic acid and Asiatic acid.

Investigation of Drug Likeness Score and Physico-chemical Properties: In the present study, we have identified and taken around eight phytoconstituents from *Eugenia jambolana* Lam. for determining drug likeness score according to Lipinskies Ro5. Lipinsk's rule of five was followed so as to find out drug likeness property of each of the phytoconstituents. The data about drug likeness was complied with adherence to Lipinski's rule. The canonical SMILES (Simplified Molecular Line Entry System) were obtained from PubChem and were applied in Molsoft software to collect the data.[3-6]

Computational and Server Based Prediction of Pharmacokinetic and Toxicological Properties The pharmacokinetic properties such as ADME of phytoconstituents play an important role in drug development process. Therefore, we used the online server admetSAR and SwissADME to predict several pharmacokinetic aspects. admetSAR and SwissADME evaluated pharmacokinetic properties such as plasma protein bindings (PPB), skin permeability, blood brain barrier (BBB) study, P-glycoprotein, Human intestinal absorption and buffer solubility along with other important aspects of ADME.[7-14]

Results

Eugenia jambolana Lam. consists of various phytoconstituents and found to exert many pharmacological and biological actions. In the present computational screening study, we have selected oleanolic acid, ursolic acid, arjunolic acid, maslinic acid, corosolic acid, asiatic acid, alphitolic acid, betulinic acid as important constituents based on Lipinskies Ro5. The molecular weight, hydrogen bond acceptor, hydrogen bond donor, LogP value and drug likeness property score of identified or selected phytoconstituents are presented in Table 1.

The admetSAR and SwissADME servers were used for describing the molecular properties important for a drug pharmacokinetic property in the human body, including their ADME. The pharmacokinetic property such as ADME of phytoconstituents plays an important role in drug development process. The admetSAR and SwissADME evaluates pharmacokinetic properties such as plasma protein binding (PPB), skin permeability, P-glycoprotein, blood brain barrier (BBB) study, human intestinal absorption and buffer solubility and toxicity prediction. The admetSAR and SwissADME profile of oleanolic acid, ursolic acid, arjunolic acid, maslinic acid, corosolic acid, asiatic acid, alphitolic acid, betulinic acid presented in Table 2.

Table 1: Phytoconstituents and Molecular Properties Prediction by Molsoft Analysis

Sl. No	Phytoconstituents	Mol. Weight (>500)	HBA (>10)	HBD (>5)	Log P (>5)	Drug likeness Score
1	Oleanolic acid	456.36	3	2	6.66	0.37
2	Maslinic acid	472.36	4	3	5.51	0.55
3	Arjunolic acid	488.35	5	4	3.84	0.64
4	Ursolic acid	456.36	3	2	6.46	0.66
5	Corosolic acid	472.36	4	3	5.3	0.6
6	Asiatic acid	488.35	5	4	3.63	0.77
7	Alphitolic acid	472.36	4	3	5.9	0.19
8	Betulinic acid	456.36	3	2	7.05	0.25

Table 2: Pharmacokinetic and toxicity predicted profile of phytocompounds

Parameters		Compounds							
		1	2	3	4	5	6	7	8
ABSORPTION	HIA	+	+	+	+	-	+	+	+
	Caco-2	+	+	-	+	-	-	+	+
	HOB	0.85	0.56	0.56	0.85	0.56	0.56	0.56	0.85
DISTRIBUTION	BBB	+	+	+	+	-	+	+	+
	P-glycoprotein (i)	-	-	-	-	-	-	-	-
	P-glycoprotein (s)	+	+	+	+	+	+	+	+
	PPB	No	Yes	Yes	No	Yes	Yes	Yes	No
METABOLISM	CYP3A4 (s)	+	+	+	+	+	+	+	+
	CYP2C9 (s)	-	-	-	-	-	-	-	-
	CYP2D6 (s)	-	-	-	-	-	-	-	-
	CYP3A4 (i)	-	-	-	-	-	-	-	-
	CYP2D6 (i)	-	-	-	-	-	-	-	-
	CYP1A2 (i)	-	-	-	-	-	-	-	-
EXCREATION	Plasma t1/2	NA	NA	NA	NA	NA	NA	NA	NA
	Renal clearance	NA	NA	NA	NA	NA	NA	NA	NA
TOXICITY	HERG	-	-	-	-	-	-	-	-
	Hepatotoxicity	+	+	+	+	+	+	+	+
	AOT	III	III	III	III	III	III	III	I
	Eye corrosion	-	-	-	-	-	-	-	-
	Carcinogenicity	-	-	-	-	-	-	-	-
	Ames mutagenesis	-	-	-	-	-	-	-	-

1-oleanolic acid, 2-maslinic acid, 3-arjunolic acid, 4-ursolic acid, 5-corosolic acid, 6-asiatic acid, 7-alphitolic acid, 8-betulinic acid. Human either-a-go-go inhibition: HERG, Plasma protein binding (PPB), Blood Brain Barrier (BBB), Human Intestinal Absorption (HIA), Human Oral Bioavailability (HOB), Acute Oral Toxicity (AOT), (i): Inhibiter, (s): Substrate

Discussion

Eugenia jambolana Lam. is a herb distributed throughout the world and documented to possess many beneficial effects. The plant was documented for the presence of various phytochemicals including primary and secondary metabolites. In the present investigation, an attempt has been made to carry out computational prediction of pharmacokinetic and toxicological properties of selected phytoconstituents from *Eugenia jambolana* Lam. We have selected oleanolic acid, ursolic acid, arjunolic acid, maslinic acid, corosolic acid, asiatic acid, alphitolic acid, betulinic acid. PubChem database was utilized to collect the canonical smiles. Molsoft server was utilized to determine the drug likeness of selected phytochemicals. The admetSAR (Structure Activity Relationship) and Swiss ADME (Absorption, Distribution, Metabolism, and Excretion) server were used for the determination of toxicity and pharmacokinetic properties.

Lipinski's rule of five also known as Pfizer's rule of five, was used to evaluate the drug likeness or to determine if chemical compounds with a specific biological or pharmacological activity have physical or chemical properties that would make it an orally active drug in human beings. The rule of five predicts that poor

permeation or absorption is more likely to exist when there is molecular weight is greater than 500, more than 5H bond donors, 10H bond acceptor and calculated logP >5. However, Lipinski specifically stated that the rule of five only holds for compounds that are not substrates for active transporter. The admetSAR and SwissADME servers are used for discussing the molecular parameters that are important in drug pharmacokinetic property in the human body.

The data obtained in study provided the drug likeness score of selected phytochemicals along with its pharmacokinetic and toxicity properties. The selected constituents such as maslinic acid, arjunolic acid, ursolic acid, oleanolic acid, corosolic acid, asiatic acid, alphitolic acid, betulinic acid were found to be better drug like candidates.

Conclusion

The proposed *In-silico* work concluded that computer aided prediction and server based investigation was important and informative in collecting the data regarding drug like candidates and pharmacokinetic and toxicological properties of bioactive compounds from plant *Eugenia jambolana* Lam. The data obtained from SwissADME and admetSAR will be useful in future to carry out work on *Eugenia jambolana* Lam. The selected constituents such as maslinic acid, arjunolic acid, ursolic acid, oleanolic acid, corosolic acid, asiatic acid, alphitolic acid and betulinic acid were found to be better drug like candidates.

Conflits of Interest

None.

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