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Research Article

IN SILICO EVALUATION OF PHARMACOKINETICS, DRUG-LIKENESS AND MEDICINAL CHEMISTRY FRIENDLINESS OF MOMORDICIN1: AN ACTIVE CHEMICAL CONSTITUENT OF *MOMORDICA CHARANTIA*

S.B. UDUGADE*[1], R.C DOIJAD[1], B. V. UDUGADE[2]

[1]*Departments of Pharmaceutics, Krishna Institute of Medical Sciences "Deemed to be University, Krishna Institute of Pharmacy, Malkapur, Karad, Maharashtra, India*

[2]*Departments of Pharmaceutical Chemistry, Satara College of Pharmacy, Degaon, Satara, Maharashtra, India*

**Corresponding author: swatiudugade@gmail.com*

ABSTRACT

In the present investigation, an attempt was made to predict pharmacokinetic, toxicity and bioactivity profile of Momordicin1; an active chemical constituent of *Momordica charantia,* by *In-silico* methods. *In-silico* prediction tools were used for prediction of Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET). First, PASS *In-Silico* tool was used to predict polypharmacological activities of Momardicin1. Second, Swiss ADME was used for prediction of physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug likeness and medicinal chemistry. Finally, XUNDRUG eMolTox *In-Silico* tool was used to predict toxicity. Result of PASS prediction tool showed that Momordicin1 can be used as apoptosis inhibitors or anti-neoplastic agent; SWISS ADME result showed that drug can be orally active, cannot cross blood brain barrier and will not have any central nervous system side effect. Bioavailability radar study indicated that Momordicin1 can be considered drug-like as physicochemical properties falls within pink area of radar plot. The lipophilicity was found to be 4.9 indicating Momardicin1 could be orally active, moderate to poor water solubility indicating efforts should be taken to enhance solubility during formulation. Molecule may be effluxed out from GIT or Brain as it is substrate for P-gp. Momordicin1 does not interact with any cytochrome P450 isoform indicating these isoforms may not be involved in biotransformation of this molecule. XUNDRUG *In-Silico* tool results showed hepatotoxicity and reproduction toxicity potential of Momordicin1. From the present study, it can be concluded that the useful pharmacokinetics, drug-likeness and medicinal chemistry friendliness of momordicin1 suggested that Momordicn1 can be a good drug candidate in future.

Keywords: Momordicin1, PASS, SWISS ADME, XUNDRUG, *in silico* ADMET prediction.

1. INTRODUCTION

Over decades properties related to absorption, distribution, metabolism, excretion and toxicity have become one of the most important issues in drug development process. Recently drug withdrawal rate is increasing the economic pressure on pharmaceutical industry as preclinical safety testing, in vivo and in vitro evaluations are costly and laborious. So, *In-silico* techniques have been widely used to estimate these properties. *In-silico* prediction has the potential to reduce the number of synthesized compounds with inadequate ADMET properties. Animal trials are currently the major method for determining the possible toxic effect of drug candidates and cosmetics. *In-silico* prediction methods represent an alternative approaches and aim to rationalize the preclinical drug development.

Momardicin I, found in bitter gourd is a constituent of leave whose ADMET prediction will help in its development.

2. MATERIALS AND METHODS

Structure of Momardicin1 in SMILES file format was copied from Pub Chem website and used for further studies.

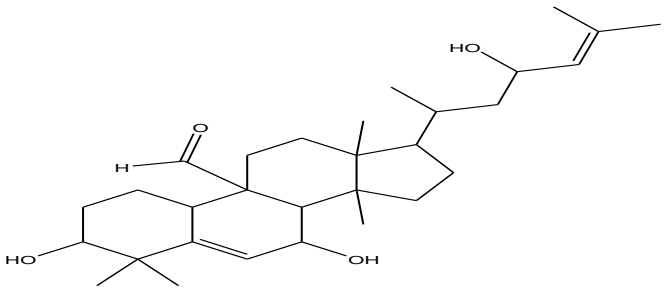


Fig. 1: Chemical structure of momordicin1

O=CC12CCC3(C(C2C(C=C2C1CCC(C2(C)C)O)O)(C)CCC3C(CC(C=C(C)C)O)C)C

Fig. 2: Canonical SMILES of momordicin1 structure

2.1. Procedure for prediction of ADME by using Swiss ADME *In-silico* tool

Swiss ADME tool permits to calculate physicochemical properties, forecast ADME parameters, drug like small molecules to sustain drug discovery process were used. Physicochemical properties, Lipophilicity, Water solubility, Pharmacokinetics, Drug likeness and Medicinal Chemistry of Momordicin1 were predicted by software [1].

2.2. Bioavailability Radar

Bioavailability radar (Fig. 3) was used for a rapid assessment of drug-likeness in which six physicochemical properties were taken into account: lipophilicity, size, polarity, solubility, flexibility and saturation. A physicochemical range on each axis was depicted as a pink area in which the radar plot of the molecule has to fall entirely to be considered drug-like.

2.3. Physicochemical Properties

Physicochemical descriptors like molecular weight (MW), molecular refractivity (MR), count of specific atom types and polar surface area (PSA) were computed because these were proven useful descriptors in many models and rules to quickly estimate some ADME properties.

2.4. Lipophilicity

The partition coefficient between *n*-octanol and water ($\log P_{o/w}$) is the classical descriptor for *Lipophilicity* due to the critical importance of this physicochemical property for pharmacokinetics drug discovery. Five freely available predictive models; i.e. XLOGP3, WLOGP, MLOGP, SILICOS-IT and iLOGP were used for determination of partition coefficient and arithmetic mean of the values predicted by the five models were calculated and mentioned as consensus $\log P_{o/w}$

2.5. Water Solubility

Water soluble molecule significantly assists many drug development activities, mainly the ease of handling and formulation. Additionally, for discovery mission intended for oral administration, solubility is one important property affecting on absorption. ESOL model and the model devolved by Ali *et al*. were used for predicting water solubility.

2.6. Pharmacokinetics

BOILED-Egg model and multiple linear regression model developed by Potts et al. were used for prediction of pharmacokinetic parameters like GI absorption, BBB permeant, P-gp substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitor and Log K_p (skin permeation).

2.7. Drug-likeness

Five different rule-based filters namely the Lipinski (Pfizer) filter, the Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer) method used for estimation of drug likeness of molecule.

2.8. Medicinal Chemistry

Medicinal chemistry parameters were predicted to support medicinal chemists in drug discovery process. PAINS (Pan Assay Interference compounds), putatively toxic chemical filter, leadlikenes and synthetic accessibility medicinal chemistry parameters were determined

2.9. Target prediction

Swiss Target Prediction tool whose predictions are based on the similarity principle, through reverse screening was used for prediction of probable macromolecular targets of a Momordicin1 which can be assumed as bioactive.

2.10. Procedure for prediction of ADME by using XUNDRUG eMolTox *In-Silico* Tool

XUNDRUG eMolTox online predictor tool which can predicts toxicity from structure was used for prediction of Hepatotoxicity, Nephrotoxicity, Cardiotoxicity, CNS Toxicity, Mutagenicity, Genotoxicity, Respiratory Toxicity, Carcinogenicity Reproduction Toxicity, Cytotoxicity, Skin Sensitisation, Mitochondrial Toxicity and Toxic Structural Alerts of Momordicn1.

2.11. Prediction of Polypharmacological activity by using PASS online In-silico Tool

PASS (Prediction of Activity Spectra for Substances) a software used as a tool for evaluating the general biological potential of an organic drug-like molecule. PASS online predictor tool which can predicts over 4000 kinds of biological activity from structure was used for prediction of polypharmacological activities of Momordicn1. Most of known biologically active

substances have many different biological activities that caused both therapeutic and side actions. PASS results shown in result section which are given as probability to be active (Pa) score which estimates the chance that the studied compound is belonging to the sub-class of active compounds.

3. RESULT AND DISCUSSION

3.1. Results of prediction of ADME by using Swiss ADME *In-silico* tool

3.1.1. Bioavailability radar for Momardicin1

The colored zone is the suitable physiochemical space for oral bioavailability and physiochemical properties of Momordicin1 molecules falls within the color zone indicating that molecule can be orally active.

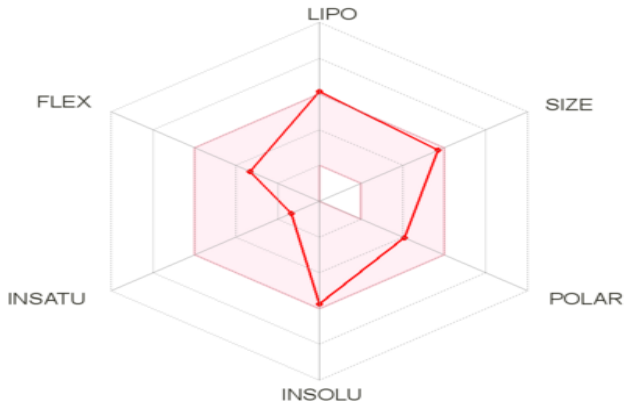


Fig. 3: Bioavailability radar for Momardicin1

LIPO=Lipophilicity, SIZE, POLAR (Polarity), INSOLU (Insolubility), INSATU (Instauration), FLEX (Flexibility)

Table 2: Predicted physicochemical properties of Momordicin1

Physicochemical Properties	Predicted Values	Program or Method used [Reference]
Formula	C30H48O4	Values are computed with OpenBabel9, version 2.3.0 [1]
Molecular weight	472.70 g/mol	
Number of heavy atoms	34	
Fraction Csp3	0.83	
Num. rotatable bonds	5	
Num. H-bond acceptors	4	
Num. H-bond donors	3	
Molar Refractivity	139.57	
TPSA (Topological Polar Surface Area)	77.76 Å²	Calculated using the fragment based technique [2]

Table 3: Predicted Lipophilicity of Momordicin1

Lipophilicity	Predicted Values	Program or Method used [Reference]
Log $P_{o/w}$ (iLOGP)	4.25	Calculated by in-house physical based method [2]
Log $P_{o/w}$ (XLOGP3)	5.26	Calculated by XLOP3 program[3]
Log $P_{o/w}$ (WLOGP)	5.46	Prediction by Atomic Contributions [4]
Log $P_{o/w}$ (MLOGP)	4.06	Calculated by topological method of Moriguchi [5]
Log $P_{o/w}$ (SILICOS-IT)	5.44	Predicted by SILICOS-IT program [6]
Consensus Log $P_{o/w}$	4.90	Average of all 5 predictions

Lipophilicity of Momordicin1 is below 5, indicating this molecule could be explored as orally active critical importance of this physicochemical property for pharmacokinetics drug discovery.

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. Momordicin1 molecule shows moderate to poor water solubility indicating efforts should be taken to enhance solubility during formulation.

Table 4: Predicted water solubility of Momordicin1

Water Solubility	Predicted Values	Program or Method used [Reference]
Log *S* (ESOL)	-5.75	Aqueous Solubility Directly from Molecular Structure [7]
Solubility	8.32e-04 mg/ml ; 1.76e-06 mol/l	
Class:	Moderately soluble	
Log *S* (Ali)	-6.64	*In Silico* Prediction of Aqueous Solubility Using QSPR Models [8]
Solubility	1.08e-04 mg/ml ; 2.28e-07 mol/l	
Class	Poorly soluble	
Log *S* (SILICOS-IT)	-4.53	Predicted by SILICOS-IT program [6]
Solubility	1.41e-02 mg/ml ; 2.98e-05 mol/l	
Class	Moderately soluble	

Log S Scale: (Insoluble < -10, Poorly < -6, Moderately < -4, souble < -2, Very <0< Highly)

Table 5: Predicted Pharmacokinetics properties of Momordicin1

Pharmacokinetics	Predicted Values	Program or Method used [Reference]
GI absorption	High	Calculated according to White of BOILD egg model [9]
BBB permeant	No	
P-gp substrate	Yes	Predicted by using support vector machine approach[10]
CYP1A2 inhibitor	No	
CYP2C19 inhibitor	No	
CYP2C9 inhibitor	No	
CYP2D6 inhibitor	No	
CYP3A4 inhibitor	No	

Human gastrointestinal absorption of Momordicin1 was found to be high with no blood-brain barrier permeability indicating molecule can be absorbed from intestine easily with no side effect in brains as it cannot passes through BBB.

The knowledge about compounds being substrate or non-substrate of the permeability glycoprotein provides information about its active efflux through biological membranes like gastrointestinal wall to the lumen or from the brain. Momordicin1 may be effluxed out from GIT or Brain as it is substrate for P-gp.

The information concerning interaction of molecules with cytochromes P450 (is critical because it plays important role in drug elimination through metabolic biotransformation. It is therefore of great importance for drug discovery to predict the tendency of the molecule to inhibit CYPs. Momordicin1 does not interact with any cytochrome P450 isoform, indicating these isoforms may not be involved in biotransformation of this molecule.

Table 6: Predicted Drug likeness of Momordicin1

Drug likeness	Predicted Values	Program or Method used [Reference]
Lipinski	Yes; 0 violation	Estimated by using computational approaches to estimate solubility and permeability developed by Lupinski's [11,12]
Ghose	No; 2 violations: MR>130, #atoms>70	Estimated by using Knowledge Based Approach developed by Ghose A K [13]
Veber (GSK) filter	Yes	Estimated by considering molecular properties that influence the oral bioavailability of drug candidates developed by Veber D F [14]
Egan (Pharmacia) filter	Yes	Estimated by using Multivariate Statistics approach developed by Egan W J [15]
Bioavailability Score	0.55	Calculated system developed by Martin YC [16]

Momordicin1 molecule bioavailability Score was 0.55, not violating any filter employed (exception Ghose filter) indicating that this molecule can be a drug could be synthesized and promoted to a further stage of a drug development pipeline.

Table 7: Predicted Medicinal Chemistry of Momordicin1

Medicinal Chemistry	Predicted Values	Program or Method used [Reference]
PAINS (Pan Assay Interferance structures)	0 alert	New Substructure Filters developed by Baell J B [17]
Brenk	2 alerts: aldehyde, isolated_alkene	Predicted by method developed by Brenk R [18]
Lead likeness	No; 2 violations: MW>350, XLOGP3>3.5	Predicted by method developed by Simon J. Teague [19]
Synthetic accessibility Score (1Easy to 10 difficult)	6.51	Calculated on basis of molecular complexity and fragment contributions [20]

Table 9: Top 15 target and target classes of Momordicin1

Rank	Target	Target Class
1	Prostanoid FP receptor	Family A G protein-coupled receptor
2	Prostanoid IP receptor	Family A G protein-coupled receptor
3	Solute carrier family 22 member 6	Electrochemical transporter
4	Glucocorticoid receptor	Nuclear receptor
5	Prostanoid EP2 receptor	Family A G protein-coupled receptor
6	Cytochrome P450 19A1	Cytochrome P450
7	Prostanoid EP1 receptor	Family A G protein-coupled receptor
8	Prostanoid EP4 receptor	Family A G protein-coupled receptor0
9	Prostanoid EP3 receptor	Family A G protein-coupled receptor
10	Protein-tyrosine phosphatase 1B	Phosphatase
11	Estrogen receptor beta	Nuclear receptor
12	Testis-specific androgen-binding protein	Secreted protein
13	Peroxisome proliferator-activated receptor gamma	Nuclear receptor
14	Prostaglandin E synthase	Enzyme
15	Peroxisome proliferator-activated receptor alpha	Nuclear receptor

Predicted results indicated that Momordicin1 can be targeted for Family A G protein-coupled receptor class. Momordicin1 can interact well with different Prostanoid receptor [21].

Momordicin1 may cause liver, endocrine, immune and nervous system injury due to ability of structure to form covalent bond with protein and DNA [22].

3.2. Results of predicted Polypharmacological activities of Momordicin1 by using PASS online tool

Study of Polypharmacological activities of Momordicin1 reveals that it can be a potential candidate as an anti neoplastic agent [23].

Table 10: Result of prediction of toxicity by using XUNDRUG In-silicoTool

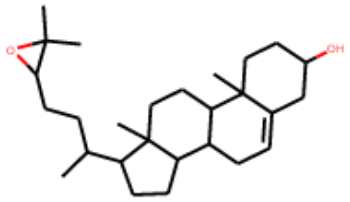
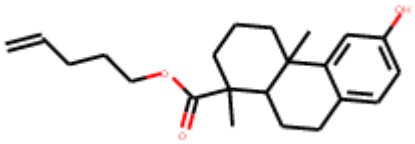
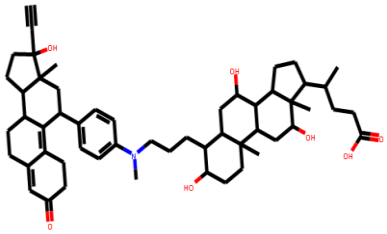
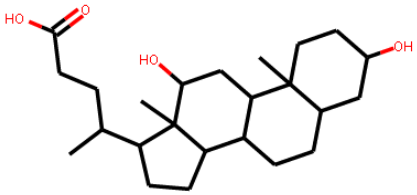
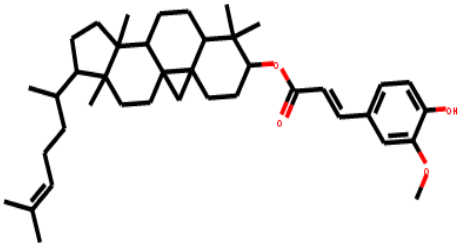
Hepatotoxicity			
Action	**Injury**	**Confidence**	**Similar active compound in database**
Agonist of Liver X receptor beta	Liver	0.993	
Agonist of Liver X receptor alpha	Liver	0.995	
Reproduction toxicity			
Modulator of Glucocorticoid receptor	Endocrine, immune, Nervous system	0.993	
Antagonist of the glucocorticoid receptor (GR) signaling pathway	Endocrine, immune, Nervous system	0.993	
Agonist of the androgen receptor (AR) signaling pathway	Endocrine, Central nervous system	0.993	

Table 11: Predicted polypharmacological activities of Momordicin1 by using PASS online In-silico Tool

Probably active Score (Pa)	Probably inactive Score (Pi)	Target
0.876	0.005	Apoptosis agonist
0.872	0.005	Antineoplastic
0.847	0.003	Chemopreventive
0.785	0.004	Antineoplastic (lung cancer)
0.790	0.010	Alkylacetylglycerophosphatase inhibitor
0.759	0.005	Hepatoprotectant
0.742	0.020	Acylcarnitine hydrolase inhibitor
0.727	0.008	Phosphatase inhibitor
0.715	0.012	Hypolipemic
0.732	0.036	Antieczematic

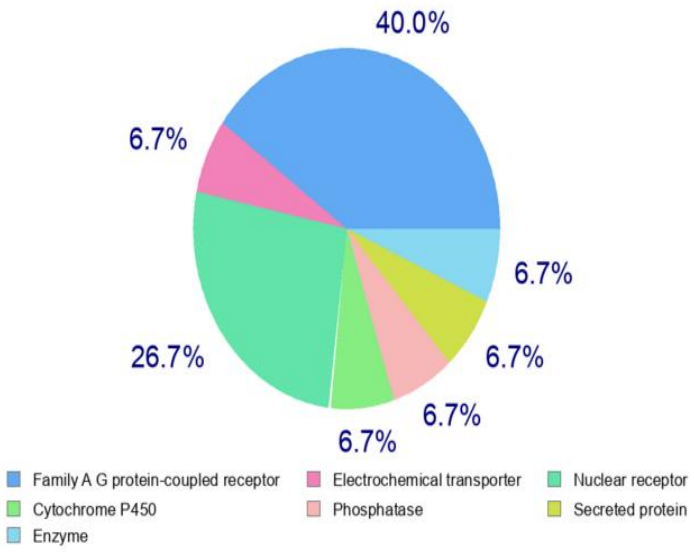


Fig. 4: Summary of target classes for Momordicin1

4. CONCLUSION

There are numerous small molecular compounds around us to affect our health, such as drugs, pesticides, food additives, industrial chemicals and environmental pollutants. Over decades properties related to absorption, distribution, metabolism, excretion and toxicity have become one of the most important issues to access the effect or risks of these compound on human body. Recent high rate drug withdrawals increase the pressure on regulators and pharmaceutical industry to improve preclinical safety testing, *in vivo* and *in vitro* evaluations are costly and laborious. Hence, *In-silico* techniques have been widely used to estimate these properties. Recent advances of *In-silico* ADMET have been available for a long time through which quality and usability can be modified. Ideally, *In-silico* ADMET models would be used before synthesis and together with potency estimation for the specific case, consequent usage of such *In-Silico* prediction has the potential to consider reduction in number of synthesized compounds with inadequate ADMET properties. Animal trials are currently the major method for determining the possible toxic effect of drug candidates and Cosmetics. *In-Silico* Prediction methods represent an alternative approach and aim to rationalize the preclinical drug development.

In-Silico Prediction tools were used for prediction of pharmacokinetic and pharmacodynamic activities. First, PASS *In-Silico* tools were used to predict Polypharmacological activities of Noscapine and results showed apoptosis agonist activity which is most predicted pharmacological activity for Momordicin1. Second, SWISS ADMET result showed that drug is orally active cannot cross BBB and will not have any side effect. Finally XUNDRUG *In-Silico* tool used to predict toxicity and Momordicin1 showed Hepatotoxicity and Reproduction toxicity. These all prediction will be useful for the further development of momordicn1 as a drug candidate.

5. ACKNOWLEDGEMENTS

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