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RESEARCH ARTICLE

In silico pharmacokinetic and toxicological properties prediction of bioactive compounds from *Andrographis paniculata*

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ABSTRACT

Background: *Andrographis paniculata* used in Siddha system of medicine as nilavembu. The scientific rationale and possible pharmacokinetic and toxicological profile of ingredients responsible for the activity are yet to be explored. **Aims and Objectives:** The aims of the study were to analyze absorption, distribution, metabolism excretion, and toxicity (ADMET) properties of certain biologically active compounds from *A. paniculata* by *in silico* computational analysis. **Materials and Methods:** This study was investigated on web-based tools PubChem to extract the chemical structure, followed by authentication and validation with the chemical formula. The two-dimensional structures are further converted to three-dimensional (3D) structure with ChemSketch software; the derived 3D structures are then screened for molecular properties and drug-likeness score, followed by absorption, distribution, metabolism, elimination, and toxicity through admetSAR software. The reports are analyzed and predicted for possible drug-like compounds from *A. paniculata*. **Results:** The results obtained indicate that the compounds screened andrographolide, neoandrographolide, 14-deoxyandrographolide, isoandrographolide, and andrographiside had the drug-likeness score −0.62, +0.17, −0.18, −0.47, and +0.04, respectively. On acute toxicity prediction andrographolide, 14-deoxyandrographolide belonged to Class III and other compounds belonged to Class I. **Conclusion:** The study confirms that among the compounds screened for *in silico* drug-likeness and ADMET profile neoandrographolide and andrographiside can be possibly developed as the effective anti-viral compound.

KEY WORDS: Nilavembu; *Andrographis paniculata*; Siddha Medicine; Pharmacokinetics; Toxicology; *In silico*

INTRODUCTION

Andrographis paniculata plant termed as nilavembu in Siddha system of medicine. In traditional Indian medicine, the ethnobotanical uses include fever, common cold, diabetes, enteritis, helminthiasis, herpes, peptic ulcer, as topical preparation in snake bite, and skin infection.[1] Siddha system of medicine is recognized by Indian government under AYUSH program. *A. paniculata* extract contains many chemical constituents among which five important biologically active compounds andrographolide, neoandrographolide, 14-deoxyandrographolide, isoandrographolide, and andrographiside were selected based on potential pharmacological activity reported in the review article.[2] The overexploitation due to the growing demand for medicinal plants of valuable resources has led to an unscientific and destructive manner without considering sustainability and quality issues.[3] Hence, medicinal plant extracts and its constituents are need of scientific validation. The chemical constituents though isolated and reported in various journals, but still, individually *A. paniculata* compounds have not

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been studied for drug-like properties prediction. Previously reported preclinical pharmacology data of andrographolide are analgesic, antipyretic, and antiulcerogenic,[4] neoandrographolide reported to have an antiherpes simplex virus,[5] 14-deoxyandrographolide reported to have antibacterial and antifungal activity,[6-8] isoandrographolide reported to have anti-inflammatory and anticancer,[9] and andrographiside has published reports of hepatoprotective activity.[10]

In silico computer simulation is considered as one of the most efficient ways to achieve the reduction of financial burden in research, refinement, and replacement of animals in research.[11] *In silico* computer simulation of research can provide predictive results of numerous compounds of more complex phenomena for which limited or no data is available in a short span of time; thereby, a lead compound with a high success rate can more easily be selected for further research and development. Hence, the current study is an attempt in search of preferred drug-like compounds from *A. paniculata* by computer simulation.

Aim and Objective

The aims of the study were to analyze absorption, distribution, metabolism excretion, and toxicity (ADMET) properties of biologically active compounds from *A. paniculata* by *in silico* methods.

MATERIALS AND METHODS

Hardware and Software

The selected compounds molecular properties of chemical structure from leaf extract of *A. paniculata* extract are carried out in Hewlett Packard 2016 Model installed with windows 11 software, java enabled with updated plugins.

Data Set

The selected compound chemical structures of *A. paniculata* with two-dimensional (2D) pictures were collected from accredited indexed published journals and other sources such as PubChem, Chembank, ChemPDB, and Asinex Ltd. After a detailed review, the structures are drawn with ChemSketch, followed by PHASE software module was used to convert the 2D structures into three-dimensional (3D) structures.[12]

Virtual Screening

ADMET predictions

The 3D structures created will be used for ADMET predictions by admetSAR version 2.0. *In silico* results of compounds on absorption, distribution, metabolism, excretion, and toxicity are acquired in the virtual screening workflow protocol, followed by a web-based tool MOLSOFT L.L.C was used to run the molecular properties evaluation and drug-likeness score igur .[13,14]

Statistical Methods and Calculation

Calculation of molecular volume and drug-likeness score is done using an interactive molecular properties calculator applet (MolSoft L.L.C. San Diego, CA, USA). The study is done in the department of pharmacology and the college library using online tools during July 2019 to January 2020. The study was self-funded from the academic allowances provided by SVIMS University, Tirupati, Andhra Pradesh, India, toward the author. Since the study does not involve animals and humans, this study is considered under the category for exemption from institutional ethics committee approval.

RESULTS

The findings of the present study are described in Tables 1-4.

DISCUSSION

The present study is designed to study and analyze the ADME and T properties followed by a prediction of a drug-like compound based on results obtained by *in silico* experimental models.

From the detailed review of literature from earlier studies andrographolide, neoandrographolide, 14-deoxyandrographolide, isoandrographolide, and andrographiside 2D chemical structure were retrieved from PubChem online compound database platform, all the five compounds were available with PubChem I.D for authentication and verification and successfully 2D structures converted to 3D structure by ChemSketch software [Table 1], the 3D structures are the processed with MOLSOFT L.L.C Software, and the molecular properties are predicted [Table 2]. The analysis of result for molecular properties revealed the octanol-water partition coefficient values of andrographolide, (1.96) and neoandrographolide (2.60) was less compared with 14-deoxyandrographolide (3.4), isoandrographolide (2.3) and andrographiside was zero. This may be predicted except andrographiside, other compounds have better water solubility. Among the five compounds the parameter for hydrogen bond donor and acceptor, andrographiside had higher values when compared to others hence predicted to have better chance of getting docked to receptors as ligand. H-bonds are generally considered to be facilitators of protein-ligand binding [Table 2]. From the analyzed report and by the structures when subjected to *in silico* drug-likeness model, andrographiside and neoandrographolide had better scores +0.04 and +0.17, thereby correlating with molecular properties, these two compounds were predicted to have

Table 1: *Andrographis paniculata* 2D-3D structure conversion with ChemSketch software

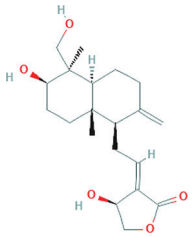
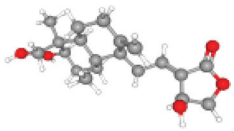
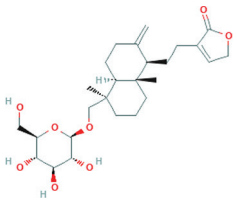
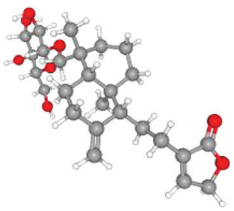
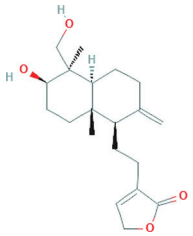
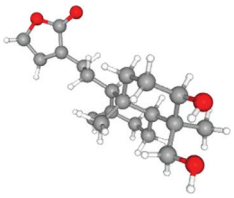
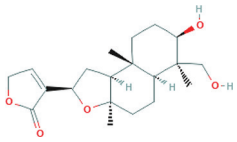
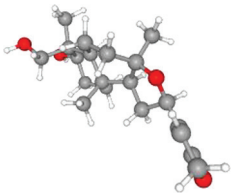
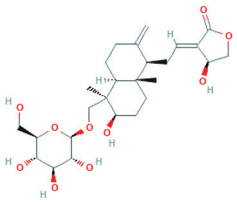
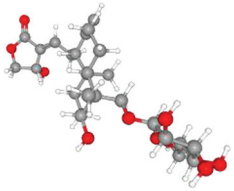
Compound (molecular formula)	2-D structures	3-D structure
Andrographolide ($C_{20}H_{30}O_5$)		
Neo Andrographolide ($C_{26}H_{40}O_8$)		
14-deoxyandrographolide ($C_{20}H_{30}O_4$)		
(8R,12R)-Isoandrographolide ($C_{20}H_{30}O_5$)		
Andrographiside ($C_{26}H_{40}O_{10}$)		

Table 2: Molecular properties and drug-likeness of *Carica papaya* leaf extract active compounds

Compounds (PUBCHEM CID)	Molecular weight (g/mol)	LogP (Octanol-water partition coefficient value)	H-bond Donor	H-Bond acceptor	Drug likeness score
Andrographolide (5318517)	350.4	1.96	3	5	−0.62
Neoandrographolide (9848024)	480.6	2.6	4	8	0.17
14-deoxyandrographolide (11624161)	334.4	3.4	2	4	−0.18
(8R,12R)-Isoandrographolide (101563020)	350.4	2.3	2	5	−0.47
Andrographiside (44593583)	512.6	0	6	10	0.04

CID-compound index, H-hydrogen

better chances as a possible drug-like candidate among the screened compounds.

The ADMET human model prediction by admetSAR software of the four compounds, 3D structures was analyzed. The absorption model predicted all the screened compounds had human intestinal absorption, whereas none had human oral absorption. The distribution model predicted all the

Table 3: ADMET predicted profile of *Carica papaya* leaf extract compounds

Compounds	Absorption			
	HIA	HOB	CaCo2	
Andrographolide	+	−	+	
Neoandrographolide	+	−	−	
14-deoxyandrographolide	+	−	+	
(8R,12R)-Isoandrographolide	+	−	+	
Andrographiside	+	−	−	
Compounds	**Distribution**			
	PPB 100%	**Pgp-substrate**	**Pgp-inhibitor**	**BBB**
Andrographolide	0.536	−	−	+
Neoandrographolide	0.828	−	−	−
14-deoxyandrographolide	0.630	−	−	+
(8R,12R)-Isoandrographolide	0.757	−	−	+
Andrographiside	0.513	−	−	−
Compounds	**Metabolism**		**Excretion**	
	CYP 450 substrate	**CYP 450 inhibitor**	**Plasma t1/2**	**Renal clearance**
Andrographolide	+	−	NA	NA
Neoandrographolide	+	−	NA	NA
14-deoxyandrographolide	+	−	NA	NA
(8R,12R)-Isoandrographolide	+	−	NA	NA
Andrographiside	+	−	NA	NA

BBB: Blood-brain barrier

Table 4: Toxicology prediction profile of *Carica papaya* leaf extract compounds

Compounds	Toxicity		
	Hepatotoxicity	**Ames test**	**Acute oral toxicity (Class)**
Andrographolide	−	−	III
Neoandrographolide	−	−	I
14-deoxyandrographolide	−	−	III
(8R,12R)-Isoandrographolide	−	−	I
Andrographiside	−	−	I

Ames-mutagenicity

compounds had <1% plasma protein binding, none of the screened compounds is P glycoprotein-substrate or inhibitor and with blood-brain barrier (BBB) model andrographolide, 14-deoxyandrographolide, and isoandrographolide were predicted to cross BBB. Based on poor plasma protein binding of <1% capacity of drugs, it was analyzed that all compounds have wider distribution. The metabolism model predicted all compounds are substrate of CYP450 and none is enzyme CYP450 inhibitor. CYP 450 one of the major enzymes responsible for metabolism and if inhibited the possibilities of drug-drug interaction side effects were predicted to be high. The elimination model has failed to predict the plasma t1/2 and renal clearance of the drug.

The toxicity model [Table 4] predicted andrographolide and 14-deoxyandrographolide to fall under Class III for acute oral toxicity testing, whereas andrographiside, deoxyandrographolide, and isoandrographolide fell under Class I positive for acute oral toxicity testing and all the five compounds appeared safer with no hepatotoxicity and AMES test negative prediction.

Traditional medicines utilization by especially females and subjects residing in rural areas were found to be significantly high. Majority of traditional medicine users were farmers.[15] *A. paniculata* in nilavembu Kudineer in Siddha medicine has published a report in treating both Chikungunya fever and dengue fever.[16] The hepatoprotective activity of *A. paniculata* its compounds is studied and published similar supportive evidence was found in the present study, as none of the compound exhibited hepatotoxicity.[17] Neoandrographolide was reported to antioxidant, anti-inflammatory, and hypolipidemic effects and, in the current research, predicts neoandrographolide with a better drug-like property.[18-20]

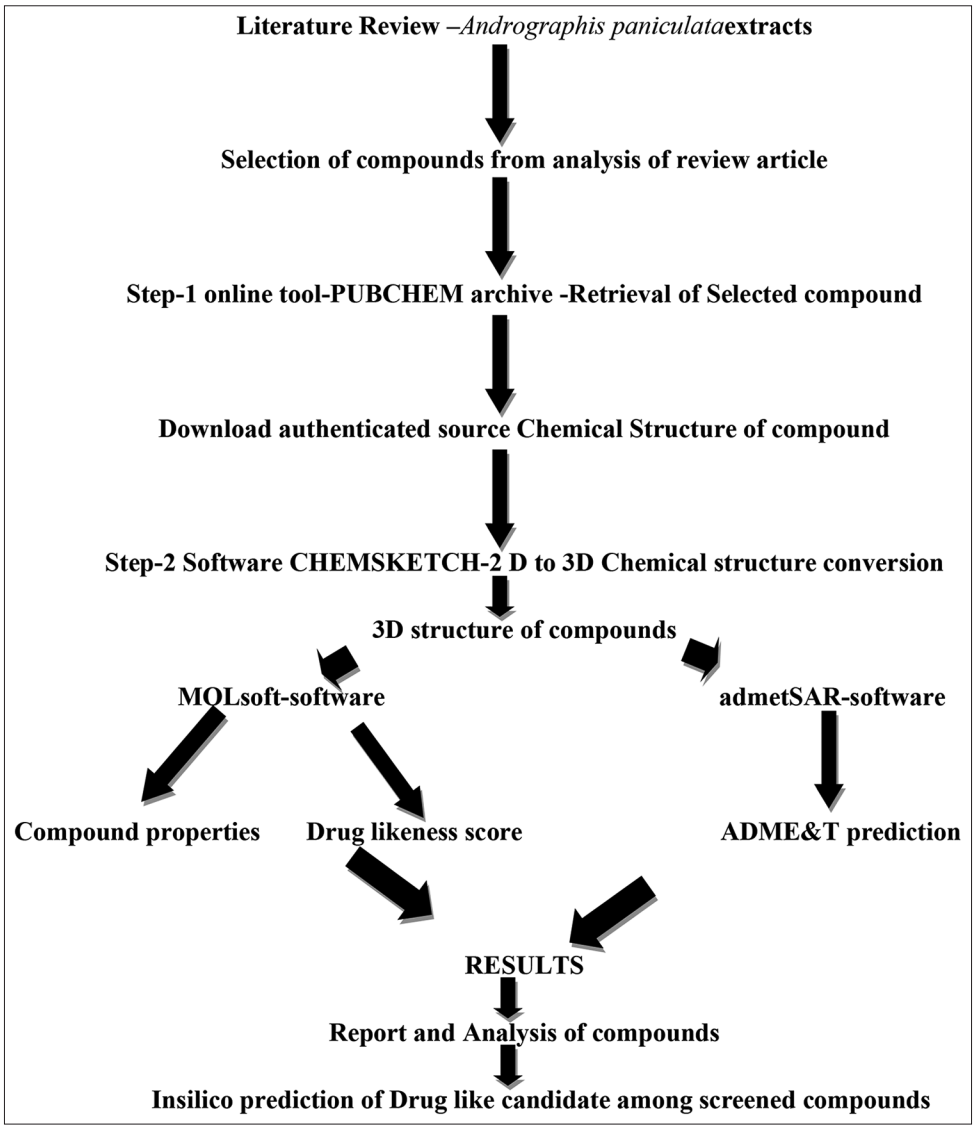


Figure 1: Flowchart of the study methodology

CONCLUSION

To conclude, the present study selected and screened five compounds based on extensive review of literature andrographolide, neoandrographolide, 14-deoxyandrographolide, isoandrographolide, and andrographiside. On the whole, based on molecular properties, drug-likeness score, and ADMET model, andrographiside and neoandrographolide are predicted to have better drug-like features with better toxicity profile. The Insilco prediction data from the present study can be applied for further research on andrographiside and neoandrographolide by wet-lab studies in relation to the potential antiviral drug for Chikungunya fever and dengue fever.

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