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In Silico Admet Profiling And Drug-Likeness Assessment Of Phytocompounds From Athiyadhi Kashayam: A Virtual Screening Approach

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Abstract

Traditional Siddha system of medicine has its own uniqueness. It is integrated into our day today life style. In India Diabetes mellitus is a serious condition that affects most of the population and leads to mortality, and it may increases massively by 2025. Athiyadhi Kashayam, a traditional Siddha polyherbal formulation, is widely used for its therapeutic benefits in treating diabetes mellitus. It is composed of Ficus racemosa, Cassia auriculata, Cassia fistula, Syzygium cumini, Salacia reticulata. This particular formulation was retrieved from Mega Nivarana Bodini Ennum Neerizhivu Maruthuvam. The above mentioned ingredientsare known for their antioxidant potential and anti-diabetic property. In the current study, virtual screening and in silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) predictions were employed using the pkCSM module to assess the pharmacokinetic behaviour, toxicity, and drug-likeness of selected phytoconstituents. Among the compounds tested, Kaempferol and Ellagic acid demonstrated favourable ADMET profiles and drug-likeness properties, highlighting their potential as lead compounds. The comprehensive evaluation offers insights into the formulation's pharmacological efficacy and safety, providing a rationale for further preclinical validation.

Keywords: *Athiyathi Kashayam, ADMET, pkCSM, phytochemicals, virtual screening, drug-likeness, In silico analysis*

INTRODUCTION

Traditional medicine systems such as Siddha have long relied on polyherbal formulations for managing various diseases. Athiyadhi Kashayam is a classical decoction traditionally used to treat conditions such as fever, inflammation, and diabetes. Despite its wide usage, the pharmacokinetic and toxicity profiles of its active phytoconstituents remain underexplored (B et al., 2022; Chandrasekaran et al., 2025; M et al., 2023). Recent advances in computational pharmacology enable in silico evaluation of ADMET properties, facilitating early drug discovery and lead optimization. This study aims to screen major phytochemicals from Athiyadhi Kashayam using pkCSM to predict their pharmacokinetic behaviour and drug-likeness (Abdullah et al., 2023; Kandeepan et al., 2022; Vegad et al., 2023).

Polyherbal formulations have long been used in traditional medical systems like Siddha to treat a variety of illnesses. A traditional remedy for ailments like fever, inflammation, and diabetes is Athiyadhi Kashayam, a traditional decoction. It is composed of Ficusracemosa, Cassia auriculata, Cassia fistula, Syzygium cumini, Salacia reticulata. This particular formulation was retrieved from Mega Nivarana Bodini Ennum Neerizhivu Maruthuvam (Hakkim P.M. Abdulla Sayabu, 1998). All the ingredientsare known for

their antioxidant potential and anti-diabetic property (Dharshini, 2017; Lakshmanakumar et al., 2023). The pharmacokinetic and toxicity profiles of its active phytoconstituents are still poorly understood despite its widespread use. Early drug discovery and lead optimization are made easier by the in-silico evaluation of ADMET properties made possible by recent developments in computational pharmacology. The purpose of this study is to use pkCSM to screen the main phytochemicals from Athiyadhi Kashayam to forecast their pharmacokinetic behavior and drug-likeness.

MATERIALS AND METHODOLOGY

2.1 Phytocompound Selection

Amyrin, Lupeol, Beta-Sitosterol, Linoleic acid, Kaempferol, Ellagic acid, Salacinol, Mangiferin, and Acarbose were the nine phytochemicalswere chosen as they are the components of Athiyadhi kashayam.

2.2 ADMET Analysis

The pkCSM web server was used for prediction of ADMET properties following the protocol by Pires et al. (2015). Parameters included water solubility, Caco2 permeability, intestinal absorption, skin permeability, distribution volume, blood-brain barrier (BBB) permeability, interaction with CYP450 enzymes, renal clearance, and toxicity indices (maximum tolerated dose, LD_{50}, hepatotoxicity, and skin sensitization).

2.3 Drug-Likeness Evaluation

Drug-likeness was assessed based on five established filters: Lipinski, Ghose, Veber, Egan, and Muegge rules, evaluating molecular weight, lipophilicity, hydrogen bond donors/acceptors, polar surface area, and other structural features.

RESULTS

3.1 Properties of Absorption

Most of the compounds showed satisfactory water solubility; however, beta-sitosterol (-6.77) and luteol (-5.86) were less soluble than kaempferol (-3.04 log mol/L) and ellagic acid (-3.18). Lupeol (95.78%) and beta-sitosterol (94.46%) had the highest intestinal absorption, indicating high oral bioavailability. Nevertheless, the systemic action of Acarbose (4.17%) and Salacinol (0%) was limited due to their minimal absorption (Table 1).

Table no 1. Parameters Pertaining to Absorption and Distribution

Compound	Water solubility (log mol/L)	Caco2 permeability (log Papp in 10-6 cm/s)	Intestinal Absorption % Absorbed	Skin Permeability Numeric (log Kp)
Amyrin	-3.809	1.292	92.32	-3.23
Lupeol	-5.861	1.226	95.78	-2.74
Beta-Sitosterol	-6.773	1.201	94.464	-2.783
Linoleic acid	-5.862	1.57	92.329	-2.723
Kaempferol	-3.04	0.032	74.29	-2.735
Ellagic acid	-3.181	0.335	86.684	-2.735
Salacinol	-1.98	-0.52	0	-2.735
Mangiferin	-2.918	-0.926	46.135	-2.735
Acarbose	-1.482	-0.481	4.172	-2.735

3.2 Profile of Distribution

The profile distribution details of the phytoconstituents are given in Table 2. Wide tissue distribution was indicated by the high volume of distribution of kaempferol and mangiferin (1.27 and 1.36 log L/kg, respectively). Higher BBB permeability (>0.7 log BB) was demonstrated by compounds like beta-sitosterol and luteol, indicating potential central effects. The majority had inadequate CNS penetration.

Table no 2:Kinetic profile pertaining to Distribution

Compound	Volume of Distribution	Fraction unbound	BBB permeability

	VDs (log L/kg)	(Fu)	(log BB)
Amyrin	0.324	0.195	0.035
Lupeol	0	0	0.726
Beta-Sitosterol	0.193	0.01	0.781
Linoleic acid	-0.587	0.054	-0.142
Kaempferol	1.274	0.178	-0.939
Ellagic acid	0.375	0.083	-1.272
Salacinol	-1.337	0.756	-1.266
Mangiferin	1.364	0.289	-1.573
Acarbose	-0.836	0.505	-1.717

3.3 Interactions in Metabolism

Except for kaempferol, none of the substances tested inhibited the CYP450 isoenzymes. Drug interactions may result from kaempferol's dual inhibition of CYP3A4 and CYP2D6 as given in Table 3. Because ellagic acid was predicted to be a CYP3A4 substrate, metabolic stability had to be considered.

Table no 3: The table presents the kinetic profile of ligand molecules in which, CYP3A4 and CYP2D6 are cytochrome enzymes and the letter (Y) denoting yes and (N) denoting No.

Compound	CYP3A4 Substrate (Y/N)	CYP2D6 Substrate (Y/N)	CYP3A4 Inhibitor (Y/N)	CYP2D6 Inhibitor (Y/N)
Amyrin	N	Y	N	N
Lupeol	N	Y	N	N
Beta-Sitosterol	N	Y	N	N
Linoleic acid	N	Y	N	N
Kaempferol	N	N	Y	Y
Ellagic acid	Y	N	N	N
Salacinol	N	N	N	N
Mangiferin	N	N	N	N
Acarbose	N	N	N	N

3.4 Properties of Elimination

With the highest total clearance (1.936 log ml/min/kg), linoleic acid appeared to be rapidly eliminated from the body (Table 4). Hepatic over renal elimination routes were indicated by the fact that none of the compounds were renal OCT2 substrates.

Table no 4:Kinetic profile pertaining to Elimination. The table presents the elimination properties of ligand molecules in which, letter (Y) denoting yes and (N) denoting No.

Compound	Total Clearance (log ml/min/kg)	Renal OCT2 substrate (Y/N)
Amyrin	0.09	N
Lupeol	0.153	N
Beta-Sitosterol	0.628	N
Linoleic acid	1.936	N
Kaempferol	0.477	N
Ellagic acid	0.537	N
Salacinol	0.959	N
Mangiferin	0.347	N
Acarbose	0.428	N

3.5 Evaluation of Bioavailability and Toxicity

Ellagic acid, beta-sitosterol, kaempferol, lupeol, and mangiferin all had good safety profiles with no signs of skin sensitization or hepatotoxicity. However, caution was advised due to the possible hepatotoxicity of amyrin and linoleic acid (Table 5).

Table no 5:Kinetic profile pertaining to Bioavailability and Toxicity. The table presents the toxicity profile of ligand molecules in which, letter (Y) denoting yes and (N) denoting No.

Compound	Bioavailability Score	Max. tolerated dose (human) (log mg/kg/day)	Oral Rat Acute Toxicity (LD50) (mol/kg)	Skin Sensitisation (Y/N)	Hepatotoxicity (Y/N)
Amyrin	0.55	-0.375	2.489	N	Y
Lupeol	0.55	-5.02	2.563	N	N
Beta-Sitosterol	0.55	-0.621	2.552	N	N
Linoleic acid	0.85	1.936	1.429	Y	Y
Kaempferol	0.55	0.531	2.449	N	N
Ellagic acid	0.85	0.476	2.399	N	N
Salacinol	0.17	1.319	1.503	N	N
Mangiferin	0.17	0.58	2.396	N	N
Acarbose	0.17	0.435	2.449	N	N

3.6 Assessment of Drug Likeness

Kaempferol had the highest potential to be a drug-like molecule among all compounds since it met all five drug-likeness filters.Because of their high polarity and size, mangiferin and acarbose did not pass any of the filters, indicating poor oral drug-likeness.

Table no 6: Drug Likeness Index. The table presents the drug likeness profile of ligand molecules, with the Drug-likeness index of ligands, with "Yes" indicating adherence to the drug-likeness index and "No" suggesting violations in drug-like properties.

Compound	Lipinski	Ghose	Veber	Egan	Muegge
Amyrin	Yes	No	Yes	No	No
Lupeol	Yes	No	Yes	No	No
Beta-Sitosterol	Yes	No	Yes	No	No
Linoleic acid	Yes	No	No	No	No
Kaempferol	Yes	Yes	Yes	Yes	Yes
Ellagic acid	Yes	No	No	Yes	Yes
Salacinol	Yes	No	No	No	No
Mangiferin	No	No	No	No	No
Acarbose	No	No	No	No	No

DISCUSSION

For a drug molecule, oral bioavailability is a critical parameter, often predicted using the Rule of Five (Ro5) established by Christopher A. Lipinski (Lipinski et al., 2001; Lipinski, 2004). In the present study, the phytocompounds identified from Athiyadhi Kashayam were evaluated for their physicochemical and pharmacokinetic properties in silico using predictive tools such as SwissADME (Daina et al., 2017) and pkCSM (Pires et al., 2015). The Ro5-based analysis considered parameters including molecular weight, hydrogen bond donors and acceptors, lipophilicity, and number of rotatable bonds, alongside the number of rule violations (Table 1 &2).

The Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) profiling provides valuable insight into the pharmacokinetic behavior and potential risk factors associated with drug candidates in

the human body (Sucharitha et al., 2022). In this study, the ADMET properties of the selected phytocompounds from Athiyadhi Kashayam were assessed using in silico tools such as pkCSM and SwissADME, and the results are summarized in Table 3.

Most of the tested compounds demonstrated favourable oral bioavailability and gastrointestinal absorption, indicating their potential suitability for oral administration. Compounds such as Amyrin, Lupeol, Beta-Sitosterol, Kaempferol, and Ellagic acid exhibited moderate to good bioavailability scores (0.55), while Linoleic acid and Ellagic acid showed the highest oral absorption potential (bioavailability score: 0.85).

In terms of toxicity, Amyrin and Linoleic acid were flagged for hepatotoxicity, while Linoleic acid alone showed skin sensitization potential. The acute oral toxicity (LD50 values) ranged from 1.429 mol/kg (Linoleic acid) to 2.563 mol/kg (Lupeol), indicating a generally acceptable safety profile across most compounds.Overall, the ADMET analysis supports the pharmacological relevance of Athiyadhi Kashayam constituents, with most compounds displaying desirable drug-like properties and manageable toxicity, warranting further experimental validation and formulation optimization.

Our results revealed that most of the compounds from Athiyadhi Kashayam complied with Ro5 criteria, with zero violations, suggesting favourable oral bioavailability. Interestingly, even some known reference inhibitors showed two Ro5 violations, indicating that occasional deviations may still be acceptable for bioactive compounds.Overall, the Ro5 analysis supports the drug-like potential of most natural constituents of Athiyadhi Kashayam, highlighting their promising candidature for further pharmacological development.

CONCLUSION

The in silico ADMET evaluation reveals that Kaempferol and Ellagic acid possess favourable pharmacokinetic and safety profiles, making them promising candidates for further preclinical research. The comprehensive ADMET analysis serves as a preliminary validation of Athiyadhi kashayam's efficacy and safety from a pharmacological standpoint. These findings may support its scientific acceptance and inspire more evidence-based exploration of Siddha formulations.

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7. Authors contribution

Dr. G. BharathKumar and Dr. B. PremKumar designed the work, Dr. C. Meenakshi and Dr. M. Ramani carried out the bench work and wrote the manuscript and Dr. S. Chithra edited the manuscript.

8. Conflict of interest

The authors declare that there are no conflicts of interest.

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