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In Silico ADMET and Molecular Interaction Profiles of Phytochemicals from Medicinal Plants in Dakshina Kannada

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Abstract

The success or failure of a potential drug depends on its absorption, distribution, metabolism, excretion and toxicity (ADMET) characteristics, and these features are usually rate-limiting in the drug development process. Hence, it is essential to know about the predicted ADMET properties of the most promising leads to avoid the risk of late-stage attrition. This project focuses on in silico screening of ADMET properties of phytochemicals found in Dakshina Kannada's medicinal plants, which include *Tinospora cordifolia*, *Azadirachta indica*, *Ocimum sanctum,* and *Plectranthus amboinicus*, mainly known for their antimicrobial properties.

The physicochemical properties, bioactivity scores, ADMET, and molecular interactions of the selected phytoconstituents were determined by QikProp, Molinspiration, ADMETlab 2.0, ProTox-II, and GLIDE. In addition, molecular docking checked for their binding interactions with target proteins 1JIJ and 4 HOE of *Staphylococcus aureus* and *Candida albicans*, respectively, as they were well known for their antimicrobial properties. In this studies, rosmarinic acid was well interacted phytochemical with both target proteins and has highest docking score.

The physicochemical properties showed that all compounds fell under the recommended molecular weight, volume, and polar surface area range. Xanosporic acid violated two rules of Lipinski's Rule of Five, indicating that it may have problems with oral bioavailability. The ADME properties for most of the phytocompounds were within the recommended ranges; hence, they are promising candidates for drug development. Most phytoconstituents showed good bioactivity scores, indicating they have good druglikeness properties. On the analysis of the toxicity, most of the phytoconstituents were found to be noncarcinogenic and nonmutagenic. Therefore, this data can further be utilized as primary tools for determining the biological actions of these plants.

Xanosporic acid was found to violate two out of three rules of Lipinski. Similarly, ursolic acid and oleanolic acid also showed a few undesirable properties. All other compounds otherwise showed desirable properties and hence are promising candidates for drug development. This data can be further utilized as primary tool for determining the biological actions of the plants.

Keywords

- physicochemical properties
- bioactivity scores
- ADMET properties
- molecular interactions

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Introduction

Pharmaceutical drug discovery is a high-risk, tedious, and expensive process that involves choosing a specific disease, target identification, lead discovery, optimization followed by preclinical and clinical trials.[1] Animal studies usually fail to predict the clinical results because of interspecies differences in transporters, biochemical pathways, and enzymes. Millions of molecules are screened, but not many get approved due to technical, safety, and efficacy issues related to absorption, distribution, metabolism, and elimination (ADME) and various toxicities (T), leading to delayed progress in drug discovery. Unfortunately, drugs with high potency may not always have the desirable pharmacokinetic profile to be approved and marketed for human use. Usually, a successful drug is not only the one with the highest potency but the one with acceptable potency, safety, and pharmacokinetics.[2] There are various online and offline tools available for analyzing the ADMET properties of a particular compound.[3] Few among the many tools available are Molinspiration, Derek Nexus, PreADMET ADMET Prediction, ProTox-II, VolSurf, ADMEWORKS Predicto, QikProp (Schrodinger, LLC, New York), ADMETlab 2.0 and admetSAR.

QikProp predicts significant physical descriptors and pharmaceutically relevant properties of organic molecules, individually or in batches. In addition to predicting molecular properties, QikProp provides ranges for comparing a particular molecule's properties with those of 95% of known drugs.[4]

Molinspiration Cheminformatics software offers fragment-based virtual screening, bioactivity prediction, and data visualization.[5]

ADMETlab 2.0 is a redesigned version of the previously widely used AMDETlab web server for the predictions of pharmacokinetics and toxicity parameter of compounds, of which the supported ADMET-related endpoints are approximately twice the number of the endpoints in the previous version.[6]

The ProTox-II is a webserver to predict toxicity and multiple toxicological endpoints for several chemical compounds have five different models such as oral acute toxicity prediction model as per six different toxicity classes; organ toxicity model especially liver toxicity prediction; toxicological (immunotoxicity model); and genotoxicological (cytotoxicity, mutagenicity and carcinogenicity model) endpoints.[7]

In the past few years, research on traditional plants with medicinal significance has seemingly surged all over the world, because the natural sources and the plant varieties encourage scientists to complement modern pharmacological approaches.[8] This project focuses on in silico screening of ADMET properties of phytochemicals found in medicinal plants of Dakshina Kannada which include, *Tinospora cordifolia* (Amrita Balli),[9] *Azadirachta indica* (Neem),[10] *Ocimum sanctum* (Tulasi),[11] and *Plectranthus amboinicus* (Indian borage).[12,13] These selected four plants are substantially found almost everywhere in Dakshina Kannada and are traditionally significant to the native population. These plants are well known for their various actions ranging from antimicrobial,[9] anti-inflammatory[10] and anti-asthmatic,[11,14] larvicidal,[12] and so on. From review of literature, it is clear that the various extracts *of Tinospora cordifolia, Azadirachta indica, Plectranthus amboinicus*, and *Ocimum sanctum* have antifungal and antibacterial activity against *Candida albicans* and *Staphylococcus aureus*, respectively. So, these four plants were selected against *S. aureus* and *C. albicans.*[15,16]

Dakshina Kannada is the abode of many such highly potent medicinal plants, containing various phytochemicals, the ADMET profiles of which, if well established, can simplify and accelerate drug discovery. Of the 500 medicinal plants listed in Arya Vaidya Sala, 320 are located in Dakshina Kannada and parts of the Udupi district. The phytoconstituents of four plants, namely *Tinospora cordifolia* (Amrita Balli), *Azadirachta indica* (Neem), *Ocimum sanctum* (Tulasi), and *Plectranthus amboinicus* (Indian borage), were selected based on their antimicrobial properties.[17–19]

Methodology

The ADMET properties of 18 phytochemicals found in Dakshina Kannada's medicinal plants were selected as *Tinospora cordifolia, Azadirachta indica, Ocimum sanctum*, and *Plectranthus amboinicus.*[19]

In Silico Platform

The computational analysis was carried out on Maestro 12.3 version (LigPrep, QikProp) (Schrödinger 2020-4)[4,20] to determine the physicochemical properties alongside ADMET properties of the selected phytoconstituents. This software is programmed on DELL Inc.27" workstation machine running on Linux –x86_64 operating system.

Bioactivity scores were predicted using the Molinspiration online tool[21] and ADMETlab 2.0 and ProTox-II online software programs were utilized to predict the toxicity profile.

Biological Data

The plants found in Dakshina Kannada were found using "Flora of Peninsular India database" developed by the research team at herbarium JCB, Centre for Ecology Sciences (CES), Indian Institute of Sciences(IISc), Bangalore.[13]

The 18 phytoconstituents were obtained from four plants, that is, four from *Tinospora cordifolia*, six from *Azadirachta indica*, five from *Ocimum sanctum*, and three from *Plectranthus amboinicus*, and were used for in silico studies.

Ligand Preparation

The SMILES of the phytoconstituents were taken from PubChem and the structures were derived based on SMILES using ChemSketch. The SMILES were imported to the Maestro in Schrödinger software. Maestro's sketch module function builds the three-dimensional structures of the 18 ligands, and the ionization states are produced at pH 7.0. OPLS3 force field executed the energy minimization, and the low-energy conformations of all 18 phytoconstituents were generated by LigPrep.[20]

Physicochemical Properties

Physicochemical properties of ligand molecules were determined by using QikProp of Schrödinger software.[4] The scores help comprehend drug-likeness properties and bioavailability. The prepared ligands were selected and incorporated into the QikProp tool and processed. The physicochemical properties like molecular weight, logP, donor HB (hydrogen bond), and acceptor HB analyses Lipinski's Rule of Five[22] were assessed. Alongside, molecular volume, polar surface area (PSA) and Jorgensen's Rule of Three[23] were also predicted.

ADMET Properties

ADMET properties of ligand molecules were determined by QikProp by Schrödinger software (Schrödinger 2020-4: QikProp).[4] The computation of ADMET parameters ahead of expensive trials can eradicate, or at the least minimize, redundant testing on leads that may not show promise in qualifying the clinical trials. The results further assist in concretizing our understanding of drug-likeness properties and bioavailability. The prepared ligands were selected and incorporated into the QikProp tool and processed. The ADMET features include Caco-2 cell permeability, blood–brain barrier (BBB) permeability, percentage human oral absorption and solvent accessible surface area (SASA), hydrophobic component of the SASA (FOSA), and hydrophilic component of the SASA (FISA), dermal penetration, plasma–protein binding, metabolism, and Half Maximal Inhibitory Concentration (IC_{50}) value for Human Ether-À-Go-Go-Related Gene Potassium Channel (HERG K+). This approach allows a researcher to focus on only those particular compounds that deserve further evaluation.[24]

Bioactivity Prediction

Bioactivity explains the adverse or beneficial effects of a drug on human body. It depends entirely on fulfillment of the ADME criteria. Hence, to be a suitable drug candidate, a chemical compound must not just be active, but must also possess the appropriate ADME properties. The automated online tool Molinspiration was therefore used to calculate the same.[25]

In the Molinspiration website, the SMILES of each of the 18 compounds were entered in the box after clicking on the "Calculation of Molecular Properties and Prediction of Bioactivity" tab. Then the command to "Predict Bioactivity" was given, and the scores were tabulated.[21]

Toxicity Prediction

The toxicity of the phytoconstituents were virtually predicted using different tools, namely ADMETlab 2.0 and ProTox-II. ADMETlab 2.0 is an enhanced version of the widely used ADMETlab for systematic evaluation of ADMET properties and some physicochemical properties, and medicinal chemistry friendliness.[6] ProTox-II is a free online virtual lab for the prediction of toxicities of small molecules, which matches the similarity of the compound with already known toxic compounds.[26,27]

With significant updates to functional modules, predictive models, explanations, and the user interface, ADMETlab 2.0 has a greater capacity to assist medicinal chemists in accelerating the drug research and development process.[28–30] The SMILES string of each compound was pasted separately and submitted. The evaluation results were then downloaded as a PDF file, and the scores were tabulated. AMES toxicity and rat oral acute toxicity scores were predicted using this tool. The mutagenicity and carcinogenicity boxes were ticked before submitting for "Search." Once the molecule was confirmed, "Start Tox Prediction" command was given. The predicted lethal dose, 50% (LD_{50}) and toxicity class along with the prediction and probability of carcinogenicity, and mutagenicity scores were calculated.

Molecular Docking

Docking studies were conducted to determine the possible interactions of 18 phyto constituents with essential enzymes, *tyrosyl-tRNA synthetase* (TyrRS) in *S. aureus*, and *dihydrofolate reductase* (DHFR) in *C. albicans*. The target proteins 1JIJ and 4HOE of TyrRS and DHFR, respectively, were downloaded from rcsb Protein Data Bank.[31] TyrRS and DHFR inhibitors are an important class of drugs, as evidenced by their use as antibacterial, antimalarial, antifungal, and anticancer agents.

Target protein 1JIJ is crystal structure of *S. aureus* TyrRS and classified as ligase with resolution of 3.20 Å. 4HOE target protein is *C. albicans* DHFR complexed with nicotinamide adenine dinucleotide phosphate (NADPH) and resolution is 1.76 Å. These all are the main selection criteria for selection of targets. Target proteins were minimized by protein preparation wizard. LigPrep application is used for preparing the phytoconstituents. The grid was generated and docking was carried between the minimized protein and phytoconstituents by GLIDE, Schrodinger, XP (extra precision) method.[32] Docking scores, hydrophobic interaction, polar interaction, and hydrogen bonding were found out.

Results and Discussions

Physicochemical Properties

The physicochemical properties were determined using QikProp. The main objective was to establish the druglikeness property, that is, to check if the phytoconstituents obeyed Lipinski's Rule of Five. The physicochemical properties of the 18 phytoconstituents are listed in ►**Table 1**. The molecular weight of all the phytoconstituents that were analyzed was found to fall within the recommended range of 130.0 to 725.00. The lipophilicity (logP) value of 16 compounds was found to be within the acceptable range of −2 to 6.5, except for ursolic acid and oleanolic acid, whose logP values were found to be above 6.5.

Lipinski used various molecular properties in formulating his "Rule of Five." The rule states that most molecules with good druglikeness have logP less than or equal to 5, MW less than or equal to 500, number of HB donors less than or equal to 5, and the number of HB acceptors less than or equal to 10. The compounds that fulfil at least three of the four criteria are said to follow the Lipinski's "Rule of Five."[22] Eleven phytoconstituents namely, tinosponone, isocolumbin, nimbin, nimbolide, mahmoodin, margolone, margolonone, eugenol, linalool, carvacrol, and *p*-cymene were found to obey

Table 1 Physicochemical properties of the phytoconstituents

Sl. no.	Phytoconstituents	Molecular weight	LogP	Donor HB	Acceptor HB	RO5	Volume	PSA
1	Tinosponone	330.38	3.672	0	0	0	609.826	0
2	Isocolumbin	358.39	1.722	1	7.25	0	968.92	101.173
3	Xanosporic acid	536.49	1.835	4	10.65	2	1355.243	185.314
4	Tinocordiside	396.48	0.73	4	11.25	0	1168.698	123.002
5	Nimbin	540.61	3.514	0	10.2	1	1511.568	132.582
6	Nimbolide	466.53	2.253	0	9.2	0	1237.134	110.386
7	Mahmoodin	526.63	3.51	1	9.95	1	1481.325	127.922
8	Margolone	300.40	3.508	1	4	0	1026.196	75.539
9	Margolonone	314.38	2.325	1	6	0	980.121	97.505
10	Quercetin	302.24	0.383	4	5.25	0	866.186	142.674
11	Eugenol	164.20	2.662	1	1.5	0	644.618	29.951
12	Linalool	154.25	3.133	1	0.75	0	701.948	18.725
13	Rosmarinic acid	360.32	0.995	5	7	0	1092.752	170.44
14	Ursolic acid	456.71	6.112	2	3.7	1	1383.256	60.609
15	Oleanolic acid	456.71	6.21	2	3.7	1	1398.423	60.67
16	Carvacrol	150.22	3.298	1	0.75	0	629.025	21.4
17	β-Caryophyllene	204.36	5.258	0	0	1	813.523	0
18	p-Cymene	134.22	3.672	0	0	0	609.826	0

Abbreviations: HB, hydrogen bond; PSA, polar surface area; RO5, Lipinski's Rule of Five.

Lipinski's Rule of Five (RO5) with no violations. On further analysis, except xanosporic acid, the remaining compounds (nimbin, mahmoodin, ursolic acid, oleanolic acid, and β-caryophyllene) were found to violate one rule, which points out that they are considered drug-like molecules, and the violations were possibly due to the complex structures of the phytoconstituents. In the case of xanosporic acid, the molecular weight of 536.49 and acceptor HB score of 10.65 were out of the recommended range, and hence, it shows two violations. The total solvent-accessible volume of all the compounds was within the desired range of 500.0 to 2000.00. The PSA, which correlates the Van der Waals surface area for polar nitrogen and oxygen atoms, was retrieved. It was found that all the phytoconstituents were in the standard limit range of 7.0 to 200.0 $Å^2$.

ADME Properties

QikProp was used to determine the ADME properties. It helps us establish the ADME of the compound and provides information related to the onset of action and how the drug crosses the barrier. The ADMET properties help the medicinal chemist to make necessary modification to improve the activity. QikProp determined the different variables such as bioavailability, BBB penetration, plasma-protein binding, metabolism, blockade of HERG K+ channels, and SASA. The results are given in ►**Tables 2** and **3**.

Prediction of Bioavailability

The parameters that assess oral absorption are the predicted aqueous solubility, logS, the predicted percentage human oral absorption, and agreement to Jorgensen's famous "Rule of Three." According to Jorgensen's RO3, if a compound complies with all or some of the rules (logS > -5.7, Caco-2 > 22 nm/s and # Primary Metabolites < 7),[23] then it is more likely to be orally available.

When examined, the log S values of the phytoconstituents showed that all, except ursolic acid and oleanolic acid, fall within the range of −6.5 to 0.5 and hence they have good aqueous solubility.

The nonactive transport for the gut–blood barrier was assessed from Caco-2 cell permeability, and the examined 18 phytocompounds showed varied results. Phytochemicals like, tinosponone, isocolumbin, nimbin, nimbolide, eugenol, linalool, carvacrol, β-caryophyllene, p-cymene with Caco-2 value higher than 500 showed the maximum permeability to the gut–blood barrier. Xanosporic acid, quercetin and rosmarinic acid were found to have poor gut–blood barrier permeability since their values fell under 25. The remaining compounds showed acceptable permeability.

Tinosponone, isocolumbin, nimbin, nimbolide, mahmoodin, margolone, margolonone, eugenol, linalool, carvacrol, and p-cymene were found to obey Jorgensen's RO3 with no violations. On the analysis of all the compounds, few violated one or two but never violated all three rules, which infers that they are orally bioavailable. Xanosporic acid yet again violated two rules out of three.

The percentage human oral absorption value was more than 80% for tinosponone, isocolumbin, nimbin, nimbolide, margolone, eugenol, linalool, ursolic acid, oleanolic acid, carvacrol, β-caryophyllene, and p-cymene. Only xanosporic

Table 2 Bioavailability properties of phytoconstituents

Sl. no.	Phytoconstituents	QPlogS	QPPCaco	RO3	%Human oral absorption	QPlogBB	#Metabolic reactions
1	Tinosponone	−3.729	9906.038	0	100	0.702	2
2	Isocolumbin	−2.725	526.91	0	85.744	−0.482	5
3	Xanosporic acid	−3.373	5.395	2	24.871	−2.486	8
4	Tinocordiside	−2.536	226.475	1	73.371	−1.361	7
5	Nimbin	−4.338	652.244	0	84.935	−0.813	6
6	Nimbolide	−2.282	747.773	0	91.571	−0.446	6
7	Mahmoodin	−4.739	296.576	0	78.788	−1.126	2
8	Margolone	−5.413	77.475	0	81.296	−1.023	2
9	Margolonone	−3.881	59.152	0	72.276	−0.97	3
10	Quercetin	−2.878	19.286	1	52.191	−2.377	5
11	Eugenol	−2.438	2984.167	0	100	−0.143	3
12	Linalool	−2.969	5211.949	0	100	0.011	4
13	Rosmarinic acid	−3.124	1.267	1	34.611	−3.556	6
14	Ursolic acid	−6.829	294.421	1	93.962	−0.399	3
15	Oleanolic acid	−7.044	294.066	1	94.529	−0.417	3
16	Carvacrol	−2.328	3696.854	0	100	0.073	3
17	β-Caryophyllene	−6.284	9906.038	1	100	1.055	5
18	p-Cymene	−3.729	9906.038	0	100	0.702	2

Table 3 ADME properties of the phytoconstituents

Sl. no.	Phytoconstituents	QPlogHERG	QPlogKp	QPlogKhsa	SASA	FOSA	FISA
1	Tinosponone	−3.709	−0.965	0.346	384.777	254.556	0
2	Isocolumbin	−3.172	−3.241	−0.102	496.509	175.27	134.363
3	Xanosporic acid	−2.221	−5.388	−0.256	676.496	294.12	281.292
4	Tinocordiside	−3.334	−3.872	−0.451	599.962	407.559	173.034
5	Nimbin	−4.635	−2.869	0.108	744.709	460.369	124.59
6	Nimbolide	−3.223	−2.949	−0.337	591.452	314.266	118.331
7	Mahmoodin	−4.28	−3.424	0.463	715.411	290.941	160.684
8	Margolone	−2.616	−4.204	0.433	589.789	386.674	159.268
9	Margolonone	−1.804	−4.47	−0.049	541.534	336.954	171.626
10	Quercetin	−5.067	−5.493	−0.343	517.181	0	285.844
11	Eugenol	−4.063	−1.624	−0.107	406.64	202.795	54.949
12	Linalool	−3.611	−1.43	0.133	432.024	359.685	29.411
13	Rosmarinic acid	−3.721	−6.084	−0.551	626.581	55.641	347.641
14	Ursolic acid	−1.713	−3.086	1.361	681.273	568.961	98.126
15	Oleanolic acid	−1.883	−3.069	1.4	693.327	575.953	98.182
16	Carvacrol	−3.597	−1.811	0.056	393.825	249.884	45.141
17	β-Caryophyllene	−3.13	−1.408	0.98	462.84	431.098	0
18	p-Cymene	−3.709	−0.965	0.346	384.777	254.556	0

Abbreviations: ADME, absorption, distribution, metabolism, and elimination; SASA, solvent accessible surface area.

acid showed poor percentage human oral absorption value (<25%), while the other compounds showed acceptable values, falling in the range of 25 to 80%.

Prediction of Blood–Brain Barrier Penetration

Too polar drugs do not cross the BBB. The blood–brain partition coefficients (logB/B) were computed and used as a predictor for access to the central nervous system. QPlogBB analyzed the entrance of a chemical to the central nervous system. Rosmarinic acid's blood/brain partition coefficient does not fall in the recommended range (−3.0–1.2), while all others can penetrate the BBB.

Prediction of Metabolism

All the 18 phytoconstituents fall inside the recommended range (1–8 reactions) of #metab that predicts the number of likely metabolic reactions they may undergo.

Prediction of Blockage of Ether-À-Go-Go-Related Gene Potassium (HERG K +) Channel

HERG K^+ channel blockers are potentially toxic, and the predicted IC_{50} value often provides reasonable prediction for the cardiac toxicity of drugs in the early stages. All phytochemicals except quercetin showed predicted IC_{50} value above −5 for HERG K+ channels, which is in compliance with the standard range.

Prediction of Dermal Penetration

The logKp value predicts the skin permeability and the same is desired to fall in the range of –8.0 and –1.0. All the phytoconstituents were found to be within the recommended range that predicts them to have good dermal penetration.

Prediction of Plasma-Protein Binding

The binding of the drugs to plasma proteins decreases the amount of drug reaching the blood circulation, affecting drug efficiency. The plasma–protein binding is determined by binding to human serum albumin (logKhsa) (recommended range is −1.5–1.5). All the compounds were found to be in the recommended range and thus are likely to reach the blood circulation freely and are hence more available to the target site.

Prediction of Solvent Accessible Surface Area (SASA, FOSA, FISA)

The measure of the contact area between the solvent and molecule represents SASA, which is usually in the range of 300.0 to 1000.0 $Å^2$ and the measure of FOSA, must be in the range of 0.0 to 750.0, which represents the hydrophobic component of the SASA (saturated carbon and attached hydrogen). All the phytocompounds were found to satisfy the SASA and FOSA criteria within the said ranges. FISA measures the hydrophilic component of the SASA (SASA on N, O, H on heteroatoms, carbonyl C) and must ideally lie between the range of 7.0 to 330.0. Tinosponone, β-caryophyllene, and p-cymene show value of 0 and rosmarinic acid shows the value of 347.641 and hence falls out of the recommended range. All other constituents fall above 7.0 and below 330.0.

Bioactivity Prediction

Molinspiration tool was used to predict the bioactivity score of the 18 phytoconstituents of *Tinospora cordifolia* (Amrita Balli), *Azadirachta indica* (Neem), *Ocimum sanctum* (Tulasi), and *Plectranthus amboinicus* (Indian borage). A molecule having a bioactivity score of more than 0.00 is considered to exhibit good biological activity, while values −0.50 to 0.00 are expected to be moderately active, and if the score is less than −0.50, it is presumed to be inactive.[27] The bioactivity score of compounds is suggestive of moderate interaction with all drug targets. Eugenol, carvacrol, and p-cymene were found to have poor bioactivity, whereas linalool was predicted to show poor-to-moderate bioactivity. The rest of the compounds were found to have good activity since they showed scores above 0.00. The results are tabulated in ►**Table 4**.

Toxicity Prediction

The in silico toxicity of the 18 compounds were found using two online tools. The AMES toxicity and rat oral acute toxicity were found with the help of ADMETlab 2.0 and; LD_{50}, toxicity class, carcinogenicity, and mutagenicity were found using ProTox-II online software. The properties are tabulated in ►**Table 5**.

AMES Toxicity

The reference for the evaluation for toxicity was taken from ADMETlab 2.0 that mentions empirical decision of 0 to 0.3 as excellent toxicity, 0.3 to 0.7 as moderate toxicity, and 0.7 to 1 as poor toxicity. Except for Tinocordiside, which was found to be moderately toxic, all the other compounds were found to have high toxicity.

Rat Oral Acute Toxicity

Except for tinosponone, isocolumbin, Tinocordiside, nimbin, nimbolide, and mahmoodin, which were found to have poor toxicity results, all the other compounds were found to be highly toxic. The reference for evaluation for toxicity was taken from ADMETlab 2.0, which mentions empirical decision of 0 to 0.3 as excellent toxicity, 0.3 to 0.7 as moderate toxicity, and 0.7 to 1 as poor toxicity.

LD_{50}

The compounds were evaluated based on the upper threshold for high toxicity according to the globally harmonized system of classification, which is 50mg/kg and any values higher than this were considered toxic. All compounds except p-cymene had a value more than 50 mg/kg and were predicted to be nontoxic. The LD_{50} of p-cymene was found to be 3mg/kg and hence was considered to be highly toxic.

Toxicity Class

Lower the class of the compound, higher is its toxicity. p-Cymene was predicted to be in class I. Tinosponone, xanosporic acid, and quercetin were predicted to be in class III. Linalool, rosmarinic acid, and β-caryophyllene were expected to be class V and the remaining compounds were found to fall under class IV.

Table 4 Bioactivity prediction of the phytoconstituents

Sl. no.	Phytoconstituents	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Tinosponone	0.74	0.11	−0.46	0.64	0.15	0.55
2	Isocolumbin	−0.12	−0.41	−0.05	0.21	−0.18	0.16
3	Xanosporic acid	−0.12	−0.41	−0.05	0.21	−0.18	0.16
4	Tinocordiside	0.10	0.04	−0.39	0.35	0.17	0.59
5	Nimbin	0.24	0.14	−0.30	0.26	0.10	0.36
6	Nimbolide	0.22	0.20	−0.36	0.32	0.04	0.36
7	Mahmoodin	0.10	−0.04	−0.44	0.44	−0.01	0.49
8	Margolone	0.31	0.14	−0.22	0.64	−0.20	0.34
9	Margolonone	0.24	0.02	−0.46	0.69	−0.19	0.36
10	Quercetin	−0.06	−0.19	0.28	0.36	−0.25	0.28
11	Eugenol	−0.86	−0.36	−1.14	−0.78	−1.29	−0.41
12	Linalool	−0.73	0.07	−1.26	−0.06	−0.94	0.07
13	Rosmarinic acid	0.17	−0.08	−0.18	0.57	0.15	0.24
14	Ursolic acid	0.28	−0.03	−0.50	0.89	0.23	0.69
15	Oleanolic acid	0.28	−0.06	−0.40	0.77	0.15	0.65
16	Carvacrol	−1.02	−0.15	−1.15	−0.70	−1.25	−0.56
17	β-Caryophyllene	−0.34	0.28	−0.78	0.13	−0.60	0.19
18	p-Cymene	−1.18	−0.61	−1.40	−1.21	−1.42	−0.78

Table 5 Toxicity prediction of the phytoconstituents

Sl. no.	Phytoconstituents	AMES toxicity	Rat oral acute toxicity	Predicted LD_{50} (mg/kg)	Predicted toxicity Class	Carcinogenicity		Mutagenicity	
						Prob-ability	Activity	Prob-ability	Activity
1	Tinosponone	0.054	0.983	274	III	0.62	Inactive	0.79	Inactive
2	Isocolumbin	0.023	0.982	555	IV	0.62	Inactive	0.79	Inactive
3	Xanosporic acid	0.229	0.042	200	III	0.64	Inactive	0.58	Inactive
4	Tinocordiside	0.339	0.777	4500	IV	0.74	Inactive	0.56	Inactive
5	Nimbin	0.012	0.98	1000	IV	0.51	Active	0.86	Inactive
6	Nimbolide	0.009	0.984	1000	IV	0.51	Active	0.86	Inactive
7	Mahmoodin	0.047	0.963	555	IV	0.52	Inactive	0.77	Inactive
8	Margolone	0.017	0.295	570	IV	0.59	Inactive	0.97	Inactive
9	Margolonone	0.043	0.281	570	IV	0.60	Inactive	0.96	Inactive
10	Quercetin	0.657	0.065	159	III	0.68	Active	0.51	Active
11	Eugenol	0.066	0.121	1930	IV	0.73	Inactive	0.97	Inactive
12	Linalool	0.006	0.02	2200	V	0.64	Inactive	0.95	Inactive
13	Rosmarinic acid	0.03	0.067	5000	V	0.66	Inactive	0.85	Inactive
14	Ursolic acid	0.012	0.183	2000	IV	0.57	Active	0.85	Inactive
15	Oleanolic acid	0.025	0.088	2000	IV	0.57	Active	0.85	Inactive
16	Carvacrol	0.034	0.217	810	IV	0.60	Inactive	0.99	Inactive
17	β-Caryophyllene	0.012	0.049	5300	V	0.70	Inactive	0.95	Inactive
	p-Cymene	0.018	0.079	3	I	0.67	Active	0.96	Inactive

Abbreviations: Ames test (salmonella typhimurium reverse mutation assay); LD50, lethal dose, 50%.

Carcinogenicity

The carcinogenicity of nimbin, nimbolide, quercetin, ursolic acid, oleanolic acid, and p-cymene was found to be active with probability ranging from 0.51 to 0.68. As for the remaining phytoconstituents, carcinogenicity was found to be inactive, with a probability ranging from 0.52 to 0.74.

Mutagenicity

The mutagenicity of quercetin was found to be active with probability of 0.51. All the other compounds were found to be inactive with a possibility ranging from 0.99 to 0.56.

Molecular Docking

All the 18 phytoconstituents obtained, four from Tinospora cordifolia, six from Azadirachta indica, five from *Ocimum sanctum*, and three from *Plectranthus amboinicus*, were docked with two proteins 1JIJ and 4HOE. Most of the phytoconstituents had excellent docking scores. Among the 18 phytoconstituents rosmarinic acid from *Ocimum sanctum* (Tulasi) showed excellent molecular interaction with TyrRS in *S. aureus* and DHFR in *C. albicans*. The docking scores of both target proteins with rosmarinic acid, quercetin, *Tinocordiside*, and carvacrol have highest docking scores compared with other phytoconstituents.

Binding with 1JIJ

Rosmarinic acid from *Ocimum sanctum* (Tulasi) interacted with the TyrRS enzyme 1JIJ with the highest docking score of −7.305 kcal/mol. The hydroxyl group of rosmarinic acid made two HBs with the amino acid Asp 177 and other hydroxyl groups made HBs with Lys 84, Asp 80, Tyr 36, Asp 40, Gly 38, and Asp 195. Hydrophobic interactions (Tyr 170, Leu 70, Tyr 36, and Ala 39) and polar interactions (Gln 190, Gln 174, Asn 124, Thr 75, Gln 196, Hie 50, Asn 199, and Thr 42), which are essential interactions for binding with the enzyme. The image of rosmarinic acid with 1JIJ gives information regarding hydrogen bonding, polar interaction, and hydrophobic interaction in ►**Fig. 1A**. Highest score from each category is as follows: Quercetin from *Azadirachta indica* (Neem) with the docking score of −7.123 kcal/mol and the hydroxyl group made two HBs with the amino acid Asp 177 and the other hydroxyl groups with Tyr 36, Gly 193 and Asp 195 (►**Fig. 2A)**. Tinocordiside from *Tinospora cordifolia* (Amrita Balli) with the docking score of -5.923kcal/mol and the hydroxyl group made two hydrogen bonds with the amino acid Asp 40 and the other

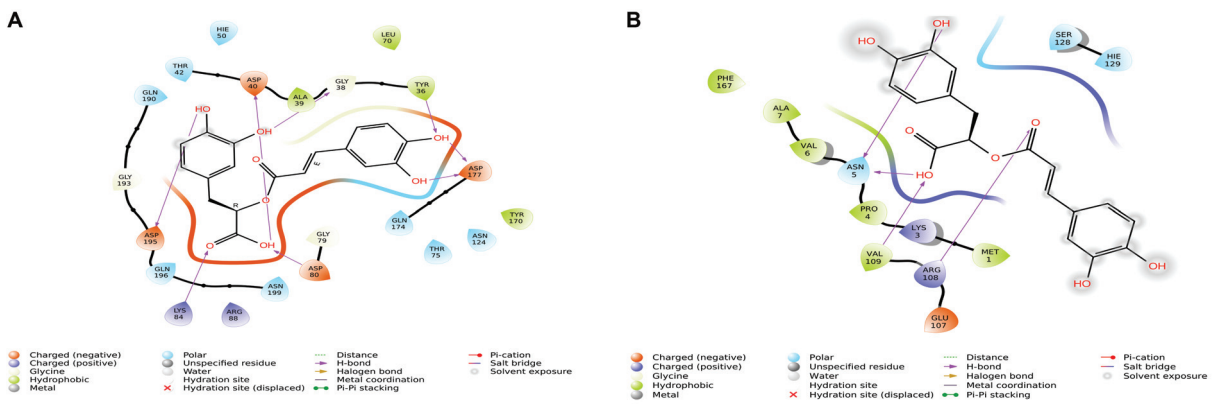

Fig. 1 (A and B) Two-dimensional docking conformation of rosmarinic acid with 1JIJ and 4HOE.

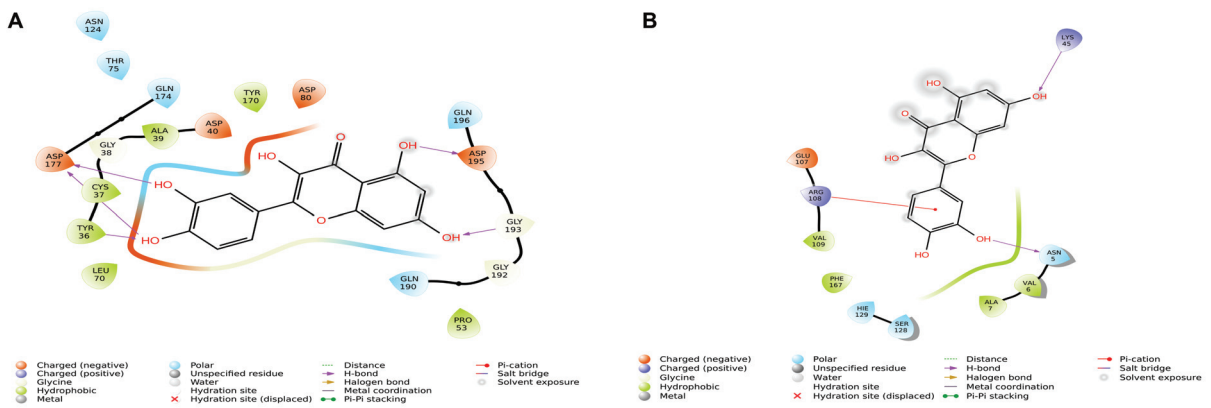

Fig. 2 (A and B) Two-dimensional docking conformation of quercetin with 1JIJ and 4HOE.

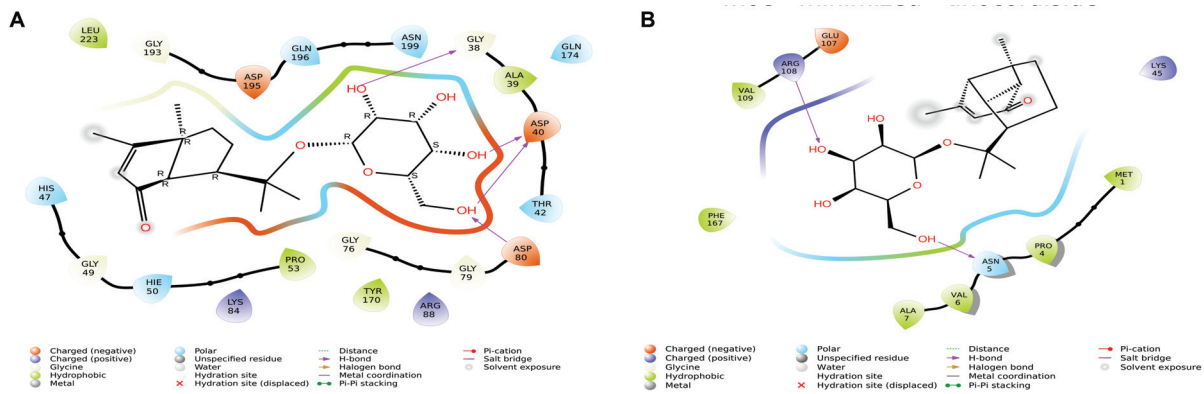

Fig. 3 (**A** and **B**) Two-dimensional docking conformation of Tinocordiside with 1JIJ and 4HOE.

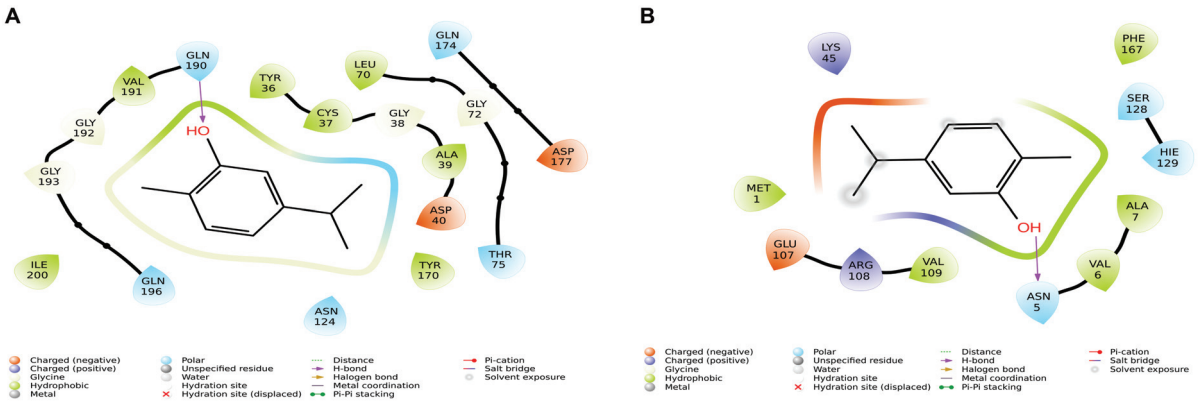

Fig. 4 (**A** and **B**) Two-dimensional docking conformation of carvacrol with 1JIJ and 4HOE.

hydroxyl groups with Gly 38 and Asp 80 as shown in ►**Fig. 3A**. Carvacrol from *Plectranthus amboinicus* (Indian Borage) with the docking score of −5.408 kcal/mol and HB with the amino acid Gln 190 as shown in ►**Fig. 4A**.

Binding with 4HOE

The highest docking score of rosmarinic acid was −8.833 kcal/mol, and hydroxyl group made two HBs with the amino acid Asn 5 and other HBs are Val 109 and Arg 108. The polar interactions are with the amino acid residues Asn 5, Hie 129, and Ser 128. Phe 167, Ala 7, Val 6, Pro 4, Val 109, and Met 1 create hydrophobic interactions with 4HOE (►**Fig. 1B**). The compound quercetin has obtained a docking score of −6.156 kcal/mol by interacting with 4HOE and the hydrogen bonding has been observed with Lys 45 and Asn 5 (►**Fig. 2B**). Based on the interaction analysis of Tinocordiside, the docking score was 5.938 kcal/mol and HBs with the amino acids are Asn 5 and Arg 108 (►**Fig. 3B**). Carvacrol showed interaction with DHFR in *C. albicans* was –4.055 kcal/mol and it has shown a HB with Asn 5 (►**Fig. 4B**).

The two-dimensional images of phytoconstituents with high docking scores with 1JIJ (►**Figs. 1A** to **4A**) and 4HOE (►**Figs. 1B** to **4B**) give information regarding hydrogen bonding, polar interaction and hydrophobic interactions. Eighteen phytoconstituents and their docking scores and binding interactions are tabulated in ►**Tables 6** and **7**.

Conclusion

In silico ADMET profiles of 18 phytoconstituents from four plants, namely Amrita Balli, Neem, Tulasi and Indian borage, abundantly found in Dakshina Kannada, were screened. The physicochemical properties when screened via QikProp showed that all compounds fell under the recommended range of molecular weight, volume, and PSA. Xanosporic acid violated two rules of RO5, indicating that it may have problems with oral bioavailability. The ADME properties include bioavailability, logS, PCaco, percentage human oral absorption, BBB permeation, log-HERG, dermal penetration, plasma protein binding, SASA for most of the phytocompounds were within the recommended ranges; hence they are promising candidates for drug development. Most of the phytoconstituents showed good bioactivity scores, which infers that they have good druglikeness properties. On the analysis of the toxicity, most of the phytoconstituents were found to be noncarcinogenic and non-mutagenic. In molecular docking studies, the 18 phytoconstituents of different categories were

Table 6 Docking score of phytoconstituents with target proteins 1JIJ and 4HOE

Sl. no.	Phytoconstituents	Docking score	
		PDB ID	
		1JIJ	4HOE
Tinospora cordifolia (Amrita Balli)			
1	Tinosponone	−5.058	−3.893
2	Isocolumbin	−5.155	−4.369
3	Xanosporic acid	−4.782	−5.156
4	Tinocordiside	−5.923	−5.938
Azadirachta indica (Neem)			
5	Nimbin	−2.460	−4.207
6	Nimbolide	−2.405	−4.079
7	Mahmoodin	−3.656	−3.155
8	Margolone	−4.723	−5.496
9	Margolonone	−4.597	−4.083
10	Quercetin	−7.123	−6.156
Ocimum sanctum (Tulasi)			
11	Eugenol	−4.629	−4.124
12	Linalool	−3.740	−3.295
13	Rosmarinic acid	−7.305	−8.833
14	Ursolic acid	−3.535	−3.990
15	Oleanolic acid	−3.068	−3.292
Plectranthus amboinicus (Indian Borage)			
16	Carvacrol	−5.408	−4.055
17	β-Caryophyllene	−3.093	−2.600
18	p-Cymene	−2.965	−2.871

Table 7 Docking Interactions of phytoconstituents with target proteins 1JIJ and 4HOE

Sl. no.	Phytoconstituent		Hydrophobic interaction	Polar interaction	Hydrogen bond
1	Tinosponone	1JIJ	Ala 39, Pro 53, Pro 222, Leu 223, Val 224	Ser 82, Thr 42, Gln 196, His 47, Hie 50	Hie 50, Asp 40, Gly 193
		4HOE	Val 6, Ala 7, Phe 110, Val 109, Phe 167, Ala 7, Val 6	Asn 5, Hie 129, Ser 128, Thr 144	Val 109
2	Isocolumbin	1JIJ	Val 224, Leu 223, Pro 222, Pro 53, Ala 39, Tyr 170	Hie 50, His 47, Gln 196, Thr 42, Ser 82	Lys 84, Gly 193
		4HOE	Ala 7, Val 6, Val 109, Phe 167	Asn 5,Hie 129	Val 109, Arg 108
3	Xanosporic acid	1JIJ	Pro 53, Leu 52, Ile 221, Pro 222, Leu 223, Val 224, Phe 232	His 47, Hie 50, Ser 82	Asp 115
		4HOE	Met 1, Pro 4, Val 109, Phe 167	Asn 5, Hie 129, Thr 44,	Arg 108.
4	Tinocordiside	1JIJ	*Tyr* 170, Ala 39, Leu 223, Pro 53	Thr 42, Asn 199, Gln 174, Gln 196, His 47, Hie 50	Gly 38, Asp 80, Asp 40.
		4HOE	Met1, Pro 4, Val 6, Ala 7, Val 109, Phe 167	Asn 5.	Asn 5, Arg 108
5	Nimbin	1JIJ	Ala 30, Cys 37, Phe 54, Pro 53, Leu 223, Val 224, Phe 232.	Ser 82,Thr 42, Gln 196, His 47, Hie 50	Gly 193
		4HOE	Met1, Pro 4, Val 106, Val 100, Phe 110, Phe 167, Ala 7	Ser 128, Hie 129	Asn 5

(*Continued*)

Table 7 (*Continued*)

Sl. no.	Phytoconstituent		Hydrophobic interaction	Polar interaction	Hydrogen bond
6	Nimbolide	1JIJ	Ala 39, Pro 53, Ile 45, Trp 241, Ala 239, Leu 223, Phe 232	Thr 42, Hie 50, His 47, Gln 196	Hie 50, lys 84, Gly 193
		4HOE	Met1, Pro 4, Val 6, Ala 7, Val 109, Phe 167	Asn 5, Ser 128, Hie 129	Asn 5
7	Mahmoodin	1JIJ	Ala 39, Ala 43, Pro 53, Ala 239, Trp 241	Thr 42, Hie 50, His 47,Gln 196, Ser 82	Gln 19, Gly 38
		4HOE	Ala 7, Val 6, Val 109, Leu 188, Phe 167	Asn 5, Thr 44, Ser128, Hie 129	Asn 5, Lys 166
8	Margolone	1JIJ	Tyr 170, Ala 39, Cys 37, Tyr 36, Leu 70, Phe 54, Pro 53	Hie 50, Gln 196, Gln 190, Gln 174,Thr 42,Thr 75	Gly 193
		4HOE	Met1, Pro 4, Val 6, Ala 7, Val 109, Phe 167	Asn 5	Val 109, Asn 5
9	Margolonone	1JIJ	Ala 39, Cys 37, Pro 53, Phe 54.	His 47, Hie 50, Gln 196, Ser 194, Gln 174	Asp 195, Hie 50
		4HOE	Met1, Pro 4, Val 106	Asn 5, Thr 41	Arg 108
10	Quercetin	1JIJ	Tyr 170, Tyr 36, Cys 37, Leu 70, Ala 39, Pro 53	Asn 124, Gln 174, Thr 75, Gln 196, Gln 190	Asp 195, Gly 193, Asp 177, Tyr 36
		4HOE	Val 109, Phe 167, Ala 7, Val 6	Asn 5, Ser 128, Hie 129	Lys 45, Asn 5
11	Eugenol	1JIJ	Tyr 170, Leu 70, Tyr 36, Cys 37, Ala 39, Ile 200, Val 191	Thr 75, Asn 124, Gln 174, Gln 196, Asn 199, Gln 190	Asp 177, Tyr 36
		4HOE	Met 1, Val 109, Val 6, Ala 7, Phe 167	Ser 128, Hie 129, Asn 5	Asn 5
12	Linalool	1JIJ	Ala 39, Cys 37, Phe 54, Pro 53	Thr 42, Hie 50,	Gly 38
		4HOE	Ala 7, Val 6, Val 109, Phe 110, Leu 131, Phe 167	Asn5, Thr 44, Ser 128, Hie 129	Val 109, Asn 5
13	Rosmarinic acid	1JIJ	Tyr 170, Leu 70, Tyr 36, Ala 39	Gln 190, Gln 174, Asn 124, Thr 75, Gln 196, Hie 50, Asn 199, Thr 42	Lys 84, Asp 80, Asp 177, Tyr 36, Asp 40, Gly 38, Asp 195
		4HOE	Phe 167, Ala 7, Val 6, Pro 4,Val 109, Met 1	Ser 128, Hie 129, Asn 5	Asn 5, Val 109, Arg 108
14	Ursolic acid	1JIJ	Phe 232, Pro 53, Leu 52, Val 224, Leu 223, Pro 222	Hie 50, His 47, Ser 19	Gly 49, Val 224
		4HOE	Met 1, Pro 4, Val 106, Phe 167	Thr 44, Asn 5, Hie 129	Asn 5
15	Oleanolic acid	1JIJ	Ala 39,Tyr 170, Leu 223	Thr 42, Gln 174, Ser 82 Asn 199, Gln 196, Ser 194, Hie 50, His 47	Lys 84, Arg 88
		4HOE	Phe 167, Leu 188	Asn 5, Thr 190, Hie 129	Glu 107
16	Carvacrol	1JIJ	Ala 39, Leu 70, Cys 37, Tyr 170, Tyr 36, Val 191, Ile 200	Gln 174, Thr 75, Asn 124, Gln 190, Gln 196	Gln 190
		4HOE	Phe 167, Leu 188.	Asn 5, Thr 190, Hie 129	Asn 5
17	β-Caryophyllene	1JIJ	Tyr 170, Ala 39, Cys 37, Phe 54, Pro 53	Gln 174, Gln 196, Hie 50	–
		4HOE	Val 109, Ala 7, Val 6, Phe 167	Asn 5, Ser 128, Hie 129.	–
18	p-Cymene	1JIJ	Ala 39, Cys 37, Phe 54, Pro 53	Hie 50, Gln 196	–
		4HOE	Val 6, Ala 7, Val 109, Phe 110, Phe 167	Asn 5, Ser 128, Hie 129	–

computationally analyzed for the possible interactions with the TyrRS enzyme target protein 1JIJ in *S. aureus* and DHFR enzyme target protein 4HOE in *C. albicans*, most of them interacted excellently. Their docking scores are the evidence for that. Therefore, this data can be utilized for forthcoming studies.

Conflict of Interest
None declared.

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