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Computational Breakthrough of Natural Lead Hits from the Genus of *Arisaema* against Human Respiratory Syncytial Virus

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ABSTRACT

Background: To date, efforts for the prevention and treatment of human respiratory syncytial virus (RSV) infection have been still vain, and there is no safe and effective clinical accepted vaccine. Arisaema genus has claimed for various traditional bioactivities, but scientific assessments are quite limited. Objective: This encouraged us to carry out our present study on around 60 phytoconstituents of different Arisaema species as a natural inhibitor against the human RSV. Materials and Methods: Selected 60 phytochemical entities were evaluated on the docking behavior of human RSV receptor (PDB: 4UCC) using Maestro 9.3 (Schrödinger, LLC, Cambridge, USA). Furthermore, kinetic properties and toxicity nature of top graded ligands were analyzed through QikProp and ProTox tools. Results: Notably, rutin (glide score: -8.49), schaftoside (glide score: -8.18) and apigenin-6,8-di-C- β -D-galactoside (glide score – 7.29) have resulted in hopeful natural lead hits with an ideal range of kinetic descriptors values. ProTox tool (oral rodent toxicity) has resulted in likely toxicity targets of apex-graded tested ligands. Conclusion: Finally, the whole efforts can be explored further as a model to confirm its anti-human RSV potential with wet laboratory experiments.

Key words: Apigenin-6,8-di-C- β -D-galactoside, Arisaema, ProTox, Rutin, Schaftoside

SUMMARY

- Rutin, schaftoside, and apigenin-6,8-di-C-β-D-galactoside showed promising top hits docking profile against human respiratory syncytial virus
- Moreover, absorption, distribution, metabolism, excretion properties (QikProp) of top hits resulted within an ideal range of kinetic descriptors
- ProTox tool highlighted toxicity class ranges, LD₅₀ values, and possible toxicity targets of apex-graded tested ligands.



Abbreviations used: RSV: Respiratory syncytial virus, PRRSV: Porcine respiratory and reproductive syndrome virus, ADME-T: Absorption, distribution, metabolism, excretion, and toxicity.

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INTRODUCTION

Human respiratory syncytial virus (RSV) represents as an important respiratory pathogens predecessor for the development of lower respiratory tract infections such as bronchiolitis and pneumonia in infants and young children worldwide. It causes diseases with an expected of 125,000 hospitalizations and 66,000-199,000 mortality rate in 2005 among children >5 years of age. To date, attempts for the prevention and treatment of RSV infection have been still unsuccessful and there is no safe and effective clinical accepted vaccine. Notably, ribavirin showed promising licensed antiviral treatment, and moreover, passive immunization with palivizumab has too resulted in 50% protection to high-risk children but due to questionable efficacy and toxicity put a big question mark among researchers.^[1,2] Thus, there is an urgent need to explore and unlock safe effective therapy for RSV. RSV is an enveloped and nonsegmented with negative-strand RNA virus (family; Paramyxoviridae) belonging to the genus Pneumovirus. Previous

studies have indicated that RNA-dependent polymerase complex offers promising targets for RSV-specific drugs. Remarkably, the ribonucleoprotein complex involves of genomic RNA encapsulated by the RSV nucleoprotein, N. This detection proceeds through interaction between the phosphoprotein P, which is the chief polymerase cofactor, and N.^[3] Thus, we have tried to explore natural chemical entities with the nucleocapsid/phosphoprotein pocket site as an alternative to synthetic drugs to reduce or

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minimize the side effects. A series of phytochemical entities are accumulated as secondary metabolites during biosynthesis. The literature findings have already documented that the nature of these chemical substances varies due to the unique form of biosynthetic processes with the particular period of the plants and may worth for exceptional antiviral action.^[4,5]

Arisaema genus consists of monocotyledon plant species belonging to family *Araceae*. Around 150 species are accessible throughout the world, out of which 140 species are found in Asia, Africa, and Arab continents.^[6] Previous study has revealed that *Arisaema franchetianum* confirmed hopeful biological spectrum against porcine respiratory and reproductive syndrome virus.^[7] Very few species of *Arisaema* genus have been documented for their biological actions to date.^[8-12] Thus, herein, an attempt was designed to computationally discover the *in silico* natural lead hits concerning their kinetic and toxicity nature against RSV [Figure 1].

MATERIALS AND METHODS

Molecular docking simulations were operated on Maestro 9.3 (Schrödinger, LLC, Cambridge, USA) furnished with Core i5 processor, 8 GB RAM, and 500 GB with Window 10 as the operating system. The tested ligands details were retrieved from various search engines such as SciFinder, PubMed, and Google Scholar.^[7,13-29]

Target protein identification and preparation

The three-dimensional crystal structure of target RSV receptor (PDB: 4UCC) with a resolution of 2.05 Å was obtained from the Research Collaboratory for Structural Bioinformatics, PDB database (Anonymous, www.rcsb.org). The protein was linked in complex with 1-[(2,4-dichlorophenyl) methyl] pyrazole-3,5-dicarboxylic acid as a reference ligand. Target receptor preparation was started in the course of protein preprocess step which agrees with the insertion of polar hydrogen and amputation of metal ions, cofactor, and water molecule outside 5 Å. In addition, ionization (pH: 6.7–7.3), optimization of hydrogen bond, and restorative energy minimization steps were also performed to attained the proper geometry of the receptor. The probable binding pocket area was indicated through grid box formation by clicking on the internal ligand.

Ligand preparation

The tested ligands were sketched in ChemDraw Ultra 10.0 (CambridgeSoft) in.mol file format, followed by exportation into Maestro software. Outstandingly, ligands preparations were done using least square OPLS_2005 force field plus conformer generations and filtration to their energy minima with probable state creation (pH 7 \pm 2.0).

Docking simulation

Extra Precision (XP) Glide docking simulations were applied to the

indicated receptor grid of human RSV protein receptor. Finally, the results outcome was analyzed by the way of XP Visualizer not only in the form of glide score but also reviewing various probable interactions such as H-bonding, π - π interactions, and hydrophobic interactions, correspondingly.^[30]

Absorption, distribution, metabolism, excretion, and toxicity prediction

Both of absorption, distribution, metabolism, excretion, and toxicity prediction (ADME-T) were accomplished using QikProp (Maestro 9.3) and ProTox tools, respectively. Various kinetic descriptors as indicated in Table 1 were scrutinized. As for the ProTox analysis, oral toxicity in rodents (LD₅₀ in mg/kg of body weight) descriptors with likely toxicity targets was too studied.^[31]

RESULTS AND DISCUSSION

Overall, the results of tested chemical entities having particular glide score with human RSV receptors are summarized in Table 2. From the results, it has been observed that out of 60 phytoconstituents of *Arisaema* genus, rutin (glide score: -8.49), schaftoside (glide score: -8.18), and apigenin-6,8-di-C- β -D-galactoside (glide score -7.29) attained top hits with an ideal range of kinetic descriptors values [Table 3].^[32] Furthermore, toxicity profiles of tested chemical constituents (ProTox) were also highlighted with probable toxicity targets as mentioned in Table 4.

Top hits phytoconstituents *Rutin*

This compound resulted as a first rank great hit with remarkably, H-bonding interactions of Glu128, Glu112, Arg132, Asp152, and Arg150, followed by hydrophobic interactions of amino acid residues such as Phe111, Met50, Tyr135, leu139, respectively. Interestingly, π - π stacking (Tyr135 and Hie151) were too seen.

Schaftoside

Schaftoside compound confirmed as the second best hit with H-bonding interactions such as Glu144, Arg132, Glu112, Glu128, Lys110, Asp152, and Lys46. Moreover, π - π stacking (Arg150) was examined. The hydrophobic interactions (Leu139, Tyr135, and Phe111) were also analyzed.

Apigenin-6,8-di-C-β-D-galactoside

Apigenin-6,8-di-C- β -D-glucopyranoside was observed as the third-ranked promising hit with capable of H-bonding (Arg132, Glu112, Glu128, Lys110, Asp152, and Lys46) and hydrophobic interactions (Tyr135, Phe111). In addition, π - π stacking (Arg150) was observed.

Among all top hits, rutin showed possible predicted interaction (LD₅₀: 5000 mg/kg rodents) with adrenoceptor beta 2 (ADR β 2) and

Table 1: Absorption, distribution, metabolism, excretion descriptors of top ranked entities from QikProp

Entities	MW	DM	SASA	FOSA	PISA	IP (EV)	QPLOGPO/W	QPLOGS	QPLOGKHSA	QPLOGKP	RULE of 5
Rutin (20)	610.524	3.238	804.232	208.548	193.218	9.066	-2.470	-2.304	-1.360	-6.816	3
Schaftoside (1)	564.499	10.456	764.960	206.985	169.730	8.757	-2.329	-2.801	-1.128	-7.021	3
Apigenin-6,8-di-C- β -D-galactoside (7)	578.526	5.539	849.974	200.056	191.360	9.023	-2.665	-3.340	-1.262	-8.138	3

MW: Molecular weight; DM: Predicted dipole moment; SASA: Solvent assessable surface area; QPLOGPO/W: Predicted octanol/water partition coefficient; QPLOGS: Predicted aqueous solubility; QPLOGKP: Predicted skin permeability; QPLOGKHSA: Predicted human serum albumin binding; RULE of 5: Lipinski violations





Figure 1: Chemical structures of chief phytoconstituents reported from *Arisaema* species

prostaglandin G/H synthase 1 targets, which might be a valuable tool for future researchers to understand its precise mechanistic nature [Figure 2].

Table 2: Phytoconstituents from Arisaema species docked with respiratory syncytial virus receptor

Plant species	Phytoconstituents	Docking score
Arisaema erubescens (Wall.) Schott	1. Schaftoside	-8.18
	2. Isoschaftoside	-6.61
	3. Aurantiamide acetate	NS
	4. Apigenin-6-C-galactosyl-8-C-arabinoside	-6.14
	5. Apigenin-6-C-arabinosyl-8-C-galactoside	-6.99
	6. Apigenin-6,8-di-C-β-D-glucopyranoside	-6.91
	7. Apigenin-6,8-di-C-β-D-galactoside	-7.29
	8. Paeonol	-3.79
	9. β-sitosterol	-1.99
Arisaema amurense Maxim	10. D-mannitol	-6.20
	11. Daucosterol	NS
	12. 2,3-dinydroxypropyi 92,122-octadeca-Dienoate	-6.57
Arisaema tortuosum (Wall.) Schott	13. Stigmasterol	INS 1.49
	15. Chalactaral	-1.40 NS
	16 Choline chloride	_2 12
	17. Stachydrine	-2.12
	18 Colchicine	-3.19
	19 Ouercetin	-5.44
	20. Rutin	-8.49
	21. Luteolin	-5.52
Arisaema triphyllum (L.) Schott	22. α -ketoadipic acid	NS
	23. Inositol	NS
	24. Maleoyl acetic acid	-3.72
Arisaema flavum (Forssk.) Schott	25. α-amyrin	-1.41
	26. β-amyrin	-1.27
	27. lup-20 (29)-en-3β-ol	-1.60
	28. lup-20 (20)-en-3β-yl acetate	-1.63
	29. (3β)-Stigmast-5-en-3-yl β-D-galactopyranoside	NS
	30. Arisaeminone	-3.61
Arisaema jacquemontii Blume	31. 2-hydroxydiplopterol	-2.60
	32. 30-nor-lanost-5-ene-3β-ol	NS
	33. 30-nor-lanost-5-ene-3-one	NS
Arisaema negishii Makino	34. Cis-ribosylzeatin	NS
Arisaema fargesii Buchet	35. Benzoic acid	-3.08
	36. Succinic acid	-2.68
Arisaema franchetianum Engl	37. (2R*,3S*,5S*)-N,2-dimethyl-3-hydroxy-5-(10-phenyldecyl) pyrrolidine	NS
	38. 5-nyaroxy-1,1,2-trimetnyl-5 (10-pnenylaecyl) 1-ri-pyrronum	185
	40. Emodin	-4.80
	4). Efficiencia	-3.62
	42 Nobiletin	-3.02
	43 Conjferin	-4 78
	44 Methyl Coniferin	-5.28
	45. 3-O-β-d-galactopyranosyl-hederagenin	NS
	28-O-β-d-xylopyranosyl $(1 \rightarrow 6)$ -β-D-galactopyranosyl ester	
	46. Qingyangshengenin	NS
	47. Syringaresinol 4'-O-β-D-glucopyranoside	-6.97
	48. Gagaminine	-5.36
	49. Perlolyrine	NS
	50. (S)-1-(1'-hydroxyethyl)-β-carboline	-4.03
	51. 1-(β-carboline-1-yl)-3,4,5-trihydroxy-1-pentanone	-5.38
	52. 1-methoxycarbonyl-β-carboline	-3.54
	53. Indolo[2,3-β]carbazole	-4.47
	54. 4-hydroxycinnamic acid methyl ester	-3.94
Arisaema decipiens Schott	55. (-)-(2R*, 3S*, 6S*)-N,2-dimethyl-3-hydroxy-6-(9-phenylnonyl) piperidine	-3.78
	56. Nimbin	-3.39
	57. 6-deacetylnimbin	-3.77
	58. 28-deoxonimbolide	-3.16
Arisaema rnizomatum C.E.C. Fisch	59. 5,/,4/-trinydroxy-3/-methoxyflavone	-4.65
Internal Licender 1 [(2.4. diables - 1 1) (1 - 1]	60. Cinnamic acid	-4.25
internal Ligand: 1-[(2,4-dichlorophenyl) methyl] p	yrazoie-ə,ə-uicardoxyiic acid	-5.95

NS: Not scored

Chemical entities	Glide score	Number of H-bonds	H-bond distance (Å)	Amino acid allied
Rutin (20)	-8.49	7	2.00	Glu128
			1.98	Glu112
			1.90	Arg132
			2.00	Asp152
			2.04	Arg150
			2.03	
			1.96	
Schaftoside (1)	-8.18	10	2.42	Glu144
			1.80	Arg132
			1.86	Glu112
			1.85	Glu128
			2.41	Lys110
			1.70	Asp152
			1.76	Lys46
			2.04	
			1.93	
			1.96	
Apigenin-6,8-di-C-β-D-galactoside (7)	-7.29	9	2.08	Arg132
			2.03	Glu112
			2.12	Glu128
			2.41	Lys110
			1.82	Asp152
			3.03	Lys46
			1.89	
			1.77	
			2.02	
1-[(2,4-dichlorophenyl) methyl] pyrazole-3,5-dicarboxylic acid	-5.95	3	1.67	Lys46
(Internal Ligand)			1.84	Hie151
			2.07	Arg150

Table 3: Binding affinity of top three hits of Arisaema species with human respiratory syncytial virus receptor



Figure 2: Binding interactions of rutin with human respiratory syncytial virus receptor

CONCLUSION

In the present study, glide scores of tested phytoconstituents of *Arisaema* genus were recorded from -1.41 to -8.49. Apex-ranked hits such as rutin, schaftoside and apigenin-6,8-di-C- β -D-glucopyranos ide have found to have superior interactions and binding affinity with human RSV. Computational ADME-T studies were also emphasized to ensure the safety and effectiveness of drugs based on natural origin. Therefore, these preliminary studies might be quite useful for future researchers to validate it with wet laboratory experiments.

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Conflicts of interest

There are no conflicts of interest.

Table 4: Toxicity profiles of top hits from ProTox database

Entities	LD ₅₀ (mg/kg)	Toxicity class*	Average similarity	Predicted accuracy	Possible toxicity targets (UniProt name)
Rutin (20)	5000	5	100	100	ADRβ2 and PGH1
Schaftoside (1)	536	4	57.26	67.38	No binding
Apigenin-6,8-di-C- β -D-galactoside (7)	536	4	56.98	67.38	No binding

*Toxicity class - Class 1: Fatal if swallowed ($LD_{50} \le 5 \text{ mg/kg}$); Class 2: Fatal if swallowed ($5 < LD_{50} \le 300 \text{ mg/kg}$); Class 3: Toxic if swallowed ($50 < LD_{50} \le 300 \text{ mg/kg}$); Class 4: Harmful if swallowed ($300 < LD_{50} \le 2000 \text{ mg/kg}$); Class 5: May be harmful if swallowed ($2000 < LD_{50} \le 5000 \text{ mg/kg}$); Class 6: Nontoxic ($LD_{50} > 5000 \text{ mg/kg}$); ADR β 2: Adrenoceptor beta 2; PGH1: Prostaglandin G/H synthase 1

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