IN- SILICO DISCOVERY OF NATURAL LEAD HITS FROM THE GENUS OF *Arisaema* AGAINST HUMAN RHINO VIRUS

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ABSTRACT

Human rhino viruses (HRVs) serve as an imperative precursor for frequent cases of the common cold among children worldwide. An in-silico molecular docking attempt was made of some chief phytochemical entities (Arisaema plant species) as inhibitors of HRVs with selective therapeutic target action and minimal side effects. Around 60 phytoconstituents of different Arisaema species were docked against HRV receptor (PDB: 2XYA). Binding conformers of test ligands were compared with internal ligand. Finally, Syringaresinol 4'-O-β-D-glucopyranoside (glide score: -10.86), Rutin (glide score: -9.04) & Apigenin-6,8-di-C-β-D-glucopyranoside (glide score: -7.88) have resulted in most promising hits which can be further act as an effective template to experimentally validate or further designed their choosy and budding analogue agents against HRVSs.

Keywords: *Arisaema*, human rhino virus, docking

INTRODUCTION

Presently, it is very imperative to mitigate the challenge of developing an antiviral drug for treatment of common cold. Common cold is a disease which is being caused by rhino viruses due to lack of specific treatment against this virus. Although, randomized therapy possess some better therapeutic effect but at the same time patients may also suffer from some adverse effects. The symptom includes some cholinergic effect on the peripheral nervous system followed by nasal stuffiness, sneezing, cough & throat infections. If symptoms are not treated for longer time they may lead to some life threatening diseases such as chronic obstructive pulmonary diseases

(COPD), asthma, cystic fibrosis etc. On the light of literature findings, there is no specific antiviral drug which can cure the diseases which in turns extend the therapy as well as cost. School children's are generally more prone for this infection and repeatedly suffering with this disease. Nasal mucosa serves the main target for this virus. Mucous produced by the cilliary glands and goblet cells are generally contain metabolic cation and anion such as Cl^-, $Na,^+$,K^+, glycoprotein and immunoglobulin. [1] These are responsible for resisting this infection & any kind of imbalance leads to infection in pulmonary cells. Currently, synthetic anti viral agents are still using in market but high cost & more adverse effects have twisted researchers focus on natural products. Globally, Herbal remedies have been researched under rigorous controls and have been approved by the Government of technologically advanced nations. There are different types of chemical entities in plants which are being accumulated as secondary metabolites during the course of biosynthesis. [2] The nature of chemical entities varies due to dissimilar form of biosynthetic processes with particular time period of the plants. The literature findings have already reported excellent antiviral potential origin via natural products. [3]

Arisaema genus comprises of monocotyledon plant species belongs to family Araceae. Around 150 species are available throughout world, out of which 140 species are found in Asia, Africa, & Arab continents. [4] Previous studies have indicated that *A. franchetianum* showed promising bioactivity against porcine respiratory & reproductive syndrome virus (PRRSV). [5] To date, very few species of *Arisaema* genus have been explored for their biological actions. Thus, present study was intended to computationally discover the *in-silico* lead hits from the genus of *Arisaema* against rhino virus.

MATERIALS & METHODS

Molecular docking simulations were run on Maestro 9.3 version (Schrodinger LLC suite) equipped with core ™ processor, 3 GB RAM and 180 GB with centrp linux as the operating system. The tested phytoconstituents chemical structures were collected from the literature (Scifinder, Pubmed, Google Scholar). [7-24]

Protein Preparation & Grid Configuration

The crystal structure of human rhino protein (PDB: 2XYA) was imported from RCSB protein bank in scrupulous PDB format. [6] The protein was accounted in complex with 2-Phenylquinolin-4-ol as an internal standard. Protein preparation was initiated through protein pre-process pace which deals with the addition of polar hydrogen and removal of metal ions, cofactor and water molecule outside $5A^0$. Furthermore, ionization (pH: 6.7-7.3), optimization of hydrogen bond and restorative energy minimization steps were too applied to obtained the appropriate geometry of the receptor. The interactions potential of binding pocket were allotted through grid box formation near clicking around the active site of the internal ligand.

Ligand library

The reported chemical entities 3-D structures were sketched in Chem Draw Ultra 10.0 (Cambridge soft) in .mol file format and at last exported into Maestro software. Remarkably, ligands preparations were finished using least square OPLS_2005 force field followed by conformer generations & filtration to their energy minima with probable state creation (pH 7±2.0).

Docking computation

Extra precision (XP) glide docking was implemented on the generated receptor grid of human rhino virus protein. Finally, results outcome were analyzed via XP visualizer not only in the form of glide score but as well reviewing various probable interactions like H-bonding, π-π interactions & hydrophobic interactions, respectively. [25]

RESULTS & DISCUSSION

The internal ligand plus phytochemicals from *Arisaema* genus (Table 1) was docked against human rhino virus receptor (PDB: 2XYA). The ranking were estimated by apex hits glide score of the tested entities. Overall, table 1 has indicated that Syringaresinol 4'-O-β-D-glucopyranoside possess higher binding affinity (first rank) with HRV receptor (Glide Score: -10.86).

Table1: Maestro docking score of phytoconstituents (*Arisaema* species) against rhino virus receptor

Sr. No.	Plant Species	Phytoconstituents	Docking Score
1	*Arisaema erubescens* (Wall.) Schott	1. Schaftoside 2. Isoschaftoside 3. Aurantiamide acetate 4. Apigenin-6-C-galactosyl-8-C-arabinoside 5. Apigenin-6-C-arabinosyl-8-C-galactoside 6. Apigenin-6,8-di-C-β-D-glucopyranoside 7. Apigenin-6,8-di-C-β-D-galactoside 8. Paeonol 9. β-sitosterol	-5.15 -5.01 -5.14 -6.35 -5.26 -7.88 -6.91 -4.37 -3.19
2	*Arisaema amurense* Maxim.	10. D-Mannitol 11. Daucosterol 12. 2,3-dihydroxypropyl 9Z,12Z-octadeca- Dienoate	-5.29 n.d -5.96
3	*Arisaema tortuosum* (Wall.) Schott	13. Stigmasterol 14. Campesterol 15. Cholesterol 16. Choline chloride 17. Stachydrine 18. Colchicine 19. Quercetin 20. Rutin 21. Luteolin	n.d -2.73 n.d -2.72 -2.15 -4.38 -5.83 -9.04 -6.54
4	*Arisaema triphyllum* (L.) Schott	22. α-Ketoadipic acid 23. Inositol 24. Maleoyl acetic acid	n.d n.d -2.68
5	*Arisaema flavum* (Forssk.) Schott	25. α-Amyrin 26. β-Amyrin 27. lup-20(29) -en-3β-ol 28. lup-20(20)-en-3β-yl acetate 29. (3ß)-Stigmast-5-en-3-yl ß-D-galactopyranoside 30. Arisaeminone	-2.69 -2.80 -1.75 -2.03 n.d -6.04

Sr. No.	Plant Species	Phytoconstituents	Docking Score
6	*Arisaema jacquemontii* Blume	31. 2-hydroxydiplopterol 32. 30-nor-lanost-5-ene-3β-ol 33. 30-nor-lanost-5-ene-3-one	-3.83 n.d n.d
7	*Arisaema negishii* Makino	34. Cis-ribosylzeatin	n.d
8	*Arisaema fargesii* Buchet	35. Benzoic acid 36. Succinic acid	-2.75 -2.48
9	*Arisaema franchetianum* Engl.	37. (2R*,3S*,5S*)-N,2-dimethyl-3-hydroxy-5-(10-phenyldecyl)pyrrolidine 38. 3-Hydroxy-1,1,2-trimethyl-5(10-phenyldecyl)1-H-pyrrolium 39. Bergenin 40. Emodin 41. Caffeic acid 42. Nobiletin 43. Coniferin 44. Methyl Coniferin 45. 3-O-β-d-galactopyranosyl-hederagenin 28-O-β-d-xylopyranosyl(1 → 6)-β-D-galactopyranosyl ester 46. Qingyangshengenin 47. Syringaresinol 4'-O-β-D-glucopyranoside 48. Gagaminine 49. Perlolyrine 50. (S)-1-(1'-hydroxyethyl)-β-carboline 51. 1-(β-carboline-1-yl)-3,4,5-trihydroxy-1-pentanone 52. 1-methoxycarbonyl-β-carboline 53. Indolo[2,3-β]carbazole 54. 4-Hydroxycinnamic acid methyl ester	n.d n.d -6.11 -5.05 -4.21 -4.42 -7.01 -5.79 n.d n.d -10.86 -4.61 n.d -4.29 -6.41 -3.17 -2.85 -3.32
10	*Arisaema decipiens* Schott	55. (-)-(2R*, 3S*, 6S*)-*N*,2-dimethyl-3-hydroxy-6-(9-phenylnonyl)piperidine 56. Nimbin 57. 6-Deacetylnimbin 58. 28-Deoxonimbolide	-3.14 -2.63 -2.05 -2.67

Sr. No.	Plant Species	Phytoconstituents	Docking Score
11	*Arisaema rhizomatum* C.E.C.Fisch.	59. 5,7,4$^{/}$-trihydroxy-3$^{/}$-methoxyflavone 60. Cinnamic acid	-6.20 -2.50
		Internal ligand (2-phenylquinolin-4-ol)	-4.91

Indicated: n.d-not docked

Top ranked Phytoconstituents

Syringaresinol 4'-O-β-d-glucopyranoside: Among all tested ligands, this compound has resulted as a most powerful hit with notably H-bonding interactions of amino acid residues like Thr142, Hie161, Ser144, Lys24 & Asn107, correspondingly. The hydrophobic interactions (Cys147, Val162, Phe25) were too studied (Table2).

Rutin: The compound confirmed as the second ranked most influential hit with H-bonding interactions (Gly164, Hie161, Lys143 & Asn22) followed by hydrophobic interactions of Tyr146, Cys147, Val162 & Phe25 as indicated in Table2 & Figure 2, respectively.

Apigenin-6, 8-di-C-β-D-glucopyranoside: The molecule was examined as the third ranked promising hit with H-bonding interactions like Asn22, Hie161, Lys143 & Gly164 respectively. In addition, π-π stacking (Phe25) was also observed.

Table 2: Binding affinity of top hits phytoconstituents of *Arisaema* species with rhino virus receptor.

Sr. No.	Chemical entities	Glide Score	No. of H-bonds	H-bond distance	Amino acid allied
1	Syringaresinol 4'-O-β-d-glucopyranoside	-10.86	7	1.91 2.29 2.15 1.84 1.63 2.39 2.60	Thr142 Hie161 Ser144 Ser144 Ser144 Lys24 Asn107

Sr. No.	Chemical entities	Glide Score	No. of H-bonds	H-bond distance	Amino acid allied
2	Rutin	-9.04	5	1.92 1.53 2.43 2.41 1.84	Hie161 Lys143 Asn22 Asn22 Gly164
3	Apigenin-6,8-di-C-β-D-glucopyranoside	-7.88	4	1.90 1.52 1.85 2.39	Hie161 Lys143 Gly164 Asn22

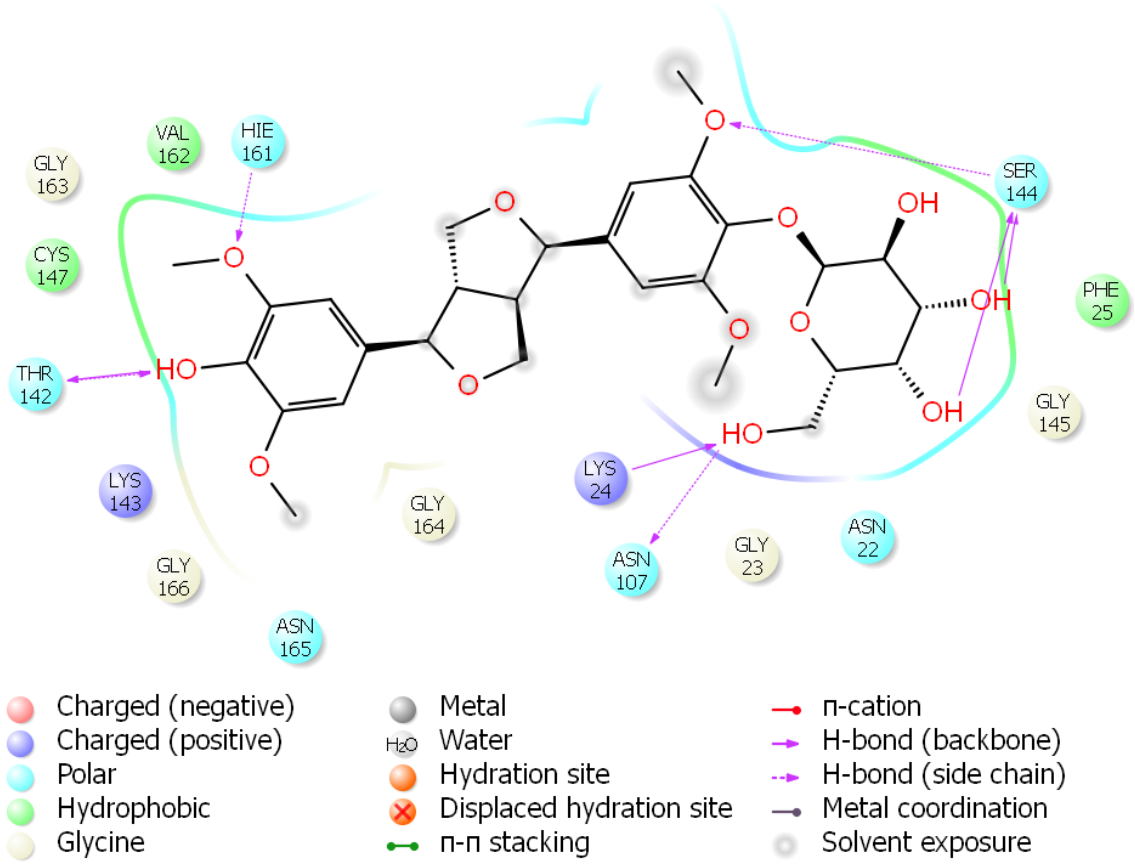

Figure 1: Binding affinity of Syringaresinol 4'-O-β-d-glucopyranoside with HRV receptor (PDB: 2XYA).

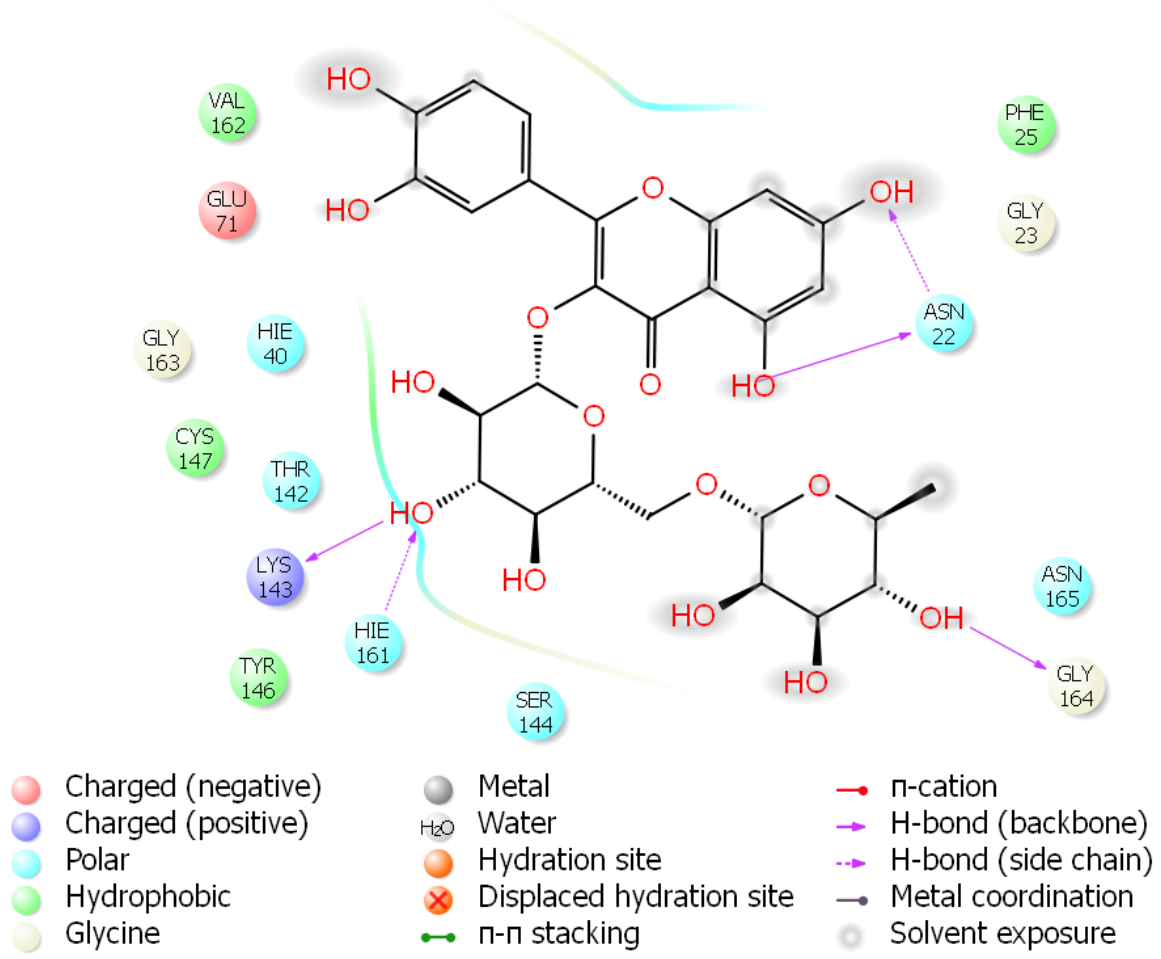

Figure 2: Binding affinity of Rutin with HRV receptor (PDB: 2XYA).

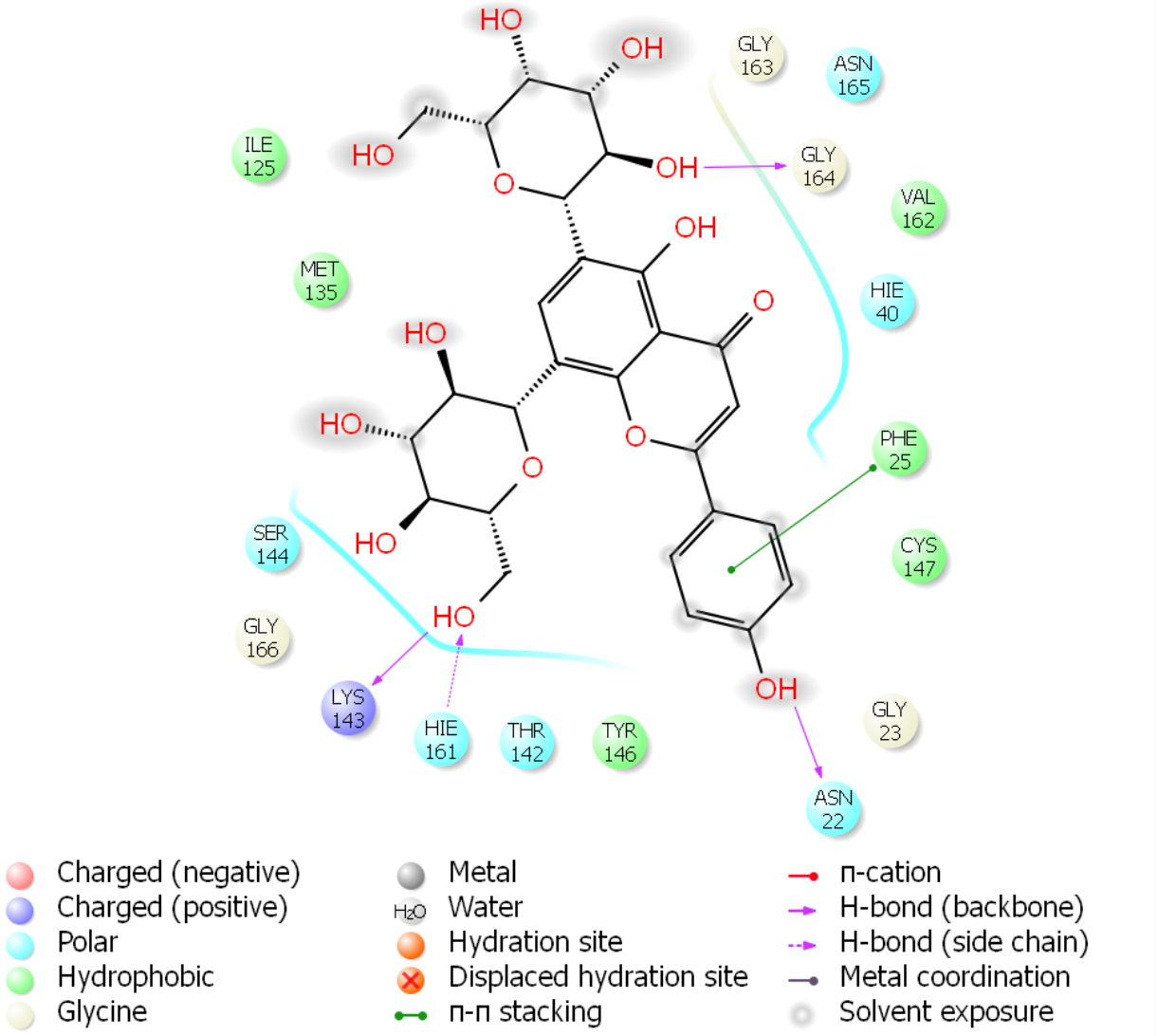

Figure 3: Binding affinity of Apigenin-6,8-di-C-β-D-glucopyranoside with HRV receptor (PDB: 2XYA).

CONCLUSION

The glide scores of phytochemical entities in *Arisaema* plant species were analyzed from -1.75 to -10.86. Top screened hits like Syringaresinol 4'-O-β-d-glucopyranoside, Rutin & Apigenin-6,8-di-C-β-D-glucopyranoside have revealed as hopeful inhibitors of HRV. However, detailed

studies (*in-vitro* & *in-vivo*) were needed to validate it experimentally & unlock the novel selective antiviral biological action with clear mechanism against HRV. The toxicity nature should be further assessed in order to minimize the adverse effects of synthetic drugs. Thus, current preliminary study might be act as an important breakthrough for future researchers to unbolt *Arisaema* species biological spectrum origin from natural sources.

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