

## Evaluation by Molecular Docking of Some *Picrasma javanica* Phytochemicals Binding to VP8\* Domain of the Outer Capsid Protein VP4 of Rotavirus A

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### Abstract

Rotavirus is one of the common causes of gastroenteritis in children; in fact nearly every child in the world will have at least one rotavirus-induced gastroenteritis (marked by watery diarrhea) before age 5. Despite the introduction of vaccines, over 200,000 children die annually from rotavirus induced severe dehydrating gastroenteritis, most of the children being in the poor countries of the world. Rotaviruses belong to the non-enveloped double-stranded RNA (dsRNA) virus group. The RNA segment encodes six structural viral proteins (VPs); among them attachment of rotavirus to host cells is mediated through the VP8\* domain of the outer capsid protein VP4. *Picrasma javanica* Blume belongs to the Simaroubaceae family and can be found in Bangladesh, India and other tropical countries. Since the plant has indigenous uses as an antiviral, it was of interest to evaluate through molecular docking studies whether phytochemicals reported from the plant can bind to VP8\* domain of the outer capsid protein VP4 of rotavirus A. Such binding has the possibility of inhibition of virus attachment to host cells and so be an effective treatment against rotavirus-induced diarrhea. In molecular docking studies carried out through AutoDock Vina, it was found that indeed several phytochemicals of the plant showed high binding affinities to the target protein and as such warrants further *in vivo* studies in experimental models of rotavirus-induced diarrhea.

**Keywords:** GI-Tract Disorders; Rotavirus; *Picrasma javanica*; Diarrhea; Gastroenteritis

### Abbreviations

dsRNA: Double-Stranded RNA; VP: Viral Protein

### Introduction

Throughout the world, in all countries rich or poor, most children by the time they have reached 5 years of age, will suffer at least once from rotavirus-induced severe dehydrating gastroenteritis. This results in more than 200,000 children deaths annually despite introduction of a vaccine against rotavirus [1]. In fact, diarrheal diseases from various causes are the leading causes of death in children under 5 years of age, and this occurs more often in the low-income countries. It has been reported that globally such diarrhea-induced deaths

number more than 500,000 annually [2]. The number of clinic visits and hospital admissions have been reported as 25 million and two million, respectively [3,4]. Children from low-income countries are more prone to this disease because of poor hygiene, lack of quality water, and lack of proper sanitary systems.

Rotaviruses belong to the non-enveloped double-stranded RNA (dsRNA) virus group. The RNA segment encodes six structural viral proteins (VPs); among them attachment of rotavirus to host cells is mediated through the VP8\* domain of the outer capsid protein VP4. Since the introduction of rotavirus vaccines, it has been observed that the vaccines perform less well in developing countries than industrialized countries, which has been attributed to possibly reduced immune responses in infants arising out of malnutrition and deficiency of micronutrients [5]. Oral rehydration therapy is the preferred mode of treatment of children with mild to moderate dehydration in children with acute diarrhea [6].

In Bangladesh, it has been found in a 5-year survey from 2012 till 2017 that around 64% of children under 5 years of age suffering from acute gastroenteritis showed rotavirus infections [7]. Group A rotaviruses (both G and P genotypes, G and P genotypes are differentiated based on differences in the genes of a glycoprotein VP7 and the spike protein VP4) cause between 6,000 to 14,000 deaths of children under 5 years of age [8]. Binding of rotavirus to human cells is mediated by the distally located VP8\* domain of the spike protein VP4 [9]. VP8\* is the least conserved among rotavirus structural proteins of the 37 P genotypes [10]. However, VP8\* is structurally conserved with a galectin-like fold.

Since the various therapies like vaccination and oral rehydration therapy, although successful in a number of aspects, have not been shown to be totally adequate for Bangladesh, we thought it might be of interest to undertake molecular docking studies between the VP8\* domain of spike protein VP4 of rotavirus A and phytochemicals of a plant *Picrasma javanica* Blume belonging to the Simaroubaceae family. Although it cannot be said with absolute certainty that a strong binding affinity in computer simulation studies between VP8\* and any given phytochemical means that the phytochemical automatically can be used *in vivo* as a rotavirus inhibitor, it at least gives a starting point for further antiviral studies.

*Picrasma javanica* was selected for our studies because the plant is found in India and Bangladesh; in India, the bark has ethnic uses, the bark decoction being taken for diabetes and hypertension, while root decoction is taken for fever and malaria [11]. Simaroubaceae family plants have been reported for anti-viral activity [12]. Moreover, not much studies have been done with plants belonging to this family. Phytochemicals reported in the present study were randomly selected from a pre-print, which gave a quite extensive list of phytochemicals of the plant [13]. Phytochemicals of plants used in ethnic medicine, if proven through further scientific studies to be correct in their ethnic uses, offers possibility of not only new drug discoveries, but also validating and as such using the plant in its traditional manner for therapeutic purposes.

## Methods

### Three-dimensional structure of receptor

We have used the pdb file (4YFW) of the VP8\* domain of the outer capsid protein VP4 of Human Rotavirus A [14]. We have added polar hydrogen and removed water from the pdb structure. Monomeric form of the protein was used for molecular docking.

### Compounds used in docking studies

We have studied phytochemicals known to occur in *Picrasma javanica*. Ligands molecules were downloaded from PubChem [15] as sdf format. They were optimized with the force field type MMFF94 using OpenBable software [16].

### Molecular docking

We have conducted molecular docking using AutoDock Vina [17] in its blind mode where the GRID box used was large enough to cover the entire protein structure. An exhaustiveness of 16 was used. Poses were ranked on the basis of estimated free energy of interaction

( $\Delta G$ , kcal/mol) and only the highest rank (i.e. with the lowest  $\Delta G$ ) pose for each ligand was considered. Also for each phytochemical, three independent docking runs were performed and the  $\Delta G$  values were reported as average.

Figures showing possible mode of interaction with the protein were made using PyMOL (<https://pymol.org/2/>) whilst the 2D ligand interaction diagrams were made using Discovery Studio [18].

## Results and Discussion

The predicted binding affinities of the phytochemicals studied with the VP8\* domain of the outer capsid protein VP4 of human rotavirus A using AutoDock Vina is shown in table 1. *Picrasma javanica* is particularly rich in quassinoids [13], a bitter group of highly oxygenated triterpenes, which can be divided into five groups, namely C-18, C-19, C-20, C-22 and C-25 based on their chemical structures. So, more emphasis was placed on quassinoids and quassinoid derivatives with a few alkaloids and triterpenoids for comparison.

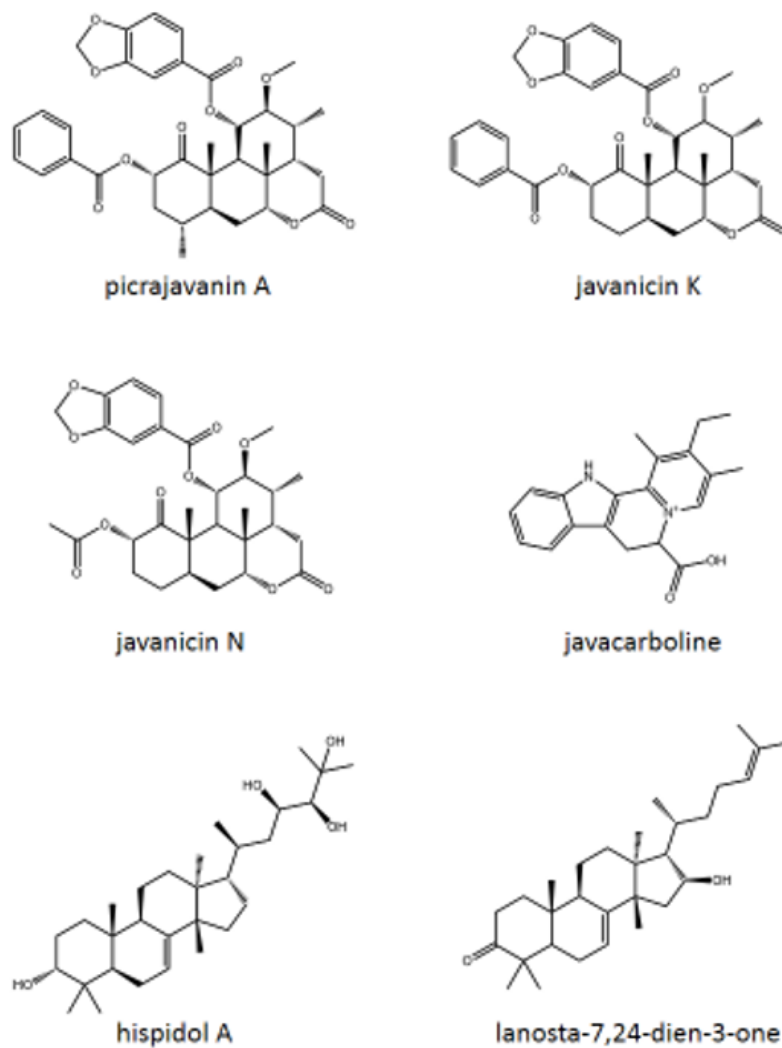
Phytochemicals	( $\Delta G$ , kcal/mol)*
5-Hydroxycrenatine (Alkaloid)	-6.9
5-Hydroxydehydrocrenatine (Alkaloid)	-6.9
Dihydrojavanicin (Quassinoid)	-6.7
<b>Hispidol A (Triterpenoid)</b>	<b>-8.2</b>
<b>Javacarboline (Alkaloid)</b>	<b>-8.3</b>
Javanicin B (Quassinoid)	-7.1
Javanicin E (Quassinoid)	-7.1
Javanicin F (Quassinoid)	-7.1
Javanicin G (Quassinoid)	-7.2
Javanicin H (Quassinoid)	-6.9
Javanicin I (Quassinoid)	-7.9
Javanicin J (Quassinoid)	-7.6
<b>Javanicin K (Quassinoid)</b>	<b>-8.0</b>
Javanicin M (Quassinoid)	-7.9
<b>Javanicin N (Quassinoid)</b>	<b>-8.0</b>
Javanicin P (Quassinoid)	-7.2
Javanicin Q (Quassinoid)	-6.9
<b>Javanicinoside D (Quassinoid glucoside)</b>	<b>-8.2</b>
<b>Javanicinoside G (Quassinoid glucoside)</b>	<b>-8.3</b>
<b>Javanicinoside K (Quassinoid glucoside)</b>	<b>-8.1</b>
<b>Javanicinoside C (Quassinoid glucoside)</b>	<b>-8.3</b>
<b>Lanosta-7,24-dien-3-one (Triterpenoid)</b>	<b>-8.2</b>
Neoquassin (Quassinoid)	-7.1
Nigakilactone B (Quassinoid)	-7.1
Nigakilactone F (Quassinoid)	-6.8
<b>Picrajavanin A (Quassinoid)</b>	<b>-9.0</b>
Picrasin A (Quassinoid)	-7.4

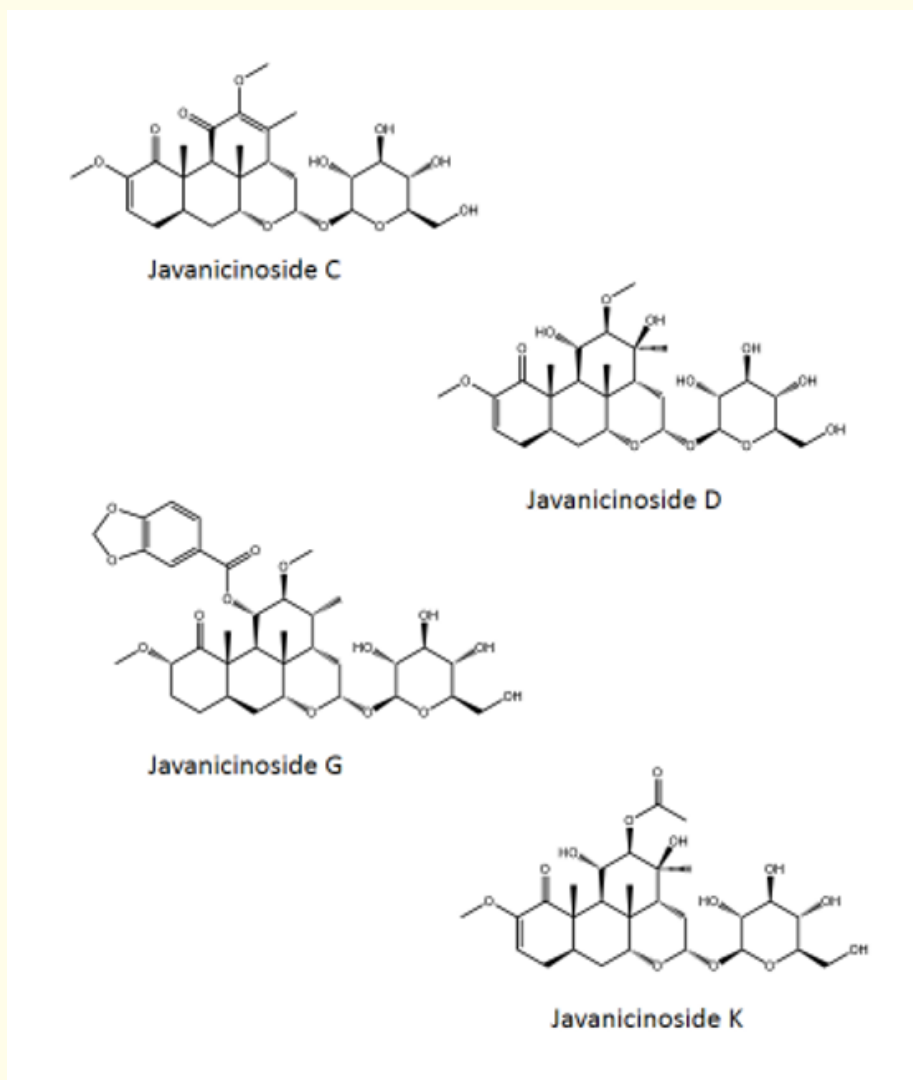
**Table 1:** Docking result of *Picrasma javanica* phytochemicals and VP8\* (PDB ID 4YFW) protein domain of rotavirus A outer capsid protein VP4 (compounds with high binding affinities are depicted in bold).

\*: Values are shown as mean  $\pm$  SEM from 3 independent docking runs in AutoDock Vina.

The lowest predicted binding energy of -9.0 kcal/mol was exhibited by a quassinoid, namely, picra javanin A (Figure 1). Other quassinoid compounds demonstrating binding energies of -8.0 or above included javanicin K and javanicin N (Figure 1). In the javanicin group of quassinoid compounds, apart from javanicin H and javanicin Q, which gave binding affinity of -6.9 kcal/mol each, the other javanicins showed binding affinities of -7.0 or above. It appears that the javanicin group of quassinoids can be potentially good inhibitors of rotavirus and merits further laboratory studies.

Javanicosides D, G, K and C all demonstrated binding energies above -8.0 kcal/mol. The structures of these javanicinosides are shown in figure 1. The binding data strongly suggest that the quassinoid glucosidic derivatives can more strongly bind to the VP8\* domain of VP4 protein of rotavirus A.





**Figure 1:** Phytochemicals from *Picrasma javanica* demonstrating good binding energies with VP8\* domain of VP4 protein of rotavirus A in molecular docking studies.

Amongst the alkaloids studied javacarboline (Figure 1) gave a high affinity with a predicted binding of -8.3 kcal/mol. Two triterpenoids, hispidol A and lanosta-7,24-dien-3-one (Figure 1) also gave high binding energies of -8.2 kcal/mol, each. Thus, besides quassinoids and quassinoid derivatives, other group of compounds from the plant may prove to be effective inhibitors of human rotavirus A. The docking of picrojavanin A, javanicin K, javanicinosides D and G, javacarboline, and hispidol A to the VP8\* domain of VP4 protein of rotavirus A is shown in figure 2-7.

The molecular docking studies demonstrate for the first time (to our knowledge) effective binding between quassinoid compounds and VP8\* domain of VP4 protein of rotavirus A. However, it remains to be seen in actual laboratory anti-rotaviral experiments whether the

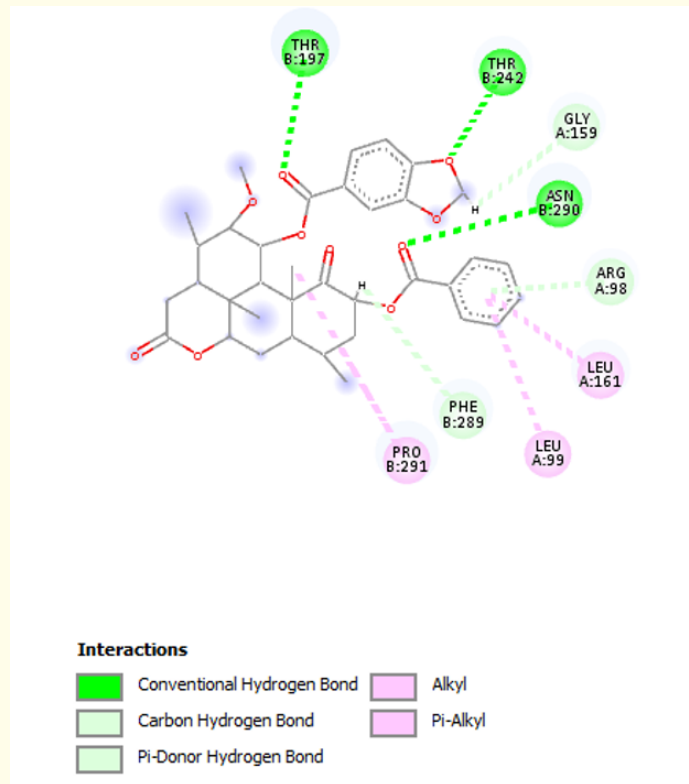


Figure 2: Binding of picrajavanin A to VP8\* domain.

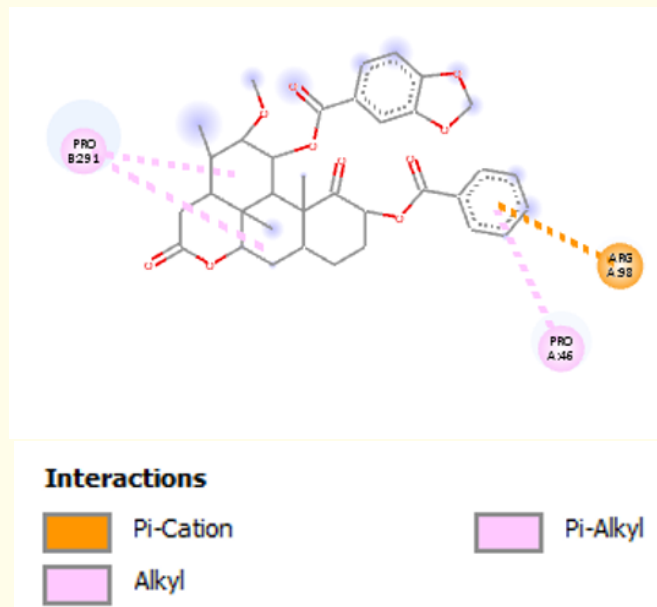


Figure 3: Binding of javanicin K to VP8\* domain.

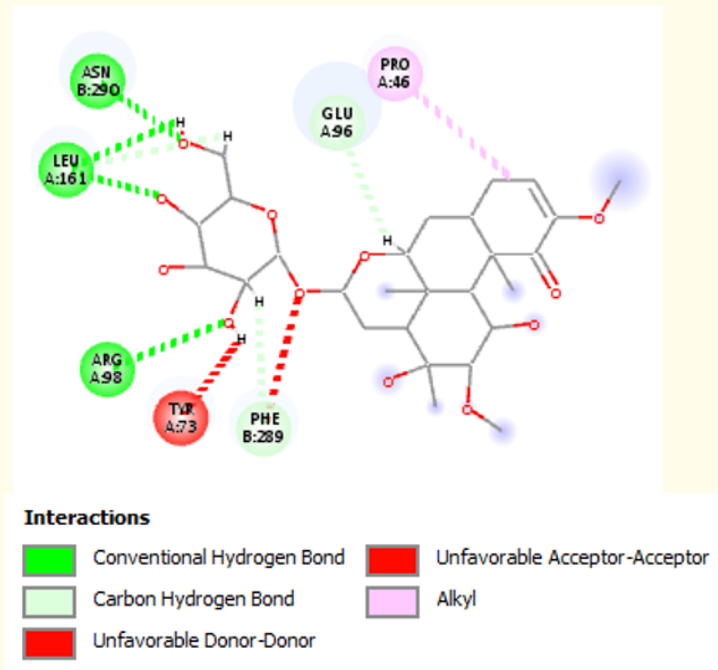


Figure 4: Binding of javanicoside D to VP8\* domain.

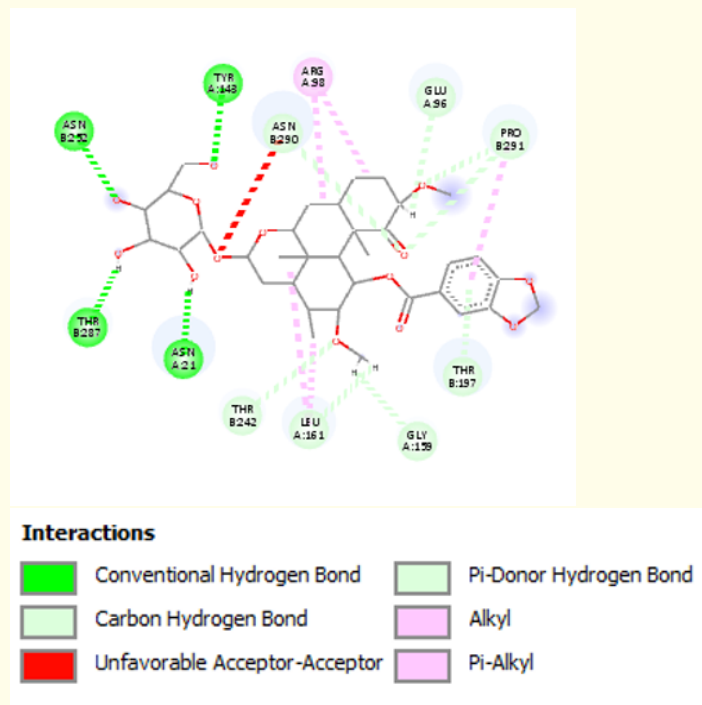


Figure 5: Binding of javanicoside G to VP8\* domain.

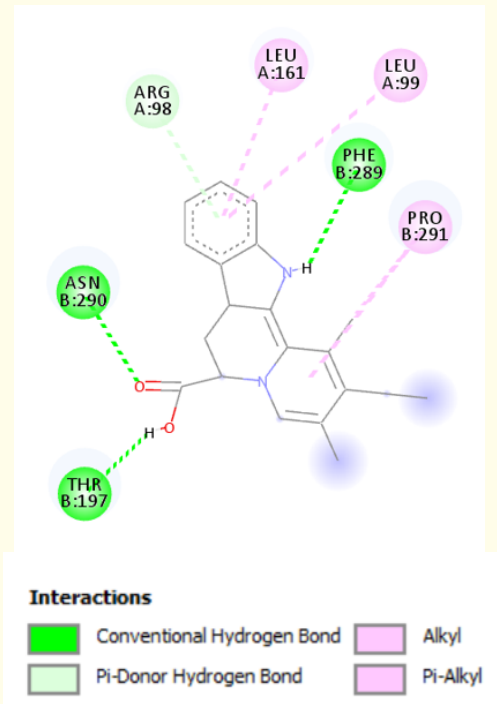


Figure 6: Binding of javacarboline to VP8\* domain.

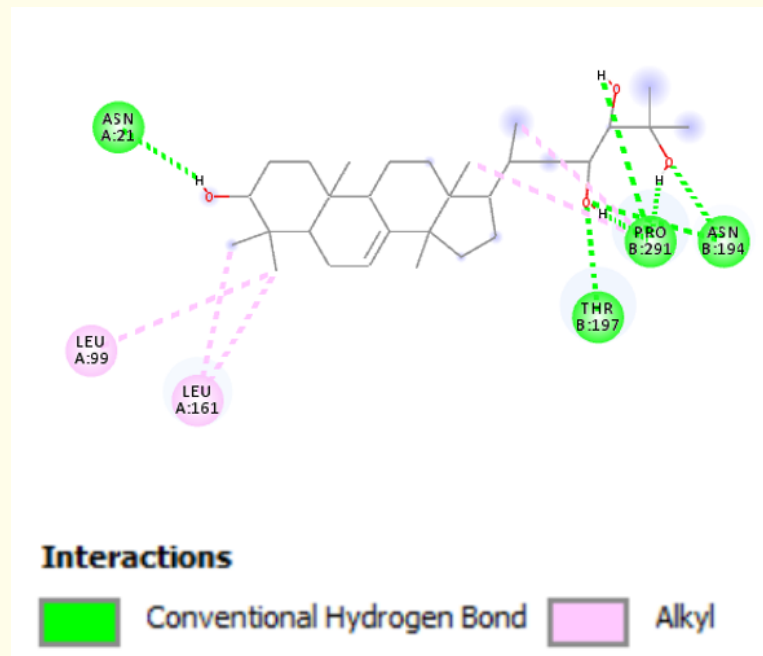


Figure 7: Binding of hispidol A to VP8\* domain.



compounds give anti-rotaviral activities *in vivo*. It can be expected from the molecular docking studies that phytochemicals from *Picrasma javanica* may prove to be alternate therapies to rotavirus A induced gastroenteritis.

### **Conclusion**

Various phytochemicals of *Picrasma javanica* demonstrated in molecular docking studies high binding affinities for the VP8\* domain of the VP4 protein of rotavirus A. As such, these compounds belonging to the quassinoid, alkaloid and triterpenoid groups may prove to be effective therapeutic agents.

### **Acknowledgements**

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### **Conflicts of Interest**

The authors declare that they have no conflicts of interest.

### **Bibliography**

1. Crawford SE., *et al.* "Rotavirus infection". *Nature Reviews Disease Primers* 3 (2017) 17083.
2. GBD Diarrhoeal Disease Collaborators. "Estimates of global, regional, and national morbidity, mortality, and aetiology of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015". *Lancet Infectious Diseases* 17 (2017) 909-948.
3. Parashar UD., *et al.* "Global illness and deaths caused by rotavirus disease in children". *Emerging Infectious Diseases* 9.5 (2003) 565-572.
4. Lanata CF., *et al.* "Child Health Epidemiology Reference Group of the World Health Organization and UNICEF. "Global causes of diarrheal disease mortality in children <5 years of age: a systematic review". *PLoS One* 8.9 (2013) e72788.
5. Glass RI., *et al.* "Rotavirus vaccines: current prospects and future challenges". *Lancet* 368.9532 (2006) 323-332.
6. Parashar UD., *et al.* "Diagnosis, management, and prevention of rotavirus gastroenteritis in children". *British Medical Journal* 347 (2013) f7204.
7. Satter SM., *et al.* "An update from hospital-based surveillance for rotavirus gastroenteritis among young children in Bangladesh, July 2012 to June 2017". *Vaccine* 36.51 (2018) 7811-7815.
8. International Centre for Diarrhoeal Disease Research, Bangladesh. Centre for Health and Population Research. "Estimated deaths due to rotavirus in Bangladesh". *Health and Science Bulletin* 4 (2006) 6-10.
9. Tate JE., *et al.* "WHO-coordinated Global Rotavirus Surveillance Network. "2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus programmes: a systematic review and meta-analysis". *The Lancet Infectious Diseases* 12.2 (2012) 136-141.
10. Trojnar E., *et al.* "Identification of an avian Group A rotavirus containing a novel VP4 gene with a close relationship to those of mammalian rotaviruses". *Journal of General Virology* 94.Pt1 (2013) 136-142.
11. Rai PK and Lalramnghinglova H. "Ethnomedicinal plants of India with special reference to an Indo-Burma hotspot region: An overview". *Ethnobotany Research and Applications* 9 (2011) 379-420.

12. Alves IABS, *et al.* "Simaroubaceae family: botany, chemical composition and biological activities". *Revista Brasileira de Farmacognosia* 24.4 (2014) 481-501.
13. Taher M., *et al.* Phytochemical constituents and pharmacological activities of *Picrasma javanica* (2019).
14. Hu L., *et al.* "Structural Basis of Glycan Specificity in Neonate-Specific Bovine-Human Reassortant Rotavirus". *Nature Communications* 6.1 (2015) 8346.
15. Ihlenfeldt W-D. "Pub Chem". In *Applied Chemoinformatics* (2018): 245-258.
16. <https://jcheminf.biomedcentral.com/articles/10.1186/1758-2946-3-33>
17. Oleg T and Olson A. "Autodock Vina: Improving the Speed and Accuracy of Docking". *Journal of Computational Chemistry* 31.2 (2010) 455-461.
18. Studio D. "Dassault Systems BIOVIA, Discovery Studio Modelling Environment, Release 4.5". Accelrys Software Inc. (2015) 98-104.

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