MARINE NATURAL PRODUCTS AS POTENTIAL INHIBITORS AGAINST PATHOGENIC *Streptococcus agalactiae* USING MOLECULAR DOCKING STUDY FOR HUMAN AND FISH DISEASE CONTROL

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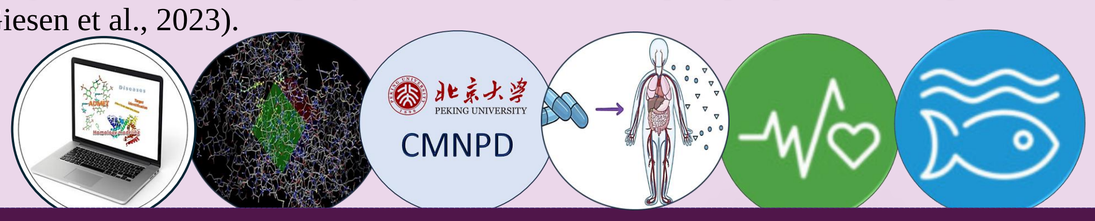
INTRODUCTION

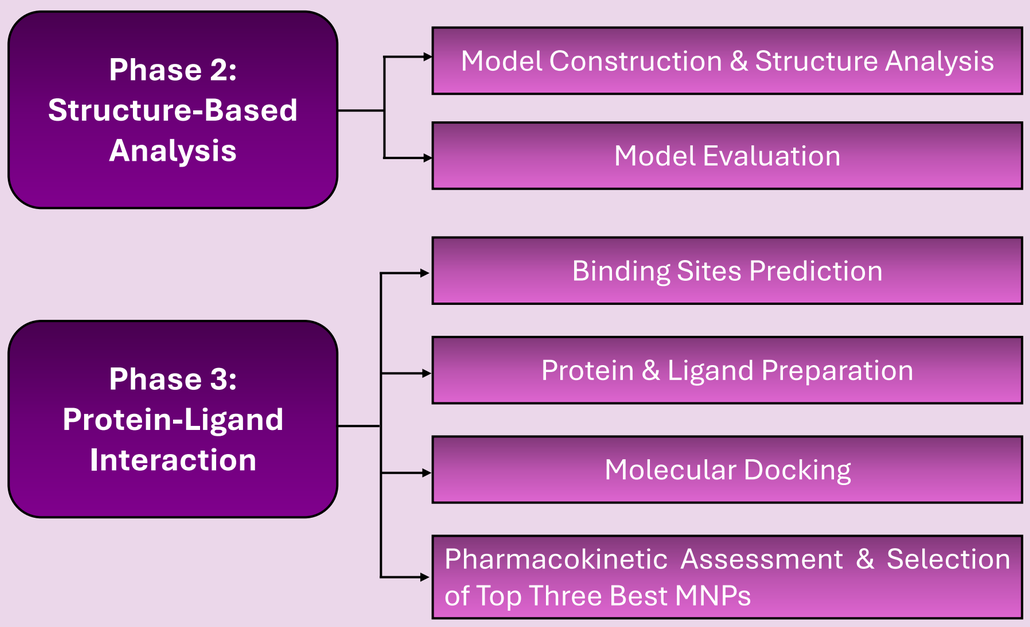
- *Streptococcus agalactiae* (UniProt ID: Q8CMH7) is a zoonotic bacterium that can cause humans to contract neonatal and urinary tract infection when they consume infected fishes (Favero et al., 2020).
- To combat *S. agalactiae* infection, eight marine natural products (MNPs), namely CMNPD30307, CMNPD30308, CMNPD30309, CMNPD30310, CMNPD30311, CMNPD30312, CMNPD30313 and CMNPD30314 had been tested as potential inhibitors to inhibit *S. agalactiae* phosphopentomutase.
- The MNPs tested in the study are helvolic acid derivatives synthesized from the marine fungus *Aspergillus fumigatus* HNMF0047 (Raffa and Keller, 2019), in which these derivatives are classified as triterpenoids (Hussain et al., 2023).
- *S. agalactiae* can no longer synthesize RNA once its phosphopentomutase gets inhibited (Van Giesen et al., 2023).



OBJECTIVES

1) To investigate the primary sequence characteristics of *S. agalactiae* phosphopentomutase.
2) To model and analyze the 3D structure of *S. agalactiae* phosphopentomutase.
3) To study the interaction between MNPs as potential inhibitors and *S agalactiae* phosphopentomutase.

METHODOLOGY



RESULTS AND DISCUSSION

Phase 1: Sequence-Based Analysis

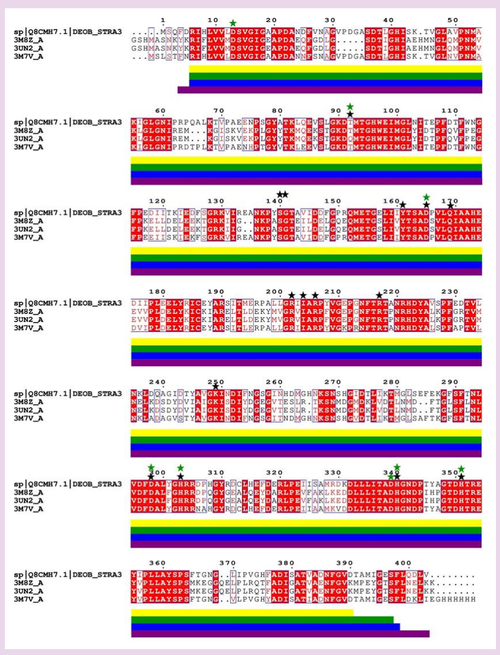


Figure 1. Illustration of MSA between *S. agalactiae* phosphopentomutase (Q8CMH7) and its three homologues (3M7V, 3M8Z, 3UN2) performed by using Clustal Omega server and visualized by using ESpript 3 server.

Phase 2: Structure-Based Analysis

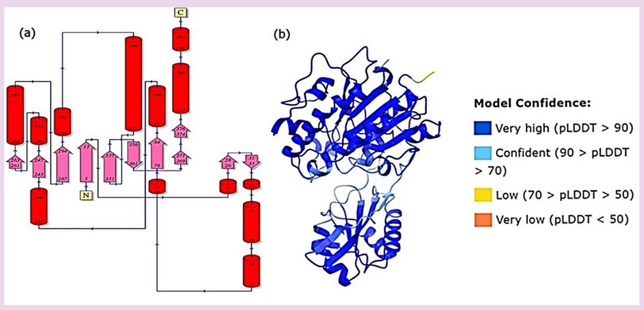


Figure 2. The (a) secondary structure of *S. agalactiae* phosphopentomutase enzyme and (b) the best predicted protein model of *S. agalactiae* phosphopentomutase by AlphaFold2.

Phase 3: Protein-Ligand Interaction

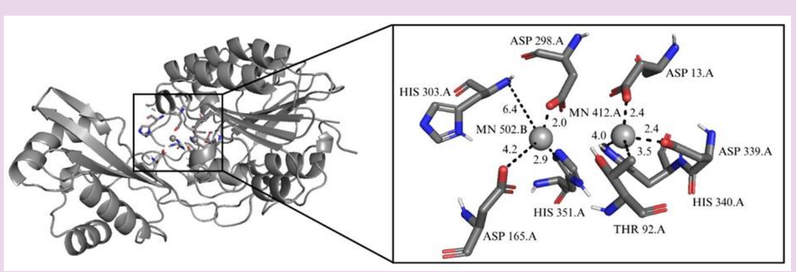


Figure 3. 8 different cofactor binding residues of *S. agalactiae* phosphopentomutase that are bound with two ions (MN 502.B and MN 412.A) , which are namely ASP-13, THR-92, ASP-165, ASP-298, HIS-303, ASP-339, HIS-340 and HIS-351.

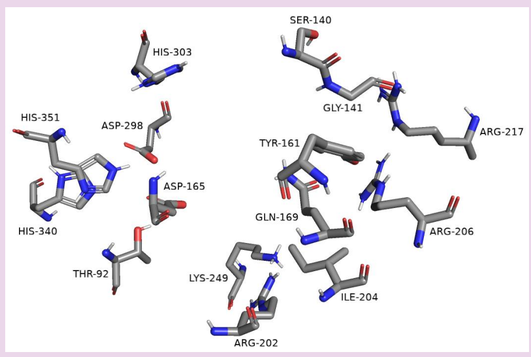


Figure 4. 15 different substrate binding residues of *S. agalactiae* phosphopentomutase, which are namely THR-92, SER-140, GLY-141, TYR-161, ASP-165, GLN-169, ARG-202, ILE-204, ARG-206, ARG-217, LYS-249, ASP-298, HIS-303, HIS-340 and HIS-351.

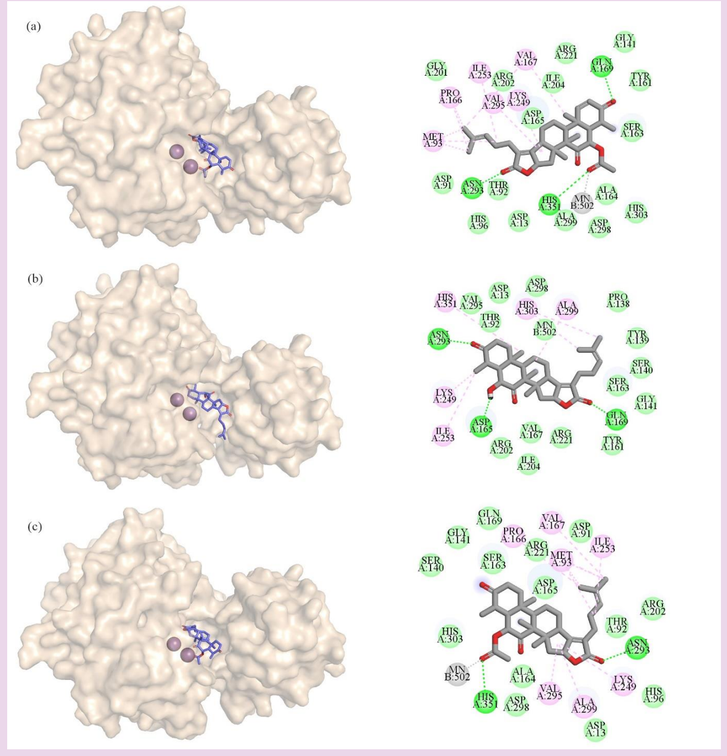


Figure 5. List of surface 3D and 2D representations of *S. agalactiae* phosphopentomutase that are bound with top three best MNPs, which are (a) CMNPD30307, (b) CMNPD30309 and (c) CMNPD30310.

Table 1. Binding energy values and pharmacokinetic properties of the top three MNPs

MNPs	Binding energy (kcal/mol)	Molecular weight (g/mol)	No. of rotatable bonds	No. of H bond acceptors	No. of H bond donors	Log $P_{o/w}$	GI absorption	Bioavailability scores
CMNPD30307	-8.32	508.65	5	6	0	4.79	High	0.55
CMNPD30309	-7.09	468.62	3	5	1	4.43	High	0.55
CMNPD30310	-8.04	510.66	5	6	0	4.90	High	0.55

- The top three best MNPs with the compound IDs of CMNPD30307, CMNPD30309 & CMNPD30310 possessed low binding energy (stable interaction), high GI absorption and high bioavailability scores in adherence to the Lipinski's rule of 5 (Benet et al., 2016).

CONCLUSION

- Through the integration of *in silico* methods for instance MSA, homology modelling and molecular docking, three of the best MNPs, which are CMNPD30307, CMNPD30309 and CMNPD30310, have been successfully identified as promising inhibitors. It is highly recommended for the wet lab scientists to further test the antibacterial properties of the three best MNPs via *in vitro* and *in vivo* study as they hold great promises for further development into potent antibiotics to combat *S. agalactiae* infection.

- By aligning the study conducted based on IR 4.0 principles with the blue economy, scientists can continue to sustainably extract, collect and utilize the MNPs for pharmaceutical research, while preserving and promoting long-term aquatic health.

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