Original Article

Screening of Jellyfish Venom Inhibitors from Beach Morning Glory (*Ipomoea pes-caprae*) against *Nemopilema nomurai*

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Abstract

Objective: This study aimed to identify potential inhibitors from the beach morning glory (*Ipomoea pes-caprae*), a plant traditionally used for treating jellyfish stings, to counteract the effects of the venom. **Materials and Methods:** We utilized homology modeling to construct three-dimensional models of the jellyfish venom metalloproteinase and validated them using the structure analysis and verification server web-based tool for stereochemical quality assessment. Molecular docking studies were conducted using AutoDock Vina to screen compounds extracted from *Ipomoea pes-caprae*, focusing on their binding affinities toward the venom metalloproteinase. Key compounds, including quercetin and isochlorogenic acids A and B, were analyzed for their potential inhibitory effects. **Results:** The homology models of the jellyfish venom metalloproteinase were successfully constructed and validated, indicating reliable structural accuracy. The molecular docking studies identified several promising compounds from *Ipomoea pes-caprae*. Quercetin exhibited a binding energy of −8.8 kcal/mol, whereas isochlorogenic acids A and B showed binding energies of −8.5 and −9.0 kcal/mol, respectively. These compounds demonstrated strong interactions with key amino acids within the active site of the metalloproteinase, suggesting their efficacy in neutralizing the venom's toxic effects. **Conclusion:** Our findings support the potential of compounds from *Ipomoea pes-caprae* as effective inhibitors of jellyfish venom metalloproteinase. This research validates the traditional use of this plant and lays the groundwork for further pharmacological and clinical studies. Future research should focus on *in vitro* and *in vivo* testing to confirm the efficacy of these compounds as new therapeutic agents for treating jellyfish stings.

Keywords: Beach morning glory, Ipomoea pes-caprae, jellyfish venom inhibitors, molecular docking, *Nemopilema nomurai* venom

Introduction

Jellyfish stings, particularly from *Nemopilema nomurai*, significantly impact marine life and human activities in East Asian seas due to their size, numbers, and toxic stings.[1] The venom of this jellyfish contains over 150 identified proteins, including phospholipase A2, serine protease, and metalloproteinases, which contribute to its toxicity.[2] Effective antidotes are necessary due to the negative effects on fishing, beach tourism, and public health.

Ipomoea pes-caprae has been traditionally used by coastal populations, such as in Vietnam and Malaysia, to treat jellyfish stings. A study in 1991 demonstrated its effectiveness in neutralizing jellyfish venom.[3] However, the active compounds responsible for this effect have not been clearly identified. This study aims to screen compounds from *Ipomoea pes-caprae* for their potential to inhibit jellyfish venom metalloproteinases, providing

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direction for efficient extraction methods and product development.

In the past decade, several studies have isolated active compounds from *Ipomoea pes-caprae* and identified various bioactivities of the plant.[4-6] Recent reviews by Korean scientists suggest that the potential applications of *Ipomoea pes-caprae* have not been fully explored, particularly its anti-venom properties, which require further molecular and mechanistic studies.[7]

Virtual screening approaches have been employed in several studies to neutralize jellyfish venom.[8,9] These studies used molecular modeling and docking techniques to identify potential chemical inhibitors of jellyfish venom metalloproteinases. However, no scientific publication has proposed the key active components in *Ipomoea pes-caprae* and their molecular mechanisms of interaction with jellyfish venom metalloproteinases. This study aims to model the protein structure of *Nemopilema nomurai* venom using advanced bioinformatics tools and screen potential inhibitory compounds from *Ipomoea pes-caprae*.

Materials and Methods

In this study, we applied a series of methods to construct and validate a model of *N. nomurai* venom metalloproteinase and screen potential active compounds from *Ipomoea pes-caprae* that can inhibit the metalloproteinase activity of the venom. The research steps are illustrated in Figure 1.

Model construction

Using homology modeling, we constructed a three-dimensional (3D) model for a disintegrin-like metalloproteinase from *N. nomurai* based on previously published gene sequences.[8] The target protein was selected based on similarity search results from published protein data stored on the National Center for Biotechnology Information (NCBI) server.[10] The SWISS-MODEL technique was used to build the 3D model of the jellyfish venom protein.[11] The reference model was chosen based on high similarity with the jellyfish venom protein from the AlphaFold database.

Model quality assessment

After constructing the 3D structure, the model's quality was assessed using the structure analysis and verification server (SAVES) online tool (UCLA-DOE LAB-SAVES v6.0—https://saves.mbi.ucla.edu/), which evaluates the geometrical and stereochemical parameters of the constructed metalloproteinase. Ramachandran plots were used to analyze the overall structure of the model and determine the accuracy of the *phi* and *psi* angles in the protein model.

Active compound screening and molecular docking

The list of active compounds from *Ipomoea pes-caprae* was compiled based on recent scientific literature reviews on the components of the plant.[3,5-7,12] The Simplified Molecular Input Line Entry System (SMILES) codes of these compounds were retrieved from the PubChem

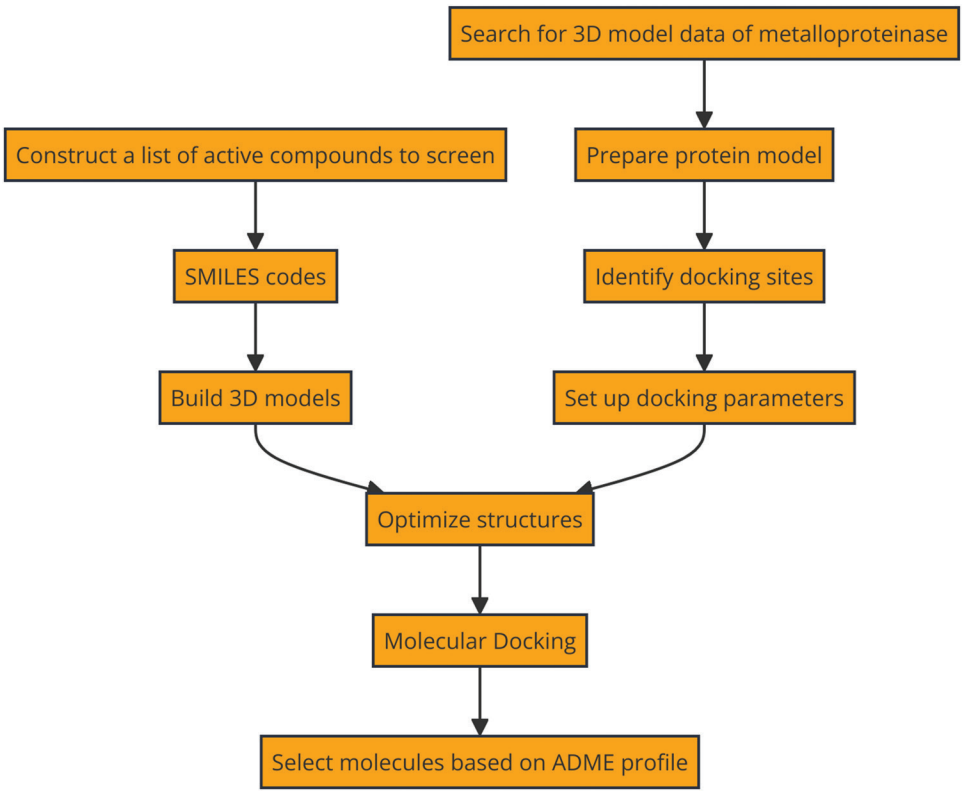

Figure 1: Research diagram

database. The SMILES codes were used to construct the 3D structures of the corresponding compounds using Chimera UCSF software (University of California, San Francisco, CA, USA) for molecular docking. AutoDock Vina software (The Scripps Research Institute, La Jolla, CA, USA) was used for docking the active compounds with the constructed metalloproteinase model. The docking results were selected based on binding affinity and ligand efficiency as previously described.[13,14] The best docking results were further analyzed for intermolecular interactions between the ligands and the metalloproteinase.

Pharmacokinetic profile and molecular interaction analysis

To propose potential active compounds, this study used Biovia Discovery Studio software (Dassault Systèmes BIOVIA, San Diego, CA, USA) to analyze detailed interactions between the compounds and the amino acids in the protein model. The information obtained from binding energy and the structure of the protein–ligand complex helps identify compounds that could potentially inhibit the jellyfish venom metalloproteinase.

Molecular interaction analysis

Biovia Discovery Studio was used to analyze the interactions between the selected compounds and the key amino acids of the venom metalloproteinase. This analysis provided insights into the binding modes and potential inhibitory mechanisms of the compounds.

Results and Discussion

Similarity search of amino acid sequence

Figure 2 presents the results of amino acid sequence searches for the *N. nomurai* venom metalloproteinase and comparison with known sequences in the zinc-dependent metalloprotease family. The data shows high similarity with known proteins, allowing for the construction of an accurate 3D model of the target protein. These data are crucial for understanding the mechanism of action and interactions of this protein, thus enhancing the efficiency of screening and designing inhibitors for jellyfish venom.

Model construction and validation

Two 3D models were designed based on homology modeling, providing visual insights into the structure of the *N. nomurai* venom metalloproteinase [Figure 3]. Although the models differ in shape and structure, they both identify potential binding regions for inhibitors extracted from *Ipomoea pes-caprae*. This helps in identifying key interaction sites for inhibitors to neutralize the activity of the venom. During the model construction, quality indices (QMEAN and GMQE) indicated that Model 2 has higher quality than that of Model 1, based on structural accuracy and predictive ability. These data are the basis for selecting the most suitable model for subsequent molecular docking studies.

Ramachandran plot analysis

The Ramachandran plots in Figure 4 show the distribution of *phi* and *psi* angles of amino acids in the protein model, reflecting the structural accuracy of the model. Most angles lie within the permissible regions, indicating that the constructed protein model has an appropriate stereochemical structure and is reliable for molecular interaction studies.

Compound screening results

The chemical components that can be isolated from *Ipomoea pes-caprae* are listed in Table 1, including

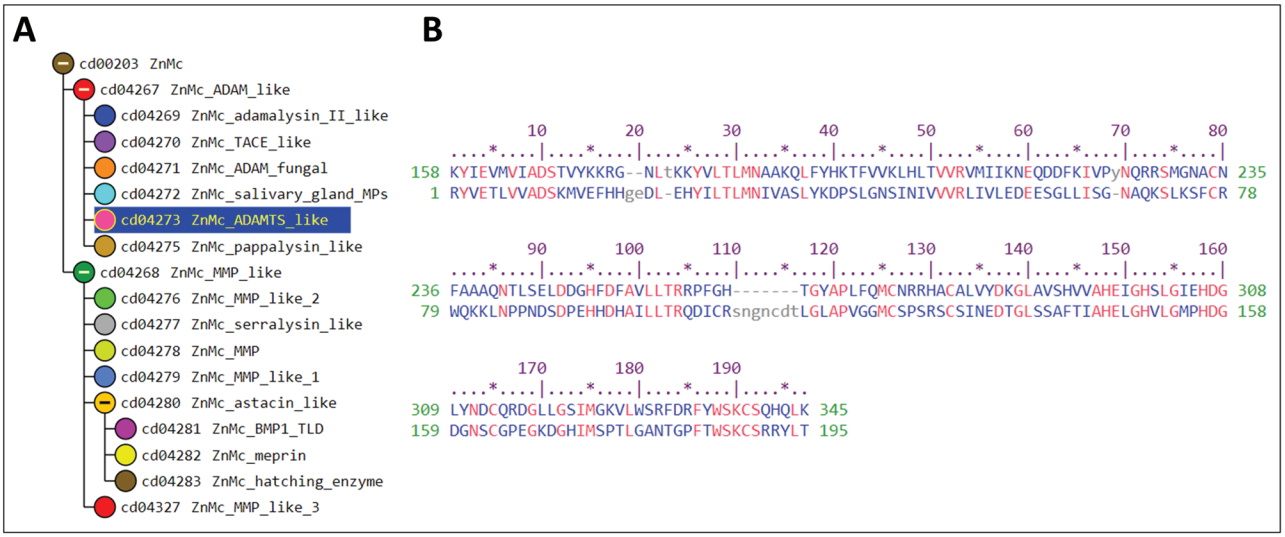

Figure 2: Results of amino acid sequence search and comparison with similar protein structures in the NCBI database. (A) Hierarchical comparison results of sub-family. (B) Sequence comparison results with zinc-dependent metalloprotease family proteins

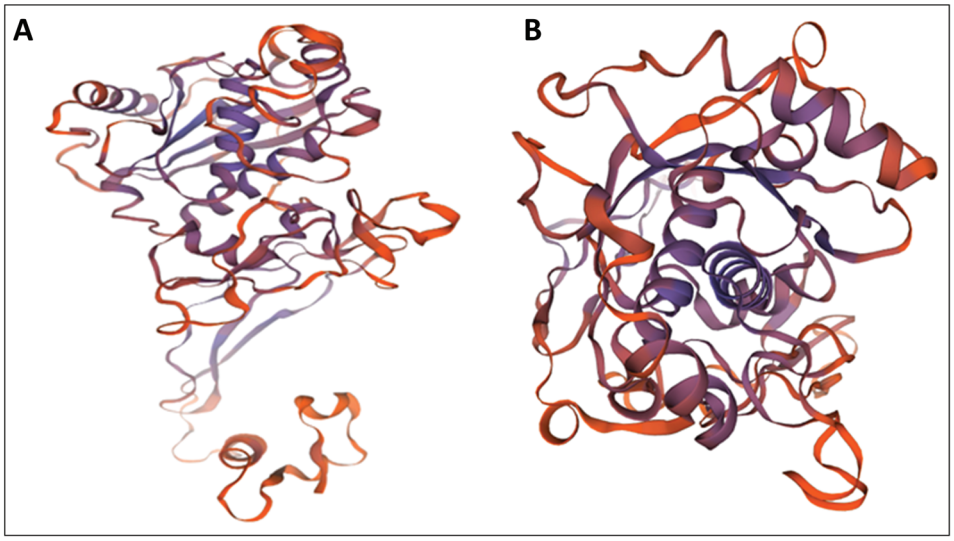

Figure 3: Models of *Nemopilema nomurai* jellyfish venom metalloproteinase constructed using homology modeling. (A) Model 1. (B) Model 2

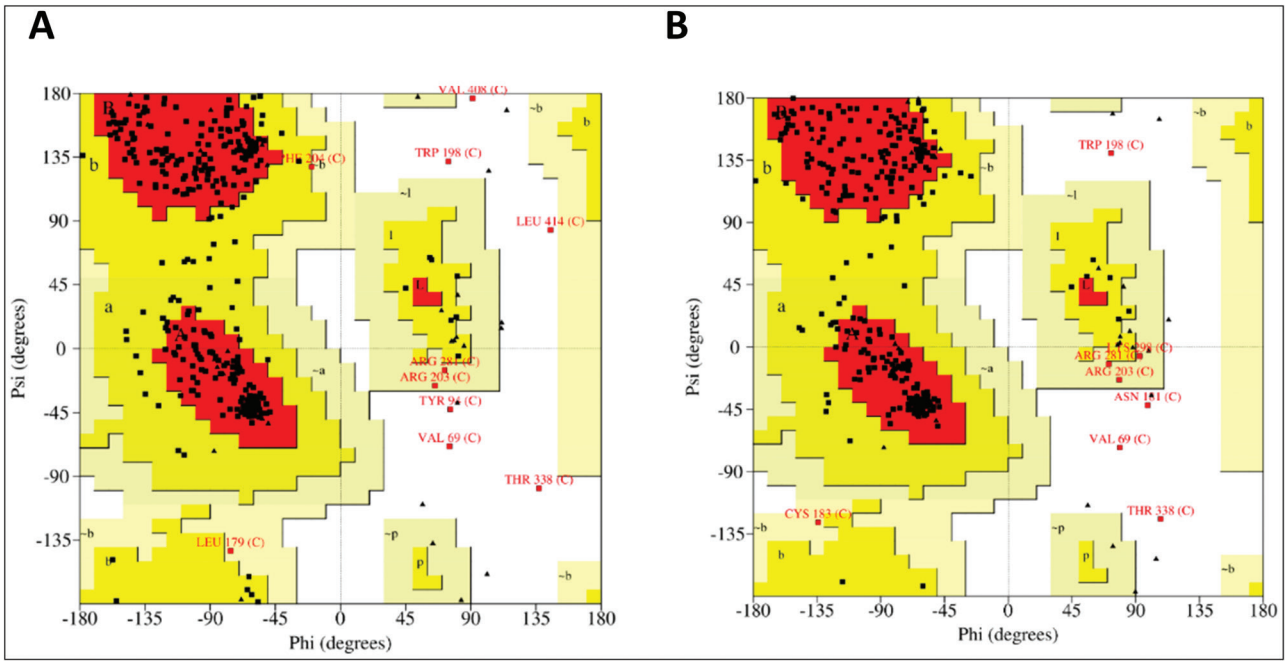

Figure 4: Ramachandran plot for evaluating the quality of the protein models. (A) Model 1. (B) Model 2

p-cymene, limonene, and quercetin, among many others. This data indicates the diversity of organic molecules in *Ipomoea pes-caprae*, which is traditionally used to alleviate jellyfish sting symptoms. The presence of isochlorogenic acids and quercetin indicates strong antioxidant potential,[15,16] which can counteract the toxic proteins in jellyfish venom. These compounds work by scavenging reactive oxygen species and reducing oxidative stress, which helps mitigate the damaging effects of venom proteins. Research studies highlight that polyphenol–protein complexes exhibit enhanced antioxidant capacities, making them effective in neutralizing toxins and protecting cells from oxidative damage.[17,18] This interaction can occur through both covalent and non-covalent bindings, which enhances the stability and functional properties of the polyphenols, furthermore, boosting their antioxidant effects.[17]

Molecular docking results

Results in Table 2 presents the results of molecular docking, highlighting compounds such as quercetin and isochlorogenic acids, which strongly bind to the jellyfish venom metalloproteinase. These results suggest that quercetin and isochlorogenic acids A and B not only bind with low docking energy but also exhibit high ligand

Table 1: Chemical components of beach morning glory (*Ipomoea pes-caprae*)

No	Compound name	References	No	Compound name	References	No	Compound name	References
1	*p*-Cymene	Akinniyi *et al.*[7]	20	β-Caryophyllene	Akinniyi *et al.*[7]	39	α-Amyrin	Akinniyi *et al.*[7]
2	Limonene	Akinniyi *et al.*[7]	21	δ-Cadinene	Akinniyi *et al.*[7]	40	β-Amyrin	Akinniyi *et al.*[7]
3	α-Pinene	Akinniyi *et al.*[7]	22	α-Humulene	Akinniyi *et al.*[7]	41	Betulinic acid	Akinniyi *et al.*[7]
4	4-Vinylguaiacol	Akinniyi *et al.*[7] and [19]	23	Germacrene D	Akinniyi *et al.*[7]	42	Quercetin 3-*O*-galactoside	Akinniyi *et al.*,[7][19], and [20]
5	Actinidols 1a	Akinniyi *et al.*[7]	24	8-Cedren-13-ol	Akinniyi *et al.*[7]	43	Isoquercetin	Akinniyi *et al.*[7]
6	α-Terpineol	Akinniyi *et al.*[7]	25	Caryophyllene oxide	Akinniyi *et al.*[7]	44	Quercetin 3-*O*-β-d-glucofuranoside	Akinniyi *et al.*[7] and [19]
7	Linaloola	Akinniyi *et al.*[7]	26	(E)-Nerolidol	Akinniyi *et al.*[7]	45	α-Amyrin acetate	Akinniyi *et al.*[7] and [19]
8	Eugenol	Akinniyi *et al.*,[7] Waterhouse *et al.*,[11] and [19]	27	α-Cadinol	Akinniyi *et al.*[7]	46	β-Amyrin acetate	Akinniyi *et al.*[7]
9	Calystegine B2	Akinniyi *et al.*[7]	28	Guaiol	Akinniyi *et al.*[7]	47	Sericic acid	Akinniyi *et al.*[7]
10	(–) Mellein	Akinniyi *et al.*[7] and [19]	29		Akinniyi *et al.*[7]	48	β-Amyrin acetate	Akinniyi *et al.*[7]
11	Caffeic acid	Akinniyi *et al.*[7] and [20]	30	E-Phytol	Akinniyi *et al.*[7]	49	Quercetin 3-*O*-acetylglucoside	Akinniyi *et al.*[7] and [20]
12	Salicylic acid	Akinniyi *et al.*[7]	31	Quercetin	Akinniyi *et al.*[7]	50	Isochlorogenic acid A	Akinniyi *et al.*[7] and [20]
13	Pescapreins I	Akinniyi *et al.*[7] and [19]	32	3-*O*-Caffeoylquinic acid	Akinniyi *et al.*[7] and [20]	51	Isochlorogenic acid B	Akinniyi *et al.*[7] and [20]
14	Xanthoxyline	Akinniyi *et al.*[7]	33	4-*O*-Caffeoylquinic acid	Akinniyi *et al.*[7] and [20]	52	Isochlorogenic acid C	Akinniyi *et al.*[7]
15	β-Damascenone	Akinniyi *et al.*[7] and [19]	34	5-*O*-Caffeoylquinic acid (chlorogenic acid)	Akinniyi *et al.*[7]	53	3,5-Di-*O*-caffeoylquinic acid methyl ester	Akinniyi *et al.*[7]
16	Actinidols 1b	Akinniyi *et al.*[7]	35	Lanosterol	Akinniyi *et al.*[7]	54	3,4-Di-*O*-caffeoylquinic acid methyl ester	Akinniyi *et al.*[7]
17	Geranyl acetate	Akinniyi *et al.*[7]	36	Stigmasterol	Akinniyi *et al.*[7]	55	4,5-Di-*O*-caffeoylquinic acid methyl ester	Akinniyi *et al.*[7]
18	2-Hydroxy-4,4,7-trimethyl-1(4H)-naphthalenone	Akinniyi *et al.*[7] and [19]	37	Sitosterol	Akinniyi *et al.*[7]	56	The quinic acid esters—3,5-di-*O*-caffeoyl-4-*O*-coumaroylquinic acid	Akinniyi *et al.*[7]
19	α-Copaene	Akinniyi *et al.*[7]	38	Glochidone	Akinniyi *et al.*[7]	57	4,5-Di-*O*-caffeoyl-1,3-di-*O*-coumaroylquinic acid	Akinniyi *et al.*[7]

Table 2: Molecular docking results of ligands with high affinity for the jellyfish venom metalloproteinase model

Ligand	Molecular weight (g/mol)	Docking energy (kcal/mol)	Ligand efficiency
Quercetin	302.24	−8.8	0.029
Isochlorogenic acid A	514.48	−8.5	0.017
Isochlorogenic acid B	516.45	−9.0	0.017

efficiency, making them potential candidates for inhibitor development. The strong binding affinities observed for quercetin and isochlorogenic acids suggest that these compounds effectively interact with the active site of the venom metalloproteinase, potentially inhibiting its function. These interactions could form the basis for developing new anti-venom therapies. Detailed analysis of their interactions with amino acids in the binding region of the protein is the next step to explore their inhibitory capabilities, suggesting their potential as inhibitors [Figure 5].

Detailed analysis from the images [Figure 5] shows how quercetin and isochlorogenic acids A and B bind to the active site of the protein, thereby inhibiting the activity of the enzyme. These results not only reinforce the potential of these compounds as metalloproteinase inhibitors but also open new avenues for designing effective anti-jellyfish venom therapies. The chemical structure of these compounds can provide insights for designing agents to neutralize jellyfish venom. Among them, quercetin [Figure 5A] shows the most promise, both in terms of intermolecular interactions and ligand efficiency [Table 2], suggesting significant potential for further research.

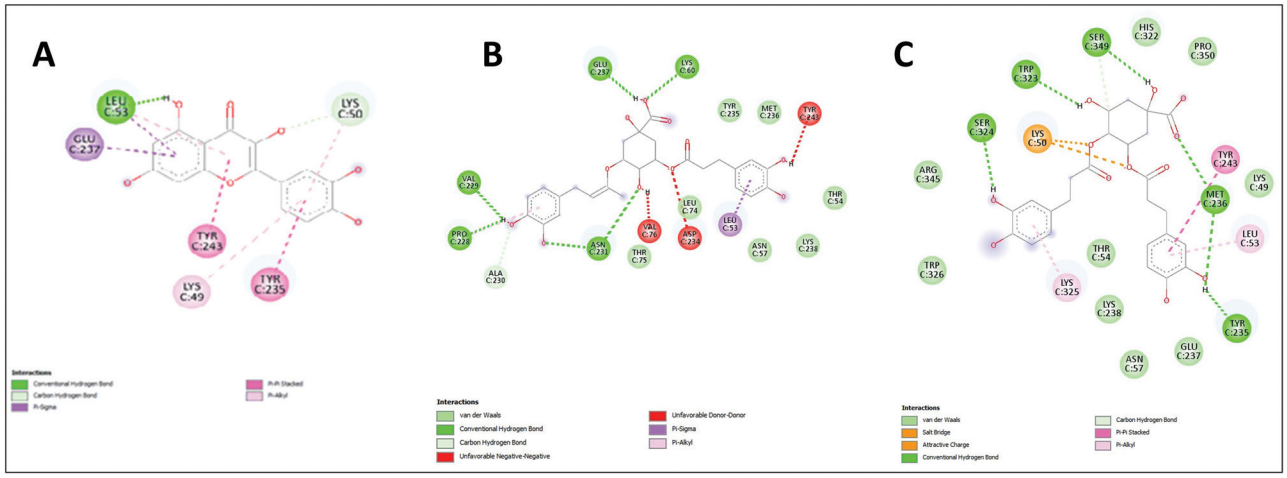

Figure 5: Analysis of interactions between selected ligands and the target protein metalloproteinase of *Nemopilema nomurai* jellyfish. (A) Quercetin. (B) Isochlorogenic acid A. (C) Isochlorogenic acid B

The detailed binding interactions observed in this study provide a deeper understanding of the inhibitory mechanisms than that of previous research studies. For instance, a recent study identified silymarin as a potential inhibitor of *N. nomurai* jellyfish venom metalloproteinase using pharmacoinformatic approaches,[8] but did not explore the binding interactions as comprehensively as in our study. The findings from our study add a new dimension to the existing literature by elucidating the specific molecular interactions between the inhibitors and the enzyme. Furthermore, research studies should elucidate the exact molecular mechanisms by which these compounds inhibit the metalloproteinase. Techniques such as molecular dynamics simulations and crystallography could provide deeper insights into these mechanisms, revealing any conformational changes in the protein structure upon binding.

Conclusion

This study identified promising compounds from *Ipomoea pes-caprae* capable of inhibiting the metalloproteinase activity of *N. nomurai* venom. Specifically, quercetin was found to be the most promising candidate for further research. This compound should be isolated and tested *in vitro* and *in vivo* for its potential as a jellyfish venom inhibitor.

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Conflicts of interest

There are no conflicts of interest.

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