

# In Silico Analysis of Bioactive Compounds from Sea Urchin (*Echinometra mathaei*) against SARS-COV-2

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SARS-CoV-2 is a kind of coronavirus that produces Covid-19 illness, which is still a public health concern in Indonesia. Meanwhile, an effective drug has not yet been found and although vaccination has been carried out, in several regions and neighboring countries there is still an increase in Covid-19 cases. This study aimed to obtain bioactive compounds from sea urchins (*Echinometra mathaei*) that have greater antiviral potential and lower toxicity than remdesivir. This research was started by predicting druglikeness with SwissADME, followed ADMET prediction with pkCSM online, and docking of molecule using the Molegro Virtual Docker (MVD) 5.5 software against the main protease (Mpro) target (PDB ID: 6W63). The results showed that six compounds from sea urchins (*Echinometra mathaei*) had antiviral activity, where the bioactive compound from sea urchins (*Echinometra mathaei*) with the highest affinity was shown by Spinochrome C a smaller rerank score compared with Remdesivir and native ligand (X77). So that Spinochrome C compounds are candidates as SARS-CoV-2 inhibitors potential developed drug.

**Keywords:** ADMET; Druglikeness; molecular docking; Sea urchin; SARS-COV-2.

Coronavirus Disease-2019 (COVID-19) is a pneumonia-like illness caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)<sup>1</sup>. SARS CoV 2 is an RNA virus with a positive strand. Symptoms of this viral infection include fever, a dry cough, and shortness of breath. However, many patients are carriers and show no symptoms. This is one of the reasons for the widespread transmission of this virus<sup>2</sup>. Since 2019 until 2022 almost three years COVID-19 has surge around the world. Some things have been done for over come COVID-19 such us vaccine or treatment therapy. Treatment of Covid-19 patients

is carried out by giving medicines that have been previously prescribed received FDA approval, such as Remdesivir, but assessment Remdesivir has little benefit on COVID-19 patients who are already being ventilated. It has a little influence on mortality or progression to ventilation in other hospitalised patients (or both)<sup>3</sup>. As time goes by, the variants COVID-19 become more variety.

This study focused on the main protease (Mpro), where Mpro is one of the CoV proteases that cleaves polyproteins. RdRp, helicase, RNA-binding protein, exoribonuclease, endoribonuclease, and 2-O-ribose methyltransferase are among the

proteins that have been removed<sup>4</sup>. This makes compounds that inhibit Mpro have broad antiviral activity<sup>2</sup>. Protease activity disruption can result in a variety of illnesses. As a result, host proteases can be exploited as possible therapeutic targets in general. Proteases serve a key role in viral replication in many viruses. As a result, proteases are frequently employed as protein targets in the development of antiviral medicine<sup>5</sup>. Molecular modeling and structure-based drug design has shown to be an effective method for discovering new inhibitors and has become a well-known approach in contemporary drug development. Until the advent of computational drug discovery, medications were discovered by accident via try and error. Computer-aided drug design facilitates and accelerates the drug design process, which includes a number of approaches for identifying new molecules<sup>6</sup>.

Sea urchin is one of the many marine biota created for medications<sup>7-12</sup>. More than 5000 chemical compounds with high pharmacological potential have been isolated and described from marine organisms<sup>8</sup>. The quinone pigments are products of the secondary metabolism of marine animals, can have complex structures and become the basis for the development of new natural products in echinoids that are modulators of chemical interactions and possible active ingredients in medicinal preparations<sup>8</sup>. The antiviral activity of sea urchin is probably due to the virus-inhibiting activity of the compounds and because of their natural potentially antioxidant properties<sup>7</sup> such as spinochrome, echinochrome, and naphthoquinone pigments<sup>9,10</sup>. According to studies (Mishchenko *et al.*, 2020), the Spinochrome amine present in sea urchins has the ability to suppress the attachment and penetration herpes simplex virus type 1 into the cell<sup>11</sup>. According to Krylova *et al.*, (2019) and Fedoreyev *et al.*, (2018) Oral administration of the antioxidant composition of echinochrome A, ascorbic acid and  $\alpha$ -tocopherol (5:5:1) protected 90% of the infected mice against death and reduced vaginal viral loads<sup>7</sup> and affect virus particle of tick-borne encephalitis virus (TBEV) and herpes simplex virus type 1 (HSV-1)<sup>12</sup>.

This study aims to further identify the antiviral activity of Sea urchin (*Echinometra mathaei*) against COVID-19. So it is hoped that it

will produce drug candidates that have the potential to be developed as anti-COVID-19 drugs.

## METHODS AND MATERIAL

### Hardware

The computer specifications are as follows: Intel® Core™ i7 8565U@ 1.80 GHz processor (CPU), Nvidia® GeForce MX230 graphics processing unit (GPU), and 8 GB Random Access Memory (RAM) running Windows 10.

### Compound Test Preparation

Eleven bioactive compounds from the sea urchin (*Echinometra mathaei*) were created in 2D and 3D models, and then they were optimized using the MMFF94 technique using Chem3D 20.0. Utilizing the Online SMILES Translator (<https://cactus.nci.nih.gov/translate/>), the structure is then converted to SMILES format.

### Drug-likeness prediction

SwissADME (<http://www.swissadme.ch/>) are used to predict drug-likeness of the test compound with SMILES file format.

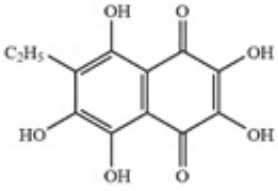
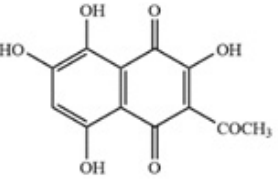
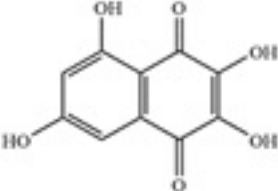
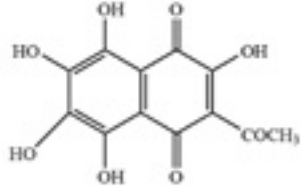
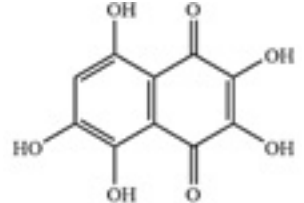
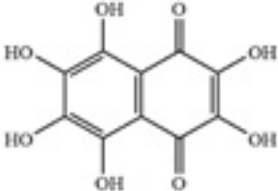
### ADMET prediction

Prediction of pharmacokinetics (ADME) and toxicity of the test compound was done by the pkCSM website (<http://biosig.unimelb.edu.au/pkcsm/prediction>) with the SMILES format.

### Molecular docking

N-nitrosourea is a COVID-19 inhibitor (4-tert-butylphenyl) -N-[(1R)-2-(cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl] In the protein data bank, -1H-imidazole-4-carboxamide (X77) was described as an inhibitor in the binding state with the Mpro (PDB ID: 6W63). Molegro Virtual Docker (MVD) 5.5 software was used to assign the structures' missing bond ordering, charges, bonds, and hybridization states<sup>13</sup>. The viral protein's 3D structure was obtained from the Protein Data Bank (PDB ID: 6W63), and the proteins were created by removing all water molecules, ligands, and cofactors and assigning bonds, bond order, hybridization, and charges with the MVD 5.5 program. Search algorithms and scoring functions docking In computation screening, the Piecewise Linear Potential (PLP) approach is used to score functions. Using the cavity prediction wizard, the cavities were predicted and limited to three; the cavity with the

**Table 1.** Drug-likeness prediction

Molecule Name	Lipinski's five-point rules (RO5) Properties	Value
 Echinochrome A	Molecular weight ( $\leq 500$ ) MLogP ( $\leq 4.15$ ) Donor of H-bonds ( $\leq 5$ ) Acceptor of H-bonds ( $\leq 10$ ) Rule Violations Meet RO5 Criteria	266.20 -1.88 5 7 0 Yes
 Spinochrome A	Molecular weight ( $\leq 500$ ) MLogP ( $\leq 4.15$ ) Donor of H-bonds ( $\leq 5$ ) Acceptor of H-bonds ( $\leq 10$ ) Rule Violations Meet RO5 Criteria	264.19 -1.96 4 7 0 Yes
 Spinochrome B	Molecular weight ( $\leq 500$ ) MLogP ( $\leq 4.15$ ) Donor of H-bonds ( $\leq 5$ ) Acceptor of H-bonds ( $\leq 10$ ) Rule Violations Meet RO5 Criteria	222.15 -1.92 4 6 0 Yes
 Spinochrome C	Molecular weight ( $\leq 500$ ) MLogP ( $\leq 4.15$ ) Donor of H-bonds ( $\leq 5$ ) Acceptor of H-bonds ( $\leq 10$ ) Rule Violations Meet RO5 Criteria	280.19 -2.48 5 8 0 Yes
 Spinochrome D	Molecular weight ( $\leq 500$ ) MLogP ( $\leq 4.15$ ) Donor of H-bonds ( $\leq 5$ ) Acceptor of H-bonds ( $\leq 10$ ) Rule Violations Meet RO5 Criteria	238.15 -2.46 5 7 0 Yes
 Spinochrome E	Molecular weight ( $\leq 500$ ) MLogP ( $\leq 4.15$ ) Donor of H-bonds ( $\leq 5$ ) Acceptor of H-bonds ( $\leq 10$ ) Rule Violations Meet RO5 Criteria	254.15 -2.98 6 8 1 Yes

	<p>Molecular weight (<math>\leq 500</math>) 265.22  MLogP (<math>\leq 4.15</math>) -1.88  Donor of H-bonds (<math>\leq 5</math>) 5  Acceptor of H-bonds (<math>\leq 10</math>) 6  Rule Violations 0  Meet RO5 Criteria Yes</p>
	<p>Molecular weight (<math>\leq 500</math>) 265.22  MLogP (<math>\leq 4.15</math>) -1.88  Donor of H-bonds (<math>\leq 5</math>) 5  Acceptor of H-bonds (<math>\leq 10</math>) 6  Rule Violations 0  Meet RO5 Criteria Yes</p>
	<p>Molecular weight (<math>\leq 500</math>) 252.18  MLogP (<math>\leq 4.15</math>) -2.16  Donor of H-bonds (<math>\leq 5</math>) 5  Acceptor of H-bonds (<math>\leq 10</math>) 7  Rule Violations 0  Meet RO5 Criteria Yes</p>
	<p>Molecular weight (<math>\leq 500</math>) 282.20  MLogP (<math>\leq 4.15</math>) -2.40  Donor of H-bonds (<math>\leq 5</math>) 4  Acceptor of H-bonds (<math>\leq 10</math>) 8  Rule Violations 0  Meet RO5 Criteria Yes</p>
	<p>Molecular weight (<math>\leq 500</math>) 253.17  MLogP (<math>\leq 4.15</math>) -2.98  Donor of H-bonds (<math>\leq 5</math>) 6  Acceptor of H-bonds (<math>\leq 10</math>) 7  Rule Violations 1  Meet RO5 Criteria Yes</p>

largest volume was chosen as the origin for the binding site. The ligands were docked with viral protein, and the best-generated postures were chosen using docking scores<sup>14</sup>. The outcome of the in-silico investigation is the Rerank Score (RS). The rerank score predicts drug-receptor interaction.

## RESULTS AND DISCUSSION

### Drug-likeness prediction

The results of the drug-likeness prediction of bioactive compounds from sea urchin (*Echinometra mathaei*) are shown in Table 1.

Table 2. ADMET prediction

Molecule Name	Absorption Intestinal absorption (human)	Skin Permeability	Distribution VDss (human)	BBB permeability	Metabolism		Excretion Total Clearance	Renal OCT2 substrate	AMES toxicity	Toxicity	
					CYP2D6 substrate	CYP2D6 inhibitor				LD <sub>50</sub>	Hepatotoxicity
Echinochrome A	52.043	-2.76	0.114	-1.515	No	No	-0.063	No	No	2.261	No
Spinochrome A	56.174	-2.924	-0.087	-1.239	No	No	0.413	No	No	1.787	No
Spinochrome B	63.14	-2.964	-0.127	-1.162	No	No	0.372	No	No	2.04	No
Spinochrome C	52.576	-2.739	0.206	-1.594	No	No	0.364	No	No	1.975	No
Spinochrome D	51.361	-2.758	0.155	-1.503	No	No	0.343	No	No	2.024	No
Spinochrome E	42.647	-2.735	0.395	-1.848	No	No	0.295	No	No	2.366	No
Echimamine A	59.833	-2.808	-0.274	-1.384	No	No	0.04	No	No	2.358	No
Echimamine B	54.695	-2.801	-0.188	-1.324	No	No	0.044	No	No	2.316	No
Spinochrome 252	56.977	-2.764	0.182	-1.423	No	No	0.327	No	No	2.205	No
Spinochrome 282	51.757	-2.774	0.164	-1.437	No	No	0.411	No	No	2.268	No
Echimamine 253	44.313	-2.736	0.029	-1.811	No	No	0.174	No	No	2.41	No

**ADMET prediction**

The results of the ADMET prediction of bioactive compounds from sea urchin (*Echinometra mathaei*) are shown in Table 2.

Prediction of toxicity (ames toxicity, hepatotoxicity, and LD50) of bioactive compounds from sea urchin were done by the pkCSM online (<https://biosig.lab.uq.edu.au/pkcsm/prediction>) with the SMILES format.

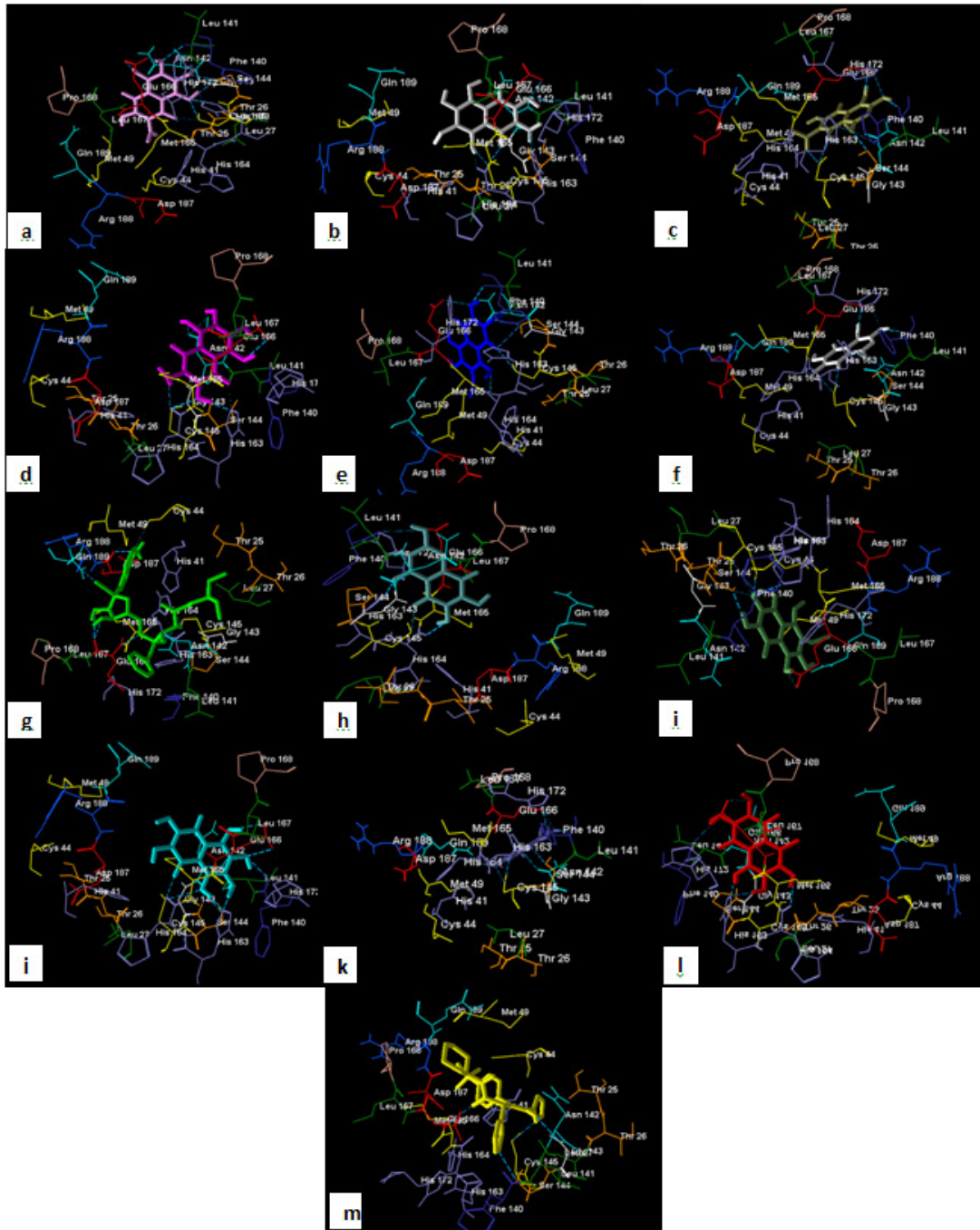
Following oral administration, the small intestine is where medication molecules are primarily absorbed. Poor absorption is defined as less than 30%. Table 2 lists bioactive substances from sea urchins (*Echinometra mathaei*), which are projected to have good oral bioavailability since they have human intestine absorption rates of over 30%. The development of transdermal drugs is particularly linked to the problem of skin permeability. The log Kp (cm/h) measurements used to represent the skin permeation coefficient are capable of forecasting a medicinal compound's skin permeability. When log Kp > -2.5, a chemical is predicted to have low skin permeability. As can be seen in Table 2, the bioactive substances from sea urchins have a lower log Kp value of < -3.0 (cm/h), indicating that they have a moderate level of skin permeability.

The theoretical volume required to hold the entire quantity of medicine delivered to disperse it while maintaining the same blood concentration is known as volume distribution (VDss). A substance that has a high VDss value is one that is dispersed more throughout the body than in blood plasma. The medication has a low distribution volume if the log VDss value is less than -0.15. In contrast, it has a larger distribution volume when the log value of VDss is bigger than 0.4511. According to Table 2, the bioactive chemicals from sea urchins have modest distribution volumes, with log VDss values ranging from 0.395 to -0.274. Drug molecules with log BB > 0.3 can cross the blood-brain barrier but cannot be distributed well with log BB < -1. The log BB value for sea urchin bioactive chemicals is between -1.848 and -0.162, according to Table 2. These chemicals can cross the BBB somewhat with this value.

In the detoxification process, cytochrome P450 is a critical and key enzyme in the liver cells. The enzyme is important in the oxidation process and aids in the excretion of foreign organic

**Table 3.** Molecular docking results ranked by the lowest Rerank Score and Interaction of ligands and amino acid residues

Compound	Rerank score (Kcal/mol)	Number of H-bonds	H-bond Interaction Site	Number of Steric bonds	Steric bonds Interaction Site
Spinochrome C	-73.3374	9	Glu166, Cys145, Leu141, His163, Ser144, Phe140	8	Glu166, Leu141, Phe140, His163, His164, Ser144, Cys145, Met165
Echinamine B	-72.5032	7	Glu166, Cys145, Leu141, His163, His164, Phe140	6	His164, Cys145, His163, Leu141, Glu166, Phe140
Spinochrome A	-71.6408	8	Glu166, Ser144, Cys145, His163, Leu141, Phe140	7	Glu166, Leu141, Phe140, His163, Ser144, Cys145, Met165
Echinamine A	-71.4374	8	Glu166, Ser144, Cys145, His163, His164, Asn142	5	Leu141, Phe140, Cys145, His163, Asn142
Echinochrome A	-70.4858	8	Glu166, Ser144, Cys145, His163, His164, Leu141, Phe140	7	Glu166, Leu141, Phe140, His163, Ser144, Cys145, His164
Spinochrome D	-70.0122	8	Glu166, Cys145, His163, His164, Leu141, Phe140	6	Glu166, Leu141, Phe140, His163, His164, Cys145
Remdesivir (standard drug)	-69.4683	9	Glu166, Cys145, Cys44, Asn142, Gln189, Asp187, Tyr54	13	Glu166, Cys145, Cys44, Asn142, Gln189, Asp187, Tyr54, His41, Met165, Met49, Gly143
Spinochrome B	-68.1089	6	Ser144, Cys145, His163, His164, Leu141	6	Glu166, Leu141, Phe140, His163, His164, Cys145
Spinochrome 282	-67.4298	5	Glu166, Ser144, Cys145, His163	8	Glu166, Leu141, Phe140, His163, Ser144, Cys145, His164, Asn142
Echinamine 253	-66.3963	9	Cys145, His164, His163, Glu166, Phe140, Ser144	7	Glu166, Leu141, Phe140, His163, Ser144, Cys145, His164
Spinochrome E	-65.5416	7	Glu166, Cys145, His163, His164, Asn142, Phe140	7	Glu166, Leu141, Phe140, His163, Ser144, Cys145, His164
Spinochrome 252	-65.0422	6	Cys145, His164, His163, Glu166, Phe140	7	Glu166, Leu141, Phe140, His163, Ser144, Cys145, His164
X77 (native ligand)	-64.0758	4	Gly143, Cys145, Ser144, Glu166	5	Asn142, Thr25, Ser144, His163, His164



**Fig. 1.** Visualization of Spinochrome C (a), Echinamine B (b), Spinochrome A (c), Echinamine A (d), Echinochrome A (e), Spinochrome D (f), Remdesivir (g), Spinochrome B (h), Spinochrome 282 (i), Echinamine 253 (j), Spinochrome E (k), Spinochrome 252 (l), X77 (m) bound to the active sites of M<sup>pro</sup> (PDB ID: 6W63)

substances such as pharmaceuticals. It is critical to understand that pharmacological molecules can decrease the activity of the cytochrome P450 enzyme. It is represented in this study by the cytochrome P3D6 isoform (CYP2D6). Table 2 shows that sea urchin bioactive chemicals have no effect on cytochrome P450 enzyme activity. The total clearance (Cl<sub>tot</sub>) and the renal organic cation transporter 2 (OCT2) substrate can be used to predict drug compound excretion. The sum of hepatic clearance (liver and bile) and renal excretion is known as Cl total.

The compound speed of excretion of bioactive chemicals from sea urchin ranges from -0.063 to 0.413 in Table 2. OCT2 is a kidney transporter that plays critical functions in the disposition and clearance of drug and endogenous chemicals in the body. Table 2 shows that bioactive chemicals from sea urchin have no impact on OCT2, allowing the substance to be readily secreted<sup>16</sup>. The Ames toxicity test is an assay used to measure the existing toxicity of a substance and has been widely used to analyze a drug's mutagenesis potential using bacteria. A positive result implies that the substance has mutagenesis capabilities and may function as a carcinogen. Table 2 reveals that sea urchin bioactive chemicals are non-toxic. This implies that the chemicals are risk-free. They were subjected to Ames and hepatotoxicity testing. When the compounds were evaluated for LD<sub>50</sub> in mice, the results ranged from 1.787 to 2.366 mol/kgBW. This demonstrates a low toxicity value, as to destroy 50% of the mice<sup>16</sup>. Furthermore, the results showed that all bioactive chemicals derived from sea urchin are non-hepatotoxic.

#### **Molecular docking**

Molecular docking is a type of computer modeling study that seeks to find ligand-receptor interactions. The RMSD number of 1.118 indicates the outcomes of docking validation, hence the docking procedure may be considered legitimate because the RMSD value is < 2<sup>17</sup>. Table 3 displays the findings of molecular docking of bioactive chemicals from sea urchin (*Echinometra mathaei*).

The assumption of greater antiviral activity of the compounds is supported by the biggest number of bond couplings between bioactive compounds from sea urchins and amino acid receptors. Table 3 further shows that, in comparison to remdesivir and native ligand,

all six sea urchin compounds (Spinochrome C, Echinamine B, Spinochrome A, Echinamine A, Echinochrome A, Spinochrome D) had a lower affinity and Rerank Score (X77). Rerank Score shows how the active substances, which are tiny molecules with molecular protein cell targets, are harmoniously bonded together. A limited affinity in the binding of molecular proteins and the chemicals indicates a stable bonding.

Moreno-gracia *et al.*, (2022) discovered that the active components that were commonly found and had pharmacological properties in a review of articles on the content of sea urchins were echinochrome A, spinochrome A, spinochrome B, gallic acid, chlorogenic acid, and naphthoquinone isolated from sea urchin shells and spine pigments from various types of sea urchins. These chemicals are expected to have significant antibacterial, antiviral, and antioxidant properties<sup>18</sup>.

As a result from this research, predictions for six sea urchin compounds' antiviral activity (Spinochrome C, Echinamine B, Spinochrome A, Echinamine A, Echinochrome A, Spinochrome D) are higher than those for Remdesivir. Spinochrome C compounds had the lowest affinity/Rerank Score, indicating that they are likely to be the most effective as anti-Covid-19 agents.

#### **CONCLUSION**

Six bioactive substances from sea urchins have been shown to suppress SARS-CoV-2, according to studies. The outcomes of this *in silico* approach's study yielded an idea of the precise and efficiency of antiviral drugs by interacting with Mpro so as to exhibit blockade and provide therapeutic therapy. In addition, among 11 bioactive compounds from sea urchins, spinochrome C is a potential compound. Spinochrome C has high affinity for 6W63 protein, spinochrome C has a smaller rerank score compare with Remdesivir and native ligand (X77). The results of this study are potentially useful, so Spinochrome C is a strong candidate for antiviral drugs as an inhibitor of SARS-CoV-2. However, further studies of bioactive compounds from sea urchins need to be done.

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None.



**Conflict of Interest**

There are no conflicts of interest.

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