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Exploring the Potency of Antiviral Marine Alkaloids Against *Japanese encephalitis* and *Ebola virus*: A Computational-Based Assessment for Drug Repurposing Applications

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Abstract: In the twenty-first century, there have been a number of outbreaks, beginning with dengue, swine flu, Nipah, Ebola, chikungunya, and Zika, which were continuously outbreaks in some specific regions. The mosquito-transmitted flavivirus *Japanese encephalitis* (JE) virus, similar to dengue fever and West Nile viruses, and the negative-single-stranded *Ebola virus* (EBOV) are the two most emerging and the WHO's most-prioritized diseases. Natural products have always served as an alternative to mainstream drugs in emergencies. Thus, due to their excellent antiviral activity, the present study focused on marine alkaloids and assessed their potency against the JE and EBOV viruses. Using various bioinformatics tools, we selected 60 different antiviral marine alkaloids for anti-JE activity against RNA-dependent RNA polymerase (PDB ID: 4HDG), NS3-helicase (PDB ID: 2Z83), and NS5-protease (PDB ID: 4K6M), as well as anti-EBOV efficacy targeting nucleoprotein (PDB ID: 4Z9P), viral protein 24 (PDB ID: 4M0Q), and viral protein 40 (PDB ID: 3TCQ). Based on previous antiviral records with combined molecular docking scores, physicochemical, toxicity, pharmacokinetic, and drug-ability profiles, the researchers concluded that manzamines A, F, and X with 6-deoxymanzamine X and 8-hydroxymanzamine may be the best among all 60 candidates for JE and EV infection control. In summary, marine alkaloids exhibit excellent antiviral potency and need to be explored as more bioactive marine candidates for mainstream drug discovery, where bioinformatics tools are a more cost-effective, resource-efficient, and time-saving platform than traditional drug discovery modules to locate most lead candidates to be used in mainstream medicine for emerging health conditions.

Introduction

Pandemics or outbreaks have plagued the last decade, beginning with dengue, Nipah, Ebola, chikungunya, Zika, and, most recently, SARS-CoV-2, an infectious version of Middle East Respiratory Syndrome (MERS) and SARS, threatening human health and the economy (Desai, 2020; Sampath et al., 2021; Schwartz et al., 2021; Read and Musacchio, 2022). Most epidemic situations in the twenty-first century emerged as a result of rapid changes in host population ecology and pathogen reservoir mutations (Jones et al., 2013; Parvez and Parveen, 2017; Seal et al., 2021; Baker et al., 2022). Generally, disease outbreaks occur when there is a high rate of transmission or infection, high mortality, and the ability to rapidly mutate in their genomes, where the pathogens are novel to humans or their hosts, and without potential treatment, an emerging health situation develops, as we have all recently witnessed with SARS-CoV-2. Viruses cause most pandemics because they can infect a wide range of species, move quickly through the body, and have higher rates of infectivity than other infectious pathogens (Seyed et al., 2020; Chams et al., 2020). Apart from SARS-CoV-2, Zika, *Ebola virus* (EBOV), *Japanese encephalitis* (JE), and Nipah, like SARS-CoV-2, can all appear at any time in any form and cause a pandemic (Tambo et al., 2020; Singh et al., 2019; WHO, 2023). Consequently, there is a global focus on viruses, with the aim of developing effective therapeutic

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options to combat pandemics caused by any virus at any given time. In addition, the World Health Organization recommends increasing resources for disease research and development, and the majority of countries invest the most in health management on an initiative basis from a socio-political standpoint to prepare for any potential pandemic.

Based on previous records, the WHO tool listed which diseases pose the greatest public health risk due to their epidemic potential and/or whether there are no or insufficient countermeasures. Along with SARS-CoV-2, Crimean-Congo haemorrhagic fever, *Ebola virus* disease (EVD), Marburg virus disease, Lassa fever, Nipah and henipaviral diseases, Rift Valley fever, JE, Zika, etc. are listed among the WHO's most prioritized diseases (Seal et al., 2021; Baker et al., 2022; WHO, 2022). Most new viruses and pandemics have originated in Asia, including West Asia (Saudi Arabia), East Asia (Japan), and African regions, and their communities have suffered at a higher rate. Briefly, the JE virus originated in Japan, belongs to the *Flaviviridae* family, is a leading member of the mosquito-transmitted flavivirus family related to dengue fever and West Nile viruses, and is primarily distributed in Asian regions, but there have been recent outbreaks in Australia too (Walsh et al., 2022; Diptyanusa et al., 2022; Suresh et al., 2022; Yakob et al., 2023). Thus, JE is an emerging mosquito-transmitted viral disease with a higher rate of mortality that mainly causes central nervous system disorders globally. Similarly, EBOV or EVD belongs to the *Filoviridae* family, which includes the Marburg and Lloviu viruses (Goeijenbier et al., 2014; Steffen et al., 2019). The negative-single-stranded RNA (-ssRNA) virus is an emerging zoonotic disease that results in homeostatic imbalance and multi-organ failure. Three documented EBOV outbreaks in the last six years have resulted in significant morbidity and mortality (Kadanali and Karagoz, 2015; Ngatu et al., 2017; Hasan et al., 2019).

From a therapeutic perspective, natural products could serve as alternative agents in a variety of potential regimens against both diseases. Based on extensive primary research, natural products are undeniably promising alternatives that could serve as a repurposing basis in emerging situations (Newman and Cragg, 2020; Atanasov et al., 2021; Anbalagan et al., 2023; Bhosale et al., 2023). Similar to phytochemicals (natural candidates derived from aromatic and medicinal plants), marine-derived constituents from marine sponge, algae, bacteria, fungi, soft corals, sea fans, tunicates, etc. also provided a number of drugs such as rifampicin, streptomycin, cytarabine, vidarabine, cephalosporin, dolastatin 10, eribulinmesylate, trabectedin, brentuximabvedotin, etc., with a higher number of candidates in clinical evaluation (Swain et al., 2015; Swain et al., 2017; Jiménez, 2018; Lu et al., 2021). Thus, in the current era, the exploration of novel marine candidates and their utilization, as determined by proper scientific validation, is a novel area of research. However, evaluating the efficacy of targeting any disease (as with JE and EBOV in the current study) must be systematic, and that systematic platform must be established prior to limiting resources and time in the drug development module. Mainly, the traditional hit-and-trial method against such contagious viruses is more expensive and time-consuming.

Therefore, the robust bioinformatics tools or computer-aided drug design (CADD) platform is currently the most viable alternative to hit-and-trial methods to locate the most potential candidates targeting specific viral targets at the primary stage. The current study gathered a diverse set of marine-derived alkaloids with broader antiviral activity against human immunodeficiency virus (HIV), swine flu (HIN1), hepatitis C virus-1 (HCV-1), CoV-A95, herpes simplex virus type 2 (HSV-2) and dengue virus (DENV2) (Table S1), and those candidates were evaluated against JEV and EVD targeting putative enzymes in a repurposing basis, followed by a systematic CADD platform. In addition, we predicted and analysed individual physiochemical, toxicity, pharmacokinetics, and drug-ability profiles to support the selection of the most potential candidates.

Materials and Methods

Selection and retrieval of ligand and receptor structure for investigation

The entire computational work on a Linux/Ubuntu 16.04 LTS workstation was carried out. A total of 60 marine alkaloids were used as ligands (Supplementary Table S1) with four mainstream anti-viral drugs: ivermectin (PubChem CID: 6321424) and novobiocin (PubChem CID: 54675769) for the JE virus, and miglustat (PubChem ID: 51634) and toremifene (PubChem ID: 3005573) for the EBOV virus (Figure 1). Primarily, we stored the retrieved marine alkaloids in (.sdf) file formats and then converted them to one of the more widely accepted formats, i.e., (.pdb), by adding explicit hydrogen using the software BIOVIA Discovery Studio Visualizer-2019 (BIOVIA-DSV-2019, Academic Version, San Diego, California, USA). We also recorded the Simplified Molecular Input Line Entry System (SMILES) in addition to the chemical structure for further analyses. Finally, using the universal force field and steepest descent algorithm in Avogadro 1.2 software,

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we optimized the geometry of all ligand structures to obtain reliable binding energy from docking studies (Swain et al., 2022a; Sahoo et al., 2022).

Similarly, three crystallographic target enzyme structures of the JE virus, such as RNA-dependent RNA polymerase or RdRps (PDB ID: 4HDG), NS3_Healicase (PDB ID: 2Z83), and NS5_Protease (PDB ID: 4K6M), and three target protein structures of the EBOV, nucleoprotein or NP (PDB ID: 4Z9P), viral protein 24 or VP24 (PDB ID: 4M0Q), and viral protein 40 or VP40 (PDB ID: 3TCQ) were retrieved from the Protein Data Bank (https://www.rcsb.org/) (Figure 2). Furthermore, before docking removed the heteroatoms, ligands, and water molecules, attached other chains, and even remodelled the protein structure with SWISS-MODEL (https://swissmodel.expasy.org/) to match the specific fragmented protein structure (Sahoo et al., 2021).

Virtual screening and molecular docking study

After ligand and target structure preparation, the PyRx 0.8 platform was used for virtual screening and AutoDock 4.2 software for a manual molecular docking study against three JE-targets (RdRps, 4HDG; NS3_Healicase, 2Z83; NS5_Protease, 4K6M) and EBOV-targets (NP, 4Z9P; VP24, 4M0Q; VP40, 3TCQ), respectively (Swain et al., 2022a; Sahoo et al., 2022a). Based on a lower binding energy or molecular docking score (kcal/mol.), indicating greater potency against the respective targets. In addition, the BIOVIA-DSV-2019 software was used to visualise the interactions of the most active protein-ligand complexes obtained from the docking study (Swain et al., 2022a; Sahoo et al., 2022a).

Physicochemical and toxicity profiles prediction

Following efficacy or potency, physiochemical and toxicity profiles are required for further clinical observation of drug-ability profiles, bioavailability profiles, and so on, as some standard parameter must be satisfied for a ligand to be chosen as the lead molecule. Therefore, computation tools also predicted such profiles as herein using individual SMILE notation, recorded physicochemical profiles from the SwissADME tool (http://www.swissadme.ch/), and toxicity profiles such as hepatotoxicity (HT), carcinogenicity (CG), immunotoxicity (IT), mutagenicity (MG), and cytotoxicity (CT) with toxicity classes (within the range of classes I to VI) from the ProTox tool (https://tox-new.charite.de/protox_II/), respectively. In addition, bioavailability (BA) and a fifty percent lethal dose (LD_{50} mg/kg) were also predicted.

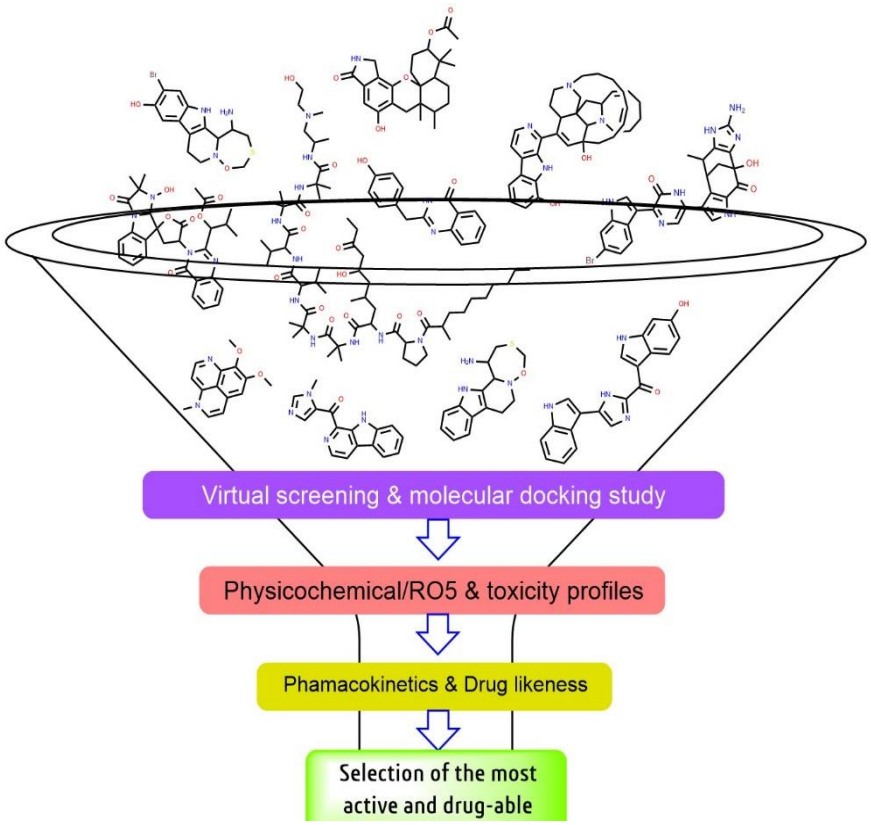

Figure 1. The overall hypothesis and screening procedure for identifying potential and drug-able lead marine alkaloids are depicted schematically.

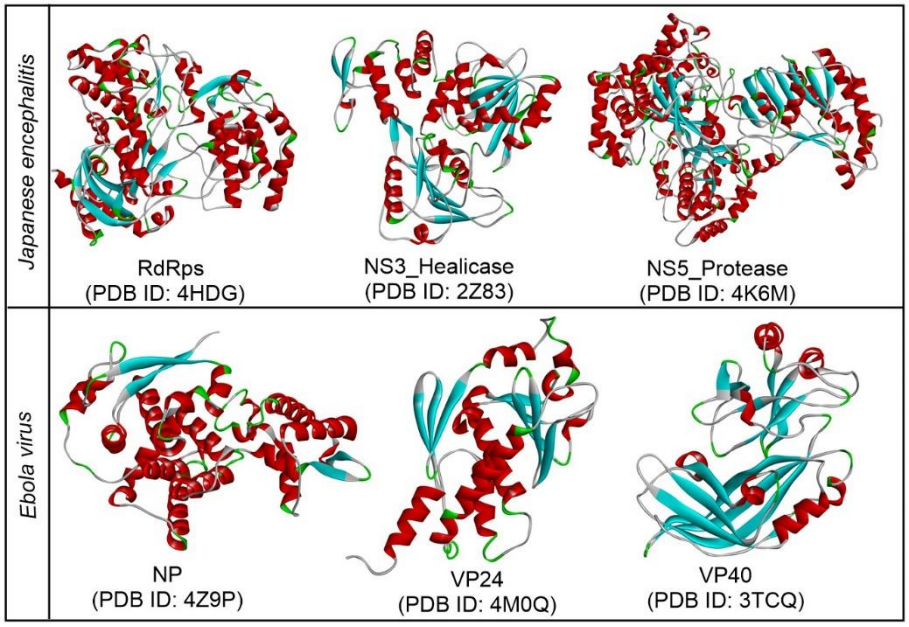

Figure 2. Three-dimensional structure of selected six target enzymes with individual PDB IDs.

Pharmacokinetics and drug-likeness profiles prediction

The pharmacokinetic profiles are also a crucial parameter after the toxicity study to analyse the metabolism of the drug after oral administration. Thus, the pharmacokinetic profiles such as gastrointestinal (GI) absorption, blood-brain barrier (BBB) permit, P-glycoprotein substrate, and cytochrome inhibitor (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) profiles were predicted from the SwissADME tool (Sahoo et al., 2022b; Swain et al., 2022a). Because all ligands are derived from natural sources, their synthetic accessibility is also predicted, with a scale ranging from 1 to 10 indicating the complexity of synthesis in laboratory conditions. The pharmacokinetic profiles are also a crucial parameter after the toxicity study to analyse the metabolism of the drug after oral administration. Thus, the pharmacokinetic profiles such as gastrointestinal (GI) absorption, blood-brain barrier (BBB) permit, P-glycoprotein substrate, and cytochrome inhibitor (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) profiles were predicted from the SwissADME tool. Because all ligands are derived from natural sources, their synthetic accessibility is also predicted, with a scale ranging from 1 to 10 indicating the complexity of synthesis under laboratory conditions. In addition, the bioinformatics also help to predict the overall drug-ability or drug-suitability score as a collective result of all the above parameters (Swain et al., 2022a; Sahoo et al., 2022a). To predict the individual drug-likeness score, the tool Molsoft (https://molsoft.com/mprop/) was used, which mostly separates the drug and non-drug molecules by a score and graph.

Result and Discussion

Virtual screening and molecular docking study

The docking score (kcal/mol.) of each individual marine candidate with four reference/standard antiviral drugs via virtual screening was recorded (Supplementary table S2). As per the recorded docking score, all candidates against three JE were within a range of -6 to -13 kcal/mol, where candidate serial numbers 42 (neosartoryadin B) and 25 (dragmacidin F) showed higher docking scores, -12.3 and 12.3 kcal/mol, against RdRps (PDB ID: 4HDG). In addition, 59 (6-deoxymanzamine X) and 60 (8-hydroxymanzamine) showed more than -10 kcal/mol against three targets of the JE virus (Supplementary Table S2). The control antiviral drugs showed docking scores within -12 kcal/mol, where ivermectin had a comparatively higher potential than novobiocin. Similarly, all candidates against EBOV-target enzymes showed within a range of -13 kcal/mol, where 39 (manzamine F) and59 (6-deoxymanzamine X) showed higher against VP40 (PDB ID: 3TCQ) at docking scores of -13.2 and 12.8 kcal/mol, respectively. At the same time, the control drugs, miglustat and toremifene, showed within -7 kcal/mol (Supplementary Table S2). The list of the 15 most active-drug-able candidates presented in Table 1 and the most lead candidates against all six target enzyme interactions were also visualised in Figure 3 and clearly indicated that all candidates interacted with a higher number of hydrogen bonds, van der Waal interactions with p-sigma

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and p-alkyl, etc. Overall, most marine candidates exhibit higher potency against JE and EBOV as per binding affinity.

accelerating the drug discovery process and is used by most academic and pharmaceutical companies to screen the most promising leads (Swain et al., 2022 a & b). In

Table 1. Among the sixty candidates, the fifteen most potent and drug-able marine alkaloids were chosen according to docking and overall drug-likeness scores.

Sl. No.	Ref. no. from total	JE-target enzymes			EBOV-target enzymes			Drug-likeness score
		RdRps (PDB ID: 4HDG)	NS3_Healicase (PDB ID: 2Z83)	NS5_Protease (PDB ID: 4K6M)	NP (PDB ID: 4Z9P)	VP24 (PDB ID: 4M0Q)	VP40 (PDB ID: 3TCQ)	
1.	**35**	-9.9	-9.7	-10.8	-9.1	-8.1	-12.4	0.41
2.	**36**	-9.2	-9.8	-10.5	-8.3	-8.1	-10.4	0.41
3.	**37**	-11.2	-10.3	-12.2	-8.8	-8.1	-12.1	0.16
4.	**38**	-9.9	-10.3	-10.8	-8.9	-8.5	-13.2	0.36
5.	**39**	-9.9	-10.8	-10.6	-9.2	-8.4	-13.2	0.81
6.	**40**	-10.7	-10.6	-11.5	-9.2	-8.5	-12.5	0.27
7.	**41**	-11.6	-9.6	-10.0	-8.8	-8.0	-11.0	0.01
8.	**42**	-12.3	-9.3	-11.0	-9.0	-8.3	-11.5	0.01
9.	**43**	-9.8	-9.0	-10.1	-8.6	-8.8	-10.7	0.90
10.	**46**	-10.3	-8.8	-8.9	-7.7	-7.1	-11.0	0.47
11.	**48**	-7.9	-7.2	-7.1	-6.5	-5.0	-8.3	0.96
12.	**49**	-11.1	-9.8	-10.0	-9.8	-8.3	-10.7	0.29
13.	**50**	-11.0	-9.9	-10.4	-9.7	-8.6	-12.0	0.52
14.	**59**	-11.3	-11.0	-11.1	-8.9	-8.4	-12.8	0.22
15.	**60**	-11.8	-10.7	-11.3	-9.9	-8.9	-12.1	0.47

Currently, CADD is a cost-effective platform for general, molecular docking offers such a strong platform

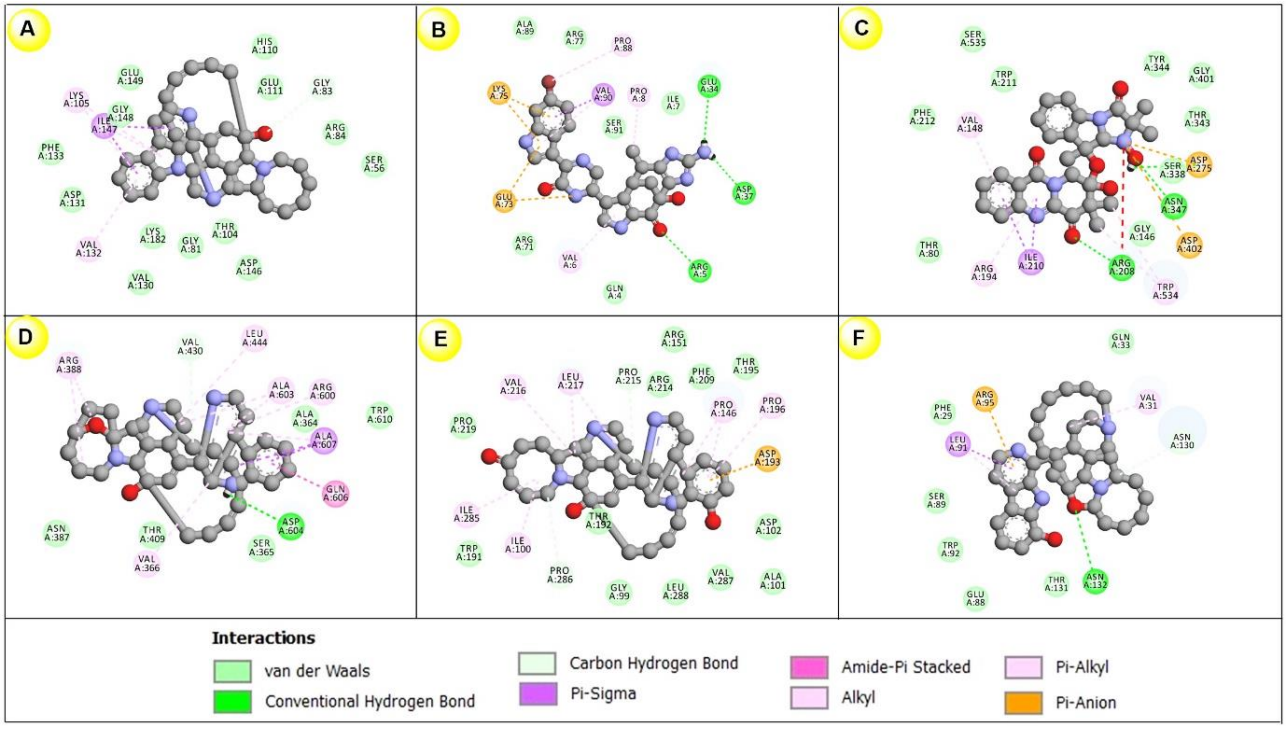

Figure 3. Protein-ligand interaction of the best ligand against each of the six targets. (A). Interaction of neosartoryadin_B with RdRps (-12.3kcal/mol) (B) Interaction of 6-deoxymanzamine_X with NS3 (-11kcal/mol) (C) Interaction of manzamine_A with NS5 (-12.2kcal/mol) of JE virus (D) Interaction of dragmacidin_F with NP (-10.6 kcal/mol) (E) Interaction of 8-Hydroxy-manzamine with VP24 (-8.9 kcal/mol) (F) Interaction of manzamine F with VP40 (-13.2 kcal/mol) of EBOV virus, respectively.

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for exposing any candidate's bioactivity based on binding affinity and targeting any disease. As bioinformatics tools able to mimic biological systems through programming and coding, which play a crucial role for selecting the most drug-able candidates before conducting an experiment or in drug repurposing strategy. Here, the selection of the most potent antiviral candidates against JE and EBOV is an ideal assessment. However, to get reliable computational results, reliable hypotheses and knowledge of bioinformatics tools and coding are essential (Shaikh et al., 2019; Dassanayake et al., 2022).

Physicochemical and toxicity profiles prediction

The physicochemical profiles, known as the Lipinski Rule of Five (RO5), of all marine alkaloids and four reference antiviral drugs were recorded (Supplementary Table S3). Among 60 marine alkaloids, only 26 candidates followed the RO5. Briefly, RO5 is a standard profile, and the ligand molecular weight should be (≤500 g/mol), the logp value (≤5), tPSA value (≤142 Å), the H-bond donor (≤5) and the H-bond acceptor (≤10). Most ligands, including ivermectin and novobiocin, cannot follow the RO5 rules due to their higher molecular weights, but not by enough to disrupt oral bioavailability (Supplementary Table S3). Thus, it is clearly indicated that most existing drugs also do not follow the RO5 profiles. Nevertheless, RO5 is a standard parameter to locate expected bioactive oral drugs that might be successful in clinical trials. Overall, applying hard or strict RO5 may result in fewer active candidates at the primary stage, but a standard set of profiles guides the selection of bioactive compounds via the CADD.

Individual marine alkaloids and antiviral drugs with concurrently predicted toxicity profiles exhibited comparatively moderate hepatotoxicity, carcinogenicity, and mutagenicity profiles with adverse immunotoxicity profiles (Supplementary Table S3). Marine alkaloids exhibited toxicity classes II and IV from toxicity class prediction, while selected potential marine alkaloids, manzamine A and 8-hydroxymanzamine, are class-II, while crambescidins 826, 830, and 844 with fromiamycalin and ptilomycalin A showed higher toxicity as indicated in the toxicity class-I category. Furthermore, acetylstachyflin, lamellarin-20-sulfate, and stachyflin were safer candidates with class VI toxicity profiles (Supplementary Table S3). Overall, most active candidates in class II with LD_{50} values less than 10 mg/kg indicated that they are toxic in nature and can help with dose preparation during JE and EBOV experimental studies.

Pharmacokinetics and drug-likeness profiles prediction

The computationally predicted pharmacokinetic profiles of individual ligands, including four control drugs, were recorded (Supplementary Table S4). The recorded profiles indicated that including all ligands, both marine candidates and standard drugs, produced diversified results. Three antiviral drugs showed lower GI absorption among all 14 marine candidates, while 17 marine candidates showed the potential to enter the BBB. Entering BBB is not ideal for all conditions if the disease is not related to the brain, but the JE virus causes central nervous system disorders, so that perspective may be used. In addition, 18 compounds do not have p-glycoprotein (p-gp) substrate ability as a plasma membrane protein associated with drug transport in the human body. Technically, the pharmacokinetic profiles of any drug candidates are associated with the physiochemical and pH profiles and indicate that most of the RO5-violated candidates exhibit pharmacokinetic properties. Thus, predicted profiles also give more drug-relevant information before expensive clinical investigations.

In each step, marine candidates face filtration by different bioinformatics tools and show diversified results, but the primary goal of filtration with various drug parameters is to identify the most drug-able candidates. Therefore, based on chemical structure, the drug-likeness score was recorded for each candidate (Supplementary Table S2). Including all antiviral drugs, 35 out of 60 marine candidates showed a positive drug-likeness score. Batzelladine C (1), batzelladine N (0.96), crambescidin_800 (1.17), crambescidin 816 (1.14), crambescidin 826 (1.28), crambescidin 830 (1.32), crambescidin 844 (1.32), dehydrobatzelladine C (0.92), dercitin (0.91), fromiamycalin (1.05), oxoglyantrypine (0.90), and ptilomycalin A (0.96) have some excellent drug-able candidates based on predicted score (Supplementary Table S2). Overall, most active candidates based on docking scores did not have an ideal drug-ability score, indicating that only one parameter, whether IC_{50}, docking scores, or toxicity profiles, was insufficient to demonstrate that potential candidates needed to be more suitable from all angles.

In face of the scarcity of potent therapeutic candidates to handle any emerging situation, the search for alternative candidates is essential, where natural products are a focus area due to their multi-potential biological activity, lower toxicity, and cost-effectiveness. Starting from our forefathers around 80% of world communities still has used natural resources for their day to day life.

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Aside from plants, most scientific groups investigated the biological potency of previously unknown sources, whereas the marine environment is a larger eco-system with many hidden bioactive unique molecules and a greater opportunity in mainstream medicine. Less than 2% of the marine ecosystem has been exposed to date, and we still need to expose it for health management purposes (Fabbri and Franzellitti, 2016; Mathur and Hoskins, 2017; Dzobo, 2022). Although alkaloids isolated from plant or marine sources are comparatively toxic compared to other chemical classes of constituents, but they are highly successful in mainstream medicine. Repurposing active molecules is a good practise for preserving sustainability and the environment. After the SARS-CoV-2 pandemic, the concept of repurposing drug discovery was widely accepted as a cost-effective and resource-saving strategy to counter the health emergency. Natural products, in addition to drugs, are gaining popularity for use in repurposing drug discovery platforms (Swain et al., 2021; Musarra-Pizzo et al., 2021; Piplani et al., 2022; Sahoo et al., 2022b). Surprisingly, a large number of marine alkaloids have been approved, with more in clinical trials. In this study, the assessment of reported marine alkaloids against specific potencies against specified JE and EBOV using bioinformatics tools may be considered a more systematic, cost-effective drug discovery platform to locate the most likely drug-like molecules for further experiments or to proceed with the most active candidates to limit resources and time in current drug discovery.

Conclusion

Opportunistically, the present study assessed the anti-JE and anti-EBOV efficacy through advanced molecular docking study against six different target enzymes associated with viral entry and replication. Based on molecular docking study, neosartoryadin_B against RdRps (-12.3 kcal/mol), 6-deoxymanzamine_X against NS3 (-11 kcal/mol), manzamine_A against NS5 (-12.2 kcal/mol) of JE virus, while dragmacidin_F against NP (-10.6 kcal/mol), 8-hydroxymanzamine against VP24 (-8.9 kcal/mol) and manzamine F with VP40 (-13.2 kcal/mol) of E virus were lead candidates against each target, respectively. Additional toxicity, physicochemical analysis, and pharmacokinetics with overall drug-likeness revealed that sponge-derived manzamine derivatives such as manzamines A, E, F, and X, 6-deoxymanzamine X, 8-hydroxymanzamine, polycitone A, fungal-originating neosartoryadins B, norquinadoline A, and quinadolines A-B and scequinadoline A are some potential-cum-drug-able antiviral candidates with higher chance of clinical success. Overall, exploring more bioactive marine candidates along with locating probable drug lead candidates through tools of bioinformatics could be a suitable strategy for current drug discovery.

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Conflict of Interest

There are no conflicts of interest.

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