Use of Marine biotoxins to modulate the tyrosine kinase domain of the human epidermal growth factor receptor

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Abstract

Inappropriate activation of the Epidermal growth factor receptor (EGFR) group of kinases has been identified in a variety of tumour cells, either due to mutation or overexpression. Although the tumour is a fatal disease, significant therapy discoveries have lately been made. The human EGFR and this family of kinases have emerged as promising targets for cancer therapy. In this molecular docking study, Natural marine toxins are employed to regulate the activity of the human EGFR tyrosine kinase domain (EGFRtkd) in the molecular docking investigation (PDB ID5JEB). Marine biotoxins can cause neurological, gastrointestinal, and cardiovascular problems, as well as severe mortality and long-term morbidity in some situations. Because there is no antidote for any of the natural marine poisons, supportive care is the mainstay of treatment. Paralytic shellfish poisoning, in particular, and puffer fish poisoning, in particular, can result in death within hours of exposure to the poisons and may require immediate medical intervention. However, this research found that marine biotoxins can modulate EGFRtkd. Furthermore, homoyessotoxin was anticipated to be an EGFRtkd modulator with a binding affinity as -9.584 kcal/mol. To employ the homoyessotoxin in tumour therapies, further knowledge of natural marine biotoxins and further toxicological research is required.

Introduction

Epidermal Growth Factor Receptor (EGFR) is a transmembrane glycoprotein receptor for epidermal growth factor. When EGFR interacts to its cognate ligand EGF, it triggers tyrosine phosphorylation and receptor dimerization with other family members, resulting in uncontrolled cell proliferation. Several anti-EGFR medicines such as monoclonal antibodies and tyrosine kinase inhibitors, have been developed, allowing doctors to identify and treat specific patient groups. (Seshacharyulu et al., 2012). EGFR is a protein located on the surface of some normal cells that help them develop. It's also possible that its present in high concentrations on cancer cells, causing them to multiply and divide (www.cancer.gov). EGFR and EGF-like peptides are widely overexpressed in human carcinomas, and *in vivo* and *in vitro* studies have shown that these proteins can accelerate cell transformation (Mendelsohn and Baselga 2000). The EGFR signal is part of a complex network that has been successfully treated as a tumour target (Oda et al., 2005). The known EGFR inhibitors show varying antitumor responses for the various EGFR mutation connected to nonsmall-cell lung cancer (Bethune et al.,2010; Sogabe et al., 2012). If the EGFR is suppressed tumour cells may not be able to multiply. In other cases, EGFR inhibitors were used to treat the malignancy (www.cancer.gov). Natural marine toxins have been tested against the EGFRtkd in DockThor-VS web portal as part of current reseach (Guedes et al., 2021). The goal of this study is to use computational tools to assess natural marine biotoxins in order to alter the EGFRtkd function. Toxic compounds exist in a variety of shapes and sizes, and there are a variety of methods for identifying them, including biological origins, toxicity, molecular mass, and structural analysis. Marine biotoxins are produced by toxicogenic algae, cyanobacteria, bacteria, and marine animals. (Bigalke and Rummel, 2005; Johnson et al., 2011).Natural marine toxins (non-protein) in man and animals induce amnesic shellfish poisoning (ASP), azaspiracid shellfish poisoning (ASP), diarrheic shellfish poisoning (DSP), neurotoxic shellfish poisoning (NSP) and paralytic shellfish

poisoning (PSP) (Lowenstine 2008). The first toxic component of paralytic shellfish poisoning to be found and studied (PSP) was saxitoxin (STX) (Wang et al 2015).This toxin inhibits neuronal transmission by binding to the voltage -gated Na+ channel (Andrinolo et al., 1999). According to research published in the late 1980s, inhalation delivery of STX to mice is around 10 times more effective than intravenous treatment (Neufeld 1980). STX is similar to low-molecular-weight toxins like tetrodotoxin, brevetoxin, and anatoxin in term of its ability to permeate the dermal barrier (Kubo et al 2008). The human percutaneous lethal dose of saxitoxin is unknown, although the equivalent brevetoxin worksin a similar way. Experiments have revealed that a percutaneous dosage of brevetoxin 20 times larger than the deadly parenteral dose does not cause death. (Supotnitskiy, 2013).

Methodology

Targeted Enzyme

EGFRtkd (PDB ID-5JEB) was chosen for this molecular docking investigation. It can be found at www.rcsb.org in the RCSB protein database. This EGFRtkd has been linked to a variety of cancers and plays a crucial role in cellular processes (Sogabe et al., 2012).

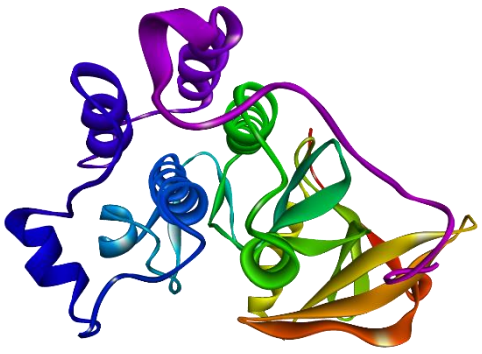

Figure 1. Structure of EGFR tyrosine kinase domain (EGFRtkd)

DockThor

The DockThor-VS web server, as well as curated libraries of currently accessible drugs and chemical data, are publicly available at www.dockthor.lncc.br. Its molecular docking and virtual screening experiments are simplified. This website was used to evaluate the natural marine toxins in order to find an EGFRtkd modulator.

Results and Discussion

Homoyessotoxin binds to the targeted receptor EGFRtkd with exceptional affinity. Fifty marine biotoxins 3D files based on KEGG chemical information were collected from the ChemSpider database. Eight compounds (#) were not processed in the chosen docking method due to an unknown fault (**Table 1**). Homoyessotoxin had the lowest binding affinity of all the ligands examined, at -9.584 kcal/mol. The BIOVIA Discovery Studio Visualizer software was used to visualize the interactive 2D posture of the receptor with homoyessotoxin docked file. Figure 2 shows the receptor-ligand interaction pattern.

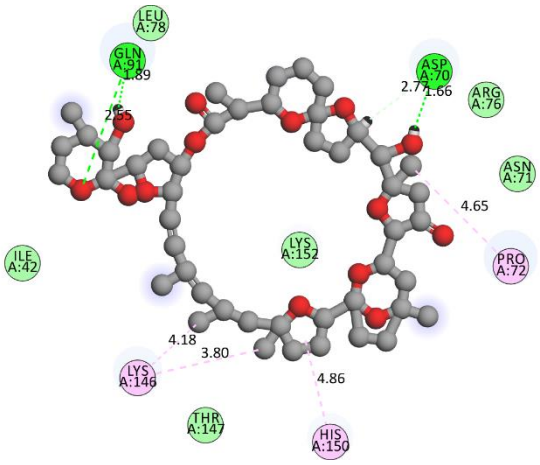

Figure 2. Receptor-Ligand (EGFRtkd-homoyessotoxin) interaction pattern in 2D

As a contaminant, homoyessotoxin is found in the digestive glands of *Mytilus galloprovincialis* (Satake et al 1997). It is potentially biotoxin (https://hmdb.ca/metabolites/HMDB0036615) and belongs to the class of organic, lipid-soluble polyether compounds consisting of 13 to 14 rings

fused by ether links into a highly stiff ladder-like structure. According to a 2003 study by Tubaro et al., homoyessotoxin treated female mice died at a dosage of 375 mg/kg. The mice were restless and leapt before death, but necroscopy revealed no substantial alterations. The LD_{50} value of homoyessotoxin-treated mice is 315–830 mg/kg. At a dose of 1 mg/kg, Oral administration of homoyessotoxin to mice did not cause any significant difference in plasmatic enzymes (AST, ALT, LDH and CK) or leukocyte percentage. In mice treated with homoyessotoxin at a dose of 1mg/kg, cytoplasmic protrusions of myocardiocytes, packed rounded mitochondria, and fibre alterations were seen using transmission electron microscopy (TEM) (Tubaro et al 2003).

Funding

This research received no funding from public, private, or non-profit organization.

Acknowledgments

The author would like to thank for the International Student fellowship from Kaohsiung Medical University (KMU). The author extends his appreciation to Office of Library and Information Services (OLIS) for providing the access to the monographs, journals, internet sources, digital materials as well as other useful software.

Conflicts of Interest

The author declared as there are no known competing financial interests.

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143 **Supporting Information**

144 **Table 1. Marine biotoxins binding affinity towards the EGFRtkd**

Marine biotoxins	KEGG compound entry	ChemSpider ID	*DockThor Ligand ID*	*Affinity kcal/mol*	*Total Energy kcal/mol*	*vdW Energy*	*Elec. Energy*
ASP-*Amnesic Shellfish Poisoning*							
Domoic acid[1]	C13732	4445428	29f824cb20	-6.523	-18.264	-1.934	-39.493
Isodomoic acid A[1]	C20027	4946671	dc8fd6f151	-6.511	-21.231	-0.094	-37.479
CFP-*Ciguatera fish poisoning*							
Ciguatoxin I[2]	C16762	4470834	60c8d84797	-9.353	107.467	-29.313	-8.358
Caribbean ciguatoxin 1[2]	C20003	10216856	b7c1db87ea	-7.402	244.765	-14.617	-41.382
CTX 3C[2]	C20001	10474447	f40814364c	-8.011	155.555	-18.881	-25.986
Ciguatoxin 4A[2]	C20002	35013551	05a6301f4	-8.788	149.372	-25.105	-16.692
Gambieric acid A[2]	C16885	27025948	b9e44b0f68	-8.910	184.602	-20.454	-22.981
Gambieric acid B[2]	C16886	9978891	5d70125b18	-9.404	194.311	-25.747	-10.070
Gambieric acid C[2]	C16887	10478379	0f4d9a62ae	-6.648	84.965	5.974	-91.040
Gambieric acid D[2]	C16888	10478380	6a798aec75	-7.261	102.434	3.392	-80.865
Gambierol[2]	C20004	4946332	e7d11eb189	-8.581	69.041	-24.837	-11.382
Gambiertoxin 4B[2]	C16852	10366292	2893bae71e	-8.220	164.485	-7.030	-47.625
Maitotoxin[2]	C16854	25991548	#	#	#	#	#
DSP-*Diarrhetic shellfish poisoning*							
Okadaic acid[3]	C01945	393845	637352dadc	-8.263	41.959	-19.833	-25.331
Acanthifolicin[3]	C20006	27022422	#	#	#	#	#
Dinophysistoxin-1[3]	C16870	16737821	7f6357dd05	-7.367	155.527	1.837	-78.085
Dinophysistoxin-4[3]	C20005	4945455	197204824a	-9.115	4.377	-26.492	-23.601
Homoyessotoxin[4]	**C20011**	**4944614**	**67b9b5ae**	**-9.584**	**59.942**	**-27.055**	**-16.251**
Yessotoxin[4]	C16872	4945067	28c096d0f8	-9.135	61.155	-24.247	-20.509
Caribenolide I[5]	C20007	10475898	b634f6bdf5	-7.392	114.925	11.641	-97.630
Goniodomin A[5]	C16899	27025933	c0caa4061c	-6.730	119.526	18.546	-75.983
Hoffmanniolide[5]	C20008	29212837	44852d982e	-7.817	24.473	-17.386	-29.255
Iriomoteolide-1a[5]	C20009	17627054	c7d5ea4232	-7.249	41.559	-12.622	-22.561
NSP-*Neurotoxic Shellfish poisoning*							
Brevetoxin A[4]	C16839	9041092	378a6ab339	-7.923	159.938	-16.731	-15.583
Brevetoxin B[4]	C16857	9041149	c4925b4b92	-8.812	93.453	-23.852	-9.887
Brevetoxin B1[4]	C20013	27026682	#	#	#	#	#
Brevetoxin B2[4]	C20014	8805247	6a8f3546ec	-8.838	142.169	-19.682	-25.245
Brevetoxin C[4]	C20015	16736106	1404334e93	-7.783	115.521	-22.669	-20.070
Hemibrevetoxin B[4]	C20016	4946882	cefb510d0f	-8.158	26.868	-20.307	-7.230
PSP-*Paralytic shellfish poisoning*							
Gonyautoxin-1[6]	C16855	30791735	b70612d0a	-6.877	-83.142	0.553	-49.812
Gonyautoxin-2[6]	C16856	9767779	69ff2d0957	-6.614	-121.898	-11.750	-30.799
Neosaxitoxin[6]	C17208	19975931	#	#	#	#	#
Saxitoxin[6]	C13757	34106	4e060a9472	-6.520	-96.572	-8.972	-25.049
Decarbamoylsaxitoxin[7]	C20021	19975972	#	#	#	#	#
Decarbamoylgonyautoxin-1[7]	C20022	30790887	b44366465c	-6.251	-55.542	-4.309	-38.583
Gonyautoxin-5[8]	C20018	94743	8f46648d7d	-6.708	-148.962	-13.217	-30.449
Gonyautoxin-6[8]	C20019	30790889	ccfa77e515	-6.842	-102.071	-16.309	-29.148

Gonyautoxin-8[8]	C20020	94734	0566d8faf5	-7.049	-176.909	-15.679	-31.061
Palytoxin[9]	C16851	9280425	#	#	#	#	#
Ostreocin D[9]	C20028	78445048	#	#	#	#	#
Tetrodotoxin[10]	C11692	23106940	ffc85130ea	-6.453	-55.305	-3.087	-36.841
11-Deoxytetrodotoxin[10]	C20026	19989712	#	#	#	#	#
Others							
Pectenotoxin-1	C16871	4942381	de9246fafa	-7.940	57.958	-13.852	-16.524
Pectenotoxin-2	C20012	4941948	4d2b95	-7.864	53.110	-12.615	-16.849
Azaspiracid	C16907	9724424	0873e863b3	-8.706	11.182	-20.035	-22.681
Gymnodimine	C20025	64854205	db2b7cd013	-7.064	89.227	-14.932	-2.517
Neosurugatoxin	C16761	29214049	a6116671	-7.462	41.290	-13.268	-30.437
Prorocentrolide	C20023	10204061	83f990486d	-7.959	261.979	-3.700	-66.466
Prorocentrolide B	C20024	10200328	cbc87dc562	-8.002	333.571	-1.433	-74.877
Pyropheophorbide a	C18064	10381282	fee4b0a482	-7.106	-2.517	36.027	-91.816

Note: *1=Kainoids; 2=Cyclic polyethers; 3=Okadaic acid and derivatives; 4=Cyclic polyethers; 5=Macrolides; 6=Carbamate derivatives; 7=Decarbamoyl derivatives; 8=N-Sulfo-carbamoyl derivatives; 9=Palytoxins; 10= Tetrodotoxins; #=unknown error in ligand preparation and docking.*

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