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RESEARCH ARTICLE

POLYCHAETE FATTY ACIDS AS POTENTIAL INHIBITOR AGAINST HUMAN GLIOBLASTOMA MULTIFORME

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ABSTRACT

Glioblastoma multiforme (GBM) is the most aggressive form of the gliomas, a collection of tumors arising from glia or their precursors within the central nervous system caused by the overexpression of EGFR (Epiderma Growth Factor Receptor), EGFRvIII and EphA2 (ephrin type A). Due to high mortality and resistance of GBM to conventional therapeutic treatments, there is an urgent need to deviate from conventional treatments and delve into molecular targeted drug therapy techniques. In the present study, the fatty acid methyl esters (FAME) of polychaete species, *Namalycastis abuima* from mangrove ecosystem was assessed for the inhibition property against GBM. Totally 29 fatty acids along with the previously reported potential compounds such as Anilinoquinazoline, Thalidomide and Tetracenomycin D3, were structurally optimized and docked against the GBM target proteins EphA2, EGFR and EGFRvIII in Arguslab software. Intriguingly all the fatty acids showed better docking energy (-14.128 to -9.224 Kcal/mol) than the previously reported drugs (-10.582 to -5.874 Kcal/mol). Among the fatty acids, polyunsaturated fatty acids (PUFA) were found to be the most effective as evident by the strong interaction with the target proteins. The *in silico* ADME results further substantiated the efficacy of fatty acids as a potential natural source which could inhibit the activity of the overexpressed mutant type EGFR.

INTRODUCTION

Glioblastoma (GBM) is known to be an extremely aggressive and malignant form of anaplastic arythrocytoma affecting the central nervous system in humans (Holland 2000). Clinically, gliomas are divided into four grades and the most aggressive among them is grade four *i.e* glioblastoma multiforme (GBM), which is unfortunately the most common in humans with a median survival of less than one year (Kleihues and Ohgaki 2007). Glioblastoma arises from the glial tissue of the brain which includes astrocytes, oligodendrocytes and ependymal cells. It has been studied that approximately 60% of the primary brain tumour detected are gliomas (Lou 2004). Glioma is a type of tumour that starts in the brain or spine and accounts for 52% of all functional tissue brain tumour and 20% of all intracranial tumours. Glioblastoma is more common in adult males and has rather severe effect on brain than the spinal cord. Lack of effective drugs, expensive cost of chemotherapeutic agents and side effects of anticancer drugs urge the continuing discovery of new anticancer agents. Glioblastoma is seen to be resistant to most of the conventional therapeutic treatments (Lipsitz *et al.,* 2003). Finding the ultimate cure for GBM remain a challenging tasks for decades. Various active compounds have been tested against a series of components of the target receptor protein to halt the growth of cancerous cell. The idea of finding cure from known pharmacologically active natural occurring compounds is intriguing and practical.

Certain receptors or molecular markers that are found overexpressed on malignant cells but are nearly absent in normal cells, act as potential drug targets. Glioblastoma gene has several regions of point mutations which establish self-activating signal transduction pathways of the tyrosine kinase receptors (Miyazaki *et al.,* 2003). EGFRvIII is one such mutated protein formed from EGFR by the genetic loss of its 270 amino acids. Even in the absence of any ligand, EGFRvIII is capable of self-activation which might results in abnormal proliferation, metastasis and inhibition of cell death ultimately leading to the formation of tumour. EGFRvIII overexpressed in about 24% to 65% of GBM cases studies (Easty and Bennett 2000). Therefore EGFR and EGFRvIII are considered to be the novel molecular targets against GBM (Massimino and Biassoni 2006). Emergence of molecular docking has open new possibilities and ways to learn molecular interaction between molecules. Molecular docking plays an important role in structure based drug design (Halperin *et al.,* 2002; Brooijmans and Kuntz 2003). Given two molecules, referred to as the receptor and the ligand, molecular docking attempts to predict the binding mode by evaluating the energy scores of different bond conformations with a scoring function. The interest of chemists, biochemists and biotechnologists in lipids and fatty acids (FA) from marine oorganisms has been stimulated in recent years, in particular, by the recognition that polyunsaturated fatty acids (PUFA) are important for the aquatic organisms as well as human health and nutrition (Chedoloh *et al.,* 2011). Polychaetes are valued by the aquaculture industry as an excellent source of PUFAs, and they have the potential to supplement fish oil as sources of essential lipid components of feeds (Fidalgo *et al.,* 2000) and hence they are also known as

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omega worms (Olive *et al.,* 1992). Fatty acids, especially Omega-3 fatty acids reduce inflammation and play an important role in brain function and cognitive development, including memory, behavior and other cognitive functions. With the dramatic increase in the capacity for biological screening and chemical synthesis, there is a colossal demand for large quantities of early information on absorption, distribution, metabolism; excretion (ADME) and toxicity data (together called ADMET data). Hence the present study was carried out to evaluate the fatty acids of polychaete as potential inhibitors of GBM and an *in silico* assessment of its ADME properties.

MATERIALS AND METHODS

Sample collection and fatty acid analysis

The preparation of fatty acid methyl esters (FAMEs) from the polychaete, *Namalycastis abuima* isolated from coastal mangrove ecosystem of Parangipettai, Tamil Nadu, India (Lat. 11º29'26.00 N; Long. 79º45'57.89 E), were performed according to the method of Anon 2000. Briefly, 100 mg of tissue samples were added to 1 ml of 1.2M NaOH in 50% aqueous methanol in a screw-cap test tube tightly sealed with teflon tape and then incubated at 100°C for 30 min. in a water bath. The saponified samples were cooled at room temperature, and then acidified and methylated by adding 2 ml of 54% 6N HCl in 46% aqueous methanol and incubated at 80° C for 10 min. in water bath. After rapid cooling, methylated fatty acids were extracted with 1.25 ml of 50% methyl-tert butyl ether (MTBE) in hexane. Each sample was mixed for 10 min. and the bottom phase removed with a Pasteur pipette. Top phase was washed with 3 ml of 0.3M NaOH. After 5 min. of mixing, the top phase was collected for analysis. Following the base wash step, the FAMEs were cleaned in anhydrous sodium sulphate and then transferred into GC sample vials for analysis. FAMEs were analyzed in GC-MS-QP (2010) (Shimadzu, Japan). One microlitre of the extract was injected in the injection port (split mode) at the temperature of 250°C and Helium (99.99% purity) was used as carrier gas. FAME profiles of the samples were identified and calibrated with standard methyl esters.

Retrieval of protein and ligand structure

The three dimensional (3D) structure of the target proteins EphA2, EGFR and EGFRvIII (PDB ID: 1MQB, 1M17 and 1I8I respectively) having the resolution of 2.3A°, 2.6A° and 1.8A° were retrieved from the protein data bank (PDB) (www.rcsb.org/pdb). The chemical structure of natural inhibitors (Anilinoquinazoline, Thalidomide and Tetracenomycin D3) *as* well as the GC-MS identified fatty acids of the polychaete, *Namalycastis abuima* were generated from SMILES notation (Simplified Molecular Input Line Entry Specification) by using the Chemsketch Software (www.acdlabs.com).

Protein-ligand Docking

Argus Lab 4.0.1 the most common and freely available software was used for docking analysis and to calculate the binding energy requirements of the fatty acids (ligands) with the target proteins, EphA2, EGFR and EGFRvIII. The active site of the target proteins were obtained from RCSB ligand explorer software. Hydrogen bonds were added to both protein and ligands followed by geometrically optimization [15]. *GA dock* was used as the docking engine and the grid resolution was set to 0.40 A°. Calculation type was set to *Dock* mode whereas *flexible mode* was selected for the ligand. Least energy represented the easy binding character of ligand and receptor. The docked structure was saved as *.pdb* file and molecular interaction between identified compounds and the receptor protein was visualized using Discovery Studio (Ver 3.1) software.

In silico ADME predictions

Pharmacokinetic properties of the fatty acids were predicted by using FAF-Drugs2 server (Lagorce *et al.*, 2011) (http:// mobyle. rpbs.univ-paris-diderot.fr/cgi-bin/portal.py?form=FAF-Drugs# forms::FAF-Drugs2). The data was uploaded in *.sdf* format. XLOGP3 was set as logP computation program. Rests of the filtering options were kept as default. ADME-Tox prediction helps in distinguishing drug-like and non-drug-like properties and predicts high probability of success or failure due to drug likeliness for the molecules. This early *in silico* prediction helps in early preclinical assessment and thereby avoiding costly late stage preclinical and clinical failures.

RESULTS

Fatty acid analysis

GC-MS analysis revealed the presence of totally 29 fatty acids dominated by 12 polyunsaturated fatty acids (PUFA), followed by 11 Monounsaturated fatty acids (MUFA) and six saturated fatty acids (SFA) in the polychaete tissue (Table 1).

Protein-ligand Docking

To understand the interactions between the fatty acids and the GBM protein and to explore their binding mode, docking study was performed using Argus Dock. The predicted active site of the target proteins are shown in Table 2. The docked ligand molecules were selected based on docking energy and good interaction with the active site residues and the results are shown in Table 3. Stupendously, compared to commercially available drugs against GBM, the fatty acids obtained from the polychaete displayed good interactions with the GBM targets as evident by better docking score (-14.128 to -9.224 Kcal/mol) compared to the standard drugs Anilinoquinazoline, Thalidomide and Tetracenomycin D3 (-10.582 to -5.874 Kcal/mol). Lesser the docking score is more the binding capacity of the ligand (Sahu *et al.,* 2012). Molecular docking of 7,10,13-Eicosatrienoic acid with EphA2 (1MQB) protein demonstrates that the inhibitor made One bonds with residues LYS646 and ASP757; and two hydrogen bonds with and SER756 with the distance of 2.4, 2.2, 1.7 and 2.5 respectively. Cis-7, 10, 13, 16-Docosatetraenoic acid exhibited two bonds with LYS646 and THR692 residues with the distance of 1.8 and 2.2 respectively. However in the case of standards, Tetracenomycin D3 showed seven H bonds followed by Thalidomide with three bonds and Anilinoquinazoline with only one bond. Except Anilinoquinazoline, both PUFA and standard drugs exhibited similar hydrogen bond with LYS646, even though the ligands are not at all structurally similar. The protein-ligand interaction as visualized in Discovery studio is shown in Fig. 2A. In the case of EGFR (1M17), the PUFA 7,10,13-Eicosatrienoic acid showed three H bonds; one with ASN818 and two with ARG817 with the distance of 1.6, 2.1 and 2.1 respectively. In the case of cis-7, 10, 13, 16-Docosatetraenoic acid only a single H bond was observed with CYS773 with the distance of 2.4.

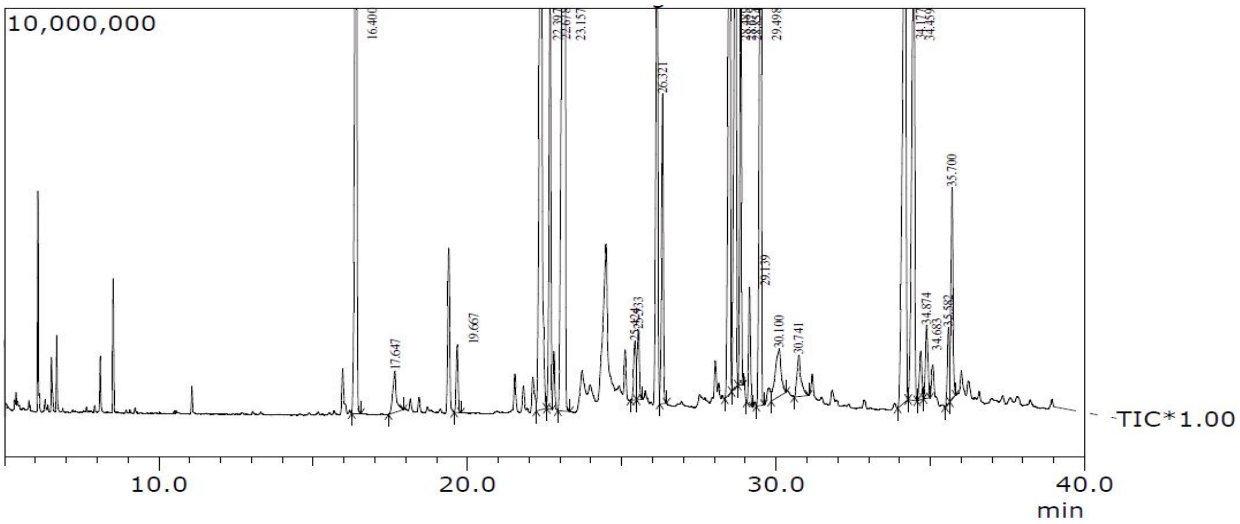


Fig.1 GC-MS chromatogram showing the Fatty Acid Methyl Ester (FAME) profile of the polychaete species, *Namalycastis abuima*

Table 1 List of fatty acids identified through GC-MS analysis and the molecular docking score against GBM target proteins

Compound code	Ligand	Docking Score (Kcal/mol)		
		EphA2 (1MQB)	EGFRIII (1I8I)	EGFR (1M17)
	PUFAs			
C1	7,10,13-Eicosatrienoic acid	-14.128	-13.654	-13.149
C2	cis-7,10,13,16-Docosatetraenoic acid	-12.228	-13.074	-12.958
C3	cis-4,7,10,13,16,19-Docosahexanoic acid	-12.416	-11.046	-12.021
C4	5,8,11,14,17-Eicosapentaenoic acid	-10.132	-9.224	-10.61
C5	5,8,11,14-Eicosatetraenoic acid	-11.609	-10.003	-11.908
C6	9,12-octadecadienoic acid	-10.087	-11.943	-11.139
C7	9-Hexadecenoic acid	-10.339	-10.736	-10.096
C8	cis-11,14-Eicosadienoic acid	-9.887	-10.056	-11.087
C9	Methyl 5,8,11,14,17-eicosapentaenoate	-10.01	-9.901	-10.131
C10	Methyl 5,11,14-eicosatrienoate	-10.19	-9.559	-10.871
C11	Methyl eicosa-5,8,11,14,17-pentaenoate	-12.043	-11.091	-11.241
C12	Methyl (Z)-5,11,14,17-eicosatetraenoate	-11.232	-10.313	-10.199
	MUFAs			
C13	5-Octadecenoic acid	-9.337	-9.998	-10.094
C14	6-Octadecenoic acid	-10.323	-11.007	-11.193
C15	9-octadecenoic acid	-11.565	-11.231	-11.001
C16	11,13-Eicosadienoic acid	-12.784	-10.783	-12.01
C17	11-eicosenoic acid	-11.433	-11.098	-11.134
C18	11-octadecenoic acid	-10.754	-9.965	-10.113
C19	13-Octadecenoic acid	-9.084	-10.043	-11.983
C20	cis-10-Heptadecenoic acid	-9.876	-10.012	-10.322
C21	cis-11-Eicosenoic acid	-9.978	-11.055	-11.073
C22	Cyclopropaneoctanoic acid	-10.876	-10.158	-11.118
C23	trans-13-Octadecenoic acid	-11.882	-11.062	-10.993
	SFAs			
C24	cis-13-Eicosenoic acid	-10.449	-9.941	-11.325
C25	cis-13-Octadecenoic acid	-10.002	-9.992	-11.098
C26	Hexadecanoic acid	-12.106	-11.463	-10.893
C27	Methyl tetradecanoate	-11.454	-10.632	-11.344
C28	Pentadecanoic acid	-11.901	-10.274	-10.773
C29	Tetradecanoic acid	-10.211	-9.732	-9.139
	Standards			
C30	Anilinoquinazoline	-7.167	-5.874	-8.43
C31	Thalidomide	-8.826	-8.399	-9.582
C32	Tetracenomycin D3	-9.005	-8.084	-10.582

Table 2 List of amino acids predicted in the active site of the target protein

S. No.	Protein (PDB ID)	Predicted amino acids in the active site
1	1I8I	ASP408, GLN412, TRP410, PHE46, GLN301, VAL302,PHE327, LYS303, ARG398
2	1MQB	MET695, THR692, ILE619, MET695, ARG743, ALA621, VAL627, LYS646, GLU693
3	1MI7	PRO779, MET831, MET769, THR766, LYS721, ARG817, ASP831, LEU694, THR830

Table 3 *In silico* ADMET screening results of the polychaete fatty acids

Compound Code	logP	logSw	HBonds	Solubility (mg/l)	Oral Bioavailability (VEBER)	Oral Bioavailability (EGAN)	Phospholipidosis	Status
C1	8.24	-5.91	2	875.75	Good	Good	NonInducer	Accepted
C2	8.68	-6.13	2	704.59	Good	Good	NonInducer	Accepted
C3	8.24	-5.88	1	860.4	Good	Good	NonInducer	Accepted
C4	7.59	-5.4	2	1333.87	Good	Good	NonInducer	Accepted
C5	5.93	-4.61	2	3136.76	Good	Good	NonInducer	Accepted
C6	6.62	-5	2	2156.19	Good	Good	NonInducer	Accepted
C7	7.59	-5.4	2	1333.87	Good	Good	NonInducer	Accepted
C8	7.59	-5.4	2	1333.87	Good	Good	NonInducer	Accepted
C9	7.3	-5.37	2	1491.46	Good	Good	NonInducer	Accepted
C10	6.91	-5.03	2	1927.37	Good	Good	NonInducer	Accepted
C11	6.51	-4.68	2	2486.84	Good	Good	NonInducer	Accepted
C12	7.2	-5.04	1	1728.35	Good	Good	NonInducer	Accepted
C13	2.86	-3.57	9	9656.3	Good	Good	NonInducer	Accepted
C14	7.05	-5.04	2	1823.54	Good	Good	NonInducer	Accepted
C15	7.99	-5.75	2	1025.14	Good	Good	NonInducer	Accepted
C16	8.68	-6.13	2	704.59	Good	Good	NonInducer	Accepted
C17	7.1	-5.11	4	1806.12	Good	Good	NonInducer	Accepted
C18	7.59	-5.4	2	1333.87	Good	Good	NonInducer	Accepted
C19	7.7	-5.72	2	1139.32	Good	Good	NonInducer	Accepted
C20	7.19	-5.2	2	1562.96	Good	Good	NonInducer	Accepted
C21	6.68	-5.24	3	1812.88	Good	Good	NonInducer	Accepted
C22	7.44	-5.21	2	1471.23	Good	Good	NonInducer	Accepted
C23	6.37	-4.84	2	2523.99	Good	Good	NonInducer	Accepted
C24	7.06	-5.22	2	1734.91	Good	Good	NonInducer	Accepted
C25	5.93	-4.61	2	3136.76	Good	Good	NonInducer	Accepted
C26	5.93	-4.61	2	3136.76	Good	Good	NonInducer	Accepted
C27	6.36	-4.49	2	2715.33	Good	Good	NonInducer	Accepted
C28	6.9	-4.85	2	2001.71	Good	Good	NonInducer	Accepted
C29	3.69	-4.75	13	3281.77	Good	Good	NonInducer	Accepted
C30	7.12	-4.99	3	1742.64	Good	Good	NonInducer	Accepted
C31	0.13	-1.61	7	51615.52	Good	Good	NonInducer	Accepted
C32	7.59	-5.4	2	1333.87	Good	Good	NonInducer	Accepted

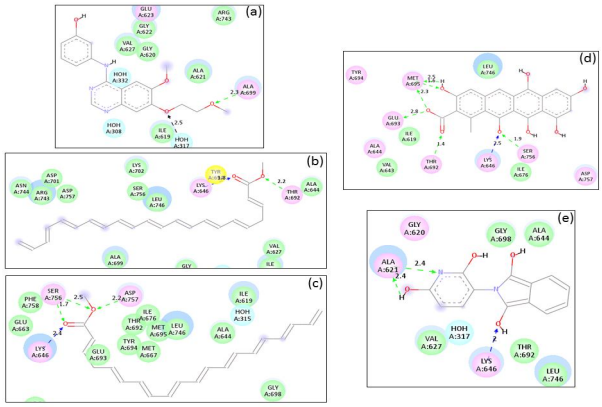
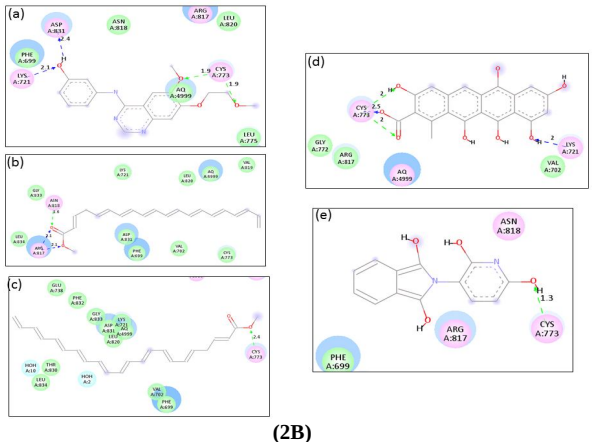
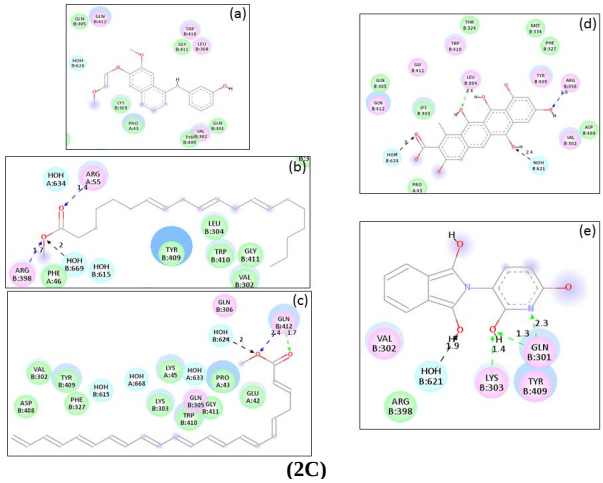


Fig 2 Figure depicting the molecular interaction of ligands with the target proteins (2A) EphA2 (1MQB); (2B) EGFR (1M17); (2C) EGFRIII (1I8I) where, (a) represents Anilinoquinazoline; (b) 7,10,13-Eicosatrienoic acid; (c) cis-7,10,13,16-Docosatetraenoic acid; (d) Tetracenomycin



(2B)



(2C)

For standard inhibitors the amino acids ASP831, LYS721, CYS773 were mainly involved in H bond formation (Fig. 2B). The receptor-ligand interaction of EGFRIII (1I8I) with 7, 10, 13-Eicosatrienoic acid and cis-7, 10, 13, 16-Docosatetraenoic acid revealed the presence of three H bonds each. Whereas, natural inhibitor Anilinoquinazoline doesn't showed any H bond. However, Tetracenomycin D3 and Thalidomide unveiled the presence of four and three bonds respectively (Fig. 2C).

In silico ADME predictions

ADMET prediction was performed in FAFDrugs2 the online tool managed by Mobyle Portal. From the assessment of ligand molecules, it was discerned that all the pharmacokinetic parameters of the tested fatty acids were within the acceptable range defined for human usage (Table 3) which coherently

divulges that the fatty acids, especially PUFA as the potent drug-like molecules.

DISCUSSION

In the present study, totally 29 fatty acids were identified from the polychaete, N. *abuima*. In aquaculture industry, polychaetes are extensively used as live feed for shrimp and ornamental fish brooders, which enable successful breeding on a large scale (Olive 1999). Among the identified fatty acids, 12 were PUFA, followed by 11 MUFA and six SFA. All marine animals, not only marine fishes but also invertebrates, characteristically accumulate various sorts of *n*-3 PUFA in their lipids, in particular docosahexaenoic acid (DHA, 22:6*n*-3) and eicosapentaenoic acid 6 (EPA, 20:5*n*-3), while *n*-6 PUFA are generally observed as the major fatty acids in terrestrial animal lipids (Saito and Aono 2013). Eighteen polychaete families from the Southern Ocean shelf and deep sea has also been analysed in order to identify trophic biomarkers and elucidate possible feeding preferences (Wurzberg *et al.,* 2011). Molecular docking analysis showed a good binding efficiency of the fatty acids especially PUFA. Compared to standard drugs, the PUFAs 7, 10, 13- Eicosatrienoic and Cis-7, 10, 13, 16 Docosatetraenoic acids exhibited better docking score against all the target proteins. LYS646 was found to be the most important interacting residue in the case of EphA2 (1MQB) protein. Similarly, for EGFR (1M17) and EGFRIII (1MQB) the H bonds were congruent with that of standard which has also been confirmed by both *in vitro* and *in vivo* studies against various cancer cells (Olano *et al.,* 2009). The eicosatrienoic acid has been reported to induce spawning in the male lugworm, *Arenicola marina* (Pacey and Bentley 1992). The ability of PUFAs, particular GLA (γ-linolenic acid) to enhance free radical generation and lipid peroxidation process specifically in tumor cells but not in normal cells seems to be their main mechanism of tumoricidal action (Das 2004). Similar observation were also made by Kirubakaran *et al.,* (2011) where, *Tetracinomycin D* has been reported as a potential inhibitor for the treatment of GBM based on *in silico* docking. Although, Thalidomide has been used as an anti-angiogenic agent, but the results have been disappointing (Fine *et al.,* 2000). Furthermore, PUFAs plays a pivotal role in synapse formation, neurite outgrowth and also have neuroprotective actions (Zhang *et al.,* 2011; Wurtman 2008). Dietary supplementation with omega-3 PUFAs has been reported to normalize BDNF (Brain-derived neurotrophic factor) levels which are reduced following brain injury (Wu *et al.,* 2004). Omega-3 enriched dietary supplement provides protection against reduced plasticity and impaired learning ability associated with brain injury in rats (Taouis *et al.,* 2002). Tumoricidal activity of Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) has been reported against glioma cells both *in vitro* and *in vivo* (Massimino and Biassoni 2006). However, the mechanisms of actions involved in the effects of PUFAs on cell regulation are complex. It has also been reported that PUFAs trigger apoptosis in glioma cells by regulating miRNA and their corresponding gene expressions (Farago *et al.,* 2011). Gliomas can occur anywhere in the brain but usually affect the cerebral hemispheres. Primary glioblastoma are associated with a high rate of overexpression or mutation of the epidermal growth factor (EGF) receptor (Watanabe *et al.,* 1996). The physicochemical properties of a drug have an important impact on its pharmacokinetic and metabolic fate in the body, and so a good understanding of these properties, coupled with their measurement and prediction, are crucial for a successful drug discovery programme. All the identified fatty acids from polychaete, passed the ADME screening and were in the acceptable range defined for human use. The predicted drug likeliness of the fatty acids follow the Lipinski "Rule of Five", all the parameter values for a compound *i.e.* Log P <5, H-bond donors <5 , H-bond acceptors <10 and molecular weight < 500 g/mol suggested that the compounds might have good absorption or permeability properties (Lipinski *et al.,* 2001). PUFAs have been shown to limit glioma cell growth, stimulate apoptosis and lipid peroxidation (Leavera *et al.,* 2004). Hence, present findings unveil and further substantiate PUFAs as better alternative than the previously reported compounds.

The idea of finding cure from known pharmacologically active natural occurring compounds is intriguing and practical. EGFR and its mutant version of EGFRvIII are known to be overexpressed case of GBM resulting in high rate of proliferation and failure in cell cycle arrest. EGFRvIII is expressed in about 62% of GBM cases and are self-activating receptors independent of ligands. The GC-MS identified 29 fatty acids (PUFA, MUFA and SFA) from *N. abuima* were analyzed and taken along with the previously reported potential anticancer compounds to dock against the GBM target proteins EphA2, EGFR and EGFRvIII. Molecular docking results shows the potency of fatty acid as effective inhibitor of GBM and the ADME screening further approves the acceptability of these fatty acids for human usage. Hence, from the present study it is discerned that the fatty acids especially polyunsaturated fatty acids could be an important source for the development of more effective tumor theraputics. Thus, a better understanding of the close interaction(s) between EGFR proteins and fatty acids (PUFAs), their metabolites may pave way for the development of newer therapeutic strategies in GBM. However, further *in vitro* and *in vivo* experiments are needed to demonstrate the effectiveness of these polychaete-derived fatty acids against GBM.

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