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RESEARCH ARTICLE

In-Silico and Pharmacokinetic Studies of Bioactive Constituents from Green Marine Macro Algae *Valoniopsis pachynema* Against Psoriasis

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Abstract

Objectives: To validate the pharmacokinetic effects of the bioactive constituents present in green marine algae *Valoniopsis pachynema* for treating Psoriasis by *in silco* methods. **Methods:** The green marine macroalga was collected from the coastal areas of Ramanathapuram, Tamil Nadu and it was confirmed as *Valoniopsis pachynema* by the CSIR- Central Marine Algal Research Station, Ramanathapuram. The GC-MS analysis of the algal extract revealed the presence of 7 different functional compounds and these ligands molecules were used for molecular docking studies with TNF-α, which is majorly involved in causing Psoriasis. The ADME Predictions of 7 compounds were computed by SwissADME and PreADMET tools. The physico-chemical properties and drug-likeness predictions of the compounds 1–7 were analysed by Molinspiration. The Molecular Docking scores and the residual amino acid interactions of 7 compounds against crystal structure of TNF-α (2AZ5) binding domain were analysed by Autodock Vina. **Findings :** The potential functional compounds present in the algal extract were found to be Cycloartenol (CAL), Eicosane (ESN), Phytol (PTL), Cis-13 Eicosenoic acid (CEA), Octadecanoic acid (ODA), Squalene (SQL) and Neophytadiene (NPN). The pharmacokinetic properties and docking studies of all 7 different ligands revealed Cycloartenol as the effective ligand having inhibitor constant 3.05μM and binding energy of -7.52 kcal/mol against TNF-α and it was found to interact with the amino acids ILE 136 and PRO 139 present in the active site domain of the protein. According to the *in silico* studies, the active component (Cycloartenol (CAL) in *Valoniopsis pachynema* reduces the amount of tumour necrosis factor which is produced in chronic skin inflammation. Thus, the seaweed metabolites were found to be the promising candidates

as TNF-inhibitors for the treatment of Psoriasis. **Novelty:** The pharmacological effect of the bioactive compounds present in marine macroalgae *V. pachynema* against skin inflammatory illnesses, particularly Psoriasis, has not been investigated yet.

Keywords: Psoriasis; Chronic skin inflammation; In silico; Valoniopsis pachynema; Bioactive constituents; TNF α

1 Introduction

Algae are creatures capable of creating bioactive molecules that can be used to create innovative medical and pharmaceutical drugs, as well as functional foods [1,2]. Algae's natural abundance, diversified origin, and worldwide availability make it a vital source of biologically useful components. Bioactive components found in edible seaweeds include soluble dietary fibres, peptides, vitamins, proteins, antioxidants and polyunsaturated fatty acids [3]. These seaweeds were previously primarily employed as thickening and gelling agents in the pharmaceutical and food sectors; however, new study has revealed their potential in alternative medicine. The anticancer, antihypertensive, antidiabetic, anticoagulant, antioxidant, immunomodulatory, anti-inflammatory, immunomodulatory, anti-hyperlipidemic, anti-microbial and tissue healing abilities have been demonstrated in red, brown, and green seaweeds [4,5]. Even though the literature works on anti-inflammatory efficacy of bioactive compounds derived from marine algae is still fewer in number.

Conventionally, medications such as cyclosporin, apremilast, and methotrexate were utilized to treat infections in Psoriasis [6]. Hence, the natural-source medications were gaining popularity. The inflammatory response is often characterized by an increase in the synthesis of prostaglandins, pro-inflammatory cytokines, and reactive oxygen species. Among those, Tumor Necrosis Factor has been reported as a major cytokine driving inflammation in the pathophysiology of psoriasis [7,8].

Currently, rigorous screening of anti-inflammatory medications derived from marine algae is being conducted and is predicted to exhibit reduced adverse effects in patients with inflammatory illnesses, particularly chronic inflammation [9,10]. Literature works on bio-active compounds isolated from various marine macroalgae have proved to act as potential anti-inflammatory agents [11–13]. Though work on marine algae has been reported *in vitro* and *in vivo*, relatively few studies have been attempted on the green marine macro algae *V. pachynema*. According to our understanding, this is the first publication on *in silico* investigations on the pharmacokinetic characteristics of functional compounds generated from *V. pachynema* extract, and we hope to prove the bioactive molecule's anti-inflammatory efficacy in the treatment of Psoriasis.

2 Materials and methods

2.1 Collection of Marine algae

The marine green macroalgae *Valoniopsis pachynema* was fetched from the shallow internal zone of the Mandapam area (Lat 9.2770° N and Lon 79.1252° E) in Ramanathapuram district, located in the east-coastal regions of Tamil Nadu. The obtained algae were rinsed with distilled water to completely remove the marks of the sand and other contaminations, dried in the shade, and stored appropriately for later study.

2.2 Validation of Marine algae

The obtained algae was examined by Dr. V. Veeragurunathan, senior scientist, CSIR- Central Marine Algal Research Station, in Mandapam, Ramanathapuram district, Tamil Nadu, India. The obtained algae was recognized as *V. pachynema*, was employed for various examination techniques.

2.3 Fabrication of Molecules involved in In silico analysis

2.3.1 Preparation of Ligands

The chemical structure of the compounds with its structure, molecular formula (M.F), and SMILES were obtained from the PubChem compound database (http://PubChem.ncbi.nlm.nih.gov) with SDF format (.sdf) Table 1. For docking analysis, the compounds were optimized by Drug Discovery Studio version 3.0 software and UCSF Chimera tool, respectively, and the obtained results were saved in SDF (.sdf) format. These coordinates had minimum energy and stable conformation; later, the ligands were converted to a PDBQT file to generate atomic coordinates.

2.3.2 Preparation of Macromolecule

The Crystal Structure of TNF-alpha, which is retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/) (PDB code: 2AZ5), serves as docking receptors with a resolution of 2.10 Å. All the bound ligands and water molecules were removed from the active site of the receptor.

2.4 Determination of Ligand properties and validation of ligand interactions with TNF-α by *In silico* analysis

2.4.1 In silico Drug-Likeness

Drug-likeness is a prediction that determines whether a particular pharmacological agent has properties consistent with being an orally active drug. This prediction is based on an already established concept called the Lipinski rule of five. Based on Lipinski's Rule of Five, (i) Molecular weight (<500 Daltons), (ii) Number of hydrogen bond donors (<5), (iii) Number of hydrogen bond acceptors(<10), (iv) Log P (<5), and (v) Molar refractivity (<140)[14] was identified and then applied to select probable compounds with maximum bioavailability by Molinspiration tool (www.molinspiration.com). For that, input was given in the form of smiles of compounds. Molinspiration calculates 13 descriptors, which are logP, polar surface area, mass, range of atoms, range of O or N, range of OH, range of rotatable bonds, volume, drug likeness including G-protein-coupled receptors (GPCR) ligands, ion channel modulator, enzymes and nuclear receptors, and range of violations to Lipinski's rule[15].

2.4.2 Prediction of Pharmacokinetic properties

The drug discovery and development process has been extensively used in ADMET screening. *In silico* ADMET (absorption, distribution, metabolism, excretion, and toxicity) analyses were performed to analyse the pharmacokinetic properties of the potent hits, such as absorption (water solubility, gastrointestinal absorption, and skin permeability), distribution blood–brain barrier (BBB) and volume of distribution at steady-state. Structures of compounds (1–7) were submitted to the SwissADME tool and converted to their canonical simplified molecular input line entry system (SMILES) to estimate the *in silico* pharmacokinetic parameters and other molecular properties based on the methodology reported by Ahmed et al., 2019[16].

SwissADME predictor provided information on the numbers of hydrogen donors, hydrogen acceptors and rotatable bonds, total polar surface area, and the synthetic accessibility of the ligands[15]. The factors such as plasma protein binding and blood-brain barrier penetration (BBB) were used for the prediction of the distribution of drugs. The selected compounds were screened against enzymes of the cytochrome P450 family, which include CYP3A4, CYP2D6, CYP2C9, and CYP2C19. These are the most important enzymes for the metabolism of drugs in humans. The selection of compounds as drug candidates was determined by a parameter called drug score. Only compounds without violating the screenings were used for the molecular docking analysis.

2.4.3 Molecular Docking Analysis (Auto Dock Vina)

The molecular docking studies were carried out using Auto Dock Vina. Docking studies with the standard protocol were used to dock the compounds (1–7) against the active site of the crystal structure of TNF-alpha (PDB ID: 2AZ5)[17]. In short, polar hydrogen atoms and Kohlman charges were assigned to the receptor proteins. Gasteiger partial charges were designated for ligands, and non-polar hydrogen atoms were merged. All torsions for ligands were allowed to rotate during the docking procedure. The program Auto Grid was used to generate the grid maps. Each grid was centred on the structure of the corresponding receptor. The grid dimensions were 80×80×80 Å with points separated by 0.375 Å. Random starting

positions, orientations, and torsions were used for all ligands. The translation, quaternion, and torsion steps were taken from default values indicated in Auto Dock.

The Lamarckian genetic algorithm method was used for minimization using default parameters. The standard docking protocol for rigid and flexible ligand docking consisted of 50 runs, using an initial population of 150 randomly placed individuals, with 2.5×10^6 energy evaluations, a maximum number of 27000 iterations, mutation rate of 0.02, crossover rate of 0.80, and an elitism value of 1.

The docked results were subjected to cluster analysis with an RMS tolerance of 1.0. The cluster with the lowest binding energy and the greatest number of conformations was chosen as the docked pose for that specific ligand. The binding energy of each cluster is the mean binding energy of all the conformations present inside the cluster. For each ligand, nine alternative conformations were created, scored using the Auto Dock Vina. The post-docking analysis used PyMOL to analyze the interactions among the target receptor and the ligands by identifying the conformations with the lowest free binding energy.

3 Results

The marine green macro-alga isolated from east-coastal areas of Ramanathapuram, Tamil Nadu was shown in Figure 1. Table 1 shows the details of the bio active compounds (ligands) selected for the study. The Swiss ADME interpretation demonstrated that all the ligand molecules (1–7) agree with the rule of Lipinski, with one violation shown in Table 2. The interaction with CYP inferred that all the ligands are CYP2C19, CYP1A2, and CYP2C9 inhibitors. Compounds 1, 3, 5, and 6 were observed to be the significant inhibitors for CYP2D6, whereas ligands 2, 4, and 7 were most likely non-inhibitors of CYP2D6. For CYP3A4, compounds 2 and 7 were shown to be the non-inhibitors, whereas ligands 1, 3-6 were observed as potential inhibitors (Table 2).

Fig 1. Distinctive morphology of the marine macro green algae *Valoniopsis pachynema* Preparation of Ligands

Table 1. Details of the compound selected for the study

S. No	Ligands	Canonical SMILES
01	Cycloartenol	CC(C)CCCC(C)C1CCC2(C1(CCC34C2CCC5C3(C4)CCC(C5(C)C)O)C)C
02	Eicosane	CCCCCCCCCCCCCCCCCCCC
03	Phytol	CC(C)CCCC(C)CCCC(C)CCCC(=CCO)C
04	Cis-13 Eicosenoic acid	CCCCCCC=CCCCCCCCCCCCC(=O)O
05	Octadecanoic acid	CCCCCCCCCCCCCCCCCC(=O)O
06	Squalene	CC(=CCCC(=CCCC(=CCCC=C(C)CCC=C(C)CCC=C(C)C)C)C)C
07	Neophytadiene	CC(C)CCCC(C)CCCC(C)CCCC(=C)C=C

A ligand molecule holding a bioactivity score of more than zero is most likely to possess considerable biological activities. At the same time, values (-0.50 to 0.00) are expected to be somewhat active, and if the score is less than (-0.50), it is presumed

Table 2. ADME Predictions of Compounds 1–7, Computed by SwissADME and PreADMET

S. No	CYP Inhibitors							Pharmacokinetics					Lipinski Rule Violations
	P-gp Substrate	CYP1A2	CYP2C19	CYP2C9	CYP2D6	GIA	BBB	Log K_p (cm/s)	S + LogP	S + LogD	Diff Coeff	M logP	
01	Yes	Yes	Yes	Yes	Yes	Low	No	-1.65	10.208	10.208	0.543	4.124	Yes / 1
02	Yes	No	No	No	No	Low	No	-0.60	10.372	10.372	0.621	3.378	Yes / 1
03	No	Yes	Yes	Yes	Yes	Low	No	-2.29	7.986	7.986	0.621	5.304	Yes / 1
04	Yes	No	Yes	No	No	Low	No	-2.00	8.030	5.764	0.621	4.721	Yes / 1
05	Yes	Yes	Yes	Yes	Yes	High	No	-2.19	7.572	5.306	0.653	4.369	Yes / 1
06	No	Yes	Yes	Yes	Yes	Low	No	-0.58	11.049	11.049	0.512	7.925	Yes / 1
07	No	No	Yes	No	No	Low	No	-1.17	9.033	9.033	0.633	6.213	Yes / 1

to be inactive[18]. The selected compounds (1 and 4) have a good, acceptable range of Kinase inhibitors, GPCR, enzyme link, nuclear receptor ligand, and ion channel modulators (Table 3).

Table 3. Drug-Likeness Predictions of Compounds 1–7, Computed by Molinspiration

S. No	Ligands	Bio-activity Properties					
		GPCR Ligand	Ion Channel Modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
01	Cycloartenol	0.22	0.08	-0.38	0.78	0.19	0.58
02	Eicosane	-0.04	0.00	-0.14	-0.05	-0.11	0.03
03	Phytol	0.11	0.16	-0.32	0.35	0.00	0.31
04	Cis-13 Eicosenoic acid	0.21	0.07	-0.14	0.28	0.14	0.25
05	Octadecanoic acid	0.11	0.05	-0.20	0.17	0.06	0.20
06	Squalene	0.04	0.01	-0.10	0.19	-0.03	0.16
07	Neophytadiene	-0.12	-0.02	-0.35	0.20	-0.11	0.14

The Kp values of each and every ligand molecule lie within the range of –0.58 to –2.29 cm/s stating low amount of skin permeability. The predicted logP values of ligands 1-5 confirmed that they have maximum lipophilicity. The physico-chemical properties prediction parameters from Molinspiration showed that the compounds 1, 4 and 5 have high gastrointestinal (G.I.) absorption, and with no blood–brain barrier (BBB) permeation (Table 4) and no compounds are substrates of permeability glycoprotein (P-gp).

Table 4. Physio-Chemical Properties of Compounds 1–7 computed by Molinspiration

S. No	Ligands	Physio-Chemical Properties								
		Molecular Formula	Molecular Weight (g/mol)	HBA	HBD	Molar Refractivity	TPSA (Å)	Rotatable bonds	GIA	BBB
01	Cycloartenol	$C_{30}H_{52}O$	428.73	1	1	135.62	20.23	05	high	No
02	Eicosane	$C_{20}H_{42}$	282.55	0	0	98.25	00.00	17	Low	No
03	Phytol	$C_{20}H_{40}O$	296.53	1	1	98.94	20.23	13	Low	No
04	Cis-13 Eicosenoic acid	$C_{20}H_{38}O_2$	310.51	2	1	99.55	37.30	17	high	No
05	Octadecanoic acid	$C_{18}H_{36}O_2$	284.48	2	1	90.41	37.30	16	High	No
06	Squalene	$C_{30}H_{50}$	410.72	0	0	143.48	00.00	15	Low	No
07	Neophytadiene	$C_{20}H_{38}$	278.52	0	0	97.31	00.00	13	Low	No

3.1 Molecular Docking against TNF-alpha

Molecular docking analysis of isolated compounds showed good docking scores within the active site of the crystal structure of TNF-alpha **(PDB ID: 2AZ5).** Compounds 1 and 5 (−7.52, −7.28 kcal/mol) showed better docking affinity. The structure of ligands and their interactions with receptor were shown in Figures 2 and 3 respectively.

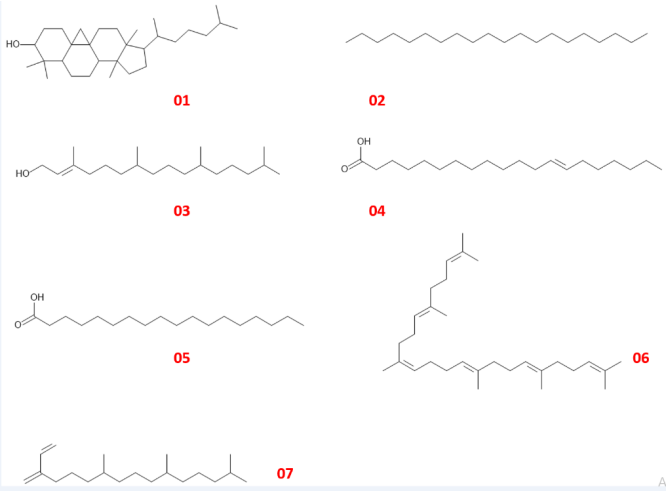

Fig 2. 2D structures of isolated compounds (01) Cycloartenol (02) Eicosane (03) Phytol (04) Cis-13 Eicosenoic acid (05) Octadecanoic acid (06) Squalene (07) Neophytadiene

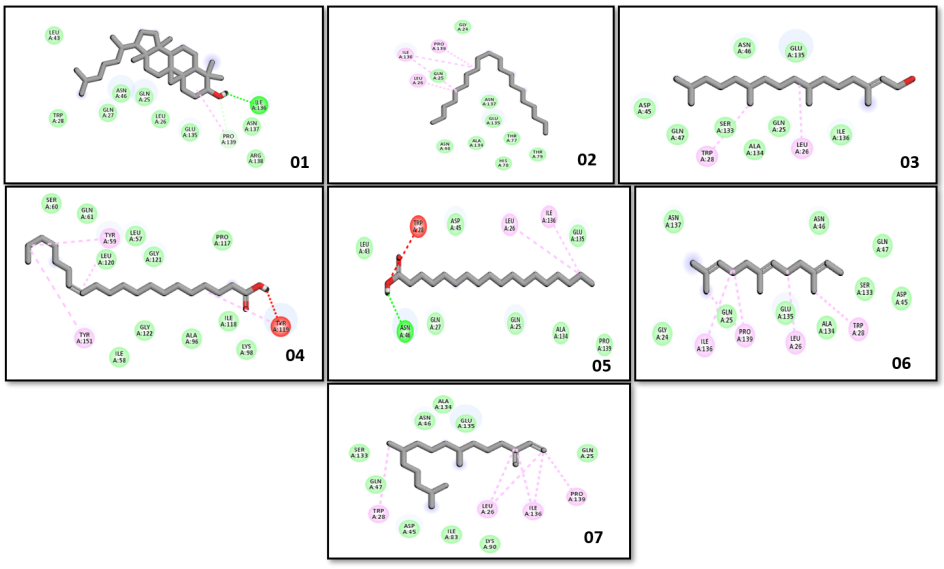

Fig 3. Molecular docking interactions of compounds (1–7) against the Crystal Structure ofthe TNF-alpha(2AZ5) Binding Domain

Compound 1 formed a hydrogen bond interaction with ILE 136 and residual hydrophobic interaction with PRO 139. Similarly, compound 5 reflected one hydrogen bond with ASN 46 and residual hydrophobic interactions with amino acids ILE 136, LEU 26, and TRP 28. However, compounds 2, 4, 6, and 7 do not show the crucial interactions with the receptor. In silico docking results confirmed that compound (ligand) 1 [Cycloartenol (CAL)] has the least docked score (−7.52 kcal/mol), suggesting that the determined compound is promising inhibitor of TNF-α which plays a crucial role in chronic skin inflammation. Figure 4 illustrates the molecular docking study of Cycloartenol (CAL)) against the Crystal Structure of TNF-alpha(2AZ5) Binding Domain and Table 5 represents the docking scores of all ligands with residual amino acid interaction.

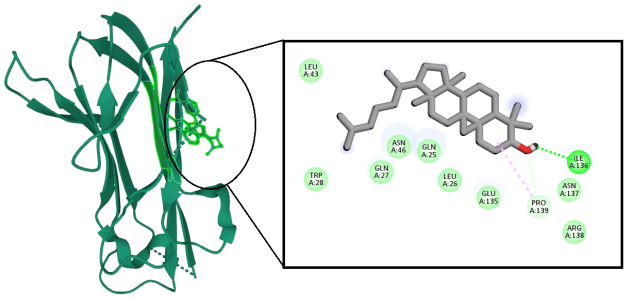

Fig 4. 2D and 3D molecular interaction view of the compound 1(Cycloartenol (CAL)) against the Crystal Structure of TNF-alpha(2AZ5) Binding Domain

Table 5. Molecular Docking Scores and Residual Amino Acid Interactions of Compounds 1–7 Against Crystal Structure of TNF-alpha(2AZ5) Binding Domain

Protein	Ligand	Binding energy	Inhibitor constant	Interactions	
				Hydrogen Bond	Residual Hydrophobic/Pi-Cation/Pi-Anion/Pi-Alkyl Interactions
2AZ5	**Cycloartenol (CAL)**	**-7.52**	**3.05 μM**	**ILE 136**	**PRO 139**
2AZ5	Eicosane **(ESN)**	-3.28	3.96 mM	Nil	ILE 136, PRO 139, LEU 26
2AZ5	Phytol **(PTL)**	-3.01	6.27 mM	Nil	TRP 28, LEU 26
2AZ5	Cis-13 Eicosenoic acid **(CEA)**	-3.33	3.6 mM	Nil	TYR 59, TYR 119, TYR 151,
2AZ5	Octadecanoic acid **(ODA)**	-7.28	9.15 mM	**ASN 46**	ILE 136, LEU 26, TRP 28
2AZ5	Squalene **(SQL)**	-3.62	2.2 mM	Nil	Ile 136, Pro 139, Leu 26, Trp 28
2AZ5	Neophytadiene **(NPN)**	-4.00	1.17 mM	Nil	Ile 136, Pro 139, Leu 26, Trp 28

4 Discussion

The phylum Chlorophyta holds numerous organic compounds that are fascinating in pharmaceutical applications. For instance, Ripol et al.[19] reported anti-inflammatory potential of five different green seaweeds, such as *Rhizoclonium riparium*, *Chaetomorpha linum, Ulva intestinalis, Ulva prolifera* and *Ulva lactuca*. All these marine macro algae shows inhibition to the enzyme cyclooxygenase-2 (COX-2), responsible for inflammation[19]. Therefore, the marine algal extract appears promising for research on metabolites that may be helpful for anti-inflammatory treatment[18].

Valoniopsis panchynema studies as an anti-inflammatory agent are particularly gaining interest for the treatment of acute and chronic inflammation[20,21]. Marine sulfated polysaccharides, polyphenols and triterpenoids, have anti-coagulant, anti-inflammatory, anti-viral, and anti-tumor properties are essential in the pharmaceutical industry[22]. Researchers have extensively researched these bioactive components for their anti-inflammatory potential.

Fucoidan, a sulphated polysaccharide produced from marine algae, has been studied for its biological properties such as anti-inflammatory and anti-oxidative effects. Besides their significant antioxidant effects, algal phlorotannins and polyphenols contain a variety of biological activities. The principal bioactive chemicals discovered in marine algae are phlorotannins. Park et al.[23] claimed that phlorotannin, a notable bio-active component which was isolated from brown marine algae *Ecklonia cava*, has anti-inflammatory properties. These data imply that this compound's anti-inflammatory activities are connected to the suppression of cyclooxygenase-2 and pro-inflammatory cytokines (TNF- and IL-6).

Furthermore, researchers discovered that the therapeutic applications of c-phycocyanin derived from the blue-green algae *Spirulina platensis* that greatly suppressed the activation of LPS-induced nitrite and iNOS protein production, as well as the synthesis of TNF-. Work on fucoxanthin in a dose-dependent way inhibited the release of cytokines TNF-, IL-1, and IL-6.[24].

Cycloartenol glycosides extracted from the root regions of *Cimicifuga simplex* have been utilized effectively as an anti-inflammatory drug in studies. Their anti-inflammatory properties were shown *in vitro* by LPS-stimulated IL-23, IL-6, and TNF-gene production in RAW cells using the Q-PCR technique [25]. The current study's findings were similarly consistent with the results. As an outcome, the bioactive components extracted from marine algae could constitute as effective anti-inflammatory drugs.

Topical treatments offer various advantages over oral delivery. The pharmacokinetics are based on skin absorption, which avoids substantial first-pass metabolism and allows for immediate access and localisation to the site of action [26,27]. Shikov et al. [28] studied the pharmacokinetics of *Fucus vesiculosus* fucoidans following topical administration. Data show that a significant amount of fucoidan-based drug was retained in the skin after the topical dose and accumulated in the striated muscle, and that it showed dose-dependent inhibition, with efficacy at higher doses equal to diclofenac gel, a synthetically derived anti-inflammatory drug in treating inflammatory diseases. The current *in silico* investigation focuses on cycloartenol, a triterpenoid produced from the green marine algae. *V. pachynema*, as a potential anti-inflammatory drug and could be exploited in topical creams for better skin absorption.

A specific docking process performed between the receptor and the inhibitor control drug using a grid box. The prediction of the interaction's potency between the ligand and receptor with respect to the binding affinity score was estimated using the docking process. A stronger interplay existed between receptor-ligand was displayed by more negative value [29,30].

Based on the docking results, seaweed metabolites possess great potential to act as inhibitors of TNF-α since the binding energy or affinity score is relatively close to control. TNF α is increased during inflammation, it is hoped that the administration of *V. pachynema* can help normalize the protein levels. Similar results were concluded in a study performed by Giriwono et al. [31] where brown algal (*Sargassum* sp.) extract at a dose of 400 mg/kg significantly reduced the expression of TNF-α as the brown algae was enriched with active substances which included triterpenoid, tannin and fucoidan.

Molecular docking was used to show the binding affinity of each drug to TNF-. The more negative scoring of binding affinity imparted the sign of a stronger relationship [32]. The cycloartenol was docked with TNF-α in this instance, and the docking results were satisfactory with binding energies close to zero (-7.52), better skin penetration ability (-1.65cm/s), and a high distribution coefficient (10.208) with maximal gastrointestinal absorption in comparison to other ligands. Though there are various bioactive compounds studied for anti-inflammatory activity, this study determined Cycloartenol as the best ligand because it has higher pharmacokinetic characteristics and pharmacological potential for the treatment of skin inflammation, particularly psoriasis.

5 Conclusion

Seaweeds are a great source of bioactive substances that might be used to create innovative functional ingredients for food and could also be used to cure or prevent chronic illnesses. Furthermore, the diverse biological activities associated with marine algae-derived bioactive substances have the potential to increase their health-beneficial value in the food and pharmaceutical industries. In conclusion, *in silico* drug-likeness analysis, molecular docking, and ADMET characteristics of seven different bioactive compounds derived from the marine algae *Valoniopsis pachynema* revealed that cycloartenol, Cis-13 Eicosenoic acid, and Octadecanoic acid had the highest gastro-intestinal absorption and no blood brain barrier diffusion. In comparison to all other ligands, the drug-likeness model score for these physiologically active compounds revealed that Cycloartenol had the highest score close to zero (-7.52 kcal/mol) with maximum stability, high skin permeation (-1.65 cm/s) and distribution coefficient (10.208), indicating that they could act as an effective candidate for treating inflammation in Psoriasis.

Abbreviations

GIA – Gastrointestinal Absorption; BBB – Blood Brain Barrier; CYP – Cytochrome P450; Diff Coeff – Differential Coefficient; Log K_p – Skin Permeation; Log P – Partition Co-efficient b/w Aqueous & and Water; Log D – Distribution Co-efficient.

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