Journal of Biological Engineering Research and Review, 2018; 5(1): 13-23
ISSN: 2349-3232 Online
DOI: 10.5281/zenodo.15351670

Research Article

Computational analysis of interaction between seaweed-derived bioactive compounds and human aldose reductase as antidiabetic target

Tomisin Happy Ogunwa [1,2]

[1]*Centre for Bio-computing and Drug Development, Adekunle Ajasin University, Akungba-Akoko, Ondo State, Nigeria.*

[2]*Department of Biochemistry, Adekunle Ajasin University, Akungba-Akoko, Ondo State, Nigeria.*

E-mail: tomisin.ogunwa@aaua.edu.ng

ARTICLE INFO:

Article History:
Received: 09/03/2018
Revised: 30/05/2018
Accepted: 05/06/2018
Available Online: 15/06/2018

Keywords:
Seaweed, Aldose reductase, Diabetes, Computational analysis, Docking, Binding signature

Citation: Ogunwa TH. Computational analysis of interaction between seaweed-derived bioactive compounds and human aldose reductase as antidiabetic target. Journal of Biological Engineering Research and Review. 2018, 5(1), 13-23.

Abstract: Diabetes still remains a rampaging metabolic disorder without a cure and current attentions are focused on the management of its associated complications particularly in type 2 diabetes. The enzyme aldose reductase is one of the validated therapeutic targets in this regard. Seaweeds (brown algae) are known to have beneficial effect in the control of hyperglycemia and other secondary complications of diabetes. Using *in silico* tools, the current study analyzed the precise interaction of selected bioactive components obtained from seaweed with aldose reductase. In the results, the compounds conveniently occupied active-site pocket flanked by the three flexible loops on top the (α/β) 8 barrel, however with varied degree of penetration (depth) and binding energy values (-5.2 kcal/mol to -9.9 kcal/mol) compared to fidarestat, the reference ligand (-9.0 kcal/mol). The favorable interaction within the catalytic pocket with less ΔG values suggests that the compounds are unique inhibitors of the protein with competitive mechanism of inhibition. Eckol showed fidarestat-comparable penetration into the cleft establishing hydrogen bonds with the partly polar anion-binding pocket residues Tyr48, His110, Leu300, Ala299, hydrophobic bonds with the aromatic amino acids Trp20 and Trp219 as well as π-stacking interactions with Trp219. Few ligands with poor active-site penetration, for instance Phlorofucofuroeckol A, are associated with poor inhibitory effect. The precise interaction patterns obtained in the current study are crucial towards understanding the mechanism responsible for the antidiabetic activity of marine brown algae while the unique binding pattern obtained may provide insights into the differences in the potency (IC50) of these algae-derived compounds.

INTRODUCTION

Diabetes is one of the most common endocrine metabolic disorders characterized by elevated blood glucose level and can cause significant morbidity and mortality in humans due to its severe complications [1]. The disease is rapidly increasing worldwide and affecting all parts of the world. According to World Health Organization, the diabetic population is likely to increase up to 300 million or more by the year 2025 [2]. Despite the introduction of hypoglycemic agents from synthetic sources, diabetes and its secondary complications continue to be a major medical problem to people. Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas, biguanid es and glinides. Many of these therapeutic agents have a number of serious adverse effects making the all-time search for more effective and safer hypoglycemic agents an important area of investigation [3,4]. Apart from medicinal plant with hypoglycemic properties that have been used in folk medicine and traditional healing systems around the world [4], the marine seaweeds have also evolved as another source of natural antidiabetic agents [5]. The preference of natural compounds for diabetes treatment mostly among people across the developing nations of the World is based on their cheaper cost and reduced adverse effects.

The human aldose reductase is a 36 kDa protein which is widely distributed in diverse tissues where it is responsible for catalytic reduction of reactive aldehydes formed from oxidative degradation of amino acids, fatty acids, and carbohydrates using NADPH as reducing cofactor [6]. The enzyme also catalyzes the rate limiting step in the polyol pathway; a metabolic pathway for the conversion of excess glucose in hyperglycemia to fructose via the intermediate sorbitol. An increased activity of this protein is observed in diabetes which eventually results in higher concentration of sorbitol that can accumulate in organs of the body including the lens [7,8]. In addition, the elevated turnover rate along the polyol pathway has been related to various biochemical compromises, including oxidative and osmotic stress,

perturbation of the NAD+/NADH ratio, formation of advanced glycosylated end products (AGEs) as well as activation of kinase signaling [9]. These characteristic imbalances play major role in the severe secondary complications of diabetes like cataract, angiopathy, retinopathy, nephropathy and neuropathy. Inhibition of human aldose reductase therefore has evolved as a promising therapeutic concept to avert such complications of diabetes [9,10].

There is growing evidence of application of seaweeds as functional foods and drugs. Reports showed that marine seaweeds have long been used in folkloric medicine as a remedy for a variety of diseases [5, 11-13]. Recent laboratory studies are investigating marine algae as for numerous promising health benefits [14]. Seaweeds can serve as rich source of vitamins and minerals. They are also known to contain array of phytochemicals like the polyphenolic compounds which confer potent antioxidant properties on them [15]. Various constituents of seaweed such as polysaccharide, carotenoids and glycoproteins have been isolated and evaluated for specific biological activities *in vitro* and *in vivo*. The therapeutic effects reported for the marine algae and their diverse constituents so far include anti-diabetic, immunomodulatory, antitumor, antioxidant, anti-coagulant, hepatoprotective and anti-hypercholesterolemic activities [16-19]. Among the marine algae with such desirable pharmacological potentials are the brown algae *Eisenia bicyclis*, *Ecklonia stolonifera*, *Ecklonia maxima* and *Ecklonia cava*. The *Eisenia bicyclis* (*E. bicyclis*) is a perennial alga commonly found in the middle Pacific coast in Japan and Korea. Locally called 'arame' in Japan, the edible seaweed belongs to the family *Laminariaceae* and has been referred to as one of the phlorotannin-rich natural sources [20]. The reported therapeutic activities of this alga and its phlorotannin constituents are anticancer, anti-microbial, algicidal, anti-skin aging, tyrosinase inhibitory, anti-inflammatory, anti-diabetic, anti-hyperlipidemic, hepatoprotective, antioxidant, anti-Alzheimer's disease, anti-atherosclerosis, anti-allergic, nitrite-scavenging, angiotensive converting enzyme- and anti-plasmin inhibitory activities [21-24]. *Ecklonia stolonifera* (*E. stolonifera*) is another brown alga which is traditionally consumed in Japan. The seaweed has been reported to contain oxylipins and phlorotannins which are responsible for its known pharmacological effects such as hepatoprotective activity [25-28]. The *Ecklonia cava* (*E. cava*), which is also called 'sea trumpet', remains one of the edible and abundant seaweed with distribution in southern coast of Korea and Japan. This marine alga has diverse bioactivities including anti-allergic, antioxidant, anti-HIV, anti-proliferative, anti-inflammatory, anti-hypertensive, anti-diabetic and radioprotective effects [29-32]. It is also reported to exhibit inhibitory potential against hyaluronidase and matrix metalloproteinase enzymes [29]. Among the biologically active components identified in this seaweed are sulphated polysaccharides, phlorotannins, carotenoids, peptides and fucoidans while most of the bioactivities have been associated with the phlorotannins content of the alga. On the other hand, *Ecklonia maxima* (*E. maxima*) which is popularly known as 'sea bamboo' is distributed in the deep waters of Africa especially along the southern Atlantic coast of South Africa to northern Namibia [29]. It is the raw material for kelpak which is consumed locally as foodstuff. Antioxidant and anti-diabetic activities of this species have also been observed [33].

Considering the significant benefit of these seaweeds in diabetes management over the years and the implication of aldose reductase in complications of diabetes with the fact that no computational study has been reported on the interactions of seaweeds components to aldose reductase in the literature, it would be very relevant to carry out *in silico* experiment to corroborate the anti-hyperglycemic potential of seaweed and to unravel the precise molecular interaction of the algae-derived compounds with human aldose reductase. Therefore, the current study was designed to provide insights into molecular mechanism of interaction between selected anti-diabetic compounds previously isolated from marine brown algae and human aldose reductase using computational approach.

MATERIALS AND METHODS

In silico methods used in this study have been described previously [34].

Preparation of target protein

The crystal structure of human aldose reductase used in this research was retrieved from the Brookhaven protein data bank (http://www.rcsb.org/pdb). The starting coordinate was the protein crystal (PDB ID: 1EF3) found in complex with fidarestat, a potent competitive inhibitor of the enzyme. The protein structure was first visualized using the molecular graphics program PyMol intended for the structural visualization of proteins. Crystallographic water molecules which were found with structure were then deleted prior molecular docking procedure. The active site of the protein was identified with reference to the co-crystallized ligand.

Ligands selection, preparation and optimization

A total of seven (7) ligands were used in this docking study. Out of these compounds, six (6) were bioactive compounds obtained from marine seaweed while the other ligand was fidarestat (co-crystallized ligand) which was employed as a reference ligand. Identification and selection of the seaweed components was based on information from the literature. The chemical structures of these compounds: eckol (CID: 145937), phlorofucofuroeckol A (CID: 130976), 7-phloroeckol (CID: 10480940), dioxinodehydroeckol (CID: 10429214), phloroglucinol (CID: 359) and dieckol (CID: 3008868) were retrieved from NCBI PubChem database (http://www.ncbi.nlm.nih.gov/pccompound) and prepared using ChemAxon software (https://www.chemaxon.com). Marvin-Sketch v15.11.30 was used to sketch the 2D-coordinates of the ligands. The structures were then cleaned up in 2D and converted to 3D geometry using the Conformers suit of the software based on the Merck molecular force field (MMFF94). The MDL SDfile (.sdf) format of the ligands were finally docked into the active site of the targets using the AutoDock 4.2.

Validation of molecular docking protocol

A key strategy towards validation of docking procedure is to accurately regenerate both the pose and the molecular interaction of the co-crystallized ligand on the

crystallographically determined protein structure [30]. In this study, the ligand found at the binding site of the experimentally determined protein crystal was deleted. Then, the ligand (.sdf format) was separately prepared using Marvin sketch as described above and re-docked into the active site. The binding pose and molecular interaction pattern was compared to that of the x-ray diffraction crystal structure.

Molecular docking and scoring

For ligand docking and target-ligand complex analysis, Autodock Vina suite on PYMOL [35, 36] was used. First, based on the already present co-crystallized ligand in the pdb file, the inhibitor binding site was defined with grid parameters and coordinate of origin (x, y and z) set as described in Table 1 and Table 2 to include all the amino acid residues at the active site. This gives enough space to enhance adequate ligand rotation and translation. The spacing between grid points was maintained at 0.375 angstroms. All optimized ligands were docked to the active site of the protein. Throughout this experiment, the rotatable bonds of the ligands were set to be free, however the protein molecule was treated as rigid structure. A total of thirty (30) docking runs were performed for each ligand with the number of modes set to 10 so as to achieve more accurate and reliable results. The best results obtained based on the binding configuration and binding affinity were chosen for further analysis.

Data analysis

Protein-ligand complex visualization and snapshots were achieved using PYMOL while Ligplot was used to depict details of protein-ligand interactions. ProteinsPlus, an online server, was used to validate the interactions especially hydrogen bond, hydrophobic bond and pie-stacking interactions [38, 39].

Table 1. Grid center coordinates (X, Y and Z) used for the docking runs.

Receptor (PDB ID)	Centre X (Å)	Centre Y (Å)	Centre Z (Å)
1EF3	-8.62	40.82	-7.18

Table 2. Grid box spacing and parameters (X, Y and Z points) used in this study for the docking.

Receptor (PDB ID)	Spacing (Å)	X point (Å)	Y point (Å)	Z point (Å)
1EF3	0.375	100	100	100

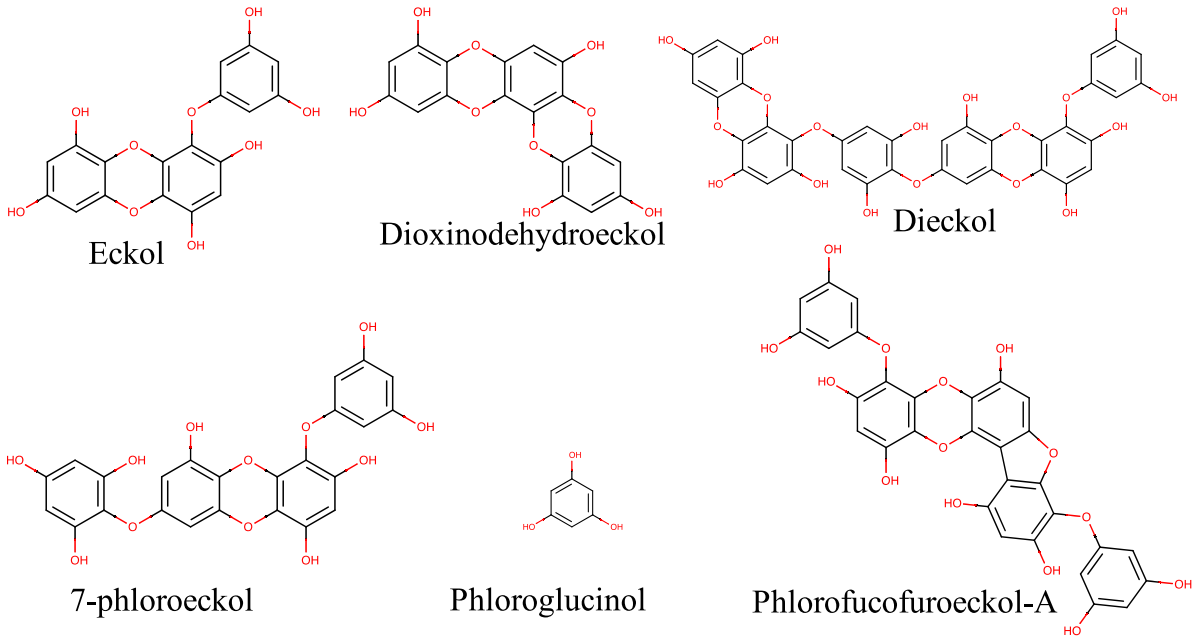


Fig. 1. 2D structure of the bioactive compounds evaluated in this study.

RESULTS AND DISCUSSION

Figure 1 shows the chemical structure of the ligands selected for this study. They are naturally-occurring phlorotannins found in marine algae for which numerous biological effects have been previously ascribed in the literature. Few authors have implicated these compounds as the bioactive ingredients responsible for the antidiabetic properties of seaweed extracts [5, 20, 22, 33]. However, the mechanisms of these claims have not been exhaustively ascertained. Therefore, research in this area is still encouraged most importantly to unravel the interaction profile of these compounds against diabetes-related proteins as targets. The current study was aimed at investigating the molecular interaction, binding mode and inhibitory potential of selected natural compounds, which had previously been isolated from various marine brown algae, on human aldose reductase. Table 3 summarizes the physicochemical parameters of the compounds (phlorotannins) which divulge them as biologically active chemical scaffolds.

To date, one of the strategies often adopted to investigate protein-ligand interactions is the *in silico* approach for generating the protein-ligand complexes [39]. Apart from the speed and relatively cheaper cost of

computational studies, the approach can also reveal the precise binding site and other binding properties of the ligands on the protein crystal structure. Meanwhile, it is important to verify the capacity of the *in silico* protocols to generate reliable and accurate binding pattern of the protein-ligand complexes. One of the acceptable ways for such validations is to test if the docking tools can successfully regenerate the ligand binding pose in a comparable pattern to the experimental results. As presented in Figure 2, both the configurational geometry and molecular interactions found in the crystallographic aldose reductase structure were reproduced by the docking protocols. This indicates that the docking tools and protocols used in the current study are reliable in generating accurate binding footprints and quality interaction between the protein and the selected ligands [40].

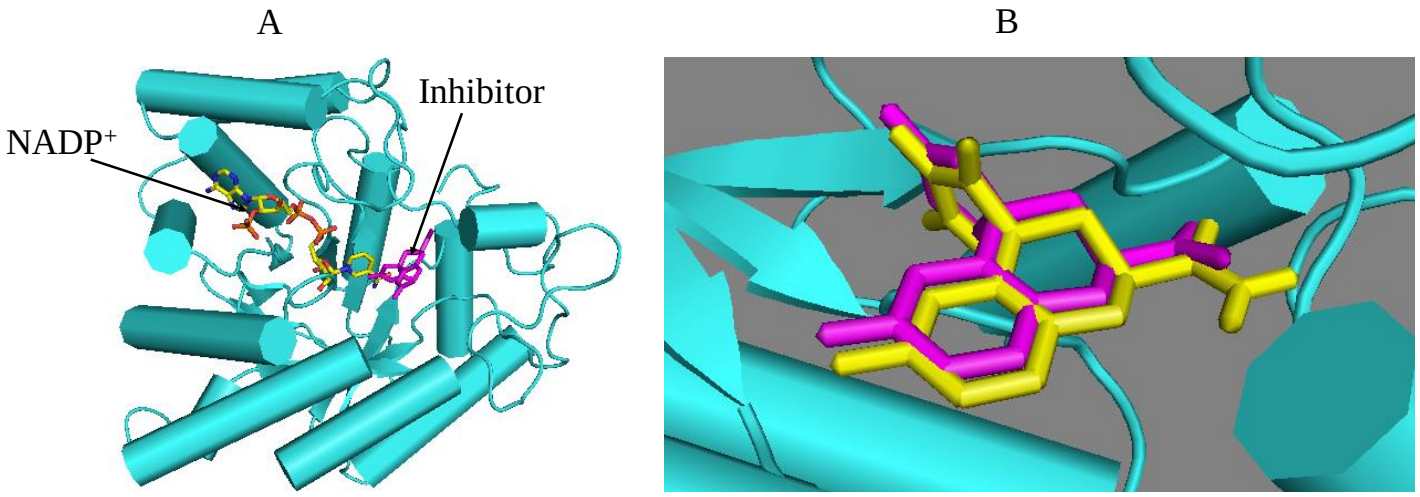


Fig. 2. (A) 3-Dimensional structure of human aldose reductase (PDB ID: 1EF3) with co-crystallized ligands (NADP+ and fidarestat). (B) Validation of docking protocol via regeneration of binding pose of the co-crystallized inhibitor. Co-crystallized ligand (yellow) and the docked ligand (magenta) shown in stick representation. NADP = Nicotinamide Adenosine Diphosphate.

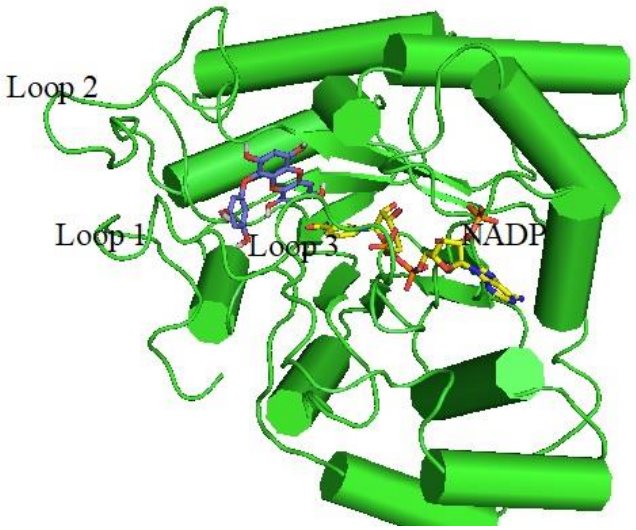


Fig. 3. Showing the three flexible loops forming the sides of human aldose reductase active site with a bound eckol molecule (blue stick). The active site of the protein is highly hydrophobic and contains few polar amino acid residues required for binding sugars with high specificity and affinity. NADP+ is shown in stick representation (yellow).

The implication of aldose reductase enzyme in degenerative complications of diabetes has made the enzyme a target for drugs used in the management of the disease. The compounds used in this study include eckol, dieckol, phlorofucofuroeckol A, 7-phloroeckol, phloroglucinol, and dioxinodehydroeckol. After molecular docking with the protein, eckol, a plorotannin molecule obtained from *E. bicyclis*, was found deeply inserted into the active-site pocket surrounded at the sides by three flexible loops located just over the proteins (α/β)8 barrel (Figure 3). In comparison with the reference ligand, investigation of the binding poses and the depth of active-site penetration for all the marine seaweed bioactive components within the protein catalytic site was carried out as shown in Figure 4. Fidarestat, which was used as the reference ligand in this study, was chosen because of previous reports showing that the inhibitor, with its spirohydantoin ring and a carbamoyl group, possessed higher activity and selectivity than other potent inhibitors of human aldose reductase [41]. The 3D structure of the protein, given in Figure 4A in complex with fidarestat (PDB ID: 1EF3) and phlorofucofuroeckol-A, reveals the active site as the preferable binding site for the all the ligands. Human aldose reductase active site has been completely described to consists of two sub-pockets, one comprising the residues reported to be involved in catalysis (Tyr48, Lys77, and His110) along with the cofactor nicotinamide moiety, while the second pocket formed by Trp111, Ala299, Leu300 and Phe122 is called specificity pocket [6]. It is known that the pattern of interaction between a protein target and its ligands contributes to the inhibitory mechanism and potency. The degree of such interactions can be measured as the binding energy which eventually suggest the affinity of the ligand to the protein. A molecule which can tightly bind to a protein might inhibit the function of the enzyme than one that binds weakly. The estimated binding energy values and amino acid residues involved in the molecular interactions in the current study are summarized in Table 4. It can be seen that the compounds display high potential to inhibit human aldose reductase at the active site.

Table 3. Physicochemical properties and plant sources of the bioactive compounds

Bioactive compounds	Chemical formula	Molecular weight	No of HB donor	No of HB acceptor	Rotatable bonds	Plant sources
Eckol	$C_{18}H_{12}O_9$	372.285	6	9	2	*E. bicyclis, E. stolonifera, E. maxima*
Dieckol	$C_{36}H_{22}O_{18}$	742.554	11	18	6	*E. bicyclis, E. stolonifera, E. cava*
7-phloroeckol	$C_{21}H_{16}O_{12}$	496.38	8	12	4	*E. cava, E. bicyclis, E. stolonifera*
Phloroglucinol	$C_6H_6O_3$	126.11	3	3	0	*E. bicyclis, E. maxima, E. stolonifera*
Dioxinodehydroeckol	$C_{18}H_{10}O_9$	370.269	5	9	0	*E. bicyclis, E. stolonifera*
Phlorofucofuroeckol A	$C_{30}H_{10}O_{14}$	602.46	9	14	4	*E. bicyclis, E. cava*

HB=Hydrogen bond

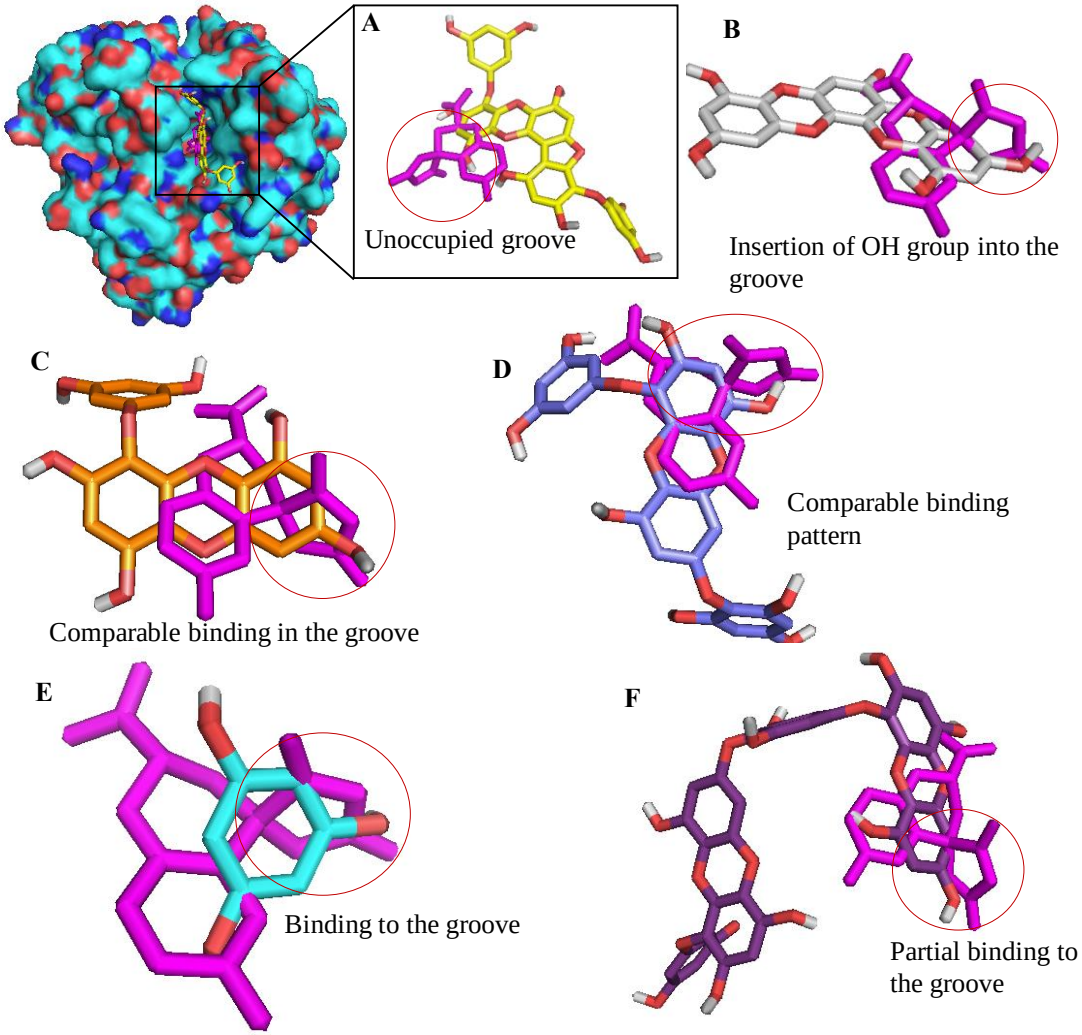


Fig. 4. Comparative analysis of binding signature of the algae antidiabetic compounds versus the reference ligand (magenta). (A) Phlorofucofuroeckol A, (B) Dioxinodehydroeckol, (C) Eckol, (D) 7-phloroeckol, (E) Phloroglucinol (F) Dieckol.

Among all the ligands selected for this *in silico* experiment, the best binding penetration into the active site of aldose reductase was observed for eckol (Figure 4C). This compound inserted the hydroxyl group of its dibenzodioxin linkage rings deep into the binding pocket in a manner comparable to the reference ligand. The other aromatic rings are positioned in the same location as the spirohydantoin moiety of fidarestat. With binding energy value of -9.0 kcal/mol, eckol is predicted as a suitable inhibitor of the enzyme which is in agreement with the IC50 value of 54.6 µM previously obtained for the compound against the enzyme *in*

vitro [44]. Hydrophilic interactions with His110, Ala299, Leu300, and Ty48 were seen in eckol-aldose reductase complex (Figure 5). Excitingly, participation of residues Tyr48, His110, and Trp111 in hydrogen bond network at the protein active site with known inhibitors has been robustly reported [42, 43]. The dimeric form of this compound (dieckol) similarly established extensive hydrogen bond with residues Trp20, Leu300, Ala299 and Asp216. The aromatic ring systems of dieckol and dioxinodehydroeckol were stacked on Trp 20. Hence, these data verify the significance of these amino acid residues in inhibitor binding to aldose reductase active site since these interactions are also found in inhibitor-bound crystal structures of the protein. Amino acid residues which formed the upper hydrophobic portion of the binding pocket, as contributed largely by Trp219 and Phe122, engaged the naturally-occurring compounds in hydrophobic interactions. The lesser binding energy (-9.8 kcal/mol) obtained for this dieckol (Table 4) and its comparable penetration at the active site compared to eckol and fidarestat (Figure 4F) indicate that dieckol is relatively more potent than eckol, a result that is consistent with the previous study showing IC50 of 42.39 μM for the compound [44].

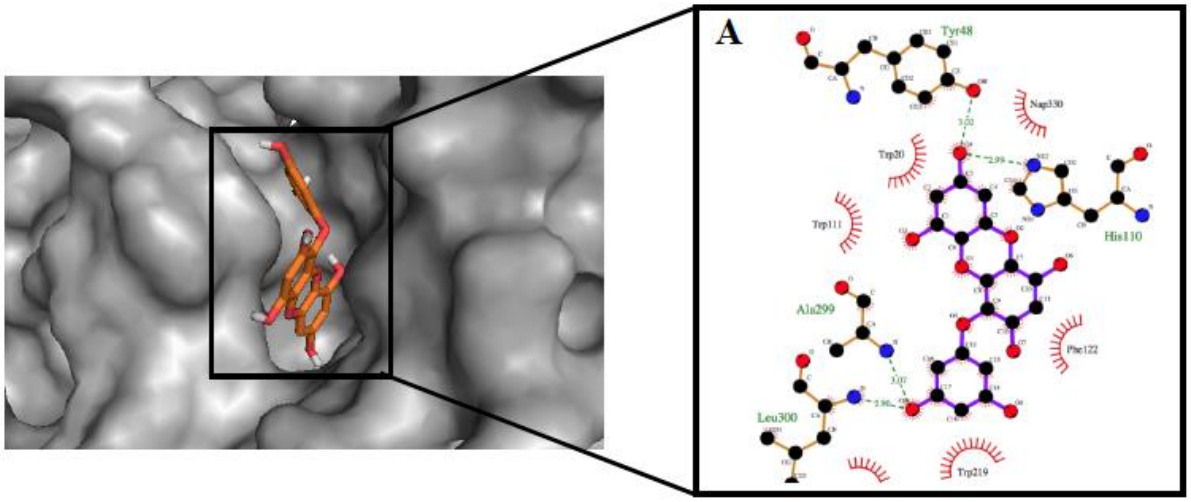
Table 4. Docking results and molecular interaction of seaweed components with aldose reductase

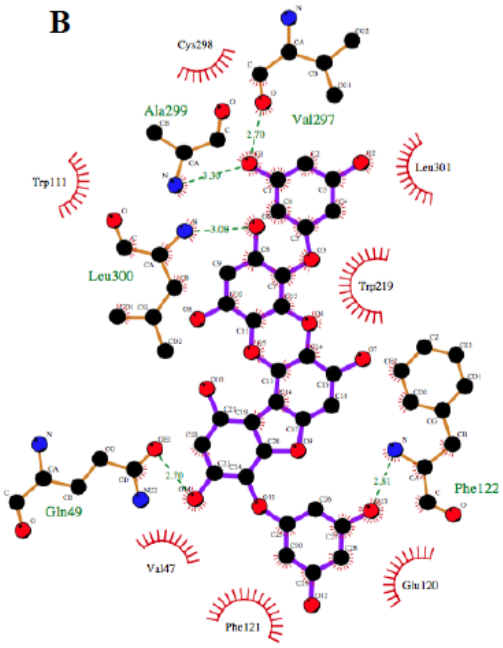
Seaweed compounds	Energy value (kcal/mol)	No of hydrogen bond	Residues involved in hydrogen bond formation	Bond length	Residues involved in hydrophobic interaction	Residues participating in π- stacking interactions
Eckol	-9.0	4	Ala299, Leu300, Tyr48, His110	3.07 2.90 3.02 2.99	Trp219, Trp20	Trp219
Dieckol	-9.8	4	Asp216, Ala299, Leu300, Trp20	2.84 3.11 2.83 3.24	Trp20	-
7-phloroeckol	-9.4	2	Ala299, Val47	3.09 2.78	Trp219	Trp20, Trp219
Dioxinodehydroeckol	-9.0	2	Leu300, Tyr48	2.84 3.24	Phe122, Leu300, Trp219, Trp20	Phe122
Phloroglucinol	-5.2	3	Trp111, His110, Tyr48	3.14 3.02 3.02	-	Trp20
Phlorofucofuroeckol-A	-9.9	5	Gln49, Phe122, Ala299, Leu300, Val297	2.70 2.81 3.30 3.08 2.70	Ph121, Phe122, Trp219	-
Fidarestat (Reference)	-9.0	4	Tyr48, Trp111 His110, Leu300	2.57 2.94 2.80 3.17	Trp219, Trp20	Trp20

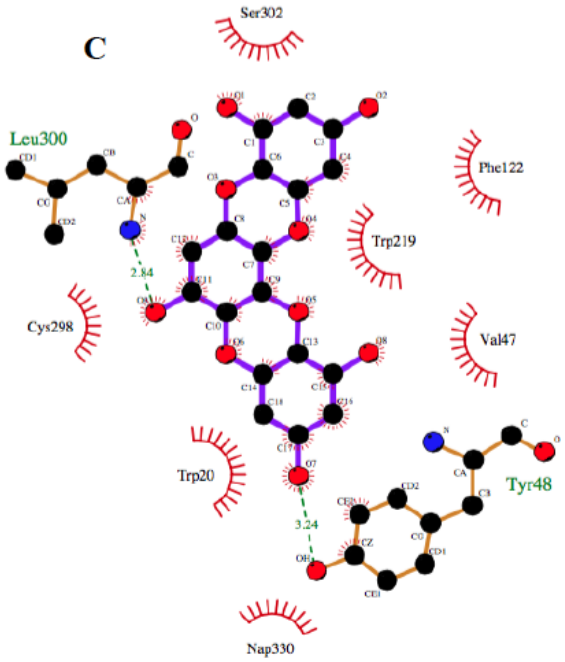
The less energy (ΔG) values and thus the high affinity predicted for dioxinodehydroeckol (-9.0 kcal/mol) in the current study is an indication of its potency in the inhibition of human aldose reductase. The finding is in agreement with an earlier report which claimed that the compound inhibited the catalytic function of aldose reductase with IC50 value of 21.95 μM [44]. Hydrogen bonds established between the hydroxyl group of Tyr48 and backbone NH group of Leu300 with the moieties of dioxinodehydroeckol (also known as eckstolonol) contributes to the complex formation and stability (Figure 5). Normally, the hydroxyl moiety of residue Tyr48 is known to protonate the oxygen atom of the enzyme substrate while His110 plays a role in orienting the substrate during catalysis [45]. Further observation of the obtained protein-dioxinodehydroeckol complex revealed that there is no interference with the $NADP^+$ binding pocket on the protein. Hence, the compound is not competitive with regards to the cofactor. In the available crystallographic structures of the protein, a $NADP^+$ cofactor is often found associating in an extended conformation across the protein binding pocket (barrel), inserting its nicotinamide ring into the bottom of a large cavity very close to the top of the barrel (Figure 3) which formed the active site around residues Cys298, His110 and Tyr48 [6].

In a related manner, 7-phloroeckol formed two hydrogen bonds but with amino acid residues Ala299 and Val47 while hydrophobic interaction was found with Trp219. These molecular interactions possibly account for aldolase-ligand complex stability and contribute to the inhibitory potential of the seaweed constituents. The binding energy value obtained from molecular docking for this compound was -9.4 kcal/mol which indicates its potential to block the catalytic function of the protein at the active site. Interestingly, this result is compatible with earlier reports from *in vitro* experiments [44]. 7-phloroeckol is one of the phlorotannins identified in *E. cava* and possibly play a crucial role in the antidiabetic and hypolipidemic effects of seaweed. Phloroglucinol and phlorofucofuroeckol-A formed three and four hydrogen bonds respectively with the enzyme at the binding pocket where they occupied without competing with the $NADP^+$. While phloroglucinol lacks hydrophobic interaction, phorofucofuroeckol-A formed three hydrophobic

bonds with Phe121, Phe122 and Trp219. These interactions are not unexpected since the active site of the aldose reductase is highly hydrophobic and contains only few polar residues that are required for binding substrates with high affinity and specificity. The estimated binding energy for the former was -9.9 kcal/mol and the later was -5.2 kcal/mol. The relatively smaller size of phloroglucinol with reduced number of moieties might contribute to its lower affinity as observed in the current study. The compound has reasonable inhibitory effect (IC50 72.54 µM) on the protein *in vitro* [44]. Although phlorofucofuroeckol A showed a lesser energy toward aldose reductase active site, its inability to deeply penetrate the binding pocket on the enzyme (Figure 4) may have resulted into the reduced inhibitory potential. Taken together, the selected bioactive compounds used in the current study displayed adequate potential to prevent diabetic complications through inhibition of aldose reductase activity in the polyol metabolic pathway (Figure 6). This represents at least one of the mechanisms underlying the antidiabetic effects of the marine algae.







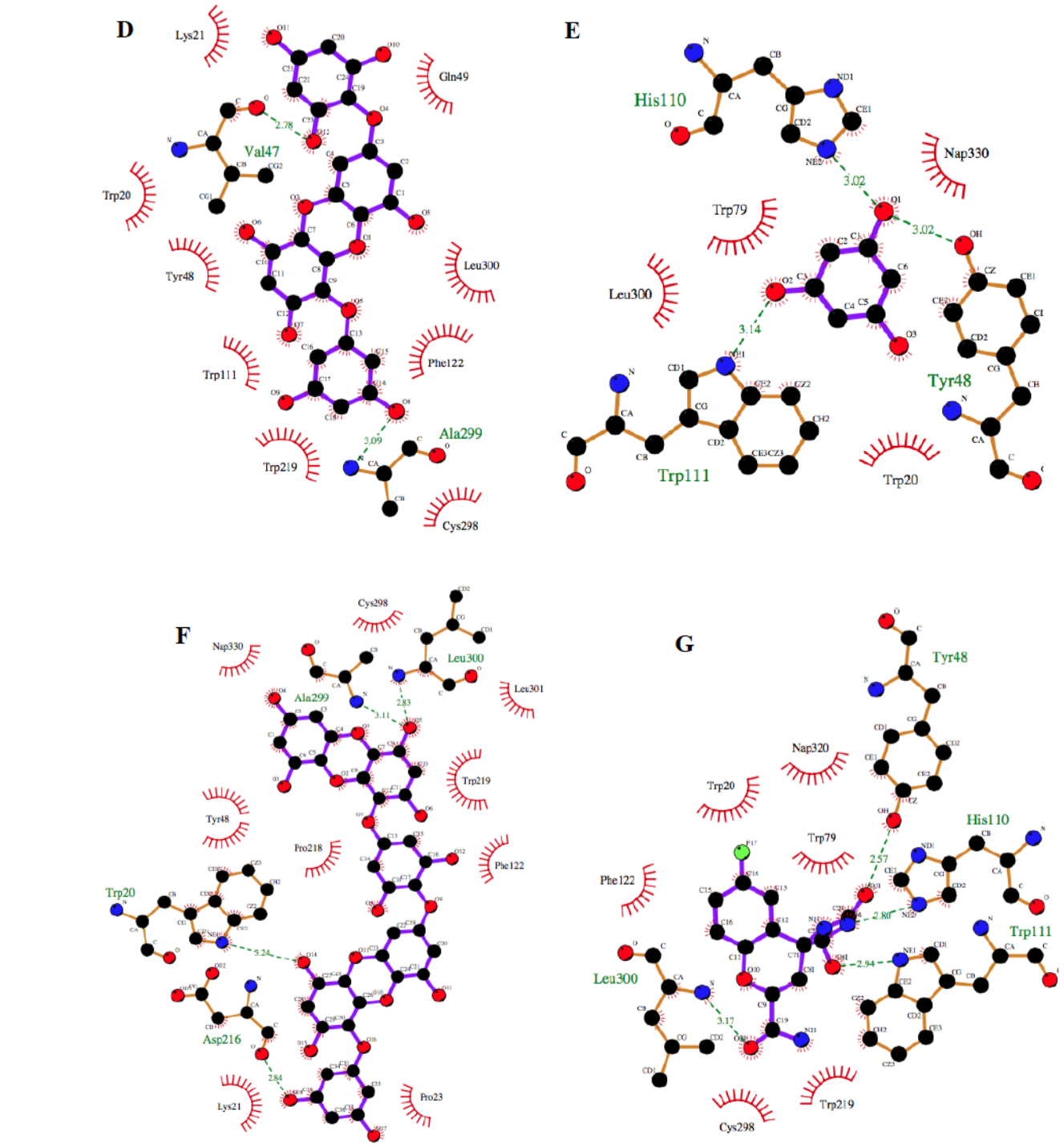
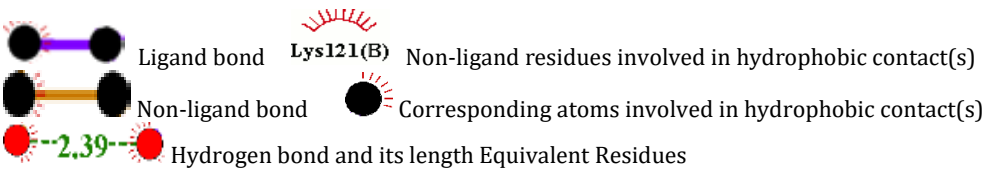


Fig. 5. Molecular interaction of the ligands within the active site of human aldose reductase. The interactions were depicted using ligplus software showing only important residues for binding within the active site that; carbons are in black, oxygens in red and nitrogens in blue. (A) Eckol, (B) Phlorofucofuroeckol A, (C) Dioxinodehydroeckol, (D) 7-phloroeckol, (E) Phloroglucinol (F) Dieckol, (G) Fidarestat.



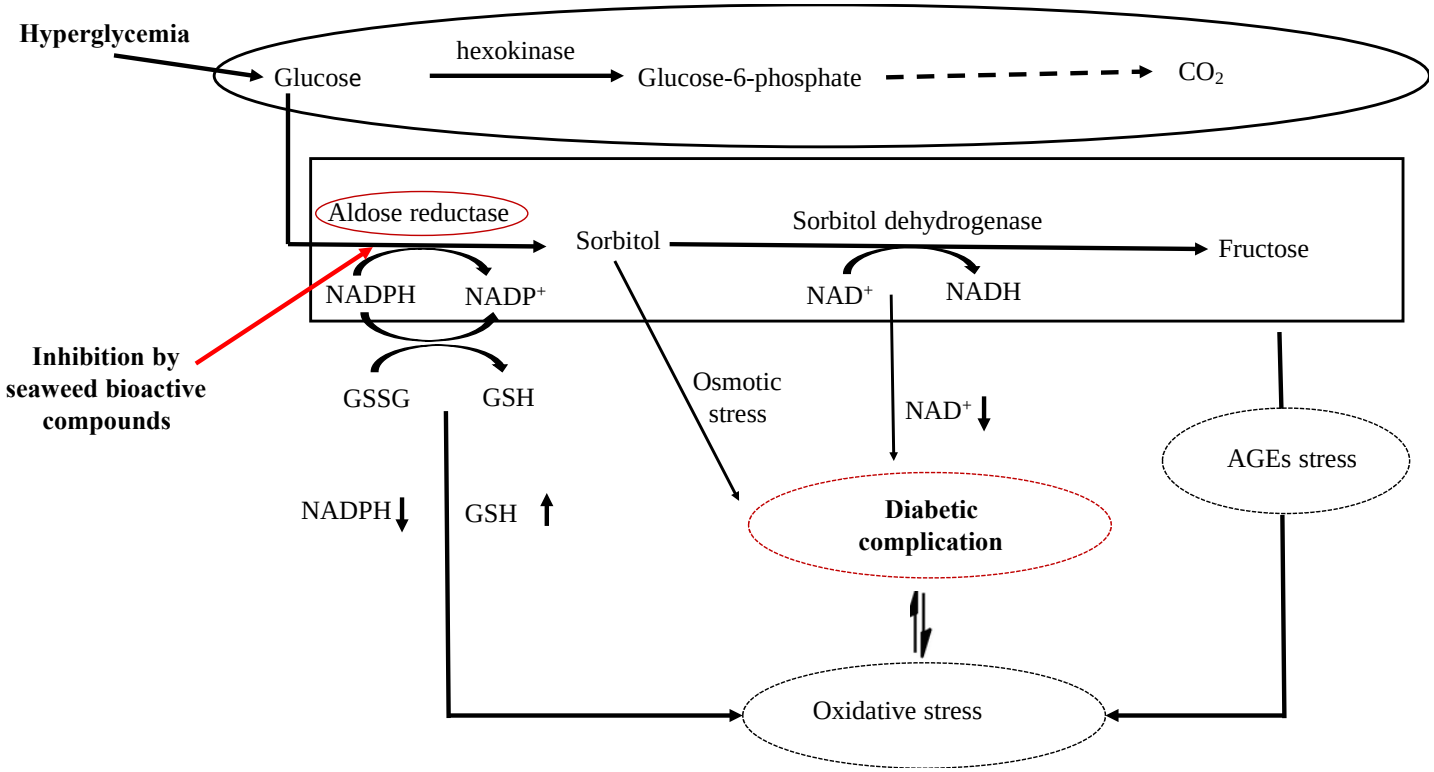


Fig. 6. Inhibition of the polyol metabolic pathway of glucose via blockage of aldose reductase activity by seaweed-derived compounds. AGEs (Advanced Glycation End Products), GSH (reduced glutathione), GSSG (oxidized glutathione), NADPH (nicotinamide adenine dinucleotide phosphate), NADH (nicotinamide adenine dinucleotide) while the upward and downward arrows indicate increase/decrease in quantity of biomolecules respectively.

CONCLUSION

In this study, the binding signature and interaction pattern of naturally-occurring bioactive ingredients isolated from various marine algae on the active site of aldose reductase were analyzed. The compounds showed favorable affinity, suitable binding poses and reasonable inhibitory potential against the protein within the active site. However, they were not competitive with $NADP^+$ in the binding cleft. The subtle differences observed in their binding poses may be responsible for the variations in the inhibitory potency against the protein *in vitro*. Eckol displayed the best binding pose to the enzyme active site which is comparable to fidarestat, a known potent inhibitor of the target which was used as the reference ligand. Results obtained for all the compounds verify the significance of the hydrophilic residues Tyr48, Trp111, His110, Leu300 in the enzyme inhibition majorly through hydrogen bond formation. According to the results, inhibition of aldose reductase contributes at least in part to the antidiabetic activity of marine brown algae while the chemical scaffold of the seaweed-derived compounds may contribute to the design and development of new antidiabetic agents targeting human aldose reductase.

ACKNOWLEDGEMENT

The technical support received from all researchers at the Centre for Bio-computing and Drug Development (CBDD), Adekunle Ajasin University, Akungba-Akoko, Ondo state, Nigeria is hereby acknowledged.

COMPETING INTERESTS

Author declares that no competing interests exist.

REFERENCES

1. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab. 2016; 20(4):546-551.
2. WHO. Global status report on noncommunicable diseases. World Health Organization. Geneva; 2010.
3. Omonkhua AA, Onoagbe IO, Fajimeye IA, Adekola MB, Imoru ZA. Long term antidiabetic and antihyperlipidaemic effects of aqueous stem bark extracts of Irvingia gabonesis in streptozotocin-induced diabetic rats. Asian Pacific J Trop. Biomed. 2012; 2:1-6.
4. Kooti W, Farokhipour M, Asadzadeh Z, Ashtary-Larky D, Asadi-Samani M. The role of medicinal plants in the treatment of diabetes: a systematic review. Electron Physician. 2016; 8(1):1832-1842.
5. Sharifuddin Y, Chin Y, Lim P, Phang S. Potential Bioactive Compounds from Seaweed for Diabetes Management. Mar. Drugs. 2015; 13:5447-5491
6. Steuber H, Zentgraf M, Gerlach C, Sotriffer CA, Heine A, Klebe G. Expect the unexpected or caveat for drug designers: Multiple structure determinations using aldose reductase crystals treated under varying soaking and co-crystallisation conditions. J. Mol. Biol. 2006; 363:174–187

7. Iwata K, Nishinaka T, Matsuno K, Kakehi T, Katsuyama M, Ibi M, Yabe-Nishimura C. The activity of aldose reductase is elevated in diabetic mouse heart. J Pharmacol Sci. 2007; 103(4):408-16.
8. Chetan S, Dharmesh SM, Malleshi NG. Inhibition of aldose reductase from cataracted eye lenses by finger millet (Eleusine coracana) polyphenols. Bioorg. Med. Chem. 2008; 16:10085–10090.
9. Ashwini DJ, Laxman NB, Tanaji AM, Madhav MJ, Akalpita UA. Strong inhibition of the polyol pathway diverts glucose flux to protein glycation leading to rapid establishment of secondary complications in diabetes mellitus. J. Diabetes and Its Complications. 2016; 30:398–405.
10. Zheng X, Zhang L, Zhai J, Chen Y, Luo H, Hu X. The molecular basis for inhibition of sulindac and its metabolites towards human aldose reductase. FEBS Lett. 2012; 586:55-59.
11. Majee SB, Avlani D, Biswas GR. Pharmacological, pharmaceutical, cosmetic and diagnostic applications of sulfated polysaccharides from marine algae and bacteria. Afr. J. Pharm. Pharmacol.2017; 11(5):68-77.
12. Albertus JS. Medicinal and pharmaceutical uses of seaweed natural products: A review. J. Applied Phycol. 2004; 16:245-262.
13. Liu L, Heinrich M, Myers S, Dworjanyn SA. Towards a better understanding of medicinal uses of the brown seaweed Sargassum in Traditional Chinese Medicine: a phytochemical and pharmacological review. J Ethnopharmacol. 2012; 142(3):591-619
14. Brown ES, Allsopp PJ, Magee PJ, Gill CI, Nitecki S, Strain CR, McSorley EM. Seaweed and human health. Nutr Rev. 2014; 72(3):205-16.
15. MacArtain P, Gill CIR, Brooks M, Campbell R, Rowland IR. Nutritional Value of Edible Seaweeds. Nutrition Reviews. 2007; 65(12):535–543,
16. Cho M, Kang IJ, Won MH, Lee HS, You S. The antioxidant properties of ethanol extracts and their solvent-partitioned fractions from various green seaweeds. J Med Food. 2010; 13(5):1232-9.
17. Kwon MJ, Nam TJ. Effects of mesangi (Capsosiphon fulvescens) powder on lipid metabolism in high cholesterol fed rats. J. Korean Soc. Food Sci. Nutr. 2006; 35(5):530-535.
18. Kim YM, Kim IH, Nam TJ. Induction of apoptosis signaling by glycoprotein of Capsosiphon fulvescens in human gastric cancer (AGS) cells. Nutr. Cancer. 2012; 64:761-769.
19. Kwon M, Nam T. A polysaccharide of the marine alga Capsosiphon fulvescens induces apoptosis in AGS gastric cancer cells via an IGF-IR-mediated PI3K/Akt pathway. Cell Biol. Int. 2007; 31(8):768–75.
20. Jung HA, Oh SH, Choi JS. Molecular docking studies of phlo¬rotannins from *Eisenia bicyclis* with BACE1 inhibitory activity. Bioorg Med Chem Lett. 2010; 20:3211-3215.
21. Noda H, Amano H, Arashima K, Hashimoto S, Nisizawa K. Studies on the antitumour activity of marine algae. Nippon Suisan Gakkaishi. 1989; 55:1259-1264.
22. Okada Y, Ishimaru A, Suzuki R, Okuyama T. A new phloro¬glucinol derivative from the brown alga *Eisenia bicyclis*: potential for the effective treatment of diabetic complications. J Nat Prod. 2004; 67:103-105.
23. Shibata T, Fujimoto K, Nagayama K, Yamaguchi K and Nakamura T. Inhibitory activity of brown algal phlorotannins against hyaluronidase. Int J Food Sci Technol. 2002; 37:703-709.
24. Shibata T, Nagayama K, Tanaka R, Yamaguchi K and Nakamura T. Inhibitory effects of brown algal phlorotannins on secretory phospholipase A2s, lipoxygenases and cyclooxygenases. J Appl Phycol. 2003; 15:61-66.
25. Takashi K, Taeko K, Hideyuki G, Takamoto S, Toshihiro Y. Varieties of antioxidant and antibacterial properties of *Ecklonia stolonifera* and Ecklonia kurome products harvested and processed in the Noto peninsula, Japan. Food Chem. 2007; 103(3): 900.
26. Lee MS, Shin T, Utsuki T, Choi JS, Byun DS, Kim HR. Isolation and identification of phlorotannins from *Ecklonia stolonifera* with antioxidant and hepatoprotective properties in tacrine-treated HepG2 Cells. J. Agric. Food Chem. 2012; 60(21):5340-9.
27. Kim YC, An RB, Yoon NY, Nam TJ, Choi JS. Hepatoprotective constituents of the edible brown alga *Ecklonia stolonifera* on tacrine-induced cytotoxicity in hep G2 cells. Arch Pharmacal Res. 2005; 28(12):1376–80
28. Yoon NY, Chung HY, Kim HR, Choi JS. Acetyl- and butyrylcholinesterase inhibitory activities of sterols and phlorotannins from *Ecklonia stolonifera*. Fish Sci. 2008; 74:200-204
29. Wijesekara I, Yoon NY, Kim S. Phlorotannins from *Ecklonia cava* (Phaeophyceae): Biological activities and potential health benefits. BioFactors. 2010; 408-414
30. Li Y, Qian ZJ, Ryu BM, Lee SH, Kim MM, Kim SK. Chemical components and its antioxidant properties *in vitro*: An edible marine brown alga, *Ecklonia cava*. Bioorg. Med. Chem. 2009; 17:1963-1973.
31. Kong CS, Kim JA, Yoon NY, Kim SK. Induction of apoptosis by phloroglucinol derivative from *Ecklonia cava* in MCF-7 human breast cancer cells. Food Chem. Toxicol. 2009; 47:1653-1658.
32. Athukorala Y, Jeon YJ. Screening for Angiotensin 1-converting enzyme inhibitory activity of *Ecklonia cava*. J. Food Sci. Nutr. 2005; 10:134-139.
33. Lee SH, Li Y, Karadeniz F, Kim MM, Kim SK. α–Glycosidase and α–amylase inhibitory activities of phloroglucinal derivatives from edible marine brown alga, *Ecklonia cava*. J. Sci. Food Agric. 89: 1552-1558.
34. Ogunwa TH, Ayenitaju FC. An insight into the precise molecular interaction and inhibitory potential of amentoflavone and its substituted derivatives on human α-amylase. Arch. Curr. Res. Int. 2017; 10(1):1-14
35. Trott O, Olson AJ. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. J. Comput. Chem.2010; 31:455-461.
36. Seelinger D, de Groot BL. Ligand docking and binding site analysis with PYMOL and Autodock/Vina. J. Comput. Aided Mol. Des.2010; 24:417-422.

37. Laskowski RA, Swindells MB. LigPlot+: multiple ligand-protein interaction diagrams for drug discovery. J Chem Inf Model. 2011; 51(10):2778-86
38. Fricker P, Gastreich M, Rarey M. Automated Generation of Structural Molecular Formulas under Constraints. J. Chem. Info. Comput. Sci. 2004; 44(3):1065-1078.
39. Cao R, Wang Y. *In silico* study of polypharmacology with protein-ligand interacting fingerprint. Receptors & Clinical Investigation 2015; 2: e976.
40. Dariusz P, Michal LN, Rafal A, Krzysztof G. Can we trust docking results? evaluation of seven commonly used programs on PDBbind database. J. Comput. Chem. 2011; 32:742-755.
41. Oka M, Matsumoto Y, Sugiyama S, Tsuruta N, Matsushima M. A potent aldose reductase inhibitor, (2S,4S)-6-fluoro-2', 5'-dioxospiro[chroman-4,4'-imidazolidine]-2-carboxamide (Fidarestat): its absolute configuration and interactions with the aldose reductase by X-ray crystallography. J. Med. Chem. 2000; 43:2479-2483
42. Brownlee JM, Carlson E, Milne AC, Pape E, Harrison DHT. Structural and thermodynamic studies of simple aldose reductase–inhibitor complexes. Bioorganic Chem. 2006; 34; 424-444
43. Urzhumtsev A, Tête-Favier F, Mitschler A, Barbanton J, Barth P, Urzhumtseva L, Biellmann JF, Podjarny AD, Moras D. A 'specificity' pocket inferred from the crystal structures of the complexes of aldose reductase with the pharmaceutically important inhibitors tolrestat and sorbinil. Structure 1997; 5(5):601-612
44. Jung HA, Yoon NY, Woo MH, Choi JS. Inhibitory activities of extracts from several kinds of seaweeds and phlorotannins from the brown alga *Ecklonia stolonifera* on glucose-mediated protein damage and rat lens aldose reductase. Fish. Sci. 2008; 74:1363-1365.
45. Bohren KM, Grimshaw CE, Lai CJ, Harrison DH, Ringe D, Petsko GA, Gabbay KH. Tyrosine-48 is the proton donor and histidine-110 directs substrate stereochemical selectivity in the reduction reaction of human aldose reductase: enzyme kinetics and crystal structure of the Y48H mutant enzyme. Biochem. 1994; 33:2021–2032.

About Author

Mr. Ogunwa Tomisin Happy is a researcher with affiliation to the Centre for Bio-computing and Drug Design (CBDD), Adekunle Ajasin University, Akungba-Akoko (AAUA), Ondo State, Nigeria. He is also a lecturer at the Department of Biochemistry, AAUA. Mr. Ogunwa obtained his BSc (Hons) in Biochemistry from the Department of Biochemistry, AAUA with a First-Class grade in 2010. He later got his MSc degree in Biochemistry from the University of Benin, Edo state, Nigeria in 2014. He is currently a PhD student at Nagasaki University, Japan after winning the Japanese Government (MONBUKAGAKUSHO: MEXT) scholarship award in 2015. His research interests include natural products research, Bioinformatics and drug design. His current project includes screening for molecular targets and unraveling possible mechanism of interaction between plant-derived compounds and their protein targets as a way of understanding the molecular basis of known bioactivities of phyto-constituents. Mr. Ogunwa has records of participation in notable Conferences including the recent annual meeting of Biophysical Society held at San Francisco, California, USA in February 2018. He has published many research papers in reputable national and international Journals.