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Computational Screening of Anti-diabetic Molecules from Microalgae Metabolites by Molecular Docking

Gurudeeban Selvaraj[1*], Satyavani Kaliamurthi[1], Zeynep Elibol Cakmak[1,2], Turgay Cakmak[1*]

[1]Department of Molecular Biology and Genetics, Faculty of Engineering and Natural Sciences, Istanbul Medeniyet University, 34730, Istanbul, Turkey
[2]Department of Biology, Faculty of Arts and Sciences, Kirikkale University, 71450, Kirikkale, Turkey

[*]**Corresponding author:** Dr. Turgay Cakmak, Phytoprocess Laboratory, Department of Molecular Biology and Genetics, Faculty of Engineering and Natural Sciences, Istanbul Medeniyet University, Istanbul, Turkey, Email: turgay.cakmak@medeniyet.edu.tr

Dr. Gurudeeban Selvaraj, Phytoprocess Laboratory, Department of Molecular Biology and Genetics, Faculty of Engineering and Natural Sciences, Istanbul Medeniyet University, Istanbul, Turkey, Tel: +90-216-280-3505, Fax: 90-216-280-2021
Email: gurudeeb99@gmail.com

Abstract

The present study aimed to evaluate the efficiency of microalgae metabolites as a ligand for anti-diabetic target proteins namely Glucokinase, Fructose-1, 6-bis-phosphatase, Glycogen synthase kinase, Cytochrome P450, multi-drug resistant protein, and Peroxisome proliferators activated receptor-γ (PPARγ) using computational approach. Three-dimensional structure of microalgal metabolites retrieved from Pub Chem database and the energy minimized. The active site of target protein predicted through PDB sum. Molecular docking has performed with microalgae metabolites using Hex 8.0 and DockThor server. Hex docking revealed binding fucoxanthin was higher with fructose 1,6 bis-phosphatase (-298.31), human multidrug resistant protein 1 (-369.67), and PPARγ (-404.18). DockThor docking suggested Zeaxanthin with Glucokinase produced higher total energy (111.23 kcal/mol) and interaction energy (-2.99 kcal/mol). Lutein with fructose 1,6 bisphosphatase, human multidrug resistant protein, glycogen synthase kinase, PPARγ, and cytochrome p450 produced higher total energy and interaction energy. Further studies will assess the anti-diabetic effect of carotenoids of microalgae, especially Lutein, Zeaxanthin, and Fucoxanthin.

Keywords: Diabetes mellitus; DockThor; Glucokinase; Microalgae; Lutein

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Introduction

Diabetes mellitus (DM) is a complex disorder incorporating severe insulin dysfunction with gross variations from the norm in glucose homeostasis, lipid and protein digestive system[1]. In the World, people with type II DM and its complication would be triple in the number at the end of 2025[2]. Type II DM mainly influences people in developing nations like Turkey. It has affected the youthful populace in the prime of their working lives and afterward represents a more prominent risk to the well-being of these people[3]. Different targets involved in regulating glucose and fatty acid metabolism reported by several researchers includes aldose reductase, cytochrome P450, fructose-1, 6-bisphosphatase, glucokinase, multidrug resistant protein and PPAR γ. The inhibitory action of these receptors is an alternative treatment to diabetes mellitus[4].

Microalgae are the rich source of high value-added compounds including pigments, carotenoids, fatty acids, sterols, and proteins. These metabolites were identified from different species *Phaeodactylum tricornutum, Arthrospira, Porphyridium, Dunaliella salina, Haematococcus pluvialis, Chlorella protothecosis, Prorocentrum minimum, Lyngbya majuscule*, and *Synechococcus*[5-8]. The extract and metabolites of microalgae showed various pharmacological activities *viz*., anti-inflamma-

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tory, analgesic, antiviral, dietary supplement antioxidants and anti-tumour agents[9,10]. To the best of our knowledge, there was no information on microalgae specific metabolites in treating diabetes mellitus. Structure-based drug design is an essential study to examine the lead compounds to prevent the drug withdrawn from the clinical and development[11]. Predicting the target sites of molecules using bioinformatics tools would be valuable and time efficient in pharmaceutical applications to make a confident elimination, avoid costly late-stage preclinical and clinical failures. It covers and identifies the lead candidate, binding pocket, determination of target structure, and evaluation of the potential lead candidate[12]. Based on this information, the present study aimed to evaluate the inhibitory action of microalgae metabolites to some target protein related to glucose metabolism and diabetes mellitus.

Materials and Methods

Tools and software: The present study performed using bioinformatics tools, biological databases like Protein Data Bank (http://www.rcsb.org/), PubChem (http://pubchem.ncbi.nlm.nih.gov/), Chimera, 3DLigandStie (http://www.sbg.bio.ic.ac.uk/3dligandsite/) and software's like Open Babel 2.3.1., DruLiTo, Hex 8.0 and DockThor (http://dockthor.lncc.br/).

Preparation of ligands: The bioactive metabolites of microalgae such as carotenoids, PUFA, sterols, alkaloids, and protein have used as ligands (Table 1). The two-dimensional (2D) chemical structures of the ligands downloaded from the PubChem database as .sdf format. The 2D of the selected ligands converted into their 3D formats using Chem Sketch and it saved as .mol format. Further, the selected .mol format of lead converted into a .pdb format using Open Babel 2.3.1. Sub-atomic adaptability considered by every ligand as a gathering of conformers communicating to various zones of the conformational space available to the particle within a given energy range. This explored adopting the best conformer with Chimera, which based on the generalized CHARMM force field implementation with default features. This program will uniformly identify the best three-dimensional arrangements of ligands, exploring the variations across the target receptors.

Preparation of Receptors: Receptors have selected based on the previous reports[4]. The PDB used to download the target proteins Glucokinase (PDB ID: 1V4S), Fructose 1, 6 bisphosphatase (PDB ID: 2JJK), Human multidrug resistance protein (PDB ID: 2CBZ), and Cytochrome P450 (PDB ID: 3LC4), PPARγ (PDB ID: 1ZGY), glycogen synthase kinase (PDB ID: 1H8F). To visualize receptors and ligands performed using the molecular graphics program PyMol.

Table 1: Physiochemical properties of selected microalgae metabolites.

No. of ligands	Name of the ligand	Molecular Weight (g/mol)	logP	Hydrogen bond acceptor	Hydrogen bond donor
Ligand 1	Astaxanthin	596.39	9.696	4	2
Ligand 2	Arachidonic acid	304.24	8.349	2	1
Ligand 3	Brassicasterol	398.35	10.50	1	1
Ligand 4	β-Stigma sterol	412.37	11.07	1	1
Ligand 5	β-Carotene	536.44	14.73	0	0
Ligand 6	Canthaxanthin	564.4	10.78	2	0
Ligand 7	Docosahexaenoic acid	328.24	8.833	2	1
Ligand 8	Eicosapentaenoic acid	302.22	8.022	2	1
Ligand 9	Fucoxanthin	658.42	9.874	6	2
Ligand 10	γ-amino butyric acid	103.06	-0.66	3	2
Ligand 11	γ-linolenic acid	278.22	7.538	2	1
Ligand 12	Lutein	568.43	11.28	2	2
Ligand 13	Lycopene	536.44	14.58	0	0
Ligand 14	Microcolin A	747.48	4.643	14	2
Ligand 15	Okadoic acid	804.47	2.973	13	5
Ligand 16	Zeaxanthin	568.43	10.56	2	2

Drug-likeness predictions: DruLiTo had used to find out lead like a candidate based on eight filters (Lipinski's rule, MDDR-like rule, Veber rule, Ghose filter, BBB rule, CMC-50 like the rule, weighted and unweighted Quantitative Estimate of Drug-likeness). Toxicity analysis of selected ligands had performed earlier with Vega-QSAR[13].

Active sites prediction: 3DLigandStie is an online tool to predict the binding site of a protein. It uses the idea of binding energy between the protein and Vander Waals test to find enthusiastically good binding pockets. Energetically favourable probe sites clustered according to their spatial nearness and clusters then ranked according to energies for sites within each cluster. These clusters placed in rank seek of the likelihood of being a binding site as showed by total binding energies for each cluster.

Docking using Hex: Hex is an Interactive Molecular Graphics Program for calculating and displaying feasible acids and small bimolecular. The program reads in molecular coordinate files and interactively displays the molecule on the screen in various representations and colour schemes. Therefore, the present study docking analysis of target proteins with microalgae metabolites carried out using HEX 8.0. Docking decides the ligand with best scores and identifying the drug-receptor complex with lowest free energy. The metabolites docked with the receptor using the following features.

1. Correlation type – Shape + Electrostatics
2. FFT Mode - 3D
3. Post Processing- MM Energies
4. Grid Dimension - 0.6
5. Receptor range – 180
6. Ligand range – 180
7. Twist range – 360
8. Distance Range – 40

Docking using DockThor server: The best scores and lowest free energy of the metabolite of Hex docking further studied with the DockThor program. It has carried out a flexible ligand and rigid-receptor grid-based method. DockThor® employs a multiple solutions genetic algorithm as the search method[14] and the MMFF94S force field as the scoring function for ranking the created poses (http://dockthor.lncc.br/). Ligand and protein setup are available on the DockThor Portal, being possible to change the amino acid residues protonation states and include cofactors (e.g. structural water molecules, metals, organic molecules) as rigid entities. Grid size 34 A°, dimension x-17; y-17; z-17 and discretization 0.35 used. Hydrogen bond contacts, lipophilic contacts, and non-bonded contacts have calculated using LIGPLOT[15].

Results

Prediction of physiochemical and Drug–likeness properties of ligands: The physiochemical property includes molecular weight, the number of hydrogen bond acceptor and donor of selected microalgae metabolites showed in Table 1. The drug-likeness properties such as compound's hydrophilicity, the polar surface area prediction, molecular refractivity, number of rotatable bonds, number of an atom, the number of acidic groups, rotatable bond count, the number of rigid bond, number of atom ring, number of hydrogen bonds, structure alerts explained in Table 2.

Table 2: Drug likeness properties of selected microalgae metabolites.

No. of ligand	Alogp	TPSA	AMR	nRB	nAtom	nAcidic Group	RC	nRigidB	nArom Ring	nHB	SAlerts
Ligand 1	7.624	74.6	196.2	10	96	0	2	35	0	6	1
Ligand 2	1.264	37.3	94.09	14	54	1	0	7	0	3	2
Ligand 3	1.933	20.2	122.21	4	75	0	4	28	0	2	1
Ligand 4	1.257	20.2	125.29	5	78	0	4	28	0	2	1
Ligand 5	8.935	0	189.29	10	96	0	2	31	0	0	1
Ligand 6	8.928	34.1	193.53	10	94	0	2	33	0	2	1
Ligand 7	2.933	37.3	111.27	14	56	1	0	9	0	3	1
Ligand 8	2.115	37.3	99	13	52	1	0	8	0	3	2
Ligand 9	6.631	96.4	202.15	12	106	0	3	38	0	8	6
Ligand 10	-1.231	63.3	23.61	3	16	1	0	3	0	5	0
Ligand 11	0.446	37.3	81.82	13	50	1	0	6	0	3	2
Ligand 12	8.621	40.5	195.47	10	98	0	2	33	0	4	2
Ligand 13	11.573	0	198.04	16	96	0	0	23	0	0	2
Ligand 14	-2.604	173.9	192.89	24	118	0	2	30	0	16	3
Ligand 15	-3.194	182.8	189.23	10	125	1	7	53	0	18	1
Ligand 16	8.49	40.5	195.39	10	98	0	2	33	0	4	1

AlogP: compound's Hydrophilicity, TPSA: The Polar Surface Area Prediction, AMR: molecular refractivity, nRB: number of Rotatable Bonds, n Atom: number of Atom, n Acidic Group: number of acidic groups, RC: Rotatable bond count, nRigidB: number of rigid bond, nAtomRing: number of Atom Ring, nHB: number of Hydrogen Bond, SAlerts: Structure alerts.

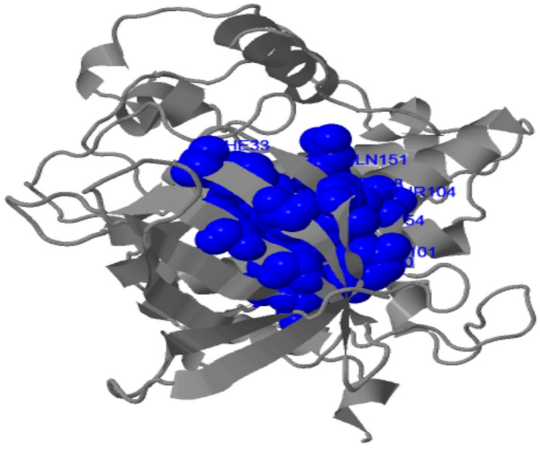

Figure 1: Predicted binding site residues of glycogen synthase kinase using Ligand Site.

Prediction of active sites residues in receptor: Computational approaches screen the possibilities of microalgae metabolites (ligand) to treat diabetes and its complication. Glucokinase has the following residues in the active sites GLU 256, PHE 152, PRO 153, THR 168, SER 151, GLY 229, GLU 290, ASP 205, GLC 500, LYS 169, ASN 204, and ASN 231. Fructose 1,6 bisphosphatase have THR 31, ALA 24, GLY 28, ARG 22, MET 18, ARG 22, ALA 24, VAL 17, THR 31, LEU 30, GLY 28, and THR 27. Human multidrug resistant proteins have GLN 713, LYS 684, VAL 680, GLY 681, THR 660, SER 686, TRP 653, ATP 1873, CYS 682 and. Cytochrome P450 have ASN 367, PHE 470, PHE 429, HIS 370, GLY 438, THR 307, TRP 128, ARG 109, HIS 109 residues in their active site. PPARγ have HIS 323, PHE 282, LEU 469, HIS 449, TYR 327, ILE 326, CYS 285, MET 364 and Glycogen synthase kinase have 28ILE, 33PHE, 36VAL, 49ALA, 51LYS, 76VAL, 99ASP, 100TYR, 101VAL,

104THR, 151GLN, 152ASN, 154LEU, 165CYS, 166 ASP residues in their active site (Figure.1).

Docking of microalgae metabolites with receptors: Hex server based docking results of the aldose reductase, cytochrome P450, Glucokinase and fructose-1, 6-bisphosphatase, permeability glycoprotein, PPARγ with ligands of microalgae metabolites interaction energy shown in Table 3. Binding of fucoxanthin simulated higher total binding energy with fructose 1,6 bis-phosphatase, multidrug resistant protein 1, and PPARγ. Lutein simulated total binding energy with glycogen synthase kinase, and Zeaxanthin simulated higher total binding energy with glucokinase and cytochrome p450. Among the 16 major microalgae metabolites Fucoxanthin, Lutein and Zeaxanthin have simulated higher binding energy with anti-diabetic target proteins. DHA, gamma linolenic acid, EPA, and GABA had shown least binding energy with targets compared to carotenoids. Microcolin A and okadaic acid stimulated higher binding energy with target proteins compared to fatty acids.

DockThor simulation carried out to confirm binding target proteins with fucoxanthin, Lutein, Zeaxanthin, microcolin A and okadaic acid. Table 4 points to the results of total energy and binding energy. Docking simulation of lutein with fructose 1,6 bisphosphatase produced higher total energy (145.66 kcal/mol) and interaction energy (-23.01 kcal/mol) on the first run. Lutein with the multidrug resistant protein produced higher total energy (1,48,085 kcal/mol) and interaction energy (-8.531 kcal/mol) on the 8th run. Zeaxanthin with glucokinase produced higher total energy (111.23 kcal/mol) and interaction energy (-2.99 kcal/mol) on the 25th run. Lutein with glycogen synthase kinase produced higher total energy (1, 59,766 kcal/mol) and interaction energy (-0.018 kcal/mol) on the 11th run. Lutein with PPARγ produced higher total energy (135.38 kcal/mol) and interaction energy (-30.604 kcal/mol) on the 8th run. Lutein with cytochrome p450 produced higher total energy (137.113 kcal/mol) and interaction energy (-30.279 kcal/mol) on the 10th run. Figure. 2 showed the molecular interaction of lead candidates with target receptor.

Table 3: Molecular Docking of Microalgae metabolites ligands using Hex.

S.No	Total energy (kcal/mol)					
	FBP	GK	CP450	MDRP 1	PPARγ	GSK
Ligand 1	-255.35	-380.75	-379.21	-371.26	-360.17	-275.43
Ligand 2	-190.95	-266.64	-276.99	-221.88	-284.43	-264.93
Ligand 3	-199.54	-312.94	-300.23	-260.21	-299.89	-261.81
Ligand 4	-218.84	-288.89	-306.25	-271.86	-306.48	-307.37
Ligand 5	-250.02	-367.48	-363.17	-357.48	-365.68	-299.81
Ligand 6	-254.87	-378.28	-388.87	-372.98	-355.12	-275.58
Ligand 7	-171.82	-285.18	-296.26	-232.31	-277.52	-253.61
Ligand 8	-191.82	-262.72	-255.94	-230.14	-286.69	-299.62
Ligand 9	-298.31	-385.36	-377.89	-369.67	-404.18	-286.01
Ligand 10	-191.95	-131.68	-138.12	-122.75	-144.56	-129.83
Ligand 11	-172.49	-269.41	-297.65	-235.28	-247.04	-242.52
Ligand 12	-248.41	-371.49	-402.54	-361.96	-373.62	-268.8
Ligand 13	-270.11	-349.86	-257.95	-343.28	-344.42	-382.39
Ligand 14	-279.61	-349.92	-340.97	-359.49	-366.06	-339.62
Ligand 15	-289.19	-363.81	-366.84	-359.49	-391.88	-331.52
Ligand 16	-247.55	-404.38	-409.42	-367.59	-373.34	-259.2

C P450 - cytochrome p450; FBP - fructose-1, 6-bisphosphatase; GK – glucokinase; GSK – glycogen synthase kinase; MDRP1 - multidrug resistance protein1; PPARγ- peroxisome proliferator-activated receptor γ;

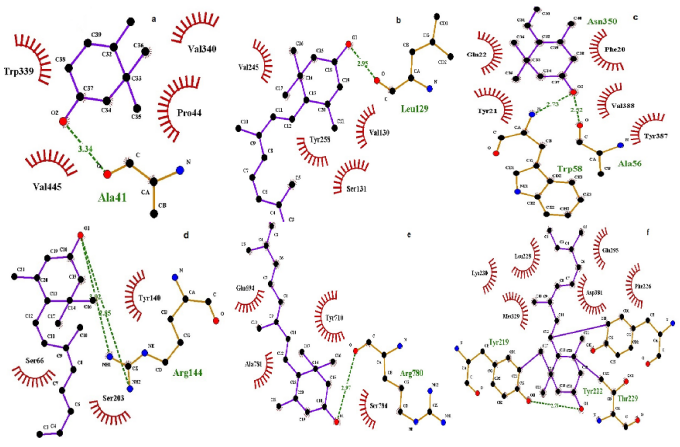

Figure 2: Docking interaction of lutein and zeaxanthin with target receptors predicted by LigPlot (blue line - ligand bonds; red line - non ligand bonds; dotted lines - hydrogen bonds and its length; half red circle – non ligand residues involved in the hydrophobic contacts; black dots - corresponding atoms involved in the hydrophobic contacts). (a) The atomic interaction between HE21 atom of the GLN267 (red colour) in the cytochrome p450 receptor and an oxygen atom of lutein; (b) The atomic interaction between OD2 atom of the ASP199 (red colour) in the fructose 1,6 bisphosphatase and oxygen atom of Lutein; (c) The atomic interaction between oxygen atom of the PRO312 and PHE 62 (red colour) in the glucokinase receptor and a hydrogen atom of zeaxanthin; (d) The atomic interaction between HN, HH21 atom of the ARG96 and ARG144 (red colour) in the glycogen synthase kinase receptor and an oxygen atom of lutein; (e) The atomic interaction between oxygen atom of the ARG 780 (red colour) in the human multidrug resistant protein and a hydrogen atom of lutein; (f) The atomic interaction between oxygen atom of the ALA300 (red colour) in the PPARγ receptor and a hydrogen atom of lutein.

Table 4: Molecular Docking of Selected ligands using DockThor Server.

Receptor	Ligand	Run	Total energy (Kcal/mol)	Interaction energy (Kcal/mol)
Fructose 1,6 bisphosphatase	Ligand 9	28	91.21	-22.31
	Ligand 12	1	145.66	-23.51
	Ligand 14	18	56.72	-25.24
	Ligand 15	18	56.72	-25.25
	Ligand 16	28	96.11	-19.99
Glucokinase	Ligand 9	10	103.49	-2.58
	Ligand 12	9	101.2	-2.07
	Ligand 14	3	75.52	-3.66
	Ligand 15	1	76.71	-3.97
	Ligand 16	25	111.23	-2.99
Human Multidrug resistant protein	Ligand 9	26	98,172	-10,209
	Ligand 12	8	1,48,085	-8,531
	Ligand 14	18	67,357	-13,554
	Ligand 15	18	67,357	-13,554
	Ligand 16	20	1,07,047	-7,888
Glycogen synthase kinase	Ligand 9	20	1,06,039	-0.016
	Ligand 12	11	1,59,766	-0.018
	Ligand 14	8	79,959	-0.033
	Ligand 15	8	79,959	-0.033
	Ligand 16	14	1,14,133	-0.014
Peroxisome proliferator activated receptor	Ligand 9	12	94.671	-22.822
	Ligand 12	8	135.384	-30.604
	Ligand 14	18	49.631	-32.991
	Ligand 15	18	49.631	-32.991
	Ligand 16	28	96.111	-19.995
Cytochrome P450	Ligand 9	8	81.088	-27.564
	Ligand 12	10	137.113	-30.279
	Ligand 14	30	52.591	-27.459
	Ligand 15	30	52.591	-27.459
	Ligand 16	13	88.041	-27.111

Discussion

Hex is an interactive modern molecular graphics program can calculate protein-ligand docking, protein –protein docking and protein– nucleotides docking modes. In protein- ligand docking, assuming the ligand is rigid, and it can superpose pairs of three-dimensional structures of molecules[16]. The superpose can use as spherical polar fourier (SPF) correlations to quicken the calculations. It encodes both surface shape and electrostatic charge and potential distributions. This study the electrostatic charge distribution of microalgae metabolites with the surface of targets calculated. The surface states of proteins using a two-term surface skin besides van der Waals steric thickness model, though the electrostatic model gets from traditional electrostatic hypothesis[17].

The DockThor Portal, developed by the group GMMSB/LNCC, is a free receptor-ligand docking server. The completed program is a flexible ligand and rigid-receptor grid-based method that employs a multiple solutions genetic algorithm along the MMFF94S molecular force field scoring. In the present study, the active site amino acids residues of targets change to confirm the binding affinity with the ligand. An enormous number of polyunsaturated fatty acids, carotenoids, carbohydrates, and sterols produce nontoxic manner under different stress condition[18]. Taouis et al[19] pointed out the attention to the healthy supplements improved with omega 3-unsaturated fats expanded the cell plasticity and reduced the inadequate insulin action caused by the store of high fatty acids. There is a strong association between the control of blood glucose and prevention rate of micro vascular complications (diabetic nephropathy, neuropathy, and retinopathy)[20]. Therefore, the present study sixteen different microalgae metabolites had evaluated in their inhibitory action against target proteins.

Glucokinase and fructose-1, 6-bisphosphatase are the most important enzymes to regulate blood glucose level in human liver. The activities of these enzymes enhanced production of glucose through glycerol or gluconeogenic amino acids[21]. The constant formation of glucose affected serious non-insulin dependent diabetic conditions. The analogs of lutein and zeaxanthin reported having a significant binding affinity with glucokinase and glycogen synthase[22]. The similar results noted in glucokinase, glycogen synthase and fructose1,6 bisphosphatase

with three different carotenoids lutein, fucoxanthin, and zeaxanthin. Permeability glycoprotein causes genetic variations in transporters protein leads to decrease the high-density lipoprotein, increase the blood glucose level, cystic fibrosis, acute damage to retina and kidney of diabetic patients[23]. Cytochrome p450 enzyme involved in regulating ADME properties of endogenous and exogenous compounds through activate or deactivate the drug molecules[24]. Surprisingly, a severe hyperglycaemic condition associated with free radical formation leads to hepatocellular damage and promoted CYP450 dependent monooxygenase enzyme in diabetic rats[25]. The dietary fucoxanthin showed greater decrease in blood glucose level, plasma insulin concentration and increase the activity of enzymatic antioxidants in diabetic/obese KK-A mice model[26]. It showed potential DPPH free radical scavenging activity than compared to other carotenoids under anaerobic condition[27]. In our study, docking of fucoxanthin with cytochrome p450, glucokinase and MDRP-1 showed potential binding[28] report fucoxanthin from edible marine seaweed *Undaria pinnatifida* could decrease the rifampin-affected Cytochrome p450 3A4 and multiple drug resistance 1 expression through attenuation of Human pregnane X receptor-mediated CYP3A4 promoter activation. Earlier studies reported fucoxanthin and fucoxanthinol have the potential to reduce body fat and lipid accumulation by restraint of 3T3-L1 adipocyte cells differentiation by control of peroxisome proliferator-activated receptor A[29]. The combined effect of PPAR active ligands such as fucoxanthin and troglitazone have potentially decreased the of colon cancer $CaCO_2$ cells. Additionally, the purified fucoxanthin ligand from showed significant DNA fragmentation in $CaCO_2$ colon cancer cell lines than compared to astaxanthin and beta-carotene[30]. Kohno et al.[31] report chemically induces colon tumorigenesis significantly inhibited by the troglitazone PPAR ligand molecules. Therefore, fucoxanthin may represent a therapeutic target to treat diabetes-induced oxidative stress and hyperlipidemic condition.

Glycogen synthase kinase is a serine or threonine kinase enzyme which involves in the glycogen and protein synthesis[32]. However, the overexpression of glycogen synthase kinase leads to insulin inability which causes a huge amount of glucose deposition in the respective muscles. There are reports on glycogen synthase kinase inhibition accelerating act insulin and glucose metabolism in type II DM patients skeletal muscles[33]. In the present study, the lutein showed high binding energy with Glycogen synthase kinase. The *in silico* findings might provide new insight to treat type II DM. Reduced level of lutein and zeaxanthin in the dietary supplement cause age-related macular degeneration diseases in humans which affect the individual central vision. Bone et al[34] reported, the graded doses treatment of lutein (2.4 to 30 mg/d) and Zeaxanthin significantly increased the serum concentration and macular pigment density in the human subjects. Prolonged hyperglycaemia conditions decreased the level of antioxidants, nitrotyrosine and increased apoptotic conditions in the retina cells. The vision losses in diabetic rats reduce by oral administration of 0.5 mg/kg of lutein up to 12 weeks[35]. Also, the lutein adjuvant therapies need further studies to improve effective drug molecules. Lutein could decrease damaging cerebral I/R in stroke patients[36]. The present study supports this information which explains to inhibit aldose reductase by lutein and zeaxanthin. Overproduction of reactive oxygen species and oxidative stress are closely associated with various health issues such as progression of atherosclerosis, hypercholesterolemia, ischemic reperfusion, and diabetes with advanced glycation products, hyperlipidemia, foot ulcer complications, cardiovascular diseases and further endothelial dysfunction[37]. PPAR γ also called as glitazone receptor, which is involved in the regulation of fatty acid storage and glucose metabolism in humans. Remarkably, the PPAR-γ concerned in the pathology of various diseases including diabetes mellitus, obesity, and atherosclerosis[38]. Astaxanthin and canthaxanthin are keto-carotenoids generously present in algae, rarely seen in plants[39]. A red fat-soluble pigment astaxanthin from *H.pluvialis* used as feed for fish. Previous studies showed the antioxidant of astaxanthin is about higher that compared to zeaxanthin, lutein, canthaxanthin, beta-carotene and alpha-tocopherol[40]. Oral administration of astaxanthin significantly reduces the plasma glucose level in alloxan-induced diabetic mice[41]. The dietary intake of 0.1% fucoxanthin significantly reduced lipid hydroperoxide levels of the liver, abdominal white adipose tissue and blood glucose levels of KK-Ay mice[42].

Conclusion

Microalgae metabolites especially lutein, fucoxanthin and zeaxanthin be an excellent source for developing the novel antidiabetic drug. Further experimental studies will confirm the therapeutic efficacy of these carotenoids.

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