REVIEW ARTICLE

Antidiabetic Activity of Red Marine Algae *In Vitro*: A Review

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Abstract

The marine ecosystem is a prosperous source of biological and chemical diversity which has been explored in the finding of unique chemicals having potential for industrial improvement as pharmaceuticals, cosmetics, nutritional supplements. Marine organisms consist of important number of novel secondary metabolites with potent pharmacological properties have been discovered. Most of the macroalgae have rich source of carotenoids, proteins, oligosaccharides, fatty acids, antioxidants, vitamins, and minerals, which are useful for medical and pharmaceutical industries. Especially, red algae are involved in photosynthesis and it also contains carrageenan, which is used for food and medicinal products. Hence, this review article is a concise of the antidiabetic effect of red algae and its bioactive components assessed *in vivo* and *in vitro* studies.

Keywords: Antidiabetic activity, Marine macroalgae, Red algae.

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Introduction

Natural products are established the best possible library with the maximum available diversity of chemical structural types. With the arrival of modern tools, they have been extremely screened. Based on traditional use (or) modern studies, natural products contribute 85% of the treatment regimens of 80% of the population in the world. The chemical intricacy of the complex natural products till now thought to be a disadvantage for drug discovery can be considered as an advantage for the drug development. Although research on marine native products started about 50 years ago, marine organisms have been used in folk medicine much before that exists.[1] Seaweeds (or) marine macroalgae are ecologically profitable marine resources, which belong to Thallophyta plant kingdom. Marine macroalgae are classified into four groups based on the presence of pigments and morphological and anatomical characters, namely Chlorophyta (green algae), Phaeophyta (brown algae), Rhodophyta (red algae), and Cyanophyta (blue-green algae).[2] Seaweeds are the groups of non-flowering marine plants commonly known as marine macroalgae having increased demand as cosmestic, pharmaceutical, and food additives.[3,4] They are photosynthesizing organisms in marine environment and produce basic biomass in the intertidal zone and have a rich source of bioactive compounds such as carotenoids, proteins, oligosaccharides, essential fatty acids, antioxidants, vitamins, and minerals, which are useful in medical and pharmaceutical industries.[5–7] Red algae are the most abundant and commercially valuable. They are found on the rocky shores from intertidal to subtidal zones. Red pigment phycoerythrin is involved in photosynthesis. Phycoerythrin masks the green pigment chlorophyll, which is also present in red algae. Many of the red species are thin and delicate. These red algae are harvested for using as a food item. It also contains a chemical called carrageenan, which is used as a binding agent in ice cream, puddings, and toothpaste. Other soft red algae supply a chemical agar, which is also used to make food and medicinal products, and prepare growth medium for bacteria growth.[8]

Diabetes mellitus (DM) is one of the metabolic disorders, which is characterized by hyperglycemia, resulting from defects in insulin secretion, action, or both.[9] Insulin is a peptide hormone produced by beta cells of the pancreatic islets.[10] It has two essential functions, without which the body ceases to function: insulin stimulates glucose uptake and lipid synthesis; insulin inhibits the breakdown of lipids, proteins, and glycogens and also causes gluconeogenesis.[11–13] According to the International Diabetes Federation (IDF), it was estimated that in 2017, there were 451 million (age 18–99 years) people with diabetes worldwide. These figures were expected to increase to 693 million by 2025. Many people affected by diabetes will eventually have a series of diabetic complications such as nephropathy, neuropathy, retinopathy, diabetic foot, ketoacidosis, and even increased risk of cardiovascular disease.[14] Complications continue to be a major medical problem. Many indigenous Indian medicinal plants including seaweeds (lower plants) have been found to be useful for successfully managing diabetes. One of the great advantages of medicinal plants is that these are readily available and have very low side effects.[15] This review gives a comprehensive knowledge of the red marine algae *in vitro* antidiabetic activity and its bioactive compounds with their target site of action to help the researchers to explore its *in vivo* activity in the future (Table 1).

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Red Algae Having Antidiabetic Activity in Different Modes of Actions

α-Amylase Inhibitory Activity

Vinoth et al. (*Champia parvula*): The crude extract of *C. Parvula* was carried out for α-amylase inhibitory activity at different concentrations (100 to 900 µg/mL), and it showed the inhibitory activity at the dose of 173 µg/mL for α-amylase activity.[16]

Table 1: Red marine algae bioactive compounds and their mechanism of action

S. no.	*Species*	*Compound name*	*Site on action*	*IC_{50} values*	*Ref.*
1	*Champia parvula*	NA	α-Amylase inhibition	173 µg/mL	16
			α-Glucosidase inhibition	81 µg/mL	
2	*Laurencia dendroidea*	NA	α-Glucosidase inhibition	3.71 µg/mL	27
			PTP1B inhibitors	1.15 µg/mL	
3	*Actinotrichia fragilis*	NA	α-Glucosidase inhibition	1.3 µg/mL	19
4	*Polysiphonia urceolata*	3-Bromo-4(3 bromo-4,5-dihydroxyphenyl methyl)-5-(hydroxymethyl)1,2-benzenediol	PTP1B inhibitors	4.9 µg/mL	32
5	*Symphocladia latiuscula*	Bis-(2,3,6-tribromo-4,5-dihyroxy-phenyl) methane	PTP1B inhibitors	4.3 µmol/L	28
		Bromophenols	Aldose reductase inhibitors	0.11 to 1.15 µg/mL	26
		2,3,6-Tribromo-4,5-dihydroxybenzyl methyl ether	PTP1B inhibitors	3.9 µmol/L	28
		1,2-Bis–(2,3,6-tribromo-4,5-dihydroxyphenyl)-ethane	PTP1B inhibitors	3.5 µmol/L	28
6	*Gracilaria Opuntia*	NA	Increase in the levels of insulin and C-peptide due to increased insulin secretion from pancreatic β-cells	125 and 175 mg/kg BW	33
7	*Portieria hornemannii*	NA	α-Amylase inhibitory	430 µg/mL	17
			α-Glucosidase inhibition	60 µg/mL	
8	*Spyridia fusiformis*	NA	α-Amylase inhibition	175 µg/mL	17
			α-Glucosidase inhibition	57 µg/mL	
9	*Halymenia durvilae*	NA	α-Glucosidase inhibition	0.32 µg/mL	20
10	*Rhodomela confervoides*	2,2′,3,3′-Tetrabromo-4,4′5,5′ tetra hydroxy diphenyl methane	PTP1B inhibitors	2.4 µM	29
		3-Bromo-4,5-bis (2,3′-dibromo-4,5-dibromobenzyl) pyrocatechol	PTP1B inhibitors	1.7 µM	29
		3,4-Dibromo-5-(methoxymethyl) benzene-1,2-diol	PTP1B inhibitors	3.4 µM	29,30
		3-(2,3-Dibromo-4,5-dihydroxyphenyl)-2-methylpropanal	PTP1B inhibitors	4.5 µM	29,30
		3,4-Dibromo-5-(2-bromo-3,4-dihydroxy-6-(isobutoxymethyl)benzyl) benzene-1,2-diol	PTP1B inhibitors	0.8 µM	29,30
11	*Laurencia similis*	1,2,5-Tribromo-3-bromoamino-7-bromomethylnaphthalene	PTP1B inhibitors	102 µg/mL	31
		3′,5′6′6-Tetrabromo-2,4 dimethyl diphenyl ether	PTP1B inhibitors	3.0 µg/mL	31
		2′,5′,6′5,6,-Pentabromo-3′,4′,3,4-tetramethoxybenzo-phenone	PTP1B inhibitors	2.7 µg/mL	31
12	*Grateloupia elliptica*	2,4,6-Tribromo phenol	α-Glucosidase inhibition	60.3 µM	21
		2,4-Dibromo phenol		110.4 µM	
13	*Odonthalia corymbifera*	2,3-Dibromo-4,5 dihydroxybenzyl	α-Glucosidase inhibition	0.4 mM.	24
14	*Polyopes lancifolia*	2,3-Dibromo-4,5 dihydroxybenzyl	α-Glucosidase inhibition	0.098 µM	23
15	*Polysiphonia morrowii*	3-Bromo-4,5-dihydroxy benzyl alcohol	α-Glucosidase inhibition	3.6 µg/mL	22
		3-Bromo-4,5-dihydroxybenzyl methyl ether	α-Glucosidase inhibition	4.8 µg/mL	22
16	*Palmaria* sp.	NA	α-Amylase inhibition	~0.1 µg/mL	18
17	*Laurencia papillosa*	NA	α-Glucosidase inhibition	>1000 µg/mL	19
18	*Palmaria palmata*	Protein hydrolysates	Dipeptidyl peptidase IV inhibition	1.65 ± 0.12 mg/mL	25

Murugesan et al. (*Portieria horemannii* and *Spyridia fusiformis*): The crude extracts of *P. horemannii* and *S. fusiformis* were assessed at the concentration of 900 µg/mL exhibited α-amylase inhibitory activity with IC_{50} values 430 and 175 µg/mL, respectively.[17]

Nwosu et al. (*Palmaria sp.*): The phenolic extract showed minimal α-amylase inhibitory activity with IC_{50} value estimated at ~0.1 µg/mL.[18]

α-Glucosidase Inhibitory Activity

Vinoth et al. (*Champia Parvula*): The crude extract of *C. Parvula* was carried out for α-glucosidase inhibitory activity at different concentrations (100 to 900 µg/mL), and it showed the inhibitory activity at the dose of 81 µg/mL for α-glucosidase activity.[16]

Osman et.al.: The crude extracts of *Actinotrichia fragilis* and *Laurencia papillosa* exhibit α-glucosidase inhibitory activity. It was carried out by using 96-well plate. About 100 µL of enzyme solution and 20 µL of crude were mixed at different concentrations (200, 500, and 1000 mg/mL), and the results showed the higher IC_{50} values 1.3 µg/mL and >1000 µg/mL, respectively.[19]

Murugesan et al. (*Portieria horemannii* and *Spyridia fusiformis*): The crude extracts of *P. horemannii* and *S. fusiformis* were assessed at the concentration of 900 µg/mL exhibited α-glucosidase inhibitory activity with IC_{50} values 60 and 57 µg/mL, respectively.[17]

Sanger et al. (*Halymenia durvilae*): α-Glucosidase inhibition of crude extract of *H. durvilae* showed that all the test concentrations (0.156, 0.312, 0.625, 1.25, 2.5 and 5 mg/mL) have highest α-glucosidase inhibitory activity at IC_{50} values 0.32 µg/mL.[20]

Kim et al. (*Grateloupia elliptica*): Two bromophenols, 2,4,6-tribromophenol and 2,4-dibromophenol, were purified from the red alga *Grateloupia elliptica*. IC_{50} values of 2,4,6-tribromophenol and 2,4-dibromophenol were 60.3 and 110.4 µM against *Saccharomyces cerevisiae* a-glucosidase, and 130.3 and 230.3 IM against *Bacillus stearothermophilus* a-glucosidase, respectively. In addition, both minimally inhibited rat-intestinal sucrase (IC_{50} of 4.2 and3.6 mM) and rat-intestinal maltase (IC_{50} of 5.0 and 4.8 mM). Therefore, bromophenols of *G. elliptica* have potential as natural nutraceuticals to prevent DM because of their high α-glucosidase inhibitory activity.[21]

Kurihara et al. (*Polysiphonia morrowii*): The crude extract of *P. morrowii* was carried out α-glucosidase inhibitory activity by using rat-intestinal maltase and sucrase assays. Bromophenol compounds 3-bromo-4,5-dihydroxy benzyl alcohol and 3-bromo-4,5-dihydroxybenzyl methyl ether showed IC_{50} 3.6 and 4.8 mM.[22]

Kim, Kurihara and Kim et al. (*Polyopes lancifolia*): *P. lancifolia* bromophenol compound, 3-dibromo-4,5 dihydroxybenzyl, was purified and identified from the *P. lancifolia* alga and the compound exhibited strongly competitive inhibition against *S. cerevisiae* α–glucosidase.[23]

Kurihara et al. (*Odanthalia corymbifera*): Bromophenol compounds were isolated from *O. corymbifera*. The novel bromophenols were determined as 4-bromo-2,3-dihydroxy-6-hydroxymethylphenyl, 2,5-dibromo-6-hydroxy-3-hydroxymethylphenyl ether, bis (2,3-dibromo-4,5-dihydroxy benzyl) ether, and 2,3-dibromo-4,5-dihydroxybenzyl alcohol. Among these bromophenols, 2,3-dibromo-4,5-dihydroxybenzyl alcohol strongly exhibits α-glucosidase of IC_{50} values 0.4 mM.[24]

Dipeptidyl Peptidase IV Inhibitory Activity

Harnedy et al. (*Palmaria palmata*): *P. palmata* protein hydrolysates generated with Alcalase and corolase *P. palmata* showed highest DPP IV inhibitory activity with aqueous protein hydrolysates, control protein sample, and the protein hydrolysate generated with flavor zyme had IC_{50} values >5 mg/mL and showed a significant increase in DPP IV of IC_{50} values 1.65 ± 0.12 mg/mL.[25]

Aldose Reductase Inhibitory Activity

Okuyama et al. (*Symphyocladia latiuscula)*: *S. latiuscula* containing high concentrations of bromophenols which were isolated like 2,2,3,6,6-penta bromo 3′,4,4′,5′-tetrahydroxy dibenzyl ether, bis (2,3,6-tribromo-4,5-dihydroxyphenyl) methane, 2,2′,3,5′,6′-pentabromo-3′,4,4′,5 tetrahydroxydiphenylmethene, 2,3,6,tribromo-4,5-dihydroxy methylbenzene, and 2,3,6-tribromo-4,5-diydroxy-benzaldehyde inhibited aldose reductase activity of IC_{50} values 0.40, 0.40, 1.15, and 0.25 µg/mL, respectively.[26]

Protein Tyrosine Phosphatase 1B Inhibitor Activity

Nguyen et al. (*L. dendroidea*): Inhibition of mammalian α-glucosidases and PTP1B of the ethyl acetate fraction was evaluated and compared with acarbose and ursolic acid as the positive controls. The fraction inhibited strongly all tested enzymes, with IC_{50} values of 3.71, 14.17, 23.31, and 1.15 µg/mL against yeast α-glucosidase, rat intestinal sucrase, rat intestinal maltase, and PTP1B, respectively.[27]

Liu et al. (*Symphyocladia latiuscula*): *S. latiuscula* was identified and structurally characterized by eight known bromophenols and then evaluated for inhibitory effects on protein tyrosine phosphatase 1B (PTP1B), a potential therapeutic drug target in the treatment of type 2 DM by using an *in vitro* assay. Bromophenol compounds such as 2,3,6-tribromo-4,5-dihydroxybenyl methyl ether, bis (2,3,6-tribromo-4,5-dihydroxy phenyl) methane, 1,2-bis (2,3,6-tribromo-4,5-dihydroxyphenyl ethane) showed strong inhibitory activity at the concentrations of 3.9, 4.3, and 3.5 µmol/L, respectively.[28]

Shi Da Yong et al. isolated bromophenol compounds such as 2,2′,3,3′-tetrabromo-4,4′5,5′ tetra hydroxy diphenyl methane, 3-bromo-4,5-Bis (2,3′-dibromo-4,5-dibromobenzyl) pyrocatechol, 3,4-dibromo-5-(methoxymethyl)benzene-1,2-diol, 3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-methylpropanal, 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(isobutoxymethyl)benzyl)benzene-1,2-diol from *Rhodomeda confervoides* which showed potent *in vitro* PTP1B inhibitory effects, with IC_{50} values at 2.4, 1.7, 3.4, 4.5 and 0.8 µM respectively.[29,30]

Qin et al. (*Laurencia similis*): Bromophenol compounds of *L. similis,* 1,2,5-tribromo-3-bromoamino-7-bromomethylnaphthalene, 3′,5′6′6-tetrabromo-2,4 dimethyl diphenyl ether, and 2′,5′,6′5,6,-pentabromo-3′,4′,3,4-tetramethoxybenzo-phenone, showed PTP1B IC_{50} values at 102, 3.0, and 2.7 µg/mL.[31]

Liu et al.: *Polysiphonia urceolata* (red alga) contains five bromophenol compounds such as as 3-bromo-4-[3-bromo-4,5-dihydroxyphenyl] methyl-5-(hydroxymethyl)-1,2-benzenediol, 3-bromo-4,5-dihydroxy-α-ethoxy-toluol, 3-bromo-4,5-dihydroxybenzyl alcohol, 3-bromo-4,5-dihydroxybenzaldehyde, 3,5-dibromo-4-hydroxybenzyl alcohol and 3,5-dibromo-4-hydroxybenzaldehyde, were isolated from the red alga *Polysiphonia urceolata* were elucidated by chemical and spectroscopic methods including 2D NMR techniques and revealed the potent effect in 3-bromo-4-[3-bromo-4, 5-dihydroxyphenyl] methyl-5-(hydroxymethyl)-1,2-benzenediol potent inhibition against PTP1B enzyme with IC_{50} = 4.9 µg/mL.[32]

In Vivo Study

Nguyen et al. : The crude extract of *L. dendroidea* showed strongly inhibitory α-glucosidase and PTP1B activity with IC_{50} values of

3.71, 14.17, 23.31 and 1.15 µg/mL against yeast α-glucosidase. Rat intestinal sucrase, maltase and PTP1B respectively showed significantly lower than positive controls.[27]

Rayapu et al. (*Gracilaria opuntia*): *G. opuntia* was extracted in different solvents like aqueous, methanolic, and ethanolic extracts, and it was given at different doses (50, 100, 125, 150, and 200 mg/kg body) in STZ-induced diabetic rats. It showed 125 and 175 mg/kg concentrations of *G. opuntia* to treat the STZ-induced diabetic rats and also reduced the blood glucose, and HbA1c levels of *G. opuntia* showed a significant increase in the levels of insulin due to increased secretion of insulin from pancreatic β-cells.[33]

Discussion

Diabetes and other metabolic disorders are major problems that the world is facing nowadays. Most of these diseases are due to improper nutritional habits and go along with the increased production of free radicals and/or insufficient antioxidant defense system.[34] Seaweeds are proved to stand as a good source of natural bioactive compounds with many therapeutic activities.[35] Preventing and treating diabetes with medications attempt these problems. They can reduce postprandial hyperglycemia by inhibiting various enzymes such as α-amylase, α-glucosidase,[36] aldose reductase, PTP1B, dipeptidyl peptidase IV found to be an effective strategy related to their activity of pancreatic β-cells (synthesis or release) or the insulin-like activity of seaweeds. All of these actions may be responsible for the reduction of diabetic complication.[37] Moreover, the cost of the drugs is high, and also, they cause adverse effects.[38] Most of the seaweeds have pharmacologically bioactive compounds such as bromophenols, alginate, carrageen, and agar as phycocolloids have been obtained from seaweeds to be used as a medicine and pharmacy.[39] Since there is increasing demand in the use of natural products with antidiabetic activity due to the side effects associated with insulin and oral hypoglycemic agents, the marine algae could be of better choice in this condition.[40]

Conclusion

The present review revealed comprehensive details of red marine algae and its use for the treatment of DM. Some of the marine algae are more potent and cost-effective for the management of diabetes. Since the allopathic drugs showed severe adverse effect for long-term usage, the natural sources such as herbal and marine algae are used as antidiabetic, dietary, and nutritional supplements. However, many other active compounds obtained from marine algae have not been well characterized. These marine red algae are useful to the health professionals, scientists, and scholars working in the field of pharmacology and therapeutics to develop antidiabetic drugs.

References

1. Gopal R, Vijaya Kumaran M, Ventatesan R, Kathiroli S. Marine organisms in Indian medicine and their future prospects. Nat Prod Rad 2008;7(2):139–145.
2. Rajakumar R, Singh APY. Biochemical investigation and GC-MS analysis of *Gracilaria edulis*. World J Pharma Res 2017;6(7):1812–1820.
3. Hill RA. Marine natural products. Ann Rep Prog Chem sect 2011;107:138–156. DOI: 10.1039/c1oc90008k.
4. Kim JK, Yarisn C, Hwang EK, Park M, Kim Y. Seaweed aquaculture: cultivation technologies, challenges and its ecosystem services. Algae 2017;32(1):1–13. DOI: 10.4490/algae.2017.32.3.3.
5. Chakarborty K, Lipton AP, Paulraj R, Chakraborty RD. Guaiane sesquiterpenes from seaweed *Ulva fasciata* delile and their antibacterial properties. Eur J Med Chem 2010;45(6):2237–2244. DOI: 10.1016/j.ejmech.2010.01.065.
6. Chakarborth K, Lipton AP, Paulraj R, Vijayan KK. Anti-bacterial labdane diterpenoids of *Ulva fasciata* delile from the southwestern coast of Indian peninsula. Food Chem 2010;119(4):1399–1408. DOI: 10.1016/j.foodchem.2009.09.019.
7. Kokabi M, Yousefzadi M, Alil Ahmadi A, Feghhi MA, Keshavarze M. Anti-oxidant activity of extracts of selected algae from the persian gulf. Iran J Pres Gulf 2013;4:45–50.
8. Sanjeeva Kumar A, Nagarjuna S, Setty VK, Raju CH, Kashinath M. A comprehensive review on marine algae and their multidisciplinary activities. Int J Adv Pharma Biolog Sci 2011;1(2):44–50.
9. Alberti KG, Zimmet PZ. . Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provision Report WHO Consult Diabet Med 1998;15(7):539–553. DOI: 10.1002/(SICI)1096-9136(199807)15:73.0.CO;2-S.
10. Joshi SR, Parikh RM, Das AK. Insulin- history, biochemistry, physiology and pharmacology. J Assoc Physicia India 2007;55:19–25.
11. Newshome P, Cruzat V, Arfuso F, Keane K. Nutrient regulation of insulin secretion and action. J Endocrinol 2014;221(3):R105–R120. DOI: 10.1530/JOE-13-0616.
12. Sonken P, Sonken J. Insulin: understanding its action in health and disease. Br J Anaeth 2000;85(1):69–79. DOI: 10.1093/bja/85.1.69.
13. Liu Y, Gao Z, Guo Q, Wang T, Lu C, Chen Y, etal. Anti-diabetic effects of CTB-APSL fusion protein in type 2 diabetic mice. Mar Drugs 2014;12(3):1512–1529. DOI: 10.3390/md12031512.
14. Soumya D, Srilatha B. Late stage complications of diabetes and insulin resistance. J Diabet Metabol 2011;2:1–7.
15. Arumugam G, Manjula P, Paari N. A review: antidiabetic medicinal plants used for diabetes mellitus. J Acute Dis 2013(3):196–200. DOI: 10.1016/S2221-6189(13)60126-2.
16. Vinoth Kumar R, Murugesan S, Shettu N. Anti-diabetic potential of marine red alga *Champia Parvula (C. agardh*) by inhibiting key metabolic enzymes. World J Pharmaceut Res 2017;6(10):1466–1474.
17. Murugesan S, Bhuvaneswari S, Sivamurugan V. Evaluation of in vitro antidiabetic activity of red seaweed *Portieria hornemannii* (Lyngbye) (sliva) and *Spyridia fusiformis* (wulfen). World J Pharmaceut Sci 2016;4(6):415–419.
18. Nwosu F, Morris J, Lund VA, Stewart D, Ross HA, McDougall GJ. Anti-proliferative and potential anti-diabetic effects of phenolic-rich extracts from edible marine algae. Food Chem 2011;126(3):1006–1012. DOI: 10.1016/j.foodchem.2010.11.111.
19. Osman NAK, Siam AA, El-manawy IM, Jeon YJ. Anti-microbial and anti-diabetic activity of six seaweeds collected from red sea, Egypt. The egyptian society For. Environment Sci 2019;19(1):55–60.
20. Sanger G, Rarung LK, Damongilala LJ, Kaseger BE, Montolaluc LADY. Phytochemical constituents and anti-diabetic activity of edible marine red seaweed(Halymenia durvilae). IOP Conf. Series. Earth Environment 2019;278:1–8.
21. Kim KV, Nam KA, Kuriharn H, Kim SM. Potent α-glucosidase inhibitors purified from the red algae Grateloupia elliptica. Phytochemistry 2008;69(16):2820–2825. DOI: 10.1016/j.phytochem.2008.09.007.
22. Kurihara H, Mithani T, Kawabata J, Takahashi K. Inhibitory potencies of bromophenols rhodomelaceae algae against α-glucosidase activity. Fisheries sciences 1999;65(2):300–303. DOI: 10.2331/fishsci.65.300.
23. Kim KY, Nguyen TH, Kurihara H, Kim SM. α-glucosidase inhibitory activity of bromophenol purified from the Red alga *Polyopes lancifolia*. J Food Sci 2010;75(5):145–150. DOI: 10.1111/j.1750-3841.2010.01629.x.
24. Kurihara H, Mithani T, Kawabata J, Takahashi K. Two new bromophenols from the red alga *Odonthalia corymbifera*. J Nat Prod 1999;62(6):882–884. DOI: 10.1021/np980324p.
25. Harnedy DA, Fitzgerald RJ. In vitro assessment of the cardio-protective, anti-diabetic and anti-oxidant potential of *Palmaria palamata* protein hydrolysates. J ApplPhycol 2013;25(6):1793–1803. DOI: 10.1007/s10811-013-0017-4.

26. Wang W, Okada Y, Shi H, Wang Y, Okuyama T. Structures and aldose reductase inhibitory effects of bromophenols from the red algae *Symphocladia latiuscula*. J Nat Prod 2005;68(4):620–622. DOI: 10.1021/np040199j.
27. Nguyen T, Nguyen T, Nguyen V, Nguyen TP, Tran TA, Do A, et al. Antidiabetic and antioxidant activities of red seaweed *Laurencia dendroidea*. Asian Pac J Trop Biomed 2019;9(12):501–509. DOI: 10.4103/2221-1691.271723.
28. Liu X, Li X, Gao L, Cui C, Li C, Li J, et al. Extraction and PtP1B inhibitory activity of bromophenols from the marine red alga symphyocladia latiuscula. Chin J Oceanol Limnol 2011;29(3):686–690. DOI: 10.1007/s00343-011-0136-1.
29. Shi D, Feng X, He J, Li J, Fan X, Han L. Inhibition of bromophenols against PTP1B and anti-hyperglycaemic effect of Rhodomela confervoides extracts in diabetic rats. Chin Sci Bull 2008;53:2476–2479.
30. Shi D, Guo S, Jiang B, Guo C, Wang T, Zhang L, et al. HPN, a synthetic analogue of bromophenol from red alga Rhodomela confervoides: synthesis and anti-diabetic effects in C57BL/KSJ-db/db mice. Mar Drugs 2013;11(2):350–362. DOI: 10.3390/md11020350.
31. Qin J, Su H, Zhang Y, Gao J, Zhu L, Wu X, et al. Highly brominated metabolites from marine red alga Laurencia similis inhibit protein tyrosine phosphatase1B. Biorogan Med Chem Lett 2010;20(23):7152–7154. DOI: 10.1016/j.bmcl.2010.08.144.
32. Liu Q, Xu H, Zhang T, Fan X, Han I. Huaxul Tongbao. Mar Nat prod 2005;25:35–94.
33. Rayapu L, Makkar F, Anandan SH, Maneesh A, Charkraborthy K, Yalluru L. Proctective role of marine marcoalgae extracts against STZ induced diabetic rats. J Coast Life Med 2017;5(12):521–530. DOI: 10.12980/jclm.5.2017J7-153.
34. Pitozzi V, Glovannelli L, Bardini G, Rotella CM, Dolara P. Oxidative DNA damage in peripheral blood cells in type-2 diabetes mellitus: Higher vulnerability of polymorphonuclear Leutocytes. Mutat Res 2003;529(1-2):129–133. DOI: 10.1016/s0027-5107(03)00114-3.
35. Ambreen AK, Hira A, Tariq R, Sultana V, Ara J. Evaluation of biochemical component and anti-microbial activity of some seaweeds occurring at Karachi coast. Pak J Bot 2012;44:1799–1803.
36. Etreberria U, De la Garza AL, Campion J, Martinez JA, Milagro FI. Anti-diabetic effects of natural plant extracts via inhibition of carbohydrates hydrolysis enzymes with emphasis on pancreatic α-amylase. Expert Opin Ther Targets 2012;16(3):269–297. DOI: 10.1517/14728222.2012.664134.
37. Mamun-or-Rashid ANM, Shamim Hossain MD, Hassan N, Dash BK, Ashrafuzzaman Sapon MD, Sen MK. A review on medicinal plants with antidiabetic activity. J Pharmacog Phytochem 2014;3(4):149–159.
38. Idsoe O, Guther T, Willeox R, Deweck AL. Nature and extent of penicillin side reaction with particular reference to fatalities from anaphylactic shock. Bull Wltto 1968;38:150–158.
39. Siddhanta AK, Mody KH, Ramavat BK, Chauchan VD, Garg HS, Goel AK, et al. Bioactivity of marine organisms: part VIII-screening of some marine flora of western coast of India. India J Exp Bio 1997;36(6):638–643.
40. Mohammed FA, Syed MK, Syed SG, Syeda SM, Shaik RA, Shai MA, et al. Antidiaetic activity of Vinca rosea extracts in alloxan-induced diabetic rats. Intl J of Endocrin 2010. 1–6.