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Development of protein tyrosine phosphatase 1B (PTPIB) Inhibitors from marine sources and other natural products-Future of Antidiabetic Therapy : A Systematic Review

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Abstract

The incidence of both obesity and Type 2 Diabetes Mellitus(DM) is increasing proportionately so that causes of deaths from these has overtaken from that of malnourishment. Hence it has been recommended to treat the 2 in parallel considering the role of diabesity on health. Important causes of T2DM are insulin resistance (IR) and /or inadequate insulin secretion. Protein tyrosine phosphatase 1B(PTPIB) has a negative impact in insulin signaling pathways and hence plays crucial role inT2DM,since its overexpression might induce IR. Thus PTPIB is considered a therapeutic target for both obesity and T2DM, there has been a search for novel ,promising natural inhibitors. We conducted a pubmed search for articles related to PTPIB inhibitors from natural causes be it marine sources or other natural sources. Out of 988 articles we selected 100 articles for review. Thus various bioactive molecules isolated from marine organisms that can acts as PTPIB Inhibitors and thus possess antidiabetic activity both in vitro/ in vivo studies ,besides products from fruits like Chinese raspberry or curcumin used as routine spices are described with their chemical classes, structure-activity relationships and potency as assessed by IC 50 values are discussed. More work is required to make this a reality.

Keywords: PTPIB Inhibitors, Diabesity, Marine Sources, Natural Products, Antidiabetic Drugs

Major classification: Health Science.

1. Introduction

Both obesity and type 2 diabetes mellitus(T2DM) incidence are on the rise globally because of mechanization, changes in lifestyle of human beings along with daily routines so much so that the combination of the 2 has been termed diabesity and an attempt to take care of the 2 together is warranted(reviewed in Al-Lawaty,2017,Xiao,2015,Kochar Kaur 2019).As per the International Diabetes Federation(IDF), it was calculated in 2017 that there were 451 million people having DM worldwide In between ages varying from 18-99 years .It was

anticipated that these figures would rise to approximately 693 million by 2045(Cho, 2018). DM occurs once there are defects in insulin action, insulin secretion or both=>persistent hyperglycaemia(ADA, 2015).

At present T2DM has become a major threat to health(Dube, 2005). In relation to increased blood glucose levels multiple complications result that include cardiovascular disorders (CVD), blindness, renal failure along with peripheral nerve damages(Brownlee, 2001).These complications are related mainly to insulin resistance(IR) along with hypoglycemic variations(Lee, 2012; Pontiroli, 2004). Hence an effective drug for controlling IR might be of benefit in improving the quality of life of T2DM patients. Various pharmacological strategies have been investigated in DM treatment, that include insulin release stimulation, inhibition of gluconeogenesis, increase in glucose transport activity and decrease in intestinal glucose absorption(Thilagam, 2013). Insulin alone or other oral antidiabetic drugs may be used alone or in combination for improving glycemic control(Jung). Problem lies in that the antidiabetic drugs either have low efficacy or have serious adverse effects(Ray, 2017). Hence an ongoing search continues to find more efficacious along with safer antihyperglycaemic agents, and are cheaper for better compliance from natural products like anthraquinones, monoterpenes, polyphenols etc.

Insulin sensitizers like thiazolidenediones(TZD's, or glitazones)are used effectively for T2DM therapy(Scheen, 1999). Once the enzyme that causes dephosphorylation of insulin receptors, known as protein-tyrosine phosphatase -1B(PTP1B) was found it was shown that inhibitors of this enzyme could be utilized as insulin sensitizing agents and hence promise to be good antidiabetic agents(Ahmad, 1995). The supposition got confirmed in mouse models, wherePTP1B gene disruption increased insulin sensitivity. Using PTP1B antisense nucleotides PTB1 gene expression got suppressed, thus confirming the hypothesis(Zinker, 2002).

Protein tyrosine phosphatases(PTP's) represent a large and structurally different family of highly controlled enzymes. Most PTP's have been considered as targets for advanced drug discovery and PTP1B is one of the well established enzymes among PTP's(Zhang, 2007; Zhang, 2007). Being the 1st isolated member of the PTP superfamily, growing literature has linked it with IR, obesity, and T2DM.Multiple studies have demonstrated that PTP1B can negatively control both insulin along with leptin signaling pathways. PTP1B dephosphorylates insulin receptor along with its substrate IRS1 in the insulin signaling pathways(Goldstein 2003), while in the leptin pathway ,it binds and dephosphorylates tyrosine kinase downstream of the Janus Activated Kinase2 (JAK2)leptin receptor(Lund, 2005). Overexpression of PTP1B in cell cultures=>a decrease in insulin stimulated phoshorylation of IR and IRS1, while PTB1 raises insulin initiated signaling levels decrease(Byon, 1998). The proposal that PTP1B expression may add to diabetes and obesity gets supported by quantitative analysis of trait loci and mutations in the human PTPB1 gene(Meshkani, 2007). PTPB1 knockout mice in, *in vivo* studies showed increased resistance to high fat diet(HFD) induced obesity and insulin sensitivity(Klaman, 2000). Additionally other studies on tissue specific PTPB1 knockout mice showed that leptin action, adiposity along with body weight get controlled by neuronal PTP1B(Bence, 2006). Many studies indicate that PTP1B1 inhibitors are a promising approach to ameliorate both obesity and T2DM.

Aryl carboxylic acids like isoxazole(Zhao, 2004), hydroxyl propionic acid(Leung, 1999), 2oxalyl-amino benzoic (OAB)acids(Andersen, 2007), and thiophene diacid (Wilson, 2007) have been identified as alternative phosphotyrosine(pTyr)surrogates to overcome the lack of cellular activity of highly charged phosphonates(fig1). Moreover it was shown that benzyl aryl α ketoacid derivatives showed significant PTP1B1 inhibitory effects in a non-competitive pattern, targeting conserved protein loop(WPD loop)open confirmation(Liu, 2008). Existence of a benzyl group in these bioactive molecules might increase PTP1B1 binding affinity, was observed and being hydrophobic in nature, it also enhanced their cell membrane permeability. It has been suggested by recent observations that PTP1B1 might become an oncogene in breast cancer(Zhang, 2007). The aim of this review is to describe the role of PTP1B1 in T2DM signaling and treatment, besides describing the most recent findings about various compounds and extracts discovered from marine organisms and their relevance regarding upcoming PTP1B1 inhibitors

Methods-Thus we used the PUBMED Search engine along with Web of Sciences using MeSH terms PTP1BI inhibitors, marine products; bromophenol; natural products; seaweeds; lichen to update the potency, isolate different compounds, structure activity relationship, in vitro and in vivo antidiabetic studies to update on the knowledge of marine compounds and other PTPIB Inhibitors from natural sources to be used as potential PTP1BI inhibitors to treat T2DM.

Results-We found a total of 988 studies from 1970's to 2019 of which we selected 100 articles for this review after removing duplicate studies and searching studies from cross references. No meta-analysis was done.

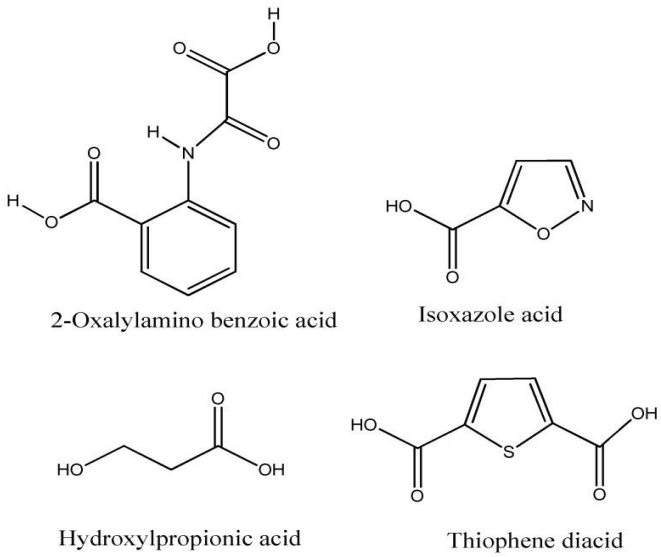

Figure 1: Structure of phosphotyrosine(pTyr)surrogate acids

2. Upcoming therapeutic Agents from Marine Sources

The marine environment is an unexploited source of bioactive compounds with high biodiversity, including fatty acids(especially polyunsaturated fatty acids) proteins, polyphenols, sterols ,sulfated polysaccharides and pigments(Lee, 2008, 2016; Mannikam, 2016; Ruocco, 2016; Saleh, 2016). Marine algae have been used increasingly as sources of metabolites having promising biological activities that include hypoglycaemic, antioxidant, hypotensive, hypolipidaemic, antibacterial and antiviral activities (Choochote, 2014; Zhao, 2014). Microalgae are thought to be healthy foods in view of their being rich in minerals along with dietary fibers. In the far east and Hawaii islands, Japan, Korea and China marine algae are taken traditionally as the common part of their diets. Over 9000species of microalgae are defined which can be classified as per their pigment composition into 3 classes, which are Phaecophyta, Rhadopyta and Chlorophyta (also known as brown, red and green algae respectively)(Khan, 2009).

Metabolites from different classes have been found from various marine plants, having in vivo pharmacological activities(Pangesturi, 2014) that are anticancer, antihyperlipidemic, antidiabetic, antihypertensive, antioxidant, antiinflammatory, anticoagulant, antiestrogenic. Antibacterial, antifungal, antiviral, immunomodulatory, neuroprotective and tissue healing properties(Mohamed, 2012). In view of characterization of a wide variety of bioactive metabolites from marine macroalgae, there has been increasing interest in the search of potential applications of macroalgae, whose metabolites act as functional constituents for human and animal health benefit(Gupta, 2011). Increasing use as food supplements along with anti diabetic purposes has been done regarding functional constituents of macroalgae(Pangesturi, 2014).Here the potential applications of marine microalgae and /or macroalgae derived bioactive metabolites for PTP1B1 inhibitory effects have been studied in detail.

3. PTP1BI Inhibitory Activity of Marine Derived Molecules

3.1. Ptb1b Inhibitory activity: In Vitro Findings

Roughly 300 natural products having PTP1BI Inhibitory activity were found and characterized from different natural sources ,many from marine origin(Jiang, 2012). The identification and isolation from deep water sponge Ircinia (unknown species) was the 1st marine metabolite that possessed PTP1BI Inhibitory activity(Scheen, 1999). Since then marine sponges have been thought to be important sourcesof PTP1BI Inhibitors having variable structures(Blunt, 2009), like polybromodiphenyl ether(Yamazalki, 2013), sequiterpenoids and sequiterpene quinines(Li, 2009). Still the novelty of marine resource scanning models has lead to the development of new studies

which target these resources for upcoming antidiabetic agents. Marine algae, seaweeds, soft corals, sponges and lichens are considered to be among these, since they exhibited PTP1BI Inhibitory effects by varying potencies.

3.1.1. Bromophenols

As they are the main parts of algae, they may be the ones that cause the antidiabetic activity which has been ascribed to marine organisms. The ability of the phenol moiety to undergo electrophilic bromination to varying degrees =>their production.

Bromophenols (Compound I-II)that are isolated from the red algae *Rhodomela confervoides* have potent PT1B1 inhibitory effects with IC_{50} values varying between 0.8 µM and 4.5µM(Kurihara 1999a, 1999b; Kwon, 2011; Shi, 2008, 2013). The changes in potencies can be due to the bromine content of these compounds or to their side chains. Conversely two bromophenols (compond12,13) from the Indonesian marine sponge *Lamello dysidea* herbacea have been found to have positive in vitro PT1B1 inhibitory effects, having IC_{50}values of 0.9µM and 1.7µM,respectively that were isolated by Yamazaki et al.(2013). Besides that other brominated phenols(compounds 14-16) that are isolated from the red algae Symphyocladia latiuscula also exerted positive PT1B1 inhibitory activity having IC_{50}values of 3.9 µM,4.3 µM and 2.7 µM respectively.

Besides these PT1B1 inhibitory activity, bromophenols also have strong α-glucosidase enzyme inhibitory effects. This α glucosidase enzyme plays a critical role in carbohydrate digestion, and thus a favoured target for antidiabetic drugs mainly in case of postprandial hyperglycemia. It has been suggested that Bis-(2,3dibromo-4,5 dihydroxybenzyl) ether (compound3 along with bis(2,3,6 –tribromo 4, 5 dihydroxybenzyl) ether, might be a future type of α glucosidase inhibitors (Kurihara, 1999a, 1999b; Kim, 2008, 2010). bis(2, 3, 6 – tribromo 4, 5 dihydroxybenzyl) ether showed the maximum potent α glucosidase inhibition activity as compared to the present series of bromophenols, having an IC_{50} value as low as 0.03µM(Kurihara 1999a). Conversely the lowest activity was shown by 2,4 dibromophenol(IC_{50}=110.4 µM).This may show that α glucosidase inhibition activity is related to bromination degree of these metabolite based on the inversely proportional relationship between their IC_{50} value and the number of bromines in metabolites. Similarly the enzymatic inhibition activity increases proportionately with the increase in number of phenyl units, Thus Bis-(2,3dibromo-4,5 dihydroxybenzyl)ether and bis(2,3,6 – tribromo 4,5 dihydroxybenzyl)ether,having a diphenyl unit ,show much greater activity than metabolites with a single phenyl unit like 3bromo-4,5 dihydroxy benzyl alcohol.Still the reason behind these changes in biological activity needs more work.

Along with PT1B1 andα- glucosidase enzyme inhibitory effects, some bromophenols also decrease aldolase reductase inhibitory effects. This aldolase reductase is thought to be the basic enzyme of the polyphenol pathway, that controls sorbitol formation from glucose and has an important role in degenerative complications resulting due to T2DM development(Susen, 2003). 2.2',3,6,6'-pentabromo-3' 4 4' 5 tetrahydroxy diphenyl methane, 2, 3, 6 tribromo,4,5dihydroxymethyl benzene and bis(2,3,6 – tribromo 4,5 dihydroxybenzyl)ether that are isolated from the red algae *S.lattiuscula* have been shown to be aldolase reductase inhibitors and hence can be of use in T2DM complications;like eye and nerve damage management (Wang, 2005).

Further Paudel et al. (2011) aimed to characterize the antidiabetic potential of 2,3,6-tribromo-4,5 dihydroxy benzyl derivatives from *Symphocladia latiuscula* via their inhibition of PTIB and α-glucosidases. Further this study used in silico monitoring and glucose uptake potential analysis in insulin resistant(IR)HepG2 cells to reveal the mechanism of antidiabetic activity. The bioassay –guided isolation led to the discovery of three potent bromophenols which act against PTIB and α-glucosidase:2.3.6- tribromo-4,5 dihydroxy benzyl alcohol(1), 2.3.6- tribromo-4,5 dihydroxy benzyl methyl ether (2) and bis-(2.3.6- tribromo-4,5 dihydroxy benzyl methyl ether(3). All compounds inhibited the target enzymes by 50% at concentrations below 10 µM. The activity of 1 and 2 was comparable to ursolic acid(IC_{50};8.66+_0.82 µM) however 3 was more potent (IC_{50};5.99+_0.08 µM) against PTP1B. Interestingly, the activity of 1and 2 against α-glucosidase was 30-110 times higher than acarbose((IC_{50};212.66+_0.35 µM).Again 3 was most potent α-glucosidase inhibitor(IC_{50};1.92+_0.02µM). Similarly 1-3 showed concentration dependent glucose uptake in IR HepG2 cells and downreguated PTPIB expression. Enzyme kinetics showed different modes of inhibition. In silico molecular docking simulations demonstrated the importance of the7-OH group for H bond formation and bromine /phenyl ring number of halogen bond interactions. These results suggest that bromophenols from *S.Latiuscula*, especially highly brominated 3 are inhibitors of, PTPIB and α-glucosidases, enhance insulin sensitivity and glucose uptake, and might represent a novel class of antidiabetic drugs(Paudel, 2019).

Li et al.(2019) used a structure based strategy to develop uncharged bromophenols as a new series of PTPIB Inhibitors. The most potent compound 22(LXQ46) inhibited PTPIB with an IC_{50} value of 0.190 µM and showed remarkable selectivity over other protein tyrosine phosphatases(PTPs, 20-200folds).In the SPR study ,increasing

concentrations of compound 22 led to concentration –dependent increases in binding responses, indicating the compound could bind to the surface of PTPIB via noncovalent means. By treating IR C2C12 myotubes with compound 22 ,enhanced insulin and leptin signaling pathways were observed. Long term oral administration of compound 22 reduced the blood glucose level of diabetic BKS db mice. The glucose tolerance tests(OGTT)and insulin tolerance test(ITT) in BKS db mice showed that oral administration of compound 22 could increase insulin sensitivity. Additionally long term oral administration of compound 22 could protect mice from obesity which was not a result of toxicity. The pharmacokinetic results of Li et al.(2019) from the rat –based assays showed that orally administered compounds 22 was absorbed rapidly from the GIT, extensively distributed to the tissues ,and rapidly eliminated from the body, all of which implied compound 22 could serve as a qualified agent for treating T2DM(Li et al., 2019).

3.1.2. Brominated Metabolites

Qin et al. (2010), assessed the in vitro PT1B1 inhibitory action of 2 brominated metabolites(compounds 17and 18)isolated from the red algae Laurencia similis. Both copounds showed PTI1BI inhibiton of IC_{50} values of 3.02 µM and 2.7 µM respectively. They also studied the activity of highly brominated merabolites(compounds 19-23)but the corresponding IC_{50}values that ranged from65.3 µg/ml to 102µg/ml. This might query the proposition that the bromination degree effect of the PT1B1 inhibitory effect in a directly proportinonate matter.

3.1.3. Poly bromodiphenyl Ether Derivatives

The Indonesian marine sponge *Lameladysidea* herbacea contains 6 polybromodiphenyl ether derivatives(compound 24-29), besides the ones mentioned above. All of these compounds showed in vitro PTP1B1 inhibitory action with IC_{50} values varying from 0.6 µM to 1,7 µM as demonstrated by Yamazaki et al. (2013). They also found out the activity of compound 24,25 in Huh -7,i.e, a well differentiated hepatocyte derived cellular carcinoma cell line which has been increasingly investigated, given its ability to secrete mitogen hepatoma-derived growth factor present in the serum. The IC_{50} values obtained for these compounds were 32 µM and 48 µM.

3.1.4. Phylorotannins

Back in 1977 Glombitza 1st introduced this term phylorotannins(Faulkner, 1977). They are a characteristic type of integral tannins found in brown algae, Alariaceae,and are mostly classified into 6 subclasses like eckols; fucols; phlorethols; fucophlorretols; fuhalols; and isofuhalols(Targett 1998; Ritta, 2008). Cellular signaling gets modulated by Phlorotannins=>regulation of various body conditions. Eckol and its derivatives(compounds30-35) that are isolated from the edible brown algae *Ecklonia stolonifera* and *Eisenia bicyclis* have been studied by a lot of workers,who found differing antidiabetic activities.The in vitro PT1B1 inhibitory action also varied, the IC_{50}values varied from 1.4 µMto 141.2 µM.

The lowest IC_{50} values were shown by phlorofurofucoeckol A(Compound 31) for both the enzymes. Conversely phloroguci nol(compound 34)that is actually the building unit of other polymer phlorotannins, had the greatest IC_{50}values for both the enzymes. Thus the activity is secondary to the product of polymerization and not due to the basic monomeric structures.

3.1.5. Sterols

More attention is required for these secondary metabolites. Few studies,that had been done in this field (Abdul, 2016; Zhou, 2014) concentrated on hydroperoxyl sterols ,epidioxy sterols and fucosterols that are contents of different marine invertebrates using sea sponge, Mycale species(Mycalidae), *Gorgionian Dichotella gemmacea* Milne Edwards and Haime(Ellisadea), algae, seaweed and diatoms. Various sterols (compounds 36-42)were identified in these various marine species, but their PT1B1 inhibitory effect has still not been determined, excepting compound 37(29-hydroperoxystigmasta-5,24(28) dien-3-ol) in which a positive effect was shown to be (IC_{50}=5.8 µM/ml)and compound 42 that showed moderate PT1B1 inhibitory action(Jung, 2013). Further studies on these compounds are encouraging with these results.

3.1.6. Terpenes

a) Sesquiterpenes

Sesquiterpene quinones (compound 43 and 44) isolated from the sea sponge Dysidea species, available in South China, were examined by different research groups(Li, 2009; Jiao, 2012; Zhang, 2009) with regards to its in vitro PT1B1 inhibitory action. These Sesquiterpene show positive PT1B1 inhibitory action, with IC_{50}values of 6.7 µM and 9.98 µM, respectively. Dehydrourysspongin A(Compound 45),another Sesquiterpene isolated from the marine sponge *Eury spongia* species, also showed positive action with an IC_{50}value of 3.6 µM(Yamazaki, 2013).

b) Diterpenes

Diterpenes were isolated from *Sarcophytontro chelliophorum*,i.e. a Hanon soft carol, received attention from Liang et al.(2013, 2014) over 2 weeks. They isolated 3 compounds (compounds 46-48], along with testing their in vitro PT1B1 inhibitory action. These diterpenes showed variable effects ,having IC_{50}values differing from 6.8 µM to 27.1 µM.

c) Sesterterpenes

The activity of 2 seterpenoids (compounds 49and 50) were examined from the sponge *Hippospongialachne* found on Yong xing island against PT1B1 via an invitro study by Piao et al(Piao, 2014). and found that they showed IC_{50}values of 5.2 µM and 8.7 µM respectively.

d) Triterpenes

Compound 51, that is a triterpene that got isolated from two sesterpenoids(compound 49and 50)from the Anarctic *Lecidella carpathica*, showed prominent in vitro antidiabetic activity through PTP family enzyme inhibition(Seo, 2011). It inhibited PT1B1(IC_{50}=3.7 µM) and T cell protein tyrosine phosphatase(TCPTP)(IC_{50}=8.4 µM) enzymes. Opposite to that, it showed greater IC_{50} values(exceeding 68 µM against the studied phosphatase enzymes. Src homology phosphatase 2(SHP-2),leukocyte antigen-related phosphatase(LAR), and protein tyrosine phosphatase receptor type C(PTPRC) also called CD 45antigen tyrosine phosphatase.
Stelletin G(Compound 52), is an isomalabaricane triterpene that got isolated from Hainon sponge *Stelletta* species by Xue et al. (2013). This compound also exhibited prominent in vitro PT1B1 inhibitory action(IC_{50}=4.1 µM). Isomalabaricanes are being tested with interest ,since most of them have shown promising in vitro cytotoxic effects(Fouad, 2006).

Further Zhang et al.(2019) showed that the methanolic extract of *Rubus chingii*(Chinese raspberry) fruits exhibited significant PT1B1 inhibitory ursane type triterpenes : ursolic acid (1), 2-oxopomolicacid (2), and 2α, 19α-dihydroxy -3oxo-urs-12-en -28-oic acid(3). Kinetic analysis revealed that 1was noncompetive PT1B1 inhibitor, and 2 and 3 were mixed type PT1B1 inhibitors. Compound 1-3 and nonstructurally related triterpenes(4-8) were further analyzed for the structure activity relationship and were evaluated for the inhibitory selectivity against 4 homologous protein tyrosine phosphatases (TCPTP,VHR,SHP-1 and SHP-2). Molecular docking simulations were also carried out ,and the result indicated that 1,3-acetoxy –urs 12-en -28-oic acid(5) and promolic acid(6) bound to the allosteric site including α 3,α 6,and α7 helix of PT1B1(Zhang, 2019).

3.1.7. Fungal Metabolites

On investigating the fungal strains derived from marine resources especially from *Penicillium* and *Eurotium* species Lee et al.(2013) and Sohn et al.(2013) found 7 compounds(compounds 53-59).These compounds showed moderate antidiabetic effects as PT1B1 inhibitors, having IC_{50}values that varied from 10.7 µM to64 µM, whereas compounds 58 and 59dispayed much lower IC_{50}values i.e. 5.3 µM and 1.9 µM respectively.

Aquastatin A (Compound 60) is also a fungal metabolite isolated from *Cosmospora* species has been highlighted by a lot of researchers(Debbab, 2010; Seo, 2009). Reason behind that is its low IC_{50}value against the PTP1B1 enzyme(0.2 µM), and secondly due to its selective inhibitory activity against others PTPs, including PCPTP, SHP-2, LAR, and CD45.

3.1.8. Miscellaneous Compounds

Furoxanthin, compound 61, is a carotenoid ,that was isolated from *Phaeodactylum tricornutum* and edible seaweeds, like *Eisenia bicyclis*(Arame), Undaria pinnatifida(Wakame), and Hi-jikia fusiformis (Hijki). Fucoxanthin lowered blood glucose and insulin levels along with water intake in diabetic/obese KKAy mice model. Marked decrease in mRNA expression levels of monocyte chemoattractant protein-1 and tumor necrosis α(TNFα) was seen that is thought to be involved in inducing insulin resistance. Significant PT1B1 inhibitory action was also found having an IC_{50}value of 4.5 µM(Jung, 2012; Maeda, 2007; Peng, 2011).
Brialmontin 1 and atraric acid(compound 62 and 63) were isolated by Seo et al.(2009), from *Lecidella carpathica,* and Antarctic lichen. Both of them had PT1B1 inhibitory action ,with IC_{50}values of 14 µM and 51.5 µM respectively.
Additionally ,crude extracts from other seaweeds, that included *Derbesia marina, Symphyocladia latiuscula,* Codium *adhaerens ,Attheya longicornis, Chatoceros socialis*. *Chatoceros furcellatus, Skeletonema marinoi,* and *Porosira glacialis* along with brown algae *Hisika fuziformis* have also been tested for their in vitro PT1B1 inhibitory action(Ingelbristen, 2015; Lauritano, 2016 ; Lee, 2007).
Moreover the ethanolic extract of brown algae, *S, serrratiofolium C. Agarth* showed broad PT1B1 and α-glucosidase inhibitory actions(IC_{50}=7.04 µg/ml and 24.16 µg/ml respectively)(Ali, 2017). Of the 4 subfractions of the ethanol extract, n-hexane showed the maximum activity(IC_{50}=1.88 and 3.16 µg/ml respectively), thus its major three plastoquinones-sargahydroquinoic acid, sarga chromenol, and sargaquinoic acid(compound 64-66) got isolated and the three compounds displayed potent PT1B1 inhibitory action. Sargachromenol displayed most promising α-glucosidase inhibitory actions having an IC_{50}value of 42.41 µM, followed by sarga quinoic acid having an IC_{50}value of 96.17+-3.48 µM, while sarga hydroquinoicacid was inactive.

Besides that curcumin and cinnamaldehyde had been few natural compounds shown to have antidiabetic and anticancer potential. Kostrzowa et al. (2019) showed that curcumin and cinnamaldehyde decreased activity of PTPIB, and had the inhibitory effects on the viability of MCF-7 cells. Curcumin had a significantly higher inhibitory effects than cinnamaldehyde which proved that curcumin can be considered a potential agent for the treatment of T2DM or cancer(Kosttrzewa, 2019)

3.2. In Vivo Findings of PT1B1 inhibitory action

Shi et al.(2008) examined the in vivo anti diabetic activity of marine plants in term of PT1B1 inhibitory action of highly brominated derivatives that were isolated from red algae *R.Conferoides*,that contains one or 2 2,3-dibromo-4,5 hydroxybenzyl units, In diabetic rats. *R. Conferoides* extract => a marked decrease in serum glucose levels. Thus these in vivo results might substantiate that the antihyperglycemic activity of R. Conferoides is partly due to the PT1B1 inhibitory action of its constituents(Shi et al., 2008). Also the antidiabetic activity of the microalgae *hapophyte Isochrys galbana* and the ochrophyte *Nannochlorosis oculata* in a diabetic rat model. Various biochemical parameters were tested, like glucose level, body weight, lipoproteins and nitrogenous compounds. Additionally gastrointestinal(GIT) histopathology was studied. Both microalgae studied => increase in low density lipoproteins(LPL)and a reduction in high density lipoprotein(HDL) levels in both control and diabetic rats.Specifically *l. galbama* reduced body weight, glucose, triglycerides and cholesterol levels and exhibited just signs of inflammation in the gut. This activity could be secondary to the high content of docosa hexaenoic acid(DHA) and the eicosa pentaenoic (EPA)fatty acids. The *N. oculan* treated diabetic group didn't show any changes in clinical values and had negative effects within the GI tract. More studies are needed to ensure the effective employment of *I, galbana* as an antidiabetic functional food.

4. Current usage and future Challenges

4.1. In vitro and in vivo concerns

T2DM in toto is a metabolic disease that is characterized by hyperglycemia and hyperinsulinemia, having the biggest risk factor as overweight or obesity(ADA, 2009). T2DM might result due to insulin secretion and or signaling deregulation by insulin receptors(IR)(Cheng, 2002). Action of PTP's in insulin signaling pathways and diabetes has been studied earlier by vanadium compounds, that are able to decrease serum glucose levels in both type1and type2 diabetic animal models (Fantus, 1995, 1998.). Vanadium compounds express both in vitro and in

vivo insullinomimetics. Hence oral administration of these compounds promote normalization of serum glucose levels in T2DM rats, increasing glucose uptake(Meyerovitch, 1987).Increased levels of hepatic cytosolic PTP action ,that reduced following insulin and vanadate treatment =>serum glucose utilization. PTB inhibition ,causing ultimate improvement of cellular tyrosine phosphorylation may explain these findings(Meyerovitch, 1989).

PTP1B enzymes =>the identification of JAK2 and tyrosine kinase 2(TYK2) as potential PTPIB substrates besides IR recognition. On interferon stimulation, both kinases were found to be hyperphosporylated in PTIB null fibroblasts(Myers, 2001). It got ascertained by the negative regulation of leptin stimulated JAK2 phosphorylation produced by PTPIB, that decreased leptin signaling in 2 models. The null PTPIB mutation was introduced into lept in deficient obese db/db mice, with a marked reduction in weight gain and enhancement of resting metabolic rates was shown in PTPIB deficient ob/ob mice. Further fat pads analysis hypothesized that weight changes could be a result of a reduction in adipose tissue(AT). Thus, in leptin absence, PTPIB loss can decrease weight gain without modifying food intake(Cheng, 2002; Zabotony, 2002). Substrate trapping trials that used caalytically inactive PTPIBD181A confirmed that leptin activated JAK2 is considered a PTPIB substrate, and leptin signaling decrease in obesity resistance mechanism in PTPIB null mice.

4.2. Human Concerns

Weight loss, along with improved insulin sensitivity are associated with reduced PTP activity along with LAR and PTP1B expression in humans in the AT(Ahmad,1997). PTP activity is not always related to its level of expression. PTP1B protein levels display a 3 to5 fold reduction in abdominal AT, in obese and diabetic subjects, whereas an appreciable reduction in PTP1B activity was observed /unit of PTP1B protein(Cheung, 1999). Another finding was that total cellular PTB, did not increase PTP1Bactivity=>a significant increase in AT in obese individuals. Further an increase in PTP activity but not an increase in PTP1Bactivity,is associated with decreased insulin –stimulated glucose transport, hypothesizing a tissue specific role in glucose homeostasis for PTP1B(Wu, 2003).

Besides that genetic evidence also links PTP1B in diabetes and obesity in humans. PTB 1B locus maps on chromosome 20 on the region of q13. 1-q13. 2, a region that is identified as a quantitative locus linked to insulin and obesity. A correlation between the role of PTP1B in IR and different polymorphisms has also been discussed. Thus a continuous need to identify new PTP1B inhibitors for diabetes and obesity control is required.

4.3. Culture Conditions-Concern

Various microalgae's antidiabetic activity cultured under stressful condition was also studied using PTP1B assay(Ingelbrigsten, 2015; Lauritano, 2016). The nonpolar fraction of five diatoms that were isolated from North Atlantic (*Attheys longicornis* ,*Chaetoceros socialis* .*Chaetoceros furcellatus* ,*Skeletonema marinoi* and *Porosira glacialis*)that were grown under different light/temperature conditions was studied by Ingelbrigtsen et al. (2015). *A. longicornis and C. furcellatus* extracts showed anti PTP1B activity. While *C. socialis* displayed activity only when cultivated under high temperature-low light conditions, on the other hand *P. glacialis* displayed activity only on cultivation in high temperature-high light conditions. But *S. marinoi* showed no activity in any studied conditions. The importance of culture conditions gets highlighted by these results in activating bioactive metabolites production.

A total of 32 crude extracts from microalgae species (four flagelles, seven dinoflagelles and 21 diatoms) were assessed by Laurinato et al.(2016) that were grown under different culturing conditions, Temperature/light stresses were more important than nutritional stress in microalgal species which had bioactive metabolites which have PTP1B enzyme inhibition.

5. Conclusions

Thus the above data stresses the importance of chemical constituents from various marine species, knowing that their PTP1B inhibition activity, plays crucial role as targets for T2DM and obesity management.
Despite various antidiabetic therapeutic strategies available at present, still a need to find more efficacious along with less toxic pharmacological agents is there. PTP1B has been identified as a promising molecular target for T2DM treatment, along with its major risk factor namely obesity. The problem faced lies in the closely related

enzymes that belong to the PTP family in view of their poor selectivity, that remains the main problem that has to be overcome for preventing side effects.

Marine metabolites recently got highlighted in the scientific community, since they are considered to represent a collection of different unexplored bioactivities and structural properties which could expand the chemical library and might provide potential targets for the discovery of novel PTP1B inhibitory agents. The other problem is in view of limited yields of marine metabolites, that interfere with their assessment through in vivo studies. Also it is seen that recent studies mainly concentrate on marine metabolites isolation and characterization as PTP1B inhibitors. Yet the underlying mechanism of action and structure activity relationship require more focus. Hence a lot of work needs to be done through high throughput screening of marine metabolites, with structural optimization and synthesis of new PTP1B inhibitors, for identification of selective ,safer and more efficacious PTP1B inhibitory agents in the coming future. Recently Efeltheriou et al.(2019) tried to find PTPIB inhibitors having high potency ,selectivity and bioavailability ,i.e. the most favourable characteristics of effective PTP1B inhibitors. They concluded that the search for finding PTP1B inhibitors started with the design of molecules that mimicked the tyrosine substrate of the enzyme. The study showed that an aromatic ring connected to a polar group, which preferably enables hydrogen bond formation, is the minimum requirement for small inhibitors binding to the active site surrounding Cys 215. Molecules bearing 2 hydrogen bond donor /acceptor (Hb d/a) groups at a distance of 8.5-11.5 A may form more stable complexes ,interacting simultaneously with a secondary area A2.Longer molecules with two Hb d/a groups at a distance of 17A or 19A may enable additional interactions with secondary sites (B and C) that confer stability as well as specificity. An aromatic ring linked to polar or Hb d/a) moieties is also used for allosteric inhibitors. A lower distance between Hb d/a moieties ,around 7.5A may favour allosteric interaction. Permanent inhibition of the enzyme by oxidation of the catalytic Cys 215 has also been referred .Moreover covalent modification of Cys 121, placed near but not inside the catalytic point has been associated with permanent inhibition of the enzyme(Elefthenou, 2019). Further Xin et al.(2019) prepared a series of cis and trans-pyrrolidine bisarylthene sulfonic acid esters and evaluated their PTP1B inhibitory potency, selectivity and membrane permeability. These novel stereoisomeric molecules especially trans-isomers exhibited remarkable inhibitory activity, significant electivity as well as good membrane permeability(e.g. compound 28a,IC_{50}=120,1940 and 267C n M against PTP1B,TCPTP and SHP2 respectively, and acid P_{app}=1.74x10^{-6}cm/s). Molecular simulations indicated that trans- pyrrolidine bisarylthene sulfonic acid esters yielded the stronger binding affinity than their cis isomers by constructing more interactions with noncatalytic sites of PTP1B.Further biological activity studies revealed that compound 28a could enhance insulin stimulated glucose uptake and insulin –mediated insulin receptor β(IRβ)phosphorylation with no significant cytotoxicity(Xin et al., 2019).

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