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The Protein Tyrosine Phosphatase PTB1B Role in the Development of Obesity, Diabetes, and Cancer and its Potential Inhibitors

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ABSTRACT

Protein tyrosine phosphatase 1 B (PTP1B) is involved in the development of obesity, type 2 diabetes, and different cancer cells, such as breast cancer and lung cancer. This makes the enzyme a promising target for the treatment of these diseases. The purpose of this review is to present the studies on the role of PTP1B in the development of obesity, diabetes, and cancer and selected inhibitors as a possible treatment. Studies have shown that PTP1B, due to its implication in obesity, type 2 diabetes, and oncogenic transformation, denotes a promising drug target. The selected compounds that are effective PTP1B inhibitors can be considered promising anti-obesity, anti-diabetic, and anticancer treatment.

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1. INTRODUCTION

Obesity and diabetes mellitus (DM) are among the greatest public health challenges of the 21st century as their incidence and prevalence are extremely increasing in the world[1, 2]. People with obesity are exposed directly to type II diabetes and various physical disabilities, psychological problems as well a high risk of developing several non-communicable diseases (NCDs), including cardiovascular disease and certain types of cancer[4, 5].The direct causes of obesity are difficult to discern due to the plethora of physiological changes associated with obesity but metabolic and genetic causes are the most important[6]. Metabolic causes are mainly due to an imbalance in the lipid metabolism which results in disruption of energy homeostasis[7, 8].Obesity is associated with an increased risk of developing multiple forms of cancer. It is estimated to cause up to 20 % of all cancers[9].

Today, diabetes is considered to be one of the most serious health problems in the world, affecting millions of adults[10]. Type 2 diabetes causes hyperglycemia due to impaired insulin secretion and/or resistance, which leads to severe complicationsincluding cardiovascular diseases, nephropathy, retinopathy, and peripheral neuropathy.Insulin, insulin secretagogues (sulfonylureas, glinides, dipeptidyl-peptidase IV inhibitors, and glucagon-like peptide-1 analogs), and insulin sensitizers(peroxisome proliferator-activated receptor (PPAR)g agonists) as well as insulin-independent drugs such as sodium-glucoseco-transporter2inhibitors can be used to treat hyperglycemia [11, 12]. Treatment of diabetic patients having insulin resistance and hyperinsulinemia with insulinsensitizersisbeneficial because these drugs are known to lower plasma glucose levelswithout increasing insulin levels, hyperinsulinemia is associated with a risk of developing obesity and cardiovascular diseases[13, 14]. In diabetic patients,pioglitazone,aPPARgagonist, has been used as an effective insulin sensitizer and it prevents macro-vasculopathy, but it may cause variousadverse effects including edema, obesity, and bone loss[15]. It is considered that PPARg agonists increase the fat mass by favoring the differentiation of adipocytes[16]. This is an indication that there is a need for insulin sensitizers that do not trigger PPARg.

Various cellular signaling pathways are involved in obesity and its complications[17, 18].Among these, signaling pathways regulated by protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs) are the most important[19-21].The mechanism by which the protein kinases and protein phosphatase enzyme regulate the signaling pathways is through phosphorylation and de-phosphorylation of proteins. PTKs mediate the phosphorylation of tyrosine residues in proteins, while protein tyrosine phosphatases (PTPs) de-phosphorylate

phosphorylated tyrosine[21, 22].They play important physiological roles and are involved in the pathogenesis of diseases such as diabetes, obesity, autoimmune disorders, cancer, and neurological disorders[22]. The reversible protein tyrosine phosphorylation catalyzed by the coordinated actions of these two families of the enzyme has great importance in the regulation of the signalingof processes in many physiological activities such as growth and proliferation, differentiation and survival or apoptosis, as well as adhesion and motility[23, 24].

From the family of PTPs the Protein tyrosine phosphatase 1B (PTP1B), a non-receptor type tyrosine phosphatase, has emerged as a critical regulator of multiple signaling networks involved in human disorders such as diabetes, obesity, and cancer because it mediates the de-phosphorylation of key proteins in different signaling pathways[25, 26]. PTP1B has been reported to be overexpressed in type II diabetes and obesity and it contributes to oncogenic properties through activation of the non-receptor tyrosine kinase Src[19, 27-29]. The genetic deletion of PTP1B increases insulin and leptin sensitivity, indicating the importance of PTP1B inhibitors[30]. In this article, scientific reports on the role of PTP1B in the development of obesity, diabetes, and cancer andits potential inhibitorswere reviewed.

2. INSULIN SIGNALIN PATHWAY

Insulin is a peptide hormone that has an anabolic effect and is produced by the B cells of the pancreas. It acts via the receptors located on the target organs like the liver, skeletal muscle, fat, and others, where it has pleiotropic effects[31-33]. In the liver, it promotes glucose storage into glycogen and decreases glucose output and in the fat, it stimulates glucose transport through translocation of GLUT4[34, 35]. All of the proteins involved in insulin action in the body, as well as the factors that regulate this action, make up the insulin signaling pathway (Fig. 1)[36, 37].Insulin's signal transduction pathway is mediated by the insulin receptor (IR) on the cell membrane[38, 39].Based on whether the IRS (insulin receptor substrate) is mediated, IR-mediated signal transduction pathways can be categorized into IRS-mediated signal transduction pathways and non-IRS-mediated signal transduction pathways[37, 40].In the insulin signal cascade, the insulin-boundinsulinreceptor (IR),insulinreceptorsubstrate(IRS),and Akt are sequentially phosphorylated, resulting in glucose up-take via the translocation of glucose transporter type 4 (GLUT4)[41-43].

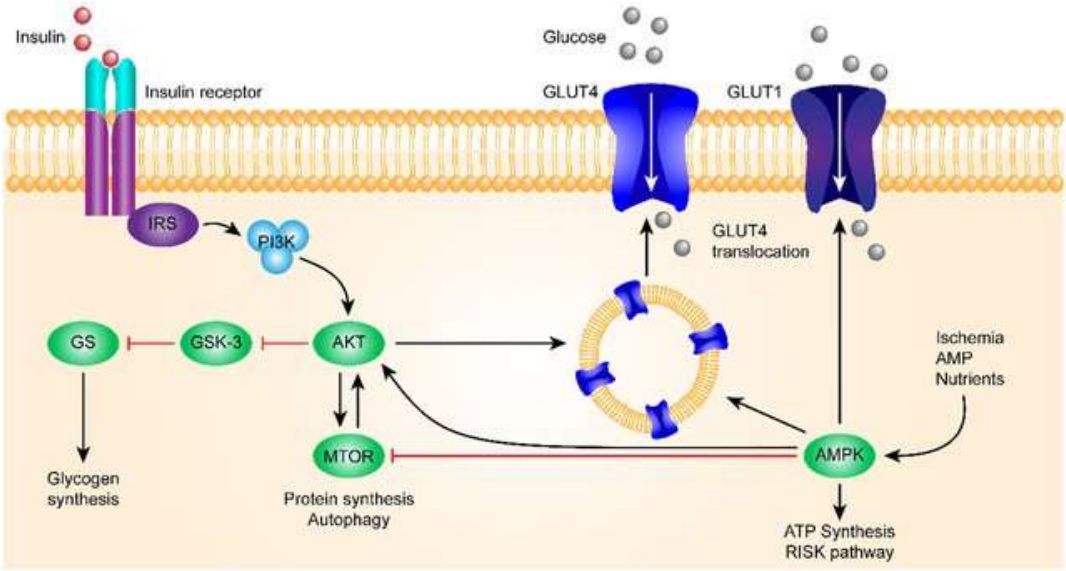


Figure1. The insulin signaling pathway, Adapted from "Metabolomics of type 1 and type 2 diabetes," by Arneth, B., Arneth, R., & Shams, M. (2019), *International journal of molecular sciences*, *20*(10), 2467[44].

3. LEPTIN SIGNALING PATHWAY

Leptin is a critical hormone that regulates mammalian energy homeostasis [45, 46]. It is primarily synthesized and secreted by white adipose tissue and mediates its effects by binding to leptin receptors (LepRs) expressed in the brain and several peripheral tissues to maintain energy balance[47, 48]. LepRb is strongly expressed in the hypothalamus and other areas of the brain[49]. Leptin plays an important role in regulation of food consumption, energy expenditure, metabolism, neuroendocrine axis and immune function[50, 51]. The binding of this hormone to its receptor in the brain leads to the activation of multiple signal transduction pathways[52, 53]. Circulating leptin levels in the blood are directly related to the amount of body fat, reflecting the state of long-term energy reserves[54, 55]. Leptin levels fluctuate with changes in caloric intake, with a marked decline during starvation and an increase in overnourished and obese states[56-58]. Leptin levels increase with insulin,

glucocorticoids and pro-inflammatory cytokines and decrease with catecholamines [59, 60]. The ob/ob mice, which are Leptin deficient and db/db mice, which are LepRb-deficient have shown hyperphagia, extreme obesity, infertility, and reduced linear growth[53]. In human loss of function or congenital deficiency of leptin or mutations of the leptin receptor (LepRb) caused hyperphagia and morbid obesity[61, 62].

3.1. **Leptin signaling and energy homeostasis**

Leptin is strongly expressed in the hypothalamus, especially in the arcuate nucleus (ARC) and the ventromedial hypothalamus (VMH)[63, 64]. Multiple signaling pathways like Janus kinase 2 (JAK2) /signal transducer and activator of transcription 3 (STAT 3) and STAT5, IRS/PI3K, SHP2/MAPK, and AMPK/ACC are activated by binding of leptin to LepRb (Fig. 2)[53, 65, 66]. The Binding of leptin to leptin receptors activates JAK2, which results in phosphorylation of the receptor, thereby recruiting signal transducer and activator of transcription 3 (STAT3)[67, 68]. STAT3isphosphorylatedbyJAK2,whichregulatesappetite and energy expenditure[69, 70].Activated JAK2 stimulates phosphorylation of STAT3 which regulates appetite and energy spending[71]. Tyrosine residues Tyr985, Tyr1077, and Tyr1138 are phosphorylated in the cytoplasmic domain of LepRb by activated JAK2[72]. LepRb affects energy homeostasis through both tyrosine-dependent and -tyrosine-independent mechanisms. Activation of JAK2/STAT3 by leptin is crucial for energy homeostasis and neuroendocrine function[48, 73].

Two neuronal populations in the ARC co-expressing proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART), and agouti-related peptide (AgRP) and neuropeptide Y (NPY) are directly targeted by leptin[72, 74]. Leptin reduces food consumption, increases spending of energy, and decreases body weight by stimulating POMC/CART expression and inhibiting AgRP/NPY expression[63, 75, 76]. In the lateral hypothalamic area (LHA), this hormone also hinders food consumption by down regulation of melanin-concentrating hormone (MCH) and orexins[77, 78]. Also, it is involved in the inhibition of feeding by stimulating the expression of brain-derived neurotrophic factor and steroidogenic factor-1 (SF-1) neurons in the VMH[79, 80]. Induction of a suppressor of cytokine signaling 3 (SOCS3) ends the leptin signaling cascade[81, 82]. SOCS3 inhibits JAK2/STAT3 signaling, providing a negative feedback mechanism[83]. Additionally, PTP1B is associated with the negative regulation of leptin signalling [84, 85]. Leptin resistance is a condition observed in obese individuals, in which there is a high level of adipose leptin expression and plasma leptin, but unable to decrease excess adiposity[47].

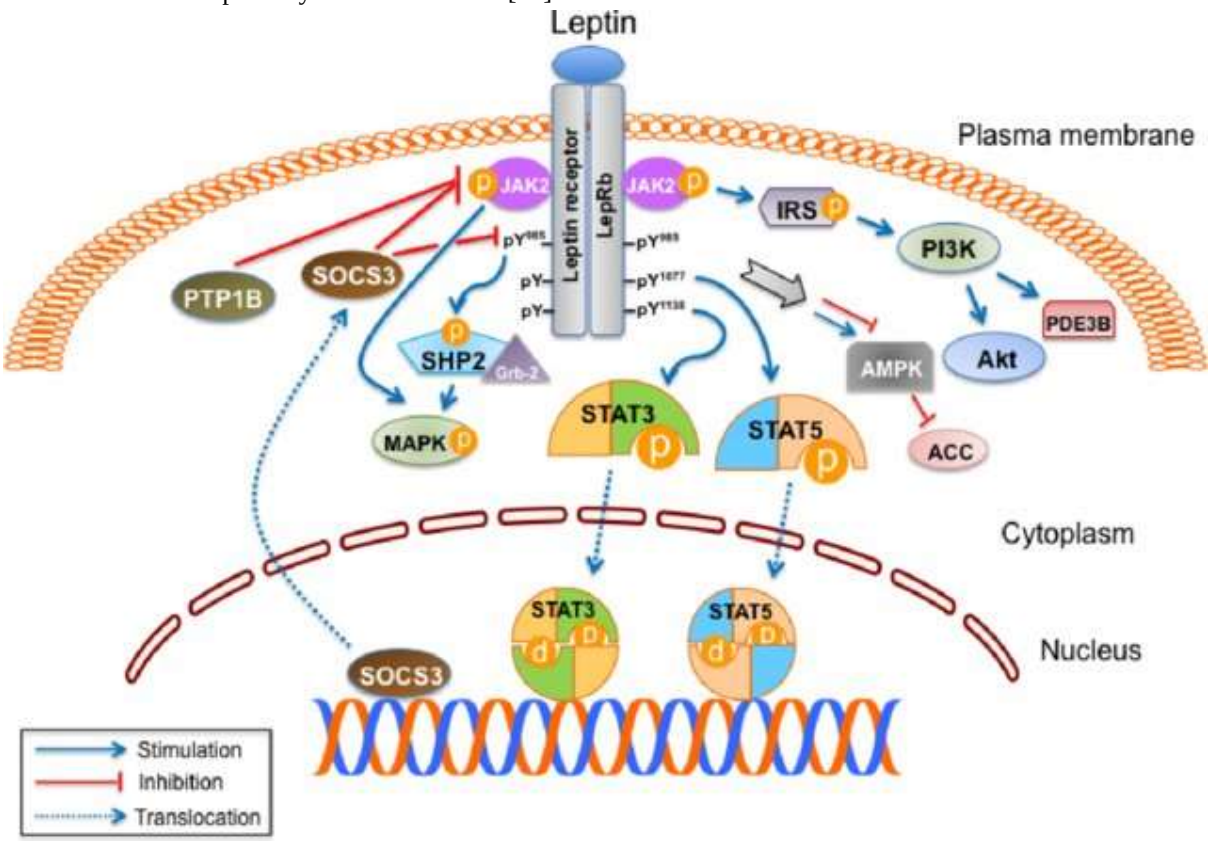


Figure 2. Multiple leptin signaling pathways, Adapted from "Leptin signaling," by Park, H. K., &Ahima, R. S. (2014), *F1000 prime reports*, *6*, 73. https://doi.org/10.12703/P6-73[53]

4. ONCOGENIC SRC KINASES

Enzymes that mediate the transfer of the phosphate group to tyrosine residues of the target protein are those belonging to

the tyrosine kinase enzyme family[86, 87]. These enzymes regulate physiological processes by transmitting signals from the surface of the cell to cytoplasmic proteins and the nucleus[88, 89]. Non-receptor tyrosine kinases (NRTK) are a sub-group of tyrosine kinases[89]. Non-receptor tyrosine kinase Src, are important components of signaling pathways that regulate fundamental cellular functions such as cell differentiation, apoptosis, survival, and proliferation[90, 91]. Deregulation, constitutively hyper-activation, and/or overexpression of non-receptor tyrosine kinase Srchas been implicated in malignant transformation and carcinogenesis[89, 92]. Src kinase activity has been reported to be higher in many cancer cell lines, like breast cancer, lung cancer, and colon cancer cells[93-95]. There are several different ways in which Src is controlled[96]. The two main phosphorylation sites on human Src are the autophosphorylation site Y419 and the negative regulatory COOH-terminal phosphorylation site Y530[97].

5. PROTEIN TYROSINE PHOSPHATESES (PTP)

Protein tyrosine phosphatases (PTPs) are enzymes that catalyze the dephosphorylation of phosphorylated tyrosine (Tyr) on the target protein[98]. PTPs are signaling enzymes involved in the control of various cellular functions in the body[99, 100]. The PTPs are involved in the development of many diseases, understanding the mechanism of action of these enzymes is important to know enzyme's activity[101]. A protein phosphatase, an enzyme that removes a phosphate group from the phosphorylated amino acid residue of its substrate protein is divided into two main groups based on substrate specificity[102]. Protein phosphatases (PPs), enzymes that specifically hydrolyze serine/threonine, and protein tyrosine phosphatases (PTPs) enzymes that hydrolyzephosphotyrosin[102, 103]. PTPs are involved in the dephosphorylation of the target proteins like mitogen-activated protein (MAP) kinases and receptor kinases, resulting in the proper regulation of various signal-transducing pathways[104, 105]. The PTP superfamily of enzymes functions in a synchronized manner with the protein tyrosine kinases to control signaling pathways that underlie several fundamental physiological processes[106]. As a superfamily, despite the diversity in size, spatial structure, or intracellular location, PTPs are characterized by a homologous PTP signature motif, (I/V) HCXAGXXR(S/T) G, and a catalytic WPD loop, which are highly conserved in the catalytic domain from bacteria to mammals[107, 108]. Among the PTP families, the Protein tyrosine phosphatase 1B (PTP1B) is the most important enzyme in obesity, diabetes, and cancer[84, 109].

6. PROTEIN TYROSINE PHOSPHATESES 1B (PTP1B)

PTP1B is one of the families of protein tyrosine phosphatese enzymes that participate in intracellular signaling and metabolism by dephosphorylation of tyrosine residue, serves as a negative regulator of leptin and insulin pathways, and has an important role in cancer development[87, 110, 111]. It is a widely expressed cytosolic soluble protein with a molecular weight of around 50 kD[112]. Full-length PTP1B comprises 435 amino acids and has a canonical PTP domain with ~280 residues in the N-terminal[108, 113]. For crystallization and enzymatic assays, shorter versions of PTP1B (298 or 321 residues) are usually employed[114]. The 298 residue version is organized in eight α helices and eleven β strands[114]. R loop (Val113–Ser118), lysine loop (Leu119–Cys121), WPD loop (Thr177–Pro185), S loop (Ser201–Gly209), Q loop (Ile261–Gln262), α3 helix (Glu186–Glu200), α6 helix (Ala264–Ile281) and α7 helix (Val287–Ser295)[114, 115]. The crystallographic studies show that the WPD loop of PTP1B exhibits an open or a closed state[116]. Opened state of the WPD loop makes the binding pocket easily accessible to the substrate[116]. When the substrate binds to the WPD loop, the conformation of the loop changed to a closed state to form a tight binding pocket. Thus, the WPD loop is essential for the catalytic function of PTP1B[117, 118]. In the dephosphorylation process by PTP1B, the enzyme and phosphotyrosine-containing substrate form an enzyme-substrate complex[119]. The binding of the substrate results in a conformational change of the enzyme by moving the WPD loop from the open state to the closed state, optimizing the interactions of its residues, Phe180 and Asp181, with phosphotyrosine[114, 120].

PTP1B is a therapeutic target for the development of drugs against obesity, type2 diabetes, and cancer[121, 122]. It has been shown that inhibition of PTP1B enhances the activity of insulin and leptin, and decreases the activity of non-receptor tyrosikinesSrc, by increasing phosphorylation at Y530 of Src[84, 85, 123]. In obesity, it negatively regulates leptin signaling through the de-phosphorylation of Janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3)[30, 124]. In the case of diabetes mellitus in the insulin signaling pathway, it has been shown to directly interact with the activated insulin receptor (IR) or insulin receptor substrate-1 to dephosphorylate phosphotyrosine residues, thus further reducing insulin sensitivity or shutting down signalling [125]. The over-expression of PTP1B has been shown to inhibit the IR signaling cascade and the expression of PTP1B increases in the insulin-resistant state[126, 127]. Different studies indicated that PTP1B is the primary phosphatase dephosphorylates Src in several human breast cancer cell lines and suggest a regulatory role of PTP1B in the control of Src-kinase activity[128, 129]. These make PTP1B a

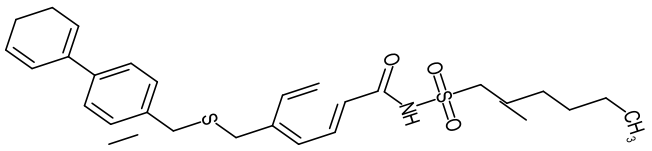
highly validated therapeutic target for obesity and diabetes[48].

7. INHIBITION OF PTP1B

Remarkable progress has been made in the development of potent and selective PTP1B inhibitors that target both active and allosteric sites [130, 131]. Inhibitors of PTP1B against the active site are difficult to discover because of the highly conserved sequence[132]. There are also multiple charge requirements of the ligands, which leads to loss of selectivity and permeability in the catalytic site[114]. A secondary allosteric site has been designated for PTP1B and several small-molecule inhibitors that occupy this site stabilize an inactive conformation of PTP1B[133]. The Discovery of the allosteric site creates opportunities to develop selective inhibitors against PTP1B[134, 135]. Allosteric inhibition of PTP1B activity using different inhibitor molecules is a promising technique to overcome the challenges of targeting the active/ catalytic site[134, 136]. Targeting the allosteric sites as drug discovery, have fewer side effects, good selectivity, higher specificity, and lower toxicity[137]. This is because it is not well conserved, possesses is substantially less polar compared with evolutionarily conserved catalytic sites[138]. More potent and orally bioavailable allosteric inhibitors are strongly desired as excellent anti-diabetic, anti-obesity, and anti-cancer drugs[139].

8. POSSIBLE INHIBITORS OF PTP1B

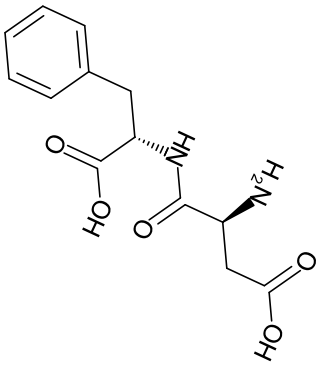
According to Morshta et al., (2017) [140]and Ito et al., (2018)[107]4-(biphenyl-4-ylmethylsulfanylmethyl)-N-(hexane-1-sulfonyl) benzoylamide (KY-226)(Fig.3) was identified asa non-competitive inhibitor which bound to the allosteric site of PTP1B with potent and selective inhibitory activity against (IC50=0.25 µM). Studies showed that the oral absorption of the compound in mice is high and there is maximum drug concentration[107, 141]. The pharmacological evaluation of KY-226 showed that the compound inhibited human PTP1B activity (IC_{50} ¼ 0.28 mM), but did not exhibit PPARg agonist activity [107]. KY-226 protects neurons from cerebral ischemic injury by inhibiting the PTP1B[141, 142]. In human hepatoma-derived cells (HepG2), KY-226 (0.3e10 mM) increased the phosphorylated insulin receptor (pIR) produced by insulin[107]. The studies concluded that KY-226 exerted anti-diabetic and anti-obesity effects by enhancing insulin and leptin signaling, respectively.



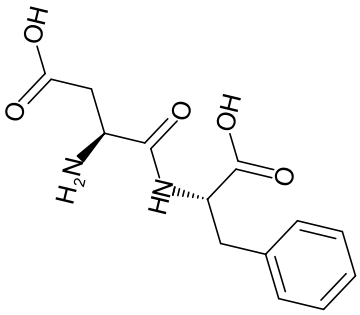
KY-226, IC50=0.25 µM [138]

Figure 3. KY 226 PTP1B allosteric inhibitor

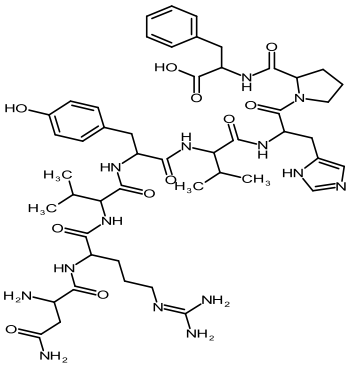
Recently, numerous studies have shown the possible treatment options for obesity, diabetes, and cancer using peptides[28]. Small peptide compounds can be used as specific inhibitors for PTPs (Fig 2.)[143]. Using peptides as PTP1B inhibitors is beneficial because peptides have less toxicity, less immunogenicity, are rapidly synthesized, and are easily modified[144, 145]. Studies showed that dipeptides and tripeptides were capable of binding and interacting to the allosteric site of PTP1B [28, 131, 143, 146]. The peptide compounds tested as inhibitors of PTP1B decreased the enzymatic activities with IC_{50} values in micro-molar ranges[147].



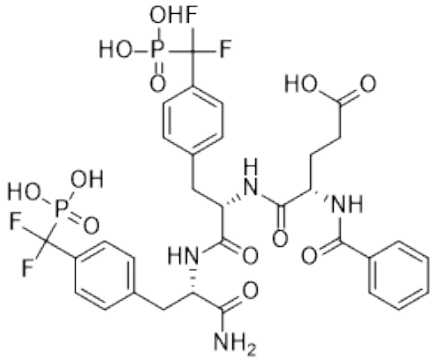
phe – Asp,
IC_{50} = 52.10 µM [143]



Asp-phe ,
IC_{50} = 52.60 µM[143]



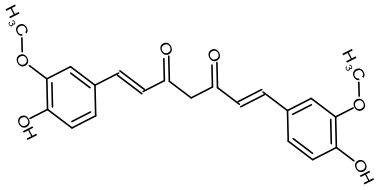
EJJ- Amide
IC_{50} = 40.00 nM[3]



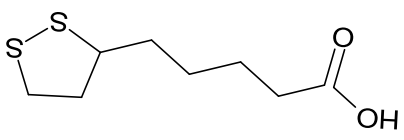
BzN-EJJ-amide
IC_{50} = 5.00 nM [8]
IC_{50} = 1.00 nM[8]

Figure 4.Selected peptide PTP1B inhibitors

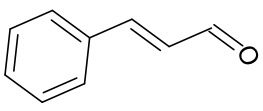
Studies indicated that different natural compounds inhibit various types of enzymes, including PTPs[148]. These inhibitorscan be considered as potential anti-obesity, anti-diabetic and anticancer agents[149, 150]. Some of these PTP inhibitors can be extracted from plants, algae, or microorganisms[151, 152]. Among natural molecules, alpha-lipoic acid**,** Curcumin, and cinnamaldehydehave beenpreviously reported to have anti-diabetic and anticancer potentials byinhibitingPTP1B [153, 154].



Curcumin [152]



Alpha-lipoic acid (ALA)
[153]



Cinnamaldehyde
[153]

Figure5. Selected natural compounds that decrease the activity of PTP1B

CONCLUSION

In conclusion, PTPs control the levels of protein tyrosine phosphorylation both in normal and disease conditions and it has both positive and negative effects on cellular signal transduction. This enzyme is involved in the development of diseases like obesity, diabetes, and cancer. PTP1B serves as a negative regulator of leptin and insulin signaling pathways and has an important role in cancer development. It is a therapeutic target for the development of drugs against these diseases.

CONFLICTS OF INTEREST

There are no conflicts of interest to disclose regarding this study.

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