

A REVIEW ON PROTEIN TYROSINE PHOSPHATASES - AN IMPORTANT TARGET FOR VARIOUS DISEASES

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ABSTRACT

The enzyme protein tyrosine phosphatase (PTP) is responsible for the regulation of cellular functions including cell growth, replication, and signal transduction. Dysregulation of this enzyme leads to various diseases including Type II diabetes and cancers as well. The PTP enzyme functions as a promising drug target for these diseases, leading to new innovations in developing new drug targets in the field of clinical studies and pharmacology. The PTP is considered as the next generation drug targets. The protein tyrosine drug targets can be targeted to cure the diseases caused due to its dysregulations. However, due to its complex structure and highly conserved active sites are the major challenges which block this strategy. Moreover, two enzyme proteins PTP A and PTP B of PTP enzyme family are essential for the survival of *Mycobacterium* in host macrophages and cause infection resulting in chronic tuberculosis. The novel drug-like properties of L335-M34 and L01Z08 compounds are selective inhibitors of this enzyme responsible for the tuberculosis virulence in mammals. Some of the commercial inhibitors such as ertiprotafib, arylbenzonaphthofurans, and arylbenzonaphthothiophenes have also proven to inhibit the enzyme's virulence. This review summarizes the latest innovations to lead a map for developing new innovative drugs against the various classes of target enzymes of tyrosine phosphatase.

Keywords: Protein tyrosine phosphatase, Diabetes, Cancer, Tuberculosis.

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INTRODUCTION

Protein tyrosine phosphatases (PTPs) (PTPase; EC 3.1.3.48) are the enzymes that cleave and remove the phosphate groups from the phosphorylated tyrosine residues present in the proteins. This process is referred to as protein tyrosine (pTyr) phosphorylation. PTP along with protein tyrosine kinases (PTKs) modulates the proper cellular level of pTyr phosphorylation process. pTyr phosphorylation is one of the typical post-translational modification processes of proteins by creating a unique idea for various processes such as cellular localization, regulation of the protein activity, and also affects protein stability, as a result of which the maintenance of appropriate levels of pTyr phosphorylation is beneficial for many cellular activities. PTPs catalyze by cleaving and removing the phosphate group that is adhered to the tyrosine residues with the help of a cysteinyl-phosphate enzyme intermediate. These enzymes play a key role in the cell signal transduction pathways, cell growth, and replication, the transformation processes and cytoskeletal activity which response to various stimuli. The PTPs also act as tumor repressors and in T-cell activation. PTP plays a major role in curing oncogenes and as well as pathogenesis caused due to bacterial infections. Improper function of the PTKs and phosphatases are related to the analysis of numerous human diseases, including cancer, diabetes, and immune dysfunction. The main attributes and functions of PTP will govern the process of phosphorylation of cell signal transduction pathways like mitogen-activated protein kinases. The major roles of this enzyme are cell growth, replication, differentiation, mitosis, the transformation of oncogenes, and receptor endocytosis (Dutta *et al.* 2015).

The active site of the enzyme

Determining the active site of the enzyme PTPs plays a major role in the inhibition of its virulence. Several studies are going onto inhibit the enzyme's activity by finding a suitable ligand that could bind to the cleft pocket efficiently. PTPB possesses similar central, canonical and also 4 stranded parallel β sheets with the PTPs. In comparison with the complexity of structure PTPs such as PTP1B and PTPB, the PTPB is intensely diverged and structurally simplified. The PTPB is structurally homologous to PTP1B (Fig. 1). With the disparity to the diverged folds,

the enzyme PTPB projects the similar active center region as that of other PTPs (Grundner *et al.*, 2005). In the active site of this enzyme, the catalytic cysteine, Cys160 is present within the loop P concurrence sequence with the amino acids His Cys Ala Gly Arg in between the $\alpha 6$ helix and $\beta 5$ sheet positions on the protein. The sulfur thiol group of the Cys160 is located for the nucleophilic attack on phosphate which makes a hydrogen-bonded ion pair with the buried side chains of amino acids Lys164 and Arg166. The phosphate group present in the protein is located at the N-amino terminal of the $\alpha 6$ present within the helix axis. The dipole of $\alpha 6$ helix, Arg166 and the partial positive charges on the loop P amide hydrogens subscribes to the binding cleft which is complementary to the phosphate group. The carbonyl oxygen of the amino acid Cys160 is in direct contact with the amide nitrogen of the amino acid Glu32 containing side chains paired with the amino acids Arg56 and Arg64 (Grundner *et al.* 2005).

The amino acid Asp82 which is corresponding to Asp181 in the enzyme PTP1B is located inside the modified motif WPD with the sequence fixed partial denture (FPD). The motif FPD is located within the loop connecting $\alpha 4$ and $\beta 3$. The active center region consists of nearly all segments that are conserved in the sample of 60 PTPB homologs. The highest conserved regions include P loop, first turn of the following helix and the FPD loop which rings the binding site of the phosphate group. The $\alpha 3$ helix influences the depth, and the efficiency of the binding of the substrate to the cleft on the enzyme and sequences preceding the kink of the $\alpha 7$ helix are also conserved elements. The buried side-chain residues this preceding sequence of $\alpha 7$ is in contact with the P loop located within the active center influences the electrostatic potential at the catalytic center (Grundner *et al.* 2005).

METHODS

PTPs importance in tuberculosis infection, diabetes, and Cancer *PTPs in tuberculosis*

Mycobacterium tuberculosis is a Gram-positive and non-motile bacterium. Theia pathogenic bacterium contains various signal transduction pathways [1,2]. The *Mycobacterium* is the causative agent



Fig. 1: Three-dimensional structure of mycobacterial enzyme protein tyrosine phosphatase B

for the deadly tuberculosis disease which affect one-third of world's total population because of its multidrug-resistant and extremely drug-resistant strains and as a result, of which there is an immediate necessity for alternative fast curative new and improved therapeutic regimen to augment the rate of treatment [1]. The main target for the mycobacteria is the host macrophages that play a major role in defense mechanism against foreign invading antigens such as a pathogen and destroy them [3]. The emerging treatment process aims to diagnose the target the virulence factors that are responsible for the development and replication of the causative microorganism [4,5]. There are two types of PTPs in *Mycobacterium* species genome: *Mycobacterium* PTPA (mPTPA) and mPTPB and lacks the PTK [5]. Both the mPTPA and mPTPB are released into the cytoplasm of the host macrophage. Although both mPTPA and mPTPB are responsible for TB infection, the major role is played by the mPTPB in TB infection in animals and humans. The two enzymes are needed for the optimal survival of the bacteria in the host macrophages as well as in animal models [6]. The mycobacteria lack endogenous PTP mPTPA and mPTPB reinforce the mycobacterial infections by acting on macrophage proteins to modulate the host-pathogen interactions. It has been revealed that the absence of tyrosine phosphorylation in the *Mycobacterium*, the mPTPA and mPTPB are likely to modify the host macrophage protein for the host-pathogen interactions. Fortunately, the genetic deletion of the mPTPB reduces the chances of survival and inhibits the survival of *Mycobacterium* in the interferon (IFN- γ) activated host macrophages, especially in the lungs of animals [6,7]. The inhibitions of both mPTPA and mPTPB activity increase the host intrinsic signaling pathways to eradicate the tuberculosis infection. The chemical inhibitors are more efficient than the biological inhibitors by reversing the modified host immune responses enhanced by the mycobacterial phosphatases and diminishing the mycobacterial survival in the host macrophages and are widely practiced [8]. Pharmacokinetic studies revealed that a chemical inhibitor isoniazid-rifampin-pyrazinamide (HRZ) is one of the effective inhibitor of tuberculosis in guinea pigs and other mammals [8].

Role of mPTPB in enhancing the survival of the Mycobacterium in host macrophage

The mPTPB secreted by the *Mycobacterium* is considered one of the most vital virulence factors which are secreted into the cytoplasm of the host macrophage which is essential for the microbe to grow and infect. The IFN- γ is the principal inflammatory cytokine which is the prime responsible factor the antimicrobial activity of the host macrophage against infectious pathogens. It is still now a hypothesis that mPTPB may promote the survival of the *Mycobacterium* in the host macrophage which targets the IFN- γ mediated signal transduction

pathways; however, the correct mechanism of this occurrence has not been clarified.

Tyrosine phosphatase as therapeutic targets for Type II diabetes

Recent studies say that PTP is a negative regulator of the insulin regulatory signaling pathways (Kennedy 1999). The non-insulin relied on diabetes or Type II diabetes mellitus reaching plague proportions in many developing and developed countries. The prime reason for the Type II diabetes in humans is mainly caused as a result of obesity; around 75% of the obese people acquire diabetes (Kennedy 1999). There was been only very negligible studies on the activity of the enzyme PTP in Type II diabetes (Kennedy 1999). The quantification of the enzyme PTP activity form the muscle tissue of the obese, and insulin-resistant non-diabetic sufferers and controls of the lean insulin-sensitive patients were reported first by McGuire *et al.* They reported and concluded that in insulin-resistant sufferers, the PTP enzyme activity was around 33% higher when compared to the controls and concluded by stating that this augmented levels of the enzyme PTP activity could be the reason for the Type II diabetes in sufferers. There were many more successive studies conducted to quantify the activity of the PTP enzyme in humans by Kusari *et al.* who quantified the activity of the enzyme from the lean controls, non-immune dependent diabetes mellitus and obese insulin-resistant non-diabetic sufferers stated concluded that there is a 21% decrease in the activity of the enzyme PTP activity in the muscle samples when compared to the lean controls, which is in contrast to the previous discovery of (McGuire *et al.*). The cause for this discrepancy between these two discoveries states that still, the role of PTP enzyme activity in humans remains unclear. On the other hand, PTP plays a major role in diabetes regimen in humans. PTP is a well-known target for obesity and Type II diabetes [9-11]. Recent studies reveal that PTP is also a potential target for breast Cancers. The PTP1B encoded by the PTPN1 gene is an expressed non-clinical receptor PTP containing 435 amino acids [12,13]. The amino acids contain the N-amino terminal domain, hydrophobic C-carboxyl terminal, and two proline amino acid-rich sequences. Biochemical studies reveal that PTP1B is a key negative regulator of leptin pathways and insulin, which are monitors and regulators of energy utilization, glucose equilibrium, and body weight balance [14]. PTP1B antibodies and inhibitors increase the insulin receptor substrates, insulin receptors, and STAT3 phosphorylation and stating that PTP1B inhibition could refine insulin sensitivity and leptin signal pathways [15,16]. The PTPN1 deficient in mice studies show the augmented insulin sensitivity and lectin sensitivity levels and exhibits lower insulin levels and lower blood glucose levels and also showed resistance to high-fat diet enhanced weight gain [17]. Diabetes mellitus a long-term metabolic disorder is caused mainly due to high blood sugar levels caused due to lack of secretion of insulin in the body by the pancreas. Type II diabetes is often due to the improper and poor nutritional diet and obesity and poor metabolism. The Type II diabetes is most common when compared to Type I diabetes in patients. With this regard, the PTP1B has been recognized as a unique novel drug target for diabetes and obesity [17]. One of the best drug target inhibitors is the second generation antisense inhibitor of PTP 1 or PTP1B is the ISIS-113715 which showed improvements significantly enhances glucose metabolism along with the reduction in the low-density lipoprotein (LDL). They are also involved in the transfer of fat molecules around the body to every cell and improper regulation of LDL result in the progression of atherosclerosis due to the oxidation of LDL in the walls of arteries.

Tyrosine phosphatase as therapeutic targets for Cancer cells

PTP1B is considered as one of the best potential tumor suppressors; however, many recent advances reveal that PTP1B also act as tumor enhancer [18]. Recent studies have found that the PTP1B activates the breast cancer cells which are a non-receptor PTK family. PTP1B enzyme dephosphorylates the negative regulatory residue of Y530 in c-Src cancer cell lines. It has been recorded that the overexpression of the PTP1B genome in 72% of the 29 human breast cancer samples tested when compared healthy controls [19]. The overexpression of

the PTP1B gene was observed and detected in all the stages of benign and malignant tumor cases, and its expression was correlated with the overexpression of the ERBB2 genome which is a most commonly amplified receptor in PTK in breast cancer [20].

To further study about the role of PTP1B in breast cancer, several experiments were performed on mice. Mice expressing activated genes of ERBB2 were interrelated by crossing with the PTPN1-null mice [20]. The results were interpreted, and when compared to reference mice, the PTPN1-null mice showed a delay in the onset of a tumor and decreased rate of lung tumor metastasis. Deferred tumor outbreak and slow rate of metastasis were also observed after its treatment with PTP1B inhibitor. PTP1B also play a positive role in colorectal cancer cells (He et al. 2014). The inhibition of PTP1B leads the way for the discovery of novel strategy for the treatment of various human tumors [20].

Selective PTP inhibitors

Inhibitors of *Mycobacterium pathogenesis*

The *Mycobacterium* virulence in mammals can be inhibited by blocking the active center of the virulence causing enzyme, PTP. There are only a few commercial inhibitors available, namely L335-M34 and L01Z08 (Dutta et al., 2015); this is due to the presence of a highly conserved active site in the enzyme, bioavailability, and many difficulties in attaining the selectivity of inhibitors. The highly conserved regions of the enzyme PTPs provide many considerable challenges and threats that tend to selectively inhibit the target enzyme without disturbing the other phosphatase enzymes. To harbor phosphor-substrates, the PTP enzyme active site possesses positive charges which complement the negatively charged molecules in the high throughput screening campaigns which ultimately agonize from poor membrane permeability. To overcome the bioavailability issues, natural compounds, and plant phytochemicals which possess pharmacological drug PTP inhibitory properties and as well as FDA approved compounds can be utilized. For example, benzofuran salicylic acid is a well-known inhibitor of the PTP enzyme. The inhibitor L335-M34 (Fig. 2) is highly specific and selective against the enzyme mPTPA with inhibitory concentration (IC_{50}) of 160 nanomolar (nM) and does not have any significant role on PTPB or at a concentration of mPTPs <3 μ M as mPTPA is a secreted virulence factor in the *Mycobacterium* that regulates the host antibacterial response [21].

The inhibitor L01Z08 (Fig. 3) of the L01 family consists of three highly selective inhibitors against mPTPB enzyme with IC_{50} of 2.5 μ M (Dutta et al., 2015). The inhibitor L01Z08 is the most potent available inhibitor for the mPTPB in the anti-tuberculosis activity [22].

The two inhibitors are the most effective commercial inhibitors used against the PTP activity thereby reducing the risk of tuberculosis in animals. Often, the two inhibitors L335-M34 and L01Z08 are used in combination which enhances the antitubercular regimen [21,22]. The two inhibitors in combination subsequently reduce the bacilli burden in the host macrophage (Dutta et al. 2015).

Inhibitors of cancer

The enzyme PTP1B of PTP enzyme class encoded by the PTPN1 gene is a non-receptor Class I PTP enzyme. This enzyme possesses a PTP domain, anchored hydrophobic endoplasmic reticulum present at the carboxyl-terminal. Recent researches revealed to activate c-Src by the dephosphorylation of inhibitory pTyr-530 [23]. This c-Src-mediated activation is required for the transformation of the MCF10A by the ErbB2 thereby contributing to the tumor development SW48 colon cancer in mammals [24,25]. P62Dok is a known substrate which p120RasGAP which shows negative regulatory functions on the Ras-Erk1/2 pathway [26]. Another feature of PTP1B is that this enzyme promotes cell migration [27]. The enzyme PTP1B is been overexpressed in several cancers/tumors such as ovarian and the breast cancers and correlates with the overexpression of ErbB2 [28]. Several studies on this enzyme reveal the mammary gland tumorigenesis in transgenic mouse models;

the deficiency of the enzyme PTP1B delays the onset of tumors which are induced by ErbB2 and possesses resistance to metastasis of lungs; whereas the overexpression of PTP1B in mammary glands of humans results to the development of mammary gland metastasis [20,29]. Hence, the effect of PTP1B deficiency performed using a transgenic mouse as models correlate with the reduced activation of Erk signaling pathway [29]. Hence, these results conclude, the enzyme PTP1B is a tumor inducer and is a therapeutic potential drug target in ErbB2 receptor breast cancer. The PTP1B also performs dual roles in cancer that is both the tumor promoter and tumor suppressor [29]. An experiment on PTP1B deficient p53 null mice is more susceptible to the B-cell lymphomas correlating with the reduced natural cell death (apoptosis) and is a negative regulator. As soon as the identification of PTP1B drug targets for cancers, several inhibitors have been discovered to inhibit its activity [30].

The compound with IC_{50} 120 nM (Fig. 4) (Han et al., 2008) acts as a potential orally bioavailable inhibitor with a very good pharmacological and pharmacokinetic property [31-33]. This compound also works efficiently against controlling blood sugar levels as well. This compound works well when administered to ErbB2 induced mammary gland tumor null mice model organism through oral administration with a dosage of 30 mg/21 consecutive days delays the mammary gland tumor development [30,31]. And also this compound was not specific to the PTP1B enzyme, and possess cross-inhibition of many other PTPs contributes to the anti-tumor effects. Hence, this research evidence

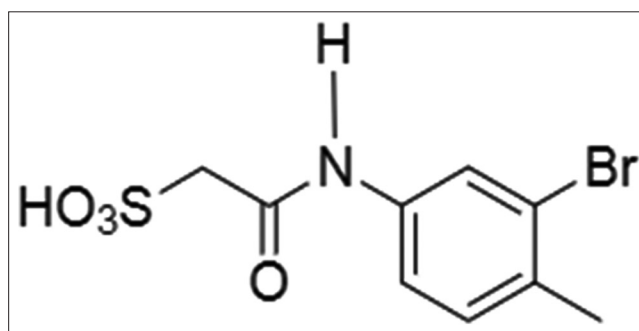


Fig. 2: Structure of the L335-M34 inhibitor

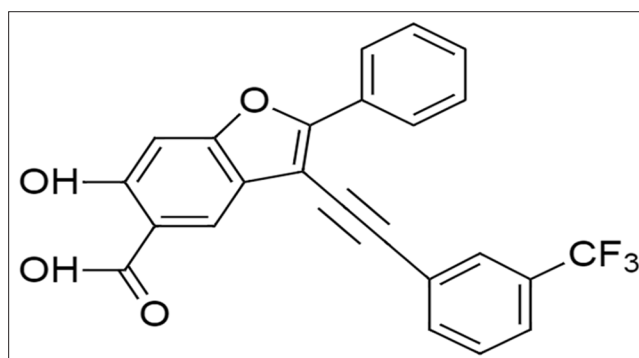


Fig. 3: Structure of the L01Z08 inhibitor

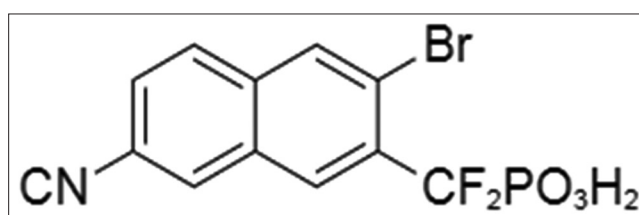


Fig. 4: Structure of the compound inhibiting protein tyrosine phosphatase 1B

contributes the truth of using PTP1B as drug targets for the intercession of ErbB2 dependent breast cancers [32,33].

Inhibitors of diabetes mellitus

After the discovery of PTP1B as molecular drug targets, there are several pharmaceutical companies involved in the discovery to inhibit the activity of the enzyme, since targeting the active site of the PTP1B enzyme will be more effective in the regimen of disease like diabetes thereby increase the insulin sensitivity in mammals [33]. The enzyme PTP1B dephosphorylates the insulin-producing receptors in the organism that is responsible for insulin signaling and secretion and thereby its contribution to its resistance to Type II diabetes in mammals [33]. However, unfortunately, it is difficult to determine a safe, selective, more efficient, and effective inhibitors of the PTP1B enzyme and is probably critical to design the inhibitor [34]. One major challenge in the development of inhibitors for Type II diabetes is due to cell permeability to reach the target. Several structure-based drug designing processes of molecular ligand-macromolecule docking are been widely performed to inhibit this enzyme [34]. Several researchers came up with the idea of using vanadium compounds as inhibitors. However, the vanadium compounds are competitive inhibitors of the enzyme PTP1B and are not considered specific to the target [35]. The K_i values (inhibition coefficient) of vanadium inhibitors are 380 nM. Vanadium is not well absorbed in the body; however, organic vanadium compounds have a lower K_i value and are well absorbed in the body [36,37].

Clinical trials were performed on vanadium compounds like vanadyl sulfate showed a better efficacy, and heavier dosage was less practiced due to augmented side effects on gastro intestine. Groves *et al.* performed several experiments and discovered that the attachment of difluoromethylene phosphonic acid group to one of the peptide substrate of PTP1B has shown to possess an effective quality of an inhibitor. Bisphosphorylated substrate tends to bind more efficiently with the binding sites of the PTP1B enzyme having a very low nM concentration of inhibition coefficient. Salmeen *et al.* showed that the PTP1B uses its second phosphate binding site through crystallographic studies of the enzyme protein, and moreover, inhibitory peptides did not bind to the second phosphate binding site, instead second phosphate group of the enzyme PTP1B has interacted with the amino acid Arg 47 [10,38]. Thus, these studies reveal that the other interactions connecting PTP1B and the insulin receptors may tend to place the second pTyr into the second phosphate binding region of the enzyme [38]. There are several other known classes of novel inhibitor compounds such as arylbenzophenofurans and arylbenzophenothiophenes that have proven to augmented insulin sensitivity in model organisms in rodents [11,39].

Ertiprotafib (Fig. 5) a lipophilic molecule (Shlomit Koren 2007), after efforts were studied and are currently used for the treatment of Type II diabetes by increasing the insulin sensitivity. This compound has successfully reached levels up to Phase II clinical trials in the regimen of Type II diabetes and showed very good effects. *In vivo* treatments of ertiprotafib on rodents showed to be inconsistent in PTP1B inhibition and are shown to be an effective inhibitor of PTP1B and also an activator of PPAR γ and α subunits [11,31,40].

Strategies that modulate PTP activity

There are many ways that modulate the activity of the PTP enzyme; one such design is that to develop mimetic dependent non-hydrolysable small molecules. This method is one of the most popularly used and has successfully produced various potential inhibitors of PTP [17,41]. However, this strategy has several challenges due to the specificity of conserved PTP structure and also due to cell permeability due to positively charged active sites of PTP and also several *in vitro* and *in vivo* studies have to be performed to determine the identification optimization specific substrates for inhibition on the target, analyzing the toxicity and pharmacological drug-like properties profiling which requires great efforts. The cell permeability and inhibitors specificity

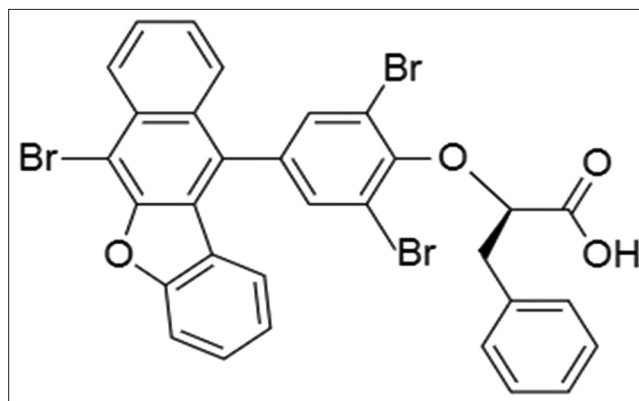


Fig. 5: Structure of ertiprotafib

are the major factors that are to be considered for creating new drug targets to inhibit the PTP activity as these enzyme domains are tumor suppressors and should not be unintentionally targeted [21].

Targeting the allosteric sites of PTP1B creates high cell permeability and high specificity inhibitors and allosteric sites are not needed to possess negative charges and as a result of which making the pharmacological properties more efficient and potent [42]. This also has challenges as the allosteric sites are not well defined as the active sites of the enzyme. Other strategies include mechanism-dependent inhibitor techniques that inactivate the PTP enzyme's catalytic cysteine amino acid residues by oxidation or by any other modifications in its terminals. This type of strategy takes place in quinone based inhibitors. The quinone based inhibitor induces reactive oxygen species and may cause *in vivo* toxicity by inactivating the redox-sensitive enzymes [43]. The *in vitro* activities are not suitable and not pleading for drug development [43,44]. The irreversible and selective kinase inhibitors have generated covalent enzyme inhibitors [44-46]. In comparison with quinone based PTP inhibitors, the irreversible inhibitors do not target all the redox-sensitive enzymes in the cell; instead, the inhibitors target only one sensitive enzyme [46]. Recent studies reveal that PTP1B and low molecular weight PTP have reported to decrease the blood glucose levels, increase the insulin regulation, and control obesity in clinical studies as a result, of which makes it is more liable for therapeutic applications [47,48]. In many conditions, small interfering RNAs can also be used in targeting PTP through similar mechanism pathways [49,50].

CONCLUSION

The PTP enzymes dysregulation is the cause for major diseases including tuberculosis, cancer, diabetes, and obesity in humans [2,51-54]. These diseases can be prevented by inhibiting the activity of the PTP enzyme and play a major role in drug discovery and development [51,55]. PTP acts as potential drug targets which enable strategies to develop modern treatment regimen [56-59]. For instance, the PTP1B and the low molecular weight PTP are well known for their activity against tumor and insulin resistance thereby suppressing the tumor/cancer [55,60]. SHP2, PRLs, and LMWPTP phosphatases are involved in controlling tumorigenesis, which led the way for the development of various drugs against metastasis tumor in humans [61]. Although a large number of PTP targets are recognized, there is a lack in the commercialization of PTP inhibitors by pharmaceutical industries; this is because of several key challenges that block the strategy for the development of PTP drug targets. Due to highly conserved active sites and diverged folds, it becomes difficult to target only PTP targets and PTP contains highly positive charges in their active site and contains cysteine amino acid residues which are catalytic [56,57]. Several natural compounds such as plant phytochemicals such as flavonoids, terpenoids, and phenolic have found to be effective inhibitors of the PTP enzyme by binding to the active center thereby inhibiting the activity of the enzyme and other secondary metabolites [62,63]. Recent discoveries on plant

phytochemicals against the PTP enzymes include *Psidium guajava* (Myrtaceae) leaf extracts which have one of the highest efficiency on the PTP enzyme active center inhibition to cure diabetes [63,64]. Natural plant phytochemicals such as curcumin as a ligand also showed high efficiency in binding with the active site of the PTP enzyme in prostate cancers through *in silico* docking analysis [65,66]. Compounds isolated from *Sorbus commixta* (Japanese flowering plant); lupeol and lupenone are also found to inhibit the PTP1B enzyme efficiently [67]. Therefore, PTP is an enzyme and is used as a novel drug target in the regimen of several mammalian diseases and disorders.

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CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest.

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