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Diterpenes as PTP1B Inhibitors for the Treatment of Diabetes Mellitus 2 and Obesity: An in-depth Literature Review and Computational Study

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Abstract: Protein tyrosine phosphatase 1B (PTP1B) negatively regulates insulin signaling pathways, reducing sensitivity to the enzyme and making it a promising therapeutic target for type 2 diabetes mellitus (DM2) and obesity treatment. This study aims to identify diterpenoids from natural sources as potential drug candidates for DM2 and obesity by inhibiting the PTP1B enzyme, evaluating drug-receptor interactions, and assessing pharmacokinetics through computational studies and literature review. A total of 96 diterpenes were analyzed for potential interactions and binding affinity with the PTP1B enzyme. The literature review utilized different electronic databases. Molecular docking was conducted to estimate binding affinities against PTP1B (PDB ID: 7LFO) and drug-receptor interactions and receptor-active sites were also examined. Physicochemical properties, drug-likeness, and pharmacokinetics of selected diterpenoids were predicted using SwissADME and ADMETlab 2.0 tools. Results showed IC_{50} values of selected diterpenes ranging from 0.90 ± 0.06 to 80.40 ± 0.60 µM, with the control oleanolic acid (OA) showing 4.71 ± 0.16 µM. In computational studies, compound 15 exhibited the highest binding affinity (–8.5 kcal/mol) toward PTP1B. Other compounds, including 17, 72, 27, 86, 85, 89, 91, 42, 43, 73, 90, 39, 51, 53, 20, 62, 67, 68, and 63, demonstrated elevated binding affinities of –8, –7.9, –7.8, –7.7, –7.7, –7.7, –7.6, –7.6, –7.6, –7.6, –7.5, –7.5, –7.5, –7.4, –7.4, –7.4, –7.4, and –7.4 kcal/mol respectively, where OA expressed binding energies of –7.7 kcal/mol.

Keywords: Diterpenes; PTP1B inhibitors; Diabetes mellitus; Molecular docking

1. Introduction

Diabetes mellitus (DM) is a metabolic condition that is rapidly spreading and affecting people all over the world. DM characterized by hyperglycemia is a condition of excessive amount of sugar in the blood stream. DM can be categorized into several types but most commonly into two types. Type 1 diabetes is also known as insulin-dependent diabetes and is mostly brought on by the destruction of pancreatic cells, which results in a lack of insulin. And type 2 diabetes is also recognized as non-insulin dependent diabetes mellitus. The primary initiating factor of type 2 diabetes is insulin deficiency (Alam et al., 2014; Bastaki, 2005). IDF reports that 537 million people (20-79 years) are living with diabetes and according to WHO, non-insulin-dependent DM represents more than 95% of the diabetes incidence. As the condition worsens, tissue or vascular damage results, which can cause serious diabetes consequences such as retinopathy, neuropathy, nephropathy, cardiovascular issues, and ulceration (Alam et al., 2014). However, currently, type 2 diabetes is treated with insulin injections and other oral hypoglycemic medications. But, in comparison to other glucose-lowering treatments, certain studies have revealed that the use of insulin is linked to an increased risk of cardiovascular events, cancer, and all-cause death (Holden et al., 2015). Additionally, alternative treatments, such as oral hypoglycemic medications, were ineffectual. Therefore, researchers from all over the world are working to develop more secure and efficient medications for treating DM. Zhang and Zhang (2007) found that the protein tyrosine phosphatase 1B (PTP1B) could be a drug target for treating obesity and type 2 diabetes (Zhang & Zhang, 2007)

PTP1B also known as protein tyrosine phosphatase non-receptor type 1 was initially discovered in a human placental protein extract

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and widely distributed in human tissues such as liver, adipose tissue, muscle, and brain (Barrett et al., 1999; Tonks, 1988; Zabolotny et al., 2008). PTP1B has negative control of both insulin and leptin signaling, making it a promising therapeutic target for the treatment of DM2 and obesity (Zhang & Zhang, 2007). In the insulin signaling pathway, PTP1B can dephosphorylate the phosphotyrosine residues of activated insulin receptor kinases (IRKs) or insulin receptor substrates (IRSs) thus reducing or shutting down insulin sensitivity (Cicirelli et al., 1990; Seely et al., 1996; Zhao et al., 2018). On the other hand, in the leptin signaling pathway, PTP1B performs the dephosphorylation of the leptin receptor (LepR) and janus kinase 2 (JAK2), which is associated with both obesity and Alzheimer's disease (Bence et al. 2006; Vieira et al. 2017). The enzyme is also involved in cancer and inflammation by regulating cytokine signaling pathways (Lessard et al., 2010; Feldhammer et al., 2013). According to a study, insulin-resistant diabetes patients have elevated protein levels, and it has been demonstrated that in mice, deleting PTP1B increases insulin sensitivity (Ahmad et al., 1997; Elchebly et al., 1999; Klaman et al., 2000). Therefore, it is suggested that PTP1B inhibition is a novel target that precisely treats insulin resistance sensitization. Inhibiting PTP1B also results in weight loss, which is beneficial for reducing obesity, a significant factor in the pathophysiology of type 2 diabetes (Koren & Fantus, 2007). Consequently, the primary focus of PTP1B inhibitor research is on natural and therapeutic plants, microbes, and animals (Nguyen et al., 2019).

Continuous attempts are being made to find new types of PTP1B inhibitors from natural sources that could be used as therapeutic candidates from natural sources a number of active chemicals have been discovered, including fatty acids, phenolics, terpenes, alkaloids, steroids, N- or S-containing compounds, and other miscellaneous compounds (Jiang et al., 2012; Zhao et al., 2018). Diterpenoids are a significant subgroup of the terpenes family of naturally occurring compounds. They have demonstrated a wide range of actions, and several of these molecules have received patent rights. Researchers report that numerous diterpenes from natural source have significant inhibition capability with strong interaction of PTP1B in treatment of DM2 (Zhao et al., 2018). Diterpenoids also have other medicinal benefits, such as the fact that naturally occurring diterpenoids also exert a number of biological effects such as anti-inflammatory action, cardiovascular effects, antimicrobial, cholesterol-lowering effect, anti-HIV, antifertility, neurotrophic, antispasmodic activities and anticancer (de Oliveira et al., 2008; Nie et al., 2021)

Nowadays, computational approaches are frequently utilized to speed up the lengthy and expensive drug discovery process (Palermo & De Vivo, 2014). The methods used in drug discovery and development allow for quick screening of a large compound library and the estimation of possible binders using modeling/ simulation and visualization tools. Additionally, it aids in the prediction of pharmacokinetics (PKs) and binding sites, both of which are essential for determining the mechanistic steps and binding when identifying and producing promising drug candidates (Sliwoski et al., 2014; Palermo & De Vivo, 2014; Ghosh et al., 2025). The objective of this study is to find diterpenoids from natural sources as promising drug candidates in the treatment of DM by inhibiting the PTP1B enzyme and to evaluate drug-receptor interactions as well as PKs through computational study and literature.

2. Methods

2.1. Literature review

The literature review of diterpenoids was drawn by PTP1B inhibition activity for the treatment of DM and obesity on the basis of PubMed, Elsevier, Springer, ScienceDirect and Google Scholar database information. The review was conducted up to 2022 and listed the information from the data sources with the aid of keyword, ‘diperpenoids', or ‘diperpenes’ pairing with PTP1B inhibitors. The review part was assessed in detail and summarized information about the source of diterpenes, IC_{50} values, and mechanism of action against the target. The data are collected from the studies which are involved *in-vitro* investigation.

2.2. Selection and preparation of ligands

We selected 96 diterpenoids for investigation and oleanolic acid (OA) as control based on literature review. 3D conformers of the selected compounds which are available in the PubChem chemical database (https://pubchem.ncbi.nlm.nih.gov/) were collected in SDF format and unavailable 3D conformers in PubChem were drawn by the aid of Chem3D 16.0 software. The compound CID (for PubChem database) which is drawn in our lab mentioned in Table 4. After collection and drawing, the 3D conformers of the chemical agents were minimized and saved in SDF files and converted into SMILES (file) through the Chem3D 16.0 program package for performing molecular docking and predicting ADMET, respectively. The two-dimensional images of the chemical agents are displayed in **Figure S1**.

2.3. Preparation of the receptor

Based on the literature review, we targeted PTP1B (PDB ID: 7LFO, source: *Homo sapiens*) responsible for the treatment of DM. 3D structure in PDB format of the targeted receptor (prepared by: X-RAY DIFFRACTION, Resolution: 1.94 Å, R-value free: 0.243, R-value work: 0.200) was gathered from the RCSB Protein Data Bank (https://www.rcsb.org/). After collection, the receptor was optimized to avoid docking interference by deleting all unnecessary molecules e.g., lipids, water molecules, and heteroatoms from the sequence of protein keeping chain ‘A’ via the PyMol software package (v2.4.1). Finally, energy minimization and geometry optimization of the receptor were carried out through the SwissPDB Viewer software package by appealing to the GROMOS96 force field and saving the PDB file to perform molecular docking (Bhuia et al., 2025a; Al Hasan et al., 2025).

2.4. Molecular docking and estimation of drug-receptor interactions

Molecular docking was performed by utilizing the PyRx software package to predict the active binding potential of the drugs against the active sites of the receptor (7LFO). For performing docking the receptor and the ligand (s) are enclosed in a grid box and the grid box dimensions were set as 76.37×55.95×83.32 Å and the calculation was run at 200 steps. The result of the docking potential is saved as.csv format and the complex of ligand-protein is collected in PDB format for collecting the ligand in pdbqt format. The interactions of ligands-receptors and the receptor’s active site were observed under the Discovery Studio Visualizer (v21.1.020298) and PyMol (v2.4.1) program packages and amino acid residues of receptor (7LFO) that interacted with the drug are listed (Bhuia et al., 2025b).

2.5. Prediction of drug-likeness and pharmacokinetics

Drug-likeness is a qualitative measurement employed in drug design and development to assess how the chemical compound acts like a drug with respect to factors like bioavailability and it is also related to ADME (Bhuia et al., 2025c). Drug-likeness and PKs of a chemical agent can be estimated through various online servers and software. In this study, we described various factors for assessing the selected molecule’s physicochemical properties and drug-likeness important in drug development with the aid of SwissADME (http://www.swissadme.ch/index.php) online tool. The PKs properties (ADME) and toxicities of the chemical

compounds were evaluated accurately and comprehensively through ADMETlab 2.0 online platform (https://admetmesh.scbdd.com/service/evaluation/index).

3. Results and discussion

3.1. Literature review

Diterpenoids are promising drug candidates for the development of a PTP1B inhibitor for the treatment of diabetes mellitus type 2. In a recent study by Gao et al. (2022) several diterpenoids were isolated from the Xisha soft coral *Clavularia viridis* and among the isolated compounds, clavurol E **(37)** exhibited a significant inhibitory activity with an IC_{50} value of 14.5 μM against PTP1B for the anti-diabetic target (Gao et al., 2022). A serrulatane diterpenoid named eremoglabrane D **(47)** was isolated from the leaf resin of *Eremophila glabra* (R.Br.) Ostenf. also showed a considerable PTP1B inhibitory activity with an IC_{50} value of 64 ± 6 μM (Petersen et al., 2022). In another study, 7-oxo-dehydroabietic acid **(11)** and 15-methoxy-7,13-abietadien-18-oic acid **(19)** diterpenes demonstrated significant inhibitory effects with IC_{50} values of 3.1 and 6.8 μM, respectively against PTP1B among 21 structurally diverse diterpenoids isolated from the leaves and twigs of the endangered conifer *Torreya jackii* Chun (Li et al., 2022). In an enzymatic investigation, acrepseudoterin **(31)** yielded by the Antarctic lichen-derived fungal strain *Acremonium* sp. SF-7394 exhibited a dose-dependent inhibition activity with an IC_{50} value of 22.8 ± 1.1 μM (Kim et al., 2021). Literature showed that the plant *Rhododendron molle* retains remarkable inhibitory activity against the enzyme and several isolated compounds from the plant demonstrated significant inhibition in an *in vitro* analysis, such as mollactone A (**59**), mollactone B **(60)**, mollactone C **(61),** rhodomollacetal A **(72)** and rhodomollanol A **(73)** with IC_{50} values of 4.24 ± 0.21, 2.69 ± 0.23, 3.33 ± 0.22, 42.42 ± 1.40 and 24.32 ± 0.56 μM respectively (Zhou et al., 2020b; Zhou et al., 2017a; Zhou et al., 2017b). In addition, two novel diterpenoids 14β,19-diacetylpimara-15-ene **(16)** and 1β,19-diacetylpimara-15-ene **(1)** isolated from the seeds of *Phalaris canariensis* L. exhibited a notable hypoglycemic activity confirmed through the *in vitro* analysis of PTP1B inhibition with IC_{50} values of 6.9 ± 2.07 and 6.5 ± 1.43 μM as well as *in vivo* hypoglycemic investigation in streptozotocin-induced diabetic mice with 54.27% and 55.65% fasting glucose level reduction respectively (Perez Gutierrez et al., 2020). Three cembrane-type diterpenoids such as jatrophainolide A **(54)**, jatrophainolide B **(55),** and jatrophainolide C **(56**) were isolated from the root bark of *Jatropha integerrima* Jacq expressed potential inhibition against the enzyme with IC_{50} values of 6.38, 25.9, and 27.4 μM, respectively (Zhang et al., 2020). A study by Zhou et al. (2020) confirmed that several diterpenes and their analogs isolated from the tuber of *Icacina oliviformis* have crucial PTP1B inhibition activity. Among the isolates, oliviformislactone A **(63)**, secopimaranlactone A **(81)**, secocleistanthone A **(79)** and 12-hydroxyicacinlactone A **(15)** demonstrated a prominent inhibition with IC_{50} values of 6.78 ± 0.41, 32.20 ± 0.59, 3.24 ± 0.14, 12.72 ± 0.53 and 58.05 ± 2.51 μM respectively (Zhou et al., 2020a). Several pimarane diterpenes such as siphonol A **(84)**, orthosiphol B **(64)**, orthosiphol I **(66)**, orthosiphol N **(67)**, and orthosiphol G **(65) were** isolated from *Orthosiphon stamineus* Benth exhibited a prominent hypoglycemic activity by inhibiting the enzyme with IC_{50} values of 8.18 ± 0.4, 9.84 ± 0.33, 0.33 ± 0.07 and 1.60 ± 0.17, and 3.82 ± 0.20 μM respectively, in their PTP1B inhibition assay (Nguyen et al., 2019). In a study by Lei et al. (2019) several diterpenoids along with other terpenes isolated from the twigs of *Pseudolarix amabilis* manifested notable hypoglycemic activity by inhibiting PTP1B in an *in vitro* investigation, and it was ascertained that the ditepenes from the plant pseudolaric acid A **(71)**, pseudolarate B **(70)** inhibit the enzyme emphatically with IC_{50} values of 8.5 ± 3.8 and 10.9 ± 1.5 μM respectively (Lei et al., 2019). The diterpenes dysokusone F **(44)**, 2-Oxoneoclerod-3, 13Z-dien-15-ol **(02)**, 3α-(4-Hydroxy-3,5-dimethoxy-benzoyloxyl)-clerod-14-ene-4β,13-diol **(03)**, 3α-(4-Hydroxybenzoyloxyl)-clerod-14-ene-4β,13-diol **(05)**, and 3α-(4-Hydroxy-3-methoxybenzoyloxyl)-clerod-14-ene-4β,13-diol **(04)** isolated from the stems of *Dysoxylum lukii* Merr also have a reliable PTP1B inhibitory effect for considering DM2 drug candidates and in their *in vitro* analysis result in noticeable inhibition with IC_{50} values of 51.62 ± 6.55, 56.74 ± 7.96, 17.04 ± 3.43, 28.96 ± 4.59, and 19.70 ± 2.57 μM, respectively (Zhang et al., 2019). In addition, the ent-labdane-type diterpenoids also provided potential antidiabetic activity by antagonizing PTP1B. A study by Liu et al. (2018) reported that the compounds 3α-hydroxy-ent-labda-8(17),12E,14-triene-18-oic acid **(06)** and 3-hydroxy-entlabda-8 (17),12E,14-triene-18-ol **(07)** inhibited the enzyme with IC_{50} values of 4.11 and 8.33 μM, respectively (Liu et al., 2018). Liang et al. investigated the PTP1B inhibitory potential of the Chinese soft coral *Sarcophyton trocheliophorum* Marenzeller *in vitro* and discovered that the isolated compounds from the coral retain significant inhibitory activity against the human PTP1B enzyme. In that bioassay, some of the isolated compounds such as 4Z,12Z,14E-sarcophytolide **(09)**, secodihydrosarsolenone **(80),** sarsolilide A **(77)**, sarsolilides B**(78),** sarcophytonolide N **(75)**, sarcrassin E **(76)**, sarcophytolide **(74)**, cembrene C **(33)**, and ketoemblide **(58)** inhibit the enzyme emphatically with the IC_{50} values of 15.4, 13.7, 6.8, 27.1, 5.95, 6.33, 15.4, 26.6 and 27.2 μM respectively (Liang et al., 2018; Liang et al., 2017; Liang et al., 2014; Liang et al., 2013). Two diterpenes, lambertianic acid **(59)** and cassipourol **(32)** among 15 isolated from the needles and twigs of the cultivated endangered pine *Pinus kwangtungensis* demonstrated potential anti-diabetic drug targets by inhibiting PTP1B with IC_{50} values of 25.5 and 11.2 μM, respectively (Hu et al., 2017). Numerous researchers have reported that the diterpene kaurenoic acid **(57)** found in various natural sources retains potential PTP1B inhibitory capability. In a few *in vitro* investigations, the compound isolated from either *Wedelia prostate or Aralia continentalis* roots exhibited significant PTP1B antagonizing potential with IC_{50} values of 28 or 4.64 ± 0.82 μM respectively, obtained from different bioassays (Abdjul et al., 2017; Jung et al., 2012). A study by Kim et al. (2017) demonstrated that the compounds cryptotanshinone **(39)**, tanshinol B **(88)**, dehydrodanshenol A **(42)**, tanshinone IIB **(91)**, tanshinonal **(89)**, 15,16-dihydrotanshinone I **(17)** and tanshinone I **(90)** isolated from the roots of *Salvia miltiorrhiza* Bunge are potential targets for developing PTP1B inhibitors because of their capability to inhibit the enzyme. And the output of the study exhibited that the compounds inhibit the enzyme with IC_{50} values of 5.5 ± 0.9, 4.7 ± 0.4, 8.5 ± 0.5, 80.4 ± 0.6, 37. 6 ± 0.7, 18.6 ± 0.4 and 27.1 ± 0.8 μM respectively (Kim et al., 2017). The endangered and rare plant *Pinus dabeshanensis* listed in the China Plant Red Data Book showed an outstanding inhibitory potential against PTP1B in the search for anti-hyperglycemic drug candidates through biological and phytochemical investigations (Hu et al., 2016). Isopimara-7-en-18-oic acid **(52)**, *trans*-abienol **(92)**, lambertianic acid **(59)** isolated from the needles, and dabeshanensin A **(41)**, 12-hydroxydehydroabietic acid **(14)**, 15-hydroxy-7-oxo-8,11,13-abietatrien-18-oic acid **(18)** isolated from the shed trunk barks of the plant have significant inhibitory activity with IC_{50} values of 14.6 ± 0.98, 37.7 ± 2.68, 22.2 ± 0.82, 7.6 ± 0.8, 35.2 ± 9.7, 5.4 ± 1.0 and 10.3 ± 0.9 μM respectively, against the enzyme (Li et al., 2017; Hu et al., 2016). The compound 5-hydroxyviscida-3,14-dien-20-oic acid **(10)** isolated from *Eremophila lucida* exhibited a moderate PTP1B inhibitory activity with an IC_{50} value of 42.0 ± 5.9 μM (Tahtah et al., 2016). The diterpenes cyrtophyllone B **(40)** and imbricatolic acid **(50)** were isolated from the stems of *Akebia quinata* and the fruits of *Cupressus sempervirens* respectively, demonstrated strong interaction and elevated PTP1B inhibitory effects with IC_{50} values of 6.77 ± 1.28 and 8.8 ± 0.00 μM respectively, resulting from studies

carried out to explore potential anti-hyperglycemic agents (An et al., 2016; Khan et al., 2016). In another investigation performed by Yang et al. (2015) several diterpenes were isolated from the green alga *Caulerpa racemosa* in search of potential PTP1B inhibitors. Among the isolates, α-tocopherol quinone **(95)** and α-tocospirone **(96)** displayed potent inhibitory effects with IC_{50} values of 3.85 ± 0.56 and 11.01 ± 0.56 μM, respectively as well as *trans*-phytol **(93)** and *trans*-phytyl acetate **(94)** demonstrated moderate inhibitory activity with IC_{50} values of 32.60 ± 1.89 and 50.02 ± 9.11 μM respectively (Yang et al., 2015). In a study by Lee et al. several diterpenes isolated from the Okinawan marine sponge *Strongylophora strongilata* demonstrated moderate to strong inhibitory potential against PTP1B for discovering more efficient anti-diabetic drugs. Isolates from the animal such as 26-*O*-ethylstrongylophorine-14 **(26)**; 26-*O*-methylstrongylophorine-16 **(27)**, strongylophorine-3 **(85)**, strongylophorine-15 **(86)** and strongylophorine-17 **(87)** inhibit the enzyme with IC_{50} values of 8.7, 8.5, 9.0, 11.9, and 14.8 μM, respectively (Lee et al., 2015). Xiong et al. (2015) investigated phytochemicals from *Chloranthus oldhamii* responsible for inhibiting PTP1B targeting DM2 and discovered that isolated diterpenes from the plant's roots, such as chlorabietol A **(34)**, chlorabietol B **(35)**, and chlorabietol C **(36)** inhibited the enzyme persistently with IC_{50} values of 12.6, 5.3, and 4.9 μM, respectively (Xiong et al., 2015). The grayanane diterpenes, principinol E **(69)** and principinol D **(68)** isolated from *Rhododendron principis* also showed potent to mild PTP1B inhibitory activity in an *in vitro* assay with IC_{50} values of 3.14 ± 0.12 and 24.46 ± 6.14 μM respectively (Liu et al., 2014). A new diterpene hueafuranoid A **(49)** isolated from the MeOH extract of *Antarctic lichen* Huea sp also exhibited inhibitory activity with an IC_{50} value of 13.9 μM against the therapeutic targeted enzyme (PTP1B) in the treatment of DM2 and obesity (Cui et al., 2012). The phytochemical ent-16βH,17-acetoxy-18-isobutyryloxy-kauran-19-oic acid **(45)** isolated from the aerial part of *Siegesbeckia glabrescens was* found to antagonize PTP1B with an IC_{50} value of 30.6 ± 2.1 μM (Kim et al., 2006). Several diterpenes such as continentalic acid **(38)**, ent-Pimarol **(46)**; 7-Oxo-ent-pimara- acid **(12)**; 16α-Hydroxy-17-isovaleryloxy-ent-kauran 19-oic acid **(23)**, 17-Hydroxy-ent-kaur-15-en-19-oic acid **(25)**, 15α,16α-Epoxy-17-Hydroxy-ent-kauran-19 -oic acid **(20)**, 1616α,17-Dihydroxy-ent-kauran-19-oic acid **(21)**, ent-Thermarol **(47)** and 4-epiruilopezol **(08)** isolated from the roots of *Aralia continentalis* exhibited strong inhibitory activity with IC_{50} values of 0.66 ± 0.18, 9.85 ± 0.20, 0.09 ± 0.06, 1.51 ± 0.07, 9.12 ± 0.92, 1.96 ± 0.06, 0.56 ± 0.10, 1.34 ± 0.56 and 10.98 ± 1.13 μM, respectively against human PTP1B in targeting for developing more efficient and safe anti-diabetic drugs. The exploration by Na et al. (2006) demonstrated that the isolated compounds diterpenes in nature from the roots of *Acanthopanax koreanum* retain mild to strong inhibitory activity against the PTP1B in the target of obesity and diabetes treatment. The compounds of the plant such as acanthol **(30)**, acanthoic acid **(28)**, 7β-Hydroxy-ent-pimara-8 (14),15-dien19-oic acid **(13)**, anthokoreoic acid A **(29)**, 16α-Hydroxy-ent-kauran-19-oic acid **(24)**, 16α H,17-isovaleryloxy-ent-kauran-19-oic acid **(22)**, 16α-Hydroxy-17-isovaleryloxy-entkauran -19-oic acid **(23)** inhibit the enzyme with IC_{50} values of >30, 23.5 ± 1.8, >30, >30, >30, 7.1 ± 0.9 and >30 μM respectively (Na et al., 2006). An investigation by Han et al. (2005) found that the isolated abietane diterpenes from the dried root of *Salvia miltiorrhiza* BUNGE such as isotanshinone IIA **(53)**, dihydroisotanshinone I **(43)**, isocryptotanshinone **(51)** inhibit PTP1B to confirm their hypoglycemic activity with IC_{50} values of 11.4 ± 0.6, 22.4 ± 0.6 and 56.1 ± 6.3 μM, respectively (Han et al., 2005). In our observation, the compounds 11, 61, 62, 79, 66, 67, 65, 95, 69, 12, 23, 20, 21, and 47 exhibited lower IC_{50} values, demonstrating more potency than the other compounds as the quantity of a medication required to have an effect; the more potent the medicine, the lower the IC_{50} value (Berrouet et al., 2020). **Table 1** represents the sources and IC_{50} of diterpenes against PTP1B.

Table 1. *In vitro* PTP1B inhibition activity of several diterpenoids from different natural sources based on literature review

Compounds	Sources	Parts	IC_{50} (μM)	References
Clavurol E **(37)**	*Clavularia viridis*	Whole parts	14.5	Gao et al., 2022
Eremoglabrane D **(47)**	*Eremophila glabra* (R.Br.) Ostenf.	Leaf	64 ± 6	Petersen et al., 2022
7-oxo-dehydroabietic acid **(11)** and 15-methoxy-7,13-abietadien-18-oic acid **(19)**	*Torreya jackii* Chun	Leaf and twigs	3.1, and 6.8, respectively	Li et al., 2022
Acrepseudoterin **(31)**	*Acremonium* sp. SF -7394	Whole parts	22.8 ± 1.1	Kim et al., 2021
Mollactone A **(60)**, Mollactone B **(61)**, Mollactone C **(62)**	*Rhododendron molle*	Leaf	4.24 ± 0.21, 2.69 ± 0.23 and 3.33 ± 0.22 respectively	Zhou et al., 2020b
14β,19-diacetylpimara-15-ene **(16)**; 1β,19-diacetylpimara-15-ene **(1)**	*Phalaris canariensis* L.	Seed	6.9 ± 2.07 and 6.5 ± 1.43 respectively	Perez Gutierrez et al., 2020
Jatrophainolide A **(54)**, jatrophainolide B **(55)**, jatrophainolide C **(56)**	*Jatropha integerrima* Jacq	Rook bark	6.38, 25.9, and 27.4, respectively	Zhang et al., 2020
Oliviformislactone A **(63)**, secopimaranlactone A **(81)**, secocleistanthone A **(79)**, 12-hydroxyicacinlactone A **(15)**	*Icacina oliviformis*	Tuber	6.78 ± 0.41, 32.20 ± 0.59, 3.24 ± 0.14, 12.72 ± 0.53 and 58.05 ± 2.51, respectively	Zhou et al., 2020a
Siphonol A **(84)**, orthosiphol B **(64)**, orthosiphol I (66), orthosiphol N **(67)**, orthosiphol G **(65)**	*Orthosiphon stamineus* Benth	Aerial parts	8.18 ± 0.41, 9.84 ± 0.33, 0.33 ± 0.07 1.60 ± 0.17, and 3.82 ± 0.20 respectively	Nguyen et al., 2019
Pseudolaric acid A **(71)**, pseudolarate B **(70)**	*Pseudolarix amabilis*	Twigs	8.5 ± 3.8 and 10.9 ± 1.5 respectively	Lei et al., 2019

Table 1. *Continued*

Compounds	Sources	Parts	IC_{50} (μM)	References
Dysokusone F **(44)**, 2-Oxoneoclerod-3, 13Z-dien-15-ol **(02)**, 3α-(4-Hydroxy-3,5 -dimethoxy-benzoyloxyl)-clerod-14-ene -4β,13-diol **(03)**, 3α-(4-Hydroxybenzoyloxyl)-clerod-14-ene-4β,13-diol **(05)**, and 3α-(4-Hydroxy-3-methoxybenzoyloxyl)-clerod-14-ene-4β,13-diol **(04)**	*Dysoxylum lukii* Merr	Stems	51.62±6.55, 56.74±7.96, 17.04±3.43, 28.96±4.59, and 19.70±2.57, respectively	Zhang et al., 2019
3α-hydroxy-ent-labda-8(17),12E,14-triene-18-oic acid (06) and 3α-hydroxy-entlabda-8(17),12E,14-triene-18-ol **(07)**	*Croton laevigatus*	Leaf	4.11 and 8.33, respectively	Liu et al., 2018
4Z,12Z,14E-sarcophytolide **(09)**	*Sarcophyton trocheliophorum*	Whole parts	15.4	Liang et al., 2018
Lambertianic acid **(59)** and cassipourol **(32)**	*Pinus kwangtungensis*	Needles and twigs	25.5 and 11.2, respectively	Hu et al., 2017
Secodihydrosarsolenone **(80)**	*Sarcophyton trocheliophorum* Marenzeller	Whole part	13.7	Liang et al., 2017
Rhodomollacetal A **(72)**	*Rhododendron molle*	Leaf	42.42 ± 1.40	Zhou et al., 2017a
Rhodomollanol A **(73)**	*Rhododendron molle*	Leaf	24.32 ± 0.56	Zhou et al., 2017b
ent-kaur-16-en19-oic acid **(57)**	*Wedelia prostata*	Roots	28	Abdjul et al., 2017
Cryptotanshinone **(39)**, tanshinol B **(88)**, dehydrodanshenol A **(42)**, Tanshinone IIB **(91),** Tanshinonal **(89)**, 15,16-Dihydrotanshinone I **(17)**, Tanshinone I **(90)**	*Salvia miltiorrhiza*	Roots	5.5 ± 0.9, 4.7 ± 0.4, 8.5 ± 0.5, 80.4 ± 0.6, 37. 6 ± 0.7, 18.6 ± 0.4 and 27.1 ± 0.8 respectively	Kim et al., 2017
Isopimara-7-en-18-oic acid **(52)**, trans-abienol **(92)**, lambertianic acid **(59)**	*Pinus dabeshanensis*	Needles	14.6±0.98, 37.7±2.68 and 22.2±0.82, respectively	Li et al., 2017
Dabeshanensin A **(41)**, 12-hydroxydehydroabietic acid **(14)**, 15-hydroxy-7-oxo-8,11,13-abietatrien-18-oic acid **(18)**	*Pinus dabeshanensis*	Shed trunk barks	7.6 ± 0.8, 35.2 ± 9.7, 5.4 ± 1.0 and 10.3 ± 0.9 respectively	Hu et al., 2016
5-hydroxyviscida-3,14-dien-20-oic acid **(10)**	*Eremophila lucida*		42.0 ± 5.9	Tahtah et al., 2016
Cyrtophyllone B **(40)**	*Akebia quinata*	Stems	6.77 ± 1.28	An et al., 2016
Imbricatolic acid **(50)**	*Cupressus sempervirens*	Fruits	8.8	Khan et al., 2016
trans-phytol **(93)**, trans-phytyl acetate **(94)**, α -tocopherol quinone **(95)**, α –tocospirone **(96)**	*Caulerpa racemosa*	Whole parts	32.60 ± 1.89, 50.02 ± 9.11, 3.85 ± 0.56 and 11.01 ± 0.56, respectively.	Yang et al., 2015
26-O-ethylstrongylophorine-14 **(26)**, 26-O-methylstrongylophorine-16 **(27)**, strongylophorine-3 **(85)**, strongylophorine-15 **(86)**, strongylophorine-17 **(87)**	*Strongylophora strongilate*	Whole parts	8.7, 8.5, 9.0, 11.9, and 14.8, respectively	Lee et al., 2015
Chlorabietol A **(34)**, chlorabietol B **(35)**, chlorabietol C **(36)**	*Chloranthus oldhamii*	Roots	12.6, 5.3, and 4.9, respectively	Xiong et al., 2015
Principinol D **(68)**, principinol E **(69)**	*Rhododendron principis*	Aerial parts	24.46±6.14 and 3.14±0.12, respectively	Liu et al., 2014
Sarsolilide A **(77)**, sarsolilides B **(78)**	*Sarcophyton trocheliophorum* Marenzeller	Whole parts	of 6.8 and 27.1 respectively	Liang et al., 2014
Sarcophytonolide N **(75)**, sarcrassin E **(76)**, sarcophytolide **(74)**, cembrene-C **(33)**, ketoemblide **(58)**	*Sarcophyton trocheliophorum* Marenzeller	Whole parts	5.95, 6.33, 15.4, 26.6 and 27.2 respectively	Liang et al., 2013
Hueafuranoid A **(49)**	*Antarctic lichen Huea* sp	Whole parts	13.9.	Cui et al., 2012

Table 1. *Continued*

Compounds	Sources	Parts	IC_{50} (μM)	References
Continentalic acid **(38)**; Kaurenoic acid **(57)**; ent-Pimarol **(46)**; 7-Oxo-ent-pimara- acid **(12)**; 16α-Hydroxy-17-isovaleryloxy-ent-kauran 19-oic acid **(23)**; 17-Hydroxy-ent-kaur-15-en-19-oic acid **(25)**; 15α,16α-Epoxy-17-Hydroxy-ent-kauran-19-oic acid **(20)**; 16α,17-Dihydroxy-ent-kauran-19-oic acid **(21)**; ent-Thermarol **(47)**, 4-epiruilopezol **(08)**	*Aralia continentalis*	Roots	0.66 ± 0.18, 4.64 ± 0.82, 9.85 ± 0.20, 0.09 ± 0.06, 1.51 ± 0.07, 9.12 ± 0.92, 1.96 ± 0.06, 0.56 ± 0.10, 1.34 ± 0.56 and 10.98 ± 1.13 respectively	Jung et al., 2012
ent-16βH,17-acetoxy-18-isobutyryloxy-kauran-19-oic acid **(45)**	*Siegesbeckia glabrescens*	Aerial parts	30.6 ± 2.1 μM	Kim et al., 2006
Acanthol **(30)**, Acanthoic acid **(28)**, 7β-Hydroxy-ent-pimara-8 **(14)**,15-dien19-oic acid **(13)**, Acanthokoreoic acid A **(29)**, ent-Kaur-16-en-19-oic acid **(57)**, 16α-Hydroxy-ent-kauran-19-oic acid **(24)**, 16α H,17-isovaleryloxy-ent-kauran-19-oic acid **(22)**, 16α-Hydroxy-17-isovaleryloxy-entkauran-19-oic acid **(23)**	*Acanthopanax koreanum*	Roots	In-vitro inhibition of PTP1B with IC_{50} values of > 30, 23.5 ± 1.8, > 30, > 30, 20.2 ± 1.3, > 30, 7.1 ± 0.9 and >30, respectively	Na et al., 2006
Isotanshinone IIA **(53)**, dihydroisotanshinone I **(43)**, isocryptotanshinone **(51)**	*Salvia miltiorrhiza* BUNGE	Roots	11.4 ± 0.6, 22.4 ± 0.6 and 56.1 ± 6.3, respectively.	Han et al., 2005
Oleanolic acid (OA)	-	-	4.71 ± 0.16	Zhou et al., 2015

3.2. In silico analysis

3.2.1. Drug-likeness and physicochemical properties

In the early stages of drug discovery and development, unwanted molecules have frequently been filtered out using drug-likeness, which is obtained from the structures and characteristics of current medications and drug candidates (Hu et al., 2018). About 30%-40% failure rate for drug development in the 1990s was largely attributed to poor biopharmaceutical qualities, also known as drug-likeness, which includes poor solubility, chemical stability, permeability, and metabolic capabilities; but currently, they only represent 10%–15% of failed drug development attempts (Kola & Landis, 2004; Venkatesh & Lipper, 2000). Current drug discovery research places a strong emphasis on the creation of novel chemical compounds and drug candidates that have similar physicochemical and biological features to those of already available drugs. Lipinski's first put forth the famous idea of drug-like rules in his rule of five, which consists of four straightforward descriptions of physicochemical parameters such as molecular weight ≤ 500, log P ≤ 5, H-bond donors ≤ 5, H-bond acceptors ≤ 10 (Lipinski, 2004), which can assist in reducing the ever-growing number of chemicals to locate those that will act most like the target medicine while also being safe for usage in humans. Drug-likeness can also be described by the ghose rules; this filter sets the following drug-likeness constraints: Calculated log P ranges from –0.4 to 5.6, 160≤ MW≤ 480, 30≤ MF≤ 140, and the total number of atoms is all between 20 and 70 (Ghose et al., 1999). Additionally, Veber's rule (VR) added the requirements of drug-likeness for developing bioavailability with less than ten rotatable bonds (RB) and a topological polar surface area (TPSA) within 140 (Veber et al., 2002; Bhuia et al., 2025d), which describes the capability of penetration of a chemical compound through the cell membrane (Pajouhesh & Lenz, 2005). In our study, according to the rule of five compounds 3, 34, 35, 36, 64, 65, 66, 67, and 84 as well as the compounds 33, 64, 93, and 94 have one violation in molecular weight more than 500 dalton and in LogP of drug likeness criteria respectively, but they are acceptable as the number of violations of rule-of-five less or equal to 1 among four parameters was defined as the criterion of drug-likeness (Lipinski, 2004). Only compound 64 (Com. No) violates two parameters in MW and HBA according to the range of rule of five. The investigation also showed that the compounds 3, 34, 35, 36, 64, 65, 66, 67 demonstrated the value of MF over the optimum range. In addition, the chemical compounds 64, 65, 66 and 67 expressed topological surface area over 140 $Å^2$ which crosses the acceptable limit described by Veber et al. All the chemical selected compounds in our study followed the rule of five, the ghose rule and the Veber rule in their drug-likeness criteria except the mentioned chemicals in above. **Table S1** shows the drug-like properties of the chosen diterpenes and their values for the different parameters.

3.2.2. ADMET analysis

The objective of PKs in drug discovery and development is to support the optimization of some characteristics such as absorption, distribution, metabolism, and excretion (ADME) of lead compound in order to develop a clinical candidate that has a concentration-time profile in the body that is sufficient for the aspirated efficacy and safety profile (Reichel & Lienau, 2015; Bithi et al., 2025). It also offers a mathematical foundation for evaluating the time course of pharmacological effects and their physiological impacts (Nishant et al., 2011). There are different elements to assess absorption properties of a drug candidate such as caco-2 permeability, p-glycoprotein (P-gp) inhibitor and human intestinal absorption interferes the absorption properties of a drug candidate. The Caco-2 permeability assay is a model of cell monolayer

absorption (Hubatsch et al., 2007). It is one of the *in vitro* methods suggested by the U.S. Food and Drug Administration for evaluating both the passive and active transport of orally delivered medicines for determining drug permeability (Press & Grandi, 2008). The model estimates the absorption rate of potential therapeutic compounds across the intestinal epithelial cell barrier, which is extraordinarily useful for screening lead compounds in drug discovery (Kerns et al., 2004). P-gp is widely distributed and expressed in the intestinal epithelium, where it pumps xenobiotics (drugs or toxins) back into the intestinal lumen, in liver cells and proximal tubule cells of the kidney, where it pumps drugs from the kidneys and liver into the urine and bile, respectively (Lin & Yamazaki, 2003). P-gp has gained the greatest attention for its function in limiting medication absorption and distribution and as a potential source of variability in drug PKs and pharmacodynamics (Hochman et al., 2002). The primary reason for inhibiting the efflux pump is to enhance the delivery of medicinal agents. The objective is to increase drug bioavailability and drug absorption in the targeted organ (Amin, 2013).

On the other hand, absorption of a therapeutic compound through the cell lining of the human intestine is an important feature for possible drug candidates (Wessel et al., 1998). To date, some predictive models have been developed to estimate the Human Intestinal Absorption (HIA) of new drug-like molecules with sufficient precision for the development of oral medicines (Wang et al., 2017). In PKs, the distribution of medications from the bloodstream to the tissues is a crucial determinant of a drug's bioavailability (Benet et al., 1996). Several parameters associated with the drug and the body influence drug distribution, including plasma or plasma protein binding (PPB), body mass, body composition, body fluid spaces (VD), and perfusion (Pleuvry, 2005; Chillistone & Hardman, 2017). Plasma proteins, external tissue proteins, and intracellular tissue proteins can bind proteins. Numerous medications in circulation are bound to plasma proteins, and because bound drugs are too big to pass through biological membranes, only free drugs are accessible for tissue distribution and pharmacological effect (Keen, 1971). PPB is significant because it alters the pharmacological action of the drug. Protein-binding may impact drug activity in one of two ways: by altering the relevant concentration of the drug at its site of action, or by altering the rate at which the drug is excreted, so modifying the length of time that effective concentrations are maintained (Davis, 2018). The volume of distribution (Vd) is a crucial PKs characteristic that represents a drug's propensity to remain in the plasma or relocate to different tissue compartments (Petersson et al., 2019). It is a crucial factor in determining a drug's half-life and dose frequency. A basic molecule will often have a greater volume of distribution than a neutral molecule for a given log P (Smith et al., 2015). The blood-brain barrier (BBB) is a unique tissue that plays a critical role in the bio-distribution of medicines from the general body to the central nervous system (CNS) (Pandit et al., 2020). BBB limits the passage of most medicines from the blood into the brain. The existence of the BBB complicates the development of novel therapies for brain illnesses and radiopharmaceuticals for neuroimaging. All biotechnological products are large-molecule drugs that cannot penetrate the BBB. While it is expected that tiny molecules are carried readily over the BBB, 98% of small molecules are not transported throughout the BBB, and the fraction is inversely related to their molecular weight (Pardridge, 2012). Evaluation of a drug candidate's potential to inhibit or inactivate cytochrome P450 (CYP) enzymes continues to be an integral component of pharmaceutical drug Discovery and Development processes. CYP enzymes are regarded as one of the most essential enzyme families involved in the clearance of the vast majority of prescription medicines. Clinical drug-drug interactions (DDI) comprising suppression or time-dependent inactivation of these enzymes can cause hazardous side effects due to decreased clearance/increased exposure of the affected medication (the "victim" drug) (O Nettleton & J Einolf, 2011). Both CYP1A2 and CYP2C19 catalyze the metabolism of several xenobiotics, influencing the pharmacokinetics of a potential medication (de Andres et al., 2021). The enzyme CYP1A2 is one of the predominant CYPs in the liver (about 13%) and metabolizes around 20% of clinically utilized drugs, while the enzyme CYP2C19 is involved in the metabolism of a vast array of therapeutic pharmaceuticals (Wang & Zhou, 2009; Myrand et al., 2008). Clearance is usually the most crucial PK characteristic for a medicinal chemist to alter in a chemical series. This is due to the fact that clearance is a factor of every other design -relevant PK parameter, including half-life, oral bioavailability, and effective dosage (Smith et al., 2018).

In addition, the drug development process requires toxicity testing for evaluating a novel chemical as a drug candidate. The harmful effects of an investigational chemical are identified via species-, organ-, and dose-specific preclinical toxicity testing on a variety of biological systems as well as predicted through various computational procedures (Parasuraman, 2011; Sliwoski et al., 2014; Tanim et al., 2025). Assessing the safety of possible drug candidates is the main goal of toxicology studies in the drug discovery process and to translate the behaviors of the animals into a comprehension of the risk to human subjects (Dorato & Buckley, 2007). The potassium channel encoded by the human ether-a-go-go related gene (hERG) is responsible for the fast delayed rectifier potassium current that is essential for the repolarization of cardiomyocytes during the cardiac action potential (Huang et al., 2010). In humans, drug-induced suppression of hERG can lengthen the electrocardiographic QT interval, which in rare cases can cause ventricular arrhythmia and abrupt cardiac death (Bjerregaard, 2018). In the majority of instances, hepatotoxicity is identified at the latter phases of drug development, either animal toxicity studies or clinical trials. Although the liver is the most prevalent target organ for drug candidates in animal toxicity studies, hepatotoxicity seldom results in the termination of preclinical drug development (Ballet, 1997). The Ames test is a sensitive screening method for suspected carcinogens. Nevertheless, despite the significant correlation, it is difficult to interpret a positive result for a specific case since a mutagen in the Ames test is not always hazardous to people (Hengstler & Oesch, 2001). On the other hand, carcinogenicity is one of the most worrisome side effects of new drug development, since the disease typically has a longer retention period prior to onset, it is necessary to conduct long-term, typically lifespan, testing on animals to determine the carcinogenic potential of a new drug company (Kille, 2017).

In our study, PKs and toxicities have been predicted by ADMETlab 2.0 and various symbols are used to represent the output values: 0-0.1(−−−), 0.1-0.3(−−), 0.3-0.5(−), 0.5- 0.7(+), 0.7-0.9(++), and 0.9-1.0(+++). The token "+++" or "++" typically denotes a molecule that is more likely to be poisonous or faulty, while "−−−" or "−−" denotes a molecule that is appropriate or harmless. The optimal value for caco-2 of a compound is over −5.15 which indicates excellent permeability. The optimal value for PPB is lower than 90% indicating a good therapeutic index. The optimal range of VD is between 0.04-20 L/kg b.w. Estimated clearance penetration of the compounds indicated by following >15 ml/min/kg: high clearance; 5-15 ml/min/kg: moderate clearance; <5 ml/min/kg: low clearance. The results of P-gpi, HIA, BBB, CYP1A2i, CYP1A2s, CYP2C19i, CYP2C19s, hERGb, H-HT, AT, Carc interprets that the output value is the probability of being toxic, within the range of 0 to 1 but their PK properties and can be estimated by the following 0 -0.3: excellent; 0.3-0.7: medium; 0.7-1.0(++): poor and the toxicities increase with the increasing of output value which mentioned above (Xiong et al., 2021; https://admetmesh.scbdd.com/explanation) (**Table S2**).

3.2.3. Molecular docking and active sites estimation

The docking results demonstrated that the tested compounds bound with the receptor by forming hydrogen and hydrophobic bonds. All the diterpenoids except 14, 21, 26, 31, 32, 33, 37, 46, 92, and 93 revealed strong binding affinity toward the targeted enzyme (PTP1B) by forming one or more hydrogen bonds (HB) as well as most of them formed several hydrophobic bonds (HPB) with the amino acid residues of the enzyme. The compound 15 demonstrated the highest binding value of –8.5 kcal/mol by forming three hydrogen bonds other than any HPBs with the amino acid residues of SER216, and GLN266, of the targeted receptor. On the other hand, the reference compound OA in this study targeting PTP1B inhibition for the treatment of DM demonstrated binding affinity –7.7 kcal/mol by forming HBs and HPBs with the amino acid residues of SER205, ARG199, GLY202, and PHE196, ARG199, and PHE280 respectively of the receptor (7LFO). The top twenty compounds 15, 17, 72, 27, 86, 85, 89, 91, 42, 43, 73, 90, 39, 51, 53, 10, 62, 67, 68, and 63 which were exhibited higher binding affinities among 96 selected diterpenoids with the values of –8.5, –8, –7.9, –7.8, –7.7, –7.7, –7.7, –7.6, –7.6, –7.6, –7.6, –7.5, –7.5, –7.5, –7.4, –7.4, –7.4, –7.4, and –7.4, kcal/mol respectively against 7LFO receptor. Docking scores of all the selected ligands against 7LFO and related amino acid residues are listed in **Table S3**. **Figure S2** illustrates the location of H-bonds in the protein formed by the ligands and 2D schematic diagram of non-bond interactions between drugs and the enzyme.

4. Conclusion

In summary, the study demonstrated that the selected diterpenoids retain strong inhibitory activity against the PTP1B enzyme with the IC_{50} values ranging from 0.90 ± 0.06 to 80.40 ± 0.60 μM. In addition, the compounds exhibited potential binding affinities toward the enzyme by forming different interactions confirmed by our computational techniques. The compound 15 demonstrated the highest binding potential (–8.5 kcal/mol) toward the receptor (PTP1B) besides the compounds 17, 72, 27, 86, 85, 89, 91, 42, 43,73, 90, 39, 51, 53, 20, 62, 67,68, 63 demonstrated elevated binding affinities of –8, –7.9, –7.8, –7.7, –7.7, –7.7, –7.6, –7.6, –7.6, –7.6, –7.5, –7.5, –7.5, –7.4, –7.4, –7.4, –7.4, –7.4 kcal/mol respectively, where the control (OA) expressed binding energies of 7.7 kcal/mol. On the basis of the *in silico* ADMET analysis, it was also hypothesized that the molecules possess favorable PKs and drug-like features. We suggest further extensive research for establishing a novel drug as a potent PTP1B inhibitor for the treatment of DM2 and obesity with favorable efficacy and safety.

Conflict of interest

The authors declare that they have no conflict of interest

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Supplementary Data Availability Statement

The supplementary files associated with this study are publicly available in the Zenodo repository under the DOI: https://doi.org/10.5281/zenodo.15164047.

Authors contributions

Each author contributed significantly to the reported work, encompassing one or more of the following: conception, study design, execution, data acquisition, analysis, and interpretation. Furthermore, all authors participated in revising or critically reviewing the article, approved the final version for publication, agreed upon the target journal, and confirmed their accountability for all aspects of the work. All authors have read and approved the published version of the manuscript.

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