Approaches to Decrease Hyperglycemia by Targeting Impaired Hepatic Glucose Homeostasis Using Medicinal Plants

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Liver plays a pivotal role in maintaining blood glucose levels through complex processes which involve the disposal, storage, and endogenous production of this carbohydrate. Insulin is the hormone responsible for regulating hepatic glucose production and glucose storage as glycogen, thus abnormalities in its function lead to hyperglycemia in obese or diabetic patients because of higher production rates and lower capacity to store glucose. In this context, two different but complementary therapeutic approaches can be highlighted to avoid the hyperglycemia generated by the hepatic insulin resistance: 1) enhancing insulin function by inhibiting the protein tyrosine phosphatase 1B, one of the main enzymes that disrupt the insulin signal, and 2) direct regulation of key enzymes involved in hepatic glucose production and glycogen synthesis/breakdown. It is recognized that medicinal plants are a valuable source of molecules with special properties and a wide range of scaffolds that can improve hepatic glucose metabolism. Some molecules, especially phenolic compounds and terpenoids, exhibit a powerful inhibitory capacity on protein tyrosine phosphatase 1B and decrease the expression or activity of the key enzymes involved in the gluconeogenic pathway, such as phosphoenolpyruvate carboxykinase or glucose 6-phosphatase. This review shed light on the progress made in the past 7 years in medicinal plants capable of improving hepatic glucose homeostasis through the two proposed approaches. We suggest that Coreopsis tinctoria, Lithocarpus polystachyus, and Panax ginseng can be good candidates for developing herbal medicines or phytomedicines that target inhibition of hepatic glucose output as they can modulate the activity of PTP-1B, the expression of gluconeogenic enzymes, and the glycogen content.

Keywords: medicinal plants, hyperglycemia, hepatic glucose output, insulin resistance, PTP-1B inhibitors, natural products

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by high blood sugar levels (hyperglycemia), caused by insulin malfunctioning, deficient insulin secretion, or both (Liu et al., 2019). Type 2 diabetes (T2D) is the most important type of DM due to its high worldwide prevalence (American Diabetes Association, 2021). It is characterized by insulin resistance, which is defined as a
poor response of insulin-sensitive tissues to normal insulin concentration (Milnar et al., 2007). The main cause of insulin resistance has been associated to an obesogenic environment in which large amounts of free fatty acids and adipokines are responsible for impairing insulin signaling by increasing serine phosphorylation that inhibits tyrosine phosphorylation of insulin receptor (IR) and insulin receptor substrates (IRSs) (DeFronzo et al., 2015). However, it has also been reported that protein tyrosine phosphatases (PTPs) could have a more important role since they are upregulated in insulin resistant states. Insulin action is negative regulated by PTPs, particularly the PTP-1B, because they promote the dephosphorylation of tyrosine residues of IR and IRSs (Saltiel and Kahn, 2001). When insulin signaling is impaired in liver by either insulin resistance or low insulin levels, the glucose storage and production is dysregulated, increasing the hepatic glucose output rates yielding hyperglycemia in diabetic patients.

Liver represents a crucial therapeutic target for treating hyperglycemia in T2D because hepatic glucose output is the pathophysiologic abnormality that contributes the most to the hyperglycemic state in fasting and postprandial state as a consequence of hepatic insulin resistance (Sharabi et al., 2015). During the overnight fast (postabsorptive state), the liver of a normal person produces glucose at a rate of approximately 1.8–2 mg/kg min. However, this rate increases around 0.5 mg/kg min in a patient with T2D, promoting a significant rise in the basal state of glucose production (Cersosimo et al., 2018). After food ingestion and the subsequent increase in insulin levels, the suppression of glucose production is slower in a diabetic patient, promoting an evident postprandial hyperglycemia due to the excess of glucose produced in addition to that from the exogenous source (Rizza, 2010).

Medicinal plants and natural products have shown to have numerous benefits on processes involved in glucose and lipid metabolism, leading to correct homeostasis imbalances that promote metabolic diseases such as T2D (Li J. et al., 2018; Xu L. et al., 2018; Saadeldeen et al., 2020). Unlike the classic “on-target” paradigm in pharmacology, namely a drug with a specific target, the polypharmacology approach, or the binding of a drug to more than one target, could be more effective against a disease as complex as T2D due to its multiple pathophysiological abnormalities (Reddy and Zhang, 2013). In this context, extract plants and phytochemicals isolated from medicinal plants exhibit multiple mechanisms of action on assorted metabolic targets that are involved in glucose homeostasis. Therefore, efforts have been made to describe all the beneficial effects on metabolism of these extracts and molecules in recent years.

The current review summarizes the medicinal plants reported from 2015 that can potentially decrease hyperglycemia resulting from imbalance in hepatic glucose metabolism by two different approaches: improving hepatic insulin resistance by inhibiting PTP-1B and decreasing hepatic glucose output by inhibiting rate-limiting enzymes involved in the storage and production of glucose.

**METHODOLOGY**

Two separate searches were performed based on the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) (Page et al., 2021) in the following databases: Scopus, Clarivate and PubMed (Figure 1). The first involved studies related to extracts or phytochemicals tested against the activity or expression of PTP-1B enzyme, while in the second, studies with extracts or phytochemicals with an effect on the glucose-producing pathways were sought. Only records related to the study of medicinal plants and their isolated compounds were considered.

**THERAPEUTIC APPROACHES TO REDUCE HYPERGLYCEMIA RESULTING FROM IMPAIRED HEPATIC GLUCOSE HOMEOSTASIS**

Each insulin-sensitive tissue presents abnormal characteristics that contribute to hyperglycemia in an insulin-resistant state. The underlying mechanisms that give rise to insulin resistance converge on deficient insulin signalling that limits the activation of factors involved in energy metabolism. In obesity and T2D, insulin resistance has been linked mainly to defects in the signalling pathway of phosphatidylinositol 3-kinase and protein kinase B (PI3K/Akt), particularly to the Akt2 isofrom (Cusi et al., 2000; Krook et al., 2000).

In normal conditions, the insulin secreted by pancreatic β cell binds to its receptor in the target cell, activating the tyrosine kinase activity, which promotes the receptor autophosphorylation and the subsequent phosphorylation of IRSs, mainly IRS-1 and IRS-2, in tyrosine residues. Afterwards, the enzyme P13K is recruited and activated by IRS to convert phosphatidylinositol 4,5-bisphosphate (PIP2) from the plasma membrane to phosphatidylinositol 3,4,5-trisphosphate (PIP3), which facilitates the phosphorylation and activation of Akt at two important sites: by phosphoinositide-dependent kinase 1 (PDK1) at residue Thr308 of the catalytic domain, and by mammalian target rapamycin complex 2 (mTORC2) at residue Ser473 of the regulatory domain (Schultz et al., 2012). Specifically in liver, the activated Akt enzyme is responsible for phosphorylating different factors that are involved in the regulation of processes such as glycogen synthesis, gluconeogenesis, and glycogenolysis, which are activated or inhibited under different nutritional circumstances (Dimitriadis et al., 2021).

Due to hepatic insulin resistance, this hormone losses its ability to regulate glucose metabolism in liver, resulting in enhanced glucose output that contributes greatly to fasting and postprandial hyperglycemia, namely glycogen synthesis is reduced, and production of glucose is increased (Figure 2). Therefore, we proposed two approaches by which medicinal plants could ameliorated hyperglycemia through enhancing hepatic glucose metabolism: improving the function of insulin in the liver by inhibiting the enzyme PTP-1B and modulating the
hepatic production/storage of glucose by regulating the enzymes involved in gluconeogenesis, glycogenolysis, and glycogenesis.

**Inhibition of Protein Tyrosine Phosphatase 1B**

The modification of proteins through phosphorylation and dephosphorylation of tyrosine residues represents one of the main mechanisms of cell signaling regulation (Alonso et al., 2016), which is carried out by two superfamilies of enzymes: protein tyrosine kinases (PTKs), and PTPs. In this regard, the classical PTP subfamily possess a domain of 240–250 amino acids characterized by a conserved site that exhibits a catalytic mechanism based on cysteine (Denu and Dixon, 1998). Specifically, the enzyme PTP-1B is a classic intracellular PTP widely distributed in mammalian tissues that is anchored on the cytoplasmic side of the endoplasmic reticulum membrane. Despite its localization, the PTP-1B enzyme can access its substrates located on the surface of the plasma membrane during endocytosis, biosynthesis, and by the movement of the endoplasmic reticulum towards the plasma membrane in specific regions (Bakke and Haj, 2015).

Since its first isolation from the human placenta in 1988 by Tonks et al., 1988 PTP-1B has become an attractive research object due to its direct link with the etiopathogenesis of insulin resistance. In addition to the processes promoted by the obesogenic inflammatory environment, such as the serine/threonine phosphorylation of IR and IRS, and their proteasomal degradation (Mlinar et al., 2007; Ahmed et al., 2021), the dephosphorylation of these components by PTP-1B has also been implied to the termination of the insulin signal (Ahmad et al., 1995; Kenner et al., 1996; Chen et al., 1997).

Experimental data obtained from various studies have shown that the PTP-1B enzyme is one of the main negative regulators of the insulin signaling pathway. For instance, studies performed in PTP-1B knock-out mice have been shown that the absence of this enzyme produces healthy organisms that exhibit enhanced insulin sensitivity, protection against the weight gain generated by high-fat diet, and increased hepatic phosphorylation of IR and IRS after an intraperitoneal insulin injection (Elchebly et al., 1999; Klaman et al., 2000). On the other hand, it has been reported an increased PTP-1B activity in hepatic cytosolic fractions isolated from streptozotocin (STZ)-hyperglycemic rats (Meyrovitch et al., 1989), while augmented hepatic microsomal enzyme...
activity, content of protein, and mRNA levels have only been observed after 2 weeks of insulin treatment in these insulinopenic organisms, suggesting that elevated insulin levels are necessary to modify PTP-1B content and activity, namely hyperinsulinemia caused by insulin resistance may lead to altered PTP-1B expression and activity (Ahmad and Goldstein, 1995). Additionally, it has also been shown that insulin rises hepatic microsomal PTP-1B activity in rat hepatoma cells (Hashimoto and Goldstein, 1992). Likewise, abnormal expression and activity of PTP-1B have been reported in skeletal muscle of insulin-resistant obese people (Ahmad et al., 1997), as well as in non-obese Goto-Kakizaki rats with spontaneously generated insulin resistance (Dadke et al., 2000), and in STZ-hyperglycemic rats fed with high-fat diet (Wu et al., 2005).

Based on the aforementioned, the PTP-1B inhibition represents a good therapeutic target for the treatment of insulin resistance-related diseases, such as DM2 (Zhang et al., 2006). Hence, an arsenal of molecules with inhibitory capacity of PTP-1B activity has been generated in recent years. The methodological approaches that have been applied are the rational design of synthetic phospho-(tyrosine)-mimetic molecules to be used as competitive inhibitors, considering the structural characteristics of the protein, and the search for molecules from natural sources (Sun et al., 2018). The latter is based on the statement that nature has a great variety of structures that present diverse pharmacological effects (Atanasov et al., 2021), so natural products can be used as a starting point for the creation of powerful inhibitors.

Table 1 summarizes all medicinal plants and their identified compounds that have proved to inhibit the activity or expression of PTP-1B since 2015. It was obtained a total of 125 medicinal plants used in various traditional medicine systems around the world, mainly represented in eastern folk, such as Chinese and Vietnamese. *Morus alba* L. (Moraceae), a plant used in the traditional Chinese system, has been the most evaluated for this purpose. In addition to direct PTP-1B activity inhibition and molecular docking studies, some extracts and compounds were assessed to improve glucose and lipid metabolism in vivo, such as lowering blood glucose levels, improved insulin resistance and glucose intolerance, and improved lipid profile. Furthermore, their effect on glucose uptake and phosphorylation of some components of insulin signaling, such as IR, IRS, and Akt, was evaluated in cell cultures under insulin-resistant conditions.

**Inhibition of Hepatic Glucose Output by Modulating Glucose Metabolism in Liver**

The liver is a key organ that plays a crucial role in the regulation of blood glucose because it manages both storage and synthesis of glucose. The latter involves two metabolic pathways: glycogenolysis and gluconeogenesis, which constitute total hepatic glucose production (HGP) (Lee et al., 2015).
| Medicinal plant (scientific name [Family]/Traditional medicine system or places where it is used) | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|---|---|---|---|---|
| Acnemla paniculata (Wall. ex DC.) R.K.Jansen [Asteraceae]/Indonesian | Aerial parts/EtOH | N-isobutyl-2E-decenamide | In vitro: PTP-1B enzyme assay/IC50 = 24 µM | Abdjul et al. (2018) |
| Agrimonia pilosa Ledeb. [Rosaceae]/Chinese | Aerial parts/EtOH | Apigenin-7-O-b-D-glucone-6"-methyl ester Quercetin-3-O-b-D-glucose Kaempferol Kaempferol-3-O-a-L-rhamnose b-sitosterol Ursolic acid Tormentic acid Methyl 2-hydroxytricosanoate Palmitic acid | In vitro: PTP-1B enzyme assay/IC50 = 14.35, 27.73, 42.93, 12.16, 49.78, 3.47, 0.5, 36.39, 0.1 µM | Na et al. (2016) |
| Akebia quinata (Thunb. ex Houtt.) Decne. [Lardizabalaceae]/Chinese | Stems/MeOH | Apigenin 7-O-b-D-glucuronide Elagic acid Agritannin Cyrtophylenes B Uncinatone 3-O-(14)-a-L-arabinopyranosyl)olean-12-en-28-oic acid 3-O-[b-glucopyranosyl (1-4)-a-L-arabinopyranosyl)olean-12-en-28-oic acid 2a,3a,23-trihydroxyolean-12-en-28-oic acid | In vitro: PTP-1B enzyme assay/IC50 = 7.14, 7.73, 17.03 µM | Nguyen et al. (2017) |
| Allium cepa L. [Amaryllidaceae] | Outer skins/MeOH | Cepadial B, C Cepabilla A-C Cepadial D | In vitro: PTP-1B enzyme assay/IC50 = 6.77, 5.41, 4.08, 21.8, 7.78 µM | An et al. (2016) |
| Alliophyly cominia (L.) Sw. [Sapindaceae]/Cuban | Leaves/MeOH | Pheophytin A, B | In vitro: PTP-1B enzyme assay/IC50 = 22.55, 22.33, 17.01, 24.07, 14.29, 1.68 µM | Semaan et al., 2017, 2018 |
| Angelica decursiva (Miq.) Franch. & Sav. [Alicaeceae]/Korean Aneoctochilus chapaensis Gagnep. [Orchidaceae]/Chinese | Whole plant/MeOH | cis-3'-Acetyl-4'-angeloylkhellactone Isorutarine | In vitro: PTP-1B enzyme assay/IC50 = 88.95, 80.09 µM | Yousof Ali et al. (2015) |
| Artocarpus nanchuanensis S.S.Chang S.C.Tan & Z.Y.Liu [Moraceae]/Chinese | Stems/EtOH | Hypargyristolbe B, D, E | In vitro: PTP-1B enzyme assay/IC50 = 3.23, 37.31, 2.53 nM | Zhang et al. (2015) |
| Artocarpus styracolius Pierre [Moraceae]/Chinese Astragalus mongholicus Bunge [Fabaceae]/Chinese | Roots/EtOH | (±)-Styrastilibene A Styrastilibene B (±)-Styrastilibene C Astragaloside IV | In vitro: PTP-1B enzyme assay/IC50 = 4.52, 2.4, 8.23 µM | Li et al. (2019b) |
| Bidens pilosa L. [Asteraceae]/Chinese | Whole plant/Aqueous in combination with Euonymus alatus (Thunb.) Siebold [Celastraceae] winged branchlet Coptis chinensis Franch. [Ranunculaceae] rhizome Cornus officinalis Siebold & Zucc. [Cornaceae] fruit Ligustrum lucidum W.T.Aiton [Oleaceae] fruit Scrophularia ningpoensis Hemsl. [Scrophulariaceae] root | Full extract | In vivo: hypertensive rats fed with HFD (2020 mg/kg b.w.) prevention of increased body weight, triglycerides, LDL, insulin resistance, glucolose tolerance, PTP-1B expression in adipose tissue | Zhu et al. (2018) |

(Continued on following page)
| Medicinal plant (scientific name [Family]/Traditional medicine system or places where it is used) | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|---|---|---|---|---|
| *Bistorta officinalis* Delarbre [Polygonaceae]/Chinese | Rhizome/EtOAc | Full extract | In vitro: PTP-1B enzyme assay/IC50 = 17.43 µg/ml Zhao et al. (2019b) | |
| *Boehmeria nivea* (L.) Gaudich. [Urticaceae]/Chinese | Root/EtOAc | Full extract | Hederagenin Pomolic acid In vitro: PTP-1B enzyme assay/IC50 = 20.19 µg/ml, 9.53, 4.89 µM Zhao et al. (2019b) | |
| *Camellia crapnelliana* Tutcher [Theaceae]/Chinese | Twigs and leaves/MeOH | Camellianol B, C, E-G A1-.barrigenol 22-O-angeloyl-A1-barrigenol Camelliaerin A 16-O-acetylcamelliaerin A 3β,11α,13β-trihydroxyolean-12-one α-arnyrtin Lupex 3β,20-dihydroxylupane In vitro: PTP-1B enzyme assay/IC50 = 4.87, 7.4, 20.03, 14.36, 11.08, 16.79, 2.56, 8.93, 10.16, 1.34, 19.26, 3.68, 12.44 µM Xiong et al. (2017) | |
| *Cassia fistula* L. [Fabaceae]/Vietnamese | Leaves/EtOAc | Full extract | In vitro: PTP-1B enzyme assay/IC50 = 24.1 µg/ml Trinh et al. (2017a) | |
| *Catharanthus roseus* (L.) G.Don [Apocynaceae]/Malaysia, India, China, South Africa, and Mexico | Leaves/DCM | Vindogentianine In vitro: PTP-1B enzyme assay/IC50 = 15.28 µg/ml In vitro: cell culture (L-TC6, C2C12)/glucose uptake Wang et al. (2017a) | |
| *Cedrus deodara* (Roxb. ex D.Don) G.Don [Pinaceae]/Taiwan | Needles/Essential oil | Caryophyllene oxide In vitro: PTP-1B enzyme assay/IC50 = 31.32 µM Wang et al. (2017a) | |
| *Centella asiatica* (L.) Urb. [Apicaceae]/Jamu | Aerial parts/Aqueous | Polyphenolic extract In vitro: cell culture (HepG2)/[PTP-1B enzyme assay/IC50 = 13.2 µg/ml Saifudin et al. (2016b) | |
| *Clematis japonica* (Thunb.) Lindl. ex Spach [Ranunculaceae]/Chinese | Fruits/acetone | Polyphenolic extract In vitro: cell culture (HepG2)/[PTP-1B enzyme assay/IC50 = 13.2 µg/ml Saifudin et al. (2016b) | |
| *Cinnamomum osmophloeum* Kaneh. [Lauraceae]/Taiwan | Twigs and leaves/acetone | Full extract n-hexane soluble fraction | In vitro: PTP-1B enzyme assay/IC50 = 1.9, 3.2, 2, 1.7, 1.9 µg/ml Lin et al. (2016) | |
| *Cipadessa baccifera* (Roth) Miq. [Melaceae]/Chinese | Leaves/EtOH | Cipacidon A In vitro: PTP-1B enzyme assay/IC50 = 16.7 µM Yu et al. (2016a) | |
| *Clausena sarcin* Perr. (P.) Molino [Rutaceae]/Chinese | Fruits/EtOH | Clausenamines A-C, E, F Euchrestifoline Dihydromupamine Clauraila B Kurryame Clausenaline F 3-formyl-1-hydroxycarbazole Coptisine, I Clausinolne, N, M In vitro: PTP-1B enzyme assay/IC50 = 16.43, 21.19, 26.14, 51.04 µM Liu et al. (2021) | |
| *Coptis chinensis* Franch. [Ranunculaceae]/Chinese | Rhizome/MeOH | Beberine Épibberine Magnoflorine Coptisine Capsiin Blut Tavinol 7.3',4'-trihydroxyflavone Quercetagtin-7-O-b-D-glucoside In vitro: PTP-1B enzyme assay/IC50 = 16.43, 21.19, 26.14, 51.04 µM Begrmatov et al. (2020) | |
| *Corydalis tinctoria* Nutt. [Oxalidaceae]/North American and Chinese | Capitula/EtOH | Full extract | In vitro: PTP-1B enzyme assay/IC50 = 20.92, 7.73, 27.93, 24.5 µM Liu et al. (2021) | |
| *Cymbopogon nardus* (L.) Rendle [Poaceae]/Jamu | Leaves/Aqueous | Full extract | In vitro: PTP-1B enzyme assay/IC50 = 10.63 µg/ml Saifudin et al. (2016b) | |
| *Dioscorea bulbifera* L. [Dioscoreaceae]/Chinese | Rhizome/EtOAc | Full extract 9,10-Dihydro-2,4,6,7-phenanthrenetolactone [1,1',2',2',3',3',6',6',7',7'-octaoctyl Cassigaroni D Biflavococbin B, F, G In vitro: PTP-1B enzyme assay/IC50 = 32.21 µg/ml, 23.79, 3.36, 13.16 µM Zhao et al. (2019b) | |
| *Dracaena cochinchinensis* (Lour.) S.C.Chen [Asparagaceae]/Chinese | Red resin/MeOH | Biflavococbin B, F, G In vitro: PTP-1B enzyme assay/IC50 = 32.21 µg/ml, 23.79, 3.36, 13.16 µM Zhao et al. (2019b) | |
| *Duranta erecta* L. [Verbenaceae]/Anuyveda | Whole plant/EtOH | Full extract | In vitro: PTP-1B enzyme assay/IC50 = 10.63 µg/ml Saifudin et al. (2016b) | |

(Continued on following page)
TABLE 1 | (Continued) Medicinal plants and their phytochemicals with PTP-1B inhibitory capacity.

| Medicinal plant (scientific name [Family])/Traditional medicine system or places where it is used | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|---|---|---|---|---|
| Elaeocarpus grandiflorus Sm. [Elaeocarpaceae]/Jamu | Fruits/Aqueous | Full extract | In vitro: PTP-1B enzyme assay/IC50 = 6.9 µg/ml | Saifudin et al. (2016b) |
| Elephantopus scaber L. [Asteraceae]/Jamu | Aerial parts/Aqueous | Full extract | In vitro: PTP-1B enzyme assay/IC50 = 2.64 µg/ml | Saifudin et al. (2016b) |
| Euphorbia hirta L. [Euphorbiaceae]/Vietnamese | Leaves/EtOH | Eucarobustol A | In vitro: PTP-1B enzyme assay/IC50 = 15.2, 12.6, 16.1, 17.1, 31, 29.4 µM | Li et al. (2017a) |
| Euphorbia hirta L. [Euphorbiaceae]/Vietnamese | Stems/MeOH | (7S,8R)-3-hydroxy-4-methoxy-balanophon (7S,8R)-5-methoxy-balanophon Balanophonin | In vitro: PTP-1B enzyme assay/IC50 = 11.59, 9.94 µM | Zhao et al. (2019a) |
| Eremophila bignonii [Berberidaceae]/Chinese | Aerial parts/MeOH | Icartin Icariside II | In vitro: PTP-1B enzyme assay/IC50 = 52.4, 41.4 µM | Pedersen et al. (2020) |
| Eremophila lucida [Scrophulariaceae]/Australian | Leaves/EtOAc | 5-hydroxyviscoda-3,14-dien-20-oic acid | In vitro: PTP-1B enzyme assay/IC50 = 42 µM | Tahtah et al. (2016) |
| Eremophila oppositifolia R.Br. [Scrophulariaceae]/Australian | Leaves/CH2CN | Type B dimeric fatty acids related to the branched-chain fatty acid (2E,4Z,6E)-5-acetoxyethyl tetradeca-2,4,6-trienic acid (Compounds 9, 12, 13a, 13b) | In vivo: 24, 4, 12, 12 µM | Pedersen et al. (2020) |
| Eriobotrya japonica (Thunb.) Lindl. [Rosaceae]/Chinese | Leaves/EtOH | Extract of triterpenoid acids (maslinic acid, corosolic acid, oleanolic acid, and ursolic acid) | In vivo: insulin-resistant mice (200 mg/kg b.w.); [insulin resistance, glucose tolerance, triglycerides, LDL, VLDL, and total cholesterol, HDL; in liver: PPARg, GLUT2, and glucokinase mRNA expression levels, PTP-1B mRNA expression levels | Li et al. (2020b) |
| Eucalyptus robusta Sm. [Myrtaceae]/Chinese | Leaves/EtOH | Eucarobustol A I Macrocarpal C | In vitro: PTP-1B enzyme assay/IC50 = 1.3, 4.3, 2.9, 4.1, 5.6, 1.8, 3.0, 1.8, 4.5 µM | Yu et al. (2016b) |
| Euphorbia hirta L. [Euphorbiaceae]/Vietnamese | Whole plant/EtOAc and n-BuOH | Full extracts | In vitro: PTP-1B enzyme assay/IC50 = 29.2, 38.3 µg/ml | Trinh et al. (2017a) |
| Ficus deltoidea Jack [Moraceae]/Malay | Leaves/EtOH | 70% EIOH extract Lupeol 3β,11β-dihydroxyolean-12-en-23-oic acid | In vitro: PTP-1B enzyme assay/IC50 = 92%, 2.88, 4.55 µM in vivo: diabetic rats (125, 250, and 500 mg/kg b.w. of 70% EIOH extract)/chronic hypoglycemic effect, [triglycerides, LDL, and total cholesterol, HDL; in liver: PGL2 levels, PEPCK, G6Pase, and PTP-1B mRNA expression levels | Abdel-Rahman et al. (2020) |
| Ficus racemosa L. [Moraceae]/Vietnamese | Fruit/EtOAc | Isoderrone Derrone Alpinumisoflavone Mucusisoflavone B γ-Mangostin 8-Deoxyartanin 1,3,7-Trihydroxy-2,8-dil-(3-methylbut-2-enyl)-xanthone α-Mangostin Garcinone E 9-Hydroxycalabaxanthone Norcocinian | In vitro: PTP-1B enzyme assay/IC50 = 22.7, 12.6, 21.2, 2.5 µM | Trinh et al. (2017a) |
| Garcinia mangostana L. [Clusiaceae]/Southeast Asia and India | Fruits/EtOH | | In vitro: PTP-1B enzyme assay/IC50 = 0.86, 1.57, 3.28, 1.34, 0.43, 12.89 µM | Hu et al. (2021) |
| Garcinia oblongifolia Champ. ex Benth [Clusiaceae]/Vietnamese | Twigs/EtOAc | | In vitro: PTP-1B enzyme assay/IC50 = 14.1 µM | Trinh et al. (2017b) |
TABLE 1 | (Continued) Medicinal plants and their phytochemicals with PTP-1B inhibitory capacity.

| Medicinal plant (scientific name [Family]/Traditional medicine system or places where it is used) | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|---|---|---|---|---|
| Geranium collinum Stephan ex Willd. [Geraniaceae]/Chinese | Root/EtOH in combination with Hypericum scabrum aerial parts (ratio: 7:3) | Full extract | In vitro: PTP-1B enzyme assay/IC50 = 0.48 µg/ml In vitro: cell culture [L6 myotubes, in the presence of insulin]/[PTP-1B protein, pAkt, pIRS-1, pGSK3β, pAMPK, glucose consumption | Edris et al. (2018) |
| | | | In vitro: PTP-1B enzyme assay/IC50 = 21.64, 6.26, 35.61, 2.19, 0.62, 0.23, 0.87 µM | Numonov et al. (2017) |
| Glycyrrhiza inflata Batalin [Fabaceae]/Japanese and Chinese | Roots and rhizomes/EtOAc | Licochalcone A Lico flavone B Full extract | In vitro: PTP-1B enzyme assay/IC50 = 0.97, 0.45, 4.5, 1.48, 0.5, 0.55, 0.84, 0.31, 0.13 µM | Lin et al. (2017) |
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| Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae]/Chinese | Rhizomes/EtOH | Licochalcone A Lico flavone B | In vitro: PTP-1B enzyme assay/IC50 = 27.95, 15.62 µM | Guo et al. (2015) |
| | | | In vitro: PTP-1B enzyme assay/IC50 = 3, 0.4 µM | Ji et al. (2016) |
| Glyptostrobus pensilis (Staunton ex D.Don) K.Koch [Cupressaceae]/Chinese | Trunk barks/MeOH | Sopropensilol A, B 3-epi-larixinol 3,2′-epi-epilarinol Abiesinol F Larixinol (Abiesinol E) | In vitro: PTP-1B enzyme assay/IC50 = 3.3, 11.2, 17.1, 4.6, 12.9, 8.1 µM | Xiong et al. (2020) |
| Gymnema latifolium Wall. ex Wight [Apochneraceae]/Vietnamese | Aerial parts/EtOH | Gymnatinoside GL2, GL3 | In vitro: PTP-1B enzyme assay/IC50 = 22.66, 19.83 µM | Pham et al. (2020) |
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| Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae]/Chinese | Rhizomes/EtOH | Licochalcone A Lico flavone B | In vitro: PTP-1B enzyme assay/IC50 = 18.2, 23.5, 28.6, 8.2, 12.5 µM | Wang et al. (2017b) |
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| Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae]/Chinese | Gum/Aqueous | Licochalcone A Lico flavone B | In vitro: PTP-1B enzyme assay/IC50 = 3.49 µg/ml | Safdudin et al. (2016b) |
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| | | | In vitro: PTP-1B enzyme assay/IC50 = 1.254, 2.016, 2.672, 1.862 µM | Ma et al. (2017) |
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| Medicinal plant (scientific name [Family]/Traditional medicine system or places where it is used) | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|---|---|---|---|---|
| Lagerstroemia speciosa (L.) Pers. [Lythraceae]/Vietnamese | Aerial parts/EtOH | 24-hydroxy-lantadene B, 3-hydroxy-lantadene C, iterogenin 4-epi-hederagenic acid, oleanolic acid, 22b-oleanolic acid, 3b-hydroxy-lantadene A, 3b-hydroxy-lantadene B, A | In vitro: PTP-1B enzyme assay/IC50 = 19.6 µg/ml | Abdul et al. (2017) |
| Lantana camara L. [Verbenaceae]/Indonesian and Japanese | Aerial parts/EtOH | Full extract | 40% inhibition at 10 μg/ml | He et al. (2020) |
| Litsea cubeba (L.) L. [Lauraceae]/Chinese | Leaves/EtOAc | (+)-9,9′-O-di-[E]-feruloyl-5,5′-dimethoxy secoisolariciresinol | In vitro: PTP-1B enzyme assay/IC50 = 13.5 µM | Li et al. (2019c) |
| Litsea cubeba (L.) L. [Lauraceae]/Chinese | Flower buds/EtOH | Lonjaponspiroside A, B | In vitro: PTP-1B enzyme assay/IC50 = 6.14, 8.42 µM | Liu et al. (2016) |
| Lithocarpus polystachyus (Wall.) M.F. Newman & Škorničk [Lauraceae]/Chinese | Aerial parts/EtOH | Full extract | In vitro: PTP-1B enzyme assay/IC50 = 16.9, 3.3 µg/ml | Trinh et al. (2017a) |
| Macaranga denticulata (Blume) Müll.Arg. [Euphorbiaceae]/Chinese | Twigs and leaves/EtOH | Macidentialcalcone 1-(5,7-dihydroxy-2,2,6-trimethyl-2H-1-benzopyran-8-yl)-3-phenyl-2-propen-1-one | In vitro: PTP-1B enzyme assay/IC50 = 21, 22 µM | Lei et al. (2016) |
| Macleaya cordata (Willd.) R.Br. [Papaveraceae]/Chinese | Aerial parts/EtOH | Macleayne | In silico: molecular docking | Sai et al. (2016) |
| Macleaya cordata (Willd.) R.Br. [Papaveraceae]/Chinese | Leaves/Aqueous | Full extract | In vitro: PTP-1B enzyme assay/IC50 = 65 µg/ml | Kim et al. (2016) |
| Magnolia aromatica (Dandy) V.S.Kumar [Magnoliaceae]/Chinese | Twigs and leaves/EtOH | (1R,6S,7S)-1-hydroxy-cadin-4,9-dien-8-one | In vitro: PTP-1B enzyme assay/IC50 = 83.5 µM | Wang et al. (2016b) |
| Magnolia aromatica (Dandy) V.S.Kumar [Magnoliaceae]/Chinese | Root barks/MeOH | Full extract | In vitro: PTP-1B enzyme assay/IC50 = 55.96 µg/ml | Sun et al. (2015) |
### TABLE 1 | (Continued) Medicinal plants and their phytochemicals with PTP-1B inhibitory capacity.

| Medicinal plant (scientific name [Family]/Traditional medicine system or places where it is used) | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|---|---|---|---|---|

**Magnolia officinalis Rehder & E.H.Wilson [Magnoliaceae]/Chinese**

| | Barks/MeOH | Magterpenoid A, C | In vitro: PTP-1B enzyme assay/IC₅₀ = 1.44, 0.81 µM | Li et al. (2018) |
|---|---|---|---|---|

**Magnolia officinalis var. biloba Rehder & E.H.Wilson**

| | (±)-Mooligomers B, D, E | | In vitro: PTP-1B enzyme assay/IC₅₀ = 0.47, 2.1, 0.35, 12.2, 0.89, 0.14 µM | Li et al. (2020a) |
|---|---|---|---|---|

**Melaleuca leucadendra (L.) L. [Myrtaceae]/Jamu**

| | Fruit/MeOH | Betulnic acid, Ursolic acid | In vitro: PTP-1B enzyme assay/IC₅₀ = 1.5, 2.3 µM | Saifudin et al. (2016a) |
|---|---|---|---|---|

**Melicope ptelefolia (Champ. ex Benth.) T.G. Hartley**

| | Roots/CH₂Cl₂/CH₃OH (1:1) | Melicoptelin B1/B2, D1/D2, E | In vitro: PTP-1B enzyme assay/IC₅₀ = 34.4, 55.2, 66.6 µM | Xu et al. (2019b) |
|---|---|---|---|---|

**Momordica charantia L.**

| | Fruits/EtOH | 25′-O-methylkaraviagein D (19R,23E)-5b,19-epoxy-19,25-dimethoxycucurbit-6,23-dien-3b-ol | In vitro: PTP-1B enzyme assay/IC₅₀ = 51.8, 54.95 µM | Yue et al. (2017) |
|---|---|---|---|---|

**Morus alba L.**

| | Roots bark/MeOH | Morusalfuran A–F, Morusalnol B, Morusibene A | In vitro: PTP-1B enzyme assay/IC₅₀ = 11.02, 8.92, 7.26, 18.02, 26.56, 17.64 µM | Ha et al. (2020) |
|---|---|---|---|---|

| | Roots/EtOAc | Kuwanon L, Mulberrofuran G, Moracenin B (Kuwanon G), Morusinol, Sanggenon G | In vitro: PTP-1B enzyme assay/IC₅₀ = 21.67, 20.03, 13.07, 30.49, 10.87, 17.48, 4.04, 9.83, 9.52, 10.71, 19, 63, 4.69, 13.28, 12.72 µg/ml | Zhao et al. (2018) |
|---|---|---|---|---|

**Morus macroura Miq.**

| | Twigs/EtOH | Notabilisin E, Taxifolin Hultenin | In vitro: PTP-1B enzyme assay/IC₅₀ = 0.87, 5.5, 1.04 µM | Wang et al. (2015) |
|---|---|---|---|---|

(Continued on following page)
### Table 1 | (Continued) Medicinal plants and their phytochemicals with PTP-1B inhibitory capacity.

| Medicinal plant (scientific name [Family]/Traditional medicine system or places where it is used) | Part/Extract | Isolated compounds | Experiment/Outcome References |
|---|---|---|---|
| Myrtus communis L. [Myrtaceae]/Italian | Leaves/chloroform | 3β-cis-p-coumaroyloxy-2α,23-dihydroxyolean-12-en-28-oic acid | In vitro: PTP-1B enzyme assay/IC₅₀ = 15.38, 14.89, 25.73, 12.21, 8.93, 26.67, 11.93, 16.05, 8.92, 14.93 µM | Liang et al. (2020) |
| Nepenthes mirabilis (Lour.) Druce [Nepenthaceae]/Vietnamese | Whole plant/EtOAc and n-BuOH | Full extract | In vitro: PTP-1B enzyme assay/IC₅₀ = 1.4, 0.4 µg/ml | Trinh et al. (2017a) |
| Nigella sativa L. [Ranunculaceae]/From Turkey to India | Aerial parts/MeOH | 3-O-[α-L-arabinopyranosyl-(1→2)-α-L-arabinopyranosyl]ederagenin | In vitro: PTP-1B enzyme assay/IC₅₀ = 91.3 µM | Parveen et al. (2020) |
| Ouret lanata (L.) Kuntze [Amaranthaceae]/Ayurveda | Leaves/MeOH | Siphonol B, D Orthosiphon B, F, G, I, N | In vitro: PTP-1B enzyme assay/IC₅₀ = 8.18, 24.75, 9.84, 27.56, 3.82, 0.33, 1.6 µM In vivo: cell culture (3T3-L1)/glucose uptake = 94.66 µg/ml In vitro: cell culture (L6 myotubes)/insulin-mediated glucose uptake/OSSTs by 18.44% | Nguyen et al. (2019) |
| Panax ginseng C. A. Meyer. [Araliaceae]/Vietnamese and Indonesian | Aerial parts/MeOH | Siphonol B, D Orthosiphon B, F, G, I, N | In vitro: PTP-1B enzyme assay/IC₅₀ = 21.27 µM In vivo: cell culture (L6 myotubes)/insulin-mediated glucose uptake/OSSTs by 18.99, 13.38 µM | Riya et al. (2015) |
| Paeonia lactiflora Pall. [Paeoniaceae]/Chinese | Seeds/EtOH | Paeonolactifloranol trans-gnetin H | In vitro: PTP-1B enzyme assay/IC₅₀ = 27.23, 27.81 µM | Zhang et al. (2019a) |
| Panax quinquefolius L. [Araliaceae]/Chinese | Stems, flowers, and fruits/EtOH | 20(R)-25-methoxydammarane-3β,12β,20-tetrol 20(R)-dammarane-3β,6α,12β,20,25-pentol 20(R)-protopanaxatriol 20(S)-panaxadiol 20(R)-protopanaxadiol | In vitro: PTP-1B enzyme assay/IC₅₀ = 16.54, 10.07, 17.98, 21.02, 21.27 µM | Yang et al. (2016) |
| Pandanus odorifer (Forrissk.) Kuntze [Pandanaceae]/Vietnamese | Crude saponins/EtOH | 20(S)-panaxadiol (20(S)-24R)-dammarane-20,24-epoxy-3β,6α,12β,20,25-tetrol 20(R)-dammarane-3β,6α,12β,20,25-pentol 20(R)-dammarane-3β,12β,20,25-tetrahydroxy-3β-O-β-D-glucopyranoside Oleandric acid 20(S)-protopanaxadiol | In vitro: PTP-1B enzyme assay/IC₅₀ = 27.23, 23.63, 10.39, 6.21, 5.91, 18.99, 13.38 µM | Han et al. (2020) |
| Pandanus odorifer (Forrissk.) Kuntze [Pandanaceae]/Vietnamese | Fruit/EtOAc and n-BuOH | Full extract | In vitro: PTP-1B enzyme assay/IC₅₀ = 20.8, 40.4 µg/ml | Trinh et al. (2017a) |
| Phyllanthus amarus Schumach. & Thonn. [Phyllanthaceae]/Vietnamese | Whole plant/EtOAc | Full extract | In vitro: PTP-1B enzyme assay/IC₅₀ = 74.4 µg/ml | Trinh et al. (2017a) |
| Phyllanthus niruri L. [Phyllanthaceae]/Jamu | Aerial parts/Aqueous | Full extract | In vitro: PTP-1B enzyme assay/IC₅₀ = 10.99 µg/ml | Salfudin et al. (2016b) |
| Phyllanthus urinaria L. [Phyllanthaceae]/Vietnamese | Whole plant/EtOAc and n-BuOH | Full extract | In vitro: PTP-1B enzyme assay/IC₅₀ = 14, 10.8 µg/ml | Trinh et al. (2017a) |

(Continued on following page)
TABLE 1 | Medicinal plants and their phytochemicals with PTP-1B inhibitory capacity.

| Medicinal plant (scientific name) | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|-----------------------------------|--------------|--------------------|-------------------|------------|
| *Pithecellobium dulce* (Roxb.) Benth. (Fabaceae)/Vietnamese | Stem/EtOAc | Full extract | In vitro: PTP-1B enzyme assay/IC₅₀: 26.1 µg/ml | Trinh et al. (2017a) |
| *Pruus amygdalus* Batsch (Rosaceae) | Fruits/EtOH | Hexane fraction Chloroform fraction | In vitro: PTP-1B enzyme assay/IC₅₀: 9.66, 37.95 µg/ml | Qureshi et al. (2019) |
| *Paicium guajava* L. (Myrtaceae)/Worldwide | Leaves/EtOAc | Psiguardiol A–J | In vitro: PTP-1B enzyme assay/IC₅₀: 4.7, 11, 11.9, 10.7, 19.1, 18.9, 6.2, 9.2, 22.8, 22.8 µM | Hou et al. (2019) |
| *Psychotria subcordatius* (DC.) Bridson (Rubiaceae)/African | Leaves/EtOH | Jejugaavone A, C | In vitro: PTP-1B enzyme assay/IC₅₀: 10.52, 9.4 µM | Ryu et al. (2021) |
| *Quercus wutaishanica* Mayr (Fagaceae)/Chinese and South Korean, and Chinese | Acorn/EtOH | Puerarin | In silico: molecular docking/PTP-1B binding energy: 6.4 kcal/mol | Ojo, (2021) |
| *Reynoutria japonica* Houtt. (Polygonaceae)/Japanese, South Korean, and Chinese | Roots/EtOAc | (trans)-emodin-physcion bianthrone (cis)-emodin-physcion bianthrone | In vitro: PTP-1B enzyme assay/IC₅₀: 5.56, 24.89, 20.56, 4.16, 3.92, 3.53, 9.58, 15.38, 20.16, 1.03 µM | Xu et al. (2018b) |
| *Reynoutria multiflora* (Thunb.) Moldenke (Polygonaceae)/Chinese | Roots/EtOH | Multiflorumiside H–K | In vitro: PTP-1B enzyme assay/IC₅₀: 1.2, 1.7, 1.5, 4.6 µM | Yang et al. (2020) |
| *Rhizophora apiculata* Blume (Rosaceae)/Vietnamese | Bark/EtOAc and n-BuOH | Full extracts | In vitro: PTP-1B enzyme assay/IC₅₀: 17.2, 1.8 µg/ml | Trinh et al. (2017a) |
| *Rhododendron fastigiatum* Franch. (Ericaceae) | Whole plant/MeOH | Arbutin | In vitro: PTP-1B enzyme assay/IC₅₀: 20.5 µM | Yuan et al. (2021) |
| *Rubus auxillae* (Thunb.) | Aerial parts/EtOH | (+)-fastinoid B (-)-fastinoid B Rubiginosin A (-)-rubiginosin A Gotrifolinone A | In vitro: PTP-1B enzyme assay/IC₅₀: 47, 54.9, 40.9, 49.2, 13 µM | Huang et al. (2019) |

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### TABLE 1 (Continued) Medicinal plants and their phytochemicals with PTP-1B inhibitory capacity.

| Medicinal plant (scientific name [Family]/Traditional medicine system or places where it is used) | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|---|---|---|---|---|
| Rhus chinensis L. [Euphorbiaceae]/Chinese | Leaves/EtOH | 3a,19-dihydroxyl-ent-pimara-8 (14,15)-diene | In vitro: PTP-1B enzyme assay/IC50 = 49.49% at 20 μg/ml | Zhang et al. (2019b) |
| Rubus idaeus L. [Rosaceae] | Fruits/EtOH | Ursolic acid 2-oxopomolic acid 2α,19a-dihydroxy-3-oxo-urs-12-en-28-oic acid | In vitro: PTP-1B enzyme assay/IC50 = 7.1, 23.7, 52.3 μM | Zhang et al. (2019c) |
| Rubus occidentalis L. [Rosaceae] | Fruits/EtOH | Cynadin-3-O-xilosulinitoside Cynadin-3-O-rutinoside Quercetin-3-O-rutinoside Elagic acid | In vitro: PTP-1B enzyme assay/IC50 = 2.58, 1.86, 2.12, 0.03 μM | Xiao et al. (2017a) |
| Salvia cinnamomea Cav. [Lamiaceae]/Mexican | Aerial parts/Aqueous | 6-hydroxymurolol Pedalin | In vitro: PTP-1B enzyme assay/IC50 = 5.5, 4.7, 37.6, 18.6, 27.1, 8.5 μM | Salinas-Arellano et al. (2020) |
| Salvia miltiorrhiza Bunge [Lamiaceae]/Chinese | Roots/EtOH | Tanshinone IIA Cryptotanshinone Tanshinone I Dehydrodanshenol A Dehydrodanshenol B | In vitro: PTP-1B enzyme assay/IC50 = 80.1, 62 μM | Kim et al. (2017b) |
| Selaginella rolandi-principis | Rhizomes/EtOH | Selaginolide A 2′-hydroxygenistein 6,7-dimethoxy-2′,4′-dihydroxysofavolane | In vitro: PTP-1B enzyme assay/IC50 = 7.4, 23.02, 11.08 μM In vitro: cell culture (3T3-L1)/glucose uptake, [pIRS-1, pPI3K, pAkt] | Nguyen et al. (2021) |
| Selaginella tamariscina (P.Beauv.) Spring [Selaginellaceae]/Chinese | Aerial parts/Methanol | Selariscin D Selariscin E | In vitro: PTP-1B enzyme assay/IC50 = 13.2, 9.8, 7.4, 6.2, 9.6, 5.4, 4.5 μM In vitro: cell culture (3T3-L1)/glucose uptake | Nguyen et al. (2015) |
| Selaginella uncinata (Desv.) Spring [Selaginellaceae]/Chinese | Whole plant/EtOH | Uncinatibflavone C 7-methyl ether Robustflavone 4′-methyl ether Robustflavone 7- methyl ether (2R)2, 3- dihydro- 4′- mero- flavone Amentoflavone Biobetin (2′S) chrysoacouflavone I Delicatiflavone (2S) 2,3-dihydro- 5′R,7′R,4′- pentahydroxy-6,6′-dimethyl-[3′′O- 4′′]-biflavanone | In vitro: PTP-1B enzyme assay/IC50 = 13.8, 14.5, 14.6, 15.9, 4.8 μM In vitro: PTP-1B enzyme assay/IC50 = 7.7, 9.2, 9.8, 16.1, 10.6, 14.6, 5.5, 6.2, 4.6 μM In vitro: cell culture [insulin-resistant HepG2]/glucose uptake, [pIRS-1, pPI3K, pAkt] (Uncinatibflavone C 7-methyl ether) | Le et al. (2017) |
| Senna obtusifolia (L.) H.S.Irwin & Barneby [Fabaceae]/Chinese | Seeds/EtOH | Physcion Chrysophanol Emodin Alatemin Obstusin Questin Chrysosobulin Aurantio-obstusin 2′-Hydroxyemodin-1 methylether | In vitro: PTP-1B enzyme assay/IC50 = 7.28, 5.86, 3.51, 1.22, 6.44, 5.69, 14.88, 27.19, 5.22 μM In vitro: cell culture [insulin-resistant HepG2]/glucose uptake (alatemin and emodin) | Jung et al. (2016) |
| Styllurus marianum (L.) Gaertn. [Asteraceae] | Seeds/EtOAc | Taxifolin Dihydrokaempferol Dihydroquercetin-4′-methyl ether Kaempferol | In vitro: PTP-1B enzyme assay/IC50 = 24.23, 27.83, 21.30, 6.79 μM | Qin et al. (2017) |
| Smilax china L. [Smilacaceae]/Thai | Leaves/EtOH | Morin Kaempferol 7-O-α-L-rhamnoside Quercetin-4′-O-β-D-glucoside 4′-methoxy-5,7-dihydroxyflavone-(3-O-7′)-4′′′,5′′′,7′′′-trihydroxyflavone Parteinse 1,3,6-trihydroxyxanthone | In vitro: PTP-1B enzyme assay/IC50 = 7.6, 10.80, 9.22, 26.8, 9.77, 24.17 μM | Zhao et al. (2016) |

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## TABLE 1  
(Continued) Medicinal plants and their phytochemicals with PTP-1B inhibitory capacity.

| Medicinal plant (scientific name [Family]/Traditional medicine system or places where it is used) | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|---|---|---|---|---|
| Sophora flavescens Aiton [Fabaceae] | Roots/EtOH | Sophobilavonoid A, C | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 0.33, 0.35 µM | Yan et al. (2019) |
| Symplocos cochinchinesis (Lour.) S. Moore. [Sympliocaceae]/Ayurveda | Bark/EtOH | Full extract | In vivo: insulin-resistant rats (250 and 500 mg/kg b.w.) | Antu et al. (2016) |
| Syzygium cumini (L.) Skeels [Myrtaceae]/Vietnamese, Ayurveda, Unani, and Chinese | Seeds/MeOH | Valoneic acid dilactone Rubuphenol Ellagic acid | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 9.37, 28.14, 25.96 µM | Sawant et al. (2015) |
| | Fruit/EtOAc | Full extract | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 27.5 µg/ml | Trinh et al. (2017a) |
| Tetradium ruticarpum (A.Juss.) T.G.Hartley [Rutaceae]/East Asia | Buds/MeOH | Schinifoline Intergifoliodiol | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 24.3, 47.7 µM | To et al. (2021) |
| Thonningia sanguinea Vahl [Balanophoraceae]/Angola | Rhizomes/MeOH | 2′-O-(3-O-galloyl-4,6-O-Sa-hexahydroxydiphenoyl-β-D-glucopyranosyl)-3′-O-(3-O-galloyl-4,6-O-Sa-hexahydroxydiphenoyl-β-D-glucopyranosyl)phloretin Thonningianin B, A | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 24.7, 23.8, 19.3, 21.7, 4.4 µM | Pompermaier et al. (2018) |
| Tinospora sagittata (Oliv.) Gagnep. [Menispermaceae]/Chinese | Rhizome/EtOAc | Full extract | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 38.5 µg/ml | Zhao et al. (2019b) |
| Tradescantia spathacea Sw. [Commelinaceae]/Vietnamese | Aerial parts/MeOH | Bracteandiolide A Latifolicinin C, A Oresbiusin A | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 7.82, 6.80, 4.55, 6.38 µM | Vo et al. (2015) |
| Ugni molinae Turcz. [Myrtaceae]/Chilean | Leaves/EtOAc | Full extract Madecassic acid Myricetin | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 97.2% at 2 µg/ml (full extract) | Arancibia-Radich et al. (2019) |
| Vaccinium myrtillus L. [Ericaceae] | Fruits/EtOH | Full extract | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 6.96 µg/ml | Xiao et al. (2017b) |
| Vaccinium uliginosum L. [Ericaceae] | Fruits/EtOH | Full extract | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 3.06 µg/ml | Xiao et al. (2017b) |
| | | Phenolic compounds Cyanidin-3-arabinoside Dephinidin-3-glucoside Cyanidin-3-galactoside Cyanidin-3-glucoside Malvidin-3-galactoside Petunidin-3-glucoside | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 8.91, 17.8, 19.8, 25.9, 34, 31.1 µM | Tian et al. (2019) |
| | | Procyanidin B1, B2 | In vitro: PTP-1B enzyme assay/IC$_{50}$ = 0.6, 4.79 µM | Li et al. (2021) |

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Glycogenolysis consists of glycogen breakdown into glucose, being half of the basal HGP in fasting and decreasing the glycogen concentration at an almost linear rate during the first 22 h (Rothman et al., 1991; Cersosimo et al., 2018). In fasting, it is controlled by glucagon and epinephrine that activate glycogen phosphorylase (GP), the major enzyme responsible for digesting glycogen by releasing glucose 1-phosphate. In feeding condition, insulin inhibits glycogen breakdown and promotes glycogen synthesis through the activation of Akt and protein phosphatase 1 (PP1), leading the deactivation of both GP and glycogen synthase kinase-3 (GSK3), which in its active form (dephosphorylated), inactivates glycogen synthase (GS) (Han et al., 2016).

Glucogenesis, on the other hand, is defined as the production of glucose from a molecule that is not a carbohydrate. Its main substrates are pyruvate, glycerol, and amino acids such as alanine (Hanson and Owen, 2013). Another way to denote glucogenesis is as “reverse glycolysis” since both share not only substrates and final products, but also many enzymes. However, the direction of the reactions catalyzed in glucogenesis goes in the opposite direction, so the steps that are not shared with glycolysis can be determined as regulatory steps. These reactions are catalyzed by four rate-limiting enzymes: pyruvate carboxylase (PC), which is responsible for converting pyruvate into oxaloacetate; phosphoenolpyruvate carboxykinase (PEPCK), that converts oxaloacetate to phosphoenolpyruvate; fructose 1,6-bisphosphatase (FBPase), that dephosphorylates fructose 1,6-bisphosphate obtaining fructose 6-phosphate; and glucose 6-phosphatase (G6Pase), which is responsible for removing the phosphate group from glucose 6-phosphate, yielding novo synthesized glucose (Postic et al., 2004).

In the diabetic state, increased rates of HGP are observed as a result of an imbalance of various factors, such as the augmented availability of gluconeogenic substrates, the resistance of the liver to the action of insulin, and elevated levels of glucagon that activate HGP (Sharabi et al., 2015). Due to all these factors, the inhibition of HGP turns out to be an important therapeutic target for the reduction of hyperglycemia observed in T2D patients. In this regard, Table 2 summarizes the works made between 2015 and 2021 with extracts or natural products from 47 medicinal plants that showed to modulate hepatic glucose metabolism by inhibiting glucose production or promoting glucogen synthesis. As it can be observed, decreasing the expression of PEPCK and G6Pase is the principal mechanism related to gluconeogenesis inhibition, while phosphorylation of GSK3, promotion of GS activity, and inhibition of GP are the main mechanisms involved in glycogen breakdown and synthesis. Furthermore, although PI3K/Akt pathway stands out as a good pharmacological target to reduce insulin resistance, medicinal plants and their phytochemicals can also decrease HGP through AMP-activated protein kinase (AMPK).

**DISCUSSION**

Insulin resistance in liver leads to the release of large amounts of glucose into the bloodstream that affects long-term homeostasis. The regulation of hepatic glucose output represents a good pharmacological target for the control of metabolic diseases such as T2D, which are characterized by the presence of this pathophysiological phenomenon. The search for new molecules capable of regulating hepatic glucose metabolism from medicinal plants has focused on screening for phytochemicals that can directly inhibit key enzymes in glucose-producing pathways. However, considering compounds with the ability to also decrease the activity of the enzymes involved in terminating the insulin signal could result in more effective glycemic control.

According to the bibliographic search, plants used in different systems of traditional medicine have shown the ability to inhibit the activity or expression of PTP-1B, which could indicate that...
TABLE 2 | Medicinal plants and their phytochemicals capable to modulate hepatic glucose metabolism.

| Medicinal plant (scientific name [Family]/Traditional medicine system or places where it is used) | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|---|---|---|---|---|
| Abelmoschus esculentus (L.) Moench [Malvaceae]/Chinese | Whole plant/EtOH | Polysaccharides | In vivo: insulin-resistant mice (200 and 400 mg/kg b.w.)/pAkt and pGSK3β | Liao et al. (2019) |
| Averrhoa bilimbi (Mocz. & Sessê ex DC.) R.M.King & H.Rob. [Asteraceae]/Mexican | Aerial parts/Aqueous | Full extract | In vivo: diabetic rats (160 mg/kg b.w.)/Glucose production in PTTs | Mata-Torres et al. (2020) |
| Aloe vera (L.) Burm.f. [Asphodelaceae]/Ayurveda | Gel/EtOH | Carbohydrate fraction | In vivo: diabetic rats (27 and 54 mg/kg b.w.)/Liver glycogen content, [G6Pase activity, [G6Pase and PEPCK expression | Govindarajan et al. (2021) |
| Althaea officinalis (Baker) D.S.Conant [Malvaceae]/Mexican | Rhizome/Aqueous | Full extract | In vitro: G6Pase inhibition assay/IC50 = 45 μg/ml in vitro: FBPase inhibition assay/IC50 = 341 μg/ml | Andrade-Cetto et al. (2021b) |
| Aster kebulifolius Maxim. [Asteraceae]/Korean | Whole plant/EtOH | Full extract | In vivo: db/db mice (50, 100, and 200 mg/kg b.w.)/GK, [G6Pase and PEPCK expression | Yin et al. (2015) |
| Averrhoa bilimbi L. [Oxalidaceae]/Indian | Fruits/Aqueous | EtOAc fraction | In vivo: diabetic rats (25 mg/kg b.w.)/[G6Pase and FBPase activity | Kurup and S. (2017) |
| Bromelia kataras L. [Bromeliaceae]/Mexican | Aerial parts/Aqueous | Full extract | In vitro: G6Pase inhibition assay/IC50 = 1,136 μg/ml | Mata-Torres et al. (2020) |
| Canthium arborescens L. [Rutaceae]/Brazilian | Flowers/EtOH | Gold nanoparticles | In vitro: cell culture (insulin-resistant HepG2)/[Glycogen content, [G6Pase and PEPCK expression and protein levels | Jiang et al. (2018a) |
| Calotropis procera (Alton) W.T.Aiton [Apocynaceae]/Indian | Aerial parts/Latex | Protein fraction | In vivo: Wistar rats (5 mg/kg b.w.)/pAMPK, [PEPCK expression, [Glucose consumption, [Glycogen storage, [G6Pase activity and expression | de Oliveira et al. (2019) |
| Caralluma fimbriata Wall. [Apocynaceae]/Indian | Stems/EtOH | Full extract | In vivo: insulin-resistant rats (200 mg/kg b.w.)/[G6Pase and FBPase activity | Gujala et al. (2017) |
| Caralluma quadriangularis (Forsk.) N.E.Br. [Apocynaceae]/Kuwait | Whole plant/MeOH | Russelioside B | In vivo: diabetic rats (50 mg/kg b.w.)/[Glycogen content, [GP activity, [G6Pase activity, [G6Pase and GSK3β expression, [G6Pase activity and expression | Abdel-Sattar et al. (2016) |
| Chrysobalanus icaco L. [Chrysobalanaceae]/Nigerian | Leaves/Aqueous | Full extract | In vivo: diabetic rats (11,076, 22,134, and 44,268 mg/kg b.w.)/[Liver glycogen content, [G6Pase activity | Ekalitke et al. (2021) |
| Cota rotunda (Vent.) Schott & Endl. [Malvaceae]/African | Seeds/Aqueous | Full extract | In vivo: diabetic rats (300 mg/kg b.w.)/[GP, G6Pase, and FBPase activities | Erukainure et al. (2019b) |
| Convolvulus althaeoides L. [Convolvulaceae]/Brazilian | Flowers/Aqueous | Full extract | In vivo: diabetic rats (500 mg/kg b.w.)/[pAMPK and pAkt, [PEPCK expression, [Glucose production in PTTs | Siqueira et al. (2016) |
| Coreopsis tinctoria Nutt. [Asteraceae]/Chinese and Portuguese | Flowers/EtOAc | Marein | In vitro: cell culture (insulin-resistant HepG2)/[G6Pase and PEPCK expression | Jiang et al. (2018a) |
| Conspernum squarrosum L. [Amaranthaceae]/Mongol | Whole plant/EtOH | Oligosaccharides | In vivo: db/db mice (380 and 750 mg/kg b.w.)/In liver: [pRS2, [pAkt, [RS2, PISK, Akt, and IR expression and protein levels | Bao et al. (2020) |
| Couroupita guianensis Aubl. [Lecythidaceae] | Leaves/Aqueous | Full extract Gold nanoparticles | In vitro: diabetic rats (100 and 2.5 mg/kg b.w.)/[Glycogen storage, [G6Pase activity and expression | Manimegalai et al. (2020) |
| Edgeworthia gardneri (Wall.) Meisn. [Thymelaeaceae]/Chinese | Flowers/Aqueous | Full extract | In vivo: cell culture (insulin-resistant HepG2)/[G6Pase uptake and consumption, [Glycogen content, [Glucose production, [pRS1, [pAkt, [pGSK3 | Zhang et al. (2020) |
| Equisetum myriochaetum Schmidt. & Cham. [Equisetaceae]/Mexican | Aerial parts/Aqueous | Full extract | In vivo: diabetic rats (330 mg/kg b.w.)/[Glucose production in PTTs | Mata-Torres et al. (2020) |
| (Continued on following page)
TABLE 2 | (Continued) Medicinal plants targeting hepatic glucose metabolism.

| Medicinal plant (scientific name [Family]/Traditional medicine system or places where it is used) | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|---|---|---|---|---|
| Eryngium cymosum F.Delaroche [Apiaceae]/Mexican | Aerial parts/Aqueous | Full extract | In vivo: diabetic rats [470 mg/kg b.w./] Glucose production in PTTs in vitro: G6Pase inhibition assay/IC50 = 782 μg/ml in vitro: FBPase inhibition assay/IC50 = 57.4 μg/ml | Espinoza-Hernández et al. (2021) |
| Eryngium longifolium Cav. [Apiaceae]/Mexican | Aerial parts/EtOH | Full extract | In vitro: G6Pase inhibition assay/IC50 = 780 μg/ml in vitro: FBPase inhibition assay/IC50 = 93 μg/ml | Andrade-Cetto et al. (2021b) |
| Ficus carica L. [Moraceae]/Spain | Leaves/MeOH | Full extract | In vivo: diabetic mice (2 g/kg b.w./) [PEPCK and G6Pase expression, pAMPK] In vitro: [PEPCK and G6Pase expression, pAMPK] | Zhang et al. (2019d) |
| Forsythia suspensa (Thunb.) Vahl [Oleaceae]/Chinese | Roots/EtOH | Full extract | In vivo: [PEPCK and G6Pase expression, pAMPK] | Zhang et al. (2016b) |
| Graptopterum paraguayense (N.E.Br.) E.Watther [Crassulaceae]/Taiwan | Aerial parts/Aqueous | Full extract | In vitro: [PEPCK and G6Pase expression, pAMPK] | Jhuang et al. (2015) |
| Hyoscyamus albus L. [Solanaceae]/Mediterranean | Seeds/EtOH | Calystegine fraction | In vitro: cell culture (insulin-resistant mice) | Kowalczyk et al. (2021) |
| Hypericum attenuatum Fisch. ex Choisy [Hypericaceae]/Chinese | Whole plant/EtOH | Full extract | In vivo: insulin-resistant mice (100, 200, and 300 mg/kg b.w./) [PEPCK and G6Pase expression and protein levels, GS expression and protein levels, pIRS, pAkt, TGSK3] | Jin et al. (2019) |
| Iris domestica (L.) Goldblatt & Mabb. [Iridaceae]/Chinese | Leaves/EtOH | Saponins and polysaccharide fraction | In vivo: diabetic rats (100, 200, and 400 mg/kg b.w./) [GK and GLUT2 expression, G6Pase and PEPCK activities, G6Pase inhibition assay/IC50, G6Pase and PEPCK expression, pAMPK, pIRS] | Guo et al. (2019) |
| Launaea acanthodes (Boiss.) Kuntze [Asteraceae]/Iran | Aerial parts/EtOH | Full extract | In vivo: diabetic rats (800 mg/kg b.w./) [Glycogen content, Liver glucose influx/FBPase expression and protein levels, GS activity, pAMPK, pAkt, TGSK3] | Marvibaigi et al. (2021) |
| Lithocarpus polystachyus (Wall. ex A.DC.) Rehder [Fagaceae]/Chinese | Leaves/Aqueous | Full extract | In vivo: insulin-resistant mice (600 mg/kg b.w./) [G6Pase activity and PEPCK expression, pAMPK, pIRS] | Wang et al. (2016a) |
| Lupinus mutabilis Sweet [Fabaceae]/Andean | Seeds/Aqueous | Protein fraction | In vitro: cell culture (HepG2)/Glucose production and PEPCK expression | Muñoz et al. (2018) |
| Myrionthus arboreus P.Beauv. [Urticaceae]/African | Root bark/EtOH | EtOAc fraction Isoroorientin, Orientin Chlorogenic acid Full extracts or fractions | In vivo: cell culture (H4IIE hepatocytes)/G6Pase activity, pAMPK In vitro: cell culture (H4IIE hepatocytes)/G6Pase activity, pAMPK In vitro: cell culture (HepG2)/G6Pase expression, pAMPK, TGSK3 | Kasangana et al. (2018) |
| Myrica rubra (Lour.) Siebold & Zucc. [Myricaceae]/Chinese | Fruits/EtOH | Full extract | In vivo: KK-A° mice (200 mg/kg b.w./) [PEPCK, G6Pase expression, G6Pase inhibition assay/IC50 expression in vitro: cell culture (HepG2)/PEPCK and G6Pase expression] | Zhang et al. (2016a) |
| Pachylobus edulis G.Don [Burseraceae]/African and Nigerian | Leaves/EtOH | BuOH fraction | In vivo: diabetic rats (150 and 300 mg/kg b.w./) [G6Pase activity and PEPCK expression, G6Pase activity and PEPCK expression, G6Pase activity and PEPCK expression, G6Pase activity and PEPCK expression] | Erukainure et al. (2020) |
| Passionflower edulis G.Don | Leaves/EtOH, Aqueous | Full extract | In vivo: G6Pase inhibition assay/IC50 = 0.66, 3.59, 0.05 μg/ml | Erukainure et al. (2017) |

(Continued on following page)
TABLE 2 | (Continued) Medicinal plants and their phytochemicals capable to modulate hepatic glucose metabolism.

| Medicinal plant (scientific name [Family]/Traditional medicine system or places where it is used) | Part/Extract | Isolated compounds | Experiment/Outcome | References |
|---|---|---|---|---|
| Panax ginseng C.A.Mey. [Araliaceae]/Korean | Roots/EtOH | Black ginseng extract | In vivo: diabetic mice (300 and 900 mg/kg b.w.)/G6Pase, PEPCK and GP expression, | Seo et al. (2016) |
| Plantago depressa Wild [Plantaginaceae]/Chinese | Seeds/EtOH | Plantadepurate A Plumbagine D Plantagoguanidinic acid | In vitro: cell culture (rat hepatocytes)/Glucagon secretion inhibition by 8.2, 18.5, and 12.5% at 40 μM | Zheng et al. (2015) |
| Raphia hookeri G.Mann & H.Wendl. [Arecaceae] | Raffia palm wine/ Concentrated in water bath | Concentrated wine | In vivo: diabetic rats (150 and 300 mg/kg b.w.)/GP, FBPase and G6Pase activity | Erukainure et al. (2019) |
| Rhizophora mangle L. [Rizophoraceae]/Mexican | Bark/EtOH | Full Extract | In vivo: diabetic rats (90 mg/kg b.w.)/Glucose production in PITTs in vitro: G6Pase inhibition assay/IC50 = 99 μg/ml | Mata-Torres et al. (2020) |
| Sarcopoterium spinosum (L.) Spach [Rosaceae]/Israel, Palestine, and Jordan | Root/Aqueous | Full extract | In vivo: insulin-resistant mice (35 and 100 mg/kg b.w.)/PπR, pAkt, TOS3, G6Pase activity | Rozenberg and Rosenzweig, (2018) |
| Senna alata (L.) Roxb. [Fabaceae]/Asia, Africa and South America | Leaves/EtOH | Full extract | In vivo: diabetic rats (400 mg/kg b.w.)/Liver glycogen content, TGS activity, GP and FBPase activities | Mohanasundaram et al. (2021) |
| Sesbania grandiflora (L.) Poir. [Fabaceae]/Ayurveda | Flowers/Aqueous | Full extract | In vivo: diabetic rats (75 mg/kg b.w.)/Glycogen storage | Uwazie et al. (2020) |
| Shrikòpsis elliptica (Hochst.) Esser [Euphorbiaceae]/Nigerian | Leaves/EtOH | Full extract | In vivo: diabetic rats (250 mg/kg b.w.)/Liver glycogen content, TGS activity, GP, G6Pase, and FBPase activities | Sureka et al. (2021) |
| Smilax moranensis M.Martens & Galeotti [Smilacaceae]/Mexican | Roots/EtOH | Full Extract | In vitro: G6Pase inhibition assay/IC50 = 84 μg/ml | Mata-Torres et al. (2020) |
| Swietenia humilis Zucc. [Melaceae]/Mexican | Seeds/Aqueous | Dried aqueous extract Mexicanolide 1 Mexicanolide 2 Mexicanolide 3 | In vitro: G6Pase inhibition assay in H4IE hepatocytes: 100 μg/ml = 40.67%; 200 μg/ml = 61.11%; 9.46 μM = 42.68%; 2: 8.79 μM = 56.51%; 3: 8.13 μM = 41.79% | Ovall-Magalanies et al. (2019) |
| Tephrosia tinctoria (L.) Pers. [Fabaceae]/Ayurveda | Stems/EtOAc | EtOAc fraction | In vivo: diabetic rats (100 and 200 mg/kg b.w.)/Liver glycogen content, G6Pase and FBPase activity | Krishnasamy and Periyasamy, (2019) |
| Terminalia catappa L. [Combretaceae]/Ayurveda | Leaves/EtOH | Full extract | In vivo: diabetic rats (300 and 500 mg/kg b.w.)/G6Pase and FBPase activity | Divya et al. (2019) |
| Trigonella foenum-graecum L. [Fabaceae]/Asia, Africa, and the Mediterranean region | Seeds/EtOH | Fenugreek flavonoids | In vivo: diabetic rats (0.5 g in 10 ml/kg)/Liver glycogen content, G6Pase and FBPase activity | Jiang et al. (2018b) |

ETOH: ethanolic extract; MeOH: methanolic extract; EtOAc: ethyl acetate extract; PTT: pyruvate tolerance test; IR: insulin receptor; IRS1: insulin receptor substrate 1; IRS2: insulin receptor substrate 2; GSK3: glycogen synthase kinase 3; Akt: protein kinase B; PK3: phosphoinositide 3-kinase; PEPCK: phosphoenolpyruvate carboxykinase; FBPase: fructose 1,6-bisphosphatase; G6Pase: glucose 6-phosphatase; GLUT4: glucose transporter 4; AMPK: AMP-activated protein kinase; GS: glycogen synthase; GP: glycogen phosphorylase.
they have a potential inhibitory effect on HGP. The determination of biological activity of full extracts and compounds isolated from medicinal plants has been approached through different perspectives. Generally, the medicinal plant is first identified using an ethnomedical approach. Afterwards, different types of extracts are elaborated (aqueous, ethanolic, methanolic, etc.) and then tested on the biological activity to be evaluated following several paths: 1) direct inhibition enzymatic assays, which can be complemented with structure-activity relationship (SAR) studies and molecular docking analysis to find the possible structures responsible for the bioactivity, relating them with the binding of amino acid residues present at the catalytic or regulatory sites (regarding isolated compounds); 2) the use of cell cultures to evaluate the effect of the extract or compound on the expression and protein levels of key enzymes; and 3) in vivo studies, where diabetic (hyperglycemic) animals induced with STZ or alloxan, or insulin-resistant animals generated by the consumption of high-fat diet are used.

Regarding PTP-1B, most of the studies published between 2015 and 2021 focused on conducting enzyme activity assays, and few of them had a multidisciplinary approach that encompassed enzyme assays and in vitro or in vivo studies. The main problem with the first type of studies is that, although the inhibition potency and selectivity of the molecule over the enzyme are directly evaluated, the pharmacokinetic properties of the compound are omitted. This particularity stands out since it has been reported that, despite having excellent inhibitory activity, many compounds lack adequate cellular permeability, namely they present poor absorption and low bioavailability (Zhang et al., 2017). Another aspect to highlight is that PTP-1B is almost identical to TC-PTP, another member of the PTP family with 74% identity at the catalytic site, so it is important that the identified inhibitors have a high selectivity towards PTP-1B to avoid unwanted effects (Dewang et al., 2005). Considering these facts, it would be necessary in the future to carry out more studies involving as many approaches as possible to obtain a more integrative panorama and to be able to evaluate potential inhibitors considering their pharmacokinetic properties and selectivity. Also, it is encouraged to directly evaluate the effect of medicinal plants and their compounds with reported PTP-1B inhibitory capacity on hepatic glucose metabolism.

In addition to exhibiting PTP-1B inhibitory capacity, some of the medicinal plants reported in Table 1 also improved hepatic glucose metabolism by promoting glucose consumption and glycogen synthesis, upregulating activity or expression of GS, decreasing activity or expression of key enzymes involved in glycogenolysis and gluconeogenesis such as GSK3, GP, PEPCK, FBPase, and G6Pase, and by modulating insulin signaling. The compounds isolated from these plants could have a greater modulatory capacity of hepatic glucose metabolism because they are capable of directly reducing both insulin resistance and glucose production. These species were Astragalus mongholicus (astragaloside IV), Chaenomeles japonica, Duranta erecta, Eriobotrya japonica (maslinic acid, corosolic acid, oleanolic acid, and ursolic acid), Symlocos cochinchinensis, Thonningia sanguinea (2′-O- (3-O-galloyl-4,6-O-Sa-hexahydroxydiphenoyl-β-D-glucopyranosyl)-3-hydroxyphloretin, 4′-O-(4,6-O-Sa-hexahydroxydiphenoyl-β-D-glucopyranosyl) phloretin, 2′-O-(3-O-galloyl-4,6-O-Sa-hexahydroxydiphenoyl-β-D-glucopyranosyl) phloretin, thonningianin A, and thonningianin B), Vaccinium uliginosum (cyaniding-3-arabinoside, delphinidin-3-glycoside, cyanidin-3-galactoside, cyanidin-3-glucoside, malvidin-3-galactoside, petunidin-3-glucoside, procyanidin B1, and procyanidin B2), and Vigna radiata. On the other hand, since Coreopsis tinctoria, Lithocarpus polystachyus, and Panax ginseng were documented in both Tables 1, 2, their isolated compounds may have better glycemic control.

This work focused on summarizing the medicinal plants with the potential capacity to reduce hyperglycemia resulting from an imbalance in the hepatic metabolism of glucose, encompassing two different approaches: the inhibition of PTP-1B (improvement of hepatic insulin resistance), and the modulation of enzymes involved in gluconeogenesis and glycogenolysis/glycogenesis (decreased hepatic glucose output). In recent years, PTP-1B research has focused on the characterization of different phytochemicals from medicinal plants, such as phenolic compounds, terpenes, and alkaloids. The main methodology used was to carry out direct enzyme inhibition tests to evaluate the potency of these molecules, omitting important aspects such as selectivity or pharmacokinetics. Therefore, it is proposed to use of multidisciplinary approaches that involve in vitro studies, such as the use of cell lines or primary culture to evaluate the effect of the extracts and compounds on expression and protein levels, and in vivo studies, where the concentration of the compound in systemic circulation and its duration is determined, as well as the transformation processes involved. In this regard, not only the inhibitory activity of the compounds is evaluated, but also the impact on other pharmacological aspects that can only be observed using animal models.

On the other hand, research on medicinal plants that modulate hepatic glucose metabolism has primarily focused on testing full extracts rather than compounds. However, it is worth mentioning that mixtures could have synergistic effects capable of regulating multiple targets (Caesar and Cech, 2019) and therefore compound fractions may exhibit more bioactivity than isolated molecules. Further studies are needed to identify potential multitarget phytochemicals in plants listed in Table 2. Finally, it is expected that this review will provide greater knowledge of medicinal plants and compounds for the development of drugs that improve hepatic glucose metabolism as a therapeutic target for the treatment of T2D. We suggest that Coreopsis tinctoria, Lithocarpus polystachyus, and Panax ginseng can be good candidates for developing herbal medicines or phytomedicines that target inhibition of hepatic glucose output as they can modulate the activity of PTP-1B, the expression of gluconeogenic enzymes, and the glycogen content. However, only their full extracts are tested until now. Therefore, compounds responsible for the effects mentioned above have not been identified, and pharmacological and toxicological tests in animal models are
required to assess their efficacy and safety, with the aim of moving forward to carry out clinical studies.

AUTHOR CONTRIBUTIONS

GM-T and FE-H performed the bibliographical research summarized in tables and wrote the first version of the manuscript. AA-C reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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