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Effect of Natural Compounds on Insulin Signaling

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Abstract: Results of several epidemiological studies have indicated that diabetes mellitus will become a global epidemic in the next decades, being more than 400 million the human subjects in the world affected by this disease in the 2030. Most of these subjects will be affected by type 2 diabetes mellitus (T2DM) whose diffusion is mainly related to excessive caloric upload, sedentary life and obesity. Typically, the treatment for T2DM is diet, weight control, physical activity or hypoglycaemic and/or lipid-lowering drugs. Unfortunately, these drugs often show low effectiveness or adverse side effects, thereby forcing patient to discontinue medical treatment. Nevertheless traditional medicine suggests the use of several formulations or medicinal foods to treat T2DM. Most of them are characterized by safety, low cost, effectiveness, and good availability. Before the advent of modern pharmacology, these remedies were used to treat diabetes and obesity or prevent their onset. Today, we know that their effectiveness is due to the presence of several bioactive compounds able to influence insulin signaling pathway and cellular metabolism. In the last decades, many efforts have been carried out to clarify their action mechanism. Here we provide a classification of the natural compounds that stimulate the insulin pathway, highlighting their effectiveness in controlling glycaemia on diabetic animal models or improving insulin signaling in cellular systems.

Keywords: AMPK, insulin signaling, natural compounds, PPAR, PTP1B inhibitors, type 2 diabetes.

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INTRODUCTION

Insulin signaling is mediated by a complex and highly integrated network that controls many physiological processes [1]. Insulin receptor (IR), a tetrameric membrane protein consisting of two extracellular α-subunits and two intracellular β-subunits, is an allosteric enzyme in which the α-subunits inhibit the intrinsic tyrosine kinase activity of the β-subunits. Insulin binding to the α-subunit enhances IR kinase activity thus triggering downstream signaling events such as insulin receptor substrates (IRSs) recruitment and phosphorylation. Tyr-phosphorylated IRS acts as a docking protein for intracellular adaptor proteins (e.g. the regulatory subunit of PI3K, and Grb2) which activate two main signaling pathways: i) the PI3K-AKT/PKB pathway, which is responsible for most of the metabolic actions of insulin (stimulation of glucose uptake; glycogen, lipids and protein synthesis; inhibition of lipolysis, glycogenolysis and gluconeogenesis ; ii) the Ras–MAPK pathway, which regulates the expression of some genes and cooperates with the PI3K pathway to control cell growth and differentiation [1] (Fig. **1**).

In 2010 285 million people worldwide was affected by diabetes and this number is estimated to about 400 million in 2030 [2]. About 95% of diabetic patients suffer from Type 2 Diabetes Mellitus (T2DM), a form characterized by a defective insulin signaling in adipose tissue, liver and muscle cells. Although the molecular mechanisms leading to the development of T2DM should be still clarified, this phenomenon has been summarized with the term *insulin resistance*. Genetic background, aging, sedentary, and mostly, high caloric uptake and excessive lipids accumulation, are considered the main causes favoring the onset of insulin resistance. This is confirmed also by the results of several epidemiological analysis that revealed a strict correlation between insulin resistance and obesity [3-5]. Therapeutic treatment of T2DM includes the administration of secretagogues (sulfonylureas) that stimulate insulin release from pancreas, α-glucosidase inhibitor (acarbose) which reduces glucose absorption, biguanides (metformin) and thiazolidinediones (pioglitazone and rosiglitazone) that contribute to reduction of fatty acid deposits and improve insulin sensitivity. Nevertheless, all available therapies have limited effects and most of the drugs used trigger unexpected side effects, forcing patients to discontinue the treatment [6]. The lack of effectiveness of current drugs in treating T2DM, the high social impact of diabetes as well as the high cost of pharmaceutical treatments determine the need to develop new therapeutic approaches to prevent the onset and the progression of this disease. In the last decades, an increasing number of studies revealed that many natural substances extracted from different organisms (plants, animals, fungi, lichens, sponges, chorals, and bacteria) modulate the IR signaling, thereby acting on carbohydrates and/or lipids metabolism [7, 8]. Interestingly, it has been demonstrated that also common fruits and vegetables contain several biologically active components (including polyphenols) able to influence energetic metabolism and glucose homeostasis, without adverse effects. Many scientists suggest that these compounds could be used as new drugs to treat T2DM or,

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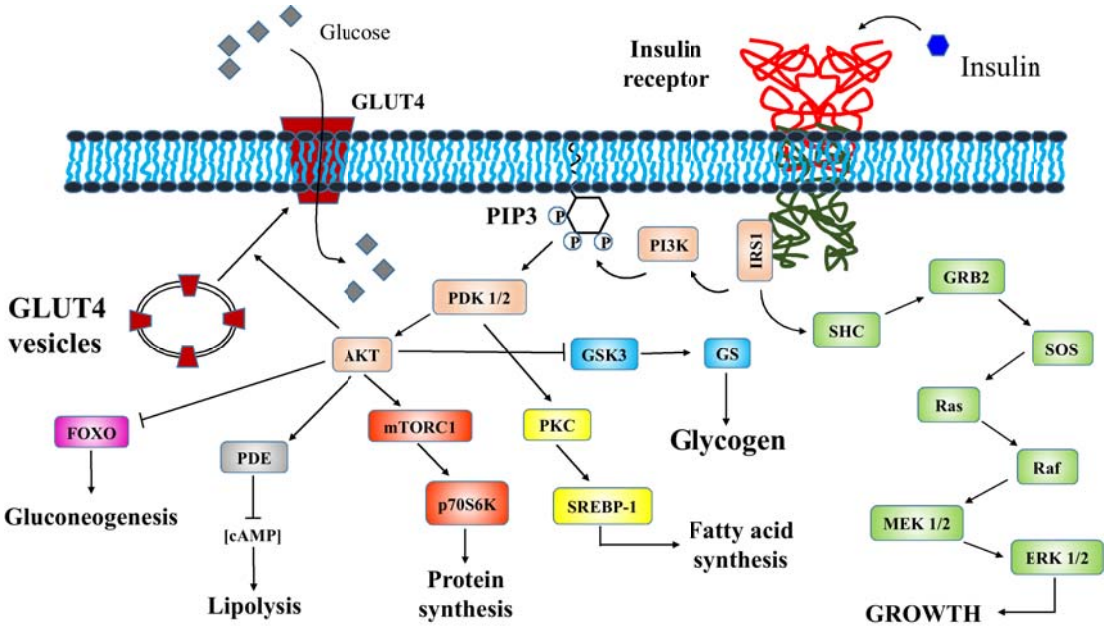


Fig. (1). The main pathways of insulin signaling. For acronyms see 'Abbreviations'.

alternatively, could represent scaffold molecules to obtain new and more specific antidiabetic drugs [9, 10]. Dietary polyphenols may be useful for supplementary treatments in T2DM and its cardiometabolic complications [11-13] inhibiting α-amylase and α-glucosidase in the intestinal lumen, thus reducing the absorption of simple sugars [14-16]. Furthermore, some polyphenols may improve glucose uptake in muscle and in adipocytes, inhibit gluconeogenesis and promote the storage of glycogen in the liver. However, the usage of these dietary polyphenols as drugs should take into account the effects that T2DM may have on their pharmacokinetics. Accordingly, an in-depth understanding of diabetes-associated changes in polyphenols absorption, distribution, metabolism, elimination and bioactivity is needed [17]. In this work we review the natural compounds so far described to influence the insulin signaling pathway, highlighting their mechanism of action and their efficacy both *in vitro* and *in vivo* models.

TYPICAL NATURAL COMPOUNDS THAT MAY AFFECT INSULIN SIGNALING

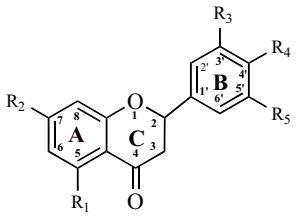
Several human foods such as tea, coffee, wine, cereal grains, vegetables, legumes, and fruits contain natural polyphenols; that are considered very important for human health. Among the 8000 phenolic compounds currently known, about half have flavonoid structures. Flavonoids (aglycones and their glycosylated derivatives) are the most important plant pigments. The basic structure of flavonoid aglycones is characterized by a C15 skeleton (Scheme **1**) having a C6-C3-C6 carbon framework which contains a 1-benzopyran (chromene) ring system, in which the aromatic ring is defined as ring A and the pyran as ring C. Another C6 aromatic ring (B) is linked to the pyran moiety of the chromene ring. Flavonoids are further divided into the following subclasses, which differ for oxidation state and connection modality of ring B to the position 2 or 3 of the heterocyclic C-ring: flavanones, flavanols, flavones, flavonols and isoflavones. Anthocyanidins, and chalchones which contain a 2-phenyl-1-benzopyrazolium, are therefore included in the flavonoid class. Chalcones, which lack the C-ring, are early intermediates in the biosynthesis of flavonoids in which the pyran ring C has not yet been formed. Some chemical structure of typical flavonoids are shown in Scheme **1**. The chemical structures of other typical compounds are shown in Schemes **2-5**.

Natural Compounds that Directly Interact and Activate Insulin Receptor

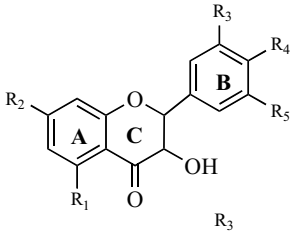
Only few natural compounds, such as demethylasterriquinone B1 (also known as L-783,281), 1,2,3,4,6-penta-O-galloyl-β-D-glucopyranose, and α-lipoic acid, directly act on IR, mimicking insulin effects (Fig. **2**) [18- 20].

Demethylasterriquinone B1 is a metabolite of the fungus species *Pseudomassaria* sp. that interacts with intracellular IR β-subunit stimulating its tyrosine kinase activity determinig increased glucose uptake. The action of this compound is selective and does not induce insulin-like proliferative effects. Oral subministration of demethylasterriquinone B1 to animal models decreases blood glucose level without inducing hypoglycaemia, both in streptozotocin-induced diabetic mice and in lean non-diabetic mice. This finding suggests that this compound is able to stimulate IR activity or to act as insulin sensitizer, thereby decreasing the amount of hormone need to obtain a physiological response [21, 22].

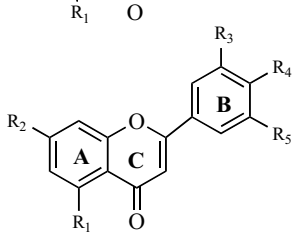
The 1,2,3,4,6-penta-O-galloyl-beta-D-glucopyranose is an ester of gallic acid with glucose, purified from *Lagerstroemia speciosa.* This compound interacts with the IR α-subunit in a binding site different from that of insulin, inducing a direct IR activation and enhancing glucose transport. The 1,2,3,4,6-penta-O-galloyl-beta-D-glucopyranose elicits an insulin-mimetic action in diabetic and obese mice reducing both blood glucose and insulin levels, with no significant



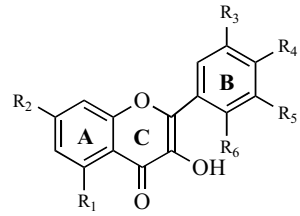
Flavanone (R_1, OH; R_2, OH)	R_3	R_4	R_5
Narigenin	HH	OH	HH
Sigmoidin B	OH	OH	-CH_2-CH=CMe_2
Hesperetin	HH	OMe	OH



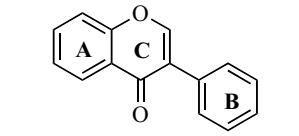
Flavanol (R_1, OH; R_2, OH)	R_3	R_4	R_5
Catechin	OH	OH	HH
Epigallocatechin	OH	OH	OH



Flavone (R_1, OH; R_2, OH)	R_3	R_4	R_5
Luteolin	HH	OH	OH
Apigenin	HH	OH	HH

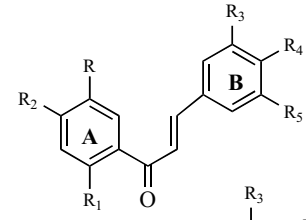


Flavonol (R_1, OH; R_2, OH)	R_3	R_4	R_5	R_6
Quercetin	OH	OH	HH	HH
Kaempferol	HH	OH	HH	HH
Myricetin	OH	OH	OH	HH
Morin	HH	OH	HH	OH

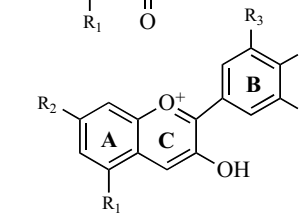


Isoflavones

(basic chemical structure)



Chalcone (R_1, OH; R_2, OH)	R	R_3	R_4	R_5
BroussochalconeA	-CH_2-CH=CMe_2	HH	OH	OH



Anthocyanidin (R_1, OH; R_2, OH)	R_3	R_4	R_5
Cyanidin	OH	OH	OH

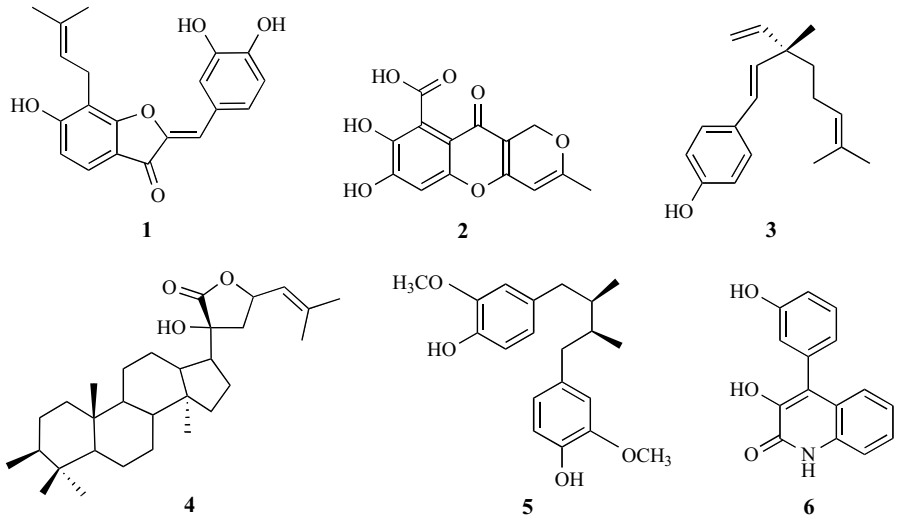
Scheme 1. Chemical structures of the main flavonoid classes, and of typical flavonoids.

changes in body weight, food intake, or physical activity with respect to the control mice [19].

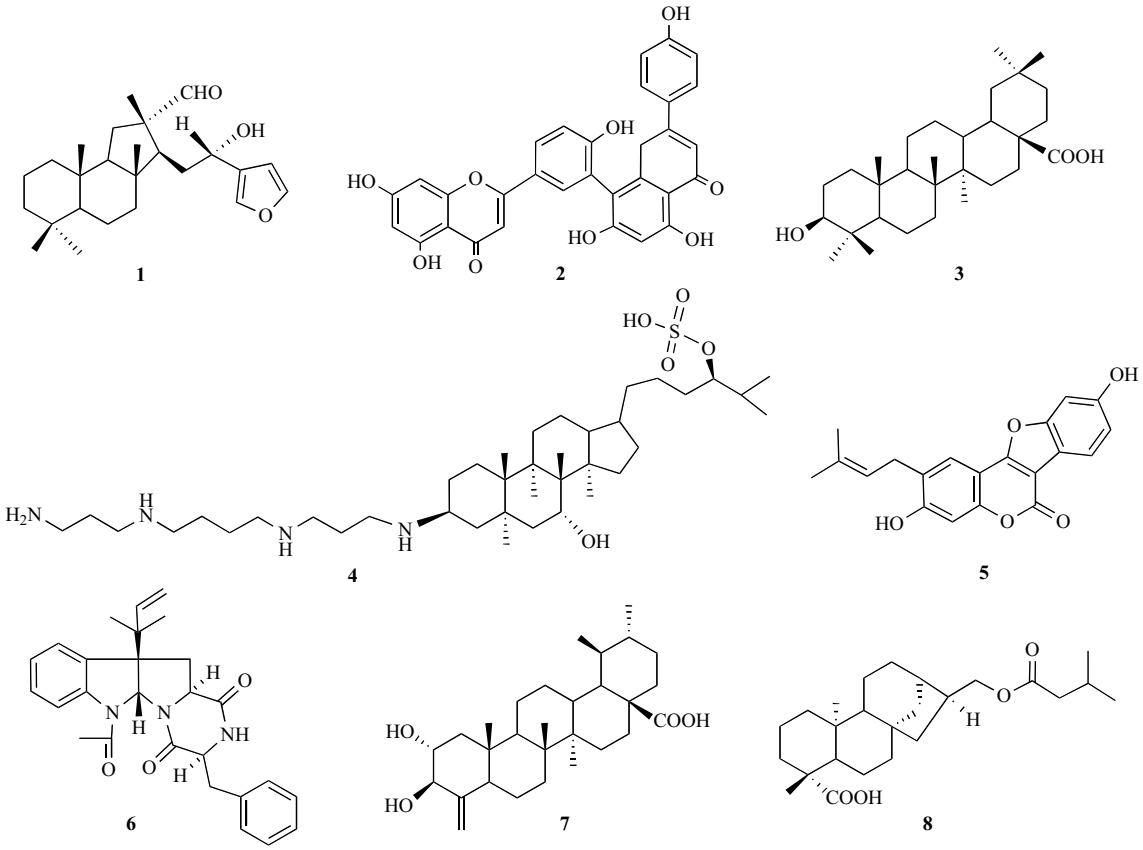
Recently, it has been reported that α-lipoic acid interacts with the tyrosine kinase domain of the insulin receptor, leading to its autophophorylation and propagation of insulin signaling. Molecular modeling studies on an α-lipoic acid-IR complex suggest that α-lipoic acid stabilizes the active form of the IR kinase domain, favoring the ATP binding to the kinase domain and contributing to its auto-activation [20].

Natural Compound Targeting Phosphotyrosine Protein Phosphatase Enzymes

In physiological conditions insulin signaling is tightly regulated by several mechanisms: i) dephosphorylation of phospho-tyrosine residues of IR and/or IRS proteins by specific protein tyrosine phosphatases (PTPs); ii) serine phosphorylation of IRS proteins by various Ser/Thr kinases; iii) binding of inhibitory proteins; iv) ligand-induced degradation [1]. It has been demonstrated that hundreds of natural



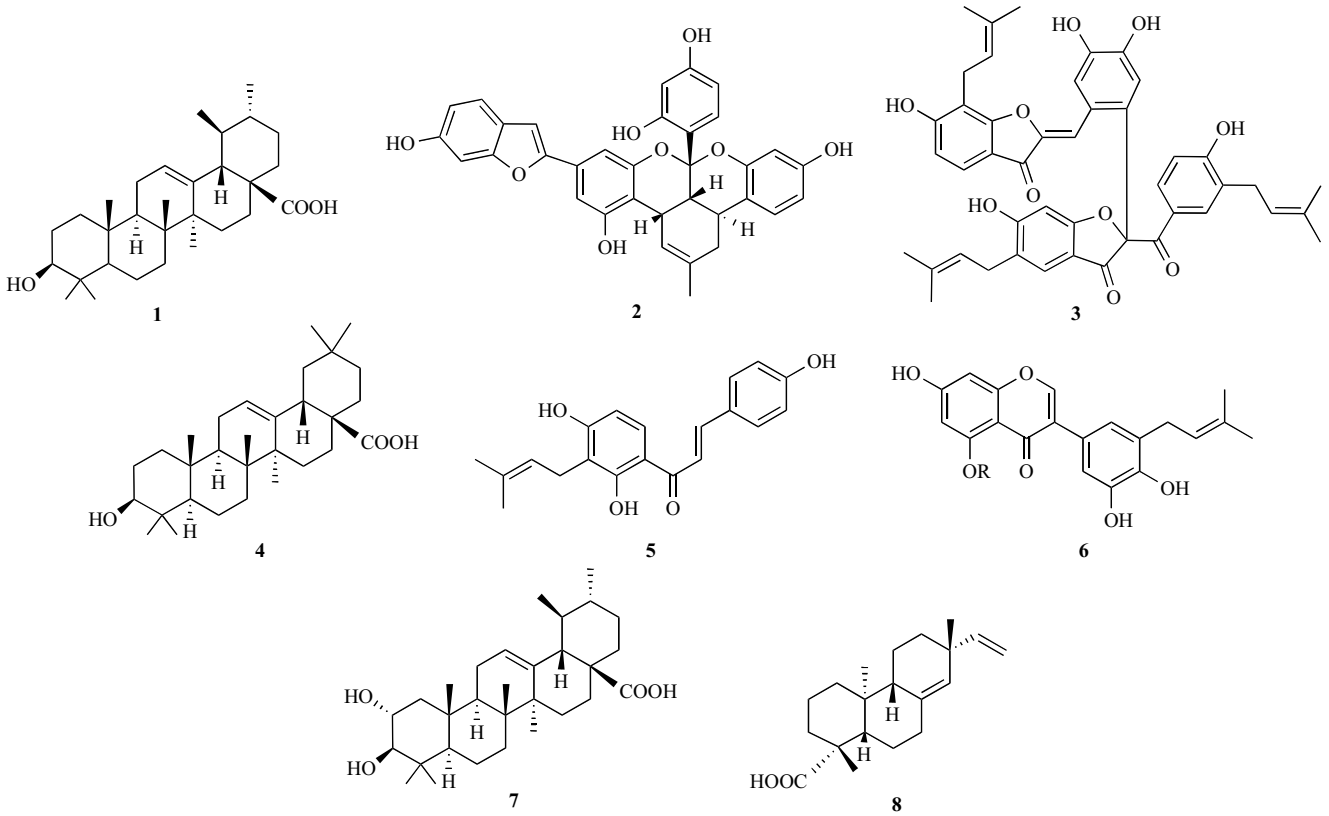
Scheme 2. Competitive inhibitors of PTP1B. Chemical structures: 1, Licoagroaurone; 2, Anhydrofulvic acid; 3, Bakuchiol; 4, (20S)-3β,20,23ξ-Trihydroxydammarane-24-en-21-oic acid-21, 23 lactone; 5, meso-Dihydroguaiaretic acid; 6, Viridicatol.



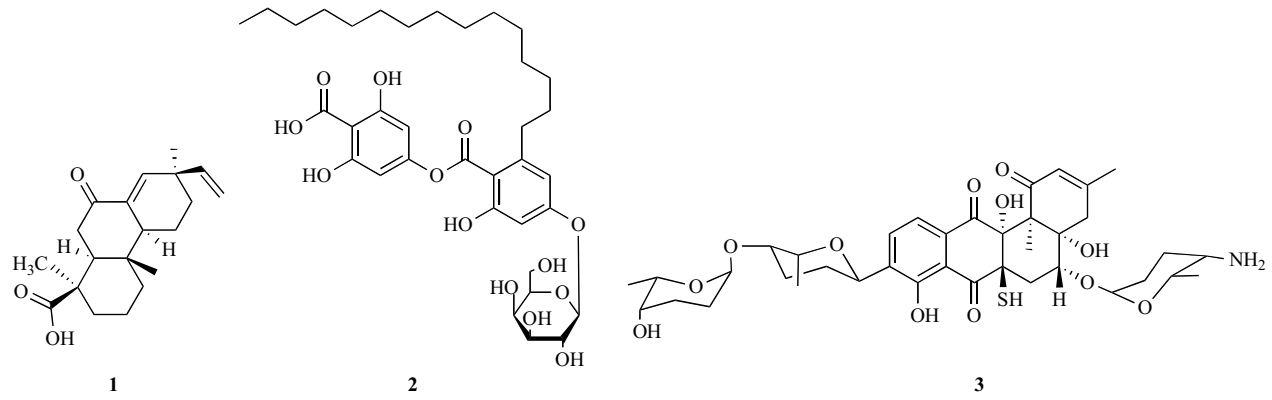
Scheme 3. Non competitive inhibitors of PTP1B. Chemical structures: 1, Hyrtiosal; 2, Amentoflavone; 3, Morolic acid; 4, Trodusquemine; 5, Psoralidin; 6, Fructigenine A; 7, Ilekudinol B; 8, 16αH,17-isovaleryloxy-ent-kauran-19-oic acid.

substances stimulate insulin signaling acting as inhibitors of protein tyrosine phosphatases (Fig. **2**), alleviating insulin resistance [23], for example: PTP1B [24], LAR (leukocyte common antigen-related PTP) [25-29], PTPα [30-34], SHP-2 [35-42], TC-PTP [43, 44], PTPε [30, 45], LMW-PTP [46, 47]; PTP-MEG2 [48].

PTP1B is one of the most important negative regulator of IR signaling in liver and muscle [49-52]. Hepatic PTP1B expression is increased in T2DM rat models [53], while mice lacking PTP1B show improved insulin sensitivity with enhanced phosphorylation of hepatic insulin receptor and IRS1 [54]. PTP1B contains an active site loop (P-loop) where the phosphate group of the substrate interacts with Arg221 and with other P-loop residues, including the catalytic Cys215 residue. The crystal structure of PTP1B–ligand complexes revealed another phosphotyrosine binding site (site B),



Scheme 4. Mixed type inhibitors of PTP1B. Chemical structures: 1, Ursolic acid; 2, Mulberrofuran G; 3, Licoagrone; 4, Oleanoic acid; 5, Isobavachalcone; 6, Glisoflavone; 7, Corosolic acid; 8, ent-pimara-8(14),15-diene-19-oic acid.



Scheme 5. The most potent natural inhibitors of PTP1B. Chemical structures: 1, 7-Oxo-ent-pimara-acid; 2, Aquastatin A; 3, Grecocycline B.

close to the conserved primary active site (site A), which contains Met258, Gly259, Gln262, Gln266, Arg24, and Arg254 [55]. While competitive inhibitors bind to site A, most non competitive and mixed type inhibitors bind to site B blocking the catalytic process. Several compounds listed in Table **1** have been characterised for their inhibition mechanisms (see below).

Natural PTP1B Inhibitors

In a detailed review Jiang *et al.* [56] described about 300 natural or synthetic products acting as PTP1B inhibitors. Tables **1** provides an updated overview of natural substances exhibiting PTP1B inhibitory activity on, their IC_{50} values and the natural resources from which they were isolated. Most of them have flavonoid or terpenoid structures. About 15% of flavonoids and almost half of terpenoids listed in Tables **1A** and **1B**, are inhibitors of PTP1B with IC_{50} values in the 2-10 μM range. Furthermore, also more than 60 % of phenolic compounds listed in Table **1C**, and about 40% of compounds listed in Table **1D** are potent inhibitors of PTP1B, with IC_{50} values in the low μM range. About 44% of compounds act as a non competitive inhibitors, 34 % as mixed-type inhibitors and 22% are competitive inhibitors respect to PTP1B (see Scheme **2-4**). The compounds 7-Oxo-ent-pimara-acid, a diterpenoid extracted from *Aralia continentalis* (IC_{50} value = 0.09 μM) [57], aquastatin A, a β-galactopyranoside extracted from a *Cosmospora* species

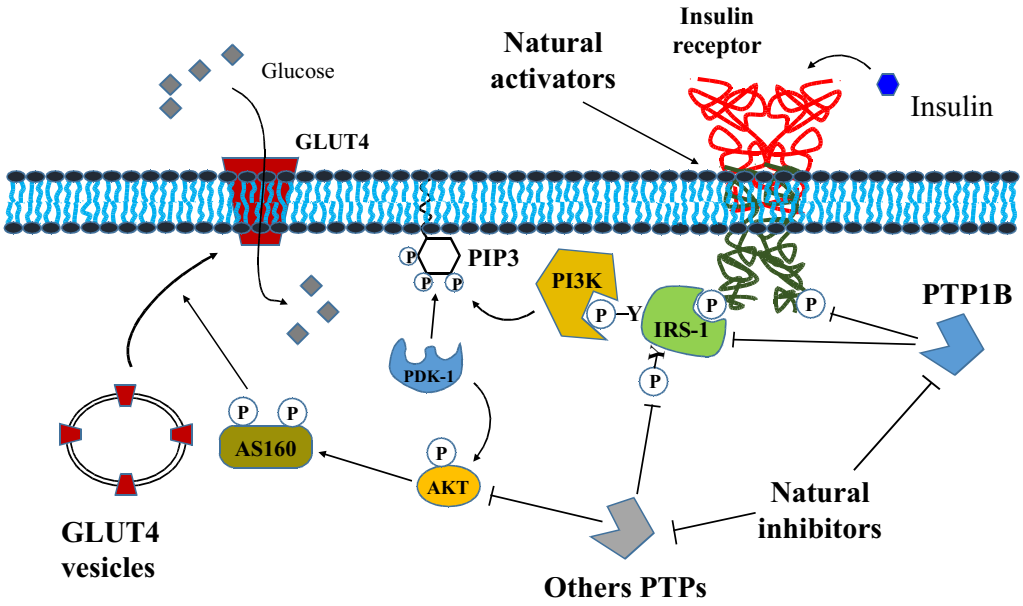


Fig. (2). Inhibition of PTPs by natural compounds improves insulin signaling. Insulin activates the IR tyrosine kinase that phosphorylates and recruits different substrate adaptors such as the IRS proteins which, in turn, recruit and activate other effectors contributing to signal propagation. Most proteins involved in insulin signaling are regulated by reversible phosphorylation on tyrosine and/or serine/threonine residues. A number of PTPs act as negative regulators of insulin signaling. One of the most important PTPs involved in the regulation of insulin receptor activity is PTP1B, which strongly contributes to downregulation of insulin signaling by dephosphorylating IR and IRS-1. Several natural molecules are able to inhibit PTP1B as well as other PTPs, thereby increasing insulin sensitivity. For an explanation of acronyms see 'Abbreviations'.

(IC_{50} value = 0.19 μM) [58], and Grecocycline B, a benzanthracene quinone extracted from a *Streptomyces* species (IC_{50} value = 0.52 μM) [59] (Table **1D**) are the most potent natural inhibitors of PTP1B (Scheme **5**). The majority of the compounds analyzed behaves as non competitive and mixed-type inhibitors. The non competitive inhibitors bind to the enzyme at a specific site usually near the active site, distorting the catalytic residues geometry and position. Mixed-type inhibitors act similarly, but they also hinder the binding of substrate. In silico docking indicated that morin, a non competitive inhibitor of PTP1B, establishes hydrogen bonds with residues near to the active site, such as Arg254, Gln262, Asp29, Met258 and Gly259 (site B), impairing the ability of the enzyme to hydrolyze substrate phosphoesteric bond [60]. Docking simulation indicated that site B residues are involved in the binding of ursolic acid, a triterpene contained in traditional Chinese medicinal herbs. Ursolic acid, due to its different steric hindrance and positioning with respect to morin, interacts also with residues at the boundary between a site A and site B, thereby influencing substrate binding [61] and behaves as a mixed-type inhibitor. Undoubtedly the ability of ursolic acid to form additional bonds with respect to morin, can explain its greater binding affinity. The diterpenoid 7-oxo-ent-pimara-8(14),15-diene-19-oic acid, acts as a non competitive inhibitor. Nevertheless, it does not interact with site B, but with the catalytic WDP loop; this stabilizes the open form of the active site, thereby blocking the catalytic process [62]. Few compounds listed in Tables **1A-D** were tested also on other PTPs. For example ascochitine (IC_{50} value = 38.5 μM on PTP1B), extracted from *Ascochyta salicorniae*, is a less potent inhibitor of PTP1B than of *M. tuberculosis* MPtpB (IC_{50} value = 11.5 μM) [63]. Dihydrocarolic acid (IC_{50} value = 38 μg/ml on PTP1B) and Penitricin D (IC_{50} value = 15.8 μg/ml on PTP1B), both extracted from *Aspergillus niger*, are less potent inhibitors versus PTP1B than versus the CD45 (IC_{50} values = 1.2 and 2.3 μg/ml, respectively) [64]. Aquastatin A (IC_{50} value = 0.19 μM on PTP1B), extracted from a fungus of the *Cosmospora* species, inhibits also TC-PTP, another enzyme involved in negative regulation of insulin-mediated signaling [58]; TC-PTP is an enzyme highly homologous with PTP1B, displaying 72% sequence identity. The compound 7-hydroxy-5,6-dimethoxy-1,4-phenantrene quinone (IC_{50} value = 38 μM on PTP1B), which is a metabolite extracted from *Dendrobium moniliforme*, is ten-fold more potent inhibitor against the dual specificity VHR PTP than against PTP1B [65]. Corosolic acid, a compound contained in several Chinese medicinal herbs, inhibits *in vitro* several diabetes-related non-receptor PTPs [66], such as PTP1B (IC_{50} value = 5.49 μM), TC-PTP (IC_{50} value = 11.31 μM), SHP1 (IC_{50} value = 24.56 μM) and SHP2 (IC_{50} value = 10.50 μM). Shi *et al.* [66] reported that corosolic acid is able to stimulate glucose uptake in cultured L6 myotubes. Furthermore, experiments performed with GLUT4 transfected CHO/hIR cells showed that corosolic acid increases GLUT4 translocation from cytoplasm to the cell membrane [66]. Both actions were blocked by wortmannin, a specific inhibitor of PI3K, a key downstream enzyme of insulin pathway. In addition, corosolic acid induces insulin receptor and Akt-Ser phosphorylation in cultured CHO/hIR cells, but it is unable to enhance AMPK phosphorylation. These authors suggest that corosolic acid might increase glucose uptake and GLUT4 translocation enhancing insulin receptor phosphorylation via the inhibition of certain PTPs that antagonize IR signaling. Ursolic acid inhibits *in vitro* some diabetes-related non-receptor PTPs such as: i) PTP1B (various IC_{50} values for PTP1B were reported:

Table 1A. Natural inhibitors of PTP1B.

Natural Flavonoids	IC_{50}	Structure type	Source
Apigenin	33 μM	Flavone	*Apium graveolens*, and other plants [60]
Quercetin	28.12 μM	Flavonol	*Ardisia japonica* [73]
8-(1,1-dimethyl-allyl)-5'-(3-methylbut-2-enyl)-3',4',5,7-tetrahydroxyflanvonol	4.3 μM	Flavonols	*Broussonetia papyrifera* [121]
3'-(3-methylbut-2-enyl)-3',4',7-trihydroxyflavane	41.5 μM	Flavan	*Broussonetia papyrifera* [121]
3,3',4',5,7-pentahydroxyflavone	23.3 μM	Flavone	*Broussonetia papyrifera* [121]
Uralenol	21.5 μM	Flavones	*Broussonetia papyrifera* [121]
Broussochalcone A	36.8 μM	Chalcones	*Broussonetia papyrifera* [121]
Quercetin-3-O-b-D-glucuronide	7.39 μM	Flavonol derivative	*Cyclocarya paliurus* [122]
Myricetin-3-O-b-D-glucuronide	9.47 μM	Flavonoid derivative	*Cyclocarya paliurus* [122]
Abyssinoflavone VI	18.9 μM	Flavanone	*Erythrina abyssinica* [123]
Abyssinoflavone VII	15.7 μM	Flavanone	*Erythrina abyssinica* [123]
Sigmoidin F	14.2 μM	Flavanone	*Erythrina abyssinica* [123]
Sigmoidin B	19.4 μM	Favanone	*Erythrina abyssinica* [123]
Abyssinin II	17.3 μM	Flavanone	*Erythrina abyssinica* [123]
Sigmoidin A	14.4 μM	Flavanone	*Erythrina abyssinica* [123]
5-Deoxyabyssinin II	19.2 μM	Favanone	*Erythrina abyssinica* [123]
3′-Prenylnaringenin	26.7 μM	Flavanone	*Erythrina abyssinica* [123]
Abyssinin I	18.2 μM	Flavanone	*Erythrina abyssinica* [123]
Abyssinone-VI	20.6 μM	Chalcone	*Erythrina abyssinica* [123]
Licoagrochalcone A	16.9 μM	Chalcone	*Erythrina abyssinica* [123]
2(S)-5,5',7-trihydroxy-2'-prenyl-(2'',2''-dimethylpyrano)-(5''6'':3',4')flavanone	13.9 μM	Flavanone	*Erythrina abyssinica* [124]
2(S)-5,7-dihydroxy-3'-methoxy-(2''-(5''-hydroxy)-methylpyrano)-(5'',6'':3',4')flavanone	17.9 μM	Flavanone	*Erythrina abyssinica* [124]
2(S)-5,7-dihydroxy-5'-prenyl-(2'2''-(3''-hydroxy)-dimethylpyrano)-(5'',6'': 3'4')flavanone	14.9 μM	Flavanone	*Erythrina abyssinica* [124]
2(S)-5,7-dihydroxy-5'-methoxy-(2'',2''-(3''-hydroxy)-dimethylpyrano)-(5'',6'':3',4')flavanone	18.2 μM	Flavanone	*Erythrina abyssinica* [124]
2(S)-5,7-dihydroxy-5'-prenyl-(2''2''-(3'',4''-dihydroxy)-dimethylpyrano))-(5'',6'':3',4')flavanone	19.0 μM	Flavanone	*Erythrina abyssinica* [124]
2(S)-5,6',7-trihydroxy-5'-prenyl-(2'',2''-dihydroxy)-dimethylpyrano)-(5'',6'':3',4')flavanone	18.2 μM	Flavanone	*Erythrina abyssinica* [124]
Burttinone	18.9 μM	Flavanone	*Erythrina abyssinica* [124]
Burttinonedehydrate	21.6 μM	Flavanone	*Erythrina abyssinica* [124]
(2S)-5,7-dihydroxy-3′-prenyl-2″ξ-(4″-hydroxyisopropyl)dihydrofurano (1″,3″:4′,5′) flavanone	15.2 μM	Flavanone	*Erythrina abyssinica* [125]
(2S)-5,7-dihydroxy-3′-methoxy-2″ξ-(4″-hydroxyisopropyl)dihydrofurano (1″,3″:4′,5′)flavanone	16.1 μM	Flavanone	*Erythrina abyssinica* [125]

(Table 1A) contd….

Natural Flavonoids	IC_{50}	Structure type	Source
(2S)-5,7-dihydroxy-3′-prenyl-2″ξ-(4″-hydroxyisopropyl)-3″-hydroxy-dihydrofurano(1″,3″:4′,5′) flavanone	17.9 μM	Flavanone	*Erythrina abyssinica* [125]
(2S)-5,7,3′-trihydroxy-2′-prenyl-2″ξ-(4″-hydroxyisopropyl)-3″-hydroxy-dihydrofurano (1″,3″:4′,5′) flavanone	18.3 μM	Flavanone	*Erythrina abyssinica* [125]
Erylatissin C	16.2 μM	Flavanone	*Erythrina abyssinica* [125]
Abyssinin III	19.6 μM	Flavanone	*Erythrina abyssinica* [125]
Erythribyssin E	15.2 μM	Isoflavanones	*Erythrina abyssinica* [126]
5-Deoxyabyssinin II	19.2 μM	5-Deoxyflavonoid deriv	*Erythrina abyssinica* [126]
7-hydroxy-2-(4-methoxy-3-(3-methylbut-2-enyl)phenyl)chroman-4-one	16.5 μM	5-Deoxyflavonoid deriv	*Erythrina abyssinica* [126]
Abyssinones V	22.6 μM	5-Deoxyflavonoid deriv	*Erythrina abyssinica* [126]
Abyssinone II	29.2 μM	5-Deoxyflavonoid deriv	*Erythrina abyssinica* [126]
Prostratol C	17.2 μM	5-Deoxyflavonoid deriv	*Erythrina abyssinica* [126]
Erythribyssin G	35.8 μM	Prenylated flavanone	*Erythrina abyssinica* [126]
Erythribyssin J	14.9 μM	Isoflavanones	*Erythrina abyssinica* [126]
Erythribyssin A	19.3 μM	Pterocarpans (Isoflavone der)	*Erythrina abyssinica* [127]
Neorautenol	7.6 μM	Pterocarpans (Isoflavone der)	*Erythrina abyssinica* [127]
Erybreadin B	4.2 μM	Pterocarpans (Isoflavone der)	*Erythrina abyssinica* [127]
3,9-Dihydroxy-4-prenyl-(6aR;11aR) pterocarpan	19.5 μM	Pterocarpans (Isoflavone der)	*Erythrina abyssinica* [127]
Folitenol	7.8 μM	Pterocarpans (Isoflavone der)	*Erythrina abyssinica* [127]
Erybreadin D	6.4 μM	Pterocarpans (Isoflavone der)	*Erythrina abyssinica* [127]
Erysubin E	8.8 μM	Pterocarpans (Isoflavone der)	*Erythrina abyssinica* [127]
Erybreadin C	7.3 μM	Pterocarpans (Isoflavone der)	*Erythrina abyssinica* [127]
5,2′,4′-trihydroxy-6-(γ,γ-dimethylallyl)-2‴,2‴-dimethyldihydropyrano(5‴,6‴) isoflavanone	4.1 μM	Isoflavanone	E*rythrina addisoniae* [128]
Orientanol E	10.1 μM	Prenylated isoflavonoid	E*rythrina addisoniae* [128]
Warangalone	42.5 μM	Prenylated isoflavonoid	E*rythrina addisoniae* [128]
2,3-Dihydroauriculatin	2.6 μM	Prenylated isoflavonoid	E*rythrina addisoniae* [128]
Erylysin A	14.8 μg/ml	Pterocarpans (Isoflavone der)	*Erythrina lysistemon Hutch* [129]
Erylysin B	6.0 μg/ml	Pterocarpans (Isoflavone der)	*Erythrina lysistemon Hutch* [129]
Isoneorautenol	18.1 μg/ml	Pterocarpans (Isoflavone der)	*Erythrina lysistemon Hutch* [129]
Phaseollin	5.1 μg/ml	Pterocarpans (Isoflavone der)	*Erythrina lysistemon Hutch* [129]
Orientanol C	8.2 μg/ml	Pterocarpans (Isoflavone der)	*Erythrina lysistemon Hutch* [129]
Erysubin D	9.7 μg/ml	Pterocarpans (Isoflavone der)	*Erythrina lysistemon Hutch* [129]
Eryvarin D	4.1 μg/ml	Pterocarpans (Isoflavone der)	*Erythrina lysistemon Hutch* [129]
Calopocarpin	7.6 μg/ml	Pterocarpans (Isoflavone der)	*Erythrina lysistemon Hutch* [129]
Erybraedin A	1.01 μg/ml	Pterocarpans (Isoflavone der)	*Erythrina lysistemon Hutch* [129]

(Table 1A) contd….

Natural Flavonoids	IC_{50}	Structure type	Source
Abyssinone-V-4′-O-methyl ether	26.3 μM	Flavonoid	*Erythrina mildbraedii* [130]
Abyssinone-IV-4′-O-methyl ether	21.2 μM	Isoprenylated Flavonoid	*Erythrina mildbraedii* [130]
Abyssinone-V	39.7 μM	Flavonoid	*Erythrina mildbraedii* [130]
Abyssinone-IV	16.0 μM	Flavonoid	*Erythrina mildbraedii* [130]
Abyssinone-VI-4-O-methyl ether	14.8 μM	Chalcone (isoprenylated Flavonoid	*Erythrina mildbraedii* [130]
Sigmoidin E	39.2 μM	Flavonoid	*Erythrina mildbraedii* [130]
Alpinumisoflavone	41.5 μM	Isoflavone	*Erythrina mildbraedii* [130]
Licoflavanone-4'-O-methyl ether	29.6 μM	flavanone	*Erythrina mildbraedii* [131]
2',7-dihydroxy-4'-methoxy-5'-(3-methylbut-2-enyl)isoflavone	21.3 μM	Isoflavone	*Erythrina mildbraedii* [131]
(3R)-2',7-dihydroxy-3'-(3-methylbut-2-enyl)-2''',2'''-dimethylpyrano(5''',6''' : 4 ',5')isoflavan	5.5 μM	Isoflavan	*Erythrina mildbraedii* [131]
Abyssinin II	40.5 μM	Flavanone	*Erythrina mildbraedii* [131]
Parvisoflavone B	42.6 μM	Isoflavone	*Erythrina mildbraedii* [131]
Licoagrone	6.0 μM	Flavonoid dimer	*Glycyrrhiza species* [132]
Licoagrodin	11.5 μM	Flavonoid dimer	*Glycyrrhiza species* [132]
Licoagroaurone	23.9 μM	Prenylated aurone	*Glycyrrhiza species* [132]
Isobavachalcone	27.3 μM	Prenylated chalcone	*Glycyrrhiza species* [132]
Glisoflavone	27.9 μM	Flavones	*Glycyrrhiza uralensis* [133]
Kuwanon J	2.7 μM	Chalcone derivative	*Morus bombycis* [134]
Kuwanon R	8.2 μM	Chalcone derivative	*Morus bombycis* [134]
Kuwanon V	13.8 μM	Chalcone derivative	*Morus bombycis* [134]
Licochalcone A	19.1 μM	Retrochalcone	*Morus bombycis* [134]
Licochalcone C	30.9 μM	Retrochalcone	*Morus bombycis* [134]
Licochalcone E	20.7 μM	Retrochalcone	*Morus bombycis* [134]
Karanjin	84.5 μM	Flavonoid (benzopyran dervative)	*Pongamia pinnata* [85]
Morin	15 μM	Flavonol	*Psidium guajava*, and other plants [60]
Amentoflavone	7.3 μM	Flavone	*Selaginella tamariscina* [77]
3',5'-Diprenylgenistein	31.75 μM	Flavonoid (genistein derv)	*Tetracera scandens* [78]
6,8-Diprenylgenistein	28.13 μM	Flavonoid (genistein derv)	*Tetracera scandens* [78]
Derrone	20.63 μM	Flavonoid (genistein derv)	*Tetracera scandens* [78]
Alpinumisoflavone	37.52 μM	Flavonoid (genistein derv)	*Tetracera scandens* [78]
OTHER NATURAL BENZOPYRAN DERIVATIVES			
Ascochitine	38.5 μM	Benzopyran derivative	*Ascochyta salicorniae* [63]
Sanggenon C	2.6 μM	Benzopyran derivative	*Morus* [135]
Sanggenon G	1.6 μM	Benzopyran derivative	*Morus* [135]
Mulberrofuran C	4.9 μM	Benzopyran derivative	*Morus* [135]
Kuwanon L	16.9 μM	Benzopyran derivative	*Morus* [135]

(Table 1A) contd….

Natural Flavonoids	IC_{50}	Structure type	Source
Anhydrofulvic acid	1.90 μM	Benzopyran derivative	*Penicillium sp* [136]
Phelligridin H	3.1 μM	Benzopyran derivative	*Phellinus igniarius* [137]
Phelligridin I	3.0 μM	Benzopyran derivative	*Phellinus igniarius* [137]
Psoralidin	9.4 μM	benzopyran derivative	*Psoralea corylifolia* [138]
Psoralidin	9.4 μM	Benzopyran derivative	*Psoralea corylifolia* [138]
NATURAL BENZOFURAN DERIVATIVES			
2-(2',4'-dihydroxy-3'-(3-methylbut-2-enyl)phenyl)-6-hydroxybenzofuran	13.6 μM	Benzofuran derivative	*Erythrina addisoniae* [139]
2-(2'-methoxy-4'-hydroxy-5'-(3-methylbut-2-enyl)phenyl)-6-hydroxybenzofuran	17.5 μM	Benzofuran derivative	*Erythrina addisoniae* [139]
2-(2'-methoxy-4'-hydroxyphenyl)-5-(3-methylbut-2-enyl)-6-hydroxybenzofuran	15.7 μM	Benzofuran derivative	*Erythrina addisoniae* [139]
Glycybenzofuran	25.5 μM	Benzofuran dervative)	*Glycyrrhiza uralensis*] [133]
Albafuran A	9.2 μM	2-arylbenzofuran	*Morus bombici* [134]
Mulberrofuran W	2.7 μM	2-arylbenzofuran	*Morus bombici* [134]
Mulberrofuran D	4.3 μM	2-arylbenzofuran	*Morus bombici* [134]
Pongamol	75.0 μM	Benzofuran dervative)	*Pongamia pinnata* [85]
Usimine A	15.0 μM	Benzofuran derivative	*Stereocaulon alpinum* [140]
Usimine B	27.7 μM	Benzofuran derivative	*Stereocaulon alpinum* [140]
Usimine C	23.2 μM	Benzofuran derivative	*Stereocaulon alpinum* [140]
Usnic acid	16.4 μM	Benzofuran derivative	*Stereocaulon alpinum* [140]

Table 1B. Natural inhibitors of PTP1B.

Natural Terpenoids	IC_{50}	Structure Type	Sources
Acanthoic acid	23.5 μM	Diterpenoid	*Acanthopanax koreanum* [141]
ent-kaur-16-en-19-oic acid	20.2 μM	Diterpenoid	*Acanthopanax koreanum* [141]
16aH,17-isovaleryloxy-ent-kauran-19-oic acid	7.1 μM	Diterpenoid	*Acanthopanax koreanum* [141]
Continentalic acid	0.66 μM	Diterpenoid	*Aralia continentalis* [57]
Kaurenoic acid	4.64 μM	Diterpenoid	*Aralia continentalis* [57]
ent-Pimarol	9.85 μM	Diterpenoid	*Aralia continentalis* [57]
7-Oxo-ent-pimara- acid	0.09 μM	Diterpenoid	*Aralia continentalis* [57]
16α-Hydroxy-17-isovaleryloxy-ent-kauran 19-oic acid	1.51 μM	Diterpenoid	*Aralia continentalis* [57]
17-Hydroxy-ent-kaur-15-en-19-oic acid	9.12 μM	Diterpenoid	*Aralia continentalis* [57]
15α,16α-Epoxy-17-Hydroxy-ent-kauran-19-oic acid	1.96 μM	Diterpenoid	*Aralia continentalis* [57]
16 16α,17-Dihydroxy-ent-kauran-19-oic acid	0.56 μM	Diterpenoid	*Aralia continentalis* [57]
ent-Thermarol	1.34 μM	Diterpenoid	*Aralia continentalis* [57]
4-Epiruilopezol	10.98 μM	Diterpenoid	*Aralia continentalis* [57]

(Table 1B) contd….

Natural Terpenoids	IC_{50}	Structure Type	Sources
ent-pimara-8(14),15-diene-19-oic acid (continentalic acid)	2.85 μM	Diterpenoids	*Aralia continentalis* [62]
7-oxo-ent-pimara-8(14),15-diene-19-oic acid	2.60 μM	Diterpenoids	*Aralia continentalis* [62]
ent-pimara-8(14),15-diene-19-ol (ent-pimarol)	12.95 μM	Diterpenoids	*Aralia continentalis* [62]
8a-hydroxy-ent-pimara-15-en-19-ol (ent-thermarol)	7.06 μM	Diterpenoids	*Aralia continentalis* [62]
ent-kaur-16-en-19-oic-acid (kaurenoic acid	8.27 μM	Diterpenoids	*Aralia continentalis* [62]
3-Oxoolean-12-en-27-oic acid	6.8 μM	Triterpene	*Astilbe koreana* [142]
3b-Hydroxyolean-12-en-27-oic acid (b-peltoboy-kinolic acid	5.2 μM	Triterpene	*Astilbe koreana* [142]
3b-Hydroxyurs-12-en-27-oic acid	4.9 μM	Triterpene	*Astilbe koreana* [142]
3a,24-Dihydroxyolean-12-en-27-oic acid	11.7 μM	Triterpene	*Astilbe koreana* [142]
3b,6b-Dihydroxyolean-12-en-27-oic acid (astilbic acid)	12.8 μM	Triterpene	*Astilbe koreana* [142]
11-keto boswellic acid	8.04 μM	Triterpene	*Boswellia carteri* [71]
Oleanolic acid	3.37 μM	Triterpene	*Calendula. officinalis* [71]
Ursolic acid	3.08 μM	Triterpenoids	*Calendula. officinalis* [71]
Corosolic acid	5.49 μM	Triterpenoids	*Calendula. officinalis* [71]
Madecassic acid	12.38 μM	Triterpene	*Centella asiatica* [71]
Ursolic acid	3.08 μM	Triterpenoids	*Cornus officinalis* [67]
O-Methyl nakafuran-8 lactone	1.58 μM	Sesquiterpenoid	*Dysidea* sp [143]
Hydroxybutenolide	8.8 μg/mL	Sesquiterpene	*Dysidea septosa* [144]
Microcionin-4	11.6 μg/mL	Sesquiterpene	*Dysidea septosa* [144]
dihydropallescensin-2	6.8 μg/mL	Sesquiterpene	*Dysidea septosa* [144]
Nakafuran-8	1.9 μg/mL	Sesquiterpenoid	*Dysidea septosa* [144]
Dysidine	6.70 μM	Sesquiterpene	*Dysidea* villosa [145]
21-Dehydroxybolinaquinone	39.50 μM	Sesquiterpene quinone	*Dysidea* villosa [145]
Betulin	15.3 μM	Triterpene	*Euphorbia micractina* [72]
(23S)-3b,20z,21z-trihydroxy-19-oxo-21,23-epoxydammarane-24-ene	19.3 μM	Triterpene	*Gynostemma pentaphyllum* [146]
(20S,24S)-3b,12b,20,24-epoxydammarane-25-triol	20.4 μM	Triterpene	*Gynostemma pentaphyllum* [146]
(20S,24S)-3b,12b,20,24-epoxy-12,25-dihydroxydammarane	21.7 μM	Triterpene	*Gynostemma pentaphyllum* [146]
(20S),3b,21-trihydroxy-25-methoxydammarane-23-ene	25.1 μM	Triterpene	*Gynostemma pentaphyllum* [146]
(20S)-3b,12b,12,25-dihydroxydammar-23-ene	28.5 μM	Triterpene	*Gynostemma pentaphyllum* [146]
(20S)-3b,20,23e-trihydroxydammarane-24-en-21-oic acid-21,23 lactone	5.3 μM	Triterpene	*Gynostemma pentaphyllum* [146]
(20R)-3b,20,23e-trihydroxydammarane-24-en-21-oic acid-21,23 lactone	5.7 μM	Triterpene	*Gynostemma pentaphyllum* [146]
Hueafuranoid A	13.9 μM	Diterpene furanoid	*Huea sp* [147]
Hyrtiosal	42 μM	Sesterterpenoid	*Hyrtios* erectus [86]
Sulfircin	29.8 μM	Sesterterpene	*Ircinia* [148]

(Table 1B) contd….

Natural Terpenoids	IC_{50}	Structure Type	Sources
(3b,6b,8a,10b)-3-acetyl-6,8,10-trihydroxyeremophil-7(11)-eno-12,8-lactone	1.34 μM	Sesquiterpene	*Ligularia fischeri* [149]
Oleanolic acid	3.4 μM	Triterpene	*Phoradendron reichenbachianum* (AEPr) [61]
Moronic acid	13.2 μM	Triterpene	*Phoradendron reichenbachianum* (AEPr) [61]
Morolic acid	9.1 μM	Triterpene	*Phoradendron reichenbachianum* (AEPr) [61]
Ursolic acid	2.3 μM	Triterpene	*Phoradendron reichenbachianum* (AEPr) [61]
Lipidyl pseudopterane A	71 μg/mL	Diterpene	*Pseudopterogorgia acerosa* [150]
Psidial B	61.7% at 10 μM	Sesquiterpenoid	*Psidium guajava L* [151]
Psidial C	38.8% at 10 μM	Sesquiterpenoid	*Psidium guajava L* [151]
Rhododendric acid A	6.3 μM	Triterpenoids	*Rhododendron brachycarpum* G. Don [70]
Ursolic acid	3.1 μM	Triterpenoids	*Rhododendron brachycarpum* G. Don [70]
Corosolic acid	7.0 μM	Triterpenoids	*Rhododendron brachycarpum* G. Don [70]
Rotundic acid	20.1 μM	Triterpenoids	*Rhododendron brachycarpum* G. Don [70]
2a,3a,23-trihydroxyursa-12,20(30)-dien-28-oic acid	17.4 μM	Triterpenoids	*Rhododendron brachycarpum* G. Don [70]
23-hydroxyursolic acid	7.4 μM	Triterpenoids	*Rhododendron brachycarpum* G. Don [70]
Actinidic acid	18.0 μM	Triterpenoids	*Rhododendron brachycarpum* G. Don [70]
Isotanshinone IIA	11.4 μM	Diterpene	*Salvia miltiorrhiza* [152]
Dihydroisotanshinone I	22.4 μM	Diterpene	*Salvia miltiorrhiza* [152]
Sarcophytonolide N	5.95 μM	Diterpenoid	*Sarcophyton trocheliophorum* [153]
Sarcrassin E	6.33 μM	Diterpenoid	*Sarcophyton trocheliophorum* [153]
4Z,12Z,14E-Sarcophytolide	15.4 μM	Diterpenoid	*Sarcophyton trocheliophorum* [153]
Cembrene-C	26.6 μM	Diterpenoid	*Sarcophyton trocheliophorum* [153]
Chetoemblide	27.2 μM	Diterpenoid	*Sarcophyton trocheliophorum* [153]
Sarcotroate B	6.97 μM	Diterpenoids	*Sarcophyton trocheliophorum* [74]
Mokko lactone	1.4 μg/mL	Sesquiterpene	*Saussurea lappa* [154]
Dehydrocostuslactone	6.5 μg/mL	Sesquiterpene	*Saussurea lappa* [154]
Betulinic acid	0.7 μg/mL	Triterpenoid	*Saussurea lappa* [154]
Betulinic acid methyl ester	0.9 μg/mL	Triterpenoid	*Saussurea lappa* [154]
ent-16betaH, 17-isobutyryloxy-kauran-19-oic acid	8.7 μM	Diterpene	*Siegesbeckia glabrescens* [155]
ent-16betaH, 17-acetoxy-18-isobutyryloxy-kauran-19-oic acid	30.6 μM	Diterpene	*Siegesbeckia glabrescens* [155]
ent-16betaH, 17-isobutyryloxy-kauran-19-oic acid	8.07 μM	Diterpene	*Siegesbeckia glabrescens* [155]
ent-16betaH, 17-acetoxy-18-isobutyryloxy-kauran-19-oic acid	30.6 μM	Diterpene	*Siegesbeckia glabrescens* [155]
Lupenone	13.07 μM	Triterpene	*Sorbus commixta* [156]
Lupeol	5.06 μM	Triterpene	*Sorbus commixta* [156]
3β-Acetoxy-28-hydroxyolean-12-ene	44.4 μM	Triterpenoid	*Styrax japonica* [157]

(Table 1B) contd….

Natural Terpenoids	IC_{50}	Structure Type	Sources
3β-Acetoxyolean-12-en-28-acid	7.8 μM	Triterpenoid	*Styrax japonica* [157]
3β-Acetoxyolean-12-en-28-aldehyde	9.3 μM	Triterpenoid	*Styrax japonica* [157]
3β-Hydroxyolean-12-en-28-oic acid	5.2 μM	Triterpenoid	*Styrax japonica* [157]
Glycyrrhetic acid	13.8 μM	Ttriterpenoid	*Styrax japonica* [157]
Ursolic acid	3.8 μM	Triterpene	*Symplocos paniculata* [68]
Corosolic acid	7.2 μM	Triterpene	*Symplocos pani culata* [68]
Ilekudinol A	29.1 μM	Triterpene	*Weigela subsessilis* [158]
Ilekudinol B	5.3 μM	Triterpene	*Weigela subsessilis* [158]
Corosolic acid	5.49 μM	Triterpene	Several traditional Chinese medicinal herbs [66]

Table 1C. Natural inhibitors of PTP1B.

Compound	IC_{50}	Structure Type	Source
Caffeic acid	3.06 μM	Cnnamic acid derivative	*Artemisia minor* [159]
Compound 1	3.7 μM	Vanillic acid derivative	*Cladophora socialis* [160]
Compound 2	1.7 μM	Vanillic acid derivative	*Cladophora socialis* [160]
Curcumin	*In vivo* PTP1B inhibitor	Phenol derivative	*Curcuma longa* [79]
Cyclospirolide	16.64 μM	Phenol derivative	*Cyclocarya paliurus* [122]
Caffeic acid	1,92 μM	Cinnamic acid derivative	*Cyclocarya paliurus* [122]
1,2,3,4,6-penta-O-galloyl-D-glucopyranose	4.8 μM	Gallic acid derivative	*Paeonia lactiflora* [75]
3,4-dihydroxy benzoic acid	52.9 μM	Benzoic acid derivative	*Phellinus linteus* [161]
Bakuchiol	20.8 μM	Phenol derivative	*Psoralea corylifolia* [138]
2,2′, 3,3′-tetrabromo-4,4′,5,5′-tetrahydroxydiphenyl methane	2.4 μM	Bromophenol derivative	*Rhodomela confervoides* [162]
3-bormo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl) pyrocatechol	1.7 μM	Bromophenol derivative	*Rhodomela confervoides* [162]
bis(2,3-dibromo-4,5-dihydroxybenzyl) ether	1.5 μM	Bromophenol derivative	*Rhodomela confervoides* [162]
2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-ethyloxymethyldiphenylmethane	0.84 μM	Bromophenol derivative	*Rhodomela confervoides* [162]
3, 4-dibromo-5-(methoxymethyl)-1, 2-benzenediol	3.4 μM	Bromophenol derivative	*Rhodomela confervoides* and *Leathesia nana* [163]
2-methyl-3-(2, 3-dibromo4, 5-dihydroxy)-propylaldehyde	4.5 μM	Bromophenol derivative	*Rhodomela confervoides* and *Leathesia nana* [163]
3-(2, 3-dibromo-4, 5-dihydroxy-phenyl)-4-bromo-5, 6-dihydroxy-1, 3-dihydroiso-benzofuran	2.8 μM	Bromophenol derivative	*Rhodomela confervoides* and *Leathesia nana* [163]
2,3-dibromo-4,5-dihydroxybenzyl methyl ether	39.0 μM	Bromophenol derivative	*Symphyocladia latiuscula* [164]
2,3,6-tribromo-4,5-dihydroxybenzaldehyde	19.4 μM	Bromophenol derivative	*Symphyocladia latiuscula* [164]
2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether	3.9 μM	Bromophenol derivative	*Symphyocladia latiuscula* [164]
bis(2,3,6-tribromo-4,5-dihydroxyphenyl)methane	4.3 μM	Bromophenol derivative	*Symphyocladia latiuscula* [164]

(Table 1C) contd….

Compound	IC_{50}	Structure Type	Source
1,2-bis(2,3,6-tribromo-4,5-dihydroxyphenyl)-ethane	3.5 μM	Bromophenol derivative	*Symphyocladia latiuscula* [164]
1-(2,3,6-tribromo-4,5-dihydroxybenzyl)-pyrrolidin-2-one	25.6 μM	Bromophenol derivative	*Symphyocladia latiuscula* [164]
Gyrophoric acid	3.6 μM	Benzoic acid derivative	*Umbilicaria antartica* [165]
lecanoric acid	31 μM	Benzoic acid derivative	*Umbilicaria antartica* [165]

Table 1D. Natural inhibitors of PTP1B.

Compound	IC_{50}	Structure Type	Sources
Maesanin	4.56 μM	Benzoquinone derivative	*Ardisia japonica* [166]
2,5-dihydroxy-3-((10Z)-pentadec-10-en-1-yl)(1,4)benzoquinone)	19.15 μM	Benzoquinone derivative	*Ardisia japonica* [166]
5-ethoxy-2-hydroxy-3-((10Z)-pentadec-10-en-1-yl)(1,4)benzoquinone	3.55 μM	Benzoquinone derivative	*Ardisia japonica* [166]
5-ethoxy-2-hydroxy-3-((8Z)-tridec-8-en-1-yl)(1,4)benzoquinone	3.01 μM	Benzoquinone derivative	*Ardisia japonica* [166]
7-hydroxy-5,6-dimethoxy-1,4-phenanthrenequinone	38.0 μM	Phenanthrene derivative	*Dendrobium moniliforme* [65]
Grecocycline B	0.52 μM	Benzanthracene quinone	*Streptomyces sp. Acta 1362* [59]
Cyclonoside A	2.11 μM	Naphtoquinone derivative	*Cyclocarya paliurus* [122]
5-hydroxynaphthalene-1,4-di-O-b-D-glucopyranoside	10.90 μM	Naphtalene derivative	*Cyclocarya paliurus* [122]
Nocardione A	14.0 μM	Naphto-furan-dione	*Nocardia sp.* TP-A0248 [167]
Ohioensins F	3.5 μM	Xanthene derivative	*Polytrichastrum alpinum* [168]
Ohioensins G	5.6 μM	Xanthene derivative	*Polytrichastrum alpinum* [168]
ohioensins A	4.3 μM	Benzonaphthoxanthenone	*Polytrichastrum alpinum* [168]
ohioensins C	7.6 μM	Benzonaphthoxanthenone	*Polytrichastrum alpinum* [168]
Berberine	Ki = 91.3 nM	Isoquinoline alkaloids	*Several plants* [82]
Papaverine	1.20 μM	Opium alkaloid	*Papaver somniferum* [81]
Caulerpin	3.77 μM	Indole derivative	*Caulerpa taxifolia* [169]
Fructigenine A	10.7 μM	Indole alkaloid	*Penicillium spp*. and *Eurotium sp.* [170]
Cyclopenol	30.0 μM	Benzodiazepine-type myco-toxins	*Penicillium spp*. and *Eurotium sp.* [170]
Viridicatol	64 μM	Quinoline derivative	*Penicillium spp*. and *Eurotium sp.* [170]
Echinulin	29.4 μM	Diketopiperazin	*Penicillium spp*. and *Eurotium sp.* [170]
Ceramide	25.1 μM	Sfingosine derivative	*Polyporus umbellatus* [171]
KS-506a	4.9 μM	Polyphenol containing an S-S bond	*Micromucor ramannianus var. angulisporus b* [172]
Piceamycin	10.1 μM	Polyketide antibiotic	*Streptomyces sp.* GB 4-2 [173]
Gymnorrhizol	14.9 μM	Macrocyclic polydisulfide	*Bruguiera gymnorrhiza* [174]

(Table 1D) contd….

Compound	IC_{50}	Structure Type	Sources
Bruguiesulfurol	17.6 μM	Cyclic disulfides	*Bruguiera gymnorrhiza* [175]
Falcarindiol	9.15 μM	Fatty alcohol	*Aegiceras corniculatum* [176]
Flavoglaucin	13.4 μM	Benzaldehyde derivative	*Penicillium spp. and Eurotium sp.* [170]
3',5',6',6-tetrabromo-2,4-dimethyldiphenyl ether	2.97 μM	Benzene derivative	*Laurencia similis* [177]
2',5',6',5,6-pentabromo-3',4',3,4-tetramethoxybenzo-phenone	2.66 μM	Benzene derivative	*Laurencia similis* [177]
Woodylide C	4.7 mg/mL	Polyketide	*Plakortis simplex* [178]
Hippolide A	23.81 μM	Acylic manoalide derivative	*Hippospongia lachne* [179]
Hippolide B	39.67 μM	Acylic manoalide derivative	*Hippospongia lachne* [179]
Manzamenone B	10.8 μM	Fatty acid derivatives	*Plakortis (unknown species)* [180]
Manzamenone E	13.5 μM	Fatty acid derivatives	*Plakortis (unknown species* [180]
Albidopyrone	128 μg/mL	Pyrone derivative	*Streptomyces sp.* NTK 227 [181]
3-Hexadecanoyl-5-hydroxymethyl tetronic acid (RK-682)	4.5 μM	Furandione derivative	*Streptomyces* [135]
Lobaric acid	0.87 μM	Depsidone-type	*Stereocaulon alpinum* [182]
Pseudodepsidone-type compound 2	6.86 μM	Pseudodepsidone-type	*Stereocaulon alpinum* [182]
Pseudodepsidone-type compound 3	2.48 μM	Pseudodepsidone-type	*Stereocaulon alpinum* [182]
Stereocalpin	40 μM	cyclic Depsipeptide	*Stereocaulon alpinum* [182]
Aquastatin A	0.19 μM	β-Galactopyranoside	*Cosmospora sp.* SF-5060 [58]
Episesamin 2,6-dicatechol	21.86 μM	Lignan derivative	*Morinda citrifolia* [69]
(−)-Pinoresinol	18.69 μM	Lignan derivative	*Morinda citrifolia* [69]
Lirioresinol B	15.01 μM	Lignan derivative	*Morinda citrifolia* [69]
Lirioresinol B dimethyl ether	16.82 μM	Lignan derivative	*Morinda citrifolia* [69]
meso-dihydroguaiaretic acid	19.6 μM	Lignan derivative	*Myristica fragrans* [183]
Otobaphenol	48.9 μM	Lignan derivative	*Myristica fragrans* [183]
Ratanhiaphenol III	20.2 μM	Lignan derivative	*Krameria lappacea* [76]
(7R,8R)-3-methoxy-1′-carboxy-4′,7-epoxy-8,3′-oxyneolignan-4,9-diol	19.56 μM	Neolignan	*Morinda citrifolia* [69]
(Z)-aglawone	1.12 μg/mL	Steroid	*Toona ciliata var. pubescens* [184]
Trodusquemine	1 μM	Aminosterol	*Squalus acanthias* [87], [185]
(2S,3S,4R,2'R)-2-(2'-hydroxytricosanoylamino)-nonadecane-1,3,4-triol	25.1 μg/mL	Steroids	*Polyporus umbellatus* [171]
19-norergosta-5,7,9,22-tetraene-3β-ol	8.9 μg/mL	Steroids	*Polyporus umbellatus* [171]
24-ethylcholesta-7,22-diene-3β,5α,6β-triol	6.5 μg/mL	Steroids	*Polyporus umbellatus* [171]
24-methylcholesta-7,22-diene-3β,5α,6β-triol	7.5 μg/mL	Steroids	*Polyporus umbellatus* [171]
Penstyrylpyrone	5.28	Pyrone derivative	*Penicillium sp* [136]
Dihydrocarolic acid	38 μg/mL	Furan derivative	*Aspergillus niger* [64]
Penitricin D	15.8 μg/mL	Cyclopropan derivative	*Aspergillus niger* [64]

IC_{50} = 3.08 μM [67], IC_{50} = 3.8 μM [68], IC_{50} = 4.12 μM [69], IC_{50} = 3.1 μM [70], IC_{50} = 2.3 μM [61]; ii) TC-PTP IC_{50} value = 3.33 μM [67]; iii) SHP2 (IC_{50} value = 2.73 μM) [67]; iv) LAR (IC_{50} value = 3.8 μM) [61]. Furthermore, ursolic acid enhances insulin receptor phosphorylation in CHO/hIR cells and stimulates glucose uptake in L6 myotubes [67]. In addition this compound shows significant antidiabetic activity in Streptozotocin-nicotinamide diabetic rats [61]. Oleanolic acid, a triterpene contained in traditional Chinese medicinal herbs [71], is another PTP1B inhibitor (IC_{50} value = 9.5 μM [61]; 4.2 μM [72]; 23.9 μM [73]; 3.37 μM [71]; 2.56 μM [74]). Oleanolic acid is active *in vivo*, showing a moderate antidiabetic activity in Streptozotocin-nicotinamide diabetic rats [61]. The lignans episesamin 2,6-dicatechol (IC_{50} value = 21.86 μM on PTP1B), lirioresinol B (IC_{50} value = 15.01 μM), and lirioresinol B dimethyl ether (IC_{50} value = 16.82 μM), extracted from *Morinda citrifolia* [69], show a strong stimulatory action on 2-NBDG uptake in 3T3-L1 adipocyte cells. The compound 1,2,3,4,6-penta-O-galloyl-D-glucopyranose (IC_{50} value = 4.8 μM on PTP1B) acts as an insulin sensitizer in human hepatoma cells [75]. The lignan ratanhiaphenol III (IC_{50} value = 20.2 μM on PTP1B) is able to increase IR phosphorylation as well as glucose uptake stimulated by insulin in cultured myotubes [76]. The treatment of 32D cells overexpressing the IR with amentoflavone, a non competititve inhibitor of PTP1B (IC_{50} value = 7.3 μM) extracted from *Selaginella tamariscina*, induces a dose-dependent increase in IR tyrosine phosphorylation [77]. The PTP1B inhibitors 3',5'-diprenylgenistein (IC_{50} value = 31.75 μM), 6,8-diprenylgenistein (IC_{50} value = 28.13 μM), derrone (IC_{50} value = 20.63 μM) and alpinumisoflavone (IC_{50} value = 37.52 μM), extracted from *Tetracera scandens*, exhibit a significant glucose-uptake activity in basal and insulin-stimulated L6 myotubes [78]. The flavonol Morin, a non-competitive inhibitor of PTP1B (IC_{50} value = 15 μM), inhibits also other two enzymes that antagonize IR signaling, i.e. TC-PTP (IC_{50} value = 19.1 μM) and LMW-PTP (IC_{50} value = 36.4 μM). Morin is able to increase IR and Akt phosphorylation as well as to inhibit gluconeogenesis and to enhance glycogen synthesis in HepG2 cells [60]. The action of morin is selective for the insulin signaling, since it is unable to stimulate phosphorylation of other tyrosine kinase receptors such as EGFR and PDGFR. Curcumin, which is a phenolic compound extracted from *Curcuma longa*, produces a number of biological actions being a PTP1B inhibitor *in vivo*. In fact, in fructose-fed rats it is able: i) to reduce serum insulin and leptin levels; ii) to increase phosphorylation of insulin receptor and IRS-1 enhancing Akt and ERK1/2 activation in the liver; iii) to increase phosphorylation of hepatic janus-activated kinase-signal transducer 2 and subsequently to stimulate activation of Akt and ERK1/2 [79]. Fructose decreases tyrosine phosphorylation of IRS1 and inhibits activation of Akt and extracellular signal-regulated kinase 1/2 (ERK1/2) in peripheral tissues of rats [80]. Papaverine, which is an opium alkaloid contained in *Papaver somniferum*, is a strong PTP1B inhibitor (IC_{50} = 1.20 μM). *In vivo*, papaverine significantly decreases fasting blood glucose level of Balb/c mice [81]. Berberine, an alkaloid contained in several plant species, mimics insulin action by increasing glucose uptake in 3T3-L1 adipocytes and L6 myocytes inhibiting the phosphatase activity of PTP1B (Ki value (competitive) = 91.3 nM) [82] and increasing the phosphorylation of IR, IRS1 and Akt. Furthermore, berberine lowers hyperglycaemia and improves impaired glucose tolerance in diabetic mice [83], as well as elicits antidiabetic effects in clinical trials [84]. The compounds pongamol and karanjin, extracted from *Pongamia pinnata* fruits, exert a moderate but significant inhibitory effect on PTP1B; in addition they are able to decrease blood glucose levels both in streptozotocin-induced diabetic rats and in db/db mice [85]. Moronic acid and morolic acid, two terpenic acids extracted from *Phoradendron reichenbachianum* and from other plants, are able to induce a significant decrease in plasma glucose concentration in streptozotocin-nicotinamide diabetic rats. Moronic acid is a mixed type inhibitor of PTP1B displaying an IC_{50} value of 13.2 μM, whereas morolic acid is a non-competitive inhibitor of PTP1B displaying and IC_{50} value of 9.1 μM [61]. Hyrtiosal, extracted from the marine sponge *Hyrtios erectus*, is a non competitive inhibitor of PTP1B (IC_{50} = 42 μM) that displays potent activity in abolishing the retardation of AKT membrane translocation caused by PTP1B overexpression in CHO cells. Furthermore hyrtiosal dramatically enhances the membrane translocation of GLUT4 in PTP1B-overexpressed CHO cells [86]. The aminosterol trodusquemine is a potent allosteric non competitive inhibitor of PTP1B. Trodusquemine's inhibition is highly selective for PTP1B, since its IC_{50} value (224 μM) for TC-PTP (70% sequence identity with PTP1B) was approximately two logs less than that against PTP1B (1μM). This compound, isolated from the liver of the dogfish shark *Squalus acanthias*, is able to inhibit PTP1B activity in HepG2 cells, resulting more potent than orthovanadate, a well known non specific tyrosine phosphatase inhibitor [87]. Lantz *et al.* [87] reported that in HepG2 cells trodusquemine enhances insulin-induced tyrosine phosphorylation of IRβ about three-fold, whereas trodusquemine by itself (in the absence of insulin) had no effect. Trodusqueamine acts also *in vivo* both on central and peripheral tissues displaying a very interesting insulin sensitizing activity. In fact, trodusquemine-treated rats show an approximately twofold increase in insulin-induced tyrosine phosphorylation of hypothalamic IRβ and a 5.4-fold increase in phosphorylation of STAT3, a downstream transcription factor. Trodusquemine itself has no effect on tyrosine phosphorylation of IRβ but induces a 2.7-fold increase of STAT3 phosphorylation in hypothalamus. Furthermore systemic administration of trodusquemine in mice results in enhanced insulin-induced phosphorylation of IRS1 andAkt in the liver, demonstrating its peripheral activity [88].

Natural Substances that Increase Glucose Uptake Acting Through the AMPK Activation

Compelling evidences suggest that in most cases antihyperglycaemic effects of natural compounds are mediated by AMPK, the same molecular target of metformin [89]. Therefore, several of these natural compounds could be used to treat T2DM or as scaffold structures to design and synthesize more potent and selective drugs. AMPK is a key player in the response to a variety of metabolic stresses and it is directly involved in the regulation of GLUT4 trafficking on the plasma membrane [90] (Fig. **3**). Unlike insulin, AMPK is activated in response to stress conditions or stimuli that cause a decrease of ATP levels such as physical activity,

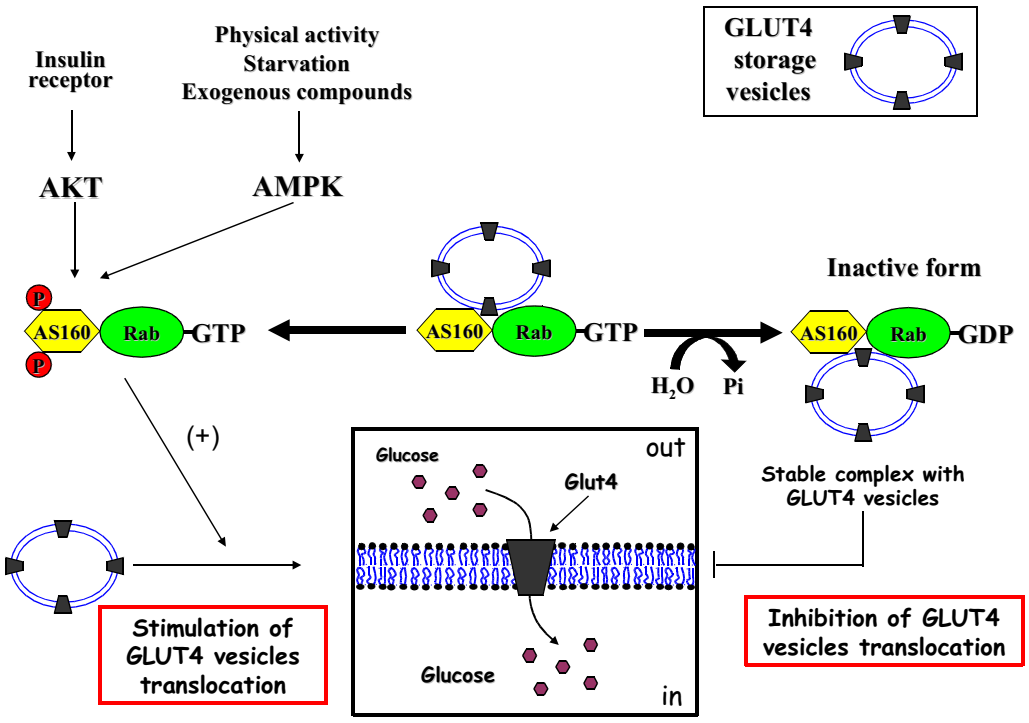


Fig. (3). Two signaling pathways involved in the regulation of GLUT4 translocation onto the plasma membrane. AKT and AMPK phosphorylate AS160 on multiple phosphorylation sites. AS160, which contains a Rab-GAP domain, is a key protein responsible for GLUT4 translocation onto plasma membrane. In insulin-sensitive cells and in the absence of hormone or stress stimuli (such as nutrient starvation or muscle contraction), Rab-GTP proteins interact with AS160; in turn, the AS160-Rab-GTP complex interacts with GLUT4 storage vesicles. Non-phosphorylated AS160 stimulates the GTPase activity of the Rab proteins which are converted in their inactive state (Rab-GDP). AS160-Rab-GDP forms a stable complex with GLUT4 storage vesicles but is unable to stimulate actin remodelling, an essential event to trigger GLUT4 vesicles translocation onto the plasma membrane. On the contrary, insulin or AMPK-mediated phosphorylation of AS160 inhibits the Rab-GAP GTPase activity, thereby eliciting accumulation of Rab-GTP. Consequently, AS160-Rab-GTP complex dissociates from GLUT4 storage vesicles, promoting actin remodeling and translocation of GLUT4 onto the plasma membrane. For an explanation of acronyms see 'Abbreviations'.

nutrients deprivation or the presence of metabolic inhibitors. High rate of ATP consumption contribute to increase intracellular levels of AMP, a potent positive allosteric effector of AMPK. Once activated, AMPK phosphorylates several key enzymes involved in the metabolic regulation, inhibiting the synthesis of macromolecules and stimulating catabolic pathways [91]. Although the mechanism by which the AMPK stimulates glucose uptake is not completely defined, most of key players involved in this process have been identified. One target of AMPK is AS160 protein. This is a GTPase activating protein that usually forms a stable complex with Rab proteins, a family of small GTP-binding proteins related to Ras and involved in the membrane trafficking regulation. After insulin stimulation, AS160 is phosphorylated by AKT on the same serine residues phosphorylated also by AMPK, thus inhibiting its functions. In the absence of insulin or metabolic stress stimuli that activate AMPK, the unphosphorylated protein AS160 stimulates the GTPase activity of Rab, converting it in its inactive GDP-bound form, unable to stimulate the transport of the GLUT4 containing vesicles towards plasma membrane. Thus, the transport of glucose from blood into muscle cells or adipocytes is inhibited. On the contrary, when stress stimuli activate AMPK, or insulin activates AKT, AS160 becomes phosphorylated, and Rab is stabilized in its active GTP-bound form inducing the fusion of the vesicles to plasma membrane [92]. AMPK regulates also the expression of many genes involved in the control of the energetic metabolism. In fact, activated AMPK induces: i) the downregulation of the fatty acid synthase (FAS) expression decreasing the cellular concentration of fatty acid; ii) the decrease of cholesterol synthesis [93-96]; iii) the upregulation of the peroxisome proliferator-activated receptor-γ coactivator-1α expression, which consequently increases the mitochondrial biogenesis [97-99]; iv) the upregulation of the hexokinase II and GLUT4 expression in muscle cells [97]. In addition, AMPK downregulates the expression of both phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase genes in the liver, thereby inhibiting gluconeogenesis [100, 101].

Natural compounds that target AMPK positively influence the insulin signaling contributing: i) to stimulate GLUT4 translocation onto the plasma membrane of adipocyte and muscle cells; ii) to increase GLUT1/4 expression and glucose uptake; iii) to phosphorylate and activate the transcriptional co-activator PPARγ coactivator-1 (PGC 1α). PGC 1α is one of the most important transcriptional regulator of mitochondrial gene expression and stimulates both the mitochondriogenesis and the mitochondrial oxidative capacity, thereby contributing to fatty acid catabolism. In the liver, natural compounds that target AMPK are able: i) to inhibit

expression of key players gluconeogenetic enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase; ii) to inhibit the expression of transcription factors involved in the regulation of lipids synthesis, such as acetyl-CoA carboxylase-1 and fatty acid synthase; iii) to increase fatty acid oxidation, through inactivation of the acetyl CoA carboxylase-2, the enzyme that catalyzed the production of malonyl-CoA, a potent inhibitor of type-1 carnitine acyl tranferase-1.

Most of compounds listed in Table **2** were tested *in vivo* and/or *in vitro* by using different cellular models, such as muscle and liver cells as well as adipocytes. *In vivo* experiments performed on diabetic or insulin resistant rats or mice, revealed that compounds such as nobiletin, EGCG, proanthocyanidins, eicosapentaenoic acid, curcumin, berberine, galegine, combrestatin A-4, arctigenin, chlorogenic acid, salicylate, shikonin stimulate and enhance both basal and insulin-mediated glucose transports in muscles, attenuate peripheral insulin resistance induced by FFAs, improve the symptoms of metabolic syndrome induced by fructose rich-diet, reduce inflammatory status, contribute to the weight loss and improves glucose tolerance in high-fat diet-induced obese mice, contributing to normalize blood glucose levels. Compelling evidences showed that *in vitro*, most of these substances (quercetin, glyceollin, ursolic acid, naringenin, retinoic acid, resveratrol, caffeic acid phenethyl ester, isoginkgetin, rutin, (*S*)-(6)-gingerol, astragalus polysaccharide, picetannol, trans-10, cis-12 conjugated linoleic acid, tangeritin, monascin and ankaflavin, capsaicin, isodihydrocapsiate, α-sitosterol, salidroside, damulin A/B, p-cumarinic acid, cinnamon, osthole, ascofuranone, tanshinone IIA, pinusolide, theasinensins, octaphlorethol A) are able to activate the AMPK enzymes, thereby stimulating GLUT4 translocation and glucose uptake in muscle cells or adipocytes. Furthermore luteolin, S-allyl-cysteine, theaflavins, and genistein are able to influence liver cells metabolism, inhibiting lipids synthesis, reducing lipid storage and improving insulin receptor sensitivity. Finally, additional evidences obtained from *in vitro* studies showed that other compounds (daidzein, β-carotene, kaempferol 3-neohesperidoside, kaempferitrin, pongamol, karanjin, pachymic acid, gallic acid, 4-hydroxyisoleucine, calophyllic acid and isocalophyllic acid, 4-hydroxypipecolic acid) stimulate GLUT4 expression and/or GLUT4 translocation to plasma membrane, both in adipocytes and muscle cells, contributing to increase the rate of glucose uptake.

PPARs Activation by Natural Agonists Increases Insulin Sensitivity

Lipid-rich diets can have deleterious effects on human health, favouring a rapid weight gain, insulin resistance and, in most cases, the development of T2DM [102]. Triacylglycerols derived from diet or synthesized by liver are transported in the blood by lipoproteins. The lipoprotein lipase present on the wall of blood vessels hydrolyzes triglycerides contained in the lipoproteins releasing free fatty acids, which are then absorbed by cells. Cellular free fatty acids bind and activate the peroxisome proliferator-activated receptors (PPARs) which, in turn, upregulates the expression of several genes involved in the fatty acid metabolism [103]. Several PPAR isotypes (α, β/δ and γ), which are expressed in tissue-specific manner, have been identified. PPARα is expressed in liver, heart, kidney and skeletal muscle; PPARγ is mainly present in adipocytes, in several kind of immune cells, in the mucosa of colon and cecum, and in placenta, whereas PPARδ can be detected in tissues controlling lipid metabolism, such as adipocytes, heart, and skeletal muscle [104]. These receptors act as metabolic sensors and are able to modulate, depending on the nutrient availability, the expression of several genes codifying enzymes involved in the control of energetic metabolism (Fig. **4**). For example, in muscle, liver and heart, PPARα stimulates the transcription of genes involved in fatty oxidation, thereby reprogramming cells to high-capacity fatty acid metabolism [105]. Nevertheless, when the fatty acids availability exceeds the cells oxidative capability, cells undergoes to metabolic overload, resulting in mitochondrial disfunction (Fig. **5**) [106]. The presence of mitochondrial abnormalities accompanied by high fatty acid levels in most of muscle and liver cells of subjects affected by insulin resistance or T2DM confirms this hypothesis [107-109]. The excess fatty acids are esterified and either stored or metabolized to various intermediates such as diacylglycerols, ceramides and triglycerides, resulting in a significant accumulation into cytoplasm or endoplasmic reticulum. Diacylglycerols activate the protein kinase C theta isoform (PKCθ) which, in turn, phosphorylates IRS-1 on serine residues, inhibiting its functions. Thus, signaling events downstream insulin receptor, such as the activation of PI3K and AKT, GLUT4 translocation onto the plasma membrane, and glycogen synthesis are impaired. On the other hand, ceramides activate protein kinase C zeta isoform (PKCζ) and protein phosphatase 2A, which collaborate to inhibit both translocation and activation of AKT onto the plasma membrane, thereby contributing to reduce insulin sensitivity [110]. Finally, accumulation of fatty acids in the endoplasmic reticulum induces a stress condition resulting in the activation of the stress activated Janus kinase (JNK), which phosphorylates IRS-1 [111]. In addition, ER stress contributes to increase PTP1B expression and leads to insulin resistance in muscle cells, suggesting a link between ER stress and the pathogenesis of obesity-associated insulin resistance (Fig. **5**) [112]. Hence, the stimulation of PPARs activity is an effective strategy to lower blood lipid levels as well as to increase the insulin sensitivity, overcoming the problem of insulin resistance [113]. In the last decades, several synthetic agonists of PPARs have been produced, but only few of them, such as fibrates (clofibrate, fenofibrate, bezafibrate) and thiazolidinediones (rosiglitazone and pioglitazone) have been approved for treatment of T2DM and metabolic syndrome. Thiazolidinediones show antidiabetic activity in patients affected by T2DM, since they increase insulin sensitivity, stimulate glucose uptake, and decrease the levels of insulin and glycated hemoglobin. The efficacy of PPARγ agonists is in part attributable to reduction of lipotoxicity in skeletal muscle and liver, and in part is probably due to their ability to stimulate the expression of glucose transporters GLUT1 and GLUT4 or of other intracellular proteins such as c-Cbl-associated protein (CAP) [114, 115]. Furthermore, it has been demonstrated that PPARγ agonists are able to stimulate adiponectin expression, which, in turn, increases fatty acid oxidation through an AMPK-dependent mechanism in liver and muscle, and decreases glucose production in liver [116]. In addition, PPARδ activation correlates with

Table 2. Natural substances that increase glucose uptake acting through the AMPK activation.

Compound	Main Biological Effects	Source
Quercetin and quercetin glycosides	Stimulation of AMPK and glucose uptake in muscle cells [186]	*Vaccinium vitis-idaea*
Glyceollin	Enhancement of insulin sensitivity in db/db mice muscle under ER stress conditions through activation of AMPK [187]	Derived from daidzein in soybeans infected by fungi
Luteolin	Activation of AMPK in HepG2 cells [188]	Several plant species
S-allyl cysteine	Activation of AMPK through Ca^{2+}/calmodulin-dependent kinase kinase [189]	*Allium sativum*
Nobiletin	Increase of phospho-Akt and GLUT1 and GLUT4 expression in white adipose tissue and muscle [190]; Increase of hepatic and peripheral insulin sensitivity [191]	Fruits of *Citrus* species
Ursolic acid	Activation of LKB1/AMPK pathway [192]	Several plant species
Epigallocatechin gallate (EGCG)	Attenuation of peripheral insulin resistance through AMPK pathway in vivo [193]; activation of IRS2 and AMPK signaling in rat pancreatic β-cells [194]; activation of the LKB1/AMPK pathway [195]; suppression of hepatic gluconeogenesis through the AMPK [196]	*Camellia sinensis*
Theaflavins	Decrease of hepatic lipid accumulation trough the LKB1/AMPK pathway [197]	Several species of tea (leaves)
Naringenin	Increases muscle cell glucose uptake via AMPK [198]	*Citrus paradisi*
Genistein	Activation of PGC-1α, upregulation of GLUT1 expression. Reversion of free fatty acid-induced insulin resistance in HepG2 hepatocytes through targeting JNK [199]	*Flemingia vestita*
Daidzein	Enhancement of insulin-stimulated glucose uptake in adipocytes by increasing the expression of GLUT4 and IRS1 via the activation of PPARγ [200]	Some plant and herb species
Proanthocyanidin-rich extract	Enhancement of IRS1 and GLUT4 expression [201]	*Malus domestica*
Retinoic acid	Activation of AMPK in skeletal muscle cells [202]	Vegetables fonts (vitamin A metabolite)
Eicosapentaenoic acid	Increase of GLUT4 expession in muscle and 2-deoxy-D-glucose uptake in C2C12 myotubes [203]	Vegetable and fish fonts
Curcumin	Activation of LKB1/AMPK pathway [204]	*Curcuma longa*
Resveratrol	Activation of PGC-1α and AMPK [205]	Fruiting berry of *Vitis vinifera*
Caffeic acid phenethyl ester	Activation of AMPK in skeletal muscle [206]	Several plants and honey
Berberine	Activation of AMPK [207]; [208]	Several Berberis species and a variety of other plant species
Isoginkgetin	Enhances adiponectin secretion through AMPK activation [209]	*Ginkgo biloba*
Galegine	Activation of AMPK. Stimulation of glucose uptake in adipocytes and L6 myotubes [210]	*Galega officinalis*
β-carotene	Enhance the expression of genes related to insulin sensitivity, including GLUT4 and adiponectin [211]. Decrease blood glucose [212]	*Daucus carota* and other plant species
Rutin	Increase of glucose uptake in rat soleus muscle, enhancing GLUT4 synthesis and translocation [213]	*Ginkgo biloba* and other plant species
Kaempferol 3-neohesperidoside	Stimulation of glucose uptake in the rat soleus muscle via the PI3K and PKC pathways, and of the synthesis of new glucose transporters [214]	Several plant species
Kaempferitrin	Activation of the classical insulin transduction pathway in adipocytes. Increased expression and translocation of GLUT4 to the membrane [215]	Leaves of various plant species
(S)-(6)-Gingerol	Enhancement glucose uptake in L6 myotubes by activation of AMPK [216]	*Zingiber officinale*

(Table 2) contd….

Compound	Main Biological Effects	Source
Astragalus polysaccharide	Stimulation of glucose uptake in L6 myotubes through the AMP-AMPK-AS160 pathway [217]	*Astragalus membranaceus*
Picetannol	Promotion of glucose uptake, AMPK phosphorylation and GLUT4 translocation in L6 myotubes [218]	*Picea abies*
trans-10, cis-12 conjugated linoleic acid	Activation of PI3K, AMPK and AS160 in skeletal muscle [219]	Produced from linoleic acid in the rumen by microbes [220]
Tangeritin	Stimulation of glucose uptake via the AMPK signaling pathways in C2C12 myotubes [221]	Fruits of *Citrus* species
Monascin and ankaflavin	Activation of AMPK in mice [222]	*Monascus purpureus*
Combrestatin A-4	Activation of AMPK in mice [223]	*Combretum caffrum*
Capsaicin	Activation of AMPK in C2C12 cells [224]	*Capsicum* species
Isodihydrocapsiate	Stimulation of glucose uptake by activation of AMPK [225]	*Capsicum* species
β-sitosterol	Activation of AMPK in L6 myotubes [226]	Several plant species
Salidroside	Stimulation of glucose uptake in skeletal muscle cells by activation of AMPK [227]	*Rhodiola rosea*
Damulin A/B	Activation of AMPK in L6 myotube cells [228]	*Gynostemma pentaphyllum*
p-Coumaric acid	Activation of AMPK in L6 skeletal muscle cells [229]	A variety of edible plants
Arctigenin	Activation of AMPK in ob/ob mice [230]	Asteraceae
Chlorogenic acid	Stimulation of glucose transport in skeletal muscle via AMPK activation [231]	Several plant species
Salicylate	Activation of AMPK [232]. Reversion of hyperglycaemia, hyperinsulinemia, and dyslipidemia in obese rodents by sensitizing insulin signaling [233]	*Salix alba*
Cinnamon extract	Enhancement of glucose uptake in 3T3-L1 Adipocytes and C2C12 Myocytes by inducing LKB1-AMPK signaling [234]	*Cinnamomum verum*
Osthole	Enhancement of glucose uptake through activation of AMPK in skeletal muscle cells [235]	*Cnidium monnieri*
Pongamol	Stimulation of both glucose transport and GLUT4 translocation to the cell surface of L6 myotubes [236]	*Pongamia pinnata*
Karanjin	Increase in glucose uptake in L6 myotubes and translocation of GLUT4 to plasma membrane associated with activation of AMPK pathway [237]	*Pongamia pinnata*
Pachymic acid	Stimulation of glucose uptake and GLUT4 expression and translocation in adipocytes . Both PI3K and AMPK are involved in the above actions [238]	*Poria cocos*
Gallic acid	Stimulation of glucose uptake and GLUT4 translocation in 3T3-L1 cells [239]	*Hippophae rhamnoides*
4-hydroxyisoleucine	Stimulation of glucose uptake and GLUT4 translocation in skeletal muscle cells in a PI3K/AKT-dependent mechanism [240]	*Trigonella foenum-graecum*
Calophyllic acid and isocalophyllic acid	Stimulation of glucose uptake and GLUT4 translocation in L6 myotubes through PI3K- and EKR1/2-dependent mechanisms (independent to the AMPK activation [241]	*Calophyllum inophyllum*
4-hydroxypipecolic acid	Stimulation of both glucose uptake and GLUT4 translocation to cell surface in skeletal muscle cells [242]	*Peganum harmala Linn*
Ascofuranone	AMPK activation in L6 myotube cells [243]	*Ascochyta viciae*
Tanshinone IIA	AMPK activation in L6 myotubes and reduction of blood glucose levels in db/db mice [244]	*Salvia miltiorrhiza bunge*

(Table 2) contd….

Compound	Main Biological Effects	Source
Pinusolide	Enhancement of IRS-1 tyrosine phosphorylation by the activating the AMPK pathway in muscle cells [245]	*Biota orientalis*
Theasinensins	Stimulation of glucose uptake through the AMPK pathway in rat skeletal muscle cells [246]	*Camellia sinensis*
Octaphlorethol A	Increase of both GLUT4 translocation to the plasma membrane and glucose uptake trough Akt and AMPK activation in differentiated L6 rat myoblast cells [247]	*Ishige foliacea*
Shikonin	Shikonin increases glucose uptake in skeletal muscle cells via an insulin-independent pathway dependent on calcium [248]	*Lithospermum erythrorhizon*

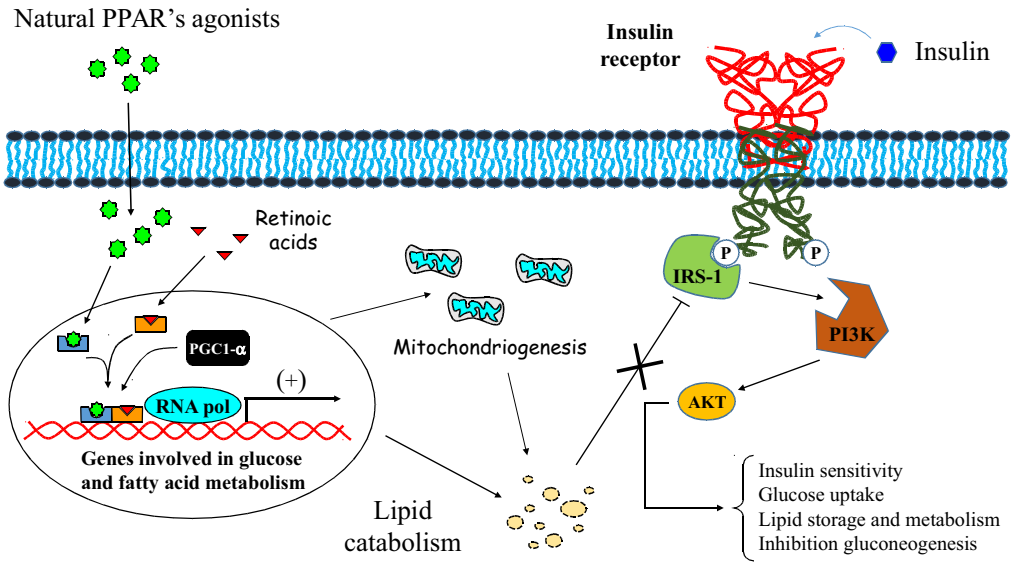


Fig. (4). Activation of PPARs by natural agonists increase insulin sensitivity. Several natural compounds, mimicking natural agonist, bind PPARs and stimulate their transcriptional activity. Consequently, the expression of several genes involved in lipids metabolism, such as those involved in fatty acid and glucose transport, β-oxidation, mitochondrial respiration and biogenesis, is strongly increased. Activation of PPARs favors adipocyte differentiation and lipid storage in the subcutaneous adipose tissue, thereby decreasing the levels of blood fatty acids. In addition, natural PPARs agonists reduce the release of inflammatory cytokines from visceral adipose tissue, thus inhibiting JNK activation in the peripheral tissues such as liver and muscle. The increase of lipid metabolism leads to reduction of intracellular depots, downregulating the activity of PKCθ, PKCζ and PP2A, thereby resulting in an increase of insulin sensitivity. The decrease of fatty acid levels in the hepatocytes and muscle cells alleviates ER stress, leading to downregulation of PTP1B expression and improving the insulin signaling pathway. For an explanation of acronyms see 'Abbreviations'.

expression of genes involved in fatty acid oxidation or/and with expression of uncoupling proteins in brown adipose tissue and in skeletal muscle [117, 118]. Compelling evidences demonstrated that in muscle cells PPARδ agonists stimulate glucose uptake through an AMPK and/or p38-MAPK-dependent signaling pathways, and that they are able to decrease glucose production in the liver [119, 120].

Although the known efficacy of the commercially available PPARs agonists, these drugs have adverse effects in humans, hence the research in this field is still very active. In the last years it has been demonstrated that many natural compounds are able to act as agonist of PPARs, contributing to stimulate insulin activity, glucose uptake and fatty acid metabolism, both *in vitro* and *in vivo*. In Table **3** most of known natural agonists of PPARs are listed.

CONCLUSION

Nowadays, the tendency to a sedentary lifestyle and obesity are becoming a serious problem in many western countries. Epidemiological analysis show that a growing number of individuals suffer of systemic insulin resistance, T2DM and/or metabolic syndrome. Drugs currently available to counteract these diseases are often characterized by a low effectiveness, unexpected side effects and ido not provide adequate protection against the many complications of these diseases. Many studies demonstrated that natural dietary compounds exert beneficial effects on human health, improving insulin signaling pathway and contributing to a better control of energy homeostasis, both in health humans that in diabetic subjects. For this reason many researches agree that assumption of natural bioactive compounds could be an

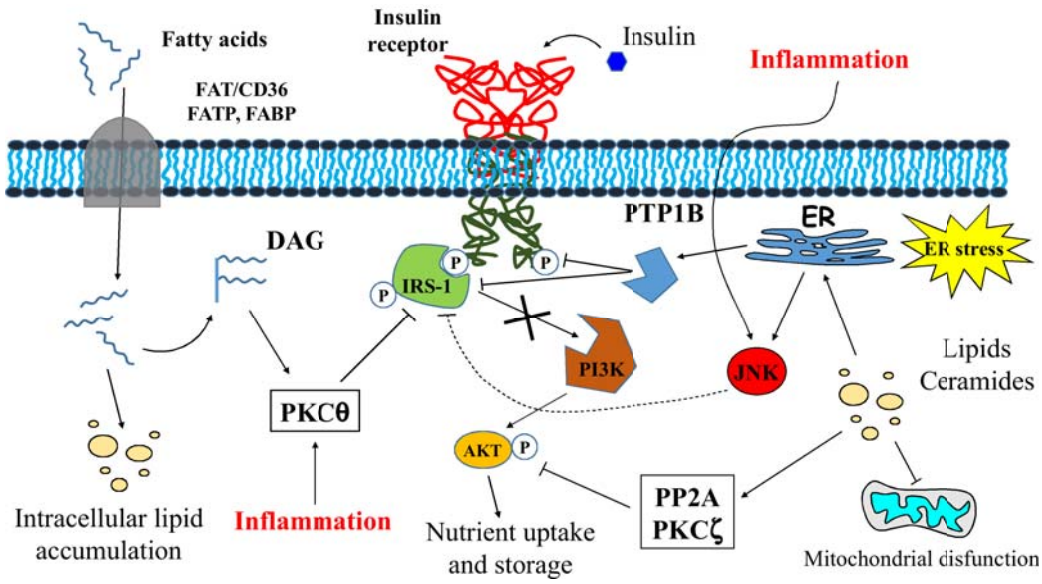


Fig. (5). Intracellular lipid overload leads to impaired insulin signaling. Intracellular lipid accumulation stimulates PKCθ activation that inhibits IRSs. Similarly, ceramides stimulate PKCζ and PP2A activation, decreasing activity of AKT. On the other hand, excessive storage of lipids into endoplasmic reticulum trigger stress response that leads to activation of JNK which increase serine phosphorylation of IRS-1, impairing insulin signaling. JNK is also activated by inflammatory cytokines, suggesting a link between obesity, chronic inflammation and insulin resistance. ER stress causes elevation in PTP1B levels, which targets IR and IRS-1, decreasing insulin sensitivity.

Table 3. Natural agonists of PPARs.

Compound	Main Biological Effects	Source
Monascin and Ankaflavin	PPARα agonist [222]	*Monascus*-fermented rice
Astaxanthin	PPAR agonist PPARγ antagonist [249]	A natural carotenoid abundant in seafood
Ursolic acid	PPARα agonist [250]	*Actinidia arguta*
Auraptene	PPARα and PPARγ agonist [251]	Fruit of *Citrus* species
Phytol	PPARα agonist [252]	a component of chlorophylls
Amorfrutin B	PPARγ agonist [253]	*Glycyrrhiza foetida*
Sargaquinoic acid and Sargahydroquinoic acid	PPARα and PPARγ agonist[254]	*Sargassum yezoense*
Ionomycin	PPARγ agonist [255]	*Streptomyces conglobatus*
Phosphoiodyns A	PPARα agonist [256]	*Placospongia sp.*
Herdmanine I and K	PPARγ agonist [257]	*Herdmania momus*
Gracilioether B and Plakilactone C	PPARγ agonist [258]	*Plakinastrella mamillaris*
Psammaplin A	PPARγ agonist [259]	*Pseudoceratina rhax*
Bixin	PPARγ agonist [260]	*Bixa orellana*
Ginsenoside 20(S)-Protopanaxatriol	PPARγ agonist [261]	Ginseng saponin
Astaxanthin	PPARα and PPARγ agonist [249]	microalgae, yeast, salmon, and most crustaceans, including krill, shrimp, crawfish, crabs, and lobster
α-Lipoic acid	PPARγ agonist [262]	broccoli, spinach and tomatoes
Paecilocin A	PPARγ agonist [263]	*Paecilomyces variotii*
Honokiol	PPARγ agonists [264]	*Magnolia* bark
Magnolol	PPARγ agonists [265]	*Magnolia officinalis*

(Table 3) contd….

Compound	Main Biological Effects	Source
Emodin	PPARγ agonists [266]	*Rheum palmatum L*
Kaempferol and Quercetin	PPARγ agonists [267]	*Euonymus alatus*
Daidzein	PPARγ agonists [200]	Soy and other plant and herb species
Artepillin C	PPARγ agonists [268]	*Baccharis dracunculifolia*
Linoleic acid, γ-Linolenic acid, Arachidonic acid and Eicosapentaenoic acid	PPARγ agonists [269]	
Ankaflavin	PPARγ agonist [270]	*Monascus*-fermented rice
Amorphastilbol	PPARα, PPARγ agonist [271]	*Amorpha fruticosa*
Luteolin	PPARγ agonist [272]	Several plant species
(-)-Catechin	PPARγ agonist [273]	*Camellia sinensis*
Ψ-baptigenin	PPARα and PPARγ agonist [274]	*Trifolium pratense*
Apigenin	PPARα and PPARγ agonist [274]	Several plants
Acacetin	PPARα and PPARγ agonist [274]	*Robinia pseudoacacia, Turnera diffusa, Asplenium normale*
Chrysoeriol	PPARα and PPARγ agonist [274]	*Artemisia copa*
Diosmetin	PPARα and PPARγ agonist [274]	Caucasian vetch plants
Chrysin	PPARα and PPARγ agonist [274]	Several plants
Kaempferol	PPARα and PPARγ agonist [274]	Several plants
Catalposide	PPARα agonist [275]	*Catalpa ovata*
Chlorophellins A	PPARγ agonist [276]	*Phellinus ribis*
Chlorophellins B	PPARγ agonist [276]	*Phellinus ribis*
Chlorophellin C	PPARγ agonist [276]	*Phellinus ribis*
Drosophilin A	PPARγ agonist [276]	*Phellinus ribis*
Hesperidin	PPARγ agonist [277]	*Citrus* fruits

effective strategy to prevent the onset and diffusion of chronic degenerative diseases such as T2DM. Traditional medicines, and in particular traditional Chinese medicine, use several plants preparations to treat diabetes and diabetic complications without side-effects. These herbal preparations contain tens of constituents, whose formulation is not standardizable. Thus in the last decades many efforts have been made attempting to identify compounds inside these preparation responsible for the hypoglycaemic effect. For example, metformin, a widely used hypoglycaemic drug, was purified from the traditional preparation of *Galega officinalis*. Several natural compounds have been shown to modulate the activity of specific enzymes and/or signaling molecules involved in the glycaemic control. Some of these compounds are in trial III phase to confirm their actual effectiveness on humans.

ABBREVIATIONS

ADP = Adenosine diphosphate

Akt/PKB = Protein kinase B

AMPK = AMP-activated protein kinase

AS160 = Akt substrate of 160 kDa

ATP = Adenosine triphosphate

CAP = Catabolite Activator Protein

CD45 = Leukocyte common antigen, protein tyrosine phosphatase

CHO/hIR = Chinese hamster ovary cell transfected with insulin receptor gene

DAG = Diacylglycerol

DM = Diabetes mellitus

EGFR = Epidermal growth factor receptor

ER = Endoplasmic reticulum

ERK = Extracellular signal-regulated kinase

ERK = extracellular signal-regulated kinases

FABP = Fatty acid binding protein

FAT/CD36 = Fatty acid transporter

FATP = Fatty acid transport proteins

FOXO = Forkhead transcription factors

GAP = GTPase activating protein

GLUT4 = Glucose transporter type 4

Grb2 = Growth factor receptor-bound protein 2

GS = Glycogen synthase

GSK3 = Glycogen synthase kinase 3

HepG2 = Human hepatocellular liver carcinoma cell line

IR = Insulin receptor

IRS = Insulin receptor substrate

JNK = c-Jun N-terminal kinases

JNK = Jun N-terminal kinase

LAR = Leucocyte antigen related phosphatase

LMW-PTP = Low Molecular Weight Protein Tyrosine Phosphatase

MAPK = Mitogen activated protein kinases

MptpB = Mycobacterium tuberculosis Protein Tyrosine Phosphatases

p70S6K = Ribosomal protein S6 kinase beta-1

PDE = Phosphodiesterase

PDGFR = Platelet derived growth factor receptor

PDK1 = Phosphoinositide-dependent kinase 1

PEPCK = Phosphoenolpyruvate carboxykinase

PGC = Peroxisome proliferator-activated receptor gamma coactivator

PI3K = Phosphatidylinositol 3-kinase

PIP3 = Phosphatidylinositol (3,4,5)-triphosphate

PKC = Protein kinase C

PKD = Protein kinase D

PPAR = Peroxisome proliferator-activated receptors

PTP1B = Protein Tyrosine Phophatases 1B

PTPs = Protein Tyrosine Phophatases

SHC = Src homology 2 domain containing) transforming protein

SHP-2 = Src homology-2 domain-containing phosphatase

SOS = Son of sevenless

SREB1 = Sterol regulatory element-binding protein 1

STAT3 = Signal transducer and activator of transcription 3

T2DM = Type 2 diabetes mellitus

TC-PTP = T-Cell Protein Tyrosine Phosphatase

TORC1 = Transcriptional coactivator for CREB1

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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