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REVIEW ARTICLE

Plant Foods and Their Phytochemicals as DPP IV and PTP1B Inhibitors for Blood Glucose Regulation: A Review

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Abstract | The increasing prevalence of diabetes has led to reducing hyperglycemia through mechanisms other than the conventional mechanism, such as α-amylase and α-glucosidase inhibition. In recent years, medicinal drugs focusing on inhibiting dipeptidyl peptidase IV (DPP IV) and protein tyrosine phosphatase 1B (PTP1B) enzymes have emerged and are being used for type 2 diabetes management. DPP IV inhibitors reduce blood glucose levels by preventing the degradation of incretin hormones such as glucagon-like peptide and glucose-dependent insulinotropic polypeptide. PTP1B has also been known to play a crucial role in reducing insulin resistance and is one of the most promising targets for managing Type 2 diabetes. Inhibition of these two enzymes is also expected to benefit other metabolic conditions such as cancer, obesity, lowered immunity, etc. The existing synthetic DPP IV and PTP1B inhibitors have been known to cause side effects. Inhibitors from natural sources are expected to be safer. The search for PTP1B inhibitors is especially necessary since the primary treatment for type 2 diabetes is to reduce insulin resistance. None of the existing PTP1B inhibitors are clinically well-approved to date. Hence, searching for antihyperglycemic components from natural sources such as foods has become a pressing need. This review has attempted to collate and analyze the existing scientific evidence to identify plant foods and their phytochemicals with in vitro and in vivo DPP IV and PTP1B inhibitory activity comprehensively. With further scientific validation and safety studies, the identified phytochemicals could be used for pharmacological applications. The foods and their extracts could be advantageous in formulating functional foods and diets suitable for type 2 diabetes, along with other physiological benefits.

Keywords: *DPP IV, PTP IB, Plant foods, Antihyperglycemic, Bioactive metabolites*

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1 Introduction

Hyperglycemia is the most characteristic symptom in all forms of diabetes. Uncontrolled hyperglycemia is associated with complications such as fluid and electrolyte disturbances and increased infection risk. Studies have reported impairment of host defenses, including decreased polymorphonuclear leukocyte mobilization, chemotaxis, and phagocytic activity related to hyperglycemia[1]. Chronic hyperglycemia has also

Hyperglycemia Abnormally high blood glucose levels. This happens when the body has too little insulin or when the body cannot utilize the insulin properly.

been associated with delayed wound healing in the diabetic population[2]. Acute hyperglycemia is also known to cause tissue injury in various organs. Consequently, glucose toxicity causes microvascular or diabetic complications such as neuropathy, retinopathy, and nephropathy[3].

Hence, the primary goal in diabetes management is reduced glycemic response to foods. Diabetic drug therapy often focuses on inhibiting enzymes implicated in diabetes to stabilize blood glucose levels. Some important target enzymes for diabetes therapy include α-amylase, α-glucosidase, dipeptidyl peptidase IV (DPP IV), and protein tyrosine phosphatase 1B (PTP1B). Specific drugs exist in the market to reduce hyperglycemia via specific mechanisms[4]. DPP IV inhibitor drugs in the market, such as sitagliptin, vildagliptin, and saxagliptin, are commonly prescribed to control hyperglycemia and reduce HbA1c levels. These drugs, however, have been reported to cause side effects such as fever, ocular hyperemia, nasopharyngitis, upper respiratory tract infection, streaming eyes, and gastrointestinal disturbances[5]. Sodium orthovanadate has been reported to be a potent inhibitor of the PTP1B enzyme. However, the safety of sodium orthovanadate remains questionable due to a lack of clinical studies[6]. Another common problem with different synthetic drugs in diabetes treatment is the occurrence of hypoglycemia[7]. Hence, the search for safer alternatives from natural sources continues to date.

Plant foods are one such natural source that has been investigated extensively for their inhibitory capacity against different target diabetic enzymes. These plant foods have several phytochemicals which exhibit significant biological activity, including DPP IV and PTP1Benzyme inhibition . Incorporating plant foods with health functionality is being recognized as a promising innovative dietary strategy for the management of type 2 diabetes and its complications[8]. There are few recent scientific reviews on DPP IV inhibitory activities of food-derived bioactive peptides[9] and some medicinal foods[10]. Synthetic and naturally isolated flavonoids have been reviewed for both DPP IV and PTP1B activities[11]. Marine-derived bioactive molecules have been reviewed for PTP1B inhibition[12]. These studies have focussed on identifying lead compounds for pharmacological applications. Activities of plant foods and their extracts have not been reviewed to date to our knowledge. This review, hence, is an attempt to collate and review the scientific information reported in the last decade on plant food extracts and their phytochemicals with DPP IV and PTP1B inhibitory activities in an attempt to scientifically identify foods that could be beneficial in a diabetic diet.

glycemic response The glycemic response to a food or meal is the effect that food or meal has on blood glucose levels after consumption. It is normal for blood glucose and insulin levels to rise after eating and then return again to fasting levels over a short period of time.

enzyme inhibition Enzyme inhibition refers to a decrease in enzyme-related processes, enzyme production, or enzyme activity. Enzyme inhibitors prevent the formation of an enzyme–substrate complex and hence prevent the formation of products. Inhibition of enzymes may be either reversible or irreversible depending on the specific effect of the inhibitor being used.

bioactive peptides Bioactive peptides (BP) are organic substances formed by amino acids joined by covalent bonds known as amide or peptide bonds. Although some BP exists free in its natural source, the vast majority of known BP are encrypted in the structure of the parent proteins and are released mainly by enzymatic processes. Some BPs have been prepared by chemical synthesis. BP plays a significant role in human health by affecting the digestive, endocrine, cardiovascular, immune, and nervous systems. BPs are considered the new generation of biologically active regulators; they can prevent oxidation and microbial degradation in foods and also improve the treatment of various diseases and disorders, thus increasing the quality of life.

2 Plant Foods and Their Phytochemicals with DPP IV Inhibitory Activity

One of the common antihyperglycemic mechanisms observed in diabetic drugs is the inhibition of the dipeptidyl peptidase IV (DPP IV/CD26) enzyme. DPP IV is a cell-surface protease belonging to the prolyl oligopeptidase family. It prevents the degradation of two key glucoregulatory incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)[13]. These incretin hormones are secreted in the intestine in response to the intake of nutrients, which in turn produce glucose-induced insulin response. DPP IV selectively removes the N-terminal dipeptide from peptides with proline or alanine in the second position. In certain metabolic conditions, GLP-1, which contains alanine, serves as a substrate for DPP IV, resulting in its inactivation. Therefore, DPP IV inhibitors have been reported to improve glucose tolerance and pancreatic islet cell function in animal models of type 2 diabetes and in diabetic patients. The DPP IV inhibitors present in functional plant foods are expected to prevent GLP-1 from being inactivated by acting as an alternative substrate for DPP IV[14]. This will result in an improvement in blood glucose levels and increased insulin production with the inhibition of glucagon secretion[10].

2.1 DPP IV Inhibitory Plant Foods

This section reviews the scientific information available in the last decade for DPP IV inhibitory activities of different foods/food products under different food groups (Table 1). For a more comprehensive idea of their glucose regulatory potential, the other mechanisms of antidiabetic action reported in the same study have also been mentioned in the descriptive text.

2.1.1 Cereals, Pulses, and Their Functional Food Products

Pigmented rice: Rice is the staple food of more than half of the world's population. Rice seeds (paddy rice) have outer shells called husk (woody, siliceous and non-edible in nature), which are removed by dehulling/de-husking process. Dehusked rice with its bran layers (nucellar, testa, and pericarp) and germ (embryo) intact is wholegrain rice, normally also referred to as brown rice,

Table 1: DPP IV inhibitory activity of plant food extracts.

Food extract	Percent inhibition or IC_{50}	Study type	References
Cereals, pulses, and their functional food products			
Indian pigmented rice methanolic extracts	Bamboo rice—4.22 µg/ml Garudan samba—1.82 µg/ml	In vitro	Haldipur and Srividya[16]
Indian pigmented rice methanolic extracts	Kattuyanam—2.18 µg/ml Chennangi—5.68 µg/ml Karungkuruvai—1.66 µg/ml	In vitro	Haldipur and Srividya[17]
Pigmented rice and pigmented rice-based extruded products with or without passion fruit powder (ethanol, hexane, and aqueous extracts)	Rice bran—42.6% Polished red rice—35.9% Optimized extrudate—25.5% Controlled extrudate—13.6%	In vitro	Samyor et al.[18]
Maize tortilla with an optimized chickpea hydrolysate	Unfortified white tortilla—11% Unfortified blue tortilla—26% Fortified white tortilla—91% Fortified blue tortilla—95%	In vitro	Acevedo-Martinez et al.[21]
Wheat and/or barley-based products enriched with three herbs (*T. chebula, T. bellerica, and E. officinalis*) (methanol and water extracts)	Methanolic extracts—4.3 to 4.6 mg/ml Water extracts—5.6 to 30.5 mg/ml Significant decrease in DPP-IV enzyme activity (p moles pNA/min/mg protein) from 1.4 to 0.64, 0.71, and 0.91 when fed with barley, wheat, and wheat-barley products in diabetic rats	In vitro In vivo (rats)	Das et al.[22]
Pre-cooked sorghum flour fortified with sorghum peptides	Unfortified pre-cooked sorghum flour—2.12 mg/ml Bioaccessible peptides from product—0.86 mg/ml	In vitro	Cian et al.[23]
Fruits, vegetables, and spices			
Indian gooseberry (*Emblica officinalis)* extract	53.2% at 4 mg/ml IC_{50}—3.8 mg/ml	In vitro	Majeed et al.[24]
Pomegranate juice consumption with resistance training	↓ DPP IV 432.74–216.63 IU/l	In vivo (human)	Akbarpour et al.[26]
Rhus Chinensis Mill. Fruits ethanolic extracts	Free phenolic extract—66 µg/ml	In vitro	Liu et al.[28]
Garlic bulb DMSO extract	70.9 µg/ml	In vitro	Kalhotra et al.[30]
Edible algae			
Edible algae—*Sargassum polycystum and Sargassum wightii* methanolic extracts	36.94 µg/ml 38.27 µg/ml	In vitro	Unnikrishnan et al.[32]
Edible algae—*Alaria esculenta* ethanolic extract and *Laminaria digitata* aqueous extract	91% 90%	In vitro	Calderwood et al.[33]

due to the color of the bran. Pigmented rice refers to whole grain rice with the bran layers varying in hues and intensities from brown, red, black, purple, green, and yellow in different varieties. In contrast, in white rice, also referred to as milled rice/polished rice, the bran layers and germ are completely removed on milling[15]. Recent studies[16,17] have reported the DPP IV inhibitory activity(IC_{50}) of methanolic extracts of Bamboo seed rice (4.2 µg/ml) and four pigmented rice varieties from India—Karungkuruvai (1.7 µg/ml), Garudan samba (1.8 µg/ml), Kattuyanam (2.2 µg/ml), and Chennangi (5.7 µg/ml). The activity was comparable to sitagliptin, the positive control (1.2 µg/ml), and significantly much higher than in white rice (IC_{50}72.6 µg/ml). The studies identified these pigmented rice varieties to be rich sources of bioactive phenolics such as gallic acid, 4-hydroxybenzaldehyde, caffeic acid 4-*O*-glucoside, *p*-coumaric acid, cirsimaritin, eriocitrin, etc. They further reported the good binding potential of these metabolites at the active site

phenolics Also known as polyphenols, are a class of compounds consisting of one or more hydroxyl groups (—OH) bonded directly to an aromatic hydrocarbon group. Phenolics are broadly distributed in the plant kingdom and are the most abundant secondary metabolites of plants. Plant polyphenols have drawn increasing attention due to their potent antioxidant properties and their marked effects in the prevention of various oxidative stress-associated diseases such as cancer. In the last few years, the identification and development of phenolic compounds or extracts from different plants have become a major area of health- and medical-related research.

IC_{50} The half maximal inhibitory concentration (IC_{50}) is a measure of the potency of a substance in inhibiting a specific biological or biochemical function.

metabolites Metabolites are intermediate products produced during metabolism, catalyzed by various enzymes that occur naturally within cells. The term metabolite is usually used for small molecules. Metabolites are the products and intermediates of cellular metabolism. Metabolites can have a multitude of functions, including energy conversion, signaling, epigenetic influence, and cofactor activity.

of the DPP IV enzyme using molecular docking. Therefore, the DPP IV inhibitory property of pigmented rice was attributed to the presence of these phenolic compounds. Additionally, Bamboo seed rice and Garudan samba were reported to inhibit the α-amylase enzyme[16], and the extracts of Kattuyanam, Karungkuruvai, and Chennangi were reported to inhibit α-amylase, α-glucosidase, and PTP IB enzymes[17].

Red rice extruded product: Another study[18] reported the in vitro DPP IV inhibitory activity of Indian red rice from Arunachal Pradesh, its bran, and extruded product. The highest inhibition was exhibited by the bran (70.5%), followed by whole red rice (42.6%) and polished red rice (35.9%). The optimized extruded product (red rice combined with 11.25% passion fruit powder) exhibited a higher (25.5%) inhibition than the control extruded product (red rice extruded alone − 13.6%).

Chickpea-fortified maize tortillas: One of the popular grains consumed worldwide is maize. Due to the presence of anthocyanins, blue and purple maize have been investigated for their anti-inflammatory, anti-adipogenic, and antidiabetic potential[19]. The maize/corn-based snacks industry has been increasing steadily, and tortillas are the most popular corn-based product[20]. To enhance the suitability of this staple food for diabetes, a recent study evaluated the effect of fortifying white and blue maize tortillas with chickpea protein hydrolysate (CPH) on in vitro DPP IV inhibition. The DPP IV inhibition increased significantly from 11 and 26% (0% fortification) to 91% and 95% in white and blue maize tortillas, respectively, when fortified with 15% CPH[21]. After simulated gastrointestinal digestion, the activity was retained but decreased to 41% and 61% in white and blue maize tortillas, respectively. Physicochemical characteristics such as texture and color were, however, found to be affected adversely.

Herb-enriched wheat and/ barley flour-based products: Wheat and/barley-based products enriched with three herbs *(T. chebula, T. bellerica, and E. officinalis*) were tested for their in vitro and in vivo DPP IV inhibitory capacity[22]. The methanolic extracts showed better in vitro DPP IV inhibition (IC_{50} 4.3–4.6 mg/mL) than the water extracts (IC_{50} 5.6–30.5 mg/mL). Studies in streptozotocin-induced diabetic rats showed a significant decrease in DPP-IV enzyme activity (p moles pNA/min/mg protein) from 1.4 to 0.64, 0.71, and 0.91 when fed with herb-enriched barley, wheat, and wheat-barley products. These products were also found to exhibit good in vitro and in vivo amylase and glucosidase inhibitory activity, low estimated glycemic index, and lower in vivo glycemic response.

Pre-cooked sorghum flour fortified with sorghum peptides: Pre-cooked sorghum flour added with 3 g/100 g of angiotensin-converting enzyme 1 (ACE-I) and DPP IV inhibitory sorghum peptides had high total peptide dialysability after simulated gastrointestinal digestion[23]. The bioaccessible peptides from the fortified product exhibited lower IC_{50}values, indicating a higher inhibitory activity than unfortified pre-cooked sorghum flour against ACE-I (1.04 ± 0.12 vs. 1.82 ± 0.09 mg protein $mL-1$, respectively) and DPP IV (0.86 ± 0.02 vs. 2.12 ± 0.08 mg protein $mL-1$, respectively) enzymes.

2.1.2 Fruits, vegetables, and spices

Amla: *Emblica officinalis*, also known as Indian gooseberry or amla in Ayurveda, is considered a powerful rejuvenator for delaying aging and degenerative process. A study[24] reported amla fruit extract to exhibit a concentration-dependent inhibitory activity in vitro against human DPP IV enzyme with the highest inhibition (53.2%) at 4 mg/ml. The fruit extract was also reported to contain phytochemicals such as β-glucogallin, and hydrolyzable tannins, including mucic acid 1,4-lactone 5-*O*-gallate, mucic acid 2-*O*-gallate, mucic acid 6-methyl ester 2-*O*-gallate, mucic acid 1-methyl ester2-*O*-gallate, and ellagic acid. The presence of these metabolites was considered the basis of the DPP IV inhibitory potential of amla. The study also reported good α-amylase and α-glucosidase inhibitory activity of amla fruit extract.

Pomegranate: In some traditional medical systems, pomegranate fruit is used in the treatment of diabetes. Pomegranate polyphenols are well-known for their antioxidant properties, which have advantages including lowering oxidative/inflammatory stress and raising protective signaling molecules like antioxidant enzymes, neurotrophic factors, and cytoprotective proteins. Some of the major compounds present in pomegranate juice, such as ellagic acid and punicalagin, inhibited α-amylase, α-glucosidase, and dipeptidyl peptidase-4 in free-cell systems and adipocyte cell lines[25]. The results from a recent study in women with type 2 diabetes[26] showed a nonsignificant decrease in DPP IV from 475.77 to 390.86 IU/L after the consumption of 100 ml of pomegranate juice for 8 weeks. When combined with resistance training, a significant decrease ($p < 0.05$)

in vitro In vitro (meaning in glass or in the glass) studies are performed to simulate biological activities at a lab level in an external environment. Colloquially called "test-tube experiments", these studies are traditionally done in labware such as test tubes, flasks, Petri dishes, and microtiter plates.

in vivo Studies that are in vivo (Latin for "within the living") are those in which the effects of various biological activities are tested on the whole, living organisms or cells, usually animals, including humans, and plants, as opposed to in an external setting of a lab. In vivo testing is often employed over in vitro because it is better suited for observing the overall effects of an experiment on a living subject.

was observed in DPP IV levels (432.74–216.63 IU/L). The combination treatment also significantly reduced LDL and glucose levels ($p = 0.0001$) and improved GLP-1, HDL, and insulin levels ($p = 0.0001$).

Rhus chinensis Mill.: Several bioactivities, including antioxidant and pancreatic lipase inhibitory actions in vitro, prevention of non-alcoholic fatty liver, and alcoholic fatty liver, have been associated with *R. chinensis* fruit, popularly known as Chinese sumac[27]. Liu et al.[28] studied the in vitro DPP IV inhibitory potential of *Rhus chinensis Mill.* fruit phenolic-rich extracts. The free phenolic extract showed the highest inhibitory activity with an IC_{50} value of 66 µg/ml. Phytochemical correlation analysis indicated di-O-galloyl-glucoside and its isomer to contribute to the above activity. The fruit phenolic-rich extracts were also found to inhibit α-glucosidase and advanced glycation end products.

Garlic: Garlic (*Allium sativum*) is a well-known spice and member of the Alliaceae family. It is also utilized as a treatment for various illnesses and physiological conditions. Garlic has been reported to have positive effects on blood pressure, cholesterol, and infections, as well as on treating metabolic disorders and cancer prevention. The antidiabetic, hepatoprotective, anthelmintic, anti-inflammatory, antioxidant, antifungal, and wound-healing properties of garlic extracts have also been reported[29]. Methanolic extract from garlic has been reported to show good inhibition of the DPP IV enzyme with an IC_{50} value of 70.9 µg/ml[30]. The study also reported the presence of phytochemicals such as catechin, caffeic acid 3-glucoside, calenduloside E, and malonylgenistin. The DPP IV inhibitory potential of garlic was attributed to the presence of these phenolic compounds, which exhibited good inhibition against DPP IV as evidenced through in silico virtual screening and molecular docking simulations studies.

2.1.3 Edible algae

Both eastern and western nations have utilized marine macroalgae, such as *Sargassum polycystum, Sargassum wightii,* etc., for food and as folk medicine. Numerous phytochemicals with diverse bioactivities, such as antidiabetic and antioxidant activities, are present in natural marine products. Significant contributions to the control of glucose-induced oxidative stress and regulation of starch-digesting enzymes have been documented for bioactive components found in these edible seaweeds[31]. Apart from these other antidiabetic mechanisms, recent studies reported the DPP IV inhibitory potential of edible algae. *Sargassum polycystum* and *Sargassum wightii* methanolic extracts exhibited IC_{50} values of 36.9 and 38.3 µg/ml, respectively[32].

Calderwood et al.[33] compared the in vitro DPP IV inhibitory activity of eleven types of red and brown algae. *Alaria esculenta* (ethanolic extract- 91%) and *Laminaria digitata* (aqueous extract-90%) exhibited the highest inhibitory potential comparable to berberine, the positive control. Extracts of *F. vesivulosus, A. nodosum,* and *A. esculenta* also exhibited glucosidase inhibition in vitro. Water and ethanolic extracts of *A. esculenta* and *U. rigida* were reported to also significantly increase GLP secretion from STC-1 cells at 25 mg/ml concentration. The proposed mechanistic action of plant food extracts against the DPP IV enzyme is presented in Fig. 1.

2.2 Food-Derived Metabolites with DPP IV Inhibitory Activity

In this section, we have reviewed the DPP IV inhibitory potential of peptides and metabolites extracted from food sources and not reported in recent earlier review articles.

2.2.1 Peptides

Peptides isolated from various food sources have been studied extensively for their DPP IV inhibitory. Two recent review articles by Liu et al.[13] and Zhang et al.[34] have reported the DPP IV inhibitory potential of peptides from several foods. In this review, we have updated the information from recent in vitro studies (Table 2).

Two peptides (IPI and IPV) hydrolyzed from quinoa exhibited DPP IV inhibitory activity with IC_{50} values of 30 µM[35]. In another study, nine peptides from oats were found to have DPP IV IC_{50} values ranging from 25.2 to 283 µM[36]. Three peptides from sorghum bicolor seed protein, LSICGEESFGTGSDHIR, SLGESLLQEDVEAHK, and QLRDIVDK, were reported to have DPP IV inhibitory potential with IC_{50} values of 73.5, 82.5, and 8.6 µM, respectively[37]. In the same study, molecular docking analysis revealed the peptides to bind at the active and secondary sites of DPP IV. The peptide QLRDIVDK exhibited the highest binding affinity. A study by Zhang et al.[38] reported the IC_{50} of pea protein peptide (IPYWTY) to be 11.04 µM. The in vitro results were further confirmed using molecular docking studies. Peptides

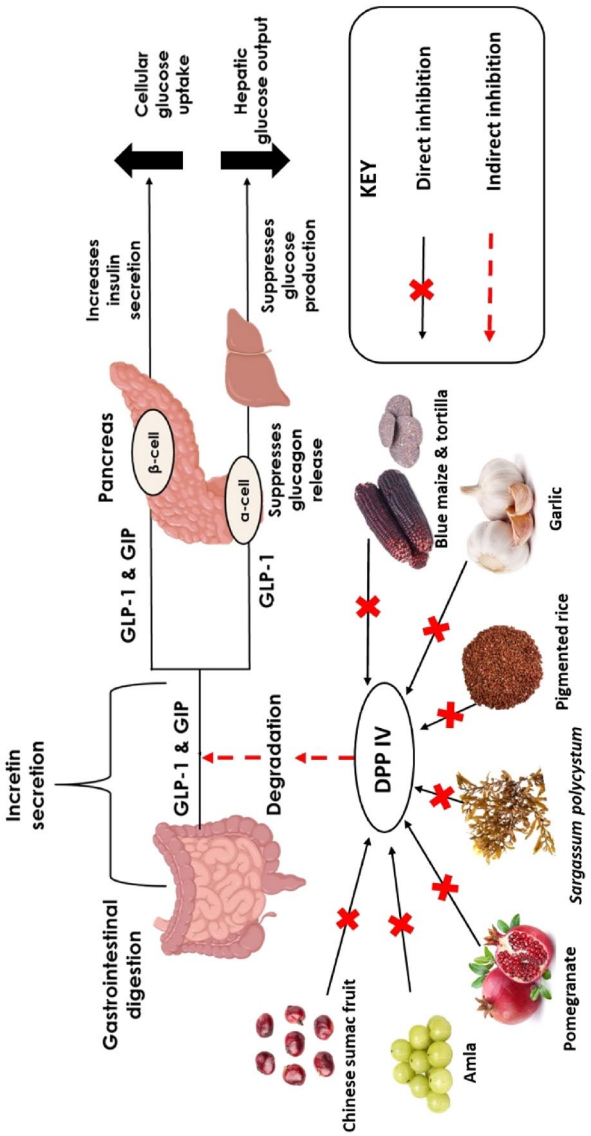

Figure 1: The proposed mechanistic action of plant food extracts against DPP IV enzyme.

Table 2: Food-derived compounds as DPP IVi.

Food-derived compounds	Percent inhibition or IC_{50}	Type of study	References
Food-derived peptides			
Quinoa peptides	IPI, IPV—30 μM	In vitro	You et al.[35]
Oats peptides	IPQHY—25.72 μM VPQHY—30.78 μM VAVVPF—33.91 μM VPLGGF—40.22 μM LPQHY—62.66 μM VAEVPF—65.33 μM PPHCP—77.14 μM MAGQVF—223.31 μM AAVPF—282.31 μM	In vitro	Wang et al.[36]
Sorghum bicolor seed protein peptide	LSICGEESFGTGSDHIR—73.5 μM SLGESLLQEDVEAHK—82.5 μM QLRDIVDK—8.55 μM	In vitro	Majid et al.[37]
Pea protein peptide	IPYWTY—11.04 μM	In vitro	Zhang et al.[38]
Germinated soybean peptides	5 to 10 KDa—0.91 mg/ml >10 KDa—1.18 mg/ml	In vitro	Gonzales-Montoya et al.[39]
Ulva spp. hydrolysates	NPF hydrolysate—2.7 mg/ml APF hydrolysate—1.21 mg/ml	In vitro	Cian et al.[40]
Black tea aqueous peptide	AGFAGDDAPR—1 mg/ml	In vitro	Lu et al.[41]
Food derived phenolics			
Extra virgin olive oil phenolics	Oleuropein—472.3 μM Oleacein—187 μM Oleocanthal—354.5 μM Hydroxytyrosol—741.6 μM Tyrosol—1112 μM	In vitro (cell line) In silico	Lammi et al.[44]
Moringa oleifera phenolic	*O*-Ethyl-4-[(α-l-rhamnosyloxy-benzyl] carbamate—798 nM	In vitro	Yang et al.[43]

from germinated soybean of 5 to 10 KDa were found to have 0.91 mg/ml $IC_{50,}$ and peptides > 10 KDa exhibited 1.18 mg/ml IC_{50}[39]. Cian et al.[40] reported the IC_{50} values of protein hydrolysates from *Ulva* spp. NPF hydrolysate exhibited 2.7 mg/ml, and APF hydrolysate exhibited 1.21 mg/ml. Lu et al.[41] reported the IC_{50} value of a black tea peptide (AGFAGDDAPR) to be 1 mg/ml.

2.2.2 Phenolics

Dietary polyphenols have drawn interest because they act as indirect insulin secretion stimulants and dipeptidyl peptidase-IV (DPP-IV) inhibitors. The DPP IV inhibitory potential of dietary polyphenols is due to their structural affinity for the active site of the DPP IV enzyme[42]. *O*-Ethyl-4-[(α-l-rhamnosyloxy-benzyl] carbamate, a phenolic glucoside derivative from *Moringa oleifera leaves,* exhibited a very low IC_{50} value of 798 nM, indicating good DPP IV inhibitory potential[43]. The phenolic metabolites, oleuropein, oleacein, oleocanthal, hydroxytyrosol, and tyrosol extracted from extra virgin olive oil exhibited DPP IV inhibition with IC_{50} ranging from 187 to 741.6 μM[44].

3 Plant Foods and Their Phytochemicals with PTP1B Inhibitory Activity

Protein tyrosine phosphatase 1B (PTP1B) is a non-transmembrane phosphatase enzyme belonging to PTPs enzymes class and is expressed in tissues targeted by insulin, such as the liver, muscle, and fat. It catalyzes the dephosphorylation of the activated insulin receptor, insulin receptor substrate-1, thereby downregulating insulin signaling through the Akt/PI3K pathway. It also negatively regulates leptin signaling, contributing to obesity and metabolic disorders. Thus, inhibition of PTP1B is considered a promising method for treating type 2 diabetes and preventing obesity[45].

Table 3: PTP1B inhibitory plant foods.

Food extract	IC_{50}	Type of study	References
Cereals			
Indian pigmented rice methanolic extracts	Kattuyanam—31.39 µg/ml Chennangi—38.57 µg/ml Karungkuruvai—30.89 µg/ml	In vitro	Haldipur and Srividya[17]
Vegetables, spices, and others			
Onion peel ethanolic and water extracts	0.3–0.86 µg/ml	In vitro	Yang et al.[47]
Moringa oleifera leaves methanolic extract	346.8 µg/ml	In vitro	Sierra-Campos et al.[50]
Moringa oleifera leaves methanolic extract	41.2%	In vitro	Saidu et al.[49]
Cinnamon extracts (*n*-hexane, ethyl acetate, *n*-butanol, and water)	1.7–3.2 µg/ml	In vitro	Lin et al.[52]
Honey ethanolic extracts	3.1–42.8 µg/ml	In vitro (cell line)	Lori et al.[54]
Tea aqueous extracts	Black tea: 0.4 g/l Oolong tea: 2 g/l Green tea: 4 g/l	In vitro	Ma et al.[56]
Punica granatum (Pomegranate) rind methanolic extract	In vitro 26.25 µg/ml In vivo 200 mg/kg extract—268.51 to 132.44 mg/dl 400 mg/kg extract—272.4 to 115.27 mg/dl	In vitro In vivo (animal model)	Jain et al.[57]
Mushrooms			
Ganoderma lucidum ethanolic extract	Reduced the expression of PTP1B mRNA in L6 cells in a dose-dependent manner until saturation (conc. > 100 µg/ml)	In vivo (animal model)	Yang et al.[58]
Morchella conica methanolic extract	26.5 µg/ml	In vitro	Begum et al.[59]
Edible algae			
Edible brown alga *Hizikia fusiformis* solvent extracts	1.69–32 µg/ml	In vitro	Han et al.[60]
Gracilaria lemaneiformis, edible algae hexane, and ethanolic extracts	17 and 68.6 µg/ml	In vitro	Guo et al.[61]

3.1 PTP1B Inhibitory Plant Food Extracts

3.1.1 Cereals

Pigmented rice: Methanolic extracts of three Indian pigmented rice varieties, namely, Kattuyanam, Karungkuruvai, and Chennangi, were found to inhibit in vitro PTP1B enzyme with IC_{50} values ranging from 30.9 to 38.6 µg/ml (Table 3)[17]. Molecular docking analysis of seven phenolic metabolites abundant in these rice varieties (3′,4′,7-trihydroxyisoflavone, 3′-*O*-methylviolanone, catechin, cirsimaritin, dihydroquercetin, isorhamnetin, and isoxanthohumol) reported in the same study demonstrated good binding potential to the active site of PTP1B enzyme. Thus, these phytochemicals were opined to contribute to the PTP1B inhibitory potential of the pigmented rice samples.

3.1.2 Vegetables and Spices

Onion: *Allium cepa* is one of the most widely grown and consumed crops and is most frequently utilized in Indian cuisine. Onion peel has been reported to be a rich source of phenolics such as quercetin and its derivatives, protocatechuic acid, isorhamnetin, coumaric acid, vanillic acid, anthocyanins, etc. and tannins[46]. In a recent study, Yang et al.[47] reported the in vitro PTP1B inhibitory potential of red and yellow onion peel extracts (Table 3). The IC_{50} values of water extracts (red—0.33, yellow—0.3) were

lower than the ethanolic extracts (red—0.76, yellow—0.86 µg/ml). The water extract also showed greater (90%) glucose uptake than ethanolic extract (70%) at 1.25 µg/ml in insulin-resistant HepG2 cells. Further, treatment of insulin-resistant HepG2 cells with water extracts was reported to significantly reduce the expression of PTP1B. The study also reported the onion peel extracts to have good antioxidant (DPPH and ABTS), α-glucosidase, and AGEs inhibitory activity. The water extract showed no toxicity in HepG2 cells up to a concentration of 100 µg/ml.

Moringa oleifera: A highly nourishing vegetable with several potential benefits for treating rheumatism, poisonous bites, and pathogenic infections is the commonly cultivated species of *Moringa oleifera* in India[48]. Saidu et al.[49] reported 41% inhibition of PTP1B in vitro at a concentration of 100 µg/ml of methanolic extract of *M. oleifera* leaves. Sierra-Campos et al.[50] also reported in vitro inhibition of the PTP1B enzyme by methanolic extract of *M. oleifera* leaves with an IC_{50} value of 346.8 µg/ml (Table 3). The study also reported it is in vitro aldose reductase activity.

Cinnamon: Consumption of cinnamon is linked to statistically significant reductions in fasting plasma glucose, total cholesterol, LDL cholesterol, and triglyceride levels, as well as an elevation of HDL cholesterol[51]. Lin et al.[52] found that different solvents and aqueous extracts of cinnamon twigs inhibited PTP 1B with IC_{50} values ranging from 1.7 to 3.2 µg/ml (Table 3). Cinnamon twig was also reported to inhibit α-amylase and α-glucosidase in the same study.

Honey: The oldest known natural sweetener is honey. Besides its sweetening property, honey is also known to be a rich source of vitamins, amino acids, proteins, mineral salts, trace elements, and other metabolites such as flavonoids, phenolic and organic acids[53]. Honey extracts from twenty samples belonging to four different floral varieties, such as honeydew, chestnut, wildflowers, and acacia, were found to inhibit PTP1B (Table 3) with IC_{50} values ranging from 3.1 to 42.8 µg/ml[54]. Highest in vitro inhibitory activity was observed in honey obtained from honeydew flowers. The honey extracts, when treated with HepG2 cells, also enhanced the expression of insulin receptors and stimulated glucose uptake.

Tea: Epidemiological research has shown that tea use lowers the risk of developing diabetes and its complications. Its antidiabetic mechanisms of action include improving insulin resistance, activating the insulin signaling pathway, playing an insulin-like role, improving oxidative stress, and alleviating inflammatory response[55]. Ma et al.[56] found that tea extracts inhibited PTP1B activity in vitro. The IC_{50} values were found to be 0.4 mg/ml (black tea), 2 mg/ml (Oolong tea), and 4 mg/ml (green tea) (Table 3). HPLC analysis revealed that polyphenols, specifically catechins, were the major bioactive compounds in the tea. When applied to cultured cells, the tea extracts also induced tyrosine phosphorylation of cellular proteins.

Pomegranate rinds: *Punica granatum* (Pomegranate) rind methanolic extract has been reported to exhibit an IC_{50} value of 26.25 µg/ml against PTP 1B enzyme[57]. Administration of 200 and 400 mg/kg of the extract to diabetic rats significantly reduced the blood glucose levels from 268.51 to 132.44 mg/dl and from 272.4 to 115.27 mg/dl, respectively, after 21 days. The extract was also reported to inhibit α-amylase and aldose reductase.

3.1.3 Mushrooms

Yang et al.[58] reported the PTP1B inhibitory potential of *Ganoderma lucidum* ethanolic extract (Table 3). It was found to reduce the expression of PTP1B mRNA in L6 cells in a dose-dependent manner until saturation (100 µg/ml). *Ganoderma lucidum* ethanolic extract also increased the glucose uptake in L6 cells, upregulated the expression of GLUT4 mRNA, and improved the phosphorylation of IRS1 on Tyr612 in PTP1B-cells in the same study. *Morchella conica* methanolic extract has been reported to exhibit PTP1B inhibition in vitro with an IC_{50} value of 26.5 µg/ml[59]. The study also reported a gradual reduction in the blood sugar level in *M. conica*-treated diabetic mice from 448 to 148 mg/dl. The extract also improved liver and kidney damage in the rats by normalizing the serum glutamic pyruvic transaminase, serum glutamic oxaloacetate, alkaline phosphatase, serum creatinine, and urea levels. The antidiabetic activity of *M. conica* was attributed to the presence of metabolites such as diethofencarb, glycyl-prolyl-lysine, enterodiol, S-Nitroso-L-glutathione, acenocoumarol, lagochiline, 16,16-dimethylprostaglandin, and quercetin 3,5,7,3′,4′-pentamethyl ether.

3.1.4 Edible Algae

Solvent extracts of edible brown alga *Hizikia fusiformis* inhibited PTP1B in vitro activity with IC_{50} values ranging from 1.69 to 32 µg/ml[60]. The extracts also exhibited good α-glucosidase and reactive oxygen species inhibition (Table 3). Another study[61] reported the IC_{50} values of *Gracilaria lemaneiformis* hexane and ethanolic extracts against PTP1B to be 17 and 68.6 µg/ml, respectively. The study attributed the inhibitory potential of *Gracilaria lemaneiformis* extracts to the presence of 2,2′-methylenebis-6-(1,1-dimethylethyl)-4-methylphenol, 2,4-di-tert-butylphenol and palmitoleic acid using molecular docking analysis. The proposed mechanistic action of plant food extracts against the PTP 1B enzyme is presented in Fig. 2.

3.2 Food-Derived Metabolites with PTP1B Inhibitory Activity

In this section, we have reviewed the PTP1B inhibitory potential of metabolites extracted from food sources (Table 4).

3.2.1 Mushroom Alkaloids and Terpenoids

Several studies have reported the PTP 1B inhibitory potential of different varieties of mushrooms. Wang et al.[62] reported the alkaloids from the edible mushroom, *Hericium erinaceus* to have good PTP1B inhibitory activity with IC_{50} values ranging from 24 to 50 µM. Sesquiterpenoids from the edible mushroom *Pleurotus citrinopileatus* were found to have IC_{50} values ranging from 30 to 100 µM[63]. In another study, Tao et al.[64] reported the IC_{50} values of sesquiterpenoids from the edible mushroom *Pleurotus cystidiosus* to range from 38 to 50 µM. Lanostane triterpenoids from the edible mushroom, *Fomitopsis pinicola,* exhibited IC_{50} values ranging from 21 to 53 µM[65].

3.2.2 Edible Algae Terpenoids

Phlorotannins from edible brown algae, *Ecklonia stolonifera, and Eisenia bicyclis* were found to have IC_{50} values ranging from 0.18 to 1.69 µg/ml[66]. Jung et al.[67] reported fucoxanthin from edible brown algae *Eisenia bicyclis* and *Undaria pinnatifida* to have an IC_{50} value of 4.80 µM. The IC_{50} values of terpenoids and organic acids from edible green alga *Caulerpa racemosa* ranged from 2.3 to 50 µM[68]. Fatty acids, sterols, phenolic compounds, homo-monoterpene, and triterpenoid glycosides from *Hizikia fusiformis* exhibited IC_{50} values ranging from 6 to 23 µM[69].

3.2.3 Metabolites from Other Food Sources

Valoneic acid dilactone (VAD) extracted from the rinds of *Punica granatum* (Pomegranate) has an IC_{50} value of 12.4 µg/ml against PTP 1B[57]. Administration of VAD at 10, 25, and 50 mg/kg for 21 days significantly reduced blood glucose levels from 259.87 to 124.66 mg/dl, 264.51 to 98.26 mg/dl, and 274.56 to 95.12 mg/dl, respectively, in alloxan-induced diabetic rats. Another study reported the PTP1B inhibitory activity of two metabolites isolated from wasted lychee seed. The IC_{50} values of pavetannin B2, procyanidin A2, and the positive control, ursolic acid, were reported to be 450.295, 338.257, and 19.686 µM, respectively[70]. Lychee seed extracts in other in vivo studies have been found to reduce insulin resistance by increasing the expression of PI3K, AKT, and mTOR and triggering the PI3K/AKT/mTOR signaling pathway[71]. However, the safety of Lychee seed is under deliberation because it contains Hypoglycin A, which has been reported to cause hypoglycemia and fatal encephalopathy in humans[72]. Cucurbitane triterpenoids from *Momordica charantia* L. exhibited IC_{50} values ranging from 10 to 28.5 µM[73]. Eleftheriou et al.[45] reported the PTP1B inhibitory activity of acetoside (IC_{50} 9.3 µM) from *Sideritis L.* (mountain tea). Procyanidins isolated from Lotus (*Nelumbo nucifera* Gaertn.) seed pods exhibited significant in vitro PTP1B inhibitory activity with an IC_{50} value of 0.33 µg/ml[74].

4 Conclusions and Future Directions

Managing diabetes through foods and bioactive food phytochemicals is gaining more emphasis due to the associated safety aspects coupled with their diverse mechanisms of action. Diabetic drugs target enzymes involved in glucose homeostasis pathways that include DPP IV and, more recently, PTP1B. This review has collated the scientific evidence for DPP IV inhibitory activity of select traditional Indian pigmented rice varieties, common fruits such as gooseberry/amla, pomegranate, and Chinese sumac, and spices such as garlic assessed by in vitro/in vivo assays. Few edible algae have also emerged as potent DPP IV inhibitors. Foods such as oats, quinoa, sorghum, pea, soybean, Moringa, and a few others have shown inhibitory activity through compounds derived/extracted from them. This review also has helped to identify plant foods such as pigmented rice varieties, onion peels, *Moringa oleifera*, cinnamon, honey, tea, mushrooms, and edible algae with (in vitro/in vivo) PTP1B inhibitory activity. Screening of the scientific literature also revealed

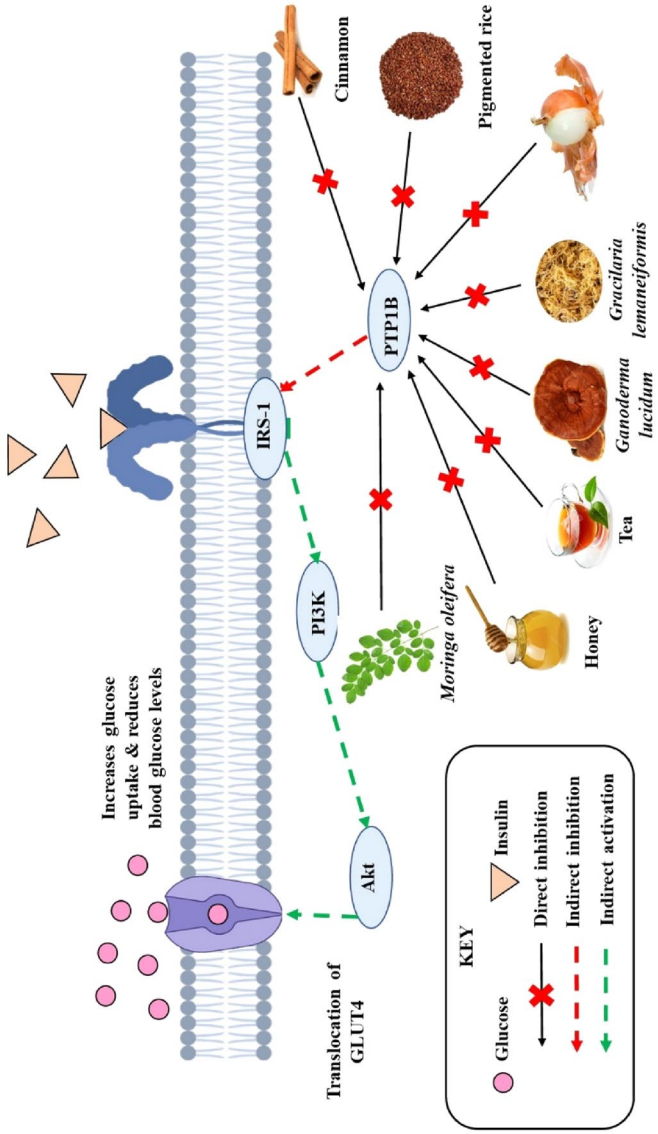

Figure 2: The proposed mechanistic action of plant food extracts against PTP 1B enzyme.

Table 4: Food-derived metabolites as PTP1B inhibitors.

Food metabolites	IC_{50}	Type of study	References
Mushrooms alkaloids and terpenoids			
Hericium erinaceus (edible mushroom) alkaloids	24–50 μM	In vitro	Wang et al.[62]
Pleurotus citrinopileatus (edible mushroom) sesquiterpenoids	30–100 μM	In vitro	Tao et al.[63]
Pleurotus cystidiosus (edible mushroom) sesquiterpenoids	38–50 μM	In vitro	Tao et al.[64]
Fomitopsis pinicola (edible mushroom) Lanostane triterpenoids	21–53 μM	In vitro	Zhang et al.[65]
Edible algae phenolics and terpenoids			
Ecklonia stolonifera and Eisenia bicyclis (edible Brown Algae) phlorotannins	0.18–1.69 μg/ml	In vitro	Moon et al.[66]
Eisenia bicyclis and *Undaria pinnatifida* (edible brown algae) fucoxanthin	4.80 μM	In vitro	Jung et al.[67]
Caulerpa racemosa (edible green alga) terpenoids	2.3–50 μM	In vitro	Yang et al.[68]
Hizikia fusiformis fatty acids, sterols, phenolic compounds, homo-monoterpene, and triterpenoid glycosides	6–23 μM	In vitro	Seong et al.[69]
Other food metabolites			
Punica granatum (Pomegranate) rind phytochemical—Valoneic acid dilactone	In vitro 12.4 μg/ml In vivo 10 mg/kg conc.—259.87 to 124.66 mg/dl 25 mg/kg conc.—264.51 to 98.26 mg/dl 50 mg/kg conc.—274.56 to 95.12 mg/dl	In vitro In vivo (animal model)	Jain et al.[57]
Wasted lychee seed	Pavetannin B2—450.295 μM Procyanidin A2—338.257 μM Ursolic acid—19.686 μM	In vitro	Choi et al.[70]
Momordica charantia L. cucurbitane triterpenoids	10 to 28.5 μM	In vitro	Yue et al.[73]
Sideritis L (mountain tea) acetoside	9.3 μM	In vitro	Eleftheriou et al.[45]
Lotus (*Nelumbo nucifera* Gaertn.) seed pods procyanidin	0.33 μg/ml	In vitro	Xiang et al.[74]

compounds isolated from a few mushrooms and edible algae to exhibit PTP1B inhibitory activity. Among the phytochemicals, peptides were found to contribute most to DPP IV inhibitory activity. For PTP1B inhibitory activity, terpenoids have been evaluated more widely. However, comparatively the few phenolic compounds studied have shown lower IC_{50} and, thereby, greater potency. Few of the foods, such as Moringa, pomegranate, and select pigmented rice varieties reviewed here, have inhibitory activity against both the target DPP IV and PTP1B enzymes. Several of them also have been reported to exhibit inhibitory properties against other diabetic target enzymes, alter plasma biomarkers, and maintain glucose homeostasis. Foods with multi-mechanistic glucose regulatory potential are expected to be promising candidates for planning preventive and therapeutic diets for diabetes.

DPP IV has also been proposed as a diagnostic or prognostic marker for various tumors, hematological malignancies, immunological,

inflammatory, psychoneuroendocrine disorders, and viral infections[75]. Similarly, PTP1B's has been proposed as an ideal therapeutic target for obesity, cancer, and immune modulation apart from type II diabetes[76]. Hence, the foods identified through this review could be promising natural candidates for the management of various other disorders.

The inhibitory activity has been attributed to several bioactive phytochemicals present in these foods. These compounds could be changed chemically and may reduce during food processing. However, few interesting studies show that the addition of phytochemicals-rich plants, herbs, and protein hydrolysates to processed food products resulted in moderate to good enzyme inhibitory activity even after simulated intestinal digestion. But the organoleptic acceptability of a few of these products appears to be a challenge.

There appears to be an urgent need as well as wide scope for the development of food products enriched with antidiabetic extracts/compounds to aid in the dietary management of this chronic disease. These will have to be further evaluated in in vivo models, and their inhibitory activity will be confirmed in human clinical trials. In line with the ancient dictum "Food is medicine", the nutrition, food, and metabolism nexus is gaining prominence and being scientifically revisited for lifestyle metabolic disorders such as diabetes. At this juncture, this review would serve as a small accelerator to further in-depth research in this area of medicinal foods for diabetes and related disorders. A healthy diet-associated metabolic signature has been reported to be inversely associated with future risk for type 2 diabetes and coronary artery disease. The association with diabetes was independent of traditional risk factors suggesting an independent beneficial effect of health-conscious dietary intake[77]. Hence, assessment using metabolomics biomarkers can be a potential futuristic area of research to provide stronger clinical evidence and validate the role of functional foods/therapeutic diets in diabetes.

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Data availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Conflict of interest

The authors declare that they have no financial or other conflicts of interest.

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