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Review Article

Sources of Food with Insulin-Secreting, Insulin-Sensitizing, and Insulin-Mimetic Properties

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Abstract

This review provides a glance at the mechanisms of diabetes, emphasizing Diabetes Mellitus type 2 and its relationship to nutrition. It also discusses several studies on sources that have insulinotropic properties. Besides it is described several species of plants and some of their phytonutrients, which are isolated or present in the extract, could be used in the development of food for diets for patients with Diabetes. Numerous studies have demonstrated that antidiabetic phytonutrients are highly effective against Diabetes patients and are almost completely without side effects. In conclusion, diabetic patients must receive medical nutrition therapy using selecting foods to meet their individual nutritional needs with insulinotropic properties. Fortunately, nature provides several sources of foods that can be useful for the implementation of these diets that must be certified institutionally through scientific confirmation. A lack of interest in the importance of herbal medicine is a primary factor contributing to unsolved health concerns. Medical communities, including nutritionists and food technologists, must take the topic into their own hands to prevent or control illness. Furthermore, there is a lack of research on the studies of these sources with clinical trials; therefore, researchers in the area must take it under control because this topic represents food and state security.ated with this disorder.

Keywords: Diabetes Mellitus; Functional Food; Insulinotropic Agents; Herbal Medicine; Medicinal Plants; Phytochemical; Phytonutrients

Introduction

In humans, the fasting normal blood glucose level is 70–110 mg/dL (4.0 to 6.0 mM) with an average of about 90 mg/dL (5 mM) [1] and is tightly regulated by maintaining the balance between the sources of glucose in the blood (diet, glycogenolysis, gluconeogenesis) and the removal of glucose from blood (glycolysis, glycogenesis, lipogenesis, uronic acid pathway etc.) through precisely hormonal regulation. This maintains the blood glucose level at a steady-state condition, called glucose homeostasis. Glucose is essential for every cell according to their specific functions. Insulin augments glycolysis, glycogenesis, lipogenesis, and protein synthesis and decreases gluconeogenesis [2]. However, due to failure in its homeostasis, the glucose levels can vary throughout the day, and glucose can build up in the blood instead of going to the cells. This condition eventually leads to Diabetes Mellitus.

The direct correlation between diet and diabetes management is well established. Diabetic patients need to receive medical nutrition therapy provided by a registered dietitian to guide them in selecting foods to meet their individual nutritional needs. The nutritional counseling provided considers the availability of food, the individual's lifestyle, their living conditions, prescribed medications, and other health goals such as lowering blood fat levels and controlling hypertension, in the development of a nutritional plan.

Nature provides several sources of food that can be useful for the implementation of these diets. This review will focus on the generalities of Diabetes Mellitus and those foods that can be useful for control or prevention, emphasising sources of foods with insulin-secreting, insulin-sensitizing, and insulin-mimetic properties reported in the literature.

Diabetes mellitus generalities

Diabetes Definition

Diabetes Mellitus (DM) is a lifelong metabolic disorder, characterized by an event of hyperglycemia in the body; due to defective insulin secretion, defective insulin action, or both [3-5].

Diabetes Mellitus Clasification

According to [4-6] diabetes can be classified as: type 1, type 2, gestational diabetes Mellitus and others specific types.

- **Type 1 (T1DM) *Diabetes Mellitus* insulin dependent*:*** Is characterized by the loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency immune-mediated or idiopathic, where beta cell loss is a T-cell mediated autoimmune attack. The disease manifest by progressive T-cell-mediated autoimmune destruction of insulin-producing β cells in the pancreatic islets of Langherans, and tendency to the ketoacidosis [7-10].
- **Type 2 *Diabetes Mellitus* (T2DM; formerly known as non-insulin dependent DM):** Is a multifactorial disease characterized by heterogeneously progressive loss of islet β cell insulin secretion usually occurring after the presence of insulin resistance (IR) it is one component of metabolic syndrome (MS), or metabolic dysfunction syndrome (MDS). T2DM is a disease with a complex and progressive pathogenesis [11,12].
- **Gestational *Diabetes Mellitus* (GDM):** Is glucose intolerance with onset or first recognition during pregnancy of non-diabetic pregnant woman, usually returning to normal condition soon after delivery [7,13].

Other specific types include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases, or drug use.

The exact cause of most types of diabetes is unknown. In all cases, glucose builds up in the bloodstream because the pancreas does not produce enough insulin. Each type of diabetes, emphasising on the type 1 and type 2, can be caused by a combination of genetic and environmental factors.

Glucose homeostasis

The body needs glucose constantly, as an important source of energy. Low blood and long-lasting elevation of blood glucose concentrations can cause body damage. Glucose homeostasis is the process, which maintains blood glucose at a steady-state [14].

Glucose absorbed from the digestive tract enters the portal blood flow and then systemic circulation. In the fed state, increased glucose stimulates insulin release from the pancreatic β-cells. Insulin acts -at the level of the liver; to inhibit hepatic gluconeogenesis, -at the skeletal muscle; to promote storage of glucose as glycogen, and -in the adipocytes; to stimulate lipogenesis. High insulin levels inhibit the release of non-esterified fatty acids.

Incretin hormones released from the small intestine in response to a meal augment pancreatic glucose-stimulated insulin secretion. Brain and red blood cells take up glucose independently of insulin in the fasting and fed state. In the fasting state, in the setting of low circulating insulin, hepatic gluconeogenesis, glycogenolysis, and release of non-esterified fatty acids [15].

In healthy subjects, insulin release is controlled to meet metabolic demands. The β cells detect changes in blood glucose and release the exact amount of insulin, given that they have a mechanism that allows them to detect the amount of insulin stored and secreted and consequently adjust its synthesis [16]. Insulin secretion is mediated by two mechanisms: one related to ATP-dependent K+ channels and another independent of these channels [17].

Because glucose does not diffuse through the lipid bilayer, it must be transported into the cell. This transport is carried out by two groups of proteins: SGLTs (sodium glucose transporters) and GLUTs (glucose transporters). The mechanisms of the transporters differ in terms of their substrate specificity, distribution, and regulatory mechanisms. SGLTs symport (transport in the same direction) glucose in conjunction with sodium ions. GLUTs transport glucose across the plasma membrane through a facilitated diffusion mechanism.

Insulin plays a partial role in glucose transport, due that some glucose transporters are insulin-dependent, while others are insulin-independent; for example, GLUT1 and GLUT2 are insulin independientye while GLUT4 is insulin dependent. Therefore, in insulin-dependent tissues like adipose tissues and muscles, intake of glucose is mediated through GLUT4, a glucose insulin-dependent transporter protein. GLUT1, the other transporter, is insulin-independent and widely expressed in most of tissue [18].

Glucose enters the cell in four stages: 1) it binds to the transporter on the outer surface of the membrane; 2) the transporter changes conformation, and glucose and its binding site are located on the inner surface of the membrane; 3) the transporter releases glucose into the cytoplasm; and 4) the free transporter changes conformation again, exposing the glucose-binding site on the outer surface and returning to its initial state [19].

Glucose is the primary stimulus for insulin secretion; although other macronutrients, such as the hormones glucagon-like peptide 1 (GLP-1), glucagon-dependent insulinotropic peptide (GIP), and incretin hormones, play a major role in stimulating insulin release. Through binding to distinct receptors on beta cells in the pancreas, incretin hormones stimulate insulin secretion and suppress glucagon release depending on the blood glucose level [20].

Pathophysiology of diabetes

As postulated by González-Mujica [18], Samuel., *et al*. and Petersen., *et al*. cited by Freeman *et al*. [21], in the state of chronic caloric surplus (chronic hyperglycemia), tissues can become resistant to insulin signaling due to impaired glucose uptake. They pointed out that the primary sites of insulin resistance are the skeletal muscle (a large reservoir for circulating glucose), the liver, and the adipose tissue.

These authors reported that in skeletal muscle, the direct result of insulin resistance is decreased glucose uptake by muscle tissue. Excess glucose that is not used as an immediate source of energy or for glycogen synthesis can be transformed through de novo lipogenesis into fat. Therefore intramuscle adipose tissue accumulates intramyocellular fatty acids, especially diacylglycerol, an intramyocellular fatty acid that signals energy excess within the cell.

The diacylglycerol activates protein kinase *C theta* (PKC-*theta*), decreasing proximal insulin signaling. The direct result is decreased glucose transporter type 4 (GLUT4) translocation to the cell membrane and reduced glucose uptake by the muscle tissue. Therefore, the excess glucose in the blood is shunted to the liver to be metabolized or stored.

Inside the liver, in an excess of energy substrate a process similar to that in skeletal muscle occurs; the diacylglycerol activates protein kinase *C epsilon* (PKC-*epsilon*), which decreases proximal insulin signaling. The glucose in excess enters hepatocytes via insulin-independent pathways stimulating *novo* lipogenesis via substrate push, creating more fatty acids from the glucose surplus. The excess fatty acid is deposited in the liver or as ectopic lipid throughout the viscera. Additionally, immune-mediated inflammatory changes contribute to excess lipolysis from adipose tissue, which is re-esterified by the liver and further adds to circulating fatty acid and ectopic lipid deposition. Finally, as reported by the authors, normal insulin-mediated suppression of gluconeogenesis is defective, and the liver continues to create more glucose, adding to the circulating glucose surplus.

It has been determined that lipolysis is sensitive to insulin. The failure of insulin to suppress lipolysis in insulin-resistant adipose tissue, especially visceral adipose tissue, increases circulating free fatty acids (FFAs). Higher levels of circulating FFAs directly affect both liver and muscle metabolism, further exacerbating insulin resistance in these tissues and contributing to lipotoxicity-induced beta-cell dysfunction.

On the other hand, Giri., *et al*. in 2018 [2], reported that when insulin resistance in peripheral tissues occurs, the pancreas produces more insulin to overcome such conditions. When the β-cells fail to compensate for this stress, apoptotic cell death occurs leading to a defect in insulin production and secretion. This consequence elevates the level of blood glucose gradually and develops hyperglycemia.

More specifically, Lu., *et al*, in 2024 [12], pointed out the vicious cycle of hyperglycemia. These authors state that a poor lifestyle and/or metabolic dysfunction syndrome leads to elevated triglycerides, non-esterified fatty acids in body. This excessive lipids is deposited in non-adipose tissue, blocking the insulin signaling pathways, then resulting in insulin resistance, especially in the liver. The excessive concentration of non-esterified fatty acids in the liver increases glucose production, and weakens the uptake of glucose, thereby increasing blood glucose and basal insulin levels. This elevated insulin promotes lipid deposition, further aggravating insulin resistance and forming the vicious circle. The elevated glucose and lipids produce hyperglucolipotoxicity to islet β cells and lipid deposition in islets, damaging the secretion function and number of pancreatic β cells, and further increasing blood glucose.

Insulin and Insuline Resistance Definition

Insulin (from the Latin word insula, meaning island) is an essential protein hormone secreted by the beta cells of the islet of Langerhans in the pancreas, which is involved in glucose utilization, cell metabolism, and mitogenesis. Recent findings suggest that some cells in the brain may also be capable of synthesizing insulin [22].

From a chemical point of view, the insulin is made up of 51 amino acids with a molecular weight of 5802, and its isoelectric point is at pH 5.5. It is composed of two chains: Chain A formed of 21 amino acids an chain B with 30 amino acids. These chains are joined together by two interchain disulphide bonds connected via cysteine residues. The A chain also has an intrachain disulphide bond. The active form of insulin is monomeric, presenting α helical structure and β-turns in both chains and β-sheet in the B-chain [18,23].

From a functional point of view, insulin is a peptide with hormonal function because it is produced by glands in the endocrine system. Insulin acts as a chemical messenger, transmitting messages to various cells or organs of the body, circulating throughout the body, and affecting only cells designed to receive its messages. Insulin augments glycolysis, glycogenesis, lipogenesis, and protein synthesis and decreases gluconeogenesis.

Insulin malfunction or that of either of its signaling components leads to the metabolic disorder or diabetes. Deficient glucose transport and glucose disposal are key pathologies leading to impaired glucose tolerance and risk of type 2 diabetes. In human subjects with prediabetes and type 2 diabetes, impaired glucose uptake in skeletal muscle, visceral adipose tissue, and the brain appears to be the best predictors of insulin resistance [21,24].

As a definition, insulin resistance is an impaired biologic state defined physiologically as a state of reduced responsiveness of insulin-target tissues to high physiological insulin levels. It primarily involves liver, muscle, and adipose tissue.

Insulin resistance is considered the pathogenic driver of many modern diseases, which metabolic consequences include metabolic syndrome (hyperglycemia, hypertension, dyslipidemia, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state), nonalcoholic fatty liver disease (NAFLD), atherosclerosis, and type 2 diabetes (T2DM) [21,25].

Incretin effect on DMT2

In humans, it is well recognized that an oral glucose load results in a greater insulin response than that of an isoglycemic intravenous glucose infusion; this response is known as the incretin effect [26,27].

This difference in insulin response is primarily attributed to: -the gastrointestinal peptides glucose-dependent insulinotropic polypeptide (GIP), -and the glucagon-like peptide-1 (GLP-1), the so-called incretin hormones. In humans and other monogastric species, GIP is synthesized in enteroendocrine *K* cells in the proximal small intestine, whereas GLP-1 is synthesized in enteroendocrine L cells in the distal ileum and colon [26].

As much as two-thirds of the insulin secreted in response to meal ingestion in humans is due to the insulinotropic action of GIP and GLP-1 [27]. A reduction in first-phase insulin secretion has been observed not only in patients with T2DM but also in patients with symptoms of prediabetes [11].

Additionally, the dipeptidyl peptidase-4 (DPP4) is an enzyme (glycoprotein, a serine-protease found in many organs and cells, and in the plasma and body fluids) that, in the body, plays a major role in glucose metabolism. It is responsible for the degradation of incretins such as GLP-1, which are key regulators of insulin release after eating. Expression of DPP4 in the body is substantially dysregulated in a variety of disease states including inflammation, cancer, obesity, and diabetes [20].

There are drugs such as; cyanopyrrolidines (sitagliptin, saxagliptin, linagliptin, vildagliptin and alogliptin) with key interactions with the DPP-4 complex that allow competitive inhibitionthat bind to the DPP-4 enzyme and reversibly inhibit the hydrolysis of endogenous incretins, thereby increasing both GIP and plasma GLP-1 levels, as well as potentiating their action, which leads to an increase in insulin response and a decrease in glucagon secretion [28]. However, there is a warning from the US Food and Drug Administration, that must be considered when using these drug [29].

Nutrition and diabetes

As has been postulated éarly, DM can be induced by daily variations in diet, lack of exercise, infection, and stress. Therefore, this review will emphasize several foods with potential properties of diet on the prevention and control of the disease.

By scientific consensus, diet in nutrition is the key to preventing or maintaining blood sugar levels in the human body; hence, it is recommended to consume healthy foods from all of the food groups that have proven scientific properties on the prevention and control of this disease.

Consequently, it is imperative to perform more research to recognize which types of food are adequate in their composition to prevent or control diabetes and to design more specific diabetic diets, using potential national sources.

This article discusses several reports of foods with these properties. In this context, several food sources with insulin-secreting, insulin-sensitizing, and insulin-mimetic potential properties have recently been scientifically reported and will be discussed below.

According to report in 2023 of the World Health Organization (WHO) [30], from 2012 data, almost half the population in many industrialized countries now regularly uses some form of traditional and complementary medicine (T and CM) (United States, 42%; Australia, 48%; France, 49%; Canada, 70%). Moreover, considerable use of some form of T and CM exists in many other countries, such as Chile (71%), Colombia (40%), and up to 80% in some African countries. This concept of complementary medicine, among other practices, uses herbal medicine or phytotherapy (which, by definition, is known as the use of plants and herbs to treat or prevent disease).

However, the WHO warns that any T and CM product or therapy should follow strict protocol and be subjected to tests and clinical trials for quality, efficacy, and patient safety. Generally speaking, T and CM products and practices are subjected to the same scrutiny (regulation, safety, and quality control) as pharmaceuticals; 124 WHO Member States have passed laws or regulation for herbal medicines.

IN nature, there are several plants containing these phytonutrients. They are catalogued as medicinal plants and they are used in the T and CM. Silveira Rabelo and Caldeira [31] define the herbal medicine or medicinal plants as those capable of alleviating or curing diseases and they have a traditional use as a remedy in a population or community. The authors pointed out that its use is one of the oldest practices for treatment, cure and prevention of diseases.

Among these medicinal plants can be mentioned

Acacia arabica, *Achyranthes aspera*, *Acosmium panamense*, *Aegle marmelose*, *Allium sativum* (garlic), *Aloe barbadensis* Miller, *Andrographis paniculat*a, *Annona squamosa*, *Argyreia nervos*a, A*rtemisia herba*, *Averrhova bilimbí*, *Azadirachta indica*, *Barleria prionitis*, *Biophytum sensitivum*, *Brassica nigra*, *Bryonia alba*, *Caesalpinia bonducella*, *Cajanus cajan*, *Carum carv*i, *Casearia esculenta*, *Chamaemelum nobile*, *Cichorium intybus*, *Citrulus colocynthis*, *Coriandrum sativum*, *Dorema aucheri*, *Eclipta alba*, *Fraxinus excersior*, *Gynostemma pentaphyllum*, *Helicteres isora*, *Hypoxis hemerocallidea*, *Lepidium sativum*, *Lupinus termis* and *Angustifolius*, *Mangifera indica*, *Myrcia bella*, *Nigella sativa*, *Ocimum sanctum*, *Origanium vulgare*, P*anax ginseng*, *Phyllanthus amarus*, *Prangos ferulacea* (L.) lindl, *Rhus coriaria* (sumac), *Salacia reticulate, Securinegra virosa*, *Stevia rebaudiana* Bertoni, *Ocimum sanctum* and *Vitis vinifera, among others.*

As reported by Frank., *et al*. [32], and Albratty and Halaw [24]. phytochemicals/phytonutrients are natural antioxidants and can act as effective medicines for humans. However, by definition, the phytochemicals are chemical compounds produced by plants, generally to help them thrive or thwart competitors, predators, or pathogens; while phytonutrients a substances found in certain plants which is believed to be beneficial to human health and help prevent various diseases; therefore it will be use the term phytonutrients.

Whatever the definitions are, these compounds could show insulinotropic activity to reduce hyperglycemia, which is the topic of this review.

In this context, Chuengsamarn., *et al*. [33], have demonstrated that a curcumin-treated diabetic patients group showed a better overall function of β-cells, with higher HOMA-β (61.58 vs. 48.72; $P < 0.01$) and lower C-peptide (1.7 vs. 2.17; $P < 0.05$) as compared with the control (not curcumin treatment). The authors used curcumin without oleoresin extracted with ethanol, from Curcuma longa Linn grown in Thailand.

The Balekari and Veeresham [34] review emphasizes the use of phytochemicals and medicinal plant extracts with insulinotropic activity to reduce hyperglycemia. The authors have indicated the role of plants and it phytochemicals as potential insulinotropic agents in diabetes, classifying the plant extracts and its phytochemicals based on their mode of action as insulin secretagogues, insulin mimetics, and both, based on in vitro and in vivo (diabetic rats) assays reported in literature.

Results, shown by Malinska *et al*.,[35], pointed out that a plant-based meal is efficient in ameliorating the postprandial oxidative and dicarbonyl stress compared to a conventional energy- and macronutrient-matched meal, indicating the therapeutic potential of plant-based nutrition in improving the progression of complications in T2D and obese patients.

Oliveira., *et al*. [36] studies suggest that a sugar-free dark chocolate bar sweetened with stevia, erythritol and inulin led to a lower blood glucose compared to the conventional dark chocolate bar in people with diabetes (13 participants consuming 1 bar (34 g) of sugar-free dark chocolate or 1 bar (34 g) of conventional dark chocolate, with glucose levels, measured before and throughout a 120-min postprandial period) in a randomized crossover design. However whilst longer-term effects on glucose control remain to be determined.

In 2024, Yonemoto., *et al*. [37] evaluated the effect of cocoa extract on glucose tolerance in terms of browning. They found that dietary supplementation with cocoa extract improved glucose intolerance in mice fed a high-fat diet, and it increased the expression levels of Ucp1 and browning-associated gene in inguinal white adipose tissue. Furthermore, in primary adipocytes of mice, cocoa extract induced Ucp1 expression through β3-adrenergic receptor stimulation. These results suggest that dietary cocoa extract improves glucose intolerance by inducing browning in white adipose tissue.

Sources of foods with insulin-secreting properties

In the context of insulin-secreting properties, the concentration of blood glucose triggers the mechanism of insulin secretion, because insulin secretion is quite sensitive to changes in blood glucose.

Consequently, glucose stimulates insulin secretion due to increased intracellular ATP levels. The increment of the ATP levels leads to closure of ATP-sensitive K+ channels with consequent membrane depolarization and opening of the Ca2+ channels (voltage-dependents). This membrane opening promotes the influx of extracellular Ca2+, inducing insulin secretion. Even though glucose is the most potent stimulator of insulin secretion, other nutrients are also capable of triggering insulin release or amplifying glucose-stimulated insulin secretions (GSISs) [38,39]. Most of the pytonutrients previously reported could activities that stimulate or potentiate insulin secretion in the pancreatic islets, acting on insulin secretagogues.

Balekari and Veeresham [34] showed secretagogues with their mechanism of action to 38 plants; some of them with the associated bioactive phytonutrient as it is shown table 1.

As reported by Ito-Nagahata *et al*. [40] , resveratrol and its derivatives, particularly the 3(OH) ST, inhibited adipocyte differentiation and enhanced glucose uptake in the myotubes. It results in improvement in glucose tolerance in vivo. Plants containing resveratrol have been used in traditional medicine for a long time. Resveratrol is in some plants, fruits, and derivatives, such as red wine.

In recent times, some studies identified phytosterols as one of the key modulators of glucose metabolism, which could lead through the AMP-activated kinase (AMPK) activation or peroxisome proliferator-activated receptors (PPARs) to transcriptional regulation pathways [41].

Ginseng radix --	*Caesalpinia bonducella*
Scutellariae radix --	*Eugenia jambolana*
Ginseng Radix Rubra --	*22 Lupinus termis and angustifolius (lupanine, 13-α-OH lupanine, and 17-oxo lupanine)*
Ginseng Radix Rubra --	*Gynostemma pentaphyllum (phanoside)*
Ginseng Radix Rubra --	*American ginseng (ginsenoside Re)*
Abutilon indicum --	*Rhizoma Coptidis (berberine)*
Angelica hirsutiflora--	*Stevia rebaudiana Bertoni (rebaudioside A)*
Acorus calamus L. (AC) --	*Genista tinctoria (genistein)*
Wilbrandia ebracteata (isovitexin and swertisin)	*Terminalia bellerica Roxb (gallic acid)*
Bauhinia variegata L. var.	*Nelumbo nucifera (nuciferene)*
Candida Voidt --	*Enicostemma littorale Blume --*
Bauhinia purpurea Linn --	*Urtica dioica --*
Berberis vulgaris Linn --	*Scoparia dulcis --*
Tabernanthe iboga Baill --	*Teucrium polium --*
Citrus medica L. cv Diamante	*Oscimum sanctum --*
Aegle marmelos (L.) Corr. aegelin, lupeol	*Desmodium gangeticum (L.). --*
Myristica fragrans	*Asparagus racemosus --*
Trachyspermum copticum	*Ichnocarpus frutescence (L.)*
Myristica malabárica	*Rehmanniae radix --*

Table 1: Several plants with secretagogues properties, some of them with its phytonutrients associated [34].

According to Kazeen and Davies [42] , several foods could have the potential to modulate insulin segregation. These foods could control insulin secretion or act as secretagogues, due to the presence of different phytonutrient in their composition, as was previously discussed.

Indeed, Rauf., *et al*. and Dias Soares., *et al*. [38,39] previously have postulated that flavonoids from some foods can act on insulin secretagogues because they are capable of triggering insulin release or amplify glucose-stimulated insulin secretions. The authors explain that flavonoids can modulate insulin secretion through alterations in Ca2+ fluxes by L-type Ca2+ channels. They also pointed out that flavonoids can act by other mechanisms, such as intracellular cAMP accumulation, activation by protein-kinase-A, activation of Ca2+/calmodulin-dependent protein kinase, or by the transcription factors or their products (genes). They conclude that flavonol and isoflavones have shown better activities of modulation.

According to researchers [43,44], the triterpenes have several antidiabetic mechanisms. They can inhibit enzymes involved in glucose metabolism, prevent the development of insulin resistance and normalize plasma glucose and insulin levels. The use of triterpenes as advanced glycation end products (AGEs) inhibitors may be a potentially effective strategy to prevent diabetic complications. Many triterpenoid compounds are present in fruits and vegetables, most of them found in the peel of the fruit, especially within the cuticle.

The Iridoid lyonofolin B potentiates glucose-induced insulin secretion and thus can serve as a new insulin secretagogue for the treatment of Diabetes [45]. Iridoids are a large group of cyclopenta[c]pyran monoterpenoids that occur widely in nature, mainly in dicotyledonous plant families like *Apocynaceae*, *Scrophulariaceae*, *Diervillaceae*, *Lamiaceae*, *Loganiaceae*, and *Rubiaceae* [46].

The review of Kazzem., *et al*. [47], attempts to present in a concise form the reports of functional foods with DPP-4 inhibition potentials, in vitro. The authors have reported that, the inhibition of dipeptidyl peptidase-4 (DPP-4), activity increases the level of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, which in turn reduces hyperglycemia by activating insulin secretion and inhibiting glucagon secretion. The authors also pointed out that some studies have reported the in vitro DPP-4 inhibitory potential of functional foods, but there is no repository of information on these reports.

To explain the classical mechanism of action of inhibition of the DPP-4, Andersen., *et al*. [48] explain that DPP-4 is present in ample amounts in the endothelial cells, which are mainly found in blood vessels, and DPP-4 exists in soluble circulating form in the plasma. The authors point out that due to the presence of alanine in the GLP-1 secreted in response to nutrient absorption, it acts as a substrate for DPP-4, which eventually inactivates the GLP-1. Therefore, the DPP-4 inhibitors from functional foods could prevent this inactivation of GLP-1, thereby resulting in increased circulating GLP-1. This could enhance insulin secretion and impede glucagon secretion. This fact could elevate glucose utilization and reduce blood glucose concentration.

The authors resume extract of plants with DPP-4 inhibition in different solvent of extraction, such as; -in methanol extract: Berberis aristate, Lippia graveolens fruits, *Moringa peregrina* leaves, *Origanum majorana* fruit, *Origanum vulgare* fruit, *Rosmarinum officinalis* fruit, *Sargassum polycystum* whole, *Sargassum wightii* whole; -in ethanol extract: *Caulerpa lentillifera* whole and *Psidium guajava* leaves; -in aqueous extract: *Syzygium cumin*i seed and *Amaranthus hypochondricus* seeds its peptides, and other phytonutrients such as cyanidin-3,5-diglucosides from *Aronia melanocarpa* fruits; anthocyanin from *Phaseolus vulgaris* seed, and the procyanidin from *Vitis vinifera* seeds.

Sources with insulin-mimetic properties

Other examples include the preparation of foods for special diets using insulin-mimetic compounds.

The insulin-mimetic trigger insulin signaling, which is characterized by rapid activation of insulin receptor substrate-1, Akt, and glycogen synthase kinase-3 independent of insulin receptor phosphorylation [49,50].

Previously, it was described the glucose uptake by the cells is facilitated by two families of transporters. GLUT family of transporters (~13 members), which mediate energy-independent bidirectional transport of glucose, and the SGLT family (~6 members), which mediate the active Na+ linked transport [51].

Among these various transporters, the GLUT4 is responsible for insulin regulation [51]. Some molecules that in the absence of insulin induce the movement or translocation of glucose transporter 4 (GLUT4) to the plasma membrane from the intracellular storage vesicles, which results in an increased uptake of glucose in muscle and adipose tissue, it is known as insulin-mimetic properties [52]. Search for thsee small molecules that can either induce or mimic the insulin action are of great interest and can be utilized to manage insulin resistance. There are several dietary phytonutrients which can potentially have insulinomimetic action (induce the translocation of GLUT4 in vitro); such as, gallic acid, tannic acid, abscisic acid, caffeic acid, and quercetin [51,53].

Komakula., *et al*. [51] have reported a technique to screen small molecules with anti-diabetic activity, which would significantly contribute towards expediting and certifying the process of drug discovery. Then, the application of insulin-mimetic compounds, i.e., substances that induce GLUT4 translocation in the absence of insulin, represents a promising strategy for the prevention and treatment of type 2 Diabetes Mellitus [53].

Moreover, Balekari and Veeresham, [34] also have shown 7 plants with insulin-mimetic properties with their mechanism of action; some of their with the associated bioactive phytonutrient as is shown in table 2.

Neuhauser., *et al*. [54] identified insulin-mimetic plants using a TIRFM based screen and verified the blood glucose reduction effects of the extracts in ovo. The findings indicate that plants, including common soapwort, lungwort, spearmint, and catechu, have potential as antidiabetic nutraceuticals.

Sources with insulin-sensitizer properties

The reduced response of the body's tissues to the hormone insulin is the most prominent feature common in Diabetes; the insulin sensitizer works mainly by reducing insulin resistance. An insulin-sensitizer is a compound that allows insulin to work more effec-

Campsis grandiflora; oleanolic acid, hederagenin acid, tormentic acid and myrianthic acid
Ginseng; Ginsenoside Rb1
Citrus grandis (L.) Osbeck; rhoifolin , cosmosiin
Lagerstroemia speciosa L. --
Vitis vinifera Procyanidines
Trigonella foenumgraecum L. --
Cornus officinalis --

Table 2: Several plants with mimetic properties, some of them with its phytonutrients associated [34].

tively on cells, decreasing the blood glucose concentration without augmenting in the concentration of insulin. Moreover, evidence shows that insulin sensitizers have not only beneficial effects on glycemic control but also have multiple effects on lipid metabolism and atherosclerotic vascular processes that could prove to be beneficial [55].

Recent studies suggest that insulin-sensitizers change mitochondrial metabolism and metabolic signals that coordinate downstream cell function. As it was postulated [56] the insulin-sensitizer binds directly to a protein complex in the inner membrane of the mitochondria, the small organelles in each cell that carry out oxidative metabolism. This complex in the mitochondria contains proteins that comprise a route through which pyruvate, an intermediate at the crossroads of metabolism, enters the mitochondria.

The effect of the insulin-sensitizer is to modify the entry of pyruvate at this site, and this adjustment affects the metabolism of other nutrients. These modifications, in turn, result in signals that coordinate cell function changes to match the perceived availability of nutrients. These changes include the regulation of the expression of gene networks specific to that cell. Thus, fitting with all available data, over-nutrition predisposes to insulin resistance and favors the progression of the diseases associated with insulin resistance. Insulin sensitizers can counter this metabolic dysfunction [49].

Robertson., *et al*. [57] pointed out that resistant starch might modulate insulin sensitivity, although the precise mechanism of this action is unknown. On the other hand, data reported by Lin., *et al*. [58] have indicated that low Pi (inorganic phosphate) in the diet regulates glucose homeostasis, partly via enhancing insulin sensitivity through upregulating insulin signals and insulin-induced glucose uptake in skeletal muscles.

Oleanolic acid (OA), a natural component of many plant foods and medicinal herbs, is endowed with a wide range of pharmacological properties whose therapeutic potential has only partly exploited. Although it directly modulates enzymes connected to carbohydrate metabolism and insulin signaling, the main OA contributions appear derived from its interaction with critical transduction pathways [59].

Also, the role of vitamin D in restraining adipose tissue inflammation and fibrosis, as well as hepatic insulin resistance and suggests that normalizing 25(OH)D levels could have metabolic benefits in targeted individuals [60,61].

Moreover, the conclusion of Belenchia., *et al*. [62] highlights that the correction of poor vitamin D status through dietary supplementation may be an effective addition to the standard treatment of obesity and its associated insulin resistance. Later, Bhattacharya in 2018 [60] suggests that vitamin D deficiency contributes to further insulin resistance and poorer long-term diabetic control in type 2 diabetes mellitus subjects.

As cited by Katz., *et al*. [63] and Mellor and Naumovski [64] the antioxidant action of the flavanols present in cocoa may ameliorate insulin resistance by reducing oxidative stress, improving endothelial function, and/or altering glucose metabolism effects and, in turn, reduce risk for diabetes. Many polyphenols, including catechin and epicatechin, have been found to alter glucose metabolism in animal and in vitro studies.

It is also informed that catechin has shown inhibition of the alpha-glucosidase activity and inhibition of the absorption of glu-

cose from the intestine, and the effects of cocoa on endothelial function, which also point to a possible effect on insulin sensitivity. They also have explained that cocoa consumption may stimulate changes in redox-sensitive signaling pathways involved in gene expression and the immune response. The evidence from these studies suggests that cocoa may be useful, in ameliorating insulin resistance in metabolic syndrome and slowing the progression to type 2 diabetes.

The objective of the Ferreira Martins., *et al*. [65] studies was to test the chemoprotective effect of concentrations of a cocoa phenolic extract and its main monomeric flavanol epicatechin on cultured human endothelial cells submitted to an oxidative challenge Its results demonstrate for the first time that a polyphenolic extract from cocoa and its main flavonoid protect human endothelial cells against an oxidative insult by modulating oxygen radical generation and antioxidant enzyme and non-enzyme defences.

Patyra., *et al*. [66] pointed out that the insulinotropic effects of three pharmacopeial angelica roots were found, the metabolite profiles and pharmacological activities of the roots were correlated, and key structures responsible for the modulation of pancreatic β-cell function were identified. These findings may have implications for the traditional use of angelica roots in treating diabetes. Active plant metabolites may also become lead structures in the search for new antidiabetic treatments.

Another ingredient to design a special diet for Diabetes could be the bone extract. Pérez., *et al*. [67] show the extract bone composition and its relationship with the improvement of diabetes suggesting that using a diet of bone extract could be a solution for controlling or preventing this illness. These authors review highlighted generalities on the Diabetes mellitus and some gaps in current T2DM nutritional strategies; emphasizing the position of the intake of bone extract or its componentes as potential diet for prevent or control of Diabetes type II.

Conclusions

Because the correlation between diet and diabetes management is well established, Diabetic patients must receive medical nutrition therapy provided by a registered dietitian to guide them in selecting foods to meet their individual nutritional needs, emphasizing those with insulinotropic phytonutrients. Nature provides several sources of foods that can be useful for the implementation of these diets that must be certified institutionally trought scientific confirmation. The use of food that could be useful for control or prevention of Diabetes, from sources with insulinotropic properties reported in the literature, i.e., substances with the ability to modulate and stimulate insulin secretion in the body, represents a promising strategy for the prevention and treatment of type 2 Diabetes Mellitus.

Despite the numerous studies reported in this review of foods with insulinotropic properties of the different food groups, there is a lack of interest and lack research on the studies of these sources with clinical trials; therefore, researchers in the area must take it under control, because it topic represent an item of food and state security.

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