Exploring the Potential of Plant-Derived Bioactive Peptides for Managing Diabetes

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Received: 10 June 2023 Revised: 30 November 2023 Accepted: 29 December 2023
Published: 30 December 2023

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https://doi.org/10.5281/zenodo.11470652

Abstract

Diabetes is characterized with symptoms of prolonged hyperglycemia, glucose intolerance, disturbance in catabolism and anabolism of carbohydrate, lipids, and proteins in a diabetic individual. The metabolic disturbance is due to lack of insulin production and impaired insulin receptor functioning or both. Many drugs such as biguanides, sulphonylurea etc. are routinely used in treating diabetes however, continuous intake of these drugs leads to certain side effects. Compared to synthetic drugs, nature-based remedies can be a counter to treat the diabetic condition. The food-derived bioactive peptides serve as an alternative to pharmacological treatments in the control of diabetes. Bioactive peptides show significant potential for use in health management strategies, particularly as components of drugs and functional foods for diabetes treatment. Many anti-diabetic bioactive peptides have been isolated and validated. The present review integrates the existing information on the plant derived bioactive peptides with a particular focus on anti-diabetic activity.

Keywords

Anti-diabetic, Bioactive peptides, Diabetes, α-amylase inhibitory activity, α glucosidase inhibitory activity.

Introduction

Diabetes is a chronic illness characterized by elevated levels of blood glucose, accompanied by disturbed metabolism of fats and proteins[1]. It is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both[2]. Diabetes is reported to be one of the most common metabolic disorders that is increasing at an alarming rate all over the world. The World Health Organization (WHO) depicts diabetes mellitus as non-communicable diseases accounting for increased number of deaths. Globally there is tremendous increase in number of diabetic individual's death. Around 31.1% increased deaths are reported between 2006 and 2016. There are more than 415 million adults suffering from diabetes, and in future the number is expected to increase to 642 million by 2040[3]. Thus, increase in diabetic cases leads to mortality, reduced life expectancy and increased disability adjusted life years. In India, the prevalence of diabetes is expected to increase from 31.7 million in 2000 to 79.4 million in 2030[4]. Additionally, a study from Indian states, reveals around 62 million individuals were reported to be suffering from diabetes mellitus[5]. Thus, looking at the increased number of incidences of diabetic population at global and national front, plant derived bioactive peptides can be a useful strategy in managing diabetes. The primary contributing factors of diabetes in individuals include exposure to unhealthy diet and physical inactivity. Other factors include aging, genetic factors, obesity, insufficient energy consumption, alcohol drinking and smoking[6,7].

Diabetes mellitus is classified into two major types - Type 1 Insulin Dependent Diabetes Mellitus (IDDM) and Type 2 Non-Insulin Dependent Diabetes Mellitus (NIDDM). Type 1 Diabetes mellitus is an autoimmune disorder characterized by the destruction of pancreatic β cells and it leads to absolute insulin deficiency[8,9]. Type 2 Diabetes mellitus is characterized by hyperglycemia, insulin resistance, and relative insulin deficiency[10]. Additionally, Diabetes is responsible for certain risk factors such as retinopathy, nephropathy, neuropathy, microangiopathy, and increased risk of cardiovascular disease[12,2]. Furthermore, based on the causes and clinical features, diabetes mellitus is categorized into various types as mentioned in Table-1.

Sr. No	Name of Disease	Clinical manifestation
1.	Type 1 Diabetes mellitus	β- cell destruction Autoimmune condition
2.	Type 2 Diabetes mellitus	Insulin resistance Insulin deficiency
3.	Gestational Diabetes mellitus	Glucose intolerance during pregnancy
4.	Other specific types of diabetes mellitus	Genetic defects of β-cell function Genetic defects in insulin action Diseases of the exocrine pancreas Endocrinopathies Drug-induced or chemical induced Infections (congenital rubella, cytomegalovirus and others) Immune mediated diabetes Genetic mutations

[11]

Table 1: Types of Diabetes and clinical manifestation

Diagnosis of diabetes

Diabetes is diagnosed and managed by checking glucose level in a blood through different tests. The oral glucose tolerance test, the random glucose test, and the fasting glucose test are the three tests that can determine blood glucose levels.

Glucose concentration for diabetes individual

1. Fasting blood glucose concentration above 7·0 mmol/L (126 mg/dL)
2. A random blood glucose concentration above 11·1 mmol/L (200 mg/dL)
3. Glycated hemoglobin and its concentration above 48 mmol/mol[11,13].

Enzymes related to glucose homeostasis

Various organs like salivary glands, the pancreas and the small intestine are involved in glucose homeostasis. Their secreted enzymes and proteins allow the digestion of carbohydrates and influence the blood glucose level. Fig. 1 shows organs involved in glucose homeostasis. α-amylase, α-glucosidase, glucagon-like peptide-1 (GLP-1) and dipeptidyl peptidase-IV (DPP-IV) are some of the enzymes in modulating blood glucose levels[7]. Initially, α-amylase is secreted from salivary glands and the pancreas, that act as a catalyst in the reaction which involves the hydrolysis of the α-1,4 glycosidic linkages of the starch, amylopectin, amylose, glycogen, and numerous maltodextrins and is responsible for starch digestion[14]. Another key enzyme, α-glucosidase, is secreted by the small intestine which plays a significant role by catalyzing the final step in the digestive process of carbohydrates. It is involved in breakdown of starch and disaccharides into glucose to increase blood glucose level[15]. The use of α-amylase and α-glucosidase inhibitors are a potential first-line therapy or in conjunction with other anti-hyperglycemic medications by the American Diabetes Association and the European Association for the Study of Diabetes[7].

Besides, glucagon like peptide-1 (GLP-1) is one of the incretin hormones secreted from the intestine enteroendocrine L cells. GLP-1 stimulates insulin and inhibits glucagon release. Therefore, regulating gastric motility and slowing gastric emptying. These actions of GLP-1 quickly reduce fluctuation of postprandial blood glucose level[16]. DPP-IV is expressed in several organs and found in blood circulation. DPP-IV cleaves oligopeptides after the second amino acid from the N-terminal end as one of its principal functions acting preferentially, if the second amino acid is alanine (as in GLP-1) or proline. This leads to GLP-1 degradation. Given the significant effect of GLP-1, receptor agonists of GLP-1 and DPP-IV inhibitors have been developed as tools to decrease blood glucose level [17].

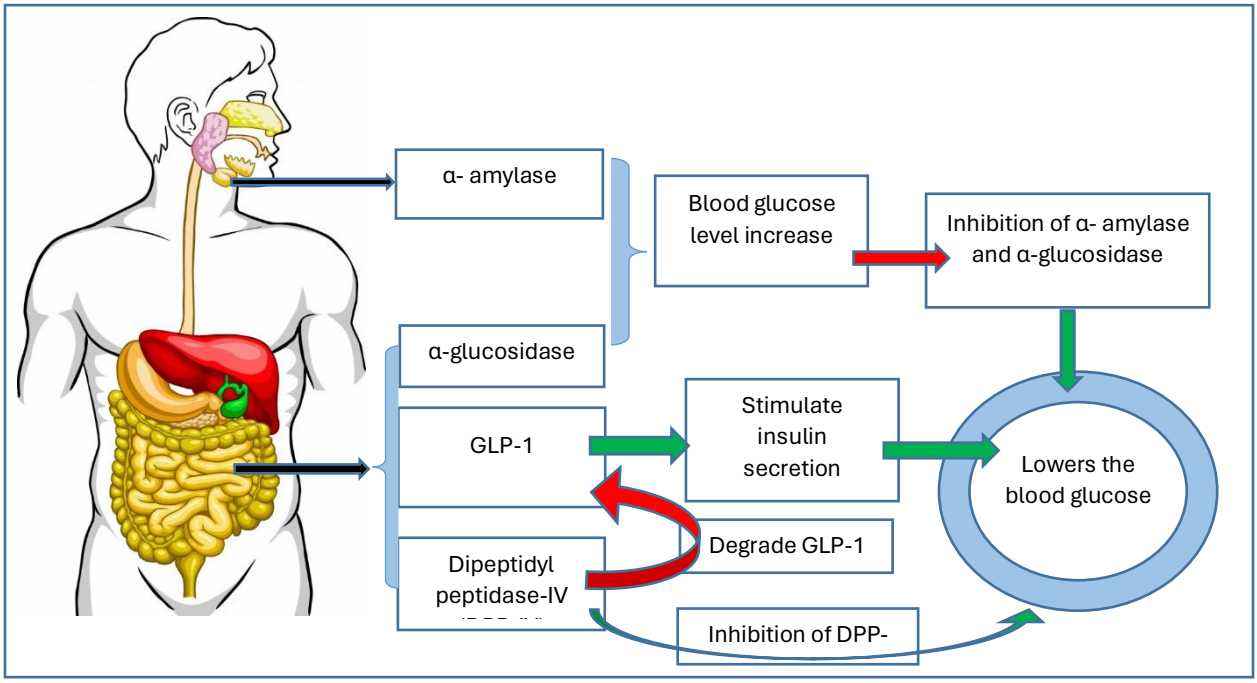

Figure 1: Enzymatic Players in Glucose Homeostasis

Hypoglycemic agents for treatment

To treat type 2 diabetes several oral hypoglycemic agents are routinely used. Some of the treatment includes use of insulin sensitizers like Biguanides (Metformin), Thiazolidinediones (Glitazones), α-Glucosidase inhibitors (Acarbose, Miglitol, Voglibose), Insulin secretagogues Sulphonylurea (Glipizide and Glimepride), Dipeptidyl peptidase-IV inhibitors (Glinides), Sodium glucose cotransporter 2 (SGLT2) inhibitors, the Glucose-dependent insulinotropic polypeptides (GLP-1) analogues and Mimetics (exanetide)[18]. However, consumption of these drugs for longer duration can exhibit certain side effects such as hypoglycemia, weight gain, tiredness, diarrhea, and risk of anemia. Also, use of such therapies includes high cost due to their periodic usage[19]. Thus, the search for new therapeutic agents and the development of new strategies for control, prevention and treatment is under major consideration for treating diabetes. A remedy dependent on natural source could be one of the alternatives ways for managing the T2DM.

Hypoglycemic molecules from Plant and animal sources are searched for their potential activity to replace the synthetic drugs. One such example of peptide drug Exendin-4 was isolated from the *Heloderma suspectum* (Gila monster) and furthermore its synthetic version is available in market

as exenatide in treatment of diabetes[20]. Besides, Liraglutide and Semaglutide peptides are reported to be structurally very close to GLP-1 with improved half-life and resistant to DPP-IV mediated degradation activity[21]. Therefore, the demand for natural source-based drugs in treatment of disease condition is steadily increasing.

Using recombinant DNA technology, many peptides are synthetized. The peptides are efficient in their activity however they are also comparatively expensive like the synthetic drugs. The interest in health-enhancing products derived from natural sources and pharmaceutical formulations incorporating bioactive peptides is experiencing a significant surge[22]. The exploration undertaken by researchers in the realm of bioactive peptides is generating significant interest as it paves the way for discovering cost-effective leads from plants to improve the care of diabetic patients[23].

Bioactive Peptides

Bioactive peptides are one of the organic substances formed by amino acids joined by covalent bonds. They are rich with hydrophobic amino acids and have multifunctional characteristics which play important roles in the metabolic functions of living organisms and positive impact on human health[24,25]. Bioactive peptides are defined as "peptide sequences within a protein that exert a beneficial effect on body functions and/or positively impact human health, beyond its known nutritional value"[26]. Most bioactive peptides have between 2 and 20 amino acid residues in their length. In some cases, much longer peptides have also been reported[28]. Bioactive peptides are usually encrypted within the primary protein structure. Within the parent protein sequence, they are present as their inactive form, but once they are released from their parental protein, they may act as physiological modulators with hormone-like activity, so they have wide range of therapeutic applications[25,29]. Bioactive peptides are released during enzymatic proteolysis of proteins and also released during food processing like cooking, fermentation, ripening. Enzymatic proteolysis occurs during gastrointestinal digestion naturally and in vitro hydrolysis carried out using proteolytic enzymes[10,30]. Different open access databases report the bioactive peptides that are being discovered including data about their main chemical and structural characteristics. Most of the bioactive peptides are reported in BIOPEP. More than 1500 different bioactive peptides have been reported in a database of BIOPEP[24]. Other bioactive databases are PEPBANK, ERP-Moscow, or Brainpeps[27].

Bioactive peptides contribute to human well-being by mitigating the risk of chronic illnesses or enhancing the body's innate immune defense[25]. Furthermore, bioactive peptides derived from food sources are recognized for their diverse therapeutic properties, including but not limited to antihypertensive, antioxidant, anti-diabetic, immunomodulatory, anticancer, antimicrobial, and lipid-lowering activities[31].

Plant derived bioactive peptides

Bioactive peptides promote human health by reducing the risk of chronic diseases or boosting natural immune protection[25]. Bioactive peptides can be obtained from plants, animal and marine protein sources[32,33]. Animal based bioactive peptides are reported from milk, eggs, meat, and fish (tuna cooking juice, salmon skin proteins etc)[18,34]. Plant derived bioactive peptides are already reported from *Phaseolus vulgaris* (black bean), *Amaranthus hypochondriacus L., Cannabis sativa L.* (Hemp), *Oryza sativa L.* (Rice bran), *Glycine max L.*(Soy) and *Lupinus albus L.* **(**Lupin), *Avena sativa L.* (Oat), *Momordica charantia L., Cuminum cyminum L.* (Cumin), *Chenopodium quinoa* Wild and *Morus alba L.* (Mulberry) [18,30]. Numerous peptides derived from various plants have been documented for their potential in treating diabetes, targeting different known pathways such as α-amylase inhibitors, α-glucosidase inhibitors, dipeptidyl peptidase-IV inhibitors, inhibitors of the glucose transporter system, and insulin mimetics. The present work elucidates the mechanistic aspect of some of the key enzymes. Amylase, also known as α-1,4-glucan-4-glucanohydrolase, plays a crucial role in accelerating the hydrolysis of the (α-1,4) glycosidic linkage found in carbohydrates and starch present in the diet. This enzyme facilitates the absorption of non-absorbable polysaccharides by converting them into absorbable monosaccharides[35]. Inhibitors of amylase function to reduce the hydrolysis of the (α-1,4) glycosidic linkage, thereby slowing down carbohydrate digestion. Consequently, this delay in digestion leads to a postponed absorption of glucose and a reduction in postprandial blood glucose levels[36]. A-glucosidase inhibitors function by competitively inhibiting the small intestinal enzyme α-glucosidase. This enzyme is responsible for converting nonabsorbable polysaccharides into absorbable monosaccharides. By doing so, these inhibitors collectively delay and reduce the elevation of postprandial plasma glucose levels. Inhibiting this enzyme has several beneficial effects, including reducing glucose toxicity (improving insulin sensitivity), relieving stress on beta cells (lowering post-meal hyperglycemia), and increasing the production of glucagon-like peptide-1 (GLP-1), thereby promoting insulin

secretion[37, 38]. DPP-IV is an enzyme responsible for rapidly cleaving the GLP-1 hormone shortly after its secretion, rendering it biologically inactive. Consequently, inhibiting DPP-IV presents the potential to counteract hyperglycemia. DPP-IV inhibitors impede the swift degradation of GLP-1, elevating the postprandial concentration of active GLP-1. This elevation subsequently diminishes liver glucagon production and triggers the beta cells of the pancreas to increase insulin secretion[17]. Moreover Table 2 emphasizes the plant derived sources, bioactive peptides sequences and their relevant anti-diabetic activity.

Plant Source	**Sequences**	**Activity**	**References**
Phaseolus vulgaris L. (Kidney bean)	INEGSLLLPH, FVVAEQAGNEEGFE	α-amylase inhibitory activity	39
Amaranthus hypochondriacus L.	PPPP, GP, PP, MP, VA, MA, KA, LA, FA, AP, FP PA, LP, VP, LL, VV, HA, IPA, IPI	DPP-IV inhibitory activity	40
Terminalia pallida Brandis	Fruit ethanolic extract	Hypoglycemic activity	41
Cannabis sativa L. (Hemp)	LR and PLMLP FY, SPVI, TGLGR, FR, INPLL, IAF	α-glucosidase inhibitory activity	42, 43
Vigna Unguiculata (Cowpea)	Less than 10kDa	DPP-IV inhibitory activity	44
Phaseolus vulgaris L. (Pinto beans)	PPHMLP, PPMHLP, PLPWGAGF, GNAACCGLPLLP, CGLPLLP, PPHMGGP, PLPPHALL, PAPFPSPHTP	α-amylase inhibitory activity	45

Cumin seeds	FFRSKLLSDGAAAAKGALLPQYW, RCMAFLLSDGAAAAQQLLPQYW, DPAQPNYPWTAVLVFRH	α-amylase inhibitory activity	46
Juglans mandshurica (Walnut)	3–10 kDa	α-glucosidase inhibitory activity	47
Phaseolus vulgaris L. (Common bean)	LLSL, QQEG, and NEGEAH TSDNPIFSDHQ, TSDNPIFSDHQK, LVNPDPKEDLRI, NPDPKEDLRIIQ, ELSKDDVFVIPAA	α-glucosidase and α-amylase inhibitory activity Black bean hydrolysate exhibits an acute glucose lowering effect after an oral glucose tolerance test.	48, 49
Ocimum basilicum (Basil seeds)	ACGNLPRMC, ACNLPRMC, and AGCGCEAMFAGA	α-amylase inhibitory activity	50
Chenopodium quinoa Wild. (Quinoa)	IQAEGGLT, DKDYPK, GEHGSDGNV	α-glucosidase inhibitory α -amylase and DPP- IV inhibitory activity	51
Glycine max (Soybean)	YPFVV, NALKPDNRIESEGG, SSPDIYNPQAGSVT, NALKPDNRIESEGG,	DPP-IV inhibitory activity	52, 53

	RQNIGQNSSPDIYNPQAG, NALKPDNRIESEGG, VVAEQAGEQGFE, HKNKNPF		
Cicer arietinum (Chickpea)	FEI, FEL, FIE, FKN, FGKG, MEE	α-glucosidase inhibitory α -amylase and DPP-IV inhibitory activity	54
Brassica napus (Rapeseed)	ELHQEEP	DPP-IV inhibitory effect in Caco-2 cell model	55

Table: 2 Plant derived Bioactive peptides exhibiting hypoglycemic activity

Studies on Wheat albumin reported inhibit α-amylase enzyme and reduced the peak of postprandial blood glucose levels in a dose-dependent manner. After receiving doses of 0.25 g, 0.5 g, and 1.0 g of wheat albumin, respectively, it demonstrated a reduction in postprandial blood glucose of 31%, 47%, and 50%. In a long-term administration study, 0.5 g of wheat albumin had no effect on fasting blood glucose levels, but it did lower glycated hemoglobin A1c levels, a measure of a diabetic's ability to control their metabolism[56]. Furthermore, studies also reported α-glucosidase inhibitory activity from plant derived peptides. *Ocimum tenuriflorum* seeds, hemp seed protein, walnut, soybean, rice, and dark tea have been indicated as the main contributors to inhibit α-glucosidase[57]. Low molecular weight peptides are known to exhibit glucosidase inhibitory activity compared to high molecular weight peptides. Studies on germinated soybeans with a molecular weight of 5 kDa demonstrated the strongest inhibitory compared to fractions exhibiting either 5-10 kDa and >10 kDa. The bioactive peptide from *Vigna angularis Wild.* (Adzuki bean) proteins exhibited α-glucosidase inhibitory activity and were also potent in in vivo condition[58]. Additionally, Oat seed proteins hydrolysate obtained by alcalase enzymatic digestion was reported to inhibit α-glucosidase enzyme. Hypoglycemic impact was further confirmed by in vivo studies on STZ-induced diabetic mice[59]. Using bromelain or papain for hydrolysis of plant protein was also

reported to exhibit DPP-IV inhibitory activity[60]. Studies on Male Sprague Dawley rats on consuming papain-hydrolyzed rice endosperm and bran protein orally and intravenously showed reduced glycemia during an intraperitoneal glucose tolerance test and decreased blood DPP-IV activity. Additionally, active peptides stimulated the cell line GLUTag for secretion of incretin GLP-1[61]. More studies on rice bran (*Oryza sativa L.*) protein hydrolysates showed DPP-IV inhibition and have IC50 1.45 ± 0.13 mg/ml[62]. Besides Pea (*Pisum sativum*), potato flour (*Solanum tuberosum*), lupin flour (*Lupinus albus*), chickpea (*Cicer arietinum*), lentil (*Lens culinaris*) and quinoa (*Chenopodium quinoa*) protein hydrolysates show DPP-IV inhibition[63.] Thus, further research on the in vivo activity of the potent bioactive sequences could help to enhance the utility of this plant in routine diet of humans.

Research gaps

Limited studies have been conducted to investigate the anti-diabetic properties of plant-derived bioactive peptides. While some plants have been tested, comprehensive in vivo testing and bioavailability testing for these peptides is lacking.

Conclusion

With increasing concerns regarding health risks, environmental considerations, and manufacturing costs, the food industry has shifted its focus towards plant-based ingredients over animal sources. Type 2 diabetes poses a significant need for effective therapies as currently available synthetic medications exhibit a range of side effects. Plants offer a promising avenue to produce bioactive peptides and functional ingredients which have been shown to possess various therapeutic properties. Notably, plant-derived bioactive peptides exhibit inhibitory effects on key enzymes such as α-glucosidase, α-amylase, and dipeptidyl peptidase-IV (DPP-IV) that play a role in type 2 diabetes. These findings highlight the potential of plant-derived bioactive peptides as a valuable resource for developing novel therapeutic interventions for diabetes management.

Future prospects

The future prospects of exploring plant-derived bioactive peptides for managing diabetes are promising as they possess potential in development of functional foods specifically for diabetic individuals. Incorporation of these peptides to regulate blood sugar levels naturally could benefit diabetes individuals to monitor their blood glucose levels. However, further studies in terms of safety, efficacy, and mode of action of the peptides would help in therapeutics of diabetes. Additionally, the inclusion of the plant derived peptides eventually would reduce the intake of synthetic drugs and thus would help in managing diabetes effectively.

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Glossary

Diabetes mellitus- Diabetes mellitus is a metabolic disease, involving inappropriately elevated blood glucose levels due to insufficient insulin secretion or insulin action.

Hyperglycemia- Hyperglycemia is the technical term for high blood glucose. Hyperglycemia is a condition in which an excessive amount of glucose circulates in the blood plasma. High blood glucose happens when the body has too little insulin or when the body can't use insulin properly.

Retinopathy- Retinopathy is any damage to the retina of the eyes which may cause vision impairment. Retinopathy often refers to retinal vascular disease or damage to the retina caused by abnormal blood flow.

Glucose homeostasis- Hormonal regulation for blood glucose.

Oral hypoglycemic agents- Oral hypoglycemic agents are a group of drugs used to help reduce the amount of sugar present in the blood. They are not insulin, but they stimulate the pancreas to produce insulin.

Insulin sensitizers- drugs that help return the blood sugar to the normal range without the risk of low blood sugars.

Insulin secretagogues- Insulin secretagogues lower blood glucose by stimulating the secretion of insulin in the body, thereby increasing insulin levels in the blood.

α-amylase inhibitor- α-Amylase inhibitors can act as carbohydrate blockers, limiting the digestibility and absorption of carbohydrate in the gastrointestinal diet.

α-glucosidase inhibitor- A-glucosidase inhibitors inhibit the absorption of carbohydrates from the small intestine. They competitively inhibit enzymes that convert complex non-absorbable carbohydrates into simple absorbable carbohydrates. T

Dipeptidyl peptidase-IV (DPP-IV) inhibitor- DPP-IV inhibitors work by blocking the action of DPP- IV, an enzyme which destroys the hormone incretin.

Dipeptidyl peptidase-IV (DPP-IV)- DPP-IV is a ubiquitous enzyme that acts on incretin hormones, mainly GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide), which maintain glucose homeostasis by increasing insulin secretion and decreasing glucagon secretion.

Natural therapeutic agents- Natural therapeutic agents are prepared from compounds found occurring in nature, which contain active components in extract form created from sources, including plants, microbes, minerals and animals.

Anti-diabetic agents- used to treat or helping to prevent diabetes.

Bioactive peptides- Bioactive peptides are a group of biological molecules that are normally buried in the structure of parent proteins and become active after the cleavage of the proteins.