Plant-Derived Bioactive Peptides: A Treatment to Cure Diabetes

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Abstract

Recent advances in analytical techniques have opened new opportunities for plant-based drug discovery in the field of peptide and proteins. Enzymatic hydrolysis of plant parent proteins forms bioactive peptides which are explored in the treatment of various diseases. In this review, we will discuss the identified plant-based bioactive proteins and peptides and the in vitro, in vivo results for the treatment of diabetes. Extraction, isolation, characterization and commercial utilization of plant proteins is a challenge for the pharmaceutical industry as plants contain several interfering secondary metabolites. The market of peptide drugs for the treatment of diabetes is growing at a fast rate. Plant-based bioactive peptides might open up new opportunities to discover economic lead for the management of various diseases.

Graphic Abstract
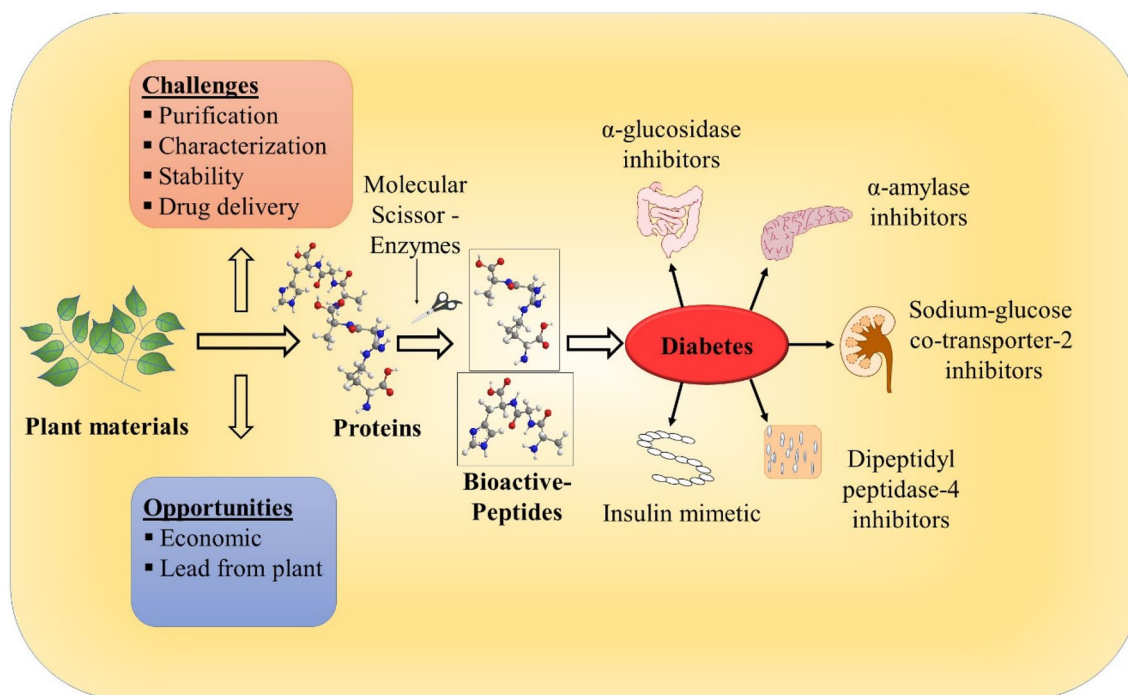
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Introduction

Biomolecules play an important role in any ligand-target interaction and their recognition in any biological system starts the cascade of signalling steps, which is an important part of the normal body function. Nucleic acids, carbohydrates, and lipids are the important ligands that bind and cause conformational changes in targets (receptors) but the messengers that release after binding and conformation changes are peptides. Any defect in these signal transduction processes cause diseases (Otvos and Wade 2014; Gautam 1999). Proteins, under the influence of proteolytic enzymes get fragmented at particular catalytic sites to form bioactive peptides. Bioactive peptides are made up of 2–20 amino acids and lack protein–protein interaction because of their small size. They have properties like tissue affinity, specificity, and efficiency (Moller et al. 2008). The structure and the overall charge and hydrophobicity/hydrophilicity of the any bioactive peptide depends on the nature of amino acids, their sequences in the peptide backbone along with the N and C terminals. The relation between structure and biological activity of the bioactive peptides are yet not confirmed but the structure is an important arbitrator for their activity (Li and Yu 2015). Bioactive and nutraceutical peptides have a positive effect in the regulation of the health of an individual (Kitts and Weiler 2003). They boost the quality of human health by preventing various ailments and by improving medical conditions related to lifestyle, metabolism, and immunity (Vitetta et al. 2005).

Peptide and protein drugs are available from the different sources for therapeutic uses, but as with many drugs, they have several advantages and disadvantages of their own. Peptide drugs are effective and specific to their biological target but devoided of some of the essential qualities of a drug to withstand in the current market of therapeutics. Proteins have a large chemical structure which makes their synthesis complex, tedious and expensive, the further low oral bioavailability of proteins limit their oral delivery hence they are administered through parenteral route (Uhlig et al. 2014). The worldwide peptide therapeutics market size valued at USD 22,071.5 million in 2017 and assumes to grow at CAGR of 9.1% over the period 2018 to 2026. (2016). Insulin is the first therapeutic peptide which has been used widely and shares good peptide market. It was first isolated by Frederick Banting and Charles Best from pancreatic islet extracts, further, J.B. Collip developed the method for extraction and purification of insulin from other animal sources (Quianzon and Cheikh 2012). Eli Lilly began producing insulin from the animal pancreas, later on, biosynthetic insulin was introduced in 1983 with the name Humulin. Novo Nordisk,

Sanofi, and Eli Lilly together share 88.7 percent of the global insulin market. Lantus (basal insulin) is a product of Sanofi accounts for approximately 22.29% of the total sales of top 10 antidiabetic drug brands, in 2016 sale of Lantus was USD 6.057 billion (Dezzani 2017). Small molecules and peptide-based drug candidate belongs to the category of New Chemical Entities (NCEs) according to the Food and Drug Administration, on the other hand, proteins used for the treatment of various diseases are classified under New Biological Entities (NBEs).

In recent years, therapeutic peptides are approved for the mitigation of various ailments mainly tumors, immunological disorders, blood disorders and metabolic disorders such as diabetes, obesity (Fig. 1) (Loganathan 2016). The peptide drug, liraglutide (Victoza) is a glucagon-like peptide-1 receptor (GLP-1R) agonist and used for the treatment of T2DM has gained popularity as a top-selling drugs in recent past, which is marketed by Novo Nordisk (Lund et al. 2014). Glatiramer acetate (Copaxone), developed by Teva is an immunomodulator and used to treat multiple sclerosis (Duda et al. 2000). Leuprolide (Lupron), developed by Abbott is useful for the treatment of cancer and estrogen-dependent conditions that respond to hormone therapy (Brito et al. 2004). Goserelin (Zoladex) from Astra Zeneca is a gonadotropin-releasing hormone agonist (GnRH agonist) that suppresses the release of different sex hormones and is useful in the treatment of breast and prostate cancer (Magon 2011). Other innovator companies include Amgen, Eli Lilly, Roche, and Pfizer have peptide and protein-based drugs in different developmental stages will reach the market soon for the treatment of various complicated diseases (Loganathan 2016).

Till date, plant secondary metabolites, mainly small molecules are the established source of new drugs to treat various diseases (Verpoorte 1998), however, advancement in analytical technique, sophisticated purification methodology and in vitro assay system pointed out the researchers
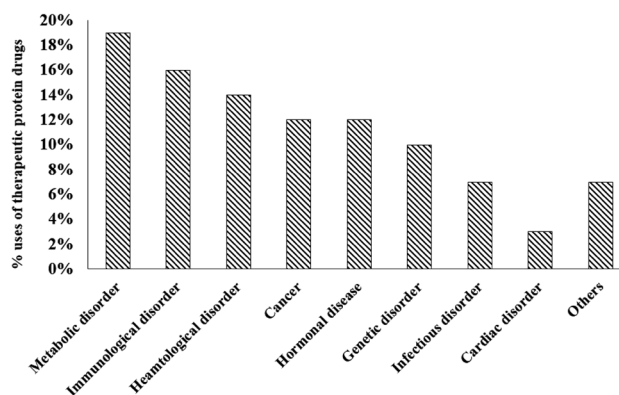
Fig. 1 Uses of therapeutic peptides and proteins in various disease conditions (Loganathan 2016)

to look beyond the small molecules. Identification of plant primary metabolites including proteins and peptides for the management of diseases have opened up a new horizon in the development of plant-based peptides as a drug candidate (Otvos 2008). This review summarizes various plant-based peptides reported for the treatment of diabetes, challenges with the development of peptide-based drugs and the future prospect of peptides as a drug.

Diabetes Mellitus

Diabetes is a metabolic disorder and can hit anyone at different stages of life. Though it is considered as one of the top health killers, its treatment is a huge challenge. Diabetes can be characterized with symptoms of prolonged hyperglycemia, glucose intolerance, disturbance in the regulatory systems for storage and utilization of metabolic energy, including catabolism and anabolism of carbohydrate, lipids, and proteins in a diabetic individual due to lack of insulin production and impaired insulin receptor functioning or both (Piero 2015; Votey and Peters 2005). Based on the causes and clinical survey, diabetes mellitus is categorized into four types as mentioned in Table 1 (Deepthi et al. 2017).

Ordinarily, the people below 18 age suffer from the type 1 diabetes, whereas type 2 diabetes mainly occurs in adult and old age group. According to the World Health Organisation, approximately 10% of all diabetes cases are type 1, and the remaining 90% cases of diabetes worldwide are of type 2 (Baynes 2015). Diabetes is ruining the life of peoples worldwide. Population suffering from diabetes is increasing and the imminence is expected to rise even more because of the current lifestyle issues. Till the year 2017, 422 million people were affected by type 2 diabetes and the number is expected to increase up to 642 million people worldwide by 2040 (Fig. 2). The data indicates that approximately 50% of diabetic patients will increase in the next two decades. The threat is every 6 s a person dies with diabetes (Roglic 2016).

From the statistics, it is clear that the population suffering from type 2 diabetes is increasing and it requires more promising therapies. Still, no promising drug is available which
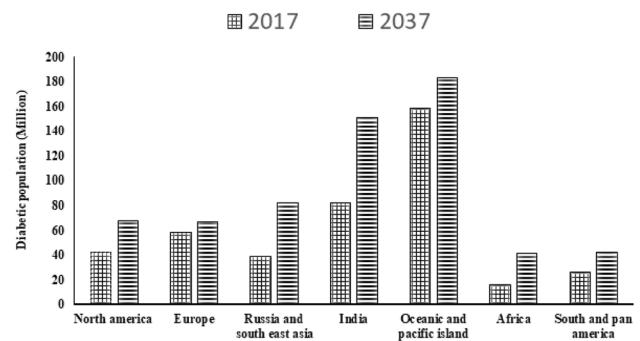

Fig. 2 Epidemiology of diabetes country wise (2017a)

has the ability to completely cure type 2 diabetes. Generally, to treat type 2 diabetes, oral hypoglycemic agents are used. The first line treatment is metformin, which is assisted with other hypoglycemic agents from different categories like thiazolidinediones, alpha-glucosidase inhibitors, sulphonylurea, dipeptidyl peptidase-IV (DPP-IV) inhibitors, sodium glucose cotransporter 2 (SGLT 2) inhibitors. The risk associated with these therapies include hypoglycemia, weight gain, tiredness, diarrhea, and anemia risk, etc. Over the period of time, these side effects lead to further complications for a visceral system like cardiovascular system and central nervous system (Nathan et al. 2009).

Peptide drugs used for the treatment of diabetes are derived from different sources, like Exendin-4 was initially isolated from the *Heloderma suspectum* (Gila monster) and its synthetic version had come to the market in the form of exenatide (Aramadhaka et al. 2013). Liraglutide and Semaglutide are structurally very close to GLP-1 with improved half-life and resistant to DPP-IV mediated degradation (Edmonds and Price 2013). Nowadays, these peptides are being produced in large scale by using recombinant DNA technology. The peptides which were obtained via synthesis or by using the recombinant technology are comparatively expensive than small molecules and are not affordable to most of the patients. The interest in health-promoting products from the natural origin and pharmaceutical formulations involving bioactive peptides are remarkably increasing

Table 1 Types of diabetes and their characteristics

Types	Characteristics
Type 1 diabetes	Destruction of the beta cell, reduced insulin secretion
Type 2 diabetes	Normal Insulin secretion Glucose storing cells developing insulin resistance
Gestational diabetes	Dysfunction of an endocrine gland present in the pancreas Endogenous disease such as rubella and Cytomegalovirus Due to drugs and chemicals exposure
Other specific diabetes	Does not last long and develops at the time of pregnancy mostly during the end of the first trimester Post delivery, the blood sugar comes to normal

(Henninot et al. 2018). Numerous scientific reports have been published on bioactive peptides obtained from animal proteins. Expedition by researchers in the field of bioactive peptides is of great interest as it opens the way to find economic lead from plants for the better care of diabetic patients (Daliri et al. 2017).

Plant-Derived Bioactive Peptides

Plentiful bioactive peptides have been reported from the animal and plant sources. Most of the peptides that had bioactivity are being derived from animal products such as milk, eggs, meat, and fish. Plant peptides are still under exploration and few bioactive peptides are reported from soy, wheat, etc (Hartmann and Meisel 2007). In animals, proteins are associated with high-fat content and lead to diseases, including high blood pressure and heart diseases if consumed in the large amount. On the other hand, plant proteins neither have associated fat nor have any side effects (Nehete et al. 2013). Previously, plant hormones were considered the only player through which cells communicate, but from the last decade as research was driven towards an understanding of plants signaling, secreted peptides, small RNAs and transcription factors emerging as a new and well-defined player in the cell to the cell communication network (Lindsey et al. 2002; Van Norman et al. 2011; Murphy et al. 2012). However, it is now clearly defined that signaling peptides of plant and animal origin are biosynthesized through the pathway that is evidently similar, although some aspects of the biosynthesis are still not identified. Peptides secreted by plants have well recognized role in preliminary processes of development like the growth of meristem, organ shedding, cell elongation, cell multiplication, cell differentiation, geotropism and protection from the invader (Ghorbani 2014). The ubiquitous presences of proteins, peptides as mediator components convey to the proposals that these messenger peptides may have emerged evolutionary in microbes and were further integrated into the complicated mediator systems of complex organisms during evolution (Roth et al. 1982). Existence of hormone-like peptides in plants including insulin-like peptide in *Spinacia oleracea* L. (Spinach) and *Lemna gibba* G-3, prolactin-like inhibitor in alfalfa, a substance with luteinizing hormone-releasing activity from leaves of *Avena sativa* L. (Oat) and somatostatin-like material in spinach support this assumption, it is speculated that the signaling peptides in plants existed from about 1 billion years ago (Collier et al. 1987; Fukushima et al. 1976; Leroith et al. 1985; Morley et al. 1980). Plant proteins containing essential amino acids are important in the food chain to fulfill human physiological needs. The proteins from plants are derived from leaves, seeds, and fruits, out of which seeds are considered as an economical source of proteins. As compared to vegetables and fruits, seeds (legumes and cereals) contain a higher amount of protein (Creighton 1993). Proteins in a mature seed represent 18–20% in *Pisum sativum* L. (Pea), *Vicia faba* L. (Faba) bean and till 35–45% in *Lupinus albus* L. (Lupin) and *Glycine max* L. (Soybean) (Gueguen and Cerletti 1994).

Reported Antidiabetic Bioactive Peptides from Plants

Many peptides are reported from different plants for the treatment of diabetes as shown in Tables 2 and 3 through various known targets such as

(a) Alpha-glucosidase inhibitors
(b) Alpha-amylase inhibitors
(c) Dipeptidyl peptidase-IV inhibitors
(d) Inhibitors of the glucose transporter system
(e) Insulin mimetics

Alpha-glucosidase Inhibitor

Alpha-glucosidase inhibitors competitively inhibit small intestinal enzyme alpha-glucosidase, which converts non-absorbable polysaccharides into absorbable monosaccharide, these effects together postpone and minimize the rise in postprandial plasma glucose level. Inhibitors of this enzyme decrease the glucose toxicity (improves insulin sensitivity), decreases stress on beta cells (decreases post-meal hyperglycemia), increases glucagon like peptide-1 (GLP-1) production hence increases insulin secretion (Scheen 2003; Mooradian and Thurman 1999). In general, normalization of postprandial hyperglycemia is difficult as compared to fasting hyperglycemia, inhibitors act specifically on the postprandial part of 24 h blood glucose curve and causes a reduction in diabetes-associated hyperglycemia which is responsible for macrovascular complication in patients (Mooradian and Thurman 1999; Ceriello et al. 2004). Glycaemic control is achieved with these agents reduces glucotoxicity which increases insulin secretion from the beta cell (Scheen 2003; Salvatore and Giugliano 1996).

All marketed alpha-glucosidase inhibitors are from natural origin, however, none of them belongs to peptide class. Few research groups have reported peptides from plants having alpha-glucosidase inhibitory activity. Peptides obtained from *Cannabis sativa* L. (Hemp) seeds contains hydrophobic amino acids (Pro and Leu), essential amino acids and branched chain amino acids in their structure and have reported to have enzyme inhibitory activity for this target (Ren et al. 2016). Oat seed proteins hydrolysate obtained by protease (alcalase) digestion gives bioactive peptides which inhibits this enzyme. In vivo study also revealed

Table 2 Reported peptides sequences from plants for antidiabetic activity

Sr. no	Plants	Sequences	Target	Study	References
1	*Amaranthus hypochon-driacus* L.	PPPP, GP, PP, MP, VA, MA, KA, LA, FA, AP, FP, PA, LP, VP, LL, VV, HA, IPA, IPI	DPP-IV inhibition	In vitro	Velarde-Salcedo et al. (2013)
2	*Cannabis sativa* L. (Hemp).	LR and PLMLP	Alpha-glucosidase inhibitory	In vitro	Ren et al. (2016)
3	*Phaseolus vulgaris* L. (Pinto)	PPHMLP, PPMHLP, PLPWGAGF, GNAAC-CGLPLLP, PPHMGGP, PLPPHALL, PAPFP-SPHTP	alpha-amylase inhibitory	In vitro	Ngoh and Gan (2016)
4	*Oryza sativa* L. (Rice bran)	LP, IP, MP, VP	DPP-IV inhibition	In vitro	Hatanaka et al. (2012, 2015)
5	*Glycine max* L. (Soy) and *Lupinus albus* L. (Lupin)	IAVPTGVA, YVVNP-DNDEN, YVVNPDN-NEN, LTFPGSAED, LILPKHSDAD, GQEQSHQDEGVIVR	DPP-IV inhibition	In vitro	Lammi et al. (2016)
6	*Phaseolus vulgaris* L. (Common bean)	AKSPLF, ATNPLF, FEELN, and LSVSVL	(GLUT2) inhibitor, (SGLT1) inhibitor	In vitro and in vivo	Mojica et al. (2017a)
7	*Avena sativa* L. (Oat)	FLQPNLDEH, DLELQNNVFPH, and TPNAGVSGAAAGA GAGGKH	Alpha-glucosidase activity	In vitro and in vivo	Zhang et al. (2015)
8	*Momordica charantia* L.	GHPYYSIKKS	Hypoglycemic	In vivo	Yuan et al. (2008)
9	*Phaseolus vulgaris* L. (Common bean)	LLSL, QQEG, and NEGEAH	alpha-glucosidase inhibition, amylase inhibition	In vitro	Oseguera-Toledo et al. (2015)
10	*Cuminum cyminum* L. (Cumin)	FFRSKLLSDGAAAAK-GALLPQYW, RCMAFLLSD-GAAAAQQLLPQYW, and DPAQPNYPWTAV-LVFRH	alpha -amylase inhibition	In vitro	Siow and Gan (2016)
11.	*Phaseolus vulgaris* L. (Common bean)	TTGGKGGK	alpha-glucosidase inhibition	In vitro and In silico	Mojica and de Mejía (2016)
12	*Chenopodium quinoa* Wild.	IQAEGGLT, DKDYPK, GEHGSDGNV	Alpha-glucosidase inhibition, alpha -amylase inhibition, DPP- IV inhibitor	In vitro	Vilcacundo et al. (2017)
13.	*Morus alba* L. (Mulberry)	WGYENAATYFWQTV	alpha-glucosidase inhibition	In vitro	Jha et al. (2018)
14.	*Glycine max* L.	YPFVV	Hypoglycemic	In vivo	Yamada et al. (2011)

G glycine, *A* alanine, *L* leucine, *M* methionine, *F* phenylalanine, *W* tryptophan, *K* lysine, *Q* glutamine, *E* glutamic acid, *S* serine, *P* proline, *V* valine, *I* isoleucine, *C* cysteine, *Y* tyrosine, *H* histidine, *R* arginine, *N* asparagine, *D* aspartic acid, *T* threonine, *kDa* kilo dalton

that oat peptides, at a higher dose, showed the hypoglycae-mic effect on STZ-induced diabetic mice, reduces the food intake, stimulates insulin secretion, improves insulin sensitivity and elevate glycogenesis (Zhang et al. 2015). Walnut hydrolyzed peptides (WHPs) from the fruit proteins of *Juglans mandshurica* Maxim. (Walnut) showed anti-diabetic activity by inhibiting the enzyme. In vitro study of WHPs showed that peptides of molecular weight (3–10 kDa) inhibit alpha-glucosidase with the inhibitory rate of (61.73%) and

they remarkably raise extracellular glucose consumption in insulin-resistant HepG2 cells. Whereas, in vivo results showed that WHPs reduce 64.82% of fasting blood glucose level by increasing insulin secretion, liver glucokinase, and glycogen level by 23.71%, 69.54%, and 76.19% respectively (Wang et al. 2018).

Vigna angularis Wild. (Adzuki bean) proteins have reported enzyme inhibitory properties in mice model KK-Ay of diabetes. The extract reduces the postprandial

Table 3 Reported protein hydrolysate from plants for antidiabetic activity

Sr. no.	Plants	Part used	Activities	Studies	References
1	*Juglans mandshurica* Maxim.	Fruits	alpha-glucosidase inhibition, reduce fasting blood glucose levels, increase in insulin secretion, liver glucokinase and glycogen levels	In vitro and in vivo	Wang et al. (2018)
2	*Hordeum vulgare* L.	Seeds	alpha-amylase inhibition	In vitro	Alu'datt et al. (2012)
3	*Spinacia oleracea* L. and *Lemna gibba* G3	Leaves and whole plant	Insulin mimetics	In vitro	Collier et al. (1987)
4	*Vigna angularis* Wild.	Seeds	alpha-glucosidase inhibition	In vivo	(Yao et al. 2014)
5	*Triticum aestivum* L.	Seeds	alpha-amylase inhibition	In vitro	Kodama et al. (2005)
6	*Linum usitatissimum* L.	Seeds	Increase glucose uptake	In vitro	Doyen et al. (2014)
7	*Glycine max* L.	Seeds	Increase glucose uptake in muscular cells via AMK activation	In vitro	Roblet et al. (2014)
8	*Phalaris canariensis* L	Seeds	DPP4 inhibition	In vitro	Estrada-Salas et al. (2014)
9	*Vigna unguiculata* L.	Seeds	Insulin mimetic	In vitro	Uruakp (2015)
10	*Momordica cymbalaria* Hook.f.	Fruits	alpha-glucosidase inhibition	In vitro and in vivo	Marella et al. (2016)
11	*Cucurbita pepo* L.	Seeds	alpha-amylase inhibitory	In vitro	(Vaštag et al. 2014)
12	*Moringa oleifera* Lam.	Seeds	alpha-amylase inhibitory	In vitro	(Gonzalez Garza et al. 2017)
13	*Citrullus lanatus* L.	Seeds	alpha-amylase inhibitory	In vitro	Arise (2016)
14	*Theobroma cacao* L.	Fruits	alpha-amylase inhibitory	In vivo	Sarmadi et al. (2012)
15	*Phaseolus vulgaris* L.	Seeds	DPP- IV inhibitor	In vitro	Mojica et al. (2017b)
16	*Chenopodium quinoa* Willd.	Seeds	DPP- IV inhibitor	In vitro	Nongonierma et al. (2015)
17	*Momordica charantia* L.	Fruit pulp	Insulin secretagogue and insulinomimetic	In vivo and in vivo	Yibchok-Anun et al. (2006)
18	*Momordica charantia* L.	Fruits, seeds	Insulin mimetic	In vivo	(Khanna et al. 1981)
19	*Momordica charantia* L.	Seed protein expressed in *E.coli*	Stimulated the phosphorylation of PDK1 and Akt, enhanced expression of GLUT-4, stimulated both the uptake of glucose in cells and the clearance of glucose	In vitro and in vivo	Lo et al. (2016)
20	*Momordica cymbalaria* Hook.f.	Fruits	Hypoglycemic	In vivo	Rajasekhar et al. (2010)
21	*Telfairia occidentalis* Hook.f. *Citrullus lanatus* L. *Lagenaria siceraria* Molina. *Cucurbita moschata* Duchesne.	Seeds	Hypoglycemic	In vivo	Teugwa et al. (2013)
22	*Zea mays* L.	Seed protein (Zein) hydrolysate	Enhance the secretion of GLP-1	In vivo	Hira et al. (2009)
23	*Glycine max* L.	Seeds	Increases the glucose uptake, enhance the expression of p-IR, p-IRS1, p-Akt and membrane GLUT4 protein improve the insulin resistance hypoglycemic	In vitro and in vivo	Lu et al. (2012)
24	*Oryza sativa* L.	Rice bran	Improve insulin resistance	In vivo	Boonloh et al. (2015)
25	*Momordica dioica* Roxb.	Fruits	Hypoglycemic	In vivo	Poovitha et al. (2017)

blood glucose in two sucrose challenge model i.e. normal and streptozocin-treated rats by 15.6% and 30.9% respectively. In vitro study of extruded adzuki bean proteins at 10 mg/mL, concentration inhibits 60.44% of rat intestinal alpha-glucosidase (Yao et al. 2014). A peptide fraction with molecular weight < 1 kDa obtained from a protein-rich extract of *Phaseolus vulgaris* L. (Pinto Durango and Negro 8025) common beans via hydrolysis and ultracentrifugation processes have shown $76.4 \pm 0.5\%$ of enzyme inhibition (Oseguera-Toledo et al. 2015). Alcalase hydrolysis of proteins from *Phaseolus vulgaris* L. (Black bean) with enzyme to substrate ratio (E/S) ratio of 1:20 and incubation time for 2 h showed 66.1% enzyme inhibition (Mojica and de Mejía 2016). In vitro digestion of the *Chenopodium quinoa* Willd. (Quinoa) protein gives bioactive peptides having amino acid sequences characterized by LC–MS/MS are IQAEGGLT, DKDYPK and GEHGSDGNV showed enzyme inhibition 55.85%, 22.16%, 30.84% respectively at 250 µM concentration (Vilcacundo et al. 2017). Oligopeptide having a molecular weight between 0.5 and 3 kDa from the leaves of the *Morus alba* L. (mulberry) showed enzyme inhibition with IC_{50} value 12.56 µg/ml (Jha et al. 2018). Protein from *Momordica cymbalaria* Hook. f. showed in vitro enzyme inhibition which decreases glucose production, improve carbohydrate metabolism in animal studies (Marella et al. 2016).

Alpha-amylase Inhibitors

Amylase (alpha-1,4-glucan-4-glucanohydrolase) is an important enzyme that speeds up the hydrolysis of (alpha-1,4) glycosidic linkage of carbohydrate and starch present in the diet and helps in absorption of non-absorbable polysaccharides after their conversion into absorbable monosaccharide (Alagesan et al. 2012). Inhibitors of amylase minimize the hydrolysis of (alpha-1,4) glycosidic linkage and help in slow digestion of carbohydrate and thus delay the absorption of glucose and reduces the postprandial glucose level in blood (Jayaraj et al. 2013).

The Pinto beans are a rich source of proteins and other nutrients but are not well explored for its therapeutic benefits. Pinto bean protein fraction was digested enzymatically using protease (Protamex) at pH 6.5, and for the incubation period of 1-h with (E/S) ratio of 1:10 at 50 °C, hydrolysed fraction was dialysed using molecular weight cutoffs and the fraction obtained with molecular weight < 3 kDa showed $62.10 \pm 3.49\%$ of enzyme inhibition (Ngoh and Gan 2016). Similarly digestion with Protease (Bromelain) and dialysis with Molecular weight cut-off < 1 kDa showed $49.9 \pm 1.4\%$ of enzyme inhibition (Oseguera-Toledo et al. 2015). The peptide obtained from *Cuminum cyminum* L. (Cumin) seeds, cumin seed peptide1 (CSP1) had shown 24.54% of alpha-amylase inhibition (Siow and Gan, 2016). In vitro study of

Triticum aestivum L. (Wheat) albumin extract showed alpha-amylase inhibition, wheat albumin restrained the peak of postprandial blood glucose levels in a dose-dependent manner. It showed the reduction in postprandial blood glucose by 31%, 47%, and 50% after administering 0.25 g, 0.5 g, and 1.0 g of wheat albumin respectively. In long-term administration study, 0.5 g of wheat albumin did not affect fasting blood glucose levels, while it reduces hemoglobin A1c levels which reflects the metabolic control of individual suffering from diabetes (Kodama et al. 2005).

A study revealed that different protein fractions isolated from the *Hordeum vulgare* L. (Barley) flour have been subjected to pancreatic hydrolysis and the obtained peptides have shown 57–77% alpha-amylase inhibitory activity (Alu'datt et al. 2012). Cucurbitin protein was obtained from the *Cucurbita pepo* L. (Pumpkin) seeds, alcalase and pepsin hydrolysed fraction of it showed the enzyme inhibition (Vaštag et al. 2014). Oligopeptides from the Mulberry showed highest enzyme inhibition with IC_{50} 16.25 µg/ml. Protein hydrolysates prepared from the seeds of *Moringa oleifera* Lam. by enzymes like trypsin, chymotrypsin and pepsin–trypsin for 2.5 and 5 h. Pepsin–trypsin digested fraction showed alpha-amylase inhibition and the IC_{50} was found to be 0.195 and 0.123 µg/ml for 2.5 h and 5 h of hydrolysis respectively (Gonzalez Garza et al. 2017). Protein hydrolysate of *Citrullus lanatus* L. (Watermelon) seeds was prepared by using enzymes like pepsin, trypsin and alcalase where alcalase hydrolysate gives the highest enzyme inhibition and the IC_{50} was found to be 0.149 mg/ml (Arise 2016). Autolysates of *Theobroma cacao* L. fruits were prepared at pH 3.5 and 5.2. Autolysate at pH 3.5 showed highest inhibition of alpha-amylase as well as helps to release the insulin, in vivo study with autolysates showed decrease in the blood glucose level (Sarmadi et al. 2012). Quinoa proteins were enzymatically hydrolyzed to obtain bioactive peptides, hydrolyzed fraction thus obtained showed 6.86% inhibition of alpha-amylase at 250 µM concentration (Vilcacundo et al. 2017).

Dipeptidyl Peptidase-IV Inhibitors

Two main gut-derived hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), also known incretin hormones are responsible for the attainment of normoglycemia. They stimulate insulin secretion, decrease glucagon, inhibit gastric emptying, reduce food intake and appetite (Drucker and Nauck 2006). In diabetic individuals, reduced secretion of incretin hormones have been observed. These gut hormones bind with their respective receptors and show their biological action (Barnett 2006). Treatment of diabetes requires to restore either normal secretion or reduce the degradation of these hormones. Dipeptidyl peptidase-IV (DPP-IV) is a protease enzyme that cleave the GLP-1

hormone within minutes after its secretion and makes it inactive for biological function. Thus, inhibition of DPP-IV has the potential to revert the hyperglycaemic condition. DPP-IV inhibitors block the rapid degradation of GLP-1 and enhance the postprandial level of active GLP-1 which further reduces the liver glucagon production and stimulate beta cells of the pancreas and increase insulin level (Ahrén 2007).

Dipeptides obtained from *Oryza sativa* L. (rice) bran protein hydrolysates showed inhibition of DPP-IV enzyme and have IC$_{50}$ 1.45 ± 0.13 mg/ml (Hatanaka et al. 2015). In another study, rice bran protein fractions have been defatted and hydrolyzed with umamizyme G and Bioprase SP. The dipeptides obtained after digestion with Umamizyme G showed inhibition of enzyme and the IC$_{50}$ was found to be 2.3 ± 0.1 mg/ml (Hatanaka et al. 2012). The proteins extracted from *Amaranthus hypochondriacus* L., have been subjected to simulated gastrointestinal digestion resulted into bioactive peptides. These peptides fraction have shown dose-dependent enzyme inhibition and have IC$_{50}$ 1.1 mg/ml (Velarde-Salcedo et al. 2013). *Glycine max* L. (Soybean) and *Lupinus albus* L. (Lupin) protein hydrolysate have been screened for the presence of bioactive peptides, and Soy 1 and Lup 1 were found to be efficient inhibitors of DPP-IV with IC$_{50}$ values 106 and 228 µM respectively (Lammi et al. 2016). Peptides obtained (CPGNK and GGGLHK) from the protein digestion of common beans showed enzyme inhibitory activity and the IC$_{50}$ (mg DW ml^{-1}) for the pure peptides were found to be 0.87 ± 0.02 and 0.61 ± 0.10 respectively (Mojica et al. 2017b). Gastrointestinal digestion of proteins obtained from *Phalaris canariensis* L. (Canary) seed showed 43.5% inhibition of DPP-IV (Estrada-Salas et al. 2014). Enzymatic digestion of Quinoa proteins with papain showed enzyme inhibition and the IC$_{50}$ for the hydrolysate-papain was found to be 0.88 ± 0.05 mg/ml (Nongonierma et al. 2015). Study was performed on quinoa protein simulated duodenal digestion and the fraction (˂ 5 kDa) obtained after 120 min of digestion showed highest DPP-IV inhibition and the IC$_{50}$ (mg protein/mL) was found to be 0.84 ± 0.07 (Vilcacundo et al. 2017).

Inhibitors of the Glucose Transporter System (GLUT and SGLT)

Glucose, the metabolic fuel of any living cell, unable to cross lipid bilayer of the membrane due to its polar nature and membrane proteins (glucose transporter) associate with lipid bilayer helps glucose to travel across (Abdul-Ghani et al. 2011). GLUT transporters facilitate the transport of glucose passively across the membrane along with its concentration gradient and do not require energy to operate, on the other hand SGLT transporters actively transport glucose across the membrane against the concentration gradient thus these types of transporters require energy to operate. In order to receive energy for operation, sodium is transported along with its concentration or electrochemical gradient thus provide the needed amount of energy for the transportation of glucose across the membrane (Musso et al. 2012; Brown 2000). In the human body, at least 12 different GLUT transporters and 7 SGLT transporters exist which belongs to membrane class of proteins. Excreted glucose is reabsorbed up to 90% in a convoluted segment of proximal tubule via high capacity, low-affinity SGLT 2 transporter while remaining 10% of glucose is reabsorbed in the distal segment of proximal tubule via high affinity, low capacity SGLT 1 transporter.

In the case of diabetes, hyperglycemia causes the high load of glucose in order to compensate for this high load of glucose, an increase in expression of a glucose transporter gene in proximal tubule occurs (Abdul-Ghani et al. 2011). Plant peptides targeting glucose transporters are less explored. However, peptides having amino acid sequences AKSPLF, ATNPLF, FEELN, and LSVSVL, isolated from the black beans have shown the ability to block the glucose transporters GLUT-2 and SGLT-1. The results of in vitro studies by using the Caco-2 cell model have shown reduced glucose re-absorption by 21.5% after 24 h treatment of these bioactive peptides. The oral glucose tolerance test in rats has shown a 24.5% decrease in postprandial glucose (p < 0.05) (50 mg hydrolyzed protein isolate/kg BW) (Mojica et al. 2017a).

Insulin Mimetics

Insulin hormone trigger several signaling events that control the metabolic fate of nutrients. Insulin binds with alpha-subunit of insulin receptor which causes the conformational changes in β-subunit of the insulin receptor, and these conformational changes in receptor activate the cytoplasmic tyrosine kinase domain. This activation further leads to the auto-phosphorylation which in turn trans-phosphorylate various intracellular substrate of the insulin receptor. These effects collectively control metabolic and mitogenic processes (Nankar and Doble, 2013). Tyrosine kinase domain activation by insulin mimetic, cause the auto-phosphorylation of receptor and trigger downstream signaling requires for metabolic activity of insulin. The other mechanism by which insulin mimetic (vanadate) works is by inhibiting the dephosphorylation of the insulin receptor via inhibition of tyrosine phosphatase (Stapleton 2000).

The reports suggest that plant extracts of spinach and *Lemna gibba* G-3 mimics like mammalian-insulin, which was confirmed by the radioimmunoassay. In an in vivo study on young rats indicated that the plant insulin-like material binds to insulin receptors on IM-9 lymphocytes and stimulates glucose oxidation and lipogenesis in isolated adipocytes (Collier et al. 1987). *Vigna unguiculate* L. (Cowpea)

containing bio-molecules have contributed in reducing the blood glucose level and enhancing the antioxidant status of patients. Study on L6 rat skeletal muscle cells was performed where cells were treated with cowpea peptides at different doses (0.1, 1, 10 and 100 ng) for 20 h or insulin (100 nM) for 30 min. Further, from the treated cells proteins were isolated for western blot analysis to check the phosphorylation of Akt (a form of protein kinase B; PKB). The results of the study showed that the cowpea peptides have the ability to phosphorylated Akt in the cell culture. This observation suggests that the treatment of cowpea peptides to the skeletal muscle cells can initiate the insulin signaling cascade. There is a possibility that cowpea peptides have the ability to mimic like insulin by inducing the same signaling cascade (Uruakp, 2015).

Linum usitatissimum L. (Flax) seed peptides obtained from the protein hydrolysate (50kD) increases glucose uptake in L6 cells (Doyen et al. 2014). MC2-1-5 peptide fraction was obtained from *Momordica charantia* L. showed hypoglycaemic effect in in vivo study. MC2-1-5 fraction decreases the blood glucose level by 61.70% and 69.18% in alloxan-induced diabetic mice with a time interval of 2 and 4 h respectively (Yuan et al. 2008). Study on protein from the pulp of *M. charantia* L. showed increase glucose uptake in C2C12 myocytes and 3T3L adipocyte, the in vivo studies showed that the protein obtained from pulp helps in secretion of the insulin as well as act like insulin to lower the glucose level (Yibchok-Anun et al. 2006). Polypeptide-P was isolated from the *M. charantia* L. acts like insulin mimetic (Khanna et al. 1981). Another 68-residue insulin receptor (IR)-binding protein (mcIRBP) was reported from the plant upon in vitro digestion yields mcIRBP-19, spanning residues 50–68 of mcIRBP which increases the binding of insulin to its receptor, stimulate the phosphorylation of PDK1 and Akt, induces the expression of glucose transporter 4, and stimulate both the uptake of glucose in cells and the clearance of glucose in diabetic mice (Lo et al. 2016). A novel protein called MCy having molecular weight 17kD was isolated from *Momordica cymbalaria* L. fruit which showed hypoglycemic effect in in vivo study (Rajasekhar et al. 2010). The peptide fraction obtained from the soybean showed increase in glucose uptake in muscular cells, it is reported that obtained peptide fraction enhances the glucose uptake via AMK activation (Roblet et al. 2014).

Protein extract of Cucurbitaceae family containing seeds like *Telfairia occidentalis* Hook.f.*, Citrullus lanatus* L., *Lagenaria siceraria* Molina., and *Cucurbita moschata* Duchesne., showed a significant decrease in blood sugar level in in vivo study (Teugwa et al. 2013). Peptide reported from the leaves of *Bauhinia variegata* L, mimics like insulin which is evidently proved from the immunological reactivity and via in vivo study *(*Azevedo et al. 2006). *Zea mays* L. (Zein) seed protein hydrolysate increase the secretion of GLP-1

directly in the ileum and indirectly in the duodenum in the rat and also confirmed with the help of GLUTag cell line study (Hira et al. 2009). Aglycine which is a bioactive peptide obtained from the soy bean increases the glucose uptake in C2C12 cell, whereas in in vivo study on diabetic model it was observed that treatment with aglycine increases the expression of p-IR, p-IRS1, p-Akt and membrane GLUT4 protein which results into hypoglycemia (Lu et al. 2012). Soymorphin-5 also called μ-opioid obtained from soy bean decreases the blood glucose level via activation of adiponectin and PPARα systems in diabetic KKAy mice (Yamada et al. 2011). Rice bran protein hydrolysate helps to improve insulin resistance and prevent metabolic diseases (Boonloh et al. 2015). Protein extracted from the fruit pulp of *Momordica dioica* Roxb. decreases the blood glucose level in a diabetic model (Poovitha et al. 2017). Plant scientist believe that there are more plants left unexplored which may contain insulin-like peptides or peptides which will mimic insulin (Xavier-Filho et al. 2003).

Challenges Associated with Peptides as a Drug

The success of any therapy and its acceptability depends on the ease of its delivery. The oral route of drug administration remains the most accepted route of drug delivery and most of the available drugs in the market are delivered through the oral route (Morishita and Peppas 2006). An orally active drug should be stable enough to withstand the gastric microenvironment and also it should be permeable through the gastrointestinal membrane. Small molecules are well tolerant to the gastric pH and permeated through the membrane whereas the large macromolecules are vulnerable to degradation in the gastrointestinal tract and are not permeable in their intact form to reach specific target successfully without being degraded in GIT (Morishita and Peppas 2006). As the medical field advances, the peptide drugs are widely explored for their therapeutic potential in the treatment of various diseases. Though these drugs are specific to their target, efficacious and potent, the oral bioavailability of peptide and peptide-based drugs always remains a challenge that limits their wide acceptance and market value. High cost of therapy is a major limitation associated with peptide drugs (Ayoub and Scheidegger 2006). With the advancement of biotechnology, the recombinant synthesis of a peptide of interest opens a door for cheap and cost-effective peptides. Also, the commercial interest for the production of bioactive peptides from the natural sources is elevated to reduce the cost but due to the lack of suitable technologies which helps to retain or increase the activity of bioactive peptides, the large-scale production gets hampered (Craik et al. 2013).

Another limitation associated with peptide-based drugs is their short half-life. When the peptides come in contact with intestinal mucosa, gastric acid in stomach and

peptidases that are present in the blood convert peptides into amino acids and gets quickly eliminated from the body, thereby reducing its half-life. In order to achieve prolonged action and to reduce the frequent dosing, it is necessary to increase the half-life of the peptides. As peptide therapeutics advances, several non-degradable polymers and polymeric matrix are available to increase the half-life of peptides and proteins thus reducing the frequent dosing (Brown 2005). Another strategy to increase the half-life of the peptide is to modify the amino acids which are susceptible to cleavage by enzymes (Adessi and Soto 2002). Oral delivery of the peptides is explored in past years but limits its use as peptides are degraded in the GIT tract (Lau et al. 2015). Novo Nordisk developed a semaglutide oral formulation which is currently in clinical trial phase 3. Other non-invasive and suitable routes for the peptide and protein-based drugs are under investigation includes the nasal and pulmonary route which directly deliver the drugs to the blood component hence, reduces the overall drug degradation which is the main drawback associated with oral delivery of peptides (Davies et al. 2017).

Future of Peptide-Based Drugs

Different therapeutic peptides have made their way to the market in recent years, and it is assumed that the market demand will increase further as peptides are specific, selective and safe in comparison to small molecules (Fosgerau and Hoffmann 2015; Loffet 2002). Traditional synthesis and drug design approaches are used by researchers and pharmaceutical companies for the development of the peptide-based drug candidate. The recombinant protein is another tool for the synthesis of the desired peptide in bacteria, yeast, and fungi. The market of peptides has now moved from the isolation of peptides from an animal source that can mimic the endogenous peptide to synthetic, semi-synthetic and recombinant peptides. Further, development in this area is drug conjugated peptides and multifunctional peptides (Fosgerau and Hoffmann 2015). Peptides are susceptible to degradation when given orally, which is supposed to be the most convenient route of administration. The preferred route for the peptide delivery is intravenous, however, more research is directed for the delivery of peptides. Recently, alternative routes are explored, which include oral, transdermal and intranasal route. As peptides are excellent biomarkers, they can also be utilized for diagnosing diseases. Further, peptides are also found to be advantageous in vaccine development (Brown 2005; Sheridan 2012).

Plant peptides have been isolated and characterized in different ways as described in Fig. 3. X-ray crystallography and NMR have contributed enormously in the field of structure elucidation of pure peptides (Gomathi and Subramanian

Fig. 3 The general scheme of isolation, purification, and characterization of plant peptides (Gomathi and Subramanian 1996; Krishnan and Rupp 2012; Sinz et al. 2015; Wysocki et al. 2005)
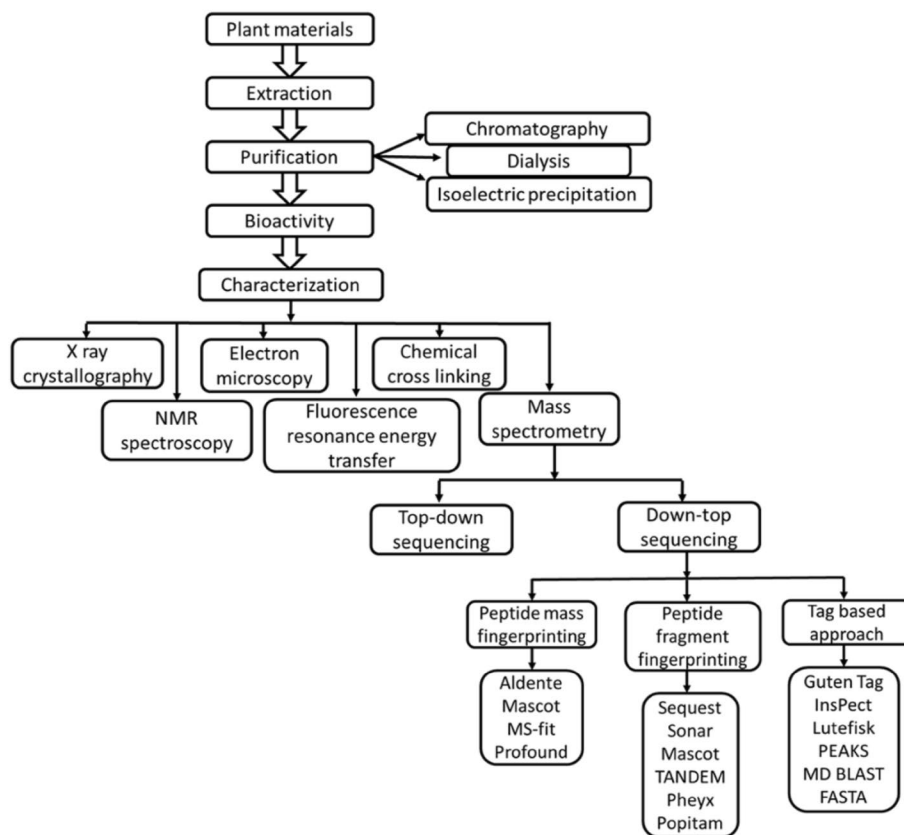
1996; Krishnan and Rupp 2012). Other techniques like electron microscopy, fluorescence resonance energy transfer, chemical cross-linking emerged in recent year for the characterization of proteins and peptides (Sinz et al. 2015). Mass spectrometry is frequently used technique in analyzing peptide mixtures and identifying their proposed structures. Amino acid sequencing in mass spectrometry can be performed by two methods namely top-down sequencing and down-top sequencing. In top–down sequencing, the proteins analysis is performed without hydrolysis and the molecular weight can be detected by fragmentation pattern of the whole protein. A common approach is down-top sequencing in which proteolytic digestion is performed followed by MS analysis. Software based on the algorithm of the amino acid sequence is available for protein identification (Wysocki et al. 2005).

Discussion

Plants remain a valuable source for developing a new drug candidate. They are still sharing their fair share of the new drug candidates and lead. As research interest is now shifted from small molecules to bio-molecules by virtue of several added benefits, plants are now under exploration for the presence of proteins and bioactive peptides for the disease management. Though plant proteins and their functions have not been defined earlier, plant hormones were only considered through which cells communicate, as our understanding to these signalling pathways become clear, several secreted peptides and small RNAs now known which regulates molecular recognition and thus, controls cell communication. From our diet we consume proteins which after gastro-intestinal digestion get converted to bioactive peptides with more tissue affinity to specific receptor. Several research publications in recent years claimed plant proteins and their bioactive peptides as a potential candidate in the treatment of various diseases specially in metabolic and life style borne diseases including cancer, diabetes and obesity. Sophisticated instrument and advancement in technology leads easy isolation, purification and characterization of proteins and peptides in a short period of time, which further reduces the overall time of discovery.

Apparently, most of the bioactive peptides available for the treatment of diabetes have emerged from the synthetic route or derived from recombinant technology, which further adds in the overall cost of the treatment. To make peptide therapy economic there is a demand to explore plant-based biomolecules. This review discusses bioactive peptide isolated from various plant parts like leaves, fruits and seeds. The trend indicates that most of the bioactive peptides are obtained from seeds, although reports are available where bioactive peptides have been also isolated from leaves, whole fruits and pulps.

It was observed in various in vitro and in vivo studies that protein hydrolysate obtained from aqueous extracts of plant are capable of inhibiting the enzymes and transporter systems responsible for the diabetes. Expedition to find molecular targets and mechanism of action of plant based bioactive peptides is needed to use these bioactive peptides as a potential drug candidate.

Conclusion

Epidemiological data reveals that type 2 diabetes requires promising therapy as the available synthetic drugs for the treatment have moderate to severe adverse effects. Plant-derived bioactive peptides inhibit the enzymes like alpha-glucosidase, alpha-amylase, dipeptidyl peptidase-IV and glucose transporter systems involved in type 2 diabetes. In vivo studies of a certain plant peptides fraction showed insulin-mimetic action in animal models. It is clear that plant-derived bioactive peptides are not explored to their full potential in comparison to other classes of natural products. The reason might be the lack of suitable instrumental techniques to identify, purify and characterize the peptides from plant source. However, the recent advancement in LCMS, LC-NMR, and X-ray crystallography has bridged the gap and this would be the right time to embark on plant peptides. In future, systematic studies including dereplication for the early identification of known peptides, target identification followed by in vivo studies would help to speed up the plant peptides research.

Compliance with Ethical Standards

Conflict of interest The authors declare there is no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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