

PLANT KINGDOM CLAIMS FOR INSULIN!!!

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ABSTRACT

*Diabetes is a multifactorial disorder affecting a great number of people across the globe. Worldwide prevalence of diabetes was estimated to be 171 million (2.8%) in 2000 and it may rise up to 366 million (4.4%) by the year 2030. Diabetes mellitus is a heterogeneous metabolic disorder characterized by hyperglycemia, glycosuria, and negative nitrogen balance leading to a number of complications like diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, peripheral vascular disease, high cholesterol and high blood pressure, atherosclerosis, and coronary artery disease etc. Of the major three types of diabetes, Type 1 diabetics primarily depends on exogenous insulin for their survival because of absolute deficiency of insulin. **Insulin** is a polypeptide hormone, possessing anabolic property playing a pivotal role in the regulation of carbohydrate metabolism, along with the metabolism of fat and proteins and regulation of certain gene expression. Insulin is required for all animal life. After knowing the importance of insulin and its role in diabetes, higher animals like horses, pigs and cows are exploited for their pancreatic hormone, insulin. Currently human insulin gene cloned in *E. coli* is considered to be a better method. By the year 2010 global market for insulin is projected to be worth around \$11.8bn, and the demand*

for insulin is predicted to rise from around 5000 kg to 16000 kg. Growing diabetic population and the complications associated with diabetes stimulates the search for new drug targets and more efficient drugs with less adverse effect. Insulin like proteins "glucokinin" is detected in various plants and microbes showing similar functions as that of vertebrate insulin. Isolated glucokinin detected and quantified by ELISA shows its structural/sequence similarity with insulin of animal origin. Peptide sequence of glucokinin isolated from certain plants were similar to that of α and β chain of insulin. Studies on the effect of glucokinin in experimental animals showed its antihyperglycemic property when administered orally/IP with protease inhibitors. Qualitative detection of glucokinin in varied species by ELISA suggests that the insulin mediated carbohydrate pathway have been conserved through evolution. This breakthrough discovery of insulin like protein in plant kingdom showing similar activity as that of animal insulin, lowering blood glucose gives a promising natural source of insulin to meet the global requirement. This article spells out some of the scientific contributions supporting the presence of insulin like hormones/proteins for bioactivity from plants.

Keywords: Insulin, glucokinin, diabetes.

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INTRODUCTION

Worldwide diabetic population is expected to approximately double between the year 2000 and 2030. The greatest increase in the number of people with diabetes will be in India. In the year 2000, diabetic population was 31,705 this number may increase to 79,441 by the year 2030 (1). Diabetes is a chronic metabolic disorder in which the body cannot metabolize carbohydrates, fats, and proteins because of a lack of or ineffective use of the hormone, insulin. Diabetes is classified into three primary types that are different disease entities but share the symptoms and complications of hyperglycemia. Type 1 (Insulin dependent diabetes mellitus [IDDM] or Juvenile onset diabetes) caused by -genetic predisposition, - environmental exposure to virus, toxin, stress, -autoimmune reaction where beta-cells of pancreas are destroyed by its own immunological system. Type 2 (Non-insulin dependent diabetes mellitus, NIDDM,

or adult-onset diabetes) caused by -insulin resistance: unable to utilize insulin produced because of cell-receptor defect, -insufficient production of insulin in response to blood glucose, -excess production of glucose from the liver, -genetic predisposition, and -obesity. The third type of diabetes, is gestational diabetes mellitus (GDM) caused by insulin resistance due to pregnancy.

However, diabetes is a manageable disease a large number of classes of drugs are being used for diabetes for the past five decades. Since, a single drug is not effective to control hyperglycemia reasonable combinations of oral agents based on their mechanism of action which includes sulfonylurea and metformin, sulfonylurea and an alpha-glucosidase inhibitor, sulfonylurea and troglitazone, repaglinide and metformin, troglitazone and metformin, insulin and metformin, and insulin and troglitazone are in clinical use now. A schematic representation of the causes of hyperglycemia and the respective drugs blocking the pathway is shown in Fig 1. Diabetes mellitus is known to man since time immemorial and the treatment for this disease from golden days is based on plants and plant derivatives (2). The standard drugs which are widely used for diabetes all over the world were derived from plants. This is in the case of metformin, which is developed from biguanides present in the leaves of the legume plant *Galga*

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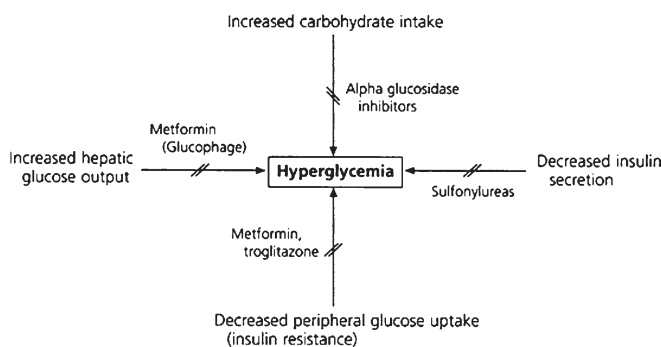


Fig. 1: Showing Pathophysiology of Hyperglycemia and the target of some antihyperglycemic drugs.

officinalis (3), salacinol, an α -glucosidase inhibitor extracted from the roots of *Salacia reticulata* (4), and cryptolepine, an indoloquinolene alkaloid isolated from the leaves of *Cryptolepis sanguinolenta* (5). Over and above a number of herbs such as *Allium cepa*, *Allium sativum*, *Aloe vera*, *Cajanus cajan*, *Coccinia indica*, *Caesalpinia bonducella*, *Ficus bengalensis*, *Gymnema sylvestre*, *Momordica charantia*, *Ocimum sanctum*, *Pterocarpus marsupium*, *Swertia chirayita*, *Syzgium cumini*, *Tinospora cordifolia*, *Trigonella foenum graecum*, *Mucuna pruriens*, *Murraya koeingii* and *Brassica juncea* (6) have been indicated/used for treating Diabetes in various traditional medicines.

Right after the discovery of insulin in young calf serum, J. B. Collip and C. H. Best reported for the presence of insulin-like substances in plant materials like green tops of onions, lettuce leaves, green bean leaves, barley roots, beet roots, etc., (7). The discovery of this hormone in tissues of the higher plants as well as in yeast opened up a new field of research in plant metabolism and afforded another remarkable example of parallelism between certain physiological processes in the plant kingdom with the animal kingdom. This review addresses some of the scientific contributions supporting the presence of insulin like animal hormones/protein capable of communicating with insulin mediated signal pathway in the plant kingdom.

GLUCOKININ OR PLANT INSULIN

Pancreatic insulin's influence on glycogen formation provoked a theoretical concept on the existence of insulin or insulin like protein hormones in organisms rich in glycogen. Collip's efforts on extracts of yeast and onion were successful in altering glucose metabolism. The term glucokinin was proposed by him in order to differentiate insulin of plant origin from that of animals. Following Collip's discovery Charles Best reported on insulin like material in germinating potatoes, rice and even in beetroot (8, 9). In plants, the growth and development process involves metabolisation of large quantity of stored starch into glucose, a process similar to that of liver glycogen mobilization for energy in animals. So a comparative study on glucokinin with insulin isolated from fresh beef pancreas and glucokinin from onion tops revealed that it promotes

maize germination (10). No research was done after this pioneering work of the 1920s. And the silence was broken when Khanna and collaborators reported on the presence of insulin in plants and patented a process for its production from the fruits of *Momordica charantia* (bitter gourd) (11). A water soluble fraction of *M.charantia* showed a single band on SDS-PAGE, smaller than recombinant insulin so, it must be less than 6 K Da. A specific fraction of *M. charantia* is about 2.5 K Da with 18 amino acid having an isoelectric point of 8.2 (12, 13). Further work on the possible presence and antihyperglycemic activity of glucokinin in *M. charantia* was done by Ng and co-workers (14). These authors utilized the seeds and employed gel filtration and ionic exchange chromatography which led to the isolation of several pure fractions exhibiting properties similar to animal insulin.

Following these reports, glucokinin was also detected in the prokaryote *Escherichia coli* and in the unicellular eukaryote *Tetrahymena* (15) as well as in fungi (8, 16, and 17) and in cyanobacterium (18). Their results suggest that "insulin may have arisen earlier in evolution than had previously been thought" and pointed to the possibility of its presence in plants. The immunoactive material from spinach and *Lemna gibba* was isolated, characterized chromatographically on C-18 hydrophobic liquid chromatography column. The protein nature of the isolated material was observed by its destruction by pronase and unaffected by inactivated enzyme. Isolated glucokinin is also similar to insulin in its net charge characteristic at low pH, since it adsorbed to a CM-Sepharose column and eluted with moderate salt concentration. Furthermore, glucokinin is similar to insulin in its behavior on a C-3 bonded silica reverse phase column. With a relatively step gradient and a short column, glucokinin eluted in the same area as the vertebrate insulin tested i.e. pork, beef, chicken and rat, but differs from guinea pig insulin which is more hydrophilic than the other vertebrate insulin. Glucokinin isolated from spinach and *Lemna gibba* is approximately 6 K Da showing similar properties of insulin immunologically as it reacts with anti-pork insulin antiserum and anti-chicken insulin antiserum, immunodepleted by anti-insulin antibodies, binds to insulin receptors and stimulates glucose metabolism in rat adipocytes (19).

Reports of Goodman and Davis showed that added exogenous insulin, insulin like growth factors I and II (IGF-I and IGF-II) accelerates the post-germinative development of fat-storing seeds of sunflower, watermelon and cucumber (20). They also measured increased activities of enzymes necessary for the conversion of fat to carbohydrate like fatty acyl CoA dehydrogenase, citrate synthase, malate dehydrogenase, isocitrate lyase, and malate synthase which suggest that plants also have a system that could respond to hormones of higher animals. Recently, a 20 kDa protein, isolated and purified by G-50 Sephadex followed by affinity chromatography through a bovine insulin

antibody-Sepharose column from maize tissue, showed IGF like activity in upregulating maize germination and seedling growth. Maize IGF enhances phosphorylation of S6 ribosomal protein on the 40 S ribosomal subunit, in a similar way as observed when bovine insulin is applied to maize axes during germination. Rapamycin, a specific inhibitor of the insulin-stimulated signal transduction pathway, prevented S6 phosphorylation. Anti-insulin antibody, heat treatment or trypsin digestion attenuated its activity which shows that this protein acts through a pathway similar to that of insulin or IGFs in animal tissues (21). The seed coat of *Canavalia ensiformis* contains protein with a sequence similar to that of bovine insulin (22). With the help of modern techniques such as immunofluorescence microscopy, insulin, insulin receptor and phosphoserine proteins were localized to an internal tissue layer of the seed coat but not in the cotyledonous tissues of *C. ensiformis*. This region was assumed to be important in the transport of the sugars to the embryo. These results proclaimed that insulin, vanadyl sulfate (an insulin mimetic compound), pinitol (a chiro inositol analogue) and glucose are capable of accelerating *C. ensiformis* seed radicle and epicotyl development. On the contrary, tyrphostin (an inhibitor of insulin receptor kinase activity) inhibited these processes (23).

Insulin like antigens were detected in leaves or aerial parts of varied species utilizing a modified ELISA and by western blotting. Plants are found to be positive for insulin like protein belonging to different phyla like Bryophyta (mosses), Psilophyta (wisk ferns), Lycopodophyta (*selaginella* sp), Sphenopsida (horsetails, *Equisetum*), Gymnosperms (Coniferophyta, Cycadophyta, Ginkgophyta) and Angiosperms (flowering plants including monocotyledons and dicotyledons). Alga like *Gracilariopsis* a common red alga, *Spirulina maxima* (Cyanobacterium) and yeast (*Saccharomyces cerevisiae*) also contain insulin like antigen. The protein isolated from *S. maxima* by acidic ethanol extraction showed a similar behavior in reverse phase chromatography as like bovine insulin and the N-terminal amino acid sequence is also shown to have homology with the sequences of proinsulins (18). Wider distribution of insulin in all organisms from unicellular bacteria to multicellular vertebrates suggests that they are conserved through evolution (24).

An ELISA assay using anti-human insulin antibody detected glucokinin in the legume *Vigna unguiculata*. The highest concentration of about 0.5ng/ μ g of protein were detected in the seed coats at 16 and 18 days after pollination. It showed similar chromatographic behavior as that of bovine insulin in RP-HPLC. The protein eluted from RP-HPLC was subjected to automated sequencing. Similarity in amino acid sequence of glucokinin with bovine insulin shows another evidence for its existence (25). More recently, isolation of insulin-like molecules from the leaves of *Bauhinia variegata* a plant widely utilized for the management of diabetes

showed partial sequence identity to bovine insulin and decreased the concentration of blood glucose when injected in both normal and alloxan induced diabetic mice. Sephadex G-50 column purified fraction which was tested by dot blot analysis showed positive for insulin like protein and was found to have partial sequence identity with that of bovine insulin. When sections of the leaves were examined by immunohistochemical and immunocytochemical microscopical analysis the protein was found to be associated with calcium containing crystals in the vacuoles of chloroplasts. Later, chloroplasts were purified and an insulin-like protein was isolated, purified by gel filtration and reverse phase chromatography. Purified protein cross-reacted with anti-human insulin antibody in an ELISA assay which confirmed the insulin like nature of the protein (26). Association of glucokinin with crystals containing calcium may protect from proteolysis when the decoctions of *Bauhinia variegata* was ingested orally.

ROLE OF GLUCOKININ

Insulin in plant exhibit metabolic functions as those of animal insulin by promoting several metabolic activities through glucose transportation into the cell and by phosphorylating proteins regulating carbohydrate metabolism as evidenced by many studies. Studies on the growth of maize seedlings showed that glucokinin isolated from onion stimulates growth of roots and tops of young maize seedlings as compared with untreated seedling controls. When growth of roots and tops of maize were compared with its endosperm weight as it is reduced much in untreated controls, glucokinin promotes growth by efficient utilization of endosperm i.e. less loss of endosperm by weight (10).

A fraction purified from *M. charantia* about 1ml in PBS (phosphate Buffer saline) given orally showed a significant reduction of blood glucose level at all points i.e. 30, 60, 90, 150 and 180 minutes in a glucose infusion study on SD rats. The same fraction was found to be effective in the prevention and treatment modes of diabetes in SD rats. In the preventive model, animals received orally 1ml (500 μ g) of glucokinin from day 1. While in the treatment model, animals received 1ml of purified fraction (500 μ g) of glucokinin at the onset of disease on day 5. Serum glucose levels were monitored daily for 15 days. It was found that purified fraction was highly effective in both preventive and treatment modes on day 10 without altering systemic insulin secretion. So, the effect of *M. charantia* on the preventive model of streptozotocin induced diabetes strongly supports its suitability in treating Type I autoimmune diabetes also (11, 12 and 13).

CM purified materials of spinach and *Lemna gibba* were able to compete with labeled insulin for binding to insulin receptors on IM-9 lymphocytes in a dose dependent manner. With increasing concentration of glucokinin there was an increase in the incorporation of 14 C from glucose into CO_2 and this stimulation was neutralized by anti-pork insulin

antiserum. Spinach glucokinin enhances lipogenesis as deduced by the conversion of D (³H) glucose into toluene extractable lipid and was neutralized by addition of anti-insulin antiserum (19).

Moreover, plant signaling pathway could respond to exogenous insulin (vertebrate insulin); accelerating seed development, increasing the activity of glyoxysomal enzymes involved in the conversion of stored fat to carbohydrate in fat storing seed species, inducing ribosomal protein synthesis in maize (20). Extracts of *Bauhinia variegata* exhibiting similar properties of bovine insulin were studied for its hypoglycemic activity in swiss albino mice. Intravenous injection of crude protein extract and protein fractions eluted from SDS-PAGE produced a significant decrease in blood glucose levels as similar to that promoted by commercial swine insulin. Total leaf extract did not show any characteristic change in glucose

level, possibly due to a lower glucokinin concentration. In the chloroplast, starch is broken down to hexoses (glucose) and transported into cytosol via a glucose translocator. Localization of glucokinin in chloroplast of *Bauhinia variegata* suggest that it might influence carbohydrate metabolism especially through transporting the sugars (26). Despite, many findings with sound techniques for the isolation, characterization and bioactivity assays, there is no direct evidence of glucokinin/vertebrate insulin effects on carbohydrate metabolism in plant. However, isolated glucokinin is found to have hypoglycemic activity in experimental animals and most of the glucokinin of different plant species shows peptide sequence homology with insulin shown in Table 1. Since, glucokinin shares amino acid sequence with human insulin it suggests that it might communicate with insulin mediated signal transduction by binding to insulin receptors.

Table 1 : A comparative tabulation of bovine insulin amino acid sequences with glucokinin isolated from plants. Fractions/subunits of *Canavalia ensiformis* and *Vigna unguiculata* showed high sequence similarity with bovine insulin.

Source	Amino acid sequence	Sequence ID
Bovine insulin á-chain â-chain	GIVEQCCASVCSLYQLENYCN FVNQHLCGSHLVEALYLVCGERGFFYTPKA	UniProtKB/Swiss-Prot P01317
<i>C. ensiformis</i> I-SC	GIVEQCCASVCSLYQLENYCN	UniProtKB/TrEMBL Q7M217
<i>C. ensiformis</i> I-LC	FVNQHLCGSHLVEALYLVCGERGFFYTPKA	
<i>V. unguiculata</i> I-SC	GIVEQXXASVXSLYQLENYXN	
<i>V. unguiculata</i> I-LC	FVNQHLXGSHLVEALYLXGERGFFYTPKA	UniProtKB/Swiss-Prot P83770
<i>B. variegata a</i> <i>B. variegata b</i>	GIVEQ FVNQH	-

INSULIN SIGNALING AND ITS PROTEIN ANALOGUE IN PLANTS

Insulin signal transducing mechanism is a very broad and crucial pathway to understand, where a number of proteins/enzymes participates. So, the insulin pathway is explained in a nutshell in relation to the current topic discussed. Increase in glucose concentration increases its metabolism in the â-cells leading to an elevation in the ATP/ADP ratio. This in turn leads to inhibition of ATP-sensitive K⁺ channels causing depolarization of the cell membrane leading to Ca²⁺ influx and insulin secretion. Insulin, in addition to its role in regulating glucose metabolism also stimulates lipogenesis, diminishes lipolysis, increases amino acid transport into cells, stimulates cellular growth and regulates certain gene's expression. Action of insulin is tissue specific promoting glycogen formation in liver and muscle, promotes glucose uptake by increasing the rate of glucose transporter's translocation in muscle and adipocytes, promotes lipogenesis in liver and adipocytes and also activates Na⁺ K⁺ pump in muscle and adipocytes.

Fig 2 shows a schematic representation of insulin's action in different tissues.

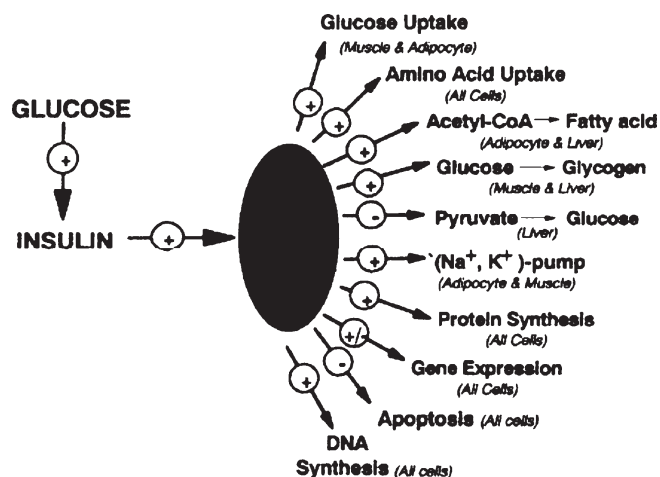
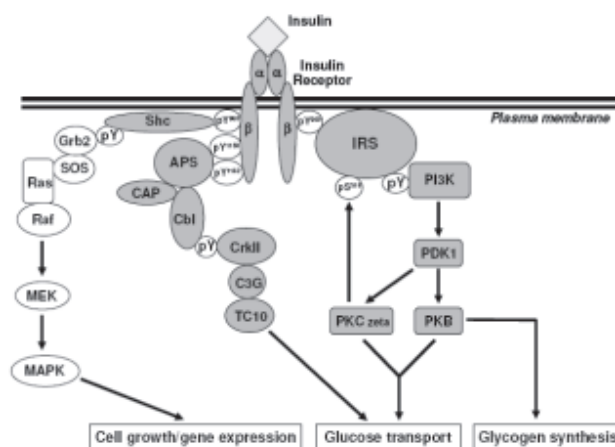


Fig. 2 : Physiological role of insulin in different cells.

Insulin mediates its action by binding to its receptor tyrosine kinases (RTK) which gets autophosphorylated provoking several cascades of signal transduction pathways. Activated RTK promotes serine-threonine phosphorylation of insulin-receptor substrates (IRS1, IRS2, IRS3 and IRS4). Phosphorylated IRS1 and IRS2 leads to binding and activation of phosphatidylinositol 3 kinase (PI3K) forming PI(3,4,5)P₃ which then binds to the plasma membrane and associates with phosphoinositide-dependent kinase-1 (PDK-1) activating protein kinase B (PKB or Akt) and PKC zeta by phosphorylation. Finally, the activated Akt is thought to initiate many of the metabolic actions of insulin. Activation of IRS-2/PI3K/Akt/PKC α is shown to be required for translocation of the glucose transport protein from storage areas to the cell surface and also for the activation of enzymes of carbohydrate metabolism.

The Mitogen-activated protein kinases (MAP kinase) pathway is also activated either through receptor activation of the protein tyrosine phosphatase (Shp-2) or growth factor receptor binding protein-2 (Grb2) which regulates various cellular activities, such as gene expression, mitosis, differentiation, and cell survival/apoptosis. The role of insulin in the stimulation of protein synthesis occurs at the level of translational initiation and elongation and is exerted primarily via a cascade leading to the activation of mammalian target of rapamycin, mTOR. Fig 3 gives a better understanding of insulin mediated signal pathway in relation to the current discussion. A great number of reports exist in literature that suggest the existence of plant proteins with functions, localization and sequences of the corresponding gene or protein, that are similar to proteins which are members of the insulin pathways characteristic of vertebrates. List of such plant protein counterparts in insulin signaling pathway is given in Table 2.



Source: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1136111/figure.pdf>

Fig. 3 : A short segment of Insulin signaling pathway showing only proteins playing crucial role in signal transduction

GLUCOKININ TOWARDS CURE

Plant insulin is found to be effective in regulating blood glucose by mimicking insulin signal in eukaryotes as mentioned before. Plant insulin ingested together with protease inhibitors is protected from hydrolysis in the digestive tract, crosses the intestinal barrier and promotes lowering of blood glucose levels (35). Additionally, galactorhamnan a polysaccharide in complex with insulin from the seed coats of Jack bean suggests that the hormone could be protected from hydrolysis in the digestive tract (36, 37). Making use of radioactive compounds, a dose dependent stimulation of glucose metabolism by CM (Carboxy Methyl cellulose) purified insulin-immunoactive material from spinach and *Lema gibba* in rat adipocytes was observed. With increasing concentration, there was an increase in the incorporation of ¹⁴C from glucose to CO₂ (19). Most recent and reliable proof was given by

Table 2 : List of proteins (except insulin) found in plants which are associated with insulin mediated signaling pathway.

Proteins of insulin pathway	Its Analogues in plant/microbes
Receptor tyrosine kinases (RTK)	Found in <i>Arabidopsis thaliana</i> (27)
Insulin receptor substrates, proteins IRS-1 and IRS-2	<i>Arabidopsis thaliana</i> -LSD1 gene shows high sequence homology (28)
Glucose transporter	Sugar beet have high sequence homology (29)
Phosphatidylinositol kinases -PI3K (PI 3-kinase)	CDNA from soyabean shows significant sequence homology (30,31)
Hexokinase	Plant hexokinase involved in sugar sensing processes are regulated by glucose (32)
MAPK pathway	Evolutionarily conserved from unicellular to eukaryote organisms associated with insulin signaling in the promotion of cellular growth in rice (33)
TOR (target of rapamycin)	A potential component of the phosphoinositide 3-kinase (PI3K) pathway in <i>Drosophila</i> and was also found in yeast and <i>Arabidopsis</i> (34)
Ribosomal S6 Kinase	A maize insulin-like growth factor signals to a transduction pathway regulating protein synthesis in maize (22)

Azevedo and coworkers that insulin-like protein isolated from *Bauhinia variegata* leaves influenced glucose levels in the serum of diabetic mice. Protein fraction caused a significant decrease in blood glucose levels in diabetic mice similar to that promoted by commercial swine insulin (26). Peptides of *Momordica charantia* (MC6 and MC2) are equally as effective as systemic injection as well as through oral administration. Hypoglycemic effect at a concentration of 500 $\mu\text{g}/\text{ml}$ on SD rats showed a significant fall of glucose in glucose tolerance test and also preventive against streptozocin induced diabetes in rats. Serum insulin level is up regulated by this peptide as revealed by radioimmunoassay (12, 13). Research on insulin like proteins in plant has a substantial action on diabetic plaque in animals and has to step into clinical trials.

FUTURE OF INSULIN THERAPY

Current methods of insulin production rely on yeast *Saccharomyces cerevisiae* and *E. coli* genetically engineered to produce synthetic human insulin. These organisms are grown in large steel bioreactors, and the products are subjected to high cost downstream process to yield highly pure protein, devoid of any contaminations. SemBioSys has been working with the transgenic plant for the past five years and its latest results show that plant-derived insulin is analytically and physiologically identical to human insulin. The product was found to be functionally equivalent to Eli Lilly's Humulin. This method achieved a 1.2 per cent accumulation of insulin within the seed protein of the plant, exceeding its commercial target. One acre of safflower would give a yield of over one kilogram of insulin - enough to supply 2,500 patients for an entire year. SemBioSys product will reach the market by as early as 2010.

Pharmaceutical heavy-weights Pfizer, Eli Lilly and Novo Nordisk are now developing new needle-free methods of insulin administration. Pfizer's inhalable insulin product Exubera is a few steps ahead of Eli Lilly's AIR Insulin System, currently undergoing Phase III clinical trials, and Novo Nordisk's AerX product is also in the final stages of clinical studies. There is also competition from US company Mankind, who's inhaled insulin product Technosphere completed Phase III trials with Type 2 diabetes in September last year, Biocon of India is also in the race. On top of this, researchers from the National Tsing Hua University in Taiwan developed insulin pill containing encapsulated insulin in such a way as to protect it from the digestive fluids in the stomach and allows the hormone to reach the bloodstream. Insulin was encased in a polymeric chitosan shell, and administered to diabetic rats. The insulin-loaded nanoparticles were found to lower blood-glucose levels, whereas plain insulin delivered orally resulted in little or no effect. However, all the above described four techniques need some more laboratory work to support their potential bioactivity and safety.

CONCLUSION

Presence of insulin-like protein in plants has been investigated since the discovery of insulin in pancreas of dog. Later contributions of people from different parts of the world with sound modern techniques, evidence the presence of insulin like protein in microbes, as well as in higher plants. All these evidence indicate that plant peptide hormones whose actions are similar to peptide hormones thought to be present only in vertebrates, namely insulin and the insulin-like growth factors, are also present in plants. Some of these have been isolated and characterized, their amino acid sequences determined and shown to share many chemical and biological properties with animal protein. And they are active molecules, effectively communicating with animal cell's signaling mechanism and mediate insulin action. Oral drugs for diabetes lose their effectiveness after an initial period of success, eventually they fail to produce a positive effect on long term treatment. Usage of synthetic drugs at minimal dose was reported to be beneficial, but in the long term they show certain untoward adverse effects such as sulphonylureas are associated with increased cardiovascular mortality, hypoglycemia, allergic skin reactions, headache, fatigue, nausea, vomiting and liver damage. Gastrointestinal intolerance such as flatulence, diarrhoea and mild pain in the abdomen are the major adverse effects of acarbos. Metformin leads to gastro-intestinal obstructions which include nausea, bloating, diarrhoea and abdominal cramping. Moreover, all the drugs are excreted by the kidneys and are complicated in patients with renal disease, liver disease, and cardiac or respiratory insufficiency. The demerits of synthetic drugs and to meet the worldwide growing diabetic population for insulin, attention of researchers, pharmacological companies and other investors in the search of alternative drugs and drug targets to manage diabetes is soaring high. Further exploration of glucokinase in various plants will pave way for a new promising therapy with lesser adverse effects from cheaper sources and also give us a clue of evolutionary existence of the insulin hormone and more. Commercial applicability of glucokinase greatly depends on the level of its expression or production, cost of its down stream processes, extended ligand-receptor interaction and also on biocompatibility.

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