“Polypeptide-k” as phytoinsulin: How much and how far

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Abstract

Diabetes mellitus (DM) is a metabolic disorder characterized by high blood glucose levels, occurs due to insulin resistance or insulin deficiency. In 2015, 415 million people worldwide suffered from DM. There have been number of antidiabetic drugs and recombinant DNA insulin used for diabetes; however, these have certain limitations in terms of side effects and cost. Need of society and efforts of scientists led to discovery of phytoinsulins. A plethora of literature is available with reports of the presence of insulin-like hormones in plants. These include bacteria (Escherichia coli), protozoa (Tetrahymena pyriformis), fungi (Neurospora crassa and Aspergillus fumigatus), and plant (Momordica charantia, Canavalia ensiformis, Vigna unguiculata, Bauhinia variegate, and Spirulina maxima) that are used to treat DM. This theory of presence of phytoinsulins has been further strengthened by presence proteins associated with insulin signaling pathways in plants. Polypeptide-k (PPK), an isolated peptide from M. charantia has shown its therapeutic potential as antidiabetic drug. It has structural similarity with insulin moreover, safety and efficacy of PPK as antidiabetic drug has been proven through various preclinical and clinical studies. Phytoinsulins like PPK have potential to replace costly recombinant DNA insulin. However, more clinical studies are required to establish PPK and other phytoinsulins to establish as first-line therapy in the management of diabetes.

Key words: Antihyperglycemic protein, diabetes mellitus, marketed formulations, Momordica charantia, polypeptide-k

INTRODUCTION

Diabetes mellitus (DM) is considered as one of the global health emergencies of the 21st century. Many people are still unaware about its complications. About 50% of people remain undiagnosed with diabetes. This lack of awareness is one of the biggest barriers in management of DM. In 2015, 415 million people worldwide suffered from DM. This number has been predicted to be increased to 649 million by 2040. DM leads to death of 5 million people worldwide in 2015. When this number is compared in terms of mortality with mortality of malaria (0.6 million), tuberculosis (1.5 million) and acquired immunodeficiency syndrome (1.5 million), this number is several times more than these.[1] Number of children with type 1 DM (T1DM) was 5,42,000 worldwide in 2015. The prevalence of DM in South East Asia in 2015 was 8.5% with 78 million peoples suffering from DM. After China, India is the second largest country with higher prevalence of diabetes with 69.2 million peoples in 2015. There were about 1.2 million deaths estimated due to DM in South East Asia out of them about 1 million, were reported only in India. In 2040, the prevalence of people with diabetes was estimated to be 140 million in South East Asia. The prevalence of children with T1DM was 81,400 in 2015 rising with rate of 13,100 every year in South East Asia. Out of these 70,200 children with T1DM live only in India.[1]

DM is a metabolic disorder characterized by high blood glucose levels, occurs due to insulin resistance or insulin deficiency.[2,3] Diabetes was reported 3000 years ago, in Egyptian manuscript.[4] Type 2 DM (T2DM) is the most common form of diabetes characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.[5]
A person is diagnosed with diabetes when his fasting plasma glucose levels >126 mg/dl or postprandial glucose levels >200 mg/dl or glycated hemoglobin (HbA1c) levels >6.5%.\(^3\)

Uncontrolled diabetes may cause various acute and chronic complications such as retinopathy, cardiovascular disease, neuropathy, nephropathy, diabetic foot, and diabetes ketoacidosis.\(^3\) Poor management of diabetes will cause early deaths and serious complications. However, a good management of diabetes and glucose levels with increase the quality of life and patient can live a long healthy life.\(^1\) United Nation has kept the goal to reduce the mortality from non-communicable disease to one-third by 2030.\(^1\)

Diabetes cannot be treated but can be managed with the help of insulin and oral antidiabetic drugs. As discussed, uncontrolled glucose levels may cause serious complications. Hence, management of diabetes is very important.\(^3\) Since no or negligible insulin is produced in T1DM hence, administration of insulin is used for management of T1DM. In T2DM, both insulin and oral antidiabetic drugs can be used.\(^6,7\) Subcutaneous administration of insulin to manage diabetes in one of the key treatment options but it has certain limitations such as painful delivery through subcutaneous route, lipid hypertrophy, and risk of hypoglycemia. Since insulin has to be administered regularly and the treatment period is long, such complications are very common to occur.\(^6,7\) There have been number of antidiabetic drugs and recombinant DNA insulin used for diabetes; however, these also have limitations in terms of side effects and cost. Various oral antidiabetic drugs used are categorized as sulfonylureas, gliptins, sodium/glucose cotransporter 2 (SGLT2) inhibitors, biguanides, α-glucosidase inhibitors, meglitinide analogs, and thiazolidinediones. Sulfonylureas usually cause hypoglycemia (especially with chlorpropamide and glibenclamide).\(^8,9\) Different types of insulin and antihyperglycemics with mechanism of action is listed in Tables 1 and 2.\(^10\)

Meglitinides may cause a range of side effects, most commonly hypoglycemia, visual disturbances, abdominal pain, diarrhea, constipation, nausea, and vomiting. Thiazolidinediones such as rosiglitazone and pioglitazone may cause edema, particularly in patient with hypertension and risks of other cardiovascular diseases. α-glucosidase inhibitors like acarbose causes abdominal discomfort associated with flatulence and diarrhea.\(^9\) Gliptins and glucagon-like peptide-1 (GLP-1) analogs can cause pancreatitis while SGLT2 inhibitor can lead to urinary tract infections.\(^9\) GLP-1 analogs administered by subcutaneous route which is painful.

Thus, all the options available for management of diabetes will have their own limitations. These will cause a variety of side effects and also need to take regularly for the management of diabetes for a lifetime. Hence, there is a need for the development of safe and effective herbal alternative for effective management of diabetes.\(^11\)

In contrast to allopathic treatments, the availability of herbal compounds from plant sources for the treatment of DM has provided a new era to rethink on indigenous remedies. The main advantage of these products relies on their safety as compared to allopathic drugs. Some of the herbal compounds used to treat DM are listed in Table 3.\(^12-155\)

### PHYTOINSULINS

Insulin is the major hormone that regulates glucose metabolism in body. Various roles of it are shown in Figure 1. Insulin is basically obtained from animal sources; however, there are various plants from which insulin type of peptides

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**Table 1: Types of insulin, their onset and duration of action, and mechanism of action\(^{10}\)**

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Onset of action (h)</th>
<th>Duration of action (h)</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>0.2-0.3</td>
<td>3-5</td>
<td>Insulin is anabolic hormone: Promotes synthesis of glycogen, lipids, and protein</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>0.2-0.3</td>
<td>3-5</td>
<td></td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>0.2-0.4</td>
<td>3-5</td>
<td></td>
</tr>
<tr>
<td>Short acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular (soluble) insulin</td>
<td>0.5-1</td>
<td>2-3</td>
<td></td>
</tr>
<tr>
<td>Intermediate acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin zinc suspension or lente</td>
<td>1-2</td>
<td>20-24</td>
<td></td>
</tr>
<tr>
<td>NPH or isophane insulin</td>
<td>1-2</td>
<td>20-24</td>
<td></td>
</tr>
<tr>
<td>Long acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>2-4</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>1-4</td>
<td>20-24</td>
<td></td>
</tr>
</tbody>
</table>

NPH: Neutral protamine hagedorn
could be obtained which work in a similar way as that of insulin. This article basically focuses on phytoinsulins with more emphasis on polypeptide-k (PPK).

**Early era of Phytoinsulins**

Drugs of herbal origin could be one of the best alternatives for management of diabetes. Plants are important source of herbal medicine used for various ailments of human body. The use of number of medicinal plants in the treatment of diabetes has been mentioned in ayurvedic literature. A number of plants have been used for treatment of diabetes mentioned in Indian, Chinese, and Egyptian literature.[11] Phyto diab care database on herbal plant used in diabetes enlists 230 plants and 155 phytochemicals having medicinal activity against diabetes.[11]

Glucokinin, an insulin-like proteins is detected in various plants and microbes showing similar functions like animal insulin.[15] A number of medicinal plants such as *Allium cepa,*

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**Table 2: Types of antihyperglycemics with MOA**

<table>
<thead>
<tr>
<th>Antidiabetic drug</th>
<th>Preparations</th>
<th>DOA (h)</th>
<th>Daily dose</th>
<th>Number of doses per day</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Rastinon (0.5 g tablets)</td>
<td>6-8</td>
<td>0.5-3 g</td>
<td>2-3</td>
<td>ATP sensitive K+ channel blockers leading to depolarization of beta cells which results to release of insulin from stored granules</td>
</tr>
<tr>
<td>Glibenclamide (glyburide)</td>
<td>Daonil, euglucotan (2.5, 5 mg tablets)</td>
<td>24</td>
<td>2.5-15 mg</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>Glynase, gled minidiab (5 mg tablet)</td>
<td>12</td>
<td>5-20 mg</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td>Glliclazide</td>
<td>Diamicron (80 mg tablet), diazide (20,80 mg tablet), glizid (30,40,80 mg tablet)</td>
<td>12-24</td>
<td>40-240 mg</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Amaryl, glypride, glimer (1.2 mg tablet)</td>
<td>24</td>
<td>1-6 mg</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td><strong>Meglitinide/phenylalanine analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Eurepa, raplin regan (0.5,1.2 mg tablet)</td>
<td>3-5</td>
<td>1-8 mg</td>
<td>3-4</td>
<td>ATP sensitive K+ channel blockers with quick and short lasting insulinemic action</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Glinate, natelide (60,120 mg tablet)</td>
<td>2-4</td>
<td>180-480 mg</td>
<td>3-4</td>
<td></td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Januvia (100 mg tablet)</td>
<td>24</td>
<td>100 mg</td>
<td>1</td>
<td>DDP-4 inhibitors, which prevent degradation of GLP-1 which induces release of insulin</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Galvus, jala, zomelis (50 mg capsule)</td>
<td>12-24</td>
<td>50-100 mg</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td><strong>Bisguanide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Glyciphage, gyomet (0.5, 0.85 g tablet, 0.5 g and 1.0 g SR tablets)</td>
<td>6-8</td>
<td>0.5-2.5 g</td>
<td>1-2</td>
<td>AMPK inhibitor, which mediate actions of biguanide</td>
</tr>
<tr>
<td><strong>Thiazolidinedione</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Pionorm, Pioresit, Piozone (15, 30 mg tablet)</td>
<td>24</td>
<td>15-45 mg</td>
<td>1</td>
<td>Selective agonists for the nuclear PPAR-α which enhances the transcription of several insulin responsive genes</td>
</tr>
</tbody>
</table>

DPP-4: Dipeptidyl peptidase 4, GLP-1: Glucagon like peptide-1, AMPK: AMP dependent protein kinase, PPAR-α: Peroxisome proliferator active receptor alpha, ATP: Adenosine tri phosphate
Allium sativum, Aloe vera, Cajanus cajan, Coccinia indica, Caesalpinia bonducella, Ficus benghalensis, Gymnema sylvestre, Momordica charantia (MC), Ocimum sanctum, Pterocarpus marsupium, Swertia chirayita, Syzygium cumini, Tinospora cordifolia, Trigonella foenum graecum, Mucuna pruriens, Murraya koenigii, and Brassica juncea have antidiabetic potential.[157]

Pancreatic insulin was discovered by Banting in 1921-1922 after a collective effort led by Frederick Banting.[158] J.B. Collip and C.H. Best first published a paper on the presence of insulin-like substances in plant materials such as green tops of onions, lettuce leaves, green bean leaves, barley roots, and beetroots.[159] Discovery of insulin-like hormones in plants opened a new field in drug discovery in DM.[156]

Collip in 1923 published a paper on plant insulin. He extracted some phytosulins by several extraction processes including the process used for extraction of insulin from pancreas. When these plant extracts were tested on normal rabbits and pancreatectomized dogs, measurable decrease in glucose levels in blood was observed. He stated that “The discovery of this hormone in tissues of the higher plants as well as in yeast opens up a new field of work in plant metabolism and affords another remarkable example of parallelism in certain physiological processes in the plant and animal kingdom.” In another passage he narrated, “As the name insulin was given by the Toronto group to an extract of pancreas prepared according to a definite method elaborated by the writer, this somewhat analogous hormone derived from plant sources must be known by a more general term. Collip named it as glucokinin in order to differentiate insulin of plant origin from that of animals.”[159]

Best in 1923 reported presence of insulin-like materials in germinating potatoes and rice.[160] They mentioned in their manuscript that: “In November, 1922, during the course of conversation with Dr. R. T. Woodyatt, in which the mechanism of the action of insulin was discussed, the idea presented itself that a hormone analogous to insulin might be present wherever glucose is metabolized, i.e., it might be present in plants.”[160] Best in 1924 also reported the presence of insulin-like materials in beetroot, which exerted the glucose lowering effect similar to insulin.[161-163] Even a step ahead, Best et al., in 1924, mentioned in their research that insulin may prove to be a constituent of every cell in which carbohydrate is metabolized.[162]

Elis and Eyster in 1924 showed action of insulin and glucokinin on maize germination. It was reported that growth process in plants involves metabolism of large quantity of starch into glucose. Similar process occurred in animals where glycogen mobilization occurred in liver. To carry out this work glucokinin was prepared from onion tops as well as from young maize seedlings and utilized inbred lines of maize. Authors reported both insulin and glucokinin promote the growth of maize seedlings.[164]

Late Era of Phytoinsulin (after 1970’s)

After initial reports of plant insulin in this era, attention has not been provided to plant insulin. Till 1970, none of the scientists...
<table>
<thead>
<tr>
<th>Botanical name</th>
<th>Common name</th>
<th>Parts used</th>
<th>Extracts</th>
<th>Active C.C</th>
<th>Family</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Aegle marmelos</em></td>
<td>Golden apple</td>
<td>Leaf, seed, fruit</td>
<td>Ethanolic, aqueous</td>
<td>Aegeline, coumarin, flavanoid, alkaloid</td>
<td>Rutaceae</td>
<td>Glucose, glycosylated hemoglobin, ↑C peptide, glucose tolerance, glycochen, insulin</td>
</tr>
<tr>
<td><em>Allium sativum</em></td>
<td>Garlic</td>
<td>Root</td>
<td>Ethanolic</td>
<td>Dialyl disulfide oxide, ajoene, allyl propyl disulfide, S-allyl cysteine, S-allyl mercaptocysteine</td>
<td>Alliaceae</td>
<td>Glucose, lipid, ↑insulin, oxidative stress</td>
</tr>
<tr>
<td><em>Averrhoa bilimbi</em></td>
<td>-</td>
<td>Leaf</td>
<td>Aqueous</td>
<td>-</td>
<td>Oxalidaceae</td>
<td>Glucose, lipid</td>
</tr>
<tr>
<td><em>Aloe vera</em></td>
<td>Barbados aloe</td>
<td>Leaf</td>
<td>Ethanolic</td>
<td>Pseudoprototinosaponin, prototinosaponin</td>
<td>Liliaceae</td>
<td>Glycosylated hemoglobin</td>
</tr>
<tr>
<td><em>Amaranthus esculentus</em></td>
<td>-</td>
<td>Whole plant</td>
<td>Oil fraction</td>
<td>-</td>
<td>Amaranthaceae</td>
<td>Glucose, insulin</td>
</tr>
<tr>
<td><em>Annona squamosa</em></td>
<td>Leaf, fruit-pulp</td>
<td>Aqueous, ethanolic</td>
<td>-</td>
<td>-</td>
<td>Annonaceae</td>
<td>Glucose, lipid, lipid peroxidation</td>
</tr>
<tr>
<td><em>Areca catechu</em></td>
<td>Betel nut</td>
<td>Fruit</td>
<td>-</td>
<td>Arecoline</td>
<td>Arecaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td><em>Andrographis paniculata</em></td>
<td>Kalmegh, King of Bitters</td>
<td>Aerial parts</td>
<td>-</td>
<td>Andrographolide</td>
<td>Acanthaceae</td>
<td>Prevents glucose absorption from gut, Glucose</td>
</tr>
<tr>
<td><em>Aerva lanata</em></td>
<td>Sunny Khur</td>
<td>Aerial parts</td>
<td>Alcoholic</td>
<td>-</td>
<td>Amaranthaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td><em>Artemisia pallens</em></td>
<td>Davana</td>
<td>Aerial parts</td>
<td>Methanolic</td>
<td>-</td>
<td>Compositae</td>
<td>Peripheral glucose utilization</td>
</tr>
<tr>
<td><em>Beta vulgaris</em></td>
<td>Beetroot</td>
<td>Whole plant</td>
<td>-</td>
<td>Sugar beet pectin, polydextrose</td>
<td>Chenopodaceae</td>
<td>-</td>
</tr>
<tr>
<td><em>Baccharis trimera</em></td>
<td>-</td>
<td>Leaf</td>
<td>Aqueous</td>
<td>-</td>
<td>Myrtaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td><em>Bryophyllum pinnatum</em></td>
<td>-</td>
<td>Leaf</td>
<td>Alcoholic</td>
<td>-</td>
<td>Crassulaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td><em>Bombax ceiba</em></td>
<td>Silk cotton tree</td>
<td>Leaf</td>
<td>Isolated compound</td>
<td>Shamimin (a flavonol glucoside)</td>
<td>Bombacaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td><em>Barleria lupulina</em></td>
<td>-</td>
<td>Aerial parts</td>
<td>-</td>
<td>-</td>
<td>Acanthaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td><em>Boerhavia diffusa</em></td>
<td>Tar vine</td>
<td>Leaf</td>
<td>Aqueous</td>
<td>-</td>
<td>Nyctaginaceae</td>
<td>Plasma insulin and improves glucose tolerance</td>
</tr>
<tr>
<td><em>Canarium schweinfurth</em></td>
<td>-</td>
<td>Steam bark</td>
<td>Methanolic, methylene chloride</td>
<td>-</td>
<td>Burseraceae</td>
<td>Glucose</td>
</tr>
<tr>
<td><em>Chamaemelum nobilis</em></td>
<td>-</td>
<td>Leaf</td>
<td>Aqueous</td>
<td>-</td>
<td>Asteraceae</td>
<td>Glucose</td>
</tr>
<tr>
<td><em>Coscinium fenestratum</em></td>
<td>-</td>
<td>Stem bark</td>
<td>Alcoholic</td>
<td>-</td>
<td>Menispermaceae</td>
<td>Glucose, glycosylated hemoglobin, glycochen, lipid, oxidative stress</td>
</tr>
</tbody>
</table>

(Contd...)
<table>
<thead>
<tr>
<th>Botanical name</th>
<th>Common name</th>
<th>Parts used</th>
<th>Extracts</th>
<th>Active C.C</th>
<th>Family</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td><strong>Caesalpinia bonducella</strong></td>
<td>Chinese cinnamon</td>
<td>Seed</td>
<td>Ethanolic</td>
<td>-</td>
<td>Cesarinaceae</td>
<td>Insulin from pancreatic cells</td>
</tr>
<tr>
<td><strong>Capparis decidua</strong></td>
<td>-</td>
<td>Fruit</td>
<td>Powdered</td>
<td>-</td>
<td>Capparidaceae</td>
<td>Glucose-6-phosphate dehydrogenase in kidney and heart</td>
</tr>
<tr>
<td><strong>Citrus colocyntsi</strong></td>
<td>Bitter apple</td>
<td>Seed</td>
<td>Aqueous, glycosidic and saponin extract</td>
<td>-</td>
<td>Cucurbitaceae</td>
<td>Insulin</td>
</tr>
<tr>
<td><strong>Cassia auriculata</strong></td>
<td>Carilla Fruit</td>
<td>Root</td>
<td>Aqueous</td>
<td>-</td>
<td>Flacourtiaceae</td>
<td>Glucose, glycosylated hemoglobin, liver hexokinase</td>
</tr>
<tr>
<td><strong>Camellia sinensis</strong></td>
<td>Green tea</td>
<td>Leaf</td>
<td>Hot water extract</td>
<td>Epigallocatechin gallate</td>
<td>Theaceae</td>
<td>Glucose, insulin</td>
</tr>
<tr>
<td><strong>Egyptian Morus alba</strong></td>
<td>-</td>
<td>Stem bark</td>
<td>Alcoholic</td>
<td>-</td>
<td>Moraceae</td>
<td>Glucose, lipid peroxidation, ↑insulin</td>
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<tr>
<td><strong>Enecostemma littorale</strong></td>
<td>Chhota chirayata</td>
<td>Whole plant</td>
<td>Aqueous</td>
<td>-</td>
<td>Gentilaceae</td>
<td>Glycosylated haemoglobin, glucose-6- phosphate activity in liver, insulin</td>
</tr>
<tr>
<td><strong>Eugenia jambolana</strong></td>
<td>Indian blackberry</td>
<td>Fruit pulp, seed</td>
<td>Aqueous, ethanolic</td>
<td>Myrtaceae</td>
<td>Glycine, lipid, glucose tolerance</td>
<td></td>
</tr>
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<td><strong>Eugenia uniflora</strong></td>
<td>Pitanga</td>
<td>Leaf</td>
<td>Ethanolic</td>
<td>-</td>
<td>Myrtaceae</td>
<td>Inhibit increase in plasma glucose level</td>
</tr>
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<td><strong>Glycyrriza glabra</strong></td>
<td>licorice</td>
<td>Root</td>
<td>-</td>
<td>Glycyrrhizinic acid</td>
<td>Fabaceae</td>
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<td>Alcoholic</td>
<td>-</td>
<td>Asclepiadaceae</td>
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<td>methanolic</td>
<td>-</td>
<td>Rubiaceae</td>
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<td>Fruit</td>
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<td>Hypoxidaceae</td>
<td>Glucose</td>
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<tr>
<td><strong>Hibiscus rosa sinensis</strong></td>
<td>China rose</td>
<td>Leaf, flower</td>
<td>Ethanolic</td>
<td>-</td>
<td>Malvaceae</td>
<td>Insulin, utilization of glucose</td>
</tr>
<tr>
<td><strong>Ipomoea batatas</strong></td>
<td>Sweet potato</td>
<td>Storage roots</td>
<td>Isolated compound</td>
<td>Diacylated anthocyanin</td>
<td>Convolvulaceae</td>
<td>Insulin resistance and acts by maltase inhibition</td>
</tr>
<tr>
<td><strong>Lepidium sativum</strong></td>
<td>-</td>
<td>Leaf</td>
<td>Aqueous</td>
<td>-</td>
<td>Brassicaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td><strong>Lycium barbarum</strong></td>
<td>Chirchita</td>
<td>Fruit</td>
<td>Crude polysaccharide extract</td>
<td>Polysaccharide</td>
<td>Solanaceae</td>
<td>Glucose, oxidative stress, GLUT-4, ↑insulin</td>
</tr>
</tbody>
</table>

*(Continued...)*
<table>
<thead>
<tr>
<th>Botanical name</th>
<th>Common name</th>
<th>Parts used</th>
<th>Extracts</th>
<th>Active C.C</th>
<th>Family</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leonotis leonurus[17,62-64]</td>
<td>-</td>
<td>Leaf</td>
<td>Aqueous</td>
<td></td>
<td>Lamiaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td>Lantana camara[133]</td>
<td>-</td>
<td>Leaf</td>
<td>Leaf juice</td>
<td></td>
<td>Verbenaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td>Momordica charantia[16,17,49-58]</td>
<td>Bitter melon</td>
<td>Whole plant</td>
<td>methanolic, aqueous, chloroform</td>
<td>Charantin, momordicin, galactosebinding lectin non-bitter, diosgenin, cholesterol, lanosterol, (\beta)-sitosterol, cucurbitacin glycoside</td>
<td>Cucurbitaceae</td>
<td>Glucose, glycosylated hemoglobin, oxidative stress, glycogen, lipid peroxidation</td>
</tr>
<tr>
<td>Momordica cymbalaria[16,17,49-58]</td>
<td>Kaarali-kanda</td>
<td>Fruit</td>
<td>Aqueous</td>
<td>Steroidal glycoside or phenolics</td>
<td>Cucurbitaceae</td>
<td>-</td>
</tr>
<tr>
<td>Mangifera indica[16,17,60,61]</td>
<td>Mango tree</td>
<td>Fruit, leaf, stem bark</td>
<td>Ethanolic</td>
<td>Mangiferin, phenolics, flavonoid</td>
<td>Anacardiaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td>Malmea depressa[24,67-70]</td>
<td>-</td>
<td>Root</td>
<td>Aqueous, ethanolic, n-butanol fraction</td>
<td></td>
<td>Annonaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td>Memecylon umbellatum[134]</td>
<td>-</td>
<td>Leaf</td>
<td>Alcoholic</td>
<td></td>
<td>Melastomataceae</td>
<td>Glucose</td>
</tr>
<tr>
<td>Mucuna pruriens[135,136]</td>
<td>Velvet bean</td>
<td>Seed, whole plant</td>
<td>Powdered seeds, alcoholic extract of plant</td>
<td>Terpen, flavonoid, strictinin, isostictinin, pedunculagin, polysaccharide</td>
<td>Leguminosae</td>
<td>Insulin, glucose</td>
</tr>
<tr>
<td>Psidium guajava[16,17,40-43]</td>
<td>Guava</td>
<td>Leaf, fruit</td>
<td>Aqueous, methanolic</td>
<td></td>
<td>Myrtaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td>Phyllanthus embica; Phyllanthus acidus[16,17,59]</td>
<td>Indian gooseberry</td>
<td>Fruit</td>
<td>Aqueous</td>
<td>Tannin</td>
<td>Euphorbiaceae</td>
<td>-</td>
</tr>
<tr>
<td>Piper betle[80,81]</td>
<td>Pan</td>
<td>Leaf</td>
<td>Aqueous</td>
<td></td>
<td>Piperaceae</td>
<td>Glucose, glycosylated hemoglobin</td>
</tr>
<tr>
<td>Picrohiza kurroa[136]</td>
<td>-</td>
<td>Leaf, bark, root, rhizomes</td>
<td>Alcoholic extract</td>
<td></td>
<td>Scrophulariaceae</td>
<td>Glucose levels in serum, serum lipid peroxides</td>
</tr>
<tr>
<td>Phyllanthus amarus[137,138]</td>
<td>-</td>
<td>Leaf</td>
<td>Methanolic extract</td>
<td></td>
<td>Euphorbiaceae</td>
<td>Glucose, glycosylated hemoglobin</td>
</tr>
<tr>
<td>Pterocarpus marsupium[139,140]</td>
<td>Vijaysar</td>
<td>Bark and heart wood</td>
<td>Isolated compounds</td>
<td>Epicatechin, marsupsin, pterosupin, pterostilbene</td>
<td>Fabaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td>Pterocarpus santalinus[154]</td>
<td>-</td>
<td>Bark</td>
<td>Aqueous</td>
<td></td>
<td>Leguminosae</td>
<td>Glucose</td>
</tr>
</tbody>
</table>

(Contd...)
<table>
<thead>
<tr>
<th>Botanical name</th>
<th>Common name</th>
<th>Parts used</th>
<th>Extracts</th>
<th>Active C.C</th>
<th>Family</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retama raetam</td>
<td>-</td>
<td>Whole plant</td>
<td>Aqueous</td>
<td>-</td>
<td>Fabaceae</td>
<td>Glucose</td>
</tr>
<tr>
<td>Raphanus sativus</td>
<td>-</td>
<td>Whole plant</td>
<td>Aqueous</td>
<td>-</td>
<td>Brassicaceae</td>
<td>Glucose, lipid, ↓insulin</td>
</tr>
<tr>
<td>Syzygium cordatum</td>
<td>-</td>
<td>Leaf</td>
<td>Aqueous</td>
<td>-</td>
<td>Myrtaceae</td>
<td>↓Glucose, ↑hepatic glycogen</td>
</tr>
<tr>
<td>Salvia officinalis</td>
<td>-</td>
<td>Leaf</td>
<td>Aqueous</td>
<td>-</td>
<td>Lamiaceae</td>
<td>↓Glucose; ↓gluconeogenesis</td>
</tr>
<tr>
<td>Scoparia dulcis</td>
<td>-</td>
<td>Whole plant</td>
<td>Aqueous</td>
<td>-</td>
<td>Scrophulariaceae</td>
<td>↓Glucose, ↓lipid, ↓oxidative stress, ↑insulin</td>
</tr>
<tr>
<td>Strobilanthes crispus</td>
<td>-</td>
<td>Leaf</td>
<td>Aqueous</td>
<td>-</td>
<td>Acanthaceae</td>
<td>↓Glucose</td>
</tr>
<tr>
<td>Salacia reticulata</td>
<td>Salacia</td>
<td>Leaf</td>
<td>Aqueous decoction</td>
<td>Salacinol (alpha–glucosidase inhibitor)</td>
<td>Celastaceae</td>
<td>↓Glucose, inhibits alpha–glucosidase activity</td>
</tr>
<tr>
<td>Salacia oblonga</td>
<td>-</td>
<td>Root</td>
<td>Aqueous methanolic extract</td>
<td>-</td>
<td>Celastaceae</td>
<td>↓Glucose, inhibits alpha–glucosidase activity</td>
</tr>
<tr>
<td>Swertia chiravita</td>
<td>Indian gentian</td>
<td>Hexane fraction of plant</td>
<td>Isolated compound</td>
<td>Swerchirin</td>
<td>Gentianaceae</td>
<td>↑Insulin secretion from islets of langerhans</td>
</tr>
<tr>
<td>Scoparia dulcis</td>
<td>Broomweed</td>
<td>Leaf</td>
<td>Aqueous</td>
<td>-</td>
<td>Scrophulariaceae</td>
<td>↓Glucose, ↓glycosylated hemoglobin, ↑plasma insulin, ↑plasma anti-oxidants</td>
</tr>
<tr>
<td>Syzygium alternifolium</td>
<td>-</td>
<td>Seed</td>
<td>Aqueous, ethanolic, hexane</td>
<td>-</td>
<td>Myrtaceae</td>
<td>↓Glucose</td>
</tr>
<tr>
<td>Sida cordifolia</td>
<td>-</td>
<td>Root</td>
<td>Methanolic chloroform, aqueous</td>
<td>-</td>
<td>Malvaceae</td>
<td>↓Glucose</td>
</tr>
<tr>
<td>Terminalia chebulic myrobalan</td>
<td>Fruit, seed</td>
<td>Shikimic, gallic, triacontanoic, palmitc acid, β-sitosterol, daucosterol</td>
<td>-</td>
<td>Combretaceae</td>
<td>↓Glucose</td>
<td></td>
</tr>
<tr>
<td>Terminalia superba</td>
<td>Stem bark</td>
<td>methanolic, methylene chloride</td>
<td>-</td>
<td>Combretaceae</td>
<td>↓Glucose</td>
<td></td>
</tr>
<tr>
<td>Terminalia pallid</td>
<td>Fruit</td>
<td>Ethanolic</td>
<td>-</td>
<td>Combretaceae</td>
<td>↓Glucose</td>
<td></td>
</tr>
<tr>
<td>Terminalia arjuna</td>
<td>Arjuna</td>
<td>Stem bark</td>
<td>Ethanolic</td>
<td>-</td>
<td>Combretaceae</td>
<td>↓Glucose-6-phosphatase, ↓fructose-1,6diphosphatase, ↓aldolase, ↑phosphoglucomerase, ↑hexokinase</td>
</tr>
</tbody>
</table>
Botanical name | Common name | Parts used | Extracts | Active C.C | Result |
--- | --- | --- | --- | --- | --- |
*Tinospora cordifolia* | - | Leaf | Hexane | ↓Glucose | ↓Glucose |
*Trigonella foenum‑graecum* | Fenugreek | Seed | Isolated compound from fibers, proteins and saponins from seeds | Isolated | ↓Glucose |
*Ziziphus spinifera* | Christ thorn | Leaf | n‑butanol fraction, hydroalcoholic | Christinin‑A, fatty acid | ↓Glucose |

| GLUT-4: Glucose transporter type 4 | | | |

Table 3: (Continued)

or research groups started research on phytoinsulins. But phytoinsulins, again came into picture when in 1970 Pusha Khanna reported the presence of insulin in plants.[165] Khanna, in 1976, patented a process for production of plant insulin from MC.[166] Phytoinsulin isolated from MC was called as polypeptide-p (PPP) or p insulin. This PPP was reported to have hypoglycemic activity.[167]

Ng et al., in 1986, further worked on plant insulin and extracted it utilizing the seeds with acid ethanol procedure from several tissues. They also concluded that the seeds of MC contain insulin-like molecules.[168] Collir et al., in 1987, published results on the isolation of proteins from etiolated rye, leaves of spinach and *Lemna gibba*, which showed properties similar to animal insulin. However, the sequence analysis was not performed on plant insulin and did not contributed further to the field.[169]

Various peptide hormones whose actions are similar to insulin and the insulin-like growth factors are also present in plants.

### Functions of Phytoinsulins and Similarity with Insulin Pathways

Plant insulin possess similar properties like animal insulin. It possesses various metabolic activities like animal insulin. They help in glucose transportation by various metabolic activities. Eyster and Elis showed similar activities in maize plant.[164]

A protein isolated from MC when given orally showed reduction in blood glucose levels at the predetermined points, i.e., 30, 60, 90, 150 and 180 min in a glucose infusion study on Sprange-Dawley rats. In another study on the preventive model of streptozotocin-induced diabetes showed, the fraction isolated from MC supported its suitability in treating Type I autoimmune diabetes.[166,167,170] Carboxymethyl cellulose (CMC) purified substances of spinach and *L. gibba* were comparable with labeled insulin for binding to insulin receptors on IM-9 lymphocytes in a dose-dependent manner.[169] An extract of *Bauhinia variegate* showed similar properties as that of bovine insulin was studied for its hypoglycemic activity in Swiss albino mice. Intravenous injection of crude protein extract and eluted protein fractions showed a significant decrease in blood glucose levels as similar to that promoted by commercial swine insulin.[171] A number of reports published that suggested 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. Table 4[172-179] enlists various plant proteins having similar mechanism of action as that of insulin signaling pathway in Figure 2.[180,181]

Insulin receptor is a member of family of ligand-activated receptor tyrosine kinase that includes receptors for many growth factors. Intracellular portion of receptor consist of tyrosine kinase activity.[182] Many plants consist of number
One such transporter was cloned from sugar beet showed high sequence homology with a mammalian glucose transporter. Hong and Verma showed homology of cloned phosphatidylinositol 3-kinase (PI3K) cDNA from soybean to mammalian PI3K. PI3K activation is one of important steps in insulin stimulation of glucose transport.

Despite this disbelief, a number of reviews have recently appeared presenting a body of circumstantial evidence that suggests that the presence of insulin in plants will be recognized.

**Table 4: Plant species having sequence homology of proteins of insulin signaling pathway**

<table>
<thead>
<tr>
<th>Proteins of insulin signaling pathway</th>
<th>Plant source</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTK</td>
<td><em>Arabidopsis thaliana</em></td>
<td>173</td>
</tr>
<tr>
<td>IRS protein</td>
<td><em>Arabidopsis thaliana</em>-LSD 1 gene</td>
<td>174</td>
</tr>
<tr>
<td>GLUT-4</td>
<td>Sugar beet</td>
<td>175</td>
</tr>
<tr>
<td>PI3K</td>
<td>Soybean from its cDNA</td>
<td>176, 177</td>
</tr>
<tr>
<td>Hexokinase</td>
<td>Plant hexokinase which is involved in sugar sensing process</td>
<td>178</td>
</tr>
<tr>
<td>MAPK pathway</td>
<td>Rice associated with insulin involved in promotion of its cellular growth</td>
<td>179</td>
</tr>
<tr>
<td>TOR</td>
<td>A potential component of the PI3K pathway in <em>Drosophila</em></td>
<td>180</td>
</tr>
</tbody>
</table>

RTK: Receptor tyrosine kinase, GLUT-4: Glucose transporter type 4, PI3K: Phosphoinositide 3-kinase, TOR: Target of Rapamycin, IRS protein: Insulin receptor substrate proteins

**MC AND ITS PHYTOINSULINS**

**MC**

MC also called as bitter gourd is a medicinal plant belonging to the family Cucurbitaceae. It is well known for its use as traditional medicine in developing countries such as “Brazil, China, Columbia, Cuba, Ghana, Haiti, India Mexico, Malaya, New Zealand, Nicaragua, Panama and Peru.” MC has antimicrobial, antihelminthic, anticancerous, antimitagenic, antitumorous, abortificient, antifertility, and antidiabetic properties. It is used for treatment of diabetes, expulsion of glucose/hexose transporters. One such transporter was cloned from sugar beet showed high sequence homology with a mammalian glucose transporter.
of intestinal gas, promotion of menstruation, treatment of measles, hepatitis, and febrile conditions.\[186\]

“In Brazil MC is used for treatment of tumours, wounds, rheumatoid arthritis, malaria, vaginal discharge, inflammation, menstrual problems, diabetes, fevers, and worms. It is also used to induce abortions, as an aphrodisiac, treatment of vaginitis, hemorrhoids, scabies, itchy rashes, eczema, leprosy and other skin problems. In Peruvian herbal medicine, the leaf or aerial parts of the plant are used to treat measles, malaria, and all types of inflammation. In Nicaragua, the leaf is commonly used for stomach pain, diabetes, fevers, colds, coughs, headaches, malaria, skin complaints, menstrual disorders, aches and pains, hypertension, infections, and as an aid in childbirth.”\[186\] In India, it is well known for antidiabetic and laxative properties. It is also used for treatment of dysmenorrhea, eczema, emmenagogue, galactagogue, gout, jaundice, kidney stones, leucorrhrea, leprosy, piles, pneumonia, scabies, and rheumatism.\[186\]

MC contains biologically active chemicals that include glycosides, saponins, alkaloids, fixed oils, triterpenes, proteins, and steroids.\[187\] Extracts of MC fruit (250 mg/kg) within 2 weeks of treatment achieved euglycemic activity.\[187\]

Antidiabetic activity has been shown by various animal and human studies.\[189-199\] MC has many pytoconstituents which act as antidiabetic and antilipidemic. A polyherbal preparations containing MC showed significant reduction in blood glucose, glycosylated hemoglobin, increase in plasma insulin and total hemoglobin in animals.\[190\] MC has shown its effectiveness in complications of diabetes such as nephropathy and neuropathy.\[190\] With the time and search of newer and safer antidiabetic agent, scientists have been able to find the active constituents responsible for antidiabetic activity of MC. The two isolated peptides having similarity with insulin and called as phyto insulin of MC that are PPP and PPK.\[166,167,200\]

PPP

PPP is a polypeptide extracted from MC with structural similarity with bovine insulin. It differs from bovine insulin in respect of extra amino acid methionine.\[195\] Three dimensional structure of PPP shows that it has 2 chains of amino acids linked together by sulfide bonds. PPP was shown to be stable at 4°C. The electrophoretic pattern also resembles that of bovine insulin. “Infrared spectrum of p-insulin is superimposable on that of standard zinc crystalline insulin.”\[199,201\]

Efficacy of PPP has been reported in animals as well as humans. Antidiabetic activity of PPP has been reported in gerbils and male langurs. For this study, 0.5 units per kg body weight dose of PPP was given subcutaneously to one group and normal saline to another group. Significant glucose lowering capacity of PPP was observed in both gerbils and langurs.\[199-201\]

In a clinical trial conducted on 9 patients, reduction of 45.8% \(\pm 13.6\)% blood glucose level was observed on single subcutaneous injection of PPP. The decrease in blood glucose level started in 30-60 min and maximum effect was observed at 4-8 h in juvenile patients and at 12 h in adults suffering from type 2 diabetes.\[199\]

Another study was conducted on 19 human subjects (type 1 diabetes mellitus: 11 subjects, type 2 diabetes: 8 subjects). PPP had significantly reduced blood glucose levels in both type 1 and type 2 diabetic patients. The results of polypeptide P were found similar to that of neutral protamine hagedorn insulin in term of action. However, no side effects were observed with PPP.\[199-201\]

Despite such a good similarity with animal insulin, in terms of structure and actions, PPP was unable to make its place in market. It may be due to ignorance of pharmaceutical companies toward this phytoinsulin over drugs of synthetic origin or, due to the challenge of cultivation and extraction. Till date, no formulation of this protein is marketed in any of the countries. Another reason for this is due to its use by subcutaneous route and its unstability via oral route. One more such protein was isolated from MC which overcomes these drawbacks of PPP.

PPK

PPK is a protein isolated from dried seeds and fruits of MC. PPK has structural and functional similarity with insulin. Work “k” is used for Karela which is Hindi name for MC.\[167,200\]

The most abundant amino acids are glutamic acid (17.08%), aspartic acid (9.71%), arginine (9.50%), and glycine (8.90%).\[159\] PPK possess a challenge in formulation development because of its limited solubility. Its solubility is reported in 10% v/v formic acid and ammonia buffer pH 9.5. It has reported stability of 18 months at room temperature.\[167,200\]

PPK has also shown to possess \(\alpha\)-glucosidase inhibitory properties, which is similar to Voglibose. An \textit{in vitro} study showed 79.18% inhibition of \(\alpha\)-glucosidase and 35.58% inhibition of \(\alpha\)-amylase with PPK. The significant inhibition of \(\alpha\)-glucosidase and \(\alpha\)-amylase revealed the potential of PPK as an antihyperglycemic agent.\[202\]

Extraction of PPK was reported in patent by Khanna et al. (2004).\[200\] Dried seeds from ripe fruits were used for extraction of PPK. These seeds were crushed to fine powder and kept in mixture of hexane and acetone in ratio of 3:1 for de-oiling. This mixture was then filtered and powder was dried and dispersed in water, pH was adjusted to 9.5 with ammonium hydroxide. Supernatant was collected and pH was adjusted to 3 with dilutesulfuric acid. Formed precipitates were filtered. These were further washed with water and acetone mixture to remove impurities. This dried precipitates were PPK.\[200,203,204\]
Various studies are available on safety and efficacy of PPK. PPK is reported to be safe even at higher doses in animals. A study published by Hakim et al., in 2011, showed safety of PPK in rats. Rats were divided into three groups with 10 rats in each group. After acclimatizing rats for 7 days, on 8th day rats were given oral dose of - 1000 mg/kg (group 1), 500 mg/kg (group 2) and 0 mg/kg (group 3). No signs of toxicity were observed even after 72 h of dosing. At the end of 72 h rats were sacrificed, organs were isolated and weighed. Weight of liver in control group, Group 2 and Group 3 was found to be 4.35, 4.12 and 4.42 g/100 g body weight, respectively. The weight of kidney in control group, Group 2 and Group 3 was found to be 6.70, 6.92 and 6.59 g/100 g body weight, respectively. Weight of heart in control group, group 2 and group 3 was found to be 3.20, 3.15 and 3.35 g/100 g body weight, respectively. Weight of lungs in control, Group 2 and Group 3 was found to be 5.89, 5.71 and 5.74 g/100 g body weight, respectively. Thus, statistically similar (P < 0.05) organ weight was observed in all the groups. Moreover, histopathological examination of liver, heart, kidney and lungs disclosed normal histopathology. The biochemical analysis such as liver function test and kidney function test revealed no change in the level of blood urea nitrogen and creatinine. There was no change observed in hematological and histological parameters of rats. It was concluded in the study that the doses of up to 100mg/kg did not have any adverse effects on rats. [205]

PPK is found to have antidiabetic activity in various human studies. Khanna reported that PPK has the ability to rejuvenate pancreas and activate insulin. Route of delivery was confirmed (i.e., Polymerase enzyme-DNA-tRNA-mRNA and then to pancreas), which leads to rejuvenation of pancreatic cells.[206] Several case studies reported 12-70 mg of PPK powder has antihyperglycemic activity. PPK showed not only antihyperglycemic activity but also reduces, blood pressure and lipids. It also reduces nephropathy and neuropathy. [167,268,207]

A study on 18 healthy human volunteers was conducted to show hypoglycemic activity of PPK supplemented soft buns. Each bun consists of 2 mg of PPK. Same buns were used in both test and control except PPK was added in buns of test group. Significant decrease in glucose was observed with PPK supplemented buns as compared to control buns at 90, 150, and 210 min.” Blood glucose level with PPK supplemented soft roll bun was further dropped to - 0.9 mmol/L after 210 min while for control soft roll bun, a slight drop of - 0.2 mmol/L in blood glucose level was observed. PPK supplemented soft roll caused decreased in sugar level as compared to control soft roll in healthy adults.[208] A significant reduction in blood glucose levels (50%) and 42% reduction in glycated hemoglobin HbA1c was observed.[209] A combination of PPK along with spirulina buccal tablet was claimed to have better antidiabetic activity than PPK alone in a patent.[210] PPK is a single small polypeptide, rejuvenates pancreas, and activate insulin. Activated insulin will effectively metabolize blood sugar to energy for daily use. Since, PPK has the ability to provide number of active insulin, its long term usage rejuvenates pancreas. When taken orally, PPK reduces level of triglycerides and cholesterol and thus benefits people with cardiovascular and weight problems.[211-212] There are only three preparations of PPK available in market- Diabegard®, Sugard®, Organic spirulina Atta noodle. Diabegard is available in the form of tablets whereas Sugard comes in powdered form. Both products are marketed by Bio-magna, Malaysia.[227-229] The various marketed preparations of PPK are shown in Table 5.

**CONCLUSION**

It is well-known fact that search for better medicine has been turned out toward natural products, particularly of plant origin. However, their successful appearance in the market is cumbersome and doubtful. The major impediments that hinder their appearance include quality in terms of stability; their method of quantification and physiochemical properties that restrict their formulation development into desired dosage form. PPK is one of the best examples to understand these bottlenecks. Despite having wide availability, ease of cultivation and simple process of extraction, its use as antidiabetic is less popular due to the poor aqueous solubility and gastric degradation. In our recent research, an attempt has been made to prepare PPK for successful oral delivery and development of self nanoemulsifying delivery systems; however, this research is still under its juvenile stage until in vivo tests will not be carried out. Nevertheless, a thoughtful process could be adopted for the development of other alternative delivery systems to make the product reach behind the bedside of patients.

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