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ADVANCES OF PHYTOCHEMICAL IN TREATMENT OF DIABETES MELLITUS

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Abstract

Endocrine system is network of glands that produce and release hormones that help control many important body functions. The most common endocrine disease diabetes a condition in which the body does not properly process glucose, a simple sugar. This is due to the lack of insulin or, Diabetes can be linked to obesity, diet and family history. Effort to harvest those medicinal plants that bear substantial amount of potential phytochemicals showing multiple beneficial effects in combating diabetes and diabetes-related complications. Therefore, there is an urgent need of identifying indigenous natural resources in order to procure them, and study in detail, their potential on different newly identified targets in order to develop them as new therapeutics. This article presents an overview of diabetes mellitus and multimodal therapeutic effect of medicinal plants/ herbal/phytochemicals and discusses the present status and future prospects of these medicines

Key words: Pharmacoecnomic, allopathic ayurvedic, diabetes mellitus, phytochemicals.

1. Introduction

Endocrine is a network of glands that produce and release hormones that help control many important body functions, including the body's ability to change calories into energy that powers cells and organs. The endocrine system influences how your heart beats, how your bones and tissues grow, even your ability to make a baby.[1] Use of phytochemicals are not only limited to dietary uses, such as food, nutrition, etc., it has its distinct role in remedy of several diseases. Herbal medicine, sometimes known as phytomedicine or botanical medicine, utilizes different parts of the plants, including its flowers, fruits, seeds, leaves, berries, bark and roots

intended for medicinal purposes. The use of medicinal plants are still continuing in this modern era, and it has been estimated that approximately one fourth of prescription medicines worldwide are derived from plants.World Health Organization has also reported the use of traditional medicine for primary health care needs in most countries.

Moreover, traditional herbal medicines may be used in combination with or as alternative to the conventional allopathic medicines. There are several complications which are targeted to treat with herbal medications, including cancer, memory impaired condition, liver disorder, peptic ulcer and other gastrointestinal disorder, inflammatory disorder, hypertension and other cardiovascular disease, diabetes mellitus, hyperlipidemia, tuberculosis, dermatological infections, along with undefined muscular pains and other diseases related to urinary tract, respiratory tract and central nervous system[2]

Diabetes mellitus is very prevelant disease affecting the citizens of both developed and developing countries. It is estimated that 25% of the world population is affected by this disease. Diabetes mellitus is caused by the abnormality of carbohydrate metabolism which is linked to low blood insulin level or insensitivity of target organs to insulin. The phytochemicals with antidiabetic activity are yet to be commercially formulated as modern medicines, even though they have been acclaimed for their therapeutic properties in the traditional systems of medicine

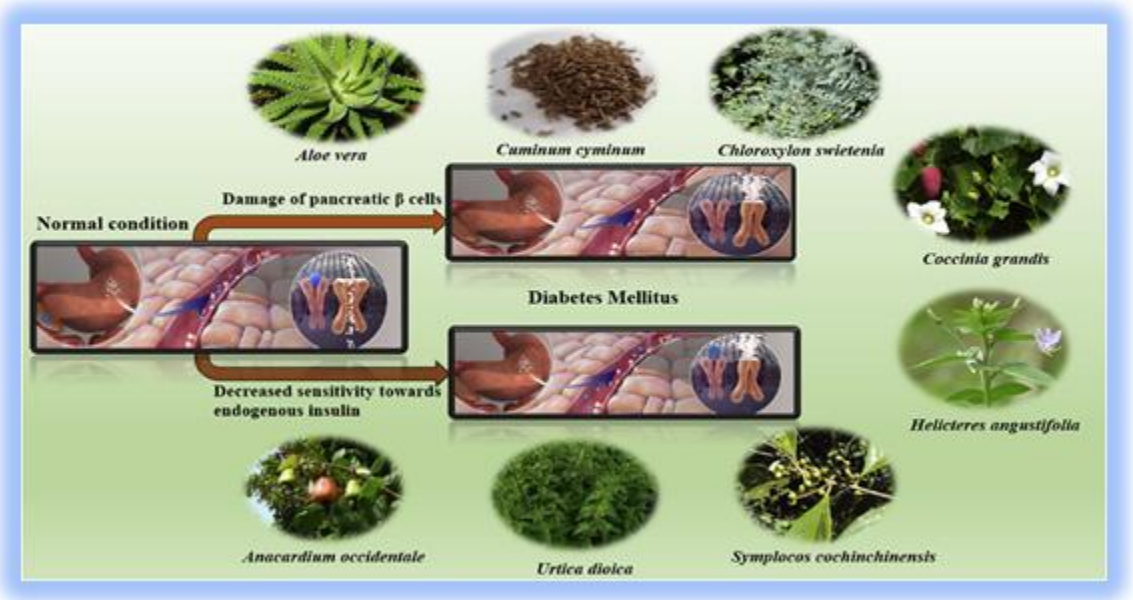
2. Overview of Diabetes Mellitus

Diabetes is a chronic disease characterized by hyperglycemia, and is categorized into two types: Type I Diabetes Mellitus (T1DM) and Type II Diabetes Mellitus (T2DM). In T1DM, b-cells of the pancreas are damaged, leading to a decreased insulin supply to the circulation. Patients will be fully dependent on exogenous insulin administration for existence. Contrarily, T2DM has been observed in majority of diabetic patients (85%) and results in peripheral insulin resistance, thereby results in decreased insulin sensitivity to the skeletal muscles, adipose tissues and liver another category of diabetes can also be categorized in pregnant women without previously diagnosed diabetes, known as gestational diabetes mellitus. Factors such as aging, obesity, physical inactivity, population growth and urbanization can gradually leads to steady increase in the number of patients with diabetes. In year 2000, prevalence of diabetes worldwide among adults is estimated to be

approximately 171 million, whereas the number has been increased to 422 million (approximately 1 in every 11 people) in 2014.The prevalence of diabetes in the world is expected to be doubled to approximately 366 million in year 2030 due to demographic changes in people of more than 65 years old and most importantly, adaptation of sedentary life style by the people in the urban areas of the world. If this disease left untreated it can lead to acute fatal complications including diabetic ketoacidosis and coma due to exceptional increase in blood glucose. Additional dreadful consequences of diabetes include vascular complications due to damage of the vessels for high glucose level, may result in macrovascular and microvascular disorders. Consequences of microvascular complications are retinopathy, neuropathy, etc., whereas, macrovascular complications lead to cardiovascular complications. Other complications for chronic diabetic conditions include dementia, sexual dysfunction, depression and lower-limb amputations[3]

3. Pharmacology of Diabetes

Type 1 diabetes always involve insulin Insulin is a peptide hormone produced by the β-cells in the pancreas. Within vertebrates the amino acid sequence is strongly conserved. Bovine insulin differs to human insulin by only three amino acids, whilst in porcine insulin the difference from human insulin is only one amino acid. Most patients are now on human insulin produced by recombinant DNA technology[4].



Fig; . Condition to develop diabetic mellitus disease and herbal approaches in the improvement of insulin secretion or improvement in insulin resistivity of the body cells.

4. Advances of Phytochemicals in Diabetes Mellitus

Plant medicine has been important in present antidiabetic drug research. The prospects of a numberof medicinal plants, herbal formulations, and natural products withanti-diabetic effects have been reported . Notable amongsuch is Astragalus membranaceus (AM)

The selection of phytochemicals for diabetes

Several medicinal plant have shown to be effective in different stages of diabetes, such as curcumin is proposed to be used as one of interventions in pre-diabetes therapy to prevent the progression of T2DM due to its proven benefits and safety profile, whereas, cinnamon can be a better option for diabetic patients who are having co-existing hypertension

4.1 Afzelia Africana

Mechanism of action:

Streptozotocin is used as an agent to induce diabetes mellitus by selective cytotoxicity effect on pancreatic beta cells. Thus it affects endogenous insulin release and as a result increases blood glucose levelThe continuous administration of aqueous extract of *A. africana* at 200 mg/kg or glibenclamide for 10 days significantly reduced the blood glucose concentration in STZ induced diabetic rats. The plant extract (200 mg/kg) showed a comparable activity with the glibenclamide treated groups. Glibenclamide is a standard antidiabetic drug that stimulates insulin secretion from beta cells of islets of Langerhans. The probable mechanisms of action of the plant extract at higher dose could be linked to potentiation of insulin from beta cells or by increasing peripheral glucose uptake[5]

Fig1: A review of afzelia Africana.

4.2 Allium cepa (Liliaceae)

The essential oil of Allium cepa in diabetic rats at 100mg/kg, p.o. for 21 days treatment, significantly decreasedthe serum lipids, lipid peroxide formation, blood glucoseand

increased serum insulin level. From the obtained result,it was found that the mode of action of Allium cepa as antidiabetic may be due to the antioxidant properties of itsessential oilcomponents, which signified its anti-diabeticand antihyperlipidaemic activity **.**

Fig-2: A review of allium cepa.

Mechanism of action:

This study demonstrated a raised blood sugar in diabetic alloxinized diabetic rabbit's models which was reduced by *A. cepa* in a dose dependent manner, with the higher percentage reduction at the higher dose. The elevated **blood glucose** in diabetes was also the finding in several previous reports ; Studies have found that *Allium cepa* (onions) has blood sugar lowering effectsThe molecular mechanism by which *A. cepa* mediate its antihyperglycocemic and antioxidative effects has not been properly elucidated. reported the active compounds of onion are mainly, sulfur-containing compounds-allyl propyl disulfide (APDS). It has been postulated that these active ingredients lower glucose levels by competing with insulin (which is also a disulfide) for insulin-inactivating sites in the liver resulting in an increase of free insulin[6]

4.3 Amaranthus caudatus (Amaranthaceae)

The methanol extracts of leaves of Amaranthus caudatus in diabetic rats at a dose of 200 and 400 mg/kg p.o. for 21 d significantly decreased the blood glucose, total cholesterol(TC), triglyceride (TG), LDL and VLDL, but increased HDLlevel, signifying its antidiabetic

activity. Further similar effect was also observed in Amaranthus spinosus and Amaranthus viridis methanolic extract in the diabetic rats.

Mechanism of action: Serum cholesterol, serum triglyceride, high density lipoprotein, low density lipoprotein

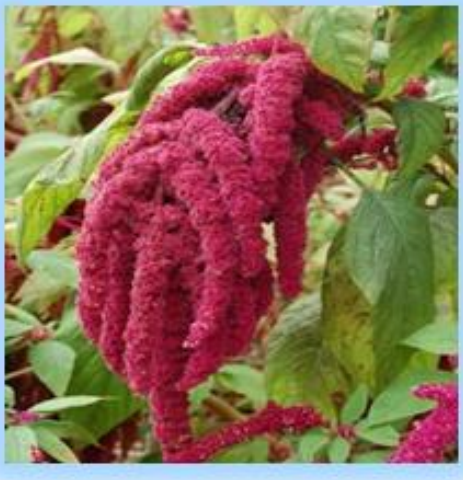


Fig-3: Amaranthus caudatus

4.4 Andrographis lineata (Acanthaceae)

The methanol and aqueous extracts of Andrographis lineatain diabetic rats400 mg/kg, p.o. for 15 days treatment, significantly reduced blood glucose, TC, LDL, VLDL leveland an increase in HDL compared to the control groupwhich signified its anti-diabetic and antihyperlipidaemicactivity.

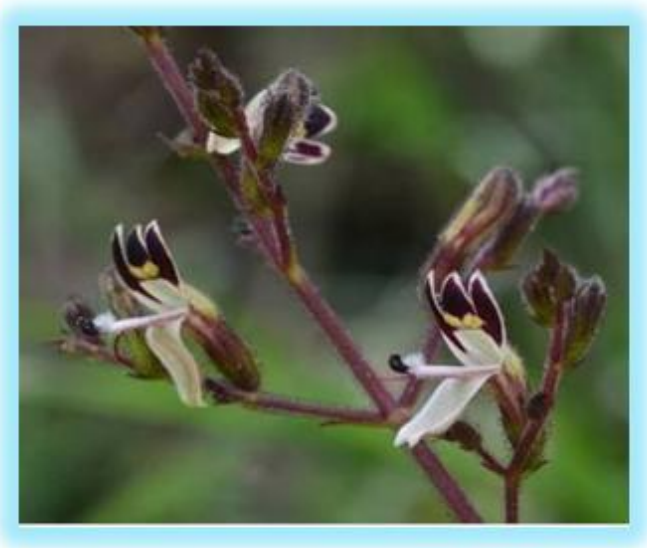


Fig-4: A review of andrographis lineata.

Mechanism of action:

increase in glucose uptake, reduction in plasma glucose, plasma insulin, total cholesterol, low density lipoprotein (LDL)-C triglyceride, glucose-6- phosphatase and fructose -1, 6- bisphosphatase, glycogen content (liver and muscle), high density lipoprotein (HDL) cholesterol, hexokinase increased[7].

Fig-5: A review of annona squamosal.

4.5 Annona squamosa (Annonaceae)

The ethanolic extract of Annona squamosa leaves indiabetic rats at 100 mg/kg, p.o. for 30 days treatmentsignificantly reduced the levels of blood glucose,glycosylated hemoglobin, urea andcreatinine. The efficacyof the Annona squamosa extract was comparable withgliclazide and the results showed that this plant has asignificant anti-diabetic potential.

Mechanism of action:

Reduced the levels of blood glucose, lipids and lipid peroxidation, increased the plasma insulin activities[8]

5. Phytochemical That Regulate Insulin Secretion

Defects in insulin secretion are the one of the main causes that leads to Diabetes Mellitus. Recently, numerous botanical herbs have demonstrated antidiabetic potential through regulation of insulin black seeds/cumin, Nigella sativa, of Ranunculaceae family possessing anti-diabetic and anti-hyperlipidemia properties. Black-colored seeds are bitter in taste and contain different chemicals than cumin seed in it, which include flavonoids,

unsaturated fatty acids, nigellone, thymoquinone, p-cymene and carvone. The N. sativa regimen also resulted in a reduction in body weight in a similar manner as metformin without any toxic effectsThese results support the use of aqueous extract of N. sativa as a traditional remedy for diabetes.[9]

Fig-6: A review of black seeds cumin.

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On the other hand, ethanolic extract of Aloe vera leaf gel, belongs to family Liliaceae, with doses of 300 mg/kg demonstrated increased levels of insulin from regenerated pancreatic beta-cells. Leaves of the same plant also has promising diabetic control properties by its insulin secretory property which is supported by its antioxidant and antiglycation properties.

Thus, medicinal plants have specific role in the improvement of diabetic condition for the healthier quality of life via ameliorating the number of pancreatic b-cells in the islets of Langerhans, acting like secretagogues, thus

increasing the insulin secretion and at the same time protect the beta-cell from destruction, however, further investigations should be conducted to study the mechanism of actions of these plants on insulin secretion.[13]

6. Herbs Have Impact on Glucose Absorption

The utilization of a-glucosidase inhibitor is one of the remedies for diabetes as it suppresses carbohydrate digestion, thus decelerating the process of glucose assimilation and resulting in significant reduction of postprandial plasma glucose and insulin level with a significant decrease of HbA1c postprandially. Several researches are ongoing in search of potential natural candidates for the effective control of diabetes consequently, several herbs, such as cinnamon, China aster, mistletoe fig and bitter oleander have been found to exhibit inhibitory actions on a-glucosidase. Other herbs that showed potential in treating diabetes include olive leaves, which has been shown to reduce digestion and absorption of starch, as well as black seed, where the inhibition of sodium-dependent glucose transport has been demonstrated. Below are examples of herbs that influence glucose absorption via their respective[10]

6.1 Cinnamomum zeylanicum (a species of cinnamon), a spice that has been traditionally consumed to cure diabetes, known to contain flavonoids, glycosides, anthraquinones, terpenoids, coumarins and tannins. Due to its affordable cost, high availability and safety profile, cinnamon is considered as one of the low risk options for diabetic patients. Therefore, cinnamon may be a potential supplement effective in controlling postprandial hyperglycemia and reducing the risk of diabetic vascular complications associated with it.[11]

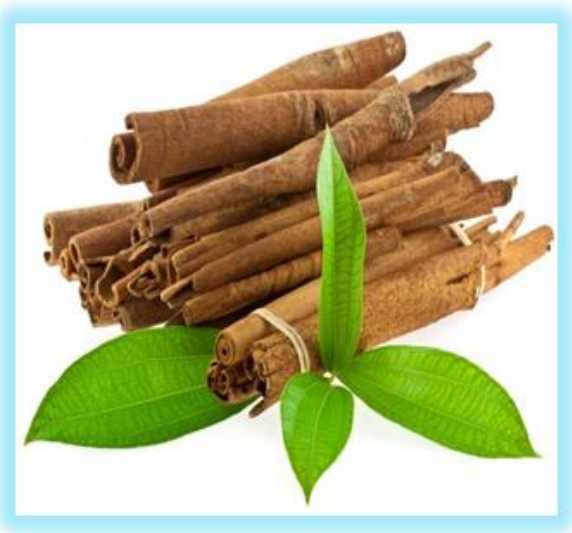

Fig6.1: A review of cinamomum zeylanicum.

7. Herbs Regulate Multiple Actions on Glucose Regulation

We have observed that hypoglycemic herbs are widely used traditionally; however, those herbal medicines are projected towards well characterized and demonstrated mechanism of diabetic control. Apart from the described herbs, several herbs investigated to have multiple mechanisms in the control of diabetic condition. Few of the medicinal herbs has been described in this section those have multiple mode of action, including regeneration of pancreatic B cells, increases insulin sensitivity, enhance glucose utilization and antioxidant property. Long term elevated blood glucose level in diabetic patients could develop variety of vascular complications due to excessive production of reactive oxygen species (ROS) and the reduction of activities of endogenous antioxidants, such as superoxide dismutase (SOD) and catalase (CAT);[12]

9.4 Curry leaves, or scientifically Murrya koenigii exhibits potent antihyperglycemic and anti-obesity effect that is useful for the glycemic control as well as maintain optimal body weight. Ethanolic extract Murrya koenigii is reported to improve glucose intolerance in hyperglycemic condition in high fat diet induced obese and diabetic rats which is associated with insulin resistance and may progress to T2DM. It has also been shown that Murrya koenigii exerts insulin sensitizing and antioxidant activities, besides its aglucosimidase inhibitory activity that can aid in glycemic control.

Fig7.1: A review of curry leaves.

ADVANCED HERBS IN CLINICAL TRIAL FOR THE TREATMENT OF DIABETES

Different active principles of herbal medications possess their individual pharmacological actions to the biological system and are in use since many centuries. Due to their positive role in medicinal field, they have an extensive and worldwide recognition along with their application as herbal medicines. However, lack of safety and efficacy profile of the herbs imposed to insufficient pharmacological, pharmacokinetic and clinical status on the majority of herbal medicinal products. This widespread gap in gathering the regulatory necessities in research on herbal medications further adds to the dilemma of regulation of herbal drugs. In this section of the manuscript a brief description was made of the herbs for diabetic control for which clinical studies has been performed.[27]

Table-1: Compositon of Polyherbal Used.

Polyherbals	Botanical composition (part used)
GSPF kwath	Gymnema sylvestre (Retz.) R.Br. (leaves), Syzygium cumini (L.) Skeels (seeds), Phyllanthus emblica L. (fruit), Curcuma longa L. (rhizome), Pterocarpus marsupium Roxb. (Heart-wood), Terminalia chebula Retz. (fruit), Cassia fistula L. (fruit), Picrorhiza kurroa Royle ex Benth. (rhizome), Swertia chirata (seeds), Terminalia bellirica (fruit)
Polyherbal formulation	Ferula assafoetida, Annona squamosal, Zingiber officinale (juice), Gymnema sylvestre (leaves), Tamarindus indica (seeds), Azadirachta indica, Trigonella foenumgraecum (seeds), Moringa oleifera (roots), Aegle marmelos (seeds), Cajanus cajan (leaves)
Polyherbal formulation	Salacia roxburghii (root and fruits), Salacia oblonga (root and fruits), Garcinia indica (fruits and seeds), Lagerstroemia parviflora (bark)
SMK001	Coptis chinensis, Trichosanthes kirilowii
DIASOL	Eugenia jambolana, Foenum graecum, Terminalia chebula, Quercus infectoria, Cuminum cyminum, Taraxacum officinale, Emblica officinalis, Gymnema sylvestre, Phyllanthrus nerui, Enicostemma littorale
DiaKure	Vetiveria zizanioides (root), Hemidesmus indicus (rhizome), Strychnos potatorum (seed), Salacia reticulata (bark), Holarhena antidysenterica (seed), Cassia auriculata (bark), Trigonella graecum (seed), Acacia catechu (bark)
ESF/AY	Aegle marmelos (leaves), Bambusa arundinacee (leaves), Eruca sativa (leaves), Aerva lanata (aerial), Catharanthus roseus (aerial), Ficus benghalensis

In continuation to our previous discussion on cinnamon, that consists of type-A procyanidin polyphenols which are responsible in preventing and treating oxidative stress and insulin resistance as well as improving cognitive function and reducing cardiovascular disease[28].Tangvarasittichai et al investigated the effect of cinnamon supplementation for 60 days on insulin sensitivity, insulin resistance, level of MDA, high sensitive-C-reactive protein and total antioxidant capacity (TAC) in diabetic patients.

The results showed that there was a marked reduction in insulin resistance, oxidative stress and inflammation while insulin sensitivity and TAC were markedly increased. Another study by Anderson et al reported that the administration of cinnamon extract (C. cassia) in people with elevated serum glucose reduced 2-hour blood postprandial glucose, fasting insulin, and homeostasis model assessment for insulin resistance (HOMA-IR). Apart from that, total cholesterol level also decreased with cinnamon treatment.[24] In addition, the effects cinnamon and Caucasian whortleberry (Vaccinium arctostaphylos L.) were studied by Mirfeizi et al, where they reported the fasting blood glucose, 2-hour postprandial glucose and HOMA-IR scores were reduced markedly in the whortleberry group while a significant difference in body mass index (BMI) was observed in cinnamon group.

However, a significant decrease of glucose control in both treatment groups was observed[29].Another study was carried out by Gul-E-Rana et al, to investigate the effect of Ficus racemosa in a group of diabetic patients who were under the treatment of oral hypoglycemics. Twenty five diabetic patients were treated with 5mL of the extract of Ficus racemosa bark twice daily for 15 days. At the end of the study, results showed that the blood glucose level (fasting and after breakfast) after taking the herb in conjunction with oral hypoglycemic drug was significantly decreased in both female and male after 1.5 h after breakfast. Antidiabetic activity of twice daily 5 g Portulaca oleracea L. seeds on T2DM subjects were compared with 1500mg metformin daily for 2months. They reported a significant decrease in fasting and post-prandial blood glucose, insulin, serum LDL cholesterol, TG, total cholesterol, liver enzymes (ALT, AST, and Gamma-Glutamyl Transferase), bilirubin, body weight and BMI while a significant increase in high density lipoprotein cholesterol (HDL-C) and albumin but non-significant change of alkaline phosphatase in herbal treatment group, whereas metformin group did not show anydifference.[30]

8. Marketed Herbal Medications for Diabetic Treatment

Enormous research of herbal products for the remedy of diabetes has developed several antidiabetic products in the market worldwide. Few of them include, Diabecon®, Glyoherb, Diabeta Plus, etc. Diabecon® is a product by Himalaya Herbal Healthcare, is one of the well marketed polyherbal formulation in diabetes care. Composion of the formulation has been depicted in table above aside from promoting b-cell repair and regeneration; it also protects the b-cells from oxidative stress and increases C-peptide levels. It mimics insulin actions by reducing HbA1c level, normalizing microalbuminuria and regulating the lipid profile. Diabecon® also possess antioxidant properties and claims to minimize complications in diabetic patients.Diabecon was compared to Hyponidd, Inolter and Cogent DB based on their effectiveness in reducing HbA1cwhere Diabecon® showed an increased fasting insulin and C peptide levels compared to the other agents Similarly, Glyoherb is also a polyherbal antihyperglyceamic formulation that has additional properties of antihyperlipidemic and antioxidant properties. It is marketed to prevent, delay or improve complications such as retinopathy, neuropathy and retinopathy Results in animal testing suggested that it increases glucose tolerance and lowers blood glucose levels in STZ-induced type 1 diabetic rats. Additionally, treatment with Glyoherb has shown to reduce serum cholesterol, TGs, VLDL, LDL levels compared to control groups but is not as effective as glibenclamide. It had also shown to increase HDL levels Glyoherb did not exert any toxic effects in STZ-induced impaired kidney and liver functions rather it improved the kidney and liver functions. On the other hand, Diabeta Plus is also an antidiabetic polyherbal formulation that has additional properties of potent immunomodulator, antihyperlipidemic, anti-stress and is hepatoprotective[13]

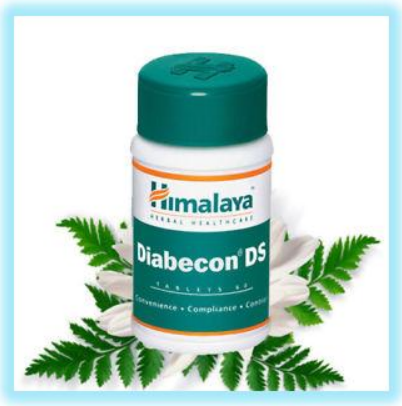

Fig 8: A review of diabecon marketed herbal tablets.

9. The future aspects of herbal remedies for diabetes mellitus.

Many herbal drugs are used by people and various native drugs are regularly being introduced into current therapeutics.

About 80% of the people, in developing countries particularly the rural people, rely on the conventional medical remedies for health care requirements.

There has been a revival of interest in herbal drugs in developed countries due to a huge amount on the preference of products from natural sources.[14]

Therefore, there's a need to differentiate between herbal drugs supplied by a medical practitioner and those herbal remedies easily accessible to the people for self-medication. The rapidly growing occurrence of diabetes mellitus is Seriousness to human physical condition in all over the world.

Recently, new active medicines have been extracted from plants and possess anti-diabetic activity with more effectiveness than oral hypoglycemicagents used in proven therapy.

In recent years, awareness has been drawn towards discoveryof plants with anti-diabetic activity that may be useful to people. It may also provide evidence for the improvement of a new oral drug for the treatment of diabetes mellitus[15]

10. Conclusion

Diabetes mellitus is a most common endocrine disorder, affecting millions of people worldwide.

It is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.

The increase in resistance and populations of patients at some risk, in conjunction with the restricted number of commercially available drugs for diabetes that still present have many side effects and also problems like unwanted hypoglycemic effect are the cause to shift the research towards traditionally available medicine which have low side effect and wide range of bio activity and do not require laborious pharmaceutical synthesis seems highly attractive.

From this review article, it may be useful to the health professionals, scientists and scholars to develop evidence-based alternative medicine to cure different kinds of diabetes problem using herbal preparation.

Substances and extracts isolated from different natural resources play very important role to design medicine and treat hyperglycemic problem in diabetes mellitus

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