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PHYTOCHEMICALS IN THE REMEDY OF DIABETES MELLITUS: A SYSTEMATIC REVIEW

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ABSTRACT

Phytomedicine or botanical medicine are synonymous, utilizes plants intended formedicinal purposes. Medicinal use of herbal medicine in the treatment and prevention of diseasesincluding diabetes has a long history compared to conventional medicine. Diabetes is one of the majorpublic health concerns over the world. Diabetes or hyperglycemia is considered to be one of the commonpublic health hazards; optimal control of which is still not possible. Persistent hyperglycemia or uncontrolleddiabetes has the potential to cause serious complications such as kidney disease, vision loss,cardiovascular disease, and lower-limb amputations which contributed towards morbidity and mortalityin diabetes. There are various approaches to treat and prevent diabetes as well as its secondary complications,one of it is herbal medicines. However, the selection of herbs might depends on severalfactors, which include the stage of progression of diabetes, types of comorbidities that the patients arehaving, availability, affordability as well as the safety profile of the herbs. This review focuses on the herbal and natural remedies that play the role in the treatment or prevention of this morbid disorder indiabetes, including their underlying mechanisms for the blood glucose-lowering property and the herbalproducts already been marketed for the remedial action of diabetes.

INTRODUCTION

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 thepancreas are damaged, leading to a decreased insulin supply to thecirculation. Patients will be fully dependent on exogenous insulinadministration for existence. Contrarily, T2DM has been observedin majority of diabetic patients (85%) and results in peripheral insulin resistance, Thereby results in decreased insulin sensitivity tothe skeletal muscles, adipose tissues and liver[1] (Fig. 1). There are estimated 143 million people worldwide sufferings from diabetes, almost five times more than the estimates ten years ago. This number may probably double by the year 2030. Therefore, the human population worldwide appears to be in the midst of an epidemic of diabetes. Reports from the World Health Organization (WHO) indicate that diabetes mellitus isone of the major killers of our time, with people in SoutheastAsia and Western Pacific being most at risk[2]. Despite the great strides that have been made in understandingand management in this disease, serious problemslike diabetic retinopathy, diabetic nephropathyand lower extremity amputationcontinue to confrontpatients and physicians. The graph of diabetes-relatedmortality is rising unabated. Certain population subgroupshave prevalence rates of disease approaching 50%and this is strongly related to the epidemic of obesity andsocio-economic inequalities that plague our society. Multiple defects in the pathophysiology of diabetes aremostly imprecisely understood, and therefore warrant notisolating a single drug target to the reversal of all ormajority of aspects of the disease, as biological systemsare too complex to be fully understood through conventionalexperimentation and also because they arenonlinear. They also may have properties that are notobvious from biological considerations alone. For example,though hyperglycemia is a classical risk factor for thedevelopment of diabetic complications, there is no consensusregarding the pathogenic links between hyperglycemiaand diabetic complications. There are a numberof equally tenable hypotheses on the origin of complicationsbeyond hyperglycemic consideration.[3] Therefore,the unidirectional therapeutic approach in the managementof diabetes does not appear to be the way to addressthis problem.

Herbal technology in diabetes

Complementary or alternative treatments using herbal medicinesdraw the attention of many diabetic patients. Numerouscommon herbs are claimed to reduce blood glucose level, therefore the possibility of having better glycemic control or being lessdependent on insulin injections by taking herbal medicines is unquestionablyappealing. However, the selection of herbs might depends on several factors, which include the stage of progressionof diabetes, types of comorbidities that the patients are having,availability, affordability as well as the safety profile of the herbs.Preclinical studies have crossed the doorstep of laboratories and reached to the bed-side of the patients. Several clinical studies inhuman patients have been conducted in recent years, reported thatmedicinal plants such as Scoparia dulcis,Cinnamomum cassia,Ficus racemosa barkand Portulaca oleracea L.

Seeds were shownto have antidiabetic potential. Subsequent research on laboratoryon herbal products has reached to the diabetic patients by thebrand name of Diabecon®, Glyoherb® and Diabeta Plus®. Thus,herbal supplements can be used as an adjuvant or as favorablealternative therapy for diabetic condition (Fig. 2).

***Herbs that regulate mechanism of insulin secretion*.**

Defects in insulin secretion are the one of the main cause's thatleads to Diabetes Mellitus. Recently, numerous botanical herbs have demonstrated antidiabetic potential through regulation of insulinsecretion (Table 1).

Cuminum cyminum in long-termdiabetes treatment since it can help in lowering the blood glucoselevel and at the same time it carries benefit of beta-cells protection.The study Patil et al showed that the diabetic rats treated with theessential oil of cumin, cuminaldehyde and cuminol, at doses of25 mg/mL for 45 days were demonstrated 3.34 and 3.85 folds increasein insulin secretion, respectively when compared to11.8 mM-glucose control. Additionally, a dose-dependent inhibitorof insulin secretion was observed and it was said to have potentbeta-cell protective action as a result from the comet assay. Besides,the high availability of this common spice and its safety profile withno reported toxicity also make it a better alternative in diabetestreatment.[4]Concurrently, a recent study indicated that the greencumin could effectively control glycemic factors along with inflammatorymediators.[5]

Nigella sativa,*N. sativa*ofRanunculaceae family possessing anti-diabetic and antihyperlipidemia properties. Black-colored seeds are bitter in tasteand contain different chemicals than cumin seed in it, whichinclude flavonoids, unsaturated fatty acids, nigellone, thymoquinone,p-cymene and carvone. Study results revealed that theblockage of sodium-dependent passage of glucose across isolatedrat jejunum was proportional to doses of N. sativa aqueous extractranging between 0.1 pg ml_1 and 100 ng ml_1, where maximuminhibition of 80% had been achieved with an IC50 ¼ 10 pg ml_1.

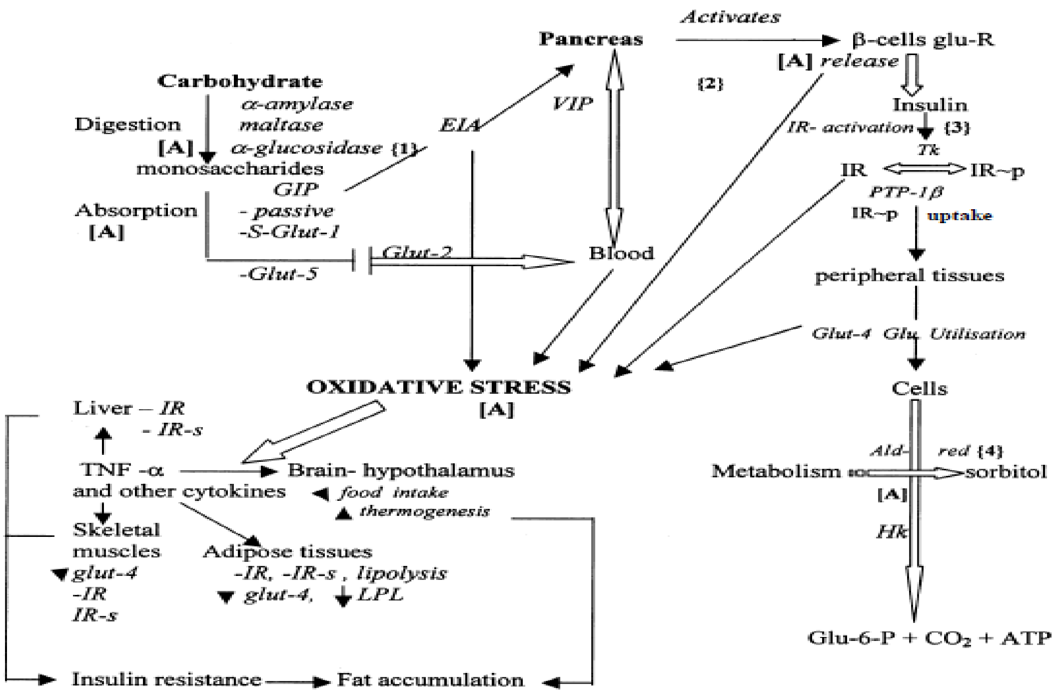

Figure 1. Carbohydrate metabolism pathways and targets where imbalance/ Insufficiencies in function lead to hyperglycemias and resultant diabetic syndrome

Figure:2 Herbal approaches in the improvement of insulin secretion or improvement in insulin resistivity of the body cells.

Table: 1 Herbals in the management of plasma glucose level, acting through secretogogues mechanism or by improvement of insulin sensitivity to the cells

Plant	Extract	Cases	Outcomes
Urtica dioica	Leaf Hydroalcoholic extract	Fructose-induced insulin resistance	The blood glucose and FIRI inhyperglycemic rats were reduced in a dose-dependentmanner with the best result obtained at 200 mg kg^{-1} bodyweight/day. The plasma insulin level was also found to be reduced intreatment group
Anacardium occidentale	Leaf Ethanol extract	STZ-induced diabetes	Blood glucose was decreased147.67 ± 6.09 mg dL^{-1} to123.83 ± 2.87 mg dL^{-1}after 30 daystreatment with plant extract. At thesame time, glycosylated haemoglobinlevel, FIRI and serum insulin level were decreased in treatment group
Afzelia africana	Stem bark Aqueous extract	STZ-induced diabetes	The blood glucose level wassignificantly reduced in a dosedependentmanner with the best result obtained at 200 mg kg^{-1} body weight per day
Helicterus angustifolia	Root Ethanol extract	STZ-induced diabetes	The blood glucose, plasma insulin leveland HOMA-IR were significantlyreduced in treatment group.
Uvaria chamae	Root Hydroethanolic extract	STZ-induced diabetes	The treatment group showedsignificant blood glucose reduction with formation of regenerated islet of Langerhans shown in photomicrographof pancreas.
Helicterus angustifolia	Root Ethanol extract	STZ-induced diabetes	The blood glucose, plasma insulin leveland HOMA-IR were significantlyreduced in treatment group
Uvaria chamae	Root Hydroethanolic extract	STZ-induced diabetes	The treatment group showedsignificant blood glucose reduction with formation of regenerated islet of Langerhans shown inphotomicrographof pancreas.
Coccinia grandis	Leaf Ethanolic extract	STZ-induced diabetes	Significant reduction in plasma glucoselevel and increase in serum insulin levelin a dose-dependent manner.
Forsythia suspensa	Fruit Ethyl acetate fraction of methanol extract	STZ-induced diabetes	Blood glucose was significantlydecreased; insulin secretion andglucose tolerance were significantly increased

Table:2- List of medicinal herbs affecting the absorption of carbohydrates from the gastrointestinal environment by inhibiting a-glucosidase and a-amylase

Plant	Extract	Chemical constituent	Outcomes dL^{-1}
Phyllanthus urinaria	Leaves 50% aqueous methanolic extract	Corilagin, gallic acid and macatannin B	Corilagin, gallic acid andmacatannin B demonstratedlow inhibitory activity againstamylase (21%, 23% and 33%respectively in 1 mmol.L_1concentration)
Cinnamomum zeylanicum	Bark Methanol extract	Tannins, flavonoids, glycosides, terpenoids, coumarins and anthraquinones	In vitro: Inhibition of yeast andmammalian a-glucosidase(IC50 =5.83 mg ml_1 & 670 mg ml_1 respectively)In vivo: Decreased postprandialhyperglycemia by 78.2% and52.0% compared to normal rats
Nigella sativa	Seeds Aqueous extract	Flavonoids, unsaturated fatty acids, nigellone, thymoquinone	In vitro: Inhibition of sodiumdependentglucose transportIn vivo: Chronic treatmentimproved glucose tolerance and

		(TQ), p-cymene and carvone	reduced body weight similarlyas metformin
Callistephus chinensis	Flower 70 % ethanol extract	Apigenin, apigenin-7-O-b-Dglucoside, hyperin, kaempferol, kaempferol-7-O-b-Dglucoside, luteolin, naringenin and quercetin	Inhibition of a-glucosidase byquercetin (IC50 = 2.04 mg ml_1)comparable to that of acarbose(IC50 =2.24 mg ml_1)
Ocimum basilicum	Leaves Aqueous extract	Cardiac glycosides, flavonoids, glycosides, reducing sugars, saponins, steroids and tannins	Inhibition of a-amylase: ratintestinal maltase and sucrase,porcine pancreatic amylase(IC50 =21.31 mg ml_1, 36.72 mg ml_1 & 42.50 mg ml_1 respectively)
Corchorus olitorius	Leaves Free & bound extracts	Caffeic acid, chlorogenic acid and isorhamnetin	Inhibition of a-amylase, aglucosidase & ACE(IC50 = 17.5 mg mL_1, 11.4 mg mL_1 & 15.7 mg mL_1, respectively)
Ficus deltoidea	Leaves Ethanolic, methanolic extracts	Vitexin, isovitexin, proanthocyanidin, flavonoids, 3-flavanol monomers and flavones glycosides	In vitro: Inhibition on aglucosidases and improvementon basal and insulin-mediatedglucose uptake into adipocytes cells
Glycine max (L.) Merrill	Soybean Free and bound phenolic extracts	Phenolic compounds	Inhibition of a-amylase, aglucosidase & ACE
Olea europaea L	Leaves Alcoholic extract	Oleuropein, hydroxytyrosol, oleuropein aglycone, and tyrosol	In vivo: Reduction in starchdigestion and absorptionRCT: Lower HbA1c (8.0%-1.5%vs. 8.9%-2.25% in placebo) andfasting plasma insulin levels (11.3-4.5 vs. 13.7e4.1 in placebo)

Table: 3 - Polyherbal Formulations Used In the Treatment of Diabetes

Sl no	Polyherbal Formulation	Ingridients
1	Diabecon	Sphaeranthus indicus, Tribulus terrestris, Tinospora cordifolia, Triphala, Curcuma longa, Rumex maritimus, Aloe vera, Swertia chirata, Ocimum sanctum, Gymnema sylvestre, Sphaeranthus indicus, Glycyrrhiza glabra, Commiphora wightii, Phyllanthus amarus, Boerhavia diffusa, Piper nigrum, Tribulus terrestris, Pterocarpus marsupium, Syzygium cumini, Tinospora cordifolia, Berberis aristata, Gmelina arborea, Asparagus racemosus, Abutilon indicum, Casearia esculenta, Berberis aristata, Gossypium herbaceum
2	Glyoherb	Gudmar (Gymnema sylvestre), Mahamejva, Katuki (Picrorhiza kurrooa), Chirayata (Swertia chirata), Karela (Momordica charantia), Indrajav (Holarrhena pubescens), Amala (Phyllanthus emblica), Gokshur (Tribulus terretris), Haritaki (Terminalia chebula), Jambu bij (Eugenia Jambolana), Methi (Trigonella foenum-graecum), Neem, Chandraprabha, Arogyavardhini, Haridra (Curcuma longa), Bang Bhasma, Devdar, Daruhaldi (Berberis aristata), Nagarmotha (Cyperus scariosus), Shuddha Shilajit, Galo
3	Diabeta Plus	Vijayasar (Pterocarpus marsupium), Gurmar (Gymnema sylves), Jamun (Syzygium cumini), Karela (Momordica charantia), Shilajit (Asphaltum), Madagascar periwinkle (Catharanthus roseus)

Oral glucose tolerance test was performed in rats ensuring the first doseas well as after continuous therapy with 2 g/kg body weight/day ofN. sativa for a period of 6weeks and a comparison was made with300 mg/kg body weight/day of metformin. The efficiency of longterm N. sativa treatment in the improvement of glucose tolerancewas found to be equivalent to metformin. The N. sativa regimen alsoresulted in a reduction in body weight in a similar manner asmetformin without any toxic effects.These results support theuse of aqueous extract of N. sativa as a traditional remedy fordiabetes[6].

Aloe vera On the other hand, ethanolic extract of Aloe vera gel , belongsto family Liliaceae, with doses of 300 mg/kg demonstratedincreased levels of insulin from regenerated pancreatic beta-cells.Besides, the plasma lipids, liver cholesterol and kidney triglycerides(TG) levels of the tested diabetic rats also being reducedafter the administration of Aloe vera extract.[7]

Chloroxylon swietenia The extracts ofChloroxylon swietenia bark were also found to have hypoglycemiceffects in streptozotocin (STZ)-induced diabetic male albino Wistarrats. The results showed that the blood glucose level was moderatelycontrolled, comparable to glibenclamide, through intragastricintubation for 45 days, as well as increased plasma insulin level, intreatment group as compared to control group.[8]Antidiabetic potentialof ethyl acetate extract of Forshythia suspense in STZ-induceddiabetic rats also reflected by the dose dependent significantreduction in blood glucose level associated with significant increasein plasma insulin level in the treatment group.

Coccinia grandis leaf of C. grandis was also found to have antidiabetic activity inSTZ induced diabetic rats, where oral treatment of ethanolic extractof C. grandis leaves at 50, 250 and 500 mg kg_1.day_1 for 21 daysresulted in significant reduction in plasma glucose level and increasein serum insulin level in a dose-dependent manner. Theblood glucose and plasma insulin level were 169.60 ± 0.70 mg dL^{-1}(p < 0.01) and 3.10 ± 0.08IU.dL_1 (p < 0.01) respectively with500 mg/kg/day extract treated rats, whereas, those levels in controldiabetic group were 312.70 ± 2.05 mg dL_1 and 1.28 ± 0.05IU.dL_1,respectively.[9]Leaves of the same plant also has promising diabeticcontrol properties by its insulin secretory property which is supportedby its antioxidant and antiglycation properties.[10]

Herbs that control and modify the insulin resistance

Majority of the diabetic patients are suffering from T2DM, due todevelopment of resistance to the endogenous insulin by the cellsand tissues of the body. Resistance to the cells can be reverted tosensitivity by the use of medicinal agents.

Urtica dioica The hydroalcoholicextract of Urtica dioica leaves showed hypoglycemic activities inmale Wistar rats with fructose-induced insulin resistance. After twoweeks of intraperitoneal injection of U. dioica extract at differentdosage to the experimental rats showed significant reduction inplasma glucose level and fasting insulin resistance index (FIRI) thanthe control group and the effects were dose-dependent.36 Besidesthat, serum insulin concentration in rats in treatment group wassignificantly lower than the control group, thus the results signifiesthat the sensitivity to the tissues and cells have been increased bythe use of leaf extraxt as evidenced by the decreased plasmaglucose level.[11]

Anacardium occidentaleThe ethanolic extract of Anacardium occidentaleleaves also demonstrated antidiabetic activities in neonatal STZinduceddiabetic rats. Oral administration of 100 mg/kg bodyweight of *A. occidentale* extract for 30 days, showed significant reductions

in fasting sugar levels, serum insulin level (11.69 ± 0.93IU.mL^{-1}) and FIRI.[12]

Allium sativumGarlic oil extracted by steam distillation ofAllium sativum shown to improve insulin and glucose tolerance andimproves glycogenesis in skeletal muscle. The hypoglycemic activityof garlic oil has shown to improve GLUT4 expression in STZinduced diabetic rats.[13]***Symplocos cochinchinesis***The ethanol extract of Symplocos cochinchinesisbark has also shown to have effects in regulating insulinresistance. The oral administration of S. cochinchinesis extract at250 and 500 mg kg_1.day_1 significantly reduced the plasmaglucose level in diabetic induced rats with insulin resistant on day20.[14]Simultaneously, it was observed that the plasma insulin leveland homeostatic model assessment score on insulin resistance(HOM-IR) in treatment group were significantly lower as comparedto control group, suggesting improved sensitivity of the cells towardsendogenous insulin.[15]

Helicterus angustifoliaEthanolic extract of Helicterusangustifolia root was also found to have antidiabeticpotential. A 200 and 400 mg/kg/day dose for a period of 28 days inSTZ-induced diabetic rats resulted in significant reduction in bloodglucose, plasma insulin level and HOMA-IR in treatment group ascompared to control group.[16]In rats receiving 400 mg/kg/dayextract, the blood glucose, plasma insulin level and HOMA-IR were23.86 ± 0.25mmol.L^{-1}6.98 ± 0.22mU.mL^{-1} and 7.41 ± 0.29,respectively whereas, those values in control diabetic group were31.47 ± 0.30mmol.L^{-1}, 7.24 ± 0.38mU.$mL^{-1}$and 10.13 ± 0.56,respectively.

Pleurotus ostreatus aqueous extract of Pleurotus ostreatusdemonstrated glucose-reducing effects in high-fat diet and STZinduced insulin resistant diabetic rats where 100, 200 and400mg kg_1.day_1 oral treatment of P. ostreatus extract for 4 weeksshowed that the fasting blood glucose level in treatment groupwere significantly lower as compared to control group at day 14, 21and 28.Besides that, the level of fasting serum insulin level (FINS)and HOM-IR were lower meanwhile the insulin sensitivity index(ISI) and the homeostatic model assessment score for beta cellfunction (HOM-b)were higher in treatment group.[17]

Afzelia africana stembark of Afzelia africana and Uvaria chamae root have also shown tohave hypoglycemic effects in STZ-induced diabetic rats, whereA. africana controls the diabetic condition in dose dependent contrary,[18]

U. chamae In explanation to the antidiabeticresearch on U. chamae extract, the authors showed thetissue histology study where the pancreas of the rats in treatmentgroup showed clusters of regenerated Islet of Langerhans of varietysize,[19]however, the plasma insulin level and HOMA-IR were notaccessed in this study.

Herbs affecting glucose absorption level

The utilization of a-glucosidase inhibitor is one of the remediesfor diabetes as it suppresses carbohydrate digestion, thus deceleratingthe process of glucose assimilation and resulting in significantreduction of postprandial plasma glucose and insulin level with asignificant decrease of HbA1c postprandially. There is a wide use ofa-glucosidase inhibitor in the control of T2DM, Several researches are ongoing in searchof potential natural candidates for the effective control of diabetesconsequently, several herbs, such as cinnamon, China aster,mistletoe fig and bitter oleander have been found to exhibitinhibitory actions on a-glucosidase. Besides that, inhibition of aamylasehas also been associated with anti-hyperglycemic actions
of medicinal herbs like Camellia sinensis, Aloe vera, basil, etc.[20]

Phyllanthus urinariaP. urinaria is a wild plant in Indonesia of Euphorbiaceaefamily being used traditionally in urinary tract disorders anddiabetes. Chromatographic separation of hydro-methanolic extractof P. urinaria leaves and subsequent purification of the active fractionsusing preparative HPLC revealed corilagin, gallic acid andmacatannin B constituents, which showed in vitro inhibitory effectagainst pancreatic amylase isolated from swine (21%, 23% and 33%,
respectively at 1 m.mol.L^{-1} concentration)[21].

Ocimum basilicumOcimum basilicum (basil) is found to beused in culinary and folk medicine. Phytochemical analysis haveshown that aqueous extract of O. basilicum leaves contains cardiacglycosides, flavonoids, glycosides, reducing sugars, saponins, steroidsand tannins. Leaf extract of the plant exhibited remarkabledose dependently inhibition of intestinal maltase and sucrase ofrats and pancreatic a-amylase of swine (IC50 ¼ 21.31 mg ml^{-1},36.72mgml^{-1}&42.50 mg ml^{-1}, respectively). Greater inhibition ofmaltase may be attributed to the high total polyphenols and flavonoidscontents.[22]

Cinnamomum zeylanicumThe bark of Cinnamomum zeylanicum (a species ofcinnamon), a spice that has been traditionally consumed to curediabetes, 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 thelow risk options for diabetic patients.52 The dose-dependent,competitive and reversible inhibitory effect of cinnamon bark extract on both yeast and mammalian a-glucosidase was evident inin vitro studies (IC50 ¼ 5.83 mg ml^{-1}& 670 mg ml^{-1}, respectively).[23]

C. cassia C. cassia is having the most established data in TD2Mtreatment. The details of the study outcomes has been depicted inclinical section.[24]Therefore, cinnamon may be a potential supplementeffective in controlling postprandial hyperglycemia andreducing the risk of diabetic vascular complications associated withit.

Callistephus chinensisHydroalcoholicextract of Callistephus chinensis flower. Further testing was carriedout on the stepwise polarity fractions of exracts and the ethyl acetatefraction was found to exhibit the greatest inhibiting action ona-glucosidase enzyme. Enzyme assay guided fractionation led tothe isolation of 8 compounds: apigenin, apigenin-7-O-b-D-glucoside,hyperin, kaempferol, kaempferol-7-O-b-D-glucoside, luteolin,naringenin and quercetin. Among the compounds isolated, quercetindemonstrated the greatest a-glucosidase inhibition(IC50 ¼ 2.04 mg ml^{-1}), which is equivalent to that of acarbose(IC50 ¼ 2.24 mg ml^{-1}).[25]

Corchorus olitoriusCorchorus olitorius (jute) leaves have been used historically as amedicinal plant to treat certain degenerative conditions due to therich contents of polyphenolic compounds and flavonoids, whichhave been reported in in vitro studies to have a-glucosidase inhibitory activity, making it a potential source of anti-diabeticagent for the management of postprandial hyperglycemia anddiabetic complications as a result of oxidative stress. A study demonstrated inhibition of a-amylase and a-glucosidase proportionalto doses of C. olitorius extracts, results showing substantiallygreater inhibition against a-amylase and a-glucosidase (IC50 ¼ 17.5 mg ml^{-1}& 11.4 mg ml^{-1}, respectively). The majorphenolic compounds were found to be chlorogenic acid and isorhamnetinin the free extract and caffeic acid in the bound extractas evidenced via reversed phase HPLC analysis.[26]

C. olitoriusThe abundance ofthese compounds in the leaves of C. olitorius may have contributedto the inhibitory activities against important enzymes associatedwith T2DM and hypertension, hence justifying its traditional use intreating these ailment. Studies also have demonstrated hypoglycemicactivity of Holarrhena antidysenterica seed extract in STZinduced diabetic rat.[27,28]

Ficus deltoidea Another medicinal herb of Moraceae family, Ficus deltoidea, hasincreased popularity as an alternative remedy for diabetes, beenexperimentally shown to lower elevated blood sugar at variousprandial states.[29]The crude extracts and fractions of two fruit varieties of F. deltoidea (var. angustifolia and var. kunstleri) has shown adose-dependent inhibition on intestinal a-glucosidases of yeastand rats.[30]However, improved basal and insulin-mediated glucoseuptake into adipocytes cells for extracts of F. deltoidea leaves aredue to the insulin-mimetic and/or insulin-sensitizing properties.[31]

Herbs regulate multiple actions on glucose regulation

We have observed that hypoglycemic herbs are widely usedtraditionally; however, those herbal medicines are projected towardswell characterized and demonstrated mechanism of diabeticcontrol. Apart from the described herbs, several herbs investigatedto have multiple mechanism in the control of diabetic condition.Fewof the medicinal herbs has been described in this section thosehave multiple mode of action, including regeneration of pancreatic B cells, increases insulin sensitivity, enhance glucose utilization andantioxidant property. Long term elevated blood glucose level indiabetic patients could develop variety of vascular complicationsdue to excessive production of reactive oxygen species (ROS) andthe reduction of activities of endogenous antioxidants, such assuperoxide dismutase (SOD) and catalase (CAT); hence, by correctingthe impaired antioxidant status in diabetic patients will be abenefit in treating diabetes mellitus and also its vascularcomplications.

PanaxginsengPanaxginseng is also known to have anticancer and anti-inflammatoryeffects where the berry and root have been explored for its antidiabeticand hypoglycemic effect, respectively. Ginsenosides are themain biological active components for the antidiabetic effect. Itsmetabolic activity is not well understood. However, it is believedthat the mode of action includes enhancement of insulin sensitivitydue to lesser insulin demand. Besides, Panax ginseng will stimulateinsulin signaling pathway such as protein kinase B and insulin receptor substrate-1 in order to increase secretion from pancreatic bcells.Its hyperglycemic effect also includes in enhancing gastrointestinalabsorption by intestinal bacteria. Increase of translocationof glucose transporter type 4 (GLUT 4) to cell membrane will alsoenhance the glucose uptake as well as glucose utilization. Antioxidanteffect of the extract is also contributed to the antidiabeticeffect. Reduction of oxidative stress can be displayed and thereforepreventing endothelial inflammation that may lead to the complicationof diabetes [32,33].

Aloe vera Aloe vera leaves are usedwidely used for the treatment of diabetes now-a-days, where theantidiabetic activity of A. vera is due to increasing secretion of insulinfrom pancreatic b-cells, along with its antioxidant property byreducing the free radical formation, in streptokinin induced diabeticadult female albino rats. This can be further explained byreduction of serum malondialdehyde (MDA) level which is theproduct of fatty acid peroxidation while there is an increase ofantioxidant enzyme such as SOD and glutathione (GSH). Antioxidantpotential is directing towards prevention of progression ofdiabetes mellitus, further, the anti-inflammatory property of Aloevera extract will also provide benefit in lowering blood glucoselevel. Emodin and mannose-6-phosphate in Aloe vera extract are believed as the main active ingredients for the anti-inflammatoryproperties, where insulin sensitivity will also increase due to preventionof inflammation.

Momordica charantia Momordica charantia L., has beenused widely for antioxidant and antidiabetic activity. Efficacy ofMomordica charantia L is evaluated with aqueous extracts and itsmain active ingredient -charantin shows hyperglycemic property inalloxan-induced diabetic mice. The mode of action includes stimulationglucose utilization of adipocytes and skeletal muscle. Besides,bitter melon extract will downregulate MAPKs and NF-kB tolower the impaired insulin signaling as well as provides protectionto pancreatic beta cells. Upregulation of peroxisome proliferatoractivatedreceptor gamma (PPAR-g gene) expression whichinvolve in glucose metabolism also one of the mechanism ofMomordica charantia L on antidiabetic effect. Modulation ofprotein-tyrosine phosphatase 1B (PTP1B) acts as negative regulatorof the insulin signaling pathway also contribute to the hypoglycemiceffect.[34,35]

Coptis chinensis Coptis chinensis is also well known for its antidiabetic effectthrough regeneration of size of the pancreatic islets of Langerhansin order to enhance the insulin secretion for glycemic control. Indue course, C. chinensis stimulate AMP-activated protein kinase(AMPK) phosphorylation in skeletal muscle and liver which isimportant for cellular energy homeostasis. AMPK activation willstimulate skeletal muscle and hepatic fatty acid oxidation, inhibitlipolysis lipogenesis as well as enhance pancreatic b-cell to secreteinsulin. Besides, C. chinensis increases glucose uptake in adiposetissue through phosphorylation of insulin receptor substrate 1 (IRS-1). IRS-1 transmit the signal from insulin to intracellular pathwaysPI3K/Akt and Erk-MAP kinase. Moreover, elevation of expression ofGLUT 4 in adipose tissue and skeletal muscle mediates glucoseuptake in response to insulin is another mode of action ofC. chinensis to control hyperglycemic condition. Insulin will increaseGLUT 4 translocation to cell membrane of adipocytes andskeletal muscle in order to aid in glucose uptake.

Murrya koenigii exhibits potentantihyperglycemic and anti-obesity effect that is useful for the glycemic control as well as maintain optimal body weight. Ethanolicextract Murrya koenigii is reported to improve glucose intolerancein hyperglycemic condition in high fat diet induced obeseand diabetic rats which is associated with insulin resistance andmay progress to T2DM. It has also been shown that Murrya koenigiiexerts insulin sensitizing and antioxidant activities, besides it's a glucosimidaseinhibitory activity that can aid in glycemic control[36,37]

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Ocimun tenuiflorum leaves of Ocimun tenuiflorum are traditionally used in diabetesin Malaysia. Investigation on the hypoglycemic effects ofO. tenuiflorum extract revealed preventing of hepatic gluconeogenesisas well as activation of glucose uptake in adipose tissues and skeletal muscle. It is also known to enhance the insulin sensitivity attributed by phenolic and flavonoids in the extract,whereas regeneration of beta cells in pancreas may account for itspotent antidiabetic effect and glycemic control. Antioxidant propertyof the plant extract contributes to the glucose homeostasis anda-amylase and a-glucosidase inhibiting activity in the control ofhyperglycemic condition.[39]

Mangifera indicaphenolic compoundof Mangifera indica seeds found to enhance glucose metabolism byinhibition of carbohydrate digesting enzymes, a-amylase and aglucosidasefor the management of T2DM. Preventing the breakdownof starch to simple sugar may lead to enhancement of glucoseuptake of circulating glucose, thus lowers the blood glucose level.Besides, inhibition of aldose reductase will prevent degradation ofsorbitol for the formation of glucose as well as alleviate the complicationsof diabetic mellitus. Moreover, inhibition of iron inducedlipid peroxidation in pancreas is also one of the modes of action forMangifera indica which will prevent disruption of the fluidity andpermeability of cell membrane and thus prevents cell death anddamage.[40]

CONCLUSION

` The use of plants is one of the ancient traditions, being imposedto current society in the urge to evaluate the mechanism of their underlying pharmacological action and their associated benefits and adverse effects. Thus, use of herbal medicines is still continued in modern society for the prevention, wellbeing and treatment of diabetes. Commercially produced drugs are largely derived from plants and form the mainstream of today's modern medicine. Therefore, many herbs have shown to have antidiabetic activity by regulating insulin secretion, insulin sensitivity to the cells, glucoseabruption, etc. in order to improve the glycemic control of the patients. Addition to the glycemic control, some of the herbsdepicted effectiveness in the control of cardiovascular complicationsby reducing TG, cholesterol levels, and BMI. Herbal medicineare always preferred treatment options by patients or as adjunctiveto conventional treatment for diabetes due to the belief on the soiland affordability, thus laboratory research has reached to thebedside of the patients though clinical trials and marketed formulations.

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