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Unique Mechanisms in Treatment of *Diabetes mellitus*: A Herbal-Based Therapeutic Approach

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Abstract

Diabetes mellitus is a chronic metabolic disease that affects millions of people worldwide, described by hyperglycemia due to impaired insulin secretion, insulin action or both. As a consequence of the persistent hyperglycemia, several microvascular and macrovascular complications arise. In herbal treatments, there are quite a variety of mechanisms and pathways that could be targeted while considering the treatment of type II diabetes mellitus (T2DM); ranging from acting on pancreatic insulin, decreasing carbohydrates digestion, to inhibiting enzymes responsible for this disease like glucosidases, maltase fructose-1,6-bisphosphatase, G6Pase and PTP1B enzymes and increasing GLUT-2 and GLUT-4 translocation. There is a diverse amount of plants that have individual active constituents that are responsible for their antidiabetic effect; such constituents belong to classes like flavonoids, phenolic compounds and alkaloids. In our review, we will report a large variety of plants and phytoconstituents that have anti-diabetic action and discuss their mechanism of action highlighting their uniqueness and thus, providing for novel targets for anti-diabetic molecules either solely or as adjunctive therapies. Ethnopharmacological studies could aid in the selection of medicinal plants to be employed in these preliminary studies. However, the exact bioactive metabolite, along with the definite mechanism of action, should be studied before experimental and clinical studies.

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INTRODUCTION

Diabetes is a heterogeneous metabolic disease that is described by hyperglycemia as a result of impaired insulin secretion, insulin action or both (Punthakee *et al.*, 2018). Impaired insulin secretion and insulin resistance contribute more or less jointly to the development of pathophysiological conditions. Impaired insulin secretion is a drop in insulin release, observed before the disease's clinical onset. Mainly, impaired glucose tolerance is caused by lowered early-phase insulin release as well as decreased postprandial insulin secretion causing hyperglycemia. Progression of the impaired pancreatic β-cell functions influences the

blood glucose control on the long-term, as it subsequently causes permanent elevation of blood glucose as depicted in Figure 1.

Insulin resistance is when insulin does not perform sufficiently in the body, proportional to its blood level. Impaired insulin activity in main target organs; for instance, liver and muscles is a common diabetic pathophysiological attribute which was revealed to be related to genetic and environmental factors (Kaku, 2010).

Morbidities and mortalities

Globally, about 5.1 million deaths of people between 20-79 years old occurred from diabetes in 2013, with a mortality of 8.4% in people from this age group (Fareed *et al.*, 2017). Based on WHO (2016), diabetes caused the death of 1.5 million people worldwide in 2012; moreover, it was the 8^{th} chief death cause among both genders and the 5^{th} chief death cause in females. Additionally, the higher-than optimal blood glucose resulted in 2.2 million deaths. The diagnostic standard is fasting blood glucose ($\geq$7.0 mmol/L, a diagnostic point for microvascular complications). However, the risk of macrovascular diseases, e.g. stroke begins to increase yet before the diagnostic point.

Prevalence

Diabetes percentage was observed to rise rapidly in countries with low and middle income. The prevalence worldwide among the adults has increased from 4.7% in 1980 up to 8.5% in 2015. By 2030, it's estimated that prevalence will rise from 366 million up to 552 million (Sherif, 2015).

The International Diabetes Federation revealed that Egypt is the ninth country for the highest numbers of patients with diabetes. At the last two decades, diabetes percentage in Egypt was tripled due to elevation in risk factors for type II diabetes. In Egypt, diabetes prevalence around 15.6%, including all adults from age 20 up to 80 years old. The prevalence was estimated to increase from 3.24 million in 1995 to 3.8 million in 2025 with increasing 3.6 times in patients less than 65 years old (Hegazi *et al.*, 2016).

Risk Factors

Demographic risk factors

According to Ley *et al.* (2015), the prevalence of diabetes escalates with age, as in most populations, its incidence is low before the age of 30 years but rises quickly and continuously with older age. Risk of diabetes is more significant in males compared with females as observed consistently in various European countries. In a study, a self-reported Asian, Hispanic, and black ethnicities were related to a greater risk of diabetes compared to whites.

Genetic risk factors

There are individual variations regarding the susceptibility towards environmental risk factors which can affect modifiable risk factors for T2DM (Ley *et al.*, 2015). Development of Type II diabetes is associated with a family history of diabetes. The pathogenesis has been assumed to involve a genetic abnormality in molecules related to the regulatory system of glucose metabolism; for instance, genetic abnormalities in insulin receptor and glucokinase genes (Kaku, 2010).

Behavioural and lifestyle risk factors

Diet was believed to be the primary lifestyle risk factor for T2DM. Still, several studies concerning diet associated with the incidence of diabetes investigated the roles of nutrients, foods, and dietary patterns on its progression. Physical inactivity and sedentary behaviours are also a risk factor. Exercises (moderate to high intensity) are shown to have advantageous effects on T2DM prevention (Ley *et al.*, 2015). Excess body fat is the most decisive risk factor in which overweight and obesity, together with physical inactivity, are estimated to cause a large proportion of the global diabetes burden (WHO, 2016).

Moreover, babies who suffered intrauterine exposure to maternal diabetes (i.e. gestational diabetes) are most probable of experiencing several problems in their early adulthood, like childhood overweight and impaired glucose tolerance.

Given that obesity and impaired glucose tolerance are risk factors for gestational diabetes in young adults, which is expected to contribute to the elevating rates of gestational diabetes and consequently, T2DM (Ley *et al.*, 2015).

Also, studies indicated a link between income and prevalence of diabetes (higher income indicates having better access to goods and services, leading to an affordable and healthier lifestyle). Active smoking increases the risk of diabetes (highest risk among heavy smokers). The risk remains elevated for about ten years after smoking cessation, which decreases rapidly for lighter smokers (WHO, 2016).

Complications

Microvascular complications

According to Møller (2016), microvascular complications may arise such as;

Hyperosmolar Hyperglycemic State

Resulting from insulin deficiency or complete absence of insulin secretion, characterized by

increasing in glucagon release.

Diabetic Retinopathy

Occurs due to many pathological mechanisms, including elevation of oxidative stress and hyperglycemia, stimulates sugar molecules flux through the polyol pathway.

Diabetic Neuropathy

Precise mechanism is still unclear but may be related to oxidative stress and accumulation of polyol due to advanced glycation products.

Diabetic Nephropathy

Occurs due to glomerular proteins glycosylation, leading to the proliferation of mesangial cells, damage of vascular endothelium.

Macrovascular complications

It includes angina, high blood pressure, heart attacks and stroke. This results from resistance of insulin and excess free fatty acids which causes protein kinase activation and advanced glycation end products receptor activation. This could be expressed in gastroparesis -which leads to damage of vagus nerves- and peripheral vascular disease "The diabetic foot" that occurs due to alteration in coagulation pathway, serum protein glycation, and modulation in levels of insulin/proinsulin. In addition to, healing impairment, as hyperglycemia leads to impairment in white blood cells function, reduced immunity, and low blood circulation.

Signs and symptoms

According to Ambady *et al.* (2013), early signs include weight loss, irritability, frequent fatigue and infections (especially in the oral cavity, genital tract, urinary tract, and skin), the appearance of dark patches on the neck, and groin (an indication for insulin resistance). The symptoms extend to extreme tiredness, polyuria, polydipsia, polyphagia, genital itching and regular episodes of thrush, delayed wound healing, tingling, or numbness, in the hands or feet, and blurred vision.

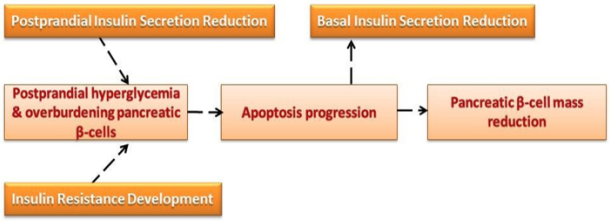

Figure 1: Pathophysiological progression of T2DM from pancreatic β-cell

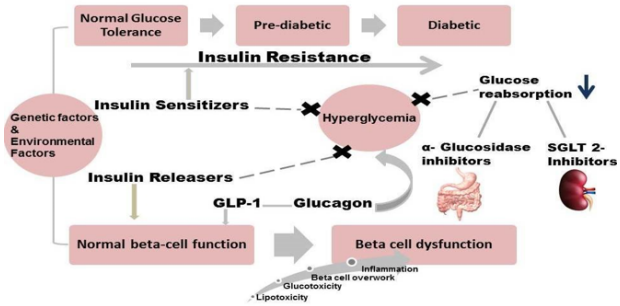

Figure 2: Common pathways targeting the treatment of T2DM

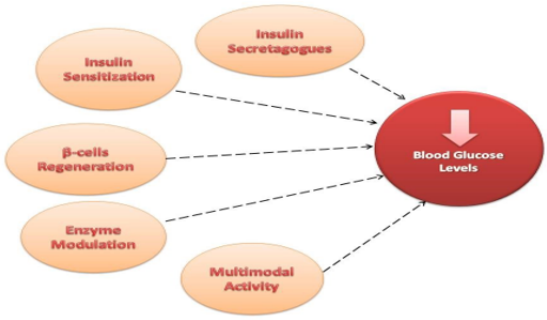

Figure 3: Mechanisms of herbal treatments of T2DM

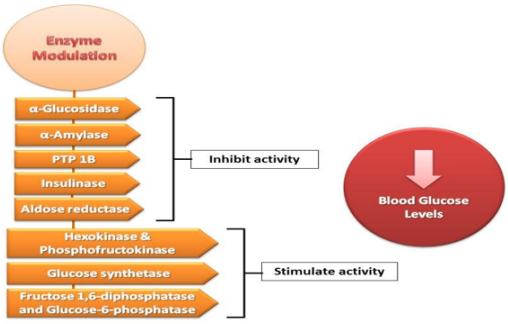

Figure 4: Enzyme modulation mechanisms adopted by plants for the treatment of T2DM

Table 1: Examples of medicinal plants exhibiting different mechanisms in the treatment of T2DM

Plant	Organ	Type of Extract	Mechanism
		Insulin Secretagogues	
Acacia arabica	Seeds	Methanolic	Stimulates the release of insulin from pancreatic β-cells.
Agrimony eupatoria	Leaves	Aqueous	
Aloe vera	Entire plant	Alcoholic	
Abies pindrow	Entire plant	Alcoholic	
Averrhoa bilimbi	Leaves and fruits	Aqueous	
Camellia sinensis	Leaves	Ethanolic	
Ocimum sanctum	Entire herb	Ethanolic	
Bridelia ndellensis	Leaves	Hydro-methanolic	
Trimenalia chebula	Seeds	Chloroform	
Alangium salvifolium	Leaves	Methanolic	Antioxidant and insulinotropic effect on insulin-secreting cells.
Bauhinia variegata	Leaves	Ethanolic	
Asparagus racemosus	Root	Ethanolic	
Zingiber officinale	Rhizome	Hydro-alcoholic	
Azadirachta indica	Leaf and seeds	Aqueous	
Bixa Orellana	Aerial parts	Ethyl acetate	
Curcuma longa	Rhizome	Aqueous	
		Insulin Sensitizers	
Bougainvillaea spectabilis	Leaves	Ethanolic	Enhances glycogenesis in the liver and increasing glucose uptake
Ipomoea potato	Leaves	Aqueous	Decreases the insulin resistance
Swertia punicea	Whole plant	Ethanolic	
Liriope spicata	Roots	Aqueous	
Elephantopus scaber	Dried powder	Acetone	Stimulates regeneration of islets of Langerhans and regenerates the granules in β-cells.
Averrhoa Oxalidaceae	Leaves	Ethanolic	Reduces gluconeogenesis and activates AMP-activated protein kinase, thus decreasing insulin resistance.
		β-Cell regeneration	
Gymnema Sylvestre	Leaves	Aqueous	Revitalizes β-cells by the aid of gymnemic acid molecules.
Caesalpinia bonducella	Seeds	Ethanolic	Prevents oxidative stress in pancreatic cells.
		Enzyme Modulators	
Viscose Dodonaea	Aerial parts	Methanolic	Modulates PTP1B enzyme levels
Brassica juncea	Seeds	Aqueous	Increases the activity of glucose synthetase.
Cassia auriculata	Seeds	Aqueous	Increases the activity of phosphofructokinase and liver hexokinase.

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Table 1 continued

Plant	Organ	Type of Extract	Mechanism
		Insulin Secretagogues	
Eugenia jambolana	Pulp of fruit	Aqueous	Inhibits the activity of insulinase.
Magnolia Officinalis	Bark	Methanolic	Enhances the phosphorylation of tyrosine levels of cellular protein, especially for insulin receptor B-subunit.
Biophytum sensitivum	Leaves	Aqueous	Inhibits fructose 1,6-diphosphatase and glucose-6-phosphatase
Andrographis paniculata	Aerial parts	Ethanolic	
Phyllanthus urinaria	Leaves	Methanolic	Inhibits α-amylase enzyme
Ocimum basilicum	Leaves	Aqueous	
Momordica miller	Leaves	Methanolic	
Cinnamomum zeylanicum	Bark	Methanolic	Inhibits α-glucosidase enzyme
Callistephus chinensis	Flower	Ethanolic	
Ficus deltoidea	Leaves and Flowers	Ethanolic	
Salacia reticulate	Roots	Aqueous	
Achyranthes Aspera	Leaves	Methanolic	
Olea europaea	Leaves	Alcoholic	
Holarrhena Antidysenterica	Seeds	Hydro-methanolic	
Glycine max	Beans	Free and bound phenolic	Inhibits α-glucosidase and α-amylase enzymes
		Multimodal activity in lowering blood glucose levels	
Trigonella Foenumgraecum	Leaves – seeds	Ethanolic - methanolic	Antioxidant / insulinotropic effect on insulin secreting cells / decreases insulin resistance / Prevents catabolism / Regenerates β-cells / Decreases glucose absorption.

Continued on next page

Table 1 continued

Plant	Organ	Type of Extract	Mechanism
		Insulin Secretagogues	
Aegle marmelos	Leaves	Aqueous – Methanolic	Stimulates the release of insulin from pancreatic β-cells / Improves pancreatic β-cells function and activity.
Coriandrum sativum	Seeds	Decoction – Ethanolic	
Cinnamomum cassia	Bark	Acetone – Ethanolic	Stimulates the release of insulin from pancreatic β-cells and increases the insulin sensitivity
Momordica charantia	Fruit	Aqueous – Alcoholic	Decreases MAPs and NF-kb regulation / Enhances insulin signaling / Modulate PTP1B / Inhibit fructose 1,6-diphosphatase and glucose-6-phosphatase / Protect β-cell, upregulate PPAR
Allium sativum	Cloves	Ethanolic	Antioxidant/insulinotropic effect on insulin-secreting cells / Stimulates reductase inhibitor, hydroxyl methyl glutaryl coA and glucose utilization.
Panax ginseng	Roots and berries	Methanolic	Inhibits α-glucosidase / Stimulates translocation of GLUT-4, insulin signalling / Antioxidant.
Carya illinoinensis	Leaves and shells	Ethanolic	Antioxidant and β-cells preserving potential
Mangifera indica	Leaves –seeds	Aqueous - ethanolic	Inhibits α-glucosidase / Inhibits aldose reductase and lipid peroxidation.
Catharanthus roseus	Leaves –seeds	Methanolic	Antioxidant / Stimulates insulin sensitivity / Inhibits α-glucosidase
Murraya koenigii	Leaves	Methanolic - Aqueous	Inhibits α-glucosidase / Antioxidant
Ocimum tenuiflorum	Leaves	Methanolic	Increases glucose uptake / Regenerates β-cells / Inhibits α-amylase and α-glucosidase.
Boerhaavia diffusa	Leaves	Chloroform – ethanolic-ethyl acetate -Aqueous	Increases insulin sensitivity / Stimulates the release of insulin from pancreatic β-cells / Inhibits fructose 1,6-diphosphatase and glucose-6-phosphatase

Table 2: Examples of bioactive metabolites exhibiting different mechanisms in the treatment of T2DM

Metabolite	Source	Mechanism
	Flavonoids and Phenolic Compounds	
Quercetin	Red onions	Inhibits renal glucose reabsorption /Decreases oxidative stress leading to protection of β-cells.
Rutin	Onions, apples, tea and red wine	Decreases blood glucose and increases insulin levels/ Inhibits lipid peroxidation/ Prevents STZ-induced oxidative stress
Trans-tiliroside	*Potentilla chinesis*	Exhibit significant glucose consumption-enhancing effects in IR-HepG2 cells
5,7-dihydroxy-6,8-dimethyl-4′ -methoxy flavone 8-2-hydroxypropyl-2-yl)-5-hydroxy-7-methoxy-6-methyl-4′-methoxy flavone	*Cirsium japonicum*	Improves the expression of adiponectin.
Diosmin	*Scrophularia Nodosa* and Citrus fruits	Stimulates the production of insulin from β-cells of pancreas / Decreases lipid peroxides, glucose and NO levels
Fisetin	Strawberries, onion and persimmon	Enhances glucose homeostasis / Stimulates glycolysis / Inhibits gluconeogenesis / Decreases IL-1β, HbA1c, NF-κB p65 and NO
Kaempferol-3-neo hesperidoside	*Bauhinia forficata* leaves	Have insulin-like action / Improves signalling of cAMP.
Apigenin	*Teucrium polium*	Increases insulin production at high concentrations of glucose.
Morin	*Prunus dulcis (Mill), Chlorophora tinctoria, Psidium guajava* and wine	Increases sensitivity of insulin / Inhibits PTP1B enzyme.
Eriodictyol	*Eriodictyon californicum, Millettia duchesnei, Eupatorium arnottianum Griseb* and lemon	Increases uptake of glucose by cells and decreases insulin resistance.
Hesperidin	*Citrus aurantium*	Decreases blood glucose level through modulating the action of glucose regulating enzymes.
Pelargonidin 3-O-α-L rhamnoside	*Ficus bengalensis* bark	Stimulates glycogen synthesis in liver and muscles / Increases glucose uptake in the peripheral tissues
Naringenin	*Cochlospermum vitifolium*, Grapefruits, oranges and tomatoes	Inhibits α-glucosidase enzyme activity in the intestine

Continued on next page

Table 2 continued

Metabolite	Source	Mechanism
	Flavonoids and Phenolic Compounds	
Baicalein	*Scutellaria baicalensis Gerogi* and *Scutellaria lateriflora*	Increases glucose tolerance and β-cell survival
Tangeretin	Citrus fruit rinds, mandarin orange and *Poncirus trifoliate*	Enhances insulin release / Increases glycogen synthesis.
Wogonin	*Scutellaria baicalensis Gerogi*	Inhibits p38 MAPK / Increases PPARα activity / Increases GLUT-2
Isorhamnetin	*Hippophae rhamnoides, Oenanthe javanica (Blume), Ginkgo biloba and Opuntia ficus-indica*	
Genistein	Fava bean, soybeans and kudzu	Inhibits α-glucosidase enzyme / Decreases protein expressions of C reactive protein, HbA1c, TNFα and TGFβ1.
Daidzein	Soybeans and nuts	Increases GLUT-4 and IRS-1.
Luteolin	*Reseda luteola*	Inhibits maltase enzyme / Increases insulin sensitivity.
Biochanin A	Red clover	Inhibits the activities of gluconeogenic enzymes: fructose-1,6-bisphosphatase and G6Pase
Procyanidins	*Theobroma cocoa*	Promotes GLUT-4 translocation / Enhances glucose uptake by incretin hormone GLP-1.
Catechin	*Cassia fistula*	Has insulin-like action / Increases glycogen in tissues / Increases expression of G6-Pase, glycogen phosphorylase, GK, GS and GTUT-4 mRNA.
Epigallocatechin	*Hypericum perforatum*	Enhances synthesis of glycogen by phosphorylation of AMP-activated protein kinase α and expression of acetyl CoA carboxylase / Reduces tyrosine-phosphorylation / Stimulates insulin receptor and IRS.
Bavachin	*Psoralea corylifolia (Fabacea)* fruit	Activates PPARγ, C/EBPα, causing plasma insulin to increase / Increases GLUT-4 translocation through activation of AMPK and Akt pathways.
Pinobanksin	Sunflower	Stimulates insulin signalling and glucose uptake in skeletal muscles / Enhance GLUT-4 translocation.
Bergenin	*Caesalpinia digyna*	Acts on pancreatic β-cells regeneration in Type II diabetes.

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Table 2 continued

Metabolite	Source	Mechanism
	Flavonoids and Phenolic Compounds	
Curcumin	*Curcuma longa*	Increases insulin levels
Resveratrol	Grapes, peanuts, cranberries, blueberries	Increases pancreatic β-cell function by inhibition of phosphodiesterase activity.
Gallic acid	Gallnuts, Sumac	Acts by adipocyte differentiation / has free radicals scavenging action.
Ferulic acid	Ferula species	Stimulates the action of G-6Pase and restores the glucose levels by the same mechanism of metformin / Decreases lipid peroxidation and glycated haemoglobin.
Anacardic acid	*Anacardium occidentale*	Enhances GLUT translocation by activation of AMPK / Increases glucose transport into C2C12 myotubes in high concentrations.
	Alkaloids	
Berberine	Goldensea, barberry, and Oregon grape	Decreases the intestinal absorption of glucose / Decreases the hepatic glucose production / Improves the action of insulin by activating AMPK enzyme.
Palmatine	*Phellodendron amurense*	Increases basal insulin release
Boldine	*Peumus boldus*	Deactivates ROS / Increases NO production by increasing phosphorylation eNOS.
Jatrorrhizine	*Enantia chlorantha*	Activates PPARα / Increases GLUT-4.
Trigonelline	*Trigonella foenumgraecum*	Increases the (GK/G6Pase) ratio in liver / Increases the translocation and expression of GLUT4 / Increases levels of plasma insulin.
Vindoline vindolidine, and vindolicine	*Catharanthus roseus,*	Increases glucose uptake in β-TC6 the same as in C2C12 cells / Inhibits PTPIB.
Catharanthine	*Catharanthus roseus*	Stimulates the release of amylase / Increases glycolysis through stimulating hexokinase activity / Inhibits glucose-fructose 1,6- bisphosphatase and 6-phosphatase.
Piperidine	*Combretum micranthum*	Inhibits the expression of phosphoenolpyruvate carboxykinase gene.
Aegeline	*Aegle marmelos*	Stimulates GLUT-4 translocation.

Diagnosis and monitoring

The diagnosis of DM comprises blood glucose concentration**,** fasting blood sugar test**,** glucose tolerance test and glucose in urine. In addition to tests for gestational diabetes, i.e. the initial glucose challenge test. It could be monitored by Glycated Hemoglobin (A1C) test as a widely used marker of chronic glycaemia, reflecting average blood glucose levels over a 2 to 3 months' period of time. As well as, Serum Fructosamine, which is a glycated serum protein, giving a reliable estimate of blood glucose level during preceding 1-3 weeks (Wild *et al.*, 2004).

Conventional treatments for T2DM

Biguanides

The first line of T2DM treatment is Metformin. Biguanides reduce glucose absorption from the intestine, enhance uptake of glucose peripherally, increase sensitivity to insulin and inhibit gluconeogenesis as depicted in Figure 2.

Thiazolidinediones

TZDs are insulin sensitizers acting on insulin-sensitive tissues (liver, adipose tissues and muscle cells) to decrease glucose production and increase its utilization as shown in Figure 2. TZDs bind to specific nuclear receptor Peroxisome Proliferator Activator Receptor-Gamma **(**PPAR-γ **)** which induces the synthesis of insulin signalling cellular molecules, e.g. GLUT-4 and Lipoprotein lipase enzyme.

Sulphonylureas and Glinides (Insulin releasers)

These are oral hypoglycemic acting by stimulating pancreatic β-cells to release insulin as illustrated in Figure 2. Mechanism of both classes depends on potassium ATP-sensitive channel (KATP-potassium channel) localized in beta cells of the pancreas. Both have different binding sites on the receptor, but they stimulate cell depolarization and channel closure leading to an increase in calcium level in cytoplasm and insulin secretion consequently (Marín-Peñalver *et al.*, 2016).

Dipeptidyl peptidase-4 inhibitors

Incretin hormones (GLP-1 and GIP), as shown in Figure 2, are secreted by L-cells in the intestine, stimulates insulin secretion and inhibit the release of glucagon. Agents that block DPP-4 action (known as gliptins) inhibit this enzyme which inactivates the incretins rapidly, increasing the duration of active incretin level which in turn enhances β-cell function and T2DM glycemic control (Barnett, 2006).

Alpha-glucosidase inhibitors

Agents from this class comprise Acarbose, Miglitol and Voglibose. They reversibly inhibit alpha-glucosidase hydrolase enzyme; inhibiting carbohydrates digestion and absorption in the brush border membrane of the small intestine as shown in Figure 2, which reduces postprandial hyperglycemia (Marín-Peñalver *et al.*, 2016).

Sodium-glucose co-transporter-2 inhibitors

Such as Canagliflozin, Dapagliflozin and Empagliflozin. It is the most recent class in T2DM treatment, works by inhibition of renal glucose reabsorption, increase glucose excretion and reduce hyperglycemia as shown in Figure 2. They block, in the proximal tubule, SGLT2 transporter which is responsible for 90% reabsorption of glucose (Kalra *et al.*, 2015).

Herbal treatments for T2DM

Plants possessing anti-diabetic potentials

According to Prabhakar and Doble (2011), there are quite a variety of mechanisms and pathways that could be targeted while considering the treatment of T2DM; ranging from acting on pancreatic insulin, decreasing carbohydrates digestion, to inhibiting enzymes responsible for this disease.

Another aspect to focus on in diabetes treatment is insulin resistance, which is mainly to increase the sensitivity of insulin receptors in cells to insulin by insulin sensitizers. However Alam *et al.* (2019) mentioned other ways of treatment which are acting on pancreatic β-cells (Malviya *et al.*, 2010; Patel *et al.*, 2012; Ríos *et al.*, 2015) and increasing insulin secretion, β-cell regeneration, enzymatic modulation and other different activities as shown in Table 1 and Figure 3 (Hawary *et al.*, 2016; Verma *et al.*, 2018; Choudhury *et al.*, 2018).

Recently, discovering and investigating enzymes that are directly involved in the diabetic pathway has been taken into full consideration. Thus, they are modulated (inhibited/stimulated) to treat and manage the disease (Alam *et al.*, 2019) as shown in Figure 4.

Bioactive metabolites possessing anti-diabetic activity

In-depth study of the plants leads to the identification of the bioactive metabolites that are responsible for the anti-diabetic effect. These metabolites belong to different classes including, phenolic compounds, flavonoids, alkaloids and saponins.

Phenolic compounds and flavonoids act by several pathways including the inhibition of renal glucose reabsorption, decreasing oxidative stress leading to protection of β-cells, stimulating insulin secretion and decreasing its resistance, enhancing glucose consumption and homeostasis, stimulating gly-

colysis, inhibition of gluconeogenesis, improving the signalling of cAMP, increasing glucose tolerance. Also, they act through the inhibition of α-glucosidase, maltase fructose-1,6-bisphosphatase, G6Pase and PTP1B enzymes and increasing GLUT-2 and GLUT-4 translocation (Ezzat *et al.*, 2018). Similar mechanisms were also reported (Venable *et al.*, 2000) for the alkaloids isolated from different plants (Table 2) (Trojan-Rodrigues *et al.*, 2012; Vanitha *et al.*, 2014; Ali *et al.*, 2015). In addition to some saponins like pseudoprototinosaponin AIII and prototinosaponinsAIII and gymnemic acid, which stimulate insulin synthesis and release from pancreatic β-cells, and lupine and protopanaxadiol, which inhibit PTP1B.

DISCUSSION

T2DM is a metabolic condition that is known by high blood glucose levels because of insulin resistance as well as impaired insulin secretion from pancreatic β-cells. This disease caused the death of approximately 5.1 million people aged between 20-79 years in 2013, accounting for 8.4% mortality of people from this age group (Fareed *et al.*, 2017). Its incidence was estimated to increase up to 552 million in 2030 (Sherif, 2015). It was observed to rise rapidly in countries of low and middle income. At the same time, the prevalence in Egypt in the last two decades was tripled due to the spread of wrong lifestyle and risk factors. Egypt was categorized by international diabetes federation as a ninth country having the highest numbers of diabetic patients (Hegazi *et al.*, 2016). However, diabetes involves various risk factors, including demographic, genetic and, behavioural and lifestyle risk factors (Ley *et al.*, 2015).

According to Møller (2016), diabetes complications are divided into microvascular and macrovascular. Microvascular complications include diabetic nephropathy, diabetic neuropathy, diabetic retinopathy and hyperosmolar hyperglycemic state. Diabetic neuropathy mechanism is still unclear, but it may be due to polyol accumulation and oxidative stress. Diabetic nephropathy occurs due to glycation of glomerular protein. Diabetic retinopathy occurs due to oxidative stress elevation and polyol pathway that causes sugar molecule flux. The hyperosmolar hyperglycemic state occurs due to deficiency of insulin and stimulation of glucagon release, while macrovascular complications include angina, stroke, heart attacks and high blood pressure. They result from an excess free fatty acid that causes activation of protein kinase. In addition to advanced glycation end products. Signs and symptoms of diabetes include irritability, weight loss, fatigue, skin patches, polyuria, polydipsia, polyphagia, genital itching, delayed wound healing, tingling, or numbness, and blurred vision (Ambady *et al.*, 2013). Diabetes can be diagnosed by blood glucose concentration**,** fasting blood sugar test**,** glucose tolerance test and glucose in urine. However, it can be monitored via glycated haemoglobin and serum fructose-amine levels tests (Wild *et al.*, 2004).

As genetic and environmental factors such as insulin resistance and beta-cell overwork lead to the risk of T2DM, current conventional treatment target the multiple pathophysiological defects including insulin sensitizers, insulin releasers, GLP-1 analogues, alpha-glucosidase inhibitors and SGLT-2 inhibitors. Insulin sensitizers include biguanides and thiazolidinediones that increase tissues sensitivity to insulin and reduce glycolysis. Insulin releasers include sulphonylureas that work by beta cell stimulation releasing insulin (Marín-Peñalver *et al.*, 2016). Alpha-glucosidase inhibitors work by decreasing glucose absorption from the intestine; while DDP-4 inhibitors stimulate insulin production (Barnett, 2006). SGLT-2 inhibitors excrete excess glucose in urine (Kalra *et al.*, 2015).

Plants have several anti-diabetic mechanisms that they work by, including insulin secretagogues, insulin sensitization, β-cells regeneration, enzyme modulation and multimodal activity (Prabhakar and Doble, 2011). Most medicinal plants act by unique mechanisms which are not found in conventional treatments (Choudhury *et al.*, 2018). Regarding enzyme modulation, some plants act on enzymes which are involved in the diabetic pathway and either inhibits or stimulates them; for example, inhibiting α-glucosidase and stimulating hexokinase enzyme (Alam *et al.*, 2019). Herbs that act as enzyme modulators (i.e. modify enzymes that contribute to glucose and insulin levels) include *Momordica charantia, Brassica juncea*, and *Andrographis paniculata*. Some herbs act through inhibition of α-glucosidase and α-amylase, which is similar to some conventional drugs. Glucosidase and amylase are enzymes that help in the breakdown of carbohydrates, thus preventing the elevation of postprandial glucose. *Phyllanthus urinaria*, *Panex ginseng* and *Glycine max* are examples of α-glucosidase and α-amylase inhibitors (Malviya *et al.*, 2010).

Furthermore, herbs which stimulate the release of insulin from pancreatic β-cells include *Acacia arabica*, *Ocimum sanctum* and *Aegle marmelos.* Also, other herbs increase insulin sensitivity such as *Cinnamomum cassia, Momordica charantia* and

Trigonella foenumgraecum. Both actions insulin-sensitizing and insulin secretagogues actions are found in conventional treatment; however, herbs such as *Gymnema Sylvestre*, *Elephantopus scaber* and *Coriandrum sativum* which improve and regenerate pancreatic β-cells function is one of the mechanisms that are not found in the conventional treatment (Verma *et al.*, 2018).

In-depth study of the plants leads to the identification of the bioactive metabolites that are responsible for the anti-diabetic effect. These constituents belong to different classes including, phenolic compounds, flavonoids, alkaloids and saponins. For example, morin, a phenolic compound and the alkaloid vindoline act by inhibition of PTP1B enzyme, this action cannot be done by conventional treatment (Venable *et al.*, 2000; Vanitha *et al.*, 2014). There are also some flavonoids such as daidzein, catechin and pinobanksin, which stimulate GLUT-4 translocation (Kim *et al.*, 2014). Besides, several constituents which act by increasing insulin release such as diosmin, kaempferol-3-neohesperidoside, apigenin and tangeretin (Trojan-Rodrigues *et al.*, 2012).

CONCLUSION

The active metabolites in different plants could act by unique mechanisms of action in the treatment of T2DM, thus, providing for novel targets for anti-diabetic molecules. Further studies in this area should be enhanced to evaluate the use of these metabolites either solely or as adjunctive therapies in anti-diabetic medications. Ethnopharmacological studies could aid in the selection of medicinal plants to be employed in these preliminary studies. However, the exact bioactive metabolite, along with the definite mechanism of action, should be studied before experimental and clinical studies.

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Conflict of interest

The authors declare no conflict of interest for this study.

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