



- REVIEW ARTICLE -

## The Potential Anti-Diabetic Effects of Some Plant Species

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### Abstract

Diabetes mellitus is a global disease, of which prevalence increases rapidly. It causes severe microvascular and macrovascular complications such as retinopathy, nephropathy, cardiomyopathy, neuropathy etc. These contribute to morbidity and mortality in diabetic patients. Therefore, it is important to find an effective therapy method(s) for the protection of body from diabetes-related complications. In this sense, herbal products are of great importance. Herein, this review will highlight the potential usage of some herbals as a preventive and/or therapeutic approach in diabetes and discusses the possible underlying mechanisms of anti-diabetic actions.

### Keywords:

Hyperglycemia, Metabolic disease, *Agrimonia eupatoria* L., *Cynara cardunculus* L., *Gastrodia elata* Blume, *Murraya koenigii*

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### Introduction

Diabetes mellitus, referred as diabetes, is a metabolic disease characterized with high blood glucose levels as a result of partial or complete lack of insulin secretion. The incidence of diabetes increases all over the world. Diabetes is generally classified as type I and type II diabetes. Type I diabetes is one of autoimmune disease, results from destroying beta ( $\beta$ ) cells of





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pancreases and reported to suffer from more than 20 million people (Pociot, 2017). Type II diabetes is also known as non-insulin dependent diabetes mellitus, which result from insulin deficiency or insulin resistance. Diabetes or hyperglycemia increases vulnerability to mortality and morbidity in patients (Olokoba et al., 2012).

There are several different therapeutic ways to manage hyperglycemia in diabetic patients such as insulin for type I and sulfonylureas or dipeptidyl peptidase IV inhibitors for type II diabetes. On the other hand, the exact medical treatment is not completely achieved (Marya et al., 2018). Therefore, herbal products only or in combination with anti-diabetic drugs take great important to manage the hyperglycemia or to create preventive strategies for diabetes related complications.

In this review, we focused on the anti-diabetic effects of some plants species (Table I) and signaling pathways that mediate the physiological actions.

Table 1. Some plant species having potential anti-diabetic action

	Scientific Name	Family Name	Common Name
 (Granica et al., 2015)	<i>Agrimonia eupatoria</i> L.	Rosaceae	Agrimony
 (Alkushi, 2017)	<i>Cynara cardunculus</i> L.	Asteraceae	Cardoon
 (An et al., 2010)	<i>Gastrodia elata</i> Blume	Orchidaceae	Tall Gastrodia
 (Ahmadi et al., 2012)	<i>Ziziphus spina-christi</i> (L.) Desf.	Rhamnaceae	Christ's thorn jujube



(Johnson et al., 2015)

*Ficus amplissima* Sm.

Moraceae

Cluster Fig Tree



(Joseph et al., 2013)

*Momordica charantia* L.

Cucurbitaceae

Bitter melon



(Miroddi et al., 2013)

*Passiflora incarnata* L.

Passifloraceae

Purple passionflower



(Mandal, 2016)

*Murraya koenigii* (L.) Spreng.

Rutaceae

Curry Leaf Tree



*Olea europaea* L.

Oleaceae

Olive

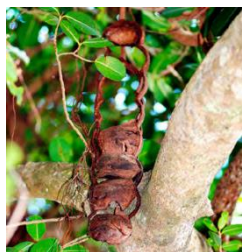


(Su et al., 2014)

*Dracaena cochinchinensis*  
(Lour.) S.C.Chen

Asparagaceae

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(Conran et al., 2014)

*Entada phaseoloides* (L.) Merr. Fabaceae

St. Thomas Bean

### Anti-diabetic Features of Some Plants

***Agrimonia eupatoria* L. (Agrimony)** is used for the treatment of diabetes. The plant includes polyphenols and exerts antioxidant properties. It is suggested to have insulin-like effect as well (Gray et al., 1998). Agrimony might inhibit  $\alpha$ -glucosidase enzyme activity that is a converting enzyme from poly and oligosaccharides to monosaccharides at  $46.31 \pm 8.76 \mu\text{g/mL}$  IC<sub>50</sub> concentration of its (Kuczmannova et al., 2016). Agrimony can be a good candidate due to its low frequency of hypoglycemia without having any gastrointestinal irritable effect against to  $\alpha$ -glucosidase enzyme inhibitors. Its water extract has also been implied to decrease advanced glycation end-products (AGEs) and receptor of AGEs (RAGE) at  $156.48 \pm 70.75 \mu\text{g/ml}$  (Kuczmannova et al., 2016). Agrimony also reduced weight lost by declining polydipsia, hyperplasia in diabetic rats. Butyrylcholinesterase (BuChE) activity might be used for therapeutic target of type II diabetes, metabolic syndrome, or obesity. Agrimony extract associated with hypolipidemic, hypocholesterolemic, hepatoprotective, and antioxidant characteristics might elevate BuChE activity compared to diabetes group that causes the decline in its hepatic activity. Moreover, the plant extract also modulated aorta vasoconstriction, probably related to its endothelial protection, resulting in eventually decreasing diabetic cardiovascular complications (DCC). One of its compounds, epicatechin, has been suggested to be responsible for its DCC by elevation of nitric oxide (NO) concentration that is well known as its endothelial vasodilatation effect and opening of NO dependent activation- iberiotoxin- sensitivity potassium (K) channel *in vitro* (Huang et al., 1999; Kuczmannova et al., 2016).

***Cynara cardunculus* L. (Cardoon)** is indicated to have antidiabetic effect due to antioxidant efficiency, resulting in decrease postprandial and fasting glucose levels (Alkushi, 2017; Kuczmannova et al., 2016). Although cardoon has been not shown any  $\alpha$ -glucosidase enzyme inhibitor effects, it has been reported to have a decline AGEs and RAGES at  $223.61 \pm 36.33 \mu\text{g/mL}$  IC<sub>50</sub> concentration of its. BuChE activity might be used for therapeutic target of type II diabetes. Diabetes causes to diminish its activity at liver. Cardoon extract based on its hypolipidemic, hypocholesterolemic, hepatoprotective and antioxidant properties might elevate its activity compared to diabetes groups. On the other hand, its protective effect on diabetes-related cardiovascular complication has not been found. However, it has been indicated to have anti-inflammatory effect in diabetic rats (Kuczmannova et al., 2016).

***Gastrodia elata* Blume (GEB)** is one of member of Orchidaceae family species, which is used for the treatment of type II diabetes in Asia. The plant has many compounds. Some of them can cross blood-brain barrier. Then, they could affect hypothalamus and hippocampus, association with peripheral glucose metabolism to improve insulin signaling which is pAkt-, pGSK-1,

resulting in enhancing peripheral glucose and energy metabolisms. After hypothalamic and hippocampus modulation, hepatic insulin resistance could improve. Therefore, GEB may be a good candidate to regulate peripheral glucose metabolism dependent on brain insulin signaling. One of previous studies showed that GEB caused a decline visceral fat mass by elevation of fatty acid  $\beta$  oxidation and decreased food consume, resulting in elevation of insulin sensitivity in obese rats. Moreover, the other compound of the plant was indicated to elevate glucose uptake induced by insulin and decrease fat accumulation in adipocytes cell culture line (3T3-L1). GEB could restore insulin sensitivity in the liver more than skeletal muscles. The plant is also reported to enhance glucose-stimulated insulin secretion by enhance phosphorylation of phosphatidylinositol 3-kinase (PI3K) and cAMP-responsive element binding protein (CREB) as well and to increase brain-derived neurotrophic factor in hippocampal cell culture line. Eventually, GEB give rise to augment pancreatic  $\beta$  cell mass and proliferation (Yang et al., 2016). Moreover, a recent study indicated that GEB improved serum insulin levels and maintained AMPK and CREB activities in rats (Kim et al., 2017). In addition, GEB enhanced leptin signaling in hypothalamus for enhancing energy metabolism by a decline to neuropeptide-Y (NPY) and agouti-related protein (AgRP). The effect of GEB on hypothalamic leptin signaling which is Janus kinase-2 and STAT-3 causes to decrease food consume and body fat, resulting in losing body weight. High fat diet (HFD) is indicated to give rise to develop hypothalamic leptin resistance, but GEB restored to leptin resistance. HFD led to increase 5' AMP-activated protein kinase (AMPK) in hypothalamus. AMPK plays a crucial role in energy and glucose metabolisms. When AMPK in hypothalamus increase, daily food consume and body weight give rise to enhance by increasing orexigenic neuropeptides, NYP, AgRP. However, GEB treatment could restore body weight and food intake by decreasing the phosphorylation of AMPK in the hypothalamus. GEB also protects brain against ischemia via decreasing  $\gamma$ -aminobutyric acid (GABA) release and GABAergic neuron activity which plays important role in regulation of daily food intake and energy metabolism, causing a decline insulin resistance and body weight in diet-induced obese mice (Park et al., 2011).

***Ziziphus spina-christi* (L.) Desf. (Christ's thorn jujube)** is also used in folk medicine and had many effects on many health conditions. The plant is reported to be antinociceptive and central depressant effect at aqueous extraction or anti-diarrheal impact at methanol extract (Abdel-Zaher et al., 2005). Moreover, it is used for diabetic therapy to decrease hyperglycemia at the butanol extract on diabetic rats by increasing insulin level after four weeks, but not normal rats (Abdel-Zaher et al., 2005; Michel et al., 2011). There is no toxic effect of *Ziziphus spina-christi* (L.) leaves on kidney or liver in rats, evidenced by examination of biochemical and histopathological parameters. Furthermore, it is reported not to change hematological parameters as well (Abdel-Zaher et al., 2005). In the mentioned study, anti-hyperglycemic effect of the plant's butanol extract is mainly based on its saponin glycoside that is known as christinin-A. The extract of the plants decreased  $\alpha$ -amylase activity at its  $IC_{50}$  concentration 0.3 mg/ml. Its high density more than 2 mg/ml almost blocked  $\alpha$ -amylase activity. The plant has some flavonols, such as quercetin, hyperoside, and quercetrin that effect on pancreatic  $\beta$ -cell function through  $Ca^{2+}$  influx and cyclic nucleotide metabolism. Quercetin is reported to decrease hyperglycemia in diabetic animals thorough enhancing pancreatic  $\beta$ -cell regeneration and translocation of glucose transporter-4 (GLUT-4) to  $\beta$ -cell membrane. Moreover, flavonoids have been shown to possess antioxidant property. Hyperglycemia accompanies with high plasma lactate levels by a decline pyruvate dehydrogenase (PDH), but not pyruvate due to enhancing glycolysis. This kind of

alternation occurs when insulin is insufficient, resulting in elevation of hepatic glucose production. Both of glucose-6-phosphatase and hexose monophosphates, hepatic gluconeogenic enzyme were reported to decrease at diabetic rats. *Ziziphus spina-christi* (L.) extract is suggested to decrease plasma lactate levels, but increase pyruvate level. Moreover, its extract treatment could modulate glycogen storage in liver and skeletal muscles by elevation of glucose-6-phosphate dehydrogenase activities and decreasing hepatic glucose-6-phosphatase (Michel et al., 2011). It is well known that ATP sensitive potassium channels ( $K_{ATP}$ ) plays a crucial role in realizing of insulin from pancreatic  $\beta$  cell. It was reported that the butanol extract pretreatment of *Ziziphus spina-christi* (L.) or chritinin-A increases glibenclamide effect, one of  $K_{ATP}$  blockers, on decreasing plasma glucose level and insulinotropic impact (Abdel-Zaher et al., 2005). Although diazoxide, one of  $K_{ATP}$  opener, cause to increase plasma glucose level by decreasing insulin releasing from pancreatic  $\beta$  cell in normal and type II diabetic animals but not in type I diabetic animals. Interestingly, when the butanol extract of the plants or chritinin-A was used for pretreatment of diabetes, the effect of diazoxide on plasma glucose level is blocked by pretreatment. According to authors' results, they concluded that *Ziziphus spina-christi* (L.) leaves naturally prevented the  $K_{ATP}$  channel at pancreas which combination is Kir 6.1, part of pore and SUR1, accessory part. It means that diabetic patients may not have to take  $K_{ATP}$  blocker such as glibenclamide to reduce blood glucose level by increasing insulin releasing.

***Ficus amplissima* Sm. (Cluster Fig Tree)** is also used in the treatment of diabetes in herbal medicine, with only the methanol extract. The plants have anti-oxidant and anti-inflammatory effects as well. Recent data has shown that its methanolic extract caused to decrease blood glucose in normoglycemic rats. Thus, it maximally enhances oral glucose tolerance test at 100 mg/kg glucose dose. Moreover, the blood glucose level is lower in diabetic rats by increasing insulin level at plasma after 21-day treatment of the extract. The authors also reported that there is similar result both glibenclamide which is one of  $K_{ATP}$  antagonist for decreasing blood glucose by enhancing insulin realizing from the pancreas and *Ficus amplissima* Sm. extract effects on hyperglycemia. The extract treatment for 21 days is shown to restore liver and muscle glycogen storages that decrease after diabetes. In diabetic animals, *Ficus amplissima* Sm. treatment for 21 days also modulates serum triglycerides and total cholesterol, which are well known to have a primary role in developing atherosclerosis and coronary heart disease. Therefore, the plant extract restores not only glucose metabolism but also lipid metabolism. Moreover, it led to enhance antioxidant and decrease oxidant status of diabetic rats that help to reduce diabetic complication linked to oxidative stress, accepted primarily to responsible for developing diabetes. Liver tissue is affected by diabetes, so the plants extract also modulate necrotic liver tissue-induced by diabetes according to histopathological and biochemical examinations (Aruna Sindhe et al., 2016; Arunachalam et al., 2013).

***Momordica charantia* L. (Bitter melon)** has the non-toxic effect on animals, which is also used for diabetic and atherosclerosis treatments. The plants belong to Cucurbitaceae family. A previous study indicated that *Momordica charantia* L. extract successfully decreased blood glucose after glucose loading within 60 minutes (Ali et al., 1993; Sekar et al., 2005). Its possible hypoglycemic effect has been reported to relate to enhancing insulin secretion from pancreatic  $\beta$ -cell or insulin sensitivity on tissues and to decrease intestinal absorption of glucose. Sekar et al. (2005) gave an alternative explanation on the anti-hyperglycemic effect of *Momordica charantia* L. to associate with alternation glucose metabolism by altering hexokinase, lactate

dehydrogenase, gluconeogenic, and glycogen synthase and glycogen phosphorylase enzymes. Diabetes gives rise to decrease hexokinase enzyme that plays essential role in converting glucose to glucose-6-phosphate that is first step in glucose utilization. Nevertheless, *Momordica charantia* L. extract is reported to restore hepatic hexokinase enzyme in the diabetic animals. Moreover, it was noticed that *Momordica charantia* L. treatment in diabetic animals led to modulate lactate dehydrogenase enzyme activity, which is important for glycolysis to change lactate/pyruvate ratio to lactate. Thereby, *Momordica charantia* L. treatment might also heal acidosis-related to diabetic complication by decreasing lactate levels due to enhancing glucose oxidation rate from mitochondria. The other pathways of *Momordica charantia* L. effect on glucose metabolism is reported to based on glucose-6-phosphatase and fructose-1,6, bisphosphatase which are gluconeogenic enzyme. Under diabetic condition, those enzymes arise due to insulin deficiency. Nevertheless, *Momordica charantia* L. treatment in diabetic animals has been indicated to attenuate those enzymes, resulting in decreasing glucose production. Liver glycogen storage is essential to maintain glucose balance. There are two crucial enzyme for glycogen storage at liver that are known as glycogen synthase and glycogen phosphorylase. Although glycogen synthase augment the storage, glycogen phosphorylase has opposite effect on glycogen storage at liver. It is well known that diabetes causes to decrease glycogen storage by decreasing glycogen synthase and enhancing glycogen phosphorylase. However, *Momordica charantia* L. extract is reported to modulate them as well (Sekar et al., 2005). *Momordica charantia* L. is named as bitter melon, karela, balsam pear, or bitter gourd. Its fruits, which is 242 kcal/ 100 g has been reported to exist many vitamins, e.g. vitamin C, A, A, B1, B2, B3 or B9 and many minerals, such as calcium, zinc, magnesium, iron or potassium. Moreover, it is suggested to be good for gastrointestinal system due to its high dietary fibers. In addition, *Momordica charantia* L. has existed very high antioxidant substrate relying on flavonoids, terpenes, isoflavones, phenols, anthroquinones, and glucosinolates that are responsible of its bitter taste as well. Moreover, its antidiabetic effects are based on protein, lipid, phenolic, inorganic, steroid and triterpene compounds. Its triterpenoids components exert its hypoglycemic effects via AMPK. Its antidiabetic effects is reported in both animals and humans studies. Charantin, polypeptide-p, and vicine are the most effective hyperglycemic compounds obtained from *Momordica charantia* L.. One of reasons for consumption of *Momordica charantia* L. is polypeptide-p or plant-insulin relied on insulin-like hypoglycemic protein. Furthermore, *Momordica charantia* L. has anticancer, anti-inflammation, antiviral, anti-mutagen and anti-cholesterol effects (Joseph et al., 2013). Antiviral effects of its associates with triggering immune system and activation of natural killer. Not only have its antiviral effects, but also it has antibacterial impact including *Staphylococcus*, *Pseudomonas*, *Salmonella*, *Staphylococcus aureus*, *Streptobacillus* or *Escherichia coli*. It is used against malaria as well. However, pregnant women are not advised to consume *Momordica charantia* L. due to its abortifacient impact. Men are not also suggested to intake *Momordica charantia* L. because it was shown that the extract might lead to infertility due to its toxic effect to seminiferous tubule and decreasing testosterone levels (Tumkiratiwong et al., 2014). Its anti-diabetic effects have been well documented (Mahmoud et al., 2017; Tahira et al., 2014). Its hypoglycemic impact is found to be relationship with enhancing peripheral uptake, blocking some important enzymes at gluconeogenesis, but stimulation of some crucial enzymes at pentose phosphate pathway inhibition adipocyte differential and gastrointestinal glucose uptake, as well as protection of  $\beta$ -cell and its functions. The protective effects of *Momordica charantia* L. on  $\beta$ -cell associated with blocking mitogen-activated protein kinases (MAPKs) which are stress-activated protein kinase/c-Jun N-terminal

kinase (SAPK/JNK), P38 and Erk1/2. *Momordica charantia* L. has restored dyslipidemia and hyperglycemia by PPAR- $\gamma$  gene expression. Hypoglycemic effects of *Momordica charantia* L. also relate to enhance  $\beta$ -cell number and recovery of impairment of the pancreatic cells. Moreover, it has been to exist cell proliferation and growth properties similar insulin. That is why *Momordica charantia* L. could recovery of pancreatic  $\beta$  cell and decrease  $\beta$ -cell lost as well. In addition, it could affect glucose metabolism by suppression of fructose 1, 6-diphosphatase, and glucose-6-phosphatase, but activation of glucose-6-phosphatase dehydrogenase. Interestingly, its juice has wortmannin that is one of phosphatidylinositol 3-kinase inhibitor. Moreover, *Momordica charantia* L. has decreased gastrointestinal glucose uptake by decreasing sodium ( $\text{Na}^+$ ) and potassium ( $\text{K}^+$ )-related glucose uptake. The diabetic patients with cataract has been suggested to recovery of retinopathy-induced by diabetes through consumption of its fruit extract due to modulation of glucose metabolism. So, the drug-obtained from *Momordica charantia* L. has been found and bought pharmacy as a capsules or tablets named as Gourdin, Karela, and Glucobetic in many countries (Joseph et al., 2013).

***Passiflora incarnata* L. (Purple passionflower)** belongs to Passifloraceae family and poses many flavonoids such as quercetin, alkaloids, i.e., harman and different phytoconstituents including carbohydrates such as raffinose. One of the recent studies show that the plant extract has hypoglycemic effect and decrease lipids levels in diabetic mice (Gupta et al., 2012). However, it should be mentioned that more studies are need to clarify anti-diabetic actions of *Passiflora incarnata* L. both *in vivo* and *in vitro*.

***Murraya koenigii* (L.) Spreng. (Curry Leaf Tree)** generally known as curry leaves, has many trace elements such as zinc, iron, and vitamins. Moreover, the plants have antioxidant activity. *Murraya koenigii* has indicated to have a hypoglycemic effect, resulting in enhancing insulin releasing by pancreatic  $\beta$ -cell proliferation due to decline oxidative stress (El-Amin et al., 2013). *Murraya koenigii* belongs to Rutaceae family. It is used for the treatment of many diseases such as diabetes, cancer, headache, stomachache, influenza, rheumatism, traumatic injury, anti-vomiting, or diarrhea, etc. Besides its hypoglycemic effects, *Murraya koenigii* might decrease cholesterol as well. Moreover, it has been proposed to have anti-microbial and anti-inflammatory impact. Its hypoglycemic effects is indicated to relate to proliferate of pancreatic  $\beta$  cells and increase insulin releasing from remnant pancreatic  $\beta$ -cell. In addition, *Murraya koenigii* treatment is shown to decrease glycosylated hemoglobin (HgA1c) levels due to the restoration of plasma glucose levels (Arulselvan et al., 2007).

***Olea europaea* L.**, known as olive, is recommended against diabetes. Its hypoglycemic effects are based on oleuropein and related to insulin releasing-induced by glucose and increase peripheral glucose uptake. *Olea europaea* L., is indicated to have a hypolipidemic impact, resulting in a decline to develop coroner heart disease and vascular disease. Diabetes is known to disrupt metabolism, including protein, glucose, and lipid as well. Elevation of protein glycation in diabetes cause to muscle weakness associated with enhancing xanthine oxidase. However, treatment of *Olea Europeae* L. has been reported to restore urea and creatinine levels (Eidi et al., 2009). *Olea Europeae* L. has antioxidant properties based on oleuropein and hydroxytyrosol by enhancing superoxide dismutase (SOD) and catalase (CAT) in the liver. *Olea europaea* L., has been reported to restore dyslipidemia by the decline of hypercholesterolemia hypertriglyceridemia (El-Amin et al., 2013).



***Dracaena cochinchinensis* (Lour.) S.C.Chen** belongs to Asparagaceae family. Sanguis draconis (SD) is a resin obtained from *Dracaena cochinchinensis* (Lour.) S.C.Chen. SD is generally used for the treatment of diabetes-related diseases. SD might restore hyperglycemia, hyperinsulinemia, and insulin resistance. Type II diabetes causes to accumulate lipid in liver by declining insulin response of the tissue, leading to inhibition of lipolysis. SD treatment of type II diabetes is recommended to decrease dyslipidemia. Type II diabetes has been well known to relate to oxidative stress-induced by hyperglycemia (Asmat et al., 2016). Therefore, type II diabetes led to decline SOD and glutathione (GSH) and increase malondialdehyde (MDA). However, a recent study indicates that SD treatment is reversely all alternation in type-2-diabetes. The pathogenesis of the disease has associated with inflammation, resulting in elevation of interleukin 6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Those cytokines cause insulin response by decreasing insulin receptor signaling and increasing C-reactive protein (CRP) in the liver. SD treatment after 21 days has been recommended to heal inflammation. Moreover, SD treatment enhances pancreatic  $\beta$  cell proliferation, which helps to alleviate type II diabetes (Chen et al., 2013).

***Entada phaseoloides* (L.) Merr. (*Entada Phaseoloides*; EP)** is early named as Bencao Gangmu, which has been used in the folk medicine against diabetes, stomachache and edema. According to a previous study, EP might potentially improve hyperglycemia in type II diabetic animals (Zheng et al., 2012). Moreover, the authors claimed that EP treatment caused to decrease plasma insulin level as well. Therefore, they suggested that EP treatment could restore insulin resistance rather than potentially enhance  $\beta$ -cell proliferation (Zheng et al., 2012). Type II diabetes is related with oxidative stress by elevation oxidant, e.g. MDA, decline antioxidant, e.g. SOD, GSH. However, the animals treated with EP had decreased oxidative stress by enhancing antioxidant and decreasing oxidant at 100 mg/kg dose. Type II diabetes is one of major risk for developing cardiovascular diseases such as metabolic disorder, e.g. dyslipidemia, steatosis. EP treatment has been indicated to attenuate dyslipidemia at 100 mg/kg more than 200 mg/kg metformin that is commonly used for against type II diabetes. Insulin resistance is important feature of type II diabetes, especially developing liver and muscle that are sensitive for insulin. The both tissues are developed the steatosis at type II diabetes. EP at 100 mg/kg dose is shown to heal steatosis in the muscle at type II diabetic animals. That is why EP could decrease to develop cardiovascular diseases at type II diabetes based on restoration of lipid metabolism (Zheng et al., 2012). Liver is the main organ to maintain glucose homeostasis. Glucose production by gluconeogenesis at liver has been reported to contribute to develop type II diabetes. Metformin is a drug to inhibit to hepatic gluconeogenesis for treatment of type II diabetes. AMPK is very important protein for doing energy sensor function at cells. AMPK can active when energy supply is low which cellular AMP: ATP ratio is high. Insulin receptor substrate-1 (IRS-1) has been indicated to block by AMPK activation that phosphorylated at Ser636/639. However, phosphatidylinositol 3-kinase (PI3K)/Akt signaling can be triggered by AMPK. Both of Akt and AMPK have been reported to block gluconeogenesis by suppression of phosphoenoyl pyruvate carboxykinase and glucose-6-phosphatase. Saponin extract of EP is also used for treatment of hepatotoxicity, hepatocellular cancer, viral hepatitis and nonalcoholic fatty liver disease. Moreover, the plant's extract has been reported to exist hypoglycemic and hypolipidemic effects against type II diabetes. A recent study suggest that EP extract's hypolipidemic and hypoglycemic effects rely on inhibition gluconeogenesis through AMPK activation signaling (Zheng et al., 2016). . In the type II diabetes, the gluconeogenesis pathways is disordered, probably related with deficiency of insulin effect on negatively regulation of gluconeogenesis gene, including phosphoenoyl pyruvate

carboxykinase and glucose-6-phosphatase. EP treatment has been reported to recovery of gluconeogenesis and impairment of glucose production by activation AMPK, Akt, GSK3 $\beta$ , PI3K. The activation of AMPK can block IRS-1 at Ser636/639 via PI3K/Akt signaling. Moreover, its activation has been suggested to enhance insulin sensitivity on liver by a decline diacylglycerol content and protein kinase-C $\epsilon$  translocation that regulates lipid metabolism. The inhibition of AMPK activation is emphasized to enhance phosphoenolpyruvate carboxykinase and glucose-6-phosphatase enzymes activity, resulting in increasing glucose production at liver that led to develop hyperglycemia. EP treatment blocks lipid accumulation and activates AMPK, eventually enhancing insulin sensitivity. Furthermore, EP has been stressed to trigger caspase-dependent apoptosis based on mitochondrial pathways. Thus, EP treatment has caused to depolarize the mitochondrial membrane potential and result in enhancing reactive oxygen species. In addition, the plant's extract treatment slightly blocks mitochondrial respiratory chain that might help to regulate hyperglycemic effect. It means that after ATP production is decreased, AMPK effect could activate by decreasing the mitochondrial membrane potential. Elevation of AMP by decreasing mitochondrial ATP production might improve glycolysis. The alternation of metabolism in cells has been reported to contribute to develop inflammation. However, activation of AMPK has resulted in inhibition of inflammation. In addition, anti-inflammation effect on it could be given another explanation, which is that its saponin extract has been reported to block pro-inflammatory cytokines, e.g. TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-8 (Zheng et al., 2016).

### Conclusion

Overall, this review has discussed the possible effects of some plants in the management of diabetes and the underlying mechanisms of their physiological actions. The plant species mentioned above have a potential to control hyperglycemia and hyperglycemia-induced dysfunctions. It is known that plants has several active compounds to be effective in the management of diabetes. However, it should be mentioned that some of them have not been completely characterized. Therefore, signaling pathways underlying the anti-diabetic effects of plants should be investigated. More preclinical and clinical studies are still necessary to clarify the effects of plants on diabetes and underlying mechanisms of their medical actions.

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