

A Systematic Review of *in vitro* Studies Conducted on Effect of Herbal Products on Secretion of Insulin from Langerhans Islets

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Received, June 4, 2012; Revised, July 23, 2012; Accepted, July 24, 2012; Published July 27, 2012

ABSTRACT - Purpose: Diabetes mellitus is the most important health problem that its prevalence is increasing. Diabetes is characterized by defects in insulin secretion, insulin action or both. Recent studies provided evidences that loss of functional β -cell mass through apoptosis is central to the development of diabetes. The management of diabetes without any side effects is still a challenge to the medical system. Recently, there has been a special interest to herbal medicine in care and management of diabetes due to their natural origin and less side effects. The current systematic review focuses on main component of antidiabetic plants with directly effect on insulin secretion of pancreas. **Methods:** All *in vitro* studies which assessed the potential effect of, main components, multi herbal, whole plant, or extract of the plants directly on pancreatic insulin secretion published from 2001 to November 2011 were included. Exclusion criteria were clinical trial studies that did not assess insulin secretion, and review articles, or letters to the editor. **Results:** The majority of these studies showed that the improvement of β -cell function and insulin secretion is possible with antioxidant compounds. Suppression of oxidative stress, cytokine-induced impairment, suppression of nuclear factor κ B a key regulator of endothelial activation, activation of uncoupling protein 2 (UCP2), insulin-like activity and increasing intracellular calcium, were among the most important indicated pathways. **Conclusions:** By considering the role of oxidative stress in pathogenesis of β -cell dysfunction, antioxidant compounds could be helpful in management of diabetes and its complications.

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INTRODUCTION

It is estimated that diabetes mellitus (DM) affects more than 366 million people worldwide and it is expected that the figure reach a staggering 552 million by 2030 (1). DM is a multifactorial disease characterized by chronic hyperglycemia due to defects in insulin secretion, insulin action or both, resulting from a deficit in β -cell mass (2, 3). Several mechanisms have been proposed for β -cell destruction, including damage from inflammatory cytokines, circulatory free fatty acids, and hyperglycemia (4, 5). The management of DM without any side effects is still a challenge to the medical system. Although, the synthetic products are widely used in clinical settings for more than 50 years, they are associated with various undesirable side effects such as hypoglycemia. In the last few years, there has been a growing interest to herbal medicine in care and management of diabetes both

in developing and developed countries, due to their natural origin and less side effects (6-9).

Wide array of plants are demonstrated to have antidiabetic activity. Biological actions of these plants are related to chemical composition of the plant products. Herbal products that are rich in phenolic compounds, alkaloids, flavonoids, terpenoids, coumarins, and glycosides usually show positive effects (6). On the other hand, many conventional drugs for treatment of diabetes such as metformin are secretagogues and have plants origin (10). The World Health Organization expert committee on diabetes has listed as one of its recommendations that traditional medical plants as methods of treatment of diabetes should be further investigated (11).

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Insulin is the most important peptide hormone that is secreted from the islet β -cells of langerhans in response to hyperglycemia but in a complex process. The first step in this process is an increase in production of adenosine triphosphate (ATP) from adenosine diphosphate which leads to an increased ATP/ADP ratio in the cytoplasm with subsequent closing of ATP-sensitive potassium channels (12). Depolarization of plasma membrane could activate the voltage-dependent Ca^{2+} channels and hence Ca^{2+} influx. The increase in intracellular concentration of Ca^{2+} triggers the insulin secretion (13). These pathways can be exhibited in diabetes and results in abnormal pattern of insulin secretion (13). Some studies provided evidences that loss of functional β -cell mass through apoptosis is central to the development of both type 1 (14) and type 2 diabetes (15). Proliferation of islet β -cells is a very important component of β -cell adaptation to increased apoptosis and insulin resistance. Similarly by the strategy to induce β -cell proliferation and preserving functional β -cell mass, it would be possible to prevent the onset of diabetes (14, 16-20). Approaches to achieve this objective are stimulation of insulin secretion and inhibition of β -cell apoptosis (21).

Many medicinal plants modulate the expression, synthesis and degradation of insulin. Induction of insulin release is the main mechanism of action for some antidiabetic plants (22); however increase in islet number and size as well as producing the antioxidative effects could be accounted as anti-diabetic mechanism of action of some other herbal medicine (7). Besides, antidiabetic effects of these compounds, the other benefit of such insulin releasers are looked in islet transplantation which is the final step in management of diabetic type 1 and sometimes progressive type 2 patients. The bottle neck in the islets transplantation is to keep them survived and functional during isolation before transplantation. The belief is that direct treatment of insulin producing cells or pancreatic islets with different herbal products improves their viability and function. Therefore, this could be a novel approach for improving the outcome of islet transplantation. The current systematic review is a novel work that focused on main components of plants with anti-diabetic effects acting directly on insulin secretion of pancreatic islet cells.

METHODS

To obtain all related studies, Google Scholar, PubMed, Web of Science, and Scopus databases from 2001 to November 2011 were searched. The search terms used were as follows: “insulin secretion”, “insulin-secreting cell”, “insulin release”, “islet” and “herbal or natural product” and their synonym in Persian databases of IranMedex, and Magiran. We found many *in vitro* studies which focused on antidiabetic plants, but they did not assess the effect on insulin secretion. Therefore all available *in vitro* studies which assessed the potential effect of, main components, multi herbal, whole plant, or extract of the plants directly on insulin secretion of isolated islet cells (or insulin-secreting cell lines such as RIN, HIT, β -TC, MIN6, INS-1) of pancreas were included. Exclusion criteria were clinical trials that did not assess insulin secretion, and review articles, or letters to the editor. Thesis and other unpublished data were not included. The title and abstract of all of search results were examined to eliminate the duplication. Also, the reference lists of articles were reviewed for additional relevant studies.

RESULTS

The number of initial search results and included studies are shown in the Figure 1. Forty-nine articles were selected as our final research database (23-71). The summary of these studies are shown in Table 1. These studies showed that herbal products can increase insulin secretion by affecting different steps of this process. Suppression of oxidative stress, cytokine-induced impairment, suppression of nuclear factor κB (NF- κB); NF- κB is a key regulator of endothelial activation; uncoupling protein 2 (UCP2) activation, and increasing intracellular Ca^{2+} , are among the most important indicated pathways (23-72).

DISCUSSION

In vitro studies on insulin secretion

The majority of experimental studies published between 2001 and 2011 were carried out on rats or mice. In addition, the most frequently drugs used for induction of diabetes were streptozotocin (STZ) and alloxan.

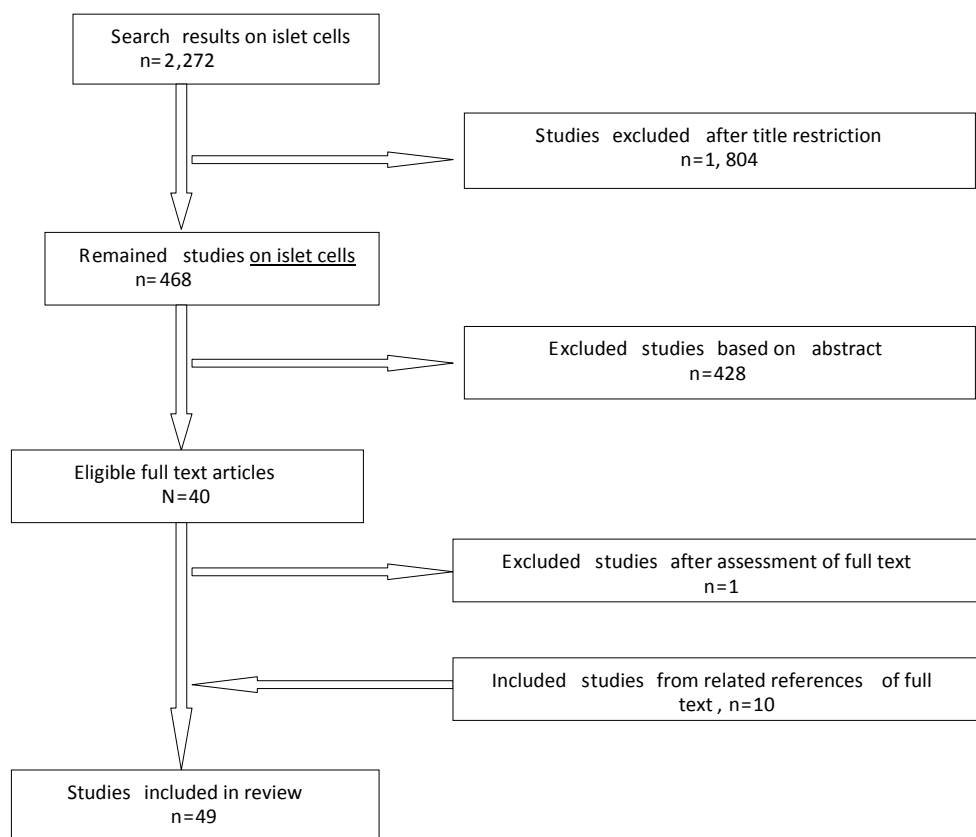


Figure 1. Flow diagram of the study selection process

It was established that these models are useful for study of multiple aspects of diabetes (73, 74). The cytotoxic action of these diabetogenic agents is mediated by reactive oxygen species (ROS) with some differences in their mechanism of action. By formation of superoxide radicals, alloxan can stimulate massive increase in cytosolic calcium concentration which leads to destruction of β -cells of pancreas (75). STZ enters the β -cell via glucose transporter 2 (GLUT2) and causes DNA alkylation. In addition, by activation of poly adenosine diphosphate ribosylation it causes nitric oxide (NO) release and necrosis of pancreatic β -cells (74).

Effect on insulin secretion by suppression of oxidative stress

We found that the potential antidiabetic activity of the published *in vitro* studies can affect different steps of insulin secretion. Because many of plants that were included in our study had more than a single active component, the observed hypoglycemic behaviors may be related to the

combined synergistic actions. Some of them showed antidiabetic activity by improving oxidative metabolisms. *Broussonitia Kazinoki* (23), *Saururus Chinensis Baill* (24), *American Ginseng* (42), *Commiphora Mukul* (43), *Germinated Fenugreek* (51), *Rhizoma Coptidis* (57), and *Curcuma Longa* (58), *Pueraria Lobata* (62) are the examples of presence of antioxidant activity in the medicinal plants. Flavonoids *Rhizoma Coptidis* (57), and *Curcuma Longa* (58), *Pueraria Lobata* (62) posse hypoglycemic as well as antioxidant properties. Quercetin is an important flavonoid that increases insulin secretion by enhancing hepatic glucokinase activity (76) or changing intracellular calcium concentration (77). Quercetin in combination with apigenin and luteolin as flavonoids increased the viability of β -cells, insulin secretion, and cytokine-induced cytotoxicity resistance, and decreased NO-synthase (iNOS) and NF- κ B activation (55). Flavonoids can also prevent cytokine-induced β -cell damage by declining NF- κ B signaling (78-80). In addition, the flavonoids have phosphodiesterase

inhibitor (PDEI) activities (81). Another main plant compounds with PDEI activity are alkaloids, saponins, lignans, and coumarins. Some benefits of PDEI activity especially in diabetic patients include anti-inflammatory and antioxidant effects (81), and improvement of isolated islet cells function (82).

Genistein and soy isoflavonoids could significantly increase the insulin secretion by enhancing KCl -stimulated insulin secretion, increasing intracellular calcium concentration, and inhibiting extracellular signal-related kinase-1/2 (ERK-1/2), Janus kinase/signal transducer and activator of transcription pathway (JAK/STAT) or NF- κ B activation (32, 56). Activated ERK1/2 plays a pivotal role in environmentally-stimulated cellular responses, including cellular proliferation, growth, and differentiation. It is observed that genistein induces a rapid ERK1/2 phosphorylation, which may be necessary for growth factors to drive β -cell proliferation (83). Puerarin, an isoflavone, could increase insulin secretion by decreasing free radical production and increasing catalase (CAT) and superoxide dismutase (SOD) activities (62). Curcumin is a polyphenolic compound that is an inhibitor of NF- κ B. Various biological activities for curcumin such as anti inflammatory and antioxidant make it helpful in increasing area and numbers of islets and secretion of insulin (40, 58).

An association has been shown between oxidative stress and occurrence of several diseases, such as cardiovascular, diabetes, and metabolic syndrome (84-86). Oxidative stress is a phenomenon associated with the action of free radicals and reactive metabolites in the organism (87). It has been shown that both types of antioxidants, enzymatic (SOD, CAT, GPx) and non-enzymatic (vitamin C, vitamin E, zinc, uric acid and selenium), act against oxidants (87). Free radicals are derived from basic radical molecules such as superoxide anion radical or NO (88). When NO is produced by catalytic action of iNOS, it can cause a damage to proteins, lipids and DNA either directly or after reaction with superoxide (89). Taking together, it is evident that increased production of free radicals has a central role in development of diabetes complications (9). The NF- κ B is activated by free fatty acids, inflammatory cytokines, and the receptor for advanced glycation end products (RAGE) (90-92). Studies in cultured endothelial cells and experimental animals have shown an association between activation of NF- κ B,

development of an inflammatory phenotype, insulin resistance, and impaired bioactivity of NO (93, 94). By considering the fact that there is a strong association between oxidative stress and diabetes, the use of antioxidants should be helpful for management of diabetes (95-99). In the recent years, the positive antioxidant effects of some antidiabetic herbal products are established. Some of these medicinal herbs include species of *Satureja* (100), *Urtica* (101), *Teucrium* (102). As islet cell transplantation procedure is faced with oxidative stress, some studies with herbal products are investigated to assess their antidiabetic effects on isolated islet cells and showed positive effects. These substances include Setarud (IMOD); a mixture of *Rosa canina*, *Tanacetumvulgare* and *Urtica dioica* comprising selenium and urea treated by pulsed electromagnetic field of high frequency (25), specific PDEIs; milrinone, rolipram, sildenafil (82), calcium channel blockers, autonomic nervous system blockers and free radical scavengers; nanoparticles of cerium (103).

Effect on insulin secretion by insulin like activity

Adipose tissue enhances lipotoxicity by increasing intracellular lipid levels and also insulin resistance (104). So, adipose tissue as a key link between obesity and diabetes was assessed for the effects of natural products on glucose uptake. On the other hand, the classic target tissues of insulin which include hepatocytes, adipose tissue and skeletal muscle play important roles in homeostasis of glucose upon glucose uptake. *Sarcopoterium Spinosum* (31), *Rooibos* (33), *Nigella Sativa L* (36), *Cichorium Intybus* (48), *Momordica Charantia* (63) are the examples of natural products with insulin-like effects. This effect is attributed to some of antidiabetic compounds such as chlorogenic acid and caffeic acid (48). Chlorogenic acid by inhibiting glucose-6-phosphatase (G6P) in microsomes of liver suppresses gluconeogenesis and glycogenolysis and consequently reduces the hyperglycemia. In addition, G6P inhibition leads to increase glucose transport and its utilization. Finally it can stimulate insulin secretion through increased production of ATP (105).

Effect on insulin secretion through increasing viability and proliferation of β -cells

It is well established that replacing β -cells by islet transplantation has the potential to cure type 1 DM

and on the other hand the efficacy of islet transplantation depends upon number and state of functional islet cells (106). Apoptosis affects the initial stage of islet transplantation which yields non-functional cells. Human pancreas contains an average one million islet cells (107) and in a good isolation process, a total of 500,000 islets with more than 80% viability can be obtained. Since the viability of islets is affected by numerous factors in the early or late period of post transplantation (108), isolated procedure would be given lower yield (109, 110). Thus, islet yield and its post-transplant survival remain major issues. During initial stage of islet transplantation, islet cells are avascular and suspected to hypoxic ischemia condition which is produced by oxidative stress (96). *Astragalus Membranaceus* Bge (38), *Codonopsis Pilosula Nannf* (38), *Lycium Chinense* Mill (38), *Green Tea* (48), *Coptidis Rhizoma* (65) are natural products with suppression effect on apoptosis. Some medicinal plants such as *Nigella Sativa L* (36) can increase insulin secretion by including proliferation of islet cells. In our study, we found other antidiabetic plants that show their effects by increasing islet cell viability. *Sarcopoterium Spinosum* (31), *Cornus Officinalis* Sieb. et Zucc (39), *Germinated Fenugreek* (51), *Rhizoma Coptidis* (57), *Curcuma Longa* (58) are the examples of plants with this effect. All of these plants have antioxidant effects and the observed antidiabetic effects may be related to combination of these mechanisms.

Effect on insulin secretion through ATP/ADP ratio and intracellular Ca^{2+} concentration

There are other mechanisms that have direct effects on insulin secretion (111, 112). These mechanisms are ATP/ADP ratio and intracellular Ca^{2+} concentration which have been described previously (12, 13). The examples of the natural products with these effects are as follows: *Angelica Hirsutiflora* (34), *Stevia Rebaudiana Bertoni* (37, 66), *Korean Red Ginseng* (41), *Asparagus Racemosus* (53), *Ocimum Sanctum* (60), and *Gardenia Jasmine Ides Ellis* (64).

Effect on insulin secretion through inhibition UCP2

UCP2 as a mitochondrial carrier protein is expressed in islets of pancreas and has negative effect on glucose-stimulated insulin secretion (113).

Animal (114, 115) and human (116, 117) studies have shown that increased UCP2 expression in islets can lead to β -cell dysfunction and development of type 2 diabetes mellitus. Thus, UCP2 deficiency can prevent β -cell dysfunction. The KYQRF formula (28) which is a combination of several medicinal plants, and *Gardenia Jasmine Ides Ellis* (64) markedly suppresses UCP2.

In this review, however, we had some limitations. We focused and included only the studies with *in vitro* analysis. Unfortunately, *in vitro* studies do not reflect all the aspect of *in vivo* application of new treatments, as most *in vitro* models consider single cell types, metabolic pathway or enzyme involvement. This greatly reduces the possibility of identifying the antidiabetic plant extracts or compounds (118). Another disadvantage of *in vitro* studies is that only acute or immediate effects are measured, whilst effects that may only appear after chronic exposure to the antidiabetic compounds are overlooked (118). Hence, there is need to carry out *in vivo* studies on these antidiabetic plants.

The major mode of action of medicinal plants with antidiabetic activity is to increase insulin secretion. Some mechanisms of actions were related to their effects on the activity of pancreatic β -cells or the insulin-like activity of the plant extracts, or directly stimulation of insulin secretion or suppression of oxidative stress. All of these actions may be responsible for the reduction and or abolition of diabetic complications. As many of the studied plants showed more than one effective mechanism in increasing islet insulin secretion, the observed hypoglycemic behaviors may be due to a combination of synergistic mechanisms. However, the benefits of antioxidants in management of diabetes could not be ignored (119). Future investigations should focus on antioxidant mixtures as an appropriate formula for management of diabetes.

ACKNOWLEDGEMENT

This paper is the outcome of an in-house study with no external financial support.

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Table1. In vitro studies in assessment of herbal and natural products on insulin secretion of pancreatic islets

Herbal/components	Substance/dose	Sample	Study design	Duration	Outcomes	Ref.
<i>Broussonetiakazinoki</i> / flavanol, flavan, diphenyl propane	Isoprenylated flavan (Kazinol U)/ 30, 60 μ m	Non-diabetic rat	Pretreated RINm5F cells and isolated islet cells with/without the substance and then treated with cytokines	48 h	Dose-dependent increase in viability of RINm5F cells, decrease in NO production, and iNOS expression, marked suppression of NF- κ B, decrease in H ₂ O ₂ production, effective prevention of caspase activation and PARP cleavage, dose-dependent recovery of cytokine-impaired insulin secretion close to that of the control	(23)
<i>Saururus Chinensis baill.</i> (<i>saururaceae</i>)/-----	Lignan (phytoestrogen) /20, 40 μ m	Non-diabetic rat	Pretreated RINm5F cells and isolated islet cells with/without the substance and then treated with cytokines	48 h	Dose-dependent increase in viability of RINm5F cells, dose-dependent decrease in NO production, and iNOS expression, marked suppression of NF- κ B, decrease in JAK/STAT, dose-dependent recovery of cytokine-impaired GSIS close to that of the control	(24)
<i>Rosa canina</i> , <i>Tanacetumvulgare</i> , <i>Urtica dioica</i> / multi herbal	Galactolipid, flavonoid, selenium, urea/0. 1, 1, 10, 100, 1000 ppm	Non-diabetic rat	Incubated isolated islet cells with/without different concentrations of the substances	24 h	Increaseed viability maximum at 1 ppm, increase in basal insulin secretion and GSIS at 0. 1 ppm, marginal increase in basal insulin secretion and GSIS at 1 ppm, decrease in basal insulin secretion and GSIS at10, 100, 1000 ppm, decrease in ROS at 0. 1 μ m	(25)
<i>Citrus medica L. cv Diamante</i> /flavonoid, flavanone	Plant extract/1-24 mg/ml	Non-diabetic mouse	Incubated MIN6 cells with/without plant extract	3 h	Suppression of α -amylase and α -glucosidase vs. acarbose, dose-dependent increase in GSIS	(26)
<i>Myristica fragrans</i> (M. F), <i>Parmelia perlata</i> (P. P), <i>Illicium verum</i> (I. V), <i>Trachyspermum copticum</i> (T. C), <i>Myristica</i>	Gallic acid, flavonoid/ 100, 200 mg/kg of each plant	Diabetic (T2DM) rat	Incubated isolated islet cells with/without the substances vs. 1. 6 mg/kg BW gliclazide as positive control, or non-diabetics,	24 h	Dose-dependent increase in insulin secretion by M. F, T. C, M. M, increase in antioxidants activity vs. ascorbic acid as positive control, increase in α -glucosidase inhibitor in P. P, M. M, M. F, T. C vs. positive	(27)

<i>malabarica</i> (M. M)/ multi herbal			or diabetics as control		control	
Berberine, <i>rhubarb</i> , <i>peony</i> root, <i>bupleurum</i> , <i>coptis</i> , root of <i>herbaceous peony</i> (named Kaiyuqinngre formula [KYQRF])/------	Unknown/5, 10, 15% respectively as low, middle and high dose treatment	Diabetic (T2DM) rat	Incubated INS-1 cells with different concentration of KYQRF vs. control or 10 μ mol/l of rosiglitazone	48 h	Increaseed viability in high dose vs. rosiglitazone, increase in GSIS at middle dose of KYQRF vs. rosiglitazone, marked suppression of UCP2 and sulfonylurea receptor 1 with all doses of KYQRF and rosiglitazone vs. control	(28)
<i>Bauhinia variegata</i> / fatty acid, protein, terpene, alkaloid, steroid, flavonoid	Ethanolic extract (EE) and roseoside(R)/ 50, 250, 500 ng/ml of EE, 1. 25, 2. 5, 5 ng/ml of R	Non-diabetic rat	Incubated INS-1 cells with different concentration of EE or R vs. 25, 50, 100 nM glibenclamide or DMSO as control	1 h	Dose-dependent increase in GSIS by EE and R vs. DMSO, increase in GSIS by EE vs. R	(29)
<i>Acoruscalamus L. (AC)</i> / α - and β -asarone, eugenol	AC or ethyl acetate fraction of AC (ACE)/ 6. 25, 12. 5, 25 μ g/ml	Non-diabetic mouse	Incubated HIT-T15 cells with different concentration of AC or one of its four fractions vs. gliclazide or negative control	24 h	Increase in insulin secretion in AC(6. 25, 12. 5 μ g/ml), and ACE (6. 25, 12. 5, 25 μ g/ml) vs. negative control close to that of the gliclazide, dose-dependent inhibition of α -glucosidase activity	(30)
<i>Sarcopoterium spinosum</i> (SS)/ triterpenoid, catechin, epicatechin	Plant extract (SSE)/0. 001-10 mg/ml	Non-diabetic mouse	Incubated RINm cells, L6 myotubes, 3T3-L1 adipocytes and AML-12 hepatocytes with/without SSE	24 h	Increase in basal insulin secretion in RINm at 0. 1 mg/ml of SSE, increase in glucose / forskolin-induced insulin secretion in RINm at 0. 001, 0. 01, 0. 1 mg/ml of SSE vs. control, increase in viability, suppression of lipolysis in adipocytes, induce glucose uptake in adipocytes, hepatocytes and myotubes, increase in glycogen synthesis in myotubes	(31)
Soy/ Isoflavone	Genistein /1, 5, 10 μ M	Non-diabetic mouse, non-diabetic human	Incubated INS-1 E cells, freshly isolated islet cells with/without the substance vs. similar doses of vehicle	48 h	Dose-dependent increase in GSIS independent of PTK, marginal effect on basal or high-glucose stimulated ATP production, increase in sodium pyruvate-stimulated insulin secretion, dose-dependent increase in Kcl-stimulated insulin secretion vs. induced high glucose or pyruvate, potentiation of glucose	(32)

					induced increase in intracellular Ca^{2+} concentration of INS-1E cells	
<i>Rooibos</i> (<i>AspalathusLinearis</i>)/ polyphenole, flavonoid, non-flavonoid	Flavonoid (Aspalathin) /1-100 μM	Diabetic (T2DM) mouse	Incubated RIN-m5F cells and L6 myotubes with/without the substance	75 h	Dose-dependent increase in glucose uptake by L6 myotubes with maximum effect at $10\mu\text{M}$, increase in GSIS in RIN-m5F at $100\mu\text{M}$	(33)
<i>Angelica hirsutiflora</i> /-----	Plant extract/ 50-150 $\mu\text{g/ml}$	Non- diabetic mouse, non- diabetic human	Cultured isolated islet cells and HIT-TI5 cells with/ without the substance	24 h	Dose-dependent increase in GSIS by all cell types, increase in extracellular Ca^{2+} at 150 $\mu\text{g/ml}$ by HIT-TI5, increase in intracellular Ca^{2+} by HIT-TI5 and islets of human, increase in phosphorylation of ERK $\frac{1}{2}$ at $150\mu\text{g/ml}$ by HIT-TI5 cells	(34)
<i>Teucrium polium</i> l (TP)/ diterpene derivative, fatty acid ester, flavonoid, steroid	TP/ 0. 01, 0. 1 mg/mL with/without 1 mM sodium molybdate or sodium orthovanadate	Non- diabetic rat	Cultured islet cells with each or combination of these substances	1 h	Increase in insulin secretion with combination therapy	(35)
<i>Nigella sativa</i> L (NS)/ volatile oil, fixed oil	Crude ethanol extract/ $200\mu\text{g/ml}$	Non- diabetic rat	Cultured INS832/13 cells, β -TC-tet cells, differentiated skeletal muscle cells, and adipocytes with/ without the substance vs. $10\mu\text{M}$ rosiglitazone	18 h	Increase in GSIS, increase in β -cell proliferation vs. vehicle, increase in basal glucose uptake in muscle cell and adipocytes, increase in triglyceride accumulation in pre-adipocytes vs. rosiglitazone	(36)
<i>Stevia rebaudiana</i> Bertoni (SrB)/ steviol, stevioside, glucoside	Steviol, diterpenic carboxylic alcohol, four molecules of D- glucose (Rebaudioside A) / $10^{-13} - 10^{-7}\text{M}$	Non- diabetic mouse	Incubated isolated MIN6 cells with/without the substance	24 h	Dose-, glucose- and Ca^{2+} dependent increase in insulin secretion, increase in ATP/ADP ratio without change in intracellular cAMP level, glucose-dependent decrease in KATP sensitive channel conduction	(37)
<i>Astragalus membranaceus</i> <i>Bge</i> , <i>Codonopsis pilosula</i> <i>Nannf</i> , <i>Lycium chinense</i> <i>Mill.</i> / -----	Water extract (linoleic acid, astragaloside IV) / $0. 78$ - $100\mu\text{g/ml}$	Non- diabetic rat	Incubated cultured RIN- m5F cells with/without the substances	24 h	Increase in viability maximum at $25\mu\text{g/ml}$, decrease in apoptosis at $25\mu\text{g/ml}$, dose- dependent decrease in iNOS until $25\mu\text{g/ml}$, decrease in expression of apoptosis-related proteins	(38)
<i>Cornus officinalis</i> Sieb.	Methanol extract,	Non-	Incubated alloxan,	48 h	Increase in viability in BRIN-BD11, potent	(39)

<i>etZucc.</i> /ursolic acid, oleanolic acid, loganin, phenolic compounds	fraction /25 mg/ml	diabetic rat	cytokine or STZ-treated BRIN-BD11 cells with/without the substances		insulin mimic activity on PEPCK expression, increase in GSIS, increase in total cell mass of H4IIE or BRIN-BD11 with fraction starting from 12. 5 or 6. 125 µg/ml, protection ofBRIN-BD11 against toxicity from cytokines or STZ starting from 12. 5or 6. 25 µg/m	
-----/-----	Curcumin/ 10µm/L	Non-diabetic rat	Cryopreservation of cultured isolated islet cells with/ without curcumin	10 d	Increase in viability, increase in insulin secretion vs. non-treated but similar to fresh isolated islets, decrease in ROS vs. non treatment non-treated, increase in level of Hsp70 and HO-1	(40)
<i>Korean red ginseng</i> /ginsenoside, acidic polysaccharide, protein, phenolic	Ginsenoside / 0. 05-1. 0 mg/ml	Non-diabetic rat	Cultured isolated islet cells with ginsenoside	2 h	Insulinotropic effect dependent on influx of Ca ²⁺ and KATP channel blockade but independent of glucose	(41)
<i>American ginseng berry</i> /ginsenoside, saponin, flavonoid, triterpenoid	Berry extract and ginsenosid Re/ 0. 1, 0. 5, 1. 0 mg/ml of berry extract, 0. 05, 0. 1 mg/ml of ginsenosid Re	Non-diabetic, unknown species	Incubated MIN-6 cells with/without the substances and assess their response to H ₂ O ₂	10 min acute, 48 h chronic	Decrease in oxidant injury in acute and chronic conditions, dose-dependent increase in insulin secretion	(42)
<i>Commiphoramukul</i> /	Cis- and trans-guggulsterone/ 12. 5, 25 µM	Non-diabetic rat	Pretreatment cultured islet cells with/ without guggulsterone and then treatment with cytokines	48 h	Decrease in cytokine-mediated cytotoxicity, decrease in NO and PGE2 production, decrease in iNOS, decrease in COX-2 mRNA and protein expression, decrease in JAK/STAT activation, decrease in NF-κB activation, decrease in down regulation of SOCS-3, restoration of insulin secretion on islet cell close to that of control	(43)
<i>Hypericum perforatum</i> (St. John'swort) (SJW)/ naphthodianthron, phloroglucinol, melatonin, flavonoid, phenolic acid	SJW extract or hyperforine (HPF)/ 25 µg/different concentrations for different assay	Non-diabetic rat, non-diabetic human	Incubated INS-1 E cells and isolated islet cells with cytokine and with/without SJW or HPF	20 h	Suppression of cytokine- impaired in GSIS at 25 µg/ml SJW or 1 µM HPF, dose-dependent decrease in apoptosis at 6. 25-50 µg/ml SJW or 0. 5-3 µg/ml HPF, dose-dependent decrease in iNOS at10-100 µg/ml SJW or 0. 25-2 µM HPF, decrease in cytokine-induced STAT-1 at 10-50 µg/ml SJW or 2 µM HPF, dose-	(44)

					dependent decrease in NF- κ B activation at 25-100 μ g/ml SJW or 1-10 μ M HPF	
<i>Rehmanniae radix, Ginseng radix, Scutellariae radix</i> /----	Unknown/50 μ g/ml	Non-diabetic rat	Incubated isolated islet cells with vehicle or each herbal extract or 2.5 nM exendin-4 as positive control	24 h	Increase in GSIS by plants but lower than level achieved with exendin-4, increase in IRS2, PDX-1 and GK mRNA, promote β -cell proliferation, increase in viability, insulinotropic agent like exendin-4	(45)
<i>Olea europaea</i> / oleic acid, phenolic constituents, squalene	Unknown/0.01, 0.05, 0.1, 1 mg/ml	Non-diabetic rat	Incubated isolated islet cells with/without the substance	0.5 h	Increase in basal insulin secretion at 0.05 mg/ml, marginal increase in GSIS	(46)
Unknown/.....	Plant-derived triterpenoid (Oleanolic acid)/30, 50 μ M vs. 100, 200 μ M tolbutamide, or 50 nM exendin-4	Non-diabetic rat	Incubated INS-1 cells and isolated islet cells with/without the substance	1 h	Increased basal insulin secretion and GSIS in INS-1 at maximum 50 μ M vs. tolbutamide but similar to exendin-4, increase in insulin secretion in GSIS at 30 μ M, increase in total cellular insulin protein, increase in mRNA level, increase in glucagon and somatostatin, no effect on intracellular Ca^{2+}	(47)
<i>Cichorium intybus</i> / phenolic compound, aesculetin, aesculin, cichoriin, glycoside	Mono-caffeoyl ester (CGA) and dicaffeoyl ester (CRA)/10, 50, 100 μ g/ml	Non-diabetic rat	Incubated INS-1E cells and islet cells with glucose and with/without CRA or CGA	1.5 h	Increase in insulin-induced glucose uptake at 100 μ g/ml CRA or CGA and in presence of insulin, increase in GSIS at 10, 50 μ g/ml CRA or CGA in INS-1E, increase in GSIS at 50 μ g/ml CRA or CGA in islet cells	(48)
<i>Rhizoma coptidis</i> / alkaloid, non-alkaloid	Isoquinoline alkaloid (Berberine)/1, 3, 10, 30 μ mol/l	Non-diabetic rat	Incubated isolated islet cells with different concentration of the substance vs. 1 μ mol/l glibenclamide or without them	24 h	Dose-dependent increase in GSIS vs. control except at 30 μ mol/l, increase in viability, increase in GK activity at 3, 10, 30 μ mol/l vs. glibenclamide or control, cytotoxicity on islet cells at 30 μ mol/l, dose-dependent up regulation of HNF4- α mRNA expression with maximum effect at 10 μ mol/l vs. glibenclamide or control	(49)
Unknown/-----	Polyphenol (Resveratrol)/3-100 μ mol/l	Non-diabetic mouse	Incubated isolated MIN6 cells, Hit-T15 cells, and RIN-m5F cells with /without the substances vs. 30, 100 μ mol/l	1 h	Dose-dependent suppression of ATP-sensitive K^+ channel vs. control, suppression of voltage-gated K^+ channel vs. control at concentration higher than 30 μ mol/l, increase in insulin secretion in all doses in RIN-m5F and Hit-T15	(50)

			glibenclamide or control		vs. control except at 100 µmol/l in MIN6	
<i>Germinated fenugreek (Trigonella foenum-graecum)/</i> phenolic, flavonoid	Powder of plant (S1), boiled aqueous extract (S2), soxhlet fractions (petroleum ether (E1), chloroform (E2), methanol (E3), aqueous soxhlet extract (E4))/ doses of S1, or S2: 2. 5, 5, 10%, doses of others: 0. 5, 2. 5, 5%	Non-diabetic mouse	Incubated isolated islet cells with/without the substances	48 h	Increase in GSIS and basal insulin secretion, increase in viability, decrease in MDA, protein carbonyls, ROS in STZ treated, highest antioxidant activity in E3, highest protection against lipid peroxidation in E3, marginal change in uric acid or glutathione, decrease in GR, SOD and increase in CAT, GPx in STZ treated	(51)
<i>Desmodium gangeticum</i> (GD)/flavones, isoflavonoid glycoside	DG extract/0. 25-2 mg/ml	Diabetic (T2DM) rat	Incubated MIN6 cells with 2mM glucose and with/without DG	1.5 h	Dose-dependent increase in insulin secretion	(52)
<i>Asparagus racemosus/</i> flavonoid, amino acid, oligosaccharide, steroidal saponin	Dried root (ethanol extract), or plant fractions (hexane, ethyl acetate, butanol, chloroform, aqueous fraction)/ 8, 40, 200, 1000, 5000 µg/ml	Non-diabetic rat	Incubated isolated clonal BRIN-BD11 cells, islet cells, and perfused pancreas with/without the substances	1 h	Increase in basal and GSIS in islet cells with all substances except aqueous fraction, increase in basal and GSIS in perfused pancreas with all substances except butanol and aqueous fraction, increase in basal and GSIS in BRIN-BD11 with all substances except hexane for basal insulin and ethyl acetate for GSIS, Ca ²⁺ -dependent increase in insulin secretion in BRIN-BD11 with all substances except ethyl acetate and butanol fractions	(53)
Green tea/flavonoid, catechin, epicatechin	Epigallocatechin-3-gallate (EGCG)/36, 72, 360 µM	Non-diabetic rat	Cultured isolated islet cells under normal or hypoxia/reoxygenation (H/R) condition with/without EGCG	48 h	Dose-dependent decrease in apoptosis, decrease in LDH, protection against decline of insulin secretion	(54)
Plant natural products/ flavonoid	Quercetin, apigenin, luteolin/25, 50 µM	Non-diabetic rat	Incubated pretreated RINm5F cells with cytokine with/ without the substances	48 h	Dose-dependent increase in viability, suppression of cytokine-mediated cytotoxicity, decrease in NO production and iNOS expression , dose-dependent decrease in	(55)

					NF_κB activation, marginal preservation of GSIS (at 20 mM glucose) in presence cytokines vs. control	
Soybean/ isoflavone	Genistein/ 5, 10, 20, 40 μM	Non-diabetic rat	Incubated cultured β-cells and RINm5F cells with/ without genistein and then treated with cytokine	48 h	Dose-dependent increase in viability, dose-dependent decrease in cytokine-induced NO production and iNOS expression, suppression of ERK-1/2 and JAK/STAT activation, decrease in NF_κB activation, suppression of MAPK pathway, dose-dependent preservation of GSIS	(56)
<i>Rhizoma Coptidis</i> / alkaloid, non-alkaloid	Plant extract/ 5, 10, 20, 50 μg/ml	Non-diabetic rat	Incubated RINm5F cells and isolated islet cells with/ without the substance and then treated with cytokine	48 h	Increased viability, decrease in NO production and iNOS expression, suppression of NF_κB activation, dose-dependent preservation of GSIS	(57)
<i>Curcuma longa</i> (Turmeric)/ curcuminoid, volatile oil sugar, protein, resin	Curcumin/10 μM vs. vehicle	Non-diabetic mouse	Incubated isolated islet cells with curcumin and then treated with STZ	24 h	Dose-dependent increase in viability, dose-dependent suppression of STZ-induced β-cell dysfunction, decrease in activated PARP, increase in Cu/Zn SOD and decrease in MDA, decrease in peroxynitrite and STZ generation of NO, increase in insulin secretion	(58)
<i>Terminalia chebula</i> Retz. (TC)/gallic acid, luteolin, tannic acid, chebulinic acid	Aqueous extract of TC / 200 μl (2 mg/ ml) for	Diabetic (T2DM) rat	Incubated islet cells with/without aqueous extract of TC vs. tolbutamide	2 h	Increase in insulin release vs. untreated diabetics and higher than tolbutamide	(59)
<i>Ocimum sanctum</i> / oleanolic acid, ursolic acid, rosmarinic acid, eugenol, carvacrol, linalool, β-caryophyllene, β-elemene, β-caryophyllene, germacrene D	Ethanol extract, aqueous, butanol, ethylacetate fractions/ dose of perfustation 1 mg/min, dose for clonal β-cells 8-5000 μg/ml	Non-diabetic rat	Incubated perfused pancreas, isolated islet cells and clonal BRIN-BD11 cells with/ without different concentration of the substances	1 h	Increase in insulin secretion by all fractions except hexane and chloroform, increase in intracellular Ca ²⁺ in clonal cells by all substances, decrease in viability at doses higher than 5000 μg/ml, increase in insulin secretion at doses higher than 5000 μg/ml by chloroform and hexane partition but concomitant decrease in viability	(60)

Fruit of <i>Eugenia jambolana</i> /oleanolic acid, ursolic acid, β -sitosterol, gallic acid	Water and ethanol extract/50, 100, 200 mg/kg of each extract or 25 mg/kg of water extract	Diabetic (T2DM) rabbit	Incubated isolated islet cells with/without fraction-III	1 h	Increase in release of insulin vs. non-treated diabetics or control	(61)
<i>Pueraria lobata</i> / flavonoid, isoflavonoid	Puerarin/10, 50, 100 μ M vs. control or 500 μ M H ₂ O ₂	Non-diabetic rat	Cultured isolated islet cells under normal or H ₂ O ₂ stress conditions with/without puerarin	48 h	Marginal protection against viability loss from H ₂ O ₂ toxicity, suppression of apoptosis at 50, 100 μ M, dose-dependent increase in basal insulin secretion and GSIS at 100 μ M vs. H ₂ O ₂ , dose-dependent decrease in ROS, dose-dependent increase in CAT at 100 μ M and SOD at 50, 100 μ M	(62)
<i>Momordica charantia</i> / Steroidal saponin, insulin-like peptide, alkaloid, momordicin, glycoside, terpenoid	Protein extract of fruit/ 10 μ g/ml	Diabetic (T2DM) rat	Perfused islet cells, incubated C ₂ C ₁₂ myocytes and 3T3-L1 adipocytes with/ without the substance	18 h	Increase in insulin secretion, increase in glucose uptake in myocytes, increase in glucose uptake in adipocytes	(63)
<i>Gardenia jasminoides</i> Ellis/ glycoside, glycoprotein, chloreogenic acid	Glycoside (genipin)/50 nM, 0.5 μ M, 5 μ M	Non-diabetic mouse (wild-type (WT) and UCP2-deficient mouse)	Incubated isolated islet cells with/without the substance	48 h	Suppression of UCP2-mediated proton leak in isolated mitochondrial, increase in mitochondrial membrane potential, and ATP level concomitant close KATP channels in WT vs. UCP2-deficient, increase in basal insulin secretion at 0.5, 5 μ M in WT, improvement in obesity induced GSIS impairment, dependent effects to iUCP2, suppression of UCP2	(64)
<i>Coptidis Rhizoma</i> / alkaloid, non-alkaloid	Plant extract (CRE)/10, 20, 50 μ g/ml	Non-diabetic rat	Pretreatment RINm5F cells with CRE then treated with 0.1 mM S-nitroso-N-acetylpenicillamine (SNAP) vs. control or SNAP without CRE	24 h	Suppression of apoptosis and necrosis, suppression of potential disruption of mitochondrial membrane, no effect on SNAP-induced NO production, retain in insulin secretion capacity in islets treated IL-1 β at 10, 50 μ g/ml CRE	(65)
<i>Stevia rebaudiana</i> Bertoni/ glycoside, stevioside, rebaudioside	Rebaudioside A/ 10 ⁻¹⁶ -10 ⁻⁶ mol/l	Non-diabetic mouse	Incubated isolated islet cells with/without the substance	140 Min	Ca ²⁺ -and glucose dose-dependent increase in insulin secretion at 10 ⁻¹⁴ -10 ⁻⁶ mol/l vs. control	(66)

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<i>Teucrium polium</i> / flavonoid, diterpene derivative, fatty acid ester, steroid	Crude extract/0.001-1 mg of plant leaf powder /ml of the culture medium	Diabetic (T2DM) rat	Incubated isolated islet cells with/without the substance	32 h	Dose-dependent increase in basal insulin secretion	(67)
<i>Anemarrhena asphodeloides</i> / glycoside, saponin, polysaccharide, norlignan	Plant ethanol extract (TH2)/2, 4, 8 mg/ml	Diabetic (T2DM) rat	Incubated or perfused isolated islet cells with/without the substances	24 h	Increased basal insulin secretion and GSIS at all doses and by all cell types	(68)
<i>Gynostemma pentaphyllum</i> / saponin (gypenosid)	Gypenosid (phanoside)/ 7.8, 15.6, 31.3, 62.5, 125, 250, 500 μ M	Non-diabetic rat	Incubated isolated islet cells with phanoside vs. control or 2 μ M glibenclamide	24 h	Dose-dependent increase in basal insulin secretion and GSIS at all doses over 50 μ U insulin/islet/h	(69)
<i>Nigella sativa</i> Linn. (<i>black cumin</i>)/ alkaloid, saponin, fixed oil, essential oil, protein	Different fractions: defatted fraction (HR II), acidic and neutral compounds (HR III), basic compounds (HR IV)/ 0.01, 0.1, 1, 5 mg/ml	Non-diabetic rat	Incubated isolated islet cells with/without the substances	2 h	Dose-dependent increase in GSIS at 0.1-5 mg/ml of HR II and HR IV vs. control, increase in GSIS at 5 mg/ml HR III vs. control	(70)
<i>Urtica dioica</i> /lectin, polysaccharide, steroid, caffeic malic acid	Different plant fractions of aqueous extract/1 ml	Non-diabetic rat	Incubated isolated islet cells with/ without the substance	2 h	Increase in basal insulin secretion and GSIS at highest dose of fraction 1	(71)

Keys: T2DM, type 2 diabetes mellitus; NO, nitric oxide; iNOS, inducible form of NO synthase; NF- κ B, nuclear factor κ B; PARP, poly ADP-ribose polymerase-1; JAK/STAT, Janus kinase /signal transducer and activator of transcription pathway; GSIS, glucose stimulated insulin secretion; ROS, reactive oxygen species; BW, body weight; UCP2, uncoupling protein 2; DMSO, dimethyl sulfoxide; PTK, protein tyrosine kinase; ATP, adenosine triphosphate; BG, blood glucose; ERK 1/2, extracellular signal-related kinase-1/2; ADP, adenosine diphosphate; KATP, potassium channel adenosine triphosphate; STZ, streptozotocin; PEPCK, phosphoenolpyruvate carboxy kinase; Hsp 70, heat shock protein 70; HO-1, hemeoxygenase-1; PGE2, prostaglandin E₂; COX-2, cyclooxygenase-2; Socs-3, suppressor of cytokine signaling-3; IRS2, insulin receptor substrate-2; PDX-1, pancreas duodenum homeobox-1; GK, glucokinase; HNF4 α , hepatic nuclear factor 4 alpha; MDA, malondialdehyde; GR, glutathione reductase; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinase; SNAP, S-nitroso-N-acetylpenicillamine.