

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.

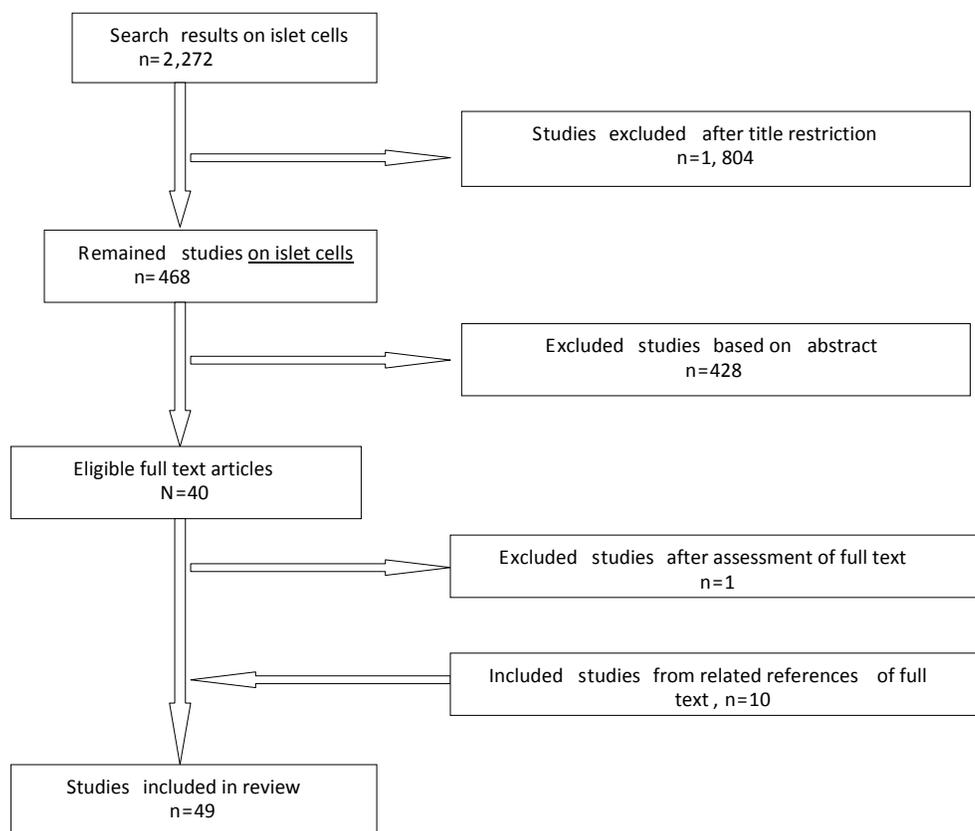


Figure 1. Flow diagram of the study selection process

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) possess 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; milrinon, 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 Ca²⁺ concentration

There are other mechanisms that have direct effects on insulin secretion (111, 112). These mechanisms are ATP/ADP ratio and intracellular Ca²⁺ 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.

REFERENCES

1. IDF diabetes atlas- fifth edition. 2011 International Diabetes Federation. Available from www.idf.org/diabetesatlas/papers.

2. WHO. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation, Part 1: diagnosis and classification of diabetes mellitus. World Health Organization 1999, Geneva.
3. Harris M, Zimmet P. Classification of diabetes mellitus and other categories of glucose intolerance, In: Alberti K, Zimmet P, Defronzo R(eds): International textbook of diabetes mellitus. 2nd ed., Chichester: John Wiley and Sons, pp 9-23, 1997.
4. Maedler K, Sergeev P, Ris F, Oberholzer J, Joller-Jemelka HI, Spinas GA, Kaiser N, Halban PA, Donath MY. Glucose-induced β cell production of IL-1 β contributes to glucotoxicity in human pancreatic islets. *J Clin Invest* 2002; 110: 851-860.
5. Shimabukuro M, Koyama K, Lee Y, Unger RH. Leptin- or troglitazone-induced lipopenia protects islets from interleukin 1 β cytotoxicity. *J Clin Invest* 1997; 100: 1750-1754.
6. Modak M, Dixit P, Londhe J, Ghaskadbi S, Paul A. Devasagayam T. Indian herbs and herbal drugs for the treatment of diabetes. *J Clin Biochem Nutr* 2007; 40: 163-173.
7. Hasani- Ranjbar S, Larijani B, Abdollahi M. A systematic review of Iranian medicinal plants useful in diabetes mellitus. *Arch Med Sci* 2008; 4: 285-292.
8. Hasani-Ranjbar S, Larijani B, Abdollahi M. A systematic review of the potential herbal sources of future drugs effective in oxidant-related diseases. *Inflamm Allergy Drug Targets* 2009; 8: 2-10.
9. Rahimi R, Nikfar S, Larijani B, Abdollahi M. A review on the role of antioxidants in the management of diabetes and its complications. *Biomed Pharmacother* 2005; 59: 365-373.
10. Grover JK, Yadav S, Vats V. Medicinal plants of India with anti-diabetic potential. *J Ethnopharmacol* 2002;81: 81-100.
11. WHO Expert committee on diabetes mellitus: second report, World Health Organ. *Tech Rep Ser* 1980; 646:1-80
12. Affourtit C, Brand MD. Stronger control of ATP/ADP by proton leak in pancreatic beta-cells than skeletal muscle mitochondria. *Biochem J* 2006; 393: 151-159.
13. Ashcroft FM, Rorsman P. Molecular defects in insulin secretion in type-2 diabetes. *Rev Endocr Metab Disord* 2004; 5: 135-142.
14. Tourrel C, Bailbe D, Lacorne M, Meile MJ, Kergoat M, Portha B. Persistent improvement of type 2 diabetes in the Goto- Kakizaki rat model by expansion of the β -cell mass during the prediabetic period with glucagon-like peptide-1 or exendin-4. *Diabetes* 2002; 51: 1443-1452.
15. Sakuraba H, Mizukami H, Yagihashi N, Wada R, Hanyu C, Yagihashi S. Reduced β -cell mass and expression of oxidative stress-related DNA damage in the islet of Japanese type II diabetic patients. *Diabetologia* 2002; 45: 85-96.
16. Suarez-Pinzon WL, Yan Y, Power R, Brand SJ, Rabinovitch A. Combination therapy with epidermal growth factor and gastrin increases β -cell mass and reverses hyperglycemia in diabetic NOD mice. *Diabetes* 2005; 54: 2596-2601.
17. Stoffers DA. The development of β -cell mass: recent progress and potential role of GLP-1. *Horm Metab Res* 2004; 36: 811-821.
18. Sreenan S, Pick AJ, Levisetti M, Baldwin AC, Pugh W, Polonsky KS. Increased β -cell proliferation and reduced mass before diabetes onset in the nonobese diabetic mouse. *Diabetes* 1999; 48: 989-996.
19. Wang Q, Brubaker PL. Glucagon-like peptide-1 treatment delays the onset of diabetes in 8-week-old db/db mice. *Diabetologia* 2002; 45: 1263-1273.
20. Rolin B, Larsen MO, Gotfredsen CF, Deacon CF, Carr RD, Wilken M, Knudsen LB. The long-acting GLP-1 derivative NN2211 ameliorates glycemia and increases β -cell mass in diabetic mice. *Am J Physiol Endocrinol Metab* 2002; 283: E745-752.
21. Ahren B. Type 2 diabetes, insulin secretion and β -cell mass. *Curr Mol Med* 2005; 5: 275-286.
22. Frode TS, Medeiros YS. Animal models to test drugs with potential antidiabetic activity. *J Ethnopharmacol* 2008; 115:173-183.
23. Bae UJ, Lee DY, Song MY, Lee SM, Park JW, Ryu JH, Park BH. A prenylatedflavan from *Broussonetiakazinoki* prevents cytokine-induced β -cell death through suppression of nuclear factor-KB activity. *Biol Pharm Bull* 2011; 34: 1026-1031.
24. Jeong GS, Lee DS, Park BH, Kwon KB, Kim YC. Sauchinone protects pancreatic β cells against cytokine-mediated toxicity. *Toxicol in Vitro* 2011; 25: 505-512.
25. Larijani B, Salimi M, Pourkhalili N, Mohammadirad A, Baeri M, Nili-Ahmadabadi A, Abdollahi M. Positive response of isolated rat pancreatic islets to IMOD; hopes for better transplant outcome and graft function. *Asian J Anim Vet Adv* 2011; 6: 1019-1025.
26. Menichini F, Tundis R, Loizzo MR, Bonesi M, Liu Bo, Jones Peter, Persaud SJ, Mastellone V, Lombardi P, Houghton PJ, Avallone L, Menichini F. C. medica cv Diamante peel chemical composition and influence on glucose homeostasis and metabolic parameters. *Food Chemistry* 2011; 124: 1083-1089.
27. Patil SB, Ghadyale VA, Taklikar SS, Kulkarni CR, Arvindekar AU. Insulin secretagogue, alpha-

- glucosidase and antioxidant activity of some selected spices in streptozotocin-induced diabetic rats. *Plant Foods Hum Nutr* 2011; 66: 85-90.
28. Tong XL, Song J, Zhao LH, Ji HY. Kaiyue formula improves insulin secretion via regulating uncoupling protein-2 and KATP channel. *Chin Med J (Engl)* 2011; 124: 2746-2750.
 29. Frankish N, Menezes FDS, Mills C, Sheridan H. Enhancement of insulin release from the β -cell line INS-1 by an ethanolic extract of *Bauhinia variegata* and its major constituent roseoside. *Planta Med* 2010; 76: 995-997.
 30. Si MM, Lou JS, Zhou CX, Shen JN, Wu HH, Yang B, He QJ, Wu HS. Insulin releasing and alpha-glucosidase inhibitory activity of ethyl acetate fraction of *Acorus calamus* in vitro and in vivo. *J Ethnopharmacol* 2010; 128:154-159.
 31. Smirin P, Taler D, Abitbol G, Brutman-Barazani T, Kerem Z, Sampson SR, Rosenzweig T. *Sarcopoterium spinosum* extract as an antidiabetic agent: in vitro and in vivo study. *J Ethnopharmacol* 2010; 129: 10-17.
 32. Fu Z, Liu D. Long-term exposure to genistein improves insulin secretory function of pancreatic β -cells. *Eur J Pharmacol* 2009; 616: 321-327.
 33. Kawano A, Nakamura H, Hata SI, Minakawa M, Miura Y, Yagasaki K. Hypoglycemic effect of aspalathin, a rooibos tea component from *Aspalathus linearis*, in type 2 diabetic model db/db mice. *Phytomedicine* 2009; 16: 437-443.
 34. Leu YL, Chen YW, Yang CY, Huang CF, Lin GH, Tsai KS, Yang RS, Liu SH. Extract isolated from *Angelica hirsutiflora* with insulin secretagogue activity. *J Ethnopharmacol* 2009; 123: 208-212.
 35. Mohseni Salehi Monfared SS, Pournourmohammadi S. *Teucrium polium* complex with molybdate enhance cultured islets secretory function. *Biol Trace Elem Res* 2010; 133: 236-241.
 36. Benhaddou-Andaloussi A, Martineau LC, Spoor D, Vuong T, Leduc C, Joly E, Burt A, Meddah B, Settaf A, Arnason JT, Prentki M, Haddad PS. Antidiabetic activity of *Nigella sativa* seed extract in cultured pancreatic β -cells, skeletal muscle cells, and adipocytes. *Pharm Biol* 2008; 46: 96-104.
 37. Abudula R, Matchkov VV, Jeppesen PB, Nilsson H, Aalkjaer C, Hermansen K. Rebaudioside A directly stimulates insulin secretion from pancreatic beta cells: a glucose-dependent action via inhibition of ATP-sensitive K^+ -channels. *Diabetes Obes Metab* 2008; 10: 1074-1085.
 38. Chan JYW, Leung PC, Che CT, Fung KP. Protective effects of an herbal formulation of *Radix Astragali*, *Radix Codonopsis* and *Cortex Lycii* on streptozotocin-induced apoptosis in pancreatic β -cells: an implication for its treatment of diabetes mellitus. *Phytother Res* 2008; 22: 190-196.
 39. Chen CC, Hsu CY, Chen CY, Liu HK. *Fructus Corni* suppresses hepatic gluconeogenesis related gene transcription, enhances glucose responsiveness of pancreatic beta-cells, and prevents toxin induced beta-cell death. *J Ethnopharmacol* 2008; 117: 483-490.
 40. Kanitkar M, Bhonde RR. Curcumin treatment enhances islet recovery by induction of heat shock response proteins, Hsp70 and heme oxygenase-1, during cryopreservation. *Life Sci* 2008; 82:182-189.
 41. Kim K, Kim HY. Korean red ginseng stimulates insulin release from isolated rat pancreatic islets. *J Ethnopharmacol* 2008; 120: 190-195.
 42. Lin E, Wang Y, Mehendale S, Sun S, Wang CZ, Xie JT, Aung HH, Yuan CS. Antioxidant protection by American Ginseng in pancreatic β -Cells. *Am J Chin Med* 2008; 36: 981-988.
 43. Lv N, Song MY, Kim EK, Park JW, Kwon KB, Park BH. Guggulsterone, a plant sterol, inhibits NF-KB activation and protects pancreatic cells from cytokine toxicity. *Mol Cell Endocrinol* 2008; 289: 49-59.
 44. Menegazzi M, Novelli M, Beffy P, D'Aleo V, Tedeschi E, Lupi R, Zoratti E, Marchetti P, Suzuki H, Masiello P. Protective effects of St. John's wort extract and its component hyperforin against cytokine-induced cytotoxicity in a pancreatic β -cell line. *Int J Biochem Cell Biol* 2008; 40: 1509-1521.
 45. Park SM, Hong SM, Sung SR, Lee JE, Kwon DY. Extracts of *Rehmannia radix*, *Ginseng radix* and *Scutellaria radix* improve glucose-stimulated insulin secretion and beta-cell proliferation through IRS2 induction. *Genes Nutr* 2008; 2: 347-351.
 46. Pournourmohammadi S, Shariffar F, Talebiyan E, Khayatian M, Rezazadeh SHA, Moslehi AH. Effect of olive leaf (*Olea europaea* L.) on glucose-stimulated insulin secretion from isolated pancreatic islets of rat. *J Med Plants* 2008; 28: 38-46.
 47. Teodoro T, Zhang L, Alexander T, Yue J, Vranic M, Volchuk A. Oleanolic acid enhances insulin secretion in pancreatic beta-cells. *FEBS Lett* 2008; 582: 1375-1380.
 48. Tousch D, Lajoix AD, Hosy E, Azay-Milhau J, Ferrare K, Jahannault C, Cros G, Petit P. Chicoric acid, a new compound able to enhance insulin release and glucose uptake. *Biochem Biophys Res Commun* 2008; 377: 131-135.
 49. Wang ZQ, Lu FE, Sleng H, Fang XS, Chen G, Wang ZS, Dong LP, Yan ZQ. Facilitating effects of berberine on rat pancreatic islets through modulating hepatic nuclear factor 4 alpha expression and glucokinase activity. *World J Gastroenterol* 2008; 14: 6004-6011.

50. Chen WP, Chi TC, Chuang LM, Su MJ. Resveratrol enhances insulin secretion by blocking KATP and KV channels of beta cells. *Eur J Pharmacol* 2007; 568: 269-277.
51. Dixit PP, Devasagayam TP, Ghaskadbi S. Formulated antidiabetic preparation Syndrex has a strong antioxidant activity. *Eur J Pharmacol* 2008; 581: 216-225.
52. Govindarajan R, Asare-Anane H, Persaud S, Jones P, Houghton PJ. Effect of *Desmodium gangeticum* extract on blood glucose in rats and on insulin secretion in vitro. *Planta Med* 2007; 73:427-432.
53. Hannan JM, Marenah L, Ali L, Rokeya B, Flatt PR, Abdel-Wahab YH. Insulin secretory actions of extracts of *Asparagus racemosus* root in perfused pancreas, isolated islets and clonal pancreatic beta-cells. *J Endocrinol* 2007; 192: 159-168.
54. Hara Y, Fujino M, Takeuchi M, Li XK. Green-tea polyphenol (-)-epigallocatechin-3-gallate provides resistance to apoptosis in isolated islets. *J Hepatobiliary Pancreat Surg* 2007; 14: 493-497.
55. Kim EK, Kwon KB, Song MY, Han MJ, Lee JH, Lee YR, et al. Flavonoids protect against cytokine-induced pancreatic β -cell damage through suppression of nuclear factor KB activation. *Pancreas* 2007; 35: e1-e9.
56. Kim EK, Kwon KB, Song MY, Seo SW, Park SJ, Ka SO, Na L, Kim KA, Ryu DG, So HS, Park R, Park JW, Park BH. Genistein protects pancreatic -cells against cytokine-mediated toxicity. *Mol Cell Endocrinol* 2007; 278: 18-28.
57. Kim EK, Kwon KB, Han MJ, Song MY, Lee JH, Lv N, Ka SO, Yeom SR, Kwon YD, Ryu DG, Kim KS, Park JW, Park R, Park BH. *Coptidis rhizoma* extract protects against cytokine-induced death of pancreatic β -cells through suppression of NF-KB activation. *Exp Mol Med* 2007; 39: 149-159.
58. Meghana K, Sanjeev G, Ramesh B. Curcumin prevents streptozotocin-induced islet damage by scavenging free radicals: A prophylactic and protective role. *Eur J Pharmacol* 2007; 577: 183-191.
59. Murali YK, Anand P, Tandon V, Singh R, Chandra R, Murthy PS. Long-term effects of *Terminalia chebula* Retz. on hyperglycemia and associated hyperlipidemia, tissue glycogen content and in vitro release of insulin in streptozotocin induced diabetic rats. *Exp Clin Endocrinol Diabetes* 2007; 115: 641-646.
60. Hannan JM, Marenah L, Ali L, Rokeya B, Flatt PR, Abdel-Wahab YH. *Ocimum sanctum* leaf extracts stimulate insulin secretion from perfused pancreas, isolated islets and clonal pancreatic beta-cells. *J Endocrinol* 2006; 189: 127-136.
61. Sharma SB, Nasir A, Prabhu KM, Murthy PS. Antihyperglycemic effect of the fruit-pulp of *Eugenia jambolana* in experimental diabetes mellitus. *J Ethnopharmacol* 2006; 104: 367-373.
62. Xiong FL, Sun XH, Gan L, Yang XL, Xu HB. Puerarin protects rat pancreatic islets from damage by hydrogen peroxide. *Eur J Pharmacol* 2006; 529: 1-7.
63. Yibchok-anun S, Adisakwattana S, Yao CY, Sangvanich P, Roengsumran S, Hsu WH. Slow acting protein extract from fruit pulp of *Momordica charantia* with insulin secretagogue and insulinomimetic activities. *Biol Pharm Bull* 2006; 29:1126-1131.
64. Zhang CY, Parton LE, Ye CP, Krauss S, Shen R, Lin CT, Porco JA Jr, Lowell BB. Genipin inhibits UCP2-mediated proton leak and acutely reverses obesity- and high glucose-induced β cell dysfunction in isolated pancreatic islets. *Cell Metab* 2006; 3: 417-427.
65. Kwon KB, Kim EK, Lim JG, Shin BC, Han SC, Song BK, Kim KS, Seo EA, Ryu DG. Protective effect of *Coptidis Rhizoma* on S-nitroso-N-acetylpenicillamine (SNAP)-induced apoptosis and necrosis in pancreatic RINm5F cells. *Life Sci* 2005; 76: 917-929.
66. Abudula R, Jeppesen PB, Rolfsen SED, Xiao J, Hermansen K. Rebaudioside a potentially stimulates insulin secretion from isolated mouse islets: studies on the dose-, glucose-, and calcium-dependency. *Metabolism* 2004; 53: 1378-1381.
67. Esmaeili MA, Yazdanparast R. Hypoglycemic effect of *Teucrium polium*: studies with rat pancreatic islets. *J Ethnopharmacol* 2004; 95: 27-30.
68. Hoa NK, Phan DV, Thuan ND, Ostenson CG. Insulin secretion is stimulated by ethanol extract of *Anemarrhena asphodeloides* in isolated islet of healthy Wistar and diabetic Goto-Kakizaki Rats. *Exp Clin Endocrinol Diabetes* 2004; 112: 520-525.
69. Norberg A, Hoa NK, Liepinsh E, Van Phan D, Thuan ND, Jörnvall H, Sillard R, Ostenson CG. A novel insulin-releasing substance, phanoside, from the plant *Gynostemma pentaphyllum*. *J Biol Chem* 2004; 279: 41361-41367.
70. Rchid H, Chevassus H, Nmila R, Guiral C, Petit P, Chokaïri M, Sauvaire Y. *Nigella sativa* seed extracts enhance glucose-induced insulin release from rat-isolated Langerhans islets. *Fundam Clin Pharmacol* 2004; 18: 525-529.
71. Farzami B, Ahmadvand D, Vardasbi S, Majin FJ, Khaghani Sh. Induction of insulin secretion by a component of *Urtica dioica* leave extract in perfused Islets of Langerhans and its in vivo effects in normal and streptozotocin diabetic rats. *J Ethnopharmacol* 2003; 89: 47-53.
72. Tabit CE, Chung WB, Hamburg NM, Vita JA. Endothelial dysfunction in diabetes mellitus:

- Molecular mechanisms and clinical implications. *Rev Endocr Metab Disord* 2010; 11: 61-74.
73. Lenzen, S., Tiedge, M., Jorns, A., Munday, R., Alloxan derivatives as a tool for the elucidation of the mechanism of the diabetogenic action of alloxan, In: Shafir E (eds), *Lessons from Animal Diabetes*. Birkhauser, Boston, pp 113-122, 1996.
 74. Mythili MD, Vyas R, Akila G, Gunasekaran S. Effect of streptozotocin on the ultrastructure of rat pancreatic islets. *Microsc Res Tech* 2004; 63: 274-281.
 75. Szkudelski T. The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. *Physiol Res* 2001; 50: 537-546.
 76. Vessal A, Hemmati M, Vasei M. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. *Comp Biochem Physiol C Toxicol Pharmacol* 2003; 135C: 357-364.
 77. Hii CS, Howell SL. Effects of flavonoids on insulin secretion and 45 Ca^{2+} handling in rat islets of Langerhans. *J Endocrinol* 1985; 107: 1-8.
 78. Kim BH, Cho SM, Reddy AM, Kim YS, Min KR, Kim Y. Down-regulatory effect of quercetin gallate on nuclear factor-KB-dependent inducible nitric oxide synthase expression in lipopolysaccharide-stimulated macrophages RAW 264.7. *Biochem Pharmacol* 2005; 69: 1577-1583.
 79. Martinez-Florez S, Gutierrez-Fernandez B, Sanchez-Campos S, González-Gallego J, Tuñón MJ. Quercetin attenuates nuclear factor-KB activation and nitric oxide production in interleukin-1 β -activated rat hepatocytes. *J Nutr* 2005; 135:1359-1365.
 80. Ruiz PA, Haller D. Functional diversity of flavonoids in the inhibition of the proinflammatory NF-KB, IRF, and AKt signaling pathways in murine intestinal epithelial cells. *J Nutr* 2006; 136: 664-671.
 81. Rahimi R, Ghiasi S, Azimi H, Fakhari S, Abdollahi M. A review of the herbal phosphodiesterase inhibitors; Future perspective of new drugs. *Cytokine* 2010; 49: 123-129.
 82. Mohammadi M, Atashpour S, Pourkhalili N, Nili-Ahmadabadi A, Baeri M, Mohammadirad A, Hassani S, Nikfar S, Abdollahi M. Comparative improvement in function of isolated rat Langerhans islets by various phosphodiesterase 3, 4 and 5 inhibitors. *Asian J Anim Vet Adv* 2011; 12: 1233-1240.
 83. Lingohr MK, Dickson LM, McCuaig JF, Hugl SR, Twardzik DR, Rhodes CJ. Activation of IRS-2-mediated signal transduction by IGF-1, but not TGF- α or EGF, augments pancreatic β -cell proliferation. *Diabetes* 2002; 51: 966-976.
 84. Ballinger SW. Mitochondrial dysfunction in cardiovascular disease. *Free Radic Biol Med* 2005; 38, 1278-1295.
 85. Muchova, J., *Diabetes mellitus and antioxidants*, In: Durackova Z, Bergendi L, Carsky J (eds), *Free Radicals and Antioxidants in Medicine (II)*, (in Slovak). SAP, Bratislava, pp 203-232, 1999.
 86. Muchova J, Liptakova A, Orszaghova Z, Garaiová I, Tison P, Cársky J, Duracková Z. Antioxidant systems in polymorphonuclear leukocytes of type 2 diabetes mellitus. *Diabet Med* 1999; 16: 74-78.
 87. Abdollahi M, Ranjbar A, Shadnia S, Nikfar S, Rezaie A. Pesticides and oxidative stress: a review. *Med Sci Monit* 2004; 10: RA 144-RA 147.
 88. Durackova, Z., Oxidants, antioxidants and oxidative stress, In: Gvozdjakova A (eds), *Mitochondrial Medicine: Mitochondrial Metabolism, Diseases, Diagnosis and Therapy*. Springer, Amsterdam, pp 19-49, 2008.
 89. Knott AB, Bossy-Wetzel E. Nitric oxide in health and disease of the nervous system. *Antioxid Redox Signal* 2009; 11: 541-553.
 90. Kim F, Gallis B, Corson MA. TNF-alpha inhibits flow and insulin signaling leading to NO production in aortic endothelial cells. *Am J Physiol Cell Physiol* 2001; 280: C1057-1065.
 91. Bierhaus A, Chevion S, Chevion M, Hofmann M, Quehenberger P, Illmer T, Luther T, Berentshtein E, Tritschler H, Müller M, Wahl P, Ziegler R, Nawroth PP. Advanced glycation end product-induced activation of NF-kappa B is suppressed by alpha-lipoic acid in cultured endothelial cells. *Diabetes* 1997; 46: 1481-1490.
 92. Bierhaus A, Schiekofer S, Schwaninger M, Andrassy M, Humpert PM, Chen J, Hong M, Luther T, Henle T, Klötting I, Morcos M, Hofmann M, Tritschler H, Weigle B, Kasper M, Smith M, Perry G, Schmidt AM, Stern DM, Häring HU, Schleicher E, Nawroth PP. Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. *Diabetes* 2001; 50: 2792-2808.
 93. Kim F, Tysseling KA, Rice J, Pham M, Haji L, Gallis BM, Baas AS, Paramsothy P, Giachelli CM, Corson MA, Raines EW. Free fatty acid impairment of nitric oxide production in endothelial cells is mediated by IKKbeta. *Arterioscler Thromb Vasc Biol* 2005; 25: 989-994.
 94. Kim F, Pham M, Maloney E, Rizzo NO, Morton GJ, Wisse BE, Kirk EA, Chait A, Schwartz MW. Vascular inflammation, insulin resistance, and reduced nitric oxide production precede the onset of peripheral insulin resistance. *Arterioscler Thromb Vasc Biol* 2008; 28: 1982-1988.
 95. Ranjbar S, Larijani B, Abdollahi M. Recent update on animal and human evidences of promising

- antidiabetic medicinal plants: a mini-review of targeting new drugs. *Asian J Anim Vet Adv* 2011; 6: 1271-1275.
96. Mohseni-Salehi-Monfared SS, Larijani B, Abdollahi M. Islet transplantation and antioxidant management: A comprehensive review. *World J Gastroenterol* 2009; 15: 1153-1161.
 97. Hosseini A, Abdollahi M. It is time to formulate an antioxidant mixture for management of diabetes and its complications: notice for pharmaceutical industries. *Int J Pharmacol* 2012; 8: 60-61.
 98. Hosseini A, Abdollahi M. Antioxidants as an appropriate approach to improve the outcome of pancreatic islet isolation: evidences from animal studies. *Asian J Anim Vet Adv* 2012; 7: 540-541.
 99. Momtaz S, Abdollahi M. An update on pharmacology of *Satureja* species; from antioxidant, antimicrobial, antidiabetes and anti-hyperlipidemic to reproductive stimulation. *Int J Pharmacol* 2010; 6: 454-461.
 100. Vosough-Ghanbari S, Rahimi R, Kharabaf S, effects of *Satureja khuzestanica* on serum glucose, lipids and markers of oxidative stress in patients with type 2 diabetes mellitus: a double-blind randomized controlled trial. *Evid Based Complement Alternat Med* 2010; 7: 465-470.
 101. Mehri A, Hasani-Ranjbar S, Larijani B, Abdollahi M. A systematic review of efficacy and safety of *Urtica dioica* in the treatment of diabetes. *Int J Pharmacol* 2011; 7: 161-170.
 102. Hassani-Ranjbar S, Nayebi N, Larijani B, Abdollahi M. A systematic review of the efficacy and safety of *Teucrium* species; from anti-oxidant to anti-diabetic effects. *Int J Pharmacol* 2010; 7: 315-325.
 103. Pourkhalili N, Pournourmohammadi S, Rahimi F, Vosough-Ghanbari S, Baeeri M, Ostad SN, Abdollahi M. Comparative effects of calcium channel blockers, autonomic nervous system blockers, and free radical scavengers on diazinon-induced hyposalivation of insulin from isolated islets of Langerhans in rats. *Arh Hig Rada Toksikol* 2009; 60: 157-164.
 104. Lelliott C, Vidal-Puig AJ. Lipotoxicity, an imbalance between lipogenesis de novo and fatty acid oxidation. *Int J Obes Relat Metab Disord* 2004; 28: 22-28.
 105. Chen PY, Csutora P, Veyna-Burke NA, Marchase RB. Glucose-6-phosphate and Ca²⁺ sequestration are mutually enhanced in microsomes from liver, brain, and heart. *Diabetes* 1998; 47: 874-881.
 106. Shapiro AM, Lakey JRT, Ryan EA, Korbitt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000; 343: 230-238.
 107. Gray H, Williams PL, Bannister LH. *Gray's anatomy: the anatomical basis of medicine and surgery*. Churchill-Livingstone, New York 1995.
 108. Deters NA, Stokes RA, Gunton JE. Islet transplantation: factors in short-term islet survival. *Arch Immunol Ther Exp* 2011; 59: 421-429.
 109. Agrawal A, Gurusamy K, Powis S, Gray DW, Fuller B, Davidson BR. A meta-analysis of the impact of the two-layer method of preservation on human pancreatic islet transplantation. *Cell Transplant* 2008; 17: 1315-1322.
 110. Kaddis JS, Danobeitia JS, Niland JC, Stiller T, Fernandez LA. Multicenter analysis of novel and established variables associated with successful human islet isolation outcomes. *Am J Transplant* 2010; 10: 646-656.
 111. Bataille D. Molecular mechanisms of insulin secretion. *Diabetes Metab* 2002; 28: 4S7-13.
 112. Maechler P. Novel regulation of insulin secretion: the role of mitochondria. *Curr Opin Investig Drugs* 2003; 4: 1166-1172.
 113. Chan CB, De Leo D, Joseph JW, McQuaid TS, Ha XF, Xu F, Tsushima RG, Pennefather PS, Salapatek AM, Wheeler MB. Increased uncoupling protein-2 levels in beta-cells are associated with impaired glucose-stimulated insulin secretion: mechanism of action. *Diabetes* 2001; 50: 1302-1310.
 114. Kassis N, Bernard C, Pusteria A, Castellia L, Penicaud L, Richard D, Ricquier D, Ktorza A. Correlation between pancreatic islet uncoupling protein-2 (UCP2) mRNA concentration and insulin status in rats. *Int J Exp Diabetes Res* 2000; 1: 185-193.
 115. Zhang CY, Baffy G, Perret P, Krauss S, Peroni O, Grujic D, Hagen T, Vidal-Puig AJ, Boss O, Kim YB, Zheng XX, Wheeler MB, Shulman GI, Chan CB, Lowell BB. Uncoupling protein-2 negatively regulates insulin secretion and is a major link between obesity, beta cell dysfunction, and type 2 diabetes. *Cell* 2001; 105: 745-755.
 116. Sasahara M, Nishi M, Kawashima H, Ueda K, Sakagashira S, Furuta H, Matsumoto E, Hanabusa T, Sasaki H, Nanjo K. Uncoupling protein 2 promoter polymorphism -866G/A affects its expression in beta-cells and modulates clinical profiles of Japanese type 2 diabetic patients. *Diabetes* 2004; 53: 482-485.
 117. Sesti G, Cardellini M, Marini MA, Frontoni S, D'Adamo M, Del Guerra S, Lauro D, De Nicolais P, Sbraccia P, Del Prato S, Gambardella S, Federici M, Marchetti P, Lauro R. A common polymorphism in the promoter of UCP2 contributes

- bto the variation in insulin secretion in glucose-tolerant subjects. *Diabetes* 2003; 52: 1280-1283.
118. van de Venter M, Roux S, Bungu LC, Louw J, Crouch NR, Grace OM, Maharaj V, Pillay P, Sewnarian P, Bhagwandin N, Folb P. Antidiabetic screening and scoring of 11 plants traditionally used in South Africa. *J Ethnopharmacol* 2008; 119: 81-86
119. Mostafalou S, Abdollahi M. The role of environmental pollution of pesticides in human diabetes. *Int J Pharmacol* 2012;8: 139-140.

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>Broussonitiakazinoki/</i> flavonol, flavan, diphenyl propane	Isoprenylated flavan (Kazinol U)/ 30, 60 μm	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 (phytoesterogen) /20, 40 μm	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, Urtica</i> <i>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	Increased 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 at 10, 100, 1000 ppm, decrease in ROS at 0. 1 μm	(25)
<i>Citrus medica L. cv</i> <i>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 10µmol/l of rosiglitazone	48 h	Increased 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	Ethanollic 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 µg/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 µg/ml), and ACE (6. 25, 12. 5, 25 µg/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 µM	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 10µM, increase in GSIS in RIN-m5F at 100µM	(33)
<i>Angelica hirsutiflora</i> /-----	Plant extract/ 50-150 µg/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 µg/ml by HIT-TI5, increase in intracellular Ca ²⁺ by HIT-TI5 and islets of human, increase in phosphorylation of ERK ½ at 150µg/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/ 200µg/ml	Non- diabetic rat	Cultured INS832/13 cells, β-TC-tet cells, differentiated skeletal muscle cells, and adipocytes with/ without the substance vs. 10 µm 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 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 µg/ml	Non- diabetic rat	Incubated cultured RIN- m5F cells with/without the substances	24 h	Increase in viability maximum at 25µg/ml, decrease in apoptosis at 25µg/ml, dose- dependent decrease in iNOS until 25µg/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 foenumgraecum)</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/l	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 (Turmeric)</i> / 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 $\frac{1}{2}$, 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.