Hypoglycemic herbs and their action mechanisms
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Abstract
Conventional drugs treat diabetes by improving insulin sensitivity, increasing insulin production and/or decreasing the amount of glucose in blood. Several herbal preparations are used to treat diabetes, but their reported hypoglycemic effects are complex or even paradoxical in some cases. This article reviews recent findings about some of the most popular hypoglycemic herbs, such as ginseng, bitter melon and Coptis chinensis. Several popular commercially available herbal preparations are also discussed, including ADHF (anti-diabetes herbal formulation), Jiangtangkeli, YGD (Yerbe Mate-Guarana-Damiana) and BN (Byakko-ka-ninjin-to). The efficacy of hypoglycemic herbs is achieved by increasing insulin secretion, enhancing glucose uptake by adipose and muscle tissues, inhibiting glucose absorption from intestine and inhibiting glucose production from hepatocytes.

Background
Diabetes mellitus is a disease in which blood glucose levels are above normal [1]. There are three main types of diabetes, namely type I diabetes (juvenile diabetes), type II diabetes and gestational diabetes. In type I diabetes, the β cells of the pancreas do not make sufficient insulin. Type II diabetes is the major form of diabetes, accounting for approximately 90–95% of all diabetic cases. This form of diabetes usually begins with insulin insensitivity, a condition in which muscle, liver and fat cells do not respond to insulin properly. The pancreas eventually loses the ability to produce and secrete enough insulin in response to food intake. Gestational diabetes is caused by hormonal changes during pregnancy or by insulin insufficiency. Glucose in the blood fails to enter cells, thereby increasing the glucose level in the blood. High blood glucose, also known as hyperglycemia, can damage nerves and blood vessels, leading to complications such as heart disease, stroke, kidney dysfunction, blindness, nerve problems, gum infections and amputation [2]. Insulin injections, glucose-lowering drugs and lifestyle changes, such as exercise, weight control and diet therapy, are recommended for treating diabetes.

Hypoglycemic herbs are widely used as non-prescription treatment for diabetes [3]. However, few herbal medicines have been well characterized and demonstrated the efficacy in systematic clinical trials as those of Western drugs.

This review article highlights the current researches on the efficacy, side effects and action mechanisms of hypoglycemic herbs in vitro, in vivo and ex-vivo systems [4].

Conventional diabetic drugs
Western diabetic drugs correct hypoglycemia by supplementing insulin, improving insulin sensitivity, increasing
Insulin secretion from the pancreas and/or glucose uptake by tissue cells. Under normal conditions, pancreatic β-cells secrete sufficient insulin to maintain blood glucose concentration within a narrow range (72–126 mg/dL) [5] (Figure 1). The insulin stimulation followed by cascade signaling enhances glucose intake, utilization and storage in various tissues (Figure 2). In diabetic patients, the body loses insulin producing capacity as a result of pancreatic β-cell apoptosis or insulin insensitivity. The cytokines, lipotoxicity and gluco-toxicity are three major stimuli for β-cell apoptosis [6] (Figure 1).

There are several types of glucose-lowering drugs [7] (Figure 3), including insulin secretagogues (sulfonylureas, meglitinides), insulin sensitizers (biguanides, metformin, thiazolidinediones), α-glucosidase inhibitors (miglitol, acarbose). New peptide analogs, such as exenatide, liraglutide and DPP-4 inhibitors, increase GLP-1 serum concentration and slow down the gastric emptying [8,9]. Most glucose-lowering drugs, however, may have side effects, such as severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit, digestive discomfort, headache, dizziness and even death [10].

Anti-diabetes herbs
Certain herbs may lower blood glucose [3,11]; however, their test results are subject to several factors. Firstly, each herb contains thousands of components, only a few of which may be therapeutically effective [12]. Secondly, different parts of an herb have different ingredient profiles. Moreover, different extraction methods may yield different active ingredients [13]. Thirdly, herbal formulae containing multiple herbs may have synergistic effects [14,15].

Ginseng
The therapeutic potency of ginseng mainly relies on its geographical locality, dosage, processing and types of diabetes. *Panax ginseng* (Chinese or Korean ginseng) has the

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**Figure 1**

**Insulin secretion and pancreatic-β-cell apoptosis.** Glucose is taken up into β-cells via glucose transporters. It is metabolized in glycolysis and Krebs cycle, resulting in an increased ratio of ATP to ADP in the cytoplasm. This closes ATP-sensitive potassium channels (KATP channels), leading to cell membrane depolarization and subsequently opening voltage-gated Ca2+ channels. These changes increase free Ca2+ concentration ([Ca2+]i) in cytoplasm and eventually triggers insulin secretion. In apoptosis, stimuli promotes the release of caspase activators from mitochondria and result in the activation of caspases procedure, by cleaving the effector caspases, which interacts with a variety of cellular proteins, resulting in directly or indirectly the morphological and biochemical characteristics of cell apoptosis. The action sites of hypoglycemia herbs are indicated with a narrow.
highest therapeutic potency. *Panax quinquefolius* (American ginseng) is the medium potency grade ginseng, while *Panax japonicus* (Japanese ginseng) is considered the low potency grade ginseng. Thus, the most commonly used therapeutic ginseng is *Panax ginseng*. The anti-tumor, angiomodulating and steroid-like activities of ginseng have been recently delineated [16].

The anti-diabetic effects of ginseng have been investigated with aqueous or ethanol ginseng extracts. A proposed action mechanism has been tested on various animal models [17]. Korean red ginseng (0.1–1.0 g/ml) significantly stimulated insulin release from isolated rat pancreatic islets at 3.3 mM glucose concentration [18]. The treatment with oral administration of H-AG (heat-processed American ginseng) at a dose of 100 mg/kg of body weight for 20 days decreased serum levels of glucose and glycosylated proteins and hemoglobin A1C in streptozotocin (STZ)-induced diabetic rats. The treatment also improved the decreased creatinine clearance level and decreased the accumulation of N (ε)-(carboxymethyl)lysine and its receptors for advanced glycation end product (AGE) expressions in kidney [19]. *Radix Ginseng Alba* improved hyperglycemia in KKAY mice, possibly by blocking intestinal glucose absorption and inhibiting hepatic glucose-6-phosphatase, while *Radix Ginseng Palva*...
has a similar effect through the up-regulation of adipocytic PPAR-γ protein expression and inhibition of intestinal glucose absorption [20].

The treatment of the C57BL/Ks db/db mice with Panax ginseng berry extract (150 mg/kg of body weight) significantly lowered the fasting blood glucose levels on day 5 and achieved euglycemia on day 12 [21]. Berry extract showed marked anti-obesity effect in obese ob/ob and db/db mice [22]. Red ginseng lowered hemoglobin A1C to normal range and improved insulin sensitivity [21]. Similarly, extract of American ginseng berry also lowered fasting blood glucose levels significantly in diabetic ob/ob mice receiving daily berry juice at 0.6 ml/kg. This hypoglycemic effect continued for at least ten days after the treatment. In addition, reduction of body weight was also observed [23].

While both ginseng root and berry possess anti-diabetic effects [24], ginseng berry seems to be more potent in anti-hyperglycemic activity [25]. Furthermore, only ginseng berry showed marked anti-obesity effects in ob/ob mice [24,26].

A total of 705 components have been isolated from ginseng, such as ginsenosides, polysaccharides, peptides and polyacetylenic alcohols, among which ginsenosides are believed to be responsible for ginseng’s efficacy [27]. Pharmacological sequential trials of three components, i.e. (1) fat-soluble components, (2) ginseng saponins and (3) a third component with hypoglycemic activity identified the most active components (100-fold more effective than the original water-soluble extract of the ginseng root). Ginseng’s clinical efficacy is thought to be mediated by multiple factors [27,28]: the component panaxans (panaxans A to E) elicits hypoglycemia in both normal and diabetic mice; the component adenosine inhibits catecholamine-induced lipolysis; both components of carboxylic acid and peptide 1400 inhibit catecholamine-induced lipolysis in rat epididymal fat pads; and the component DPG-3-2 provokes insulin secretion in diabetic and glucose-loaded normal mice [29]. EPG-3-2, a

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**Figure 3**

**Action sites of western medicine in diabetes treatment.** Hypoglycemic medicines restore euglycemia via several types, including insulin secretagogues (sulfonylureas, meglitinides), insulin sensitizers (biguanides, metformin, thiazolidinediones), alpha-glucosidase inhibitors (miglitol, acarbose).
fraction related to DPG-3-2, also exhibits an anti-lipolytic activity related to anti-obesity effects. Ginsenoside Rg3 inhibits adipocyte differentiation via PPAR-γ pathway in rosiglitazone-treated cells and activates AMPK, a pathway involved in the control of nutritional and hormonal modulation [30]. Ginsenoside Rh2 improves insulin sensitivity in rats fed with fructose rich chow [31]. Therefore, we suggest that the whole extract of ginseng contains multiple biologically active components that stimulate insulin secretion, blocking intestinal glucose absorption and enhancing glucose peripheral utilization.

Ginseng treatment for type II diabetes has been tested in both animal models and human clinical trials. Panax quinquefolius (10 g/1 kg diet) increases body weight and decreases cholesterol levels, PPAR actions and triglyceride metabolism in male Zucker diabetic fatty (ZDF) rats [32]. In human clinical trials, Panax quinquefolius improves post-prandial glycemia in type II diabetic patients [33]. Single intravenous injection of ginsenoside Rh2 decreases plasma glucose concentrations within 60 minutes in a dose-dependent manner in rats fed with fructose rich chow and STZ-induced insulin resistant rats [30]. A possible mechanism is that ginsenoside Rh2 promotes the release of ACh from nerve terminals which stimulate muscarinic M (3) receptors in pancreatic cells to increase insulin secretion [34].

Ginseng is also used to treat type I diabetic patients. Ginsenosides at 0.1–1.0 g/mL inhibited cytokine-induced apoptosis of β-cells. The action mechanism involves the reduction of nitric oxide (NO), production of reactive oxygen species (ROS) [35], inhibition on p38/p21 expression and inhibition on cleavage of caspasase and poly (ADP-ribose) polymerase (PARP) [36].

Not only does ginseng benefit serum glucose control in diabetic patients, but also aids central nervous system complications in them. Alternation expression of NOS gene is implicated in the pathogenesis of numerous secondary complications in diabetic patients. In animal models, enhanced NOS expression was detected in the hippocampus of diabetic rats and the administration of ginseng root suppressed NOS expression [33]. Pharmacological studies confirmed that ginseng possesses multiple actions (central nervous system, neuroprotective, immunomodulation and anticancer effects). Ginsenosides have antioxidant, anti-inflammatory, anti-apoptotic and immuno-stimulant properties [36].

Side-effects of ginseng include insomnia, diarrhea, vaginal bleeding, breast pain, severe headache, schizophrenia and fatal Stevens-Johnson syndrome [37]. The recommended dosage of ginseng application is 1–3 g of root or 200–600 mg of extract [38]. Ginseng has the potential to prolong bleeding time and therefore should not be used concomitantly with warfarin. Moreover, ginseng may cause headache, tremulousness, and manic episodes in patients treated with phenelzine sulfate [39]. Ginseng may interfere with the actions of estrogens or corticosteroids and may impede digoxin metabolism or digoxin monitoring [40].

Momordica charantia (bitter melon)

Hypoglycemic effects of bitter melon were demonstrated in cell culture, animal models [41] and human studies [42]. The anti-diabetic components in bitter melon include charantin, vicine, polypeptide-p, alkaloids and other non-specific bioactive components such as anti-oxidants. The major compounds in bitter melon methanol extract, including 5-β, 19-epoxy-3-β, 25-dihydroxycucurbita-6,23(E)-dien (4) and 3-β,7-β,25-trihydroxycucurbita-5,23(E)-dien-19-al (5) showed hypoglycemic effects in the diabetic male ddY mice at 400 mg/kg [43]. Olea-nolic acid glycosides, compounds from bitter melon, improved glucose tolerance in Type II diabetics by preventing sugar from being absorbed into intestines. Saponin fraction (SF) extracted from bitter melon with PEG/salt aqueous two-phase systems showed hypoglycemic activity in alloxan-induced hyperglycemic mice [44]. Bitter melon increased the mass of β cells in the pancreas and insulin production [45,46]. With edible portion of bitter melon at 10% level in the diet STZ-induced diabetic rats, an amelioration of about 30% in fasting blood glucose was observed [45].

Biochemical studies indicated that bitter melon regulated cell signaling pathways in pancreatic β-cell, adipocytes and muscles. Ethyl acetate (EA) extract of bitter melon activates peroxisomal proliferator receptors (PPARs) α and γ [46,47], modulates the phosphorylation of IR and its downstream signaling pathway, thereby lowering plasma apoB-100 and apoB-48 in mice fed with high-fat diet HFD. The momordicidioses (Q, R, S and T) stimulate GLUT4 translocation of the cell membrane and increase the activity of AMP-activated protein kinase (AMPK) in both L6 myotubes and 3T3-L1 adipocytes, thereby enhancing fatty acid oxidation and glucose disposal during glucose tolerance tests in both insulin-sensitive and insulin-insensitive mice [48].

Bitter melon can be used as a dietary supplement herbal medicine for the management of diabetes and/or metabolic syndromes [49]. Reported adverse effects of bitter melon include hypoglycemic coma, convulsions in children, reduced fertility in mice, a favism-like syndrome, increased enzyme activities of γ-glutamyl transferase and alkaline phosphatase in animals and headaches in
humans. Bitter melon has an additive effect with other glucose-lowering agents [50]. Bitter melon also reduces adiposity in rats fed with HF diet [51].

**Coptis chinensis (Huanglian)**

*Coptis chinensis* is commonly used to treat diabetes in China. Found in plant roots, rhizomes, stems and barks, berberine is an isoquinoline alkaloids and the active ingredient of *Coptis chinensis*.

Intragastric administration of berberine (100 and 200 mg/kg) in diabetic rats decreased fasting blood glucose levels and serum content of TC, TG, LDL-c, increased HDL-c and NO level, and blocked the increase of SOD and GSH-px levels [52,53]. Multiple mechanisms may be responsible for weight reduction and increased insulin response induced by berberine. Glucose’s uptake by adipocytes is enhanced by berberine via GLUT1, adenosine monophosphate-activated protein kinase and acetyl-coenzyme A carboxylase phosphorylation [54]. Berberine also increases the PPAR α/β/γ protein expression in liver [55], increases insulin receptor expression in liver and skeletal muscle cells and improves cellular glucose consumption in the presence of insulin [56]. Berberine increases GLUT4 translocation in adipocytes and myo-tubes [57], increases AMPK activity, decreases glucose-stimulated insulin secretion (GSIS) and palmitate-potent-ial insulin secretion in MIN6 cells and rat islets [58]. Furthermore, berberine decreases significantly the enzyme activity of intestinal disaccharidases and β-glucuronidase in STZ-induced diabetic rats [59]. Recently, dihydroberberine (dhBBR), an identified BBR berberine derivative, demonstrated in vivo beneficial effects in rodents fed with high-fat [60].

Berberine may also relieve some diabetic complications. Studies showed that berberine restored damaged pancreas tissues in diabetic rats induced by alloxan [61]. Berberine ameliorates renal dysfunction in rats with diabetic nephropathy through controlling blood glucose, reduction of oxidative stress and suppressing the polyol pathway [61]. Berberine ameliorates renal injury in STZ-induced diabetes, not by suppression in both oxidative stress and aldose reductase activities [61].

As berberine is an oral hypoglycemic agent in clinical studies, the hypoglycemic effect of berberine was similar to that of metformin in 36 adult patients of recently diagnosed type II diabetes [62]. Berberine also lowered fasting blood glucose and postprandial blood glucose in 48 adult patients of poorly controlled type II diabetes during a 3-month period [62]. In the same trials, the fasting plasma insulin, insulin insensitivity index, the total cholesterol and low-density lipoprotein cholesterol reduced significantly [62].

**Chinese herbal preparations for diabetes**

**ADHF (anti-diabetes herbal formulation)**

ADHF was studied in diet-induced type II diabetic animals (C57BL/6 mouse model). The blood glucose level dropped markedly in the mice fed with a diet containing 4% or 8% ADHF. Other diabetic parameters such as insulin insensitivity, histopathological changes in the pancreas and liver were also improved significantly in the mice fed with ADHF [63].

**Jiangtangkli**

Jiangtangkli, a Chinese medicine formulation containing *Radix Ginseng (Renshen)*, improves insulin insensitivity by modulating muscle fiber composition and TNF-α in skeletal muscles in hypertensive and insulin-insensitive fructose-fed rats [64].

**YGD (Yerbe Mate-Guarana-Damiana)**

YGD contains Yerbe Mate (leaves of *Ilex paraguayensis*), Guarana (seeds of *Paullinia cupana*) and Damiana (leaves of *Turnera diffusa*). The YGD capsule delayed the gastric emptying significantly, and increased the time to feel gastric fullness and reduced body weight significantly over 45 days on over-weighted patients treated in a primary health care context.

**BN (Byakko-ka-ninjin-to)**

BN contains *Radix Ginseng (Renshen)*, *Rhizoma Anemarrhena (Zhimu)*, *Radix Glycyrrhizae Uralensis (Gancao)*, gyp-sum (*Shigao*) and rice. BN lowered blood glucose levels in diabetic mice. Furthermore, ginseng-anemarrhena (or ginseng-licorice) reduced the blood glucose levels more than any individual component did. The study results indicate that the anti-hyperglycemic effect of BN relies on the cooperation of four crude therapeutic components and Ca^{2+} [65].

The major goal in treating diabetes is to minimize elevation of blood glucose without causing abnormally low levels of blood glucose. The action mechanisms for hypoglycemic herbs are multiple (Figure 4), such as increasing insulin secretion, enhancing glucose uptake by adipose and muscle tissues, inhibiting glucose absorption from intestine and inhibiting glucose production from heptocytes.

Our literature search [66-99] reveals some commonly used herbs for the management of diabetes mellitus (Table 1).

**Concerns over herbal treatment for diabetes**

While the herbs discussed in this paper have shown efficacy in lowering blood glucose in diabetes patients, the line between whether an herb is a ‘drug’ or a dietary supplement is unclear. The issues of standardization, charac-
Herb-drug interaction and herb-herb interaction is another concern. Contrary to some beliefs, herbs can have side-effects. Unfortunately, herb-drug interactions in diabetic treatments have not been well documented. A number of supplements are known to have intrinsic effects on serum glucose, for example, ginseng is hypoglycemic in diabetic patients. Gliclazide is an oral hypoglycemic (anti-diabetic) classified as a sulfonfonylurea. St John's Wort increases the apparent clearance of gliclazide significantly. Diabetic patients receiving these at the same time should be closely monitored for possible signs of reduced efficacy [100].

### Conclusion
Hypoglycemic herbs are used in Chinese medicine to treat diabetes mellitus. Ginseng, bitter melon and *Coptis chinensis* are used in both types I and II diabetes. The efficacy of hypoglycemic herbs is achieved by increasing insulin secretion, enhancing glucose uptake by adipose and muscle tissues, inhibiting glucose absorption from intestine and inhibiting glucose production from hepatocytes.

### Abbreviations
ADP: adenosine diphosphate; AGE: advanced glycation end product; AMPK: AMP-activated protein kinase; ATP: adenosine triphosphate; BUN: blood urea nitrogen; Cr: Creatinine; DPP-4 (DDP IV): dipeptidyl peptidase IV; GLP-1: glucagon-like peptide-1; Grb2: growth factor receptor-binding protein 2; GLUTs: hexose transporter protein; GLUT4: glucose transporter-4; HDL: high-density lipoprotein; HFD: high-fat diet; IRS-1 and IRS-2: insulin receptor substrate-1 and insulin receptor substrate-2; LDL-C: lower-density lipoprotein cholesterol; MRSA: methicillin resistant staphylococcus aureus; NO: nitric oxide; PPAR: peroxisome proliferator receptors; ROS: reactive oxygen species; PARP: poly (ADP-ribose) polymerase; STZ: streptozotocin; SHC: src-homology-collagen-like protein; SOD: superoxide dismutase; TC: total cholesterol; TG: triglyceride; TNF-alpha: tumor necrosis factor.
### Table 1: Herbs commonly used in diabetes management

| Herbs                     | Components                                                                 | Anti-diabetic Mechanism                                                                 | Models of experiments or tests | Application and recommend dosage | Ref  |
|---------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------|----------------------------------|------|
| Myrcia                    | Flavanone glucosides (myrciacitrins) and acetophenone glucosides myriaphenones | Inhibit activity of aldose reductase and alpha-glucosidase                              | Streptozotocin diabetic rats  | Type II DM                       | 66   |
| Cinnamon                  | Cinnulin PF(R)                                                            | Improve insulin sensitivity, Decrease fasting blood glucose                            | Human                         | Type II DM                       | 67, 68, 69 |
| Enicostemma litorale Blume|                                                                              | Increase the serum insulin through K(+) -ATP channel dependent pathway but did not require Ca2+ influx | Alloxan-induced diabetic rats  | Type II DM                       | 70   |
| Biophytum sensitivum      |                                                                           | Stimulating the synthesis/release of insulin from the beta cells of Langerhans         | Alloxan-induced diabetic rabbits | Type II DM                       | 71   |
| Ipomoea batatas           | Caiapo (ipomoea batatas)                                                 | Decrease insulin insensitivity, increase adiponecin and decrease fibrinogen levels    | Type II diabetic patients      | Type II (4 g/d) DM               | 72, 73 |
| Tithonia diversifolia     |                                                                           | Reducing insulin insensitivity                                                        | KK-Ay-mice                     | Type II DM                       | 74   |
| Sangzhi                   |                                                                           | Alpha-glucosidase inhibitory effects                                                 | Alloxan induced diabetic rats  | Type II DM                       | 75   |
| Galega officinalis        |                                                                           | Hypoglycemic effects is independent on a reduction of food intake                    | ob/ob animals                  | Type II DM                       | 76   |
| Fenugreek leaves          |                                                                           | Similar to glibenclamide, hypoglycemic property and an anti-hyperlipidemic via interferenceing carbohydrate metabolic enzymes | Streptozotocin induced diabetic rats, human | Type II DM                       | 77, 78 |
| Pterocarpus marsupium     |                                                                           | Decrease HK (hexokinase), GK (glucokinase) and PFK (phosphofructokinase)             | Human, alloxon-induced diabetic rats | Type II DM                       | 79, 80 |
| Vanadium                  |                                                                           | Regulate activity of carbohydrate-metabolizing enzymes, and enhance expression of IRS-1 and GLUT4 mRNA in adipocytes | STZ-induced diabetic rats, dexamethasone-induced insulin insensitivity in 3T3-L1 adipocytes | Type II DM                       | 81, 82 |
| Artemisia scoparia scoparia| Scoparone (6,7-dimethoxycoumarin)                                        | Anti-atherogenic effect; free radical scavenging properties; inhibited iNOS gene expression and inhibited NF-kappaB activation | Hyperlipidaemic diabetic rabbits, cytokine-induced beta-cell dysfunction | Type I DM, Type II DM            | 83, 84 |
| Gymnema sylvestre         | Gymnemic acids                                                            | Controls the activities of phosphorylase, gluconeogenic enzymes and sorbitol dehydrogenase | Alloxan diabetic rabbits       | Type II DM complication          | 85, 86 |
| Daio (Rhe Rhizoma)        |                                                                           | Improve kidney function                                                              | Patients                       | Diabetic nephropathy              | 87   |
| Lupinus termis            | Lupinus termis                                                            | Regulates acetyl cholinesterase activity, AST (Aspartate aminotransferase), ALT (alanine aminotransferase) and LDH (lactate dehydrogenase) | Alloxan-induced diabetes, patients | Type II DM                       | 88, 89 |
| Tea                       | EGCG                                                                      | Reduction of IL-1beta and IFN-gamma-induced nitric oxide (NO) production and levels of NO synthase (iNOS) | STZ-treated islets             | Type I DM, Type II DM            | 90, 91 |
| Coccinia indica leaves    | Coccinia indica leaf ethanolextract (CLEt)                               | Antioxidant property of CLEt                                                         | Streptozotocin-diabetic rats   | Type II DM                       | 92   |
| Clausena anisata (Wild)   | Terpenoid and coumar                                                      | Similar to glibenclamide                                                             | Diabetic rats                  | Type II DM                       | 93   |
alpha; UP24h: urine protein for 24 hours; ZDF: Zucker diabetic fatty rats.

**Competing interests**

The authors declare that they have no competing interests.

**Authors' contributions**

HH conceived and drafted the paper. GT and VLG critically reviewed the literature and revised the manuscript.

**Acknowledgements**

This work was partially supported by the NIH Funding of the UCLA Center for Excellence in Pancreatic Diseases (PO1AT003960). We thank Ms Lilia Grigoryan for her assistance in editing the manuscript.

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