Review Article

Advances in Research on the Protective Mechanisms of Traditional Chinese Medicine (TCM) in Islet β Cells

Na Li, Hongli Zhang, and Xiaohua Li

Department of Endocrinology, Seventh People’s Hospital Affiliated to Shanghai University of TCM, Shanghai 200137, China

Correspondence should be addressed to Hongli Zhang; hongliting@sina.com and Xiaohua Li; wendylee_tcm@shutcm.edu.cn

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The dysfunction and decreased number of islet β cells are central to the main pathogenesis of diabetes. Improving islet β cell function and increasing the number of β cells are effective approaches to treat diabetes and constitute the main direction of diabetes drug development. The role of Chinese medicine in the treatment of diabetes began to be recognized. In recent years, Chinese medicine monomers have been found to increase insulin synthesis and secretion, reduce β cell-apoptosis, and protect the function of β cells. The results of in vivo animal experiments and in vitro studies on insulinoma cells also suggested TCMs could promote the proliferation of pancreatic islet β cells and induce other cells differentiation or transdifferentiation to islet β cells. Thereby, they may play a role in the treatment of diabetes. In this paper, we will review islet β cell protection with TCMs and the related mechanisms found in recent studies. An in-depth explanation of the role of TCM in islet β cell protection can provide a theoretical basis and research ideas for the development of TCM-based diabetes treatment drugs.

1. Introduction

According to the WHO, the number of patients with type 2 diabetes mellitus (T2DM) will reach 300 million by 2025. Islet β cell function failure is the core principle of diabetes pathogenesis and the pathophysiological basis for the occurrence and development of the disease. Insulin function failure include decrease in the number of islet β cells, defect of insulin secretion and synthesis of mature insulin. In traditional Chinese medical science, diabetes is called consumptive thirst (XIAO KE). T2DM is categorized as “Xiao Ke” in TCM mentioned in “Huang Di Nei Jing Su Wen” (Pre-Qin Dynasty to Han Dynasty). TCM theorizes that the internal organ weakness, excessive intake of fat and sugar, and mood disorders are the main causes of “Xiao Ke.” The pathogenesis involves an insufficiency of Yin and excessive dryness in vivo, and its governance involves clearing the lungs, moistening dryness, and invigorating the lungs and kidneys. The key etiology of diabetes mellitus included phlegm, heat, dryness, and blood stasis, and the diseased organs were the spleen, lung, stomach, and kidney. Therefore, Chinese medicine often treats diabetes by Triple-jiao deficiencies argument. Diabetes is classified into three types in Chinese medicine including damp-heat trapping spleen, gastrointestinal heat retention, and dry-heat damaging Yin. At present, it is believed that islet β cell damage is mainly caused by qi, blood, and a Yin Yang deficiency, complicated by damp-turbid phlegm, heat, and heat retention. As a complementary and alternative medicine, traditional Chinese medicine (TCM), which has been practiced for thousands of years, has been shown to possess satisfactory clinical effectiveness for diabetes mellitus and its complications, using medications such as Gegen Qinlian Decoction [1], JinQi Jiangtang (JQJT) [2], and Xiaokeeping (XKP) [3]. Pueraria (Ge Gen), Astragali (Huang Qi), ginseng (Ren Sheng), digitalis (Di Huang), Anemarrhena (Zhi Mu), Berberine (Ber) (Huang Lian), rhubarb (Da Huang), and other TCMs often have a hypoglycemic effect. There are currently more than 100 types of Chinese medicines that treat diabetes. Huangqi (“Gan” flavor) Bunge and Huanglian (“Ku” flavor) are some of the most frequently prescribed herbs [4]. At present, the active ingredients of TCMs, such as alkaloids, polysaccharides,
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3. Increasing Islet \( \beta \) Cell Mass

There emerged a consensus that progressive \( \beta \)-cell decline is a characteristic of islet pathology in type 2 diabetes, and restoring an effective \( \beta \)-cell mass is a therapy for diabetes. \( \beta \) cell mass is dictated by a dynamic balance between neogenesis, proliferation, and apoptosis. Several TCMs have been implicated to promote the proliferation and regeneration of pancreatic islet \( \beta \) cells in vivo animal experiments and in vitro studies on isletoma cells.

3.1. Promotion of \( \beta \) Cell Proliferation. Studies have shown that Salidroside (Hongjingtian) [18] promotes the mRNA expression of insulin, PDX-1, GLP-1R, and other genes, reduces the level of IL-1\( \beta \), and promotes the proliferation of \( \beta \) cells. Cortex Lycii (Digui) (2 g/L) [19] increased the proliferation rate of islet \( \beta \) cells and inhibited the apoptosis of islet \( \beta \) cells. Portulaca oleracea L. (POP I) [20] activates JNK, PDX-1, PPAR\( \gamma \), and ERK, which affects islet \( \beta \) cell mitosis and promotes cell proliferation. Puerarin [21] can upregulate the expression of PDX-1 and promote the proliferation of islet \( \beta \) cells. Baicalein [22] can increase islet \( \beta \) cell mass in mice. Baicalein-treated diabetic mice displayed fewer apoptotic islet \( \beta \) cells and increased viability of clonal islet \( \beta \) cells and human islet cells.

3.2. Induction of Stem Cell Differentiation to Islet \( \beta \) Cells. Stem cells, including embryonic and adult stem cells, have the ability to renew and undergo multipotent differentiation. Pancreatic duct epithelial cells have stem cell properties [23]. Tripterygium wilfordii polysaccharide (TWP) [24] can induce islet stem cells to differentiate into spherical islet cell structures that produce an elongated tubule connected to the extracellular environment through the expression of \( \beta \) cell functional proteins. This finding indicates that TWP can induce islet stem cells to differentiate into \( \beta \) cell-containing islet cell clusters when cultured in vitro. Resveratrol (Baillie) [25] induces embryonic stem cells and the pluripotent stem cell line (hiPSC) MSUH-001 to differentiate into cells expressing specific protein markers of islet \( \beta \) cell function, such as PDX-1, that have an insulin secretion function. Differentiated cells accumulate in islet-like clusters when transplanted into mice with streptozotocin- (STZ-) induced diabetes. The cells secrete insulin and decrease blood glucose of STZ-treated mice. It indicated that resveratrol can promote stem cell differentiated to islet \( \beta \) cell and improves \( \beta \) cell maturation. In another study, it has been found Syzygium cumini (L.) Skeels SC2 [26] could induce \( \beta \) cell neogenesis in islets of STZ-treated mice.

3.3. Transformation of Islet \( \alpha \) Cells into Islet \( \beta \) Cells. The epithelium of the pancreas includes \( \beta \) cells, duct cells, acinar cells, and \( \alpha \) cells. When pancreatic damage, metabolic stress, and genetic manipulation occur, other pancreatic epithelial cells may be induced to transdifferentiate into \( \beta \) cells, which may then be induced to differentiate or dedifferentiate into immature \( \beta \) cells [27]. Islet \( \alpha \) and \( \beta \) cells are derived from the

flavonoids, terpenoids, and saponins, are widely studied [5]. This paper aims to summarize the mechanisms of TCM that protect \( \beta \) cells and the prospects for future research.

2. Improvement in Insulin Secretion in Islet \( \beta \) Cells

2.1. Promotion of Insulin Synthesis and Secretion from Islet \( \beta \) Cells. In both type 1 (T1D) and type 2 diabetes (T2D), the deterioration of glycemic control over time is primarily caused by an inadequate mass and progressive dysfunction of \( \beta \) cell, leading to the impaired insulin secretion. The beta cell senses an elevated level of glucose in the plasma by glucokinase. Glucose enters the tricarboxylic acid cycle (TCA) through solute carrier family 2 (facilitated glucose transporter), resulting in the productin of NADH and FADH2 which promote the ATP production. The rise of the ATP:ADP ratio in the cytoplasm closes the plasmalemmal ATP-sensitive potassium channel (KATP). This results in an influx of Ca\(^{2+}\) into the cell that triggers the exocytosis of insulin granules [6].

Studies have shown that ginsenosides can regulate islet \( \beta \) cell mitochondrial function, increase ATP content, reduce UCP2 content, and increase insulin synthesis and secretion. Ginsenoside Rb2 [7](0.5 \( \mu \)g/mL) can promote insulin synthesis, and ginsenoside Rg3 [8](10 \( \mu \)M) increases insulin secretion by INS-1 cells in a high-glucose environment by 47%. Guavenoic acid (GA) [9] (1 mmol/L) promotes the synthesis and secretion of insulin, possibly via down-regulation of PTP1b mRNA and upregulation of the PPAR-\( \gamma \) and PDX-1 genes. Guava leaf extract (GLE) [10] may improve the ability of islet \( \beta \) cells to secrete insulin and may ameliorate oxidative stress in islet \( \beta \) cells.

Berberine [11] can increase the expression of the HNF-1a/PDX-1 pathway and insulin secretion, and this effect becomes larger with increasing concentrations. Baicalein (Huangqin) [12] regulates insulin secretion by inhibiting regulation of the intracellular Ca\(^{2+}\) concentration in islet \( \beta \) cells by voltage-dependent K\(^+\) channels in the cell membrane. Resveratrol and curcumin [13] can regulate the expression and activity of phosphodiesterases (PDEs), increase the level of AMP, and stimulate insulin secretion. Syzygium cumini (L.) Skeels SC2 [14] stimulates and modulates insulin release from islet \( \beta \) cells.

2.2. Promotion of Proinsulin Cleavage into Insulin. Proinsulin is an insulin precursor synthesized in the endoplasmic reticulum. It is folded into active insulin by modification and shearing by a series of enzymes [15]. The presence of unfolded or misfolded insulin increases the level of nonnaturally folded polypeptide in the endoplasmic reticulum, thereby causing an imbalance of proinsulin homeostasis, an increased proinsulin/insulin ratio, a decrease in active insulin, and islet \( \beta \) cell dysfunction [16]. Lycium barbarum polysaccharides [17] increase the transcription and expression of proinsulin genes and proteins as well as the transformation of proinsulin into mature insulin.
same progenitor cells and express homologous proteins that sense blood glucose levels and promote hormone release, but α cells have the opposite effect on regulating blood glucose levels. Studies have shown that when the Pax4 gene is ectopically expressed, α cells are induced to differentiate into β cells [28]. Pax4 and Arx are the main regulatory genes that induce the differentiation of α cells into β cells, and Arx represents the main trigger of α cell-mediated β-like cell regeneration. Artemisinin (Qinghao) [29] increases GABA signaling, and artemether induces ARX transport from the nucleus to the cytoplasm, eliminates ARX from chromatin, and prevents α cells from secreting glucagon. The α cells acquire the characteristics of β cell and then transform into mature β cells with insulin-secreting function.

3.4. Reduction of β Cell Apoptosis. Apoptosis plays important roles in the pathophysiology of T2DM, which resulted in defective insulin secretion and loss of β-cell mass. β-cell apoptosis is mediated through a milliard of caspase family cascade machinery in T2DM. Hyperglycemia-induced β-cell apoptosis has been extensively studied on the balance of proapoptotic Bcl-2 proteins (Bad, Bid, Bik, and Bax) and antiapoptotic Bcl family (Bcl-2 and Bcl-xL) toward apoptosis in vitro isolated islets and insulinoma cell culture. Many pathways, for example, PI3K/AKT, MAPK, and autophagy, involved in apoptosis. There are several kinds of TCMs for treating T2DM, and their mechanisms to lower blood glucose levels include reduction of β cell apoptosis. Ginsenoside Rg3 [30] can inhibit β cell apoptosis through activating phosphorylation of ERK and p38 MAPK or regulating P44/42 MAPK activation in the β cells. Red ginseng [31] can inhibit the expression of bcl-2, reduce the level of Bax and the activity of caspase-3, reduce the production of proinflammatory cytokines, and inhibit cell apoptosis in β cells of CsA-induced injury. Panax notoginseng saponins (PNS) [32] can upregulate the expression of mir-181b and caspase-3 and increase the expression of bcl-2 and activation of the PI3K-AKT-mTOR pathway, which blocks the expression of the autophagy gene beclin-1 and the autophagosome membrane marker LC3-II, thereby reducing apoptosis and autophagy. Berberine [11] can reduce the expression of PTEN, activate the PI3K/Akt signaling pathway, decrease the expression of caspase-3, and significantly reduce the rate of apoptosis. Puerarin [21] and Cortex Mori Radicis with drug serum [33] may downregulate caspase-3 expression, upregulate bcl-2, downregulate Bax expression, and inhibit islet cell apoptosis through the PI3K/Akt pathway. Ophiopogonis Radix [34] protects islet β cells by inhibiting the expression of NF-κB to reduce apoptosis. The Jin Li Da (JLD) granules contain over a dozen Chinese medicinal herbs (CHM) [35], including ginseng (Renshen), puerarin (Gegen), Coptis chinensis (Huanglian), and Radix polygonati officinalis (Yuezhu). JLD might decrease β cell apoptosis through AMP-activated protein kinase activation.

3.5. Maintenance of Islet Cell Structure Integrity. TCMs can protect and repair the structural integrity of islet β cells. The number of islet and endocrine cells in a diabetic model treated with total flavonoids of Lycium barbarum (TFLB) [36] was increased compared to that of the control group, and the islet cell volume was slightly increased. In addition, the number of vacuolar cells decreased, the cell arrangement was uniform, and the structure and morphology were normal. In red ginseng-treated [31] islet cells with CsA-induced injury, the islet size was increased, insulin immunity activity was enhanced, islet cell morphology was well preserved, the islet cell boundary was irregular, and vacuolization was reduced. After treatment with puerarin, oleic acid, and astragaloside [37], the islet cells were structurally intact, and the islet cell boundary was clear and similar to the normal structure. In the ginsenoside Rgl-treated group [38], the islet cell volume was increased, the areas of islet cells were significantly increased, mitochondria were slightly swollen, the crista were expanded in the endoplasmic reticulum, and Golgi body expansion was obviously reduced. The endocrine β cell morphology and the number of secretory granules were similar to those of normal cells, and aging characteristics were not obvious. Administration of Astragalus total saponins and curcumin in a ratio of 3:7 obviously reduced the pathological changes of pancreatic tissue [39]. GLE-treated [10] diabetic rats had islet cells with normal granules and exhibited cell hyperplasticity.

4. Reduction of Oxidative Stress (OS) Damage in Islet β Cells

Insulin secretion abnormalities, high glucose, fat accumulation toxicity, apoptosis, and inflammatory reactions cause increases in highly active ROS, such as H₂O₂ and RNS. Under these conditions, the activity of SOD, CAT, GSH-Px, and other antioxidants is inhibited and the antioxidant enzyme level in islet β cells is decreased, which resulted in the defect of repairing DNA after oxidative damage ROS can directly damage islet β cells, promote apoptosis, and affect the insulin signal transduction pathway, indirectly inhibiting islet β cell function. The flavonoids, polysaccharides, and glycosides in TCMs can enhance antioxidant enzyme activity, reduce peroxide accumulation, block the protein kinase C signaling pathway and cytokine activity, and repair OS damage in islet β cells. Cordyceps sinensis (CS) [40] can decrease NO and ROS production, reduce Ca²⁺ concentration, and enhance the expression of UCP-2 protein in islet cells damaged by IL-1β, effectively scavenge free radicals, and reduce oxidative damage. Puerarin [41] reduces the MDA content, increases SOD activity, reduces serum levels of PGE₂, ET, H₂O₂, and NO, and inhibits the mRNA and protein expression of ICAM-1, NOX2, and NOX4. Salidroside [42] can down-regulate TXNIP mRNA and upregulate TRX mRNA levels, resulting in low ROS levels. Total flavonoids of Lycium barbarum (TFLB) [36] can increase SOD and GSH levels and reduce MDA content. Anoectochilus roxburghii [43] can remove DPPH and ABTS, thereby reducing NO production, and the expression of iNOS, COX-2, and IL-1β reduces OS. Oleic acid [37] inhibits α-glucosidase activity, OS, and the inflammatory reaction. Cinnamonaldehyde [44] directly
increases the antioxidant enzyme activity of islet cells and reduces the production of free radicals. GA [45] can inhibit the production of ROS in INS-1 cells and alleviate OS. Many TCMs can exert their biological functions through the JNK signaling pathway to reduce oxidative stress. GinsenosideRb1 [46] inhibits the JNK signaling pathway, as well as JNK1 and c-Jun expression in STZ-induced diabetic rats, thereby resulting in negative regulation of the expression of the inflammatory molecules IL-6, IL-1β, and TNF-α, which reduces inflammation and OS damage. POP I [20] down-regulates the expression of the JNK1, P38, and ERK proteins in the JNK pathway and alleviates the damage induced by oxygen-free radicals. Crude Portulaca Oleracea L. Poly-saccharide (CPOP) [47], which is an antioxidant with an antidiabetic and anti-inflammatory effect, reduces MDA content and increases SOD activity in the diabetic rats. Mogroside [48] can significantly reduce the ROS content in NIT-1 cells, upregulate the expression of GLUT-2 and the pyruvate kinase gene, inhibit the activation of the JNK signal transduction pathway, and reverse the effect of Foxo1, which slows OS damage and protects islet secretion. Carcumin [49, 50] antagonistically binds to TLR-4 and prevents caspase-8 from activating apoptotic DNA fragments, reducing the number of cells affected by proinflammatory cytokines (such as GM-CSF, G-CSF, and IL-6), NK T cells, and macrophage infiltration. Administration of 4–8 g/kg of Polygonatum odoratum [51] can reduce interferon IFN-γ and IL-4 levels, inhibit inflammatory cell infiltration and the polarization of Th1 cells, and reduce the oxidation of islet β cells after stimulation.

5. Promotion of GLP-1 Secretion

GLP-1 is a peptide hormone secreted by intestinal L cells and acts on islet β cells to promote insulin gene transcription, increase insulin synthesis and secretion, stimulate the proliferation and differentiation of β cells, and inhibit β cell apoptosis. Several TCMs have been demonstrated to simulate GLP1 secretion. The active ingredients of Rhizoma copidis [52] can increase the secretion of GLP-1. In vivo and in vitro experiments on rats and STC-1 cell lines have demonstrated that emodin [53] promotes the secretion of GLP-1 by regulating PPARγ in a dose-dependent manner. The accumulation of ginsenosideRe [54] in the intestine inhibits the activity of α-glucosidase and promotes the secretion of GLP-1 by L cells as well as the secretion of glucagon.

6. Other Functions

The protective and regenerative effects of TCMs on islet β cells have been utilized in surgical transplantation. Li et al. found extract of trichosanthin [55] could slow reject reaction and protect the transplanted β cells when it was applied in transplantation cases. Serum containing Euonymus fortunei [56] can increase the insulin and GSH content of islet cells, protect the islet cell secretion function, increase the cell survival rate, and reduce ROS-induced islet cell damage before transplantation. Gastrodin (GAS) [57] regulates Nrf2, affects mitochondrial dysfunction, and exhibits antioxidant, anti-inflammatory, and antiapoptotic effects in response to redox damage. Gastrodia elata Blume (GEB) water extract [58] dose-dependently improved hypothalamic insulin signaling, enhanced systemic insulin sensitivity during a euglycemic hyperinsulenic clamp, and increased insulin secretion under high glucose stimulation. Tangminling (TML) pills [59] mainly contain Rhizoma copidis, Rheum officinale Baill, Scutellaria baicalensis Georgi, and Bupleurum chinense DC and might improve β cell function in T2DM patients. Tianmai Xiaoke Pian (TMLKP) [60] is composed of Tian-huafen, Maidong, and Wuwei and could improve ischemia-reperfusion through the PI3K/AKT pathway.

7. Outlook

Type 2 diabetes is characterized by hyperglycaemia due to insulin resistance in peripheral tissues and a defect of β cell function. Many factors have been implicated in β cell dysfunction in T2DM. Traditional Chinese medicine (TCM) has been implicated in practical use in China for thousands of years and has accumulated substantial front-line experience in treating T2DM. In this review, we have highlighted the mechanism of TCMs in protecting β cell function. The current research is mainly focused on improving insulin secretion of β cell, promoting islet cell proliferation, reducing OS damage, and inhibiting apoptosis. The list of the TCM and their role in protective β cell are summarized in Table 1. It is of note that the effects of TCMs on β cell function are mainly evaluated in cellular and rodent models. Whether the effectiveness of improvement of islet β cell function of TCM is shown in animal studies remains unclear. Clinical data are required to access their efficacy and side effects on patients in the future.

In summary, though great efforts are still needed to better understand its mechanisms and clinical relevance, TCM possesses great potential as a vast and readily available source for finding and developing new drugs to treat T2DM. In this review, we have highlighted the mechanism of TCMs in protecting β cell function. The current research is mainly focused on improving insulin secretion of β cell, promoting islet cell proliferation, reducing OS damage, and inhibiting apoptosis. The list of the TCM and their role in protective β cell are summarized in Table 1. It is of note that the effects of TCMs on β cell function are mainly evaluated in cellular and rodent models. Whether the effectiveness of improvement of islet β cell function of TCM is shown in animal studies remains unclear. Clinical data are required to access their efficacy and side effects on patients in the future.

### Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| ABTS: | 2,2′-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) |
| ATP: | Adenosine triphosphate |
| ATG: | Arctigenin |
| Ber: | Berberine |
| CAT: | Catalase |
| cAMP: | Cyclic adenosine monophosphate |
| Caspase: | Cysteinyl aspartate specific protease |
| C-Blc2: | B-cell lymphoma-2 |
| COX-2: | Cyclooxygenase-2 |
| CPOP: | Crude Portulaca oleracea L. polysaccharide |
| CHM: | Chinese herbal medicines |
| CS: | Cordyceps sinensis |
| DPPH: | 1,1-diphenyl-2-picrylhydrazyl |
| ET: | Endothelin |
| ERK: | Extracellular regulated protein kinases |
| TCM                        | Functions                                                                 | Genes/proteins                                                                 | References |
|----------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------|
| Puerarin                   | Promotes β cell proliferation                                            | PDX-1↑                                                                          | [21]       |
|                            | Reduces islet OS damage                                                   | MDA↓, activity of SOD1, PGE2, ET, H2O2, NO levels↓, ICAM-1, NOX2, NOX4 mRNA, and protein expression↓ | [41]       |
| Oleanolic acid             | Reduces islet OS damage                                                  | α-glucosidase activity↓                                                        | [37]       |
| Ginsenoside Rg3            | Reduces β cell apoptosis                                                 | Phosphorylation of ERK and p38MAPK↑, P44/42MAPK↑                             | [30]       |
| Rg1                        | Reduces islet OS damage                                                  | SIL-2R↑, CD4/CD8 and NK cell activity↑, autophagy↑, caspase-39↑, Blc2↑        | [9]        |
| Rb1                        | Reduces islet OS damage                                                  | JNK pathway↑, JNK1 and c-Jun↑, IL-6, IL-1β, TNF-α↓                             | [46]       |
| Red ginseng                | Maintains the integrity of the islet structure                           | Islet size↑, insulin immunoreactivity↑, islet boundary was irregular, vacuolization↓ | [31]       |
|                            | Promotes the synthesis and secretion of insulin                          | PTP1BmRNA↑, PPARγ genes and PDX-1↑                                            | [9]        |
| Berberine                  | Reduces islet OS damage                                                  | ROS↓                                                                           | [45]       |
| Baicalein                  | Promotes the synthesis and secretion of insulin                          | β cell membrane K+ channel voltage-dependent current↑, intracellular Ca2+ concentration in β cell | [12]       |
| Resveratrol                | Promotes β cell proliferation                                            | Through cAMP-mediated mechanism                                               | [22]       |
| curcumin                   | Reduces islet OS damage                                                  | TLR-4↑, caspase-8↑, GM-CSF, G-CSF, IL-6↓, T cell, NK cell↓                     | [49], [50] |
| Resveratrol and curcumin   | Promotes the synthesis and secretion of insulin                          | Regulate the expression and activity of PDEs, cAMP level↑                      | [13]       |
| POP I                      | Promotes β cell proliferation                                            | JNK↑, PDX-1, PPARγ, ERK↑                                                      | [20]       |
| CPOP                       | Reduces islet OS damage                                                  | MDA content and SOD activity↑                                                 | [47]       |
| Salidroside                | Promotes β cell proliferation                                            | Insulin, Pdx-1, GLP-1r mRNA↑, IL-1β level↑                                    | [42]       |
| TWP                        | Reduces OS damage                                                        | TXNIP m RNA↓, TRX m RNA↑, ROS↓                                                | [42]       |
| SC2                        | Induces stem cell differentiation into β cells                           | Stem cell —→ the cell which expression of β cell functional proteins          | [24]       |
| Artemisinin                | Induces islet α cells into β cells                                       | Stem cell —→ new insulin-secreting cells                                       | [26]       |
|                            | Reduces β cell apoptosis                                                 | GABA signaling↑, ARX transport from the nucleus to the cytoplasm↑, ARX from chromatin↑, α cell secreting glucagon↑, α — β cell | [29]       |
| PNS                        | Reduces islet OS damage                                                  | mir-181b, caspase-3, Bcl-2↑, activation of PI3K- Akt-mTOR pathway↑, Beclin1, LC3-II↑ | [32]       |
| cortex mori radicis        | Reduces β cell apoptosis                                                 | PI3K/Akt↑, caspase-3↑, Bcl-2↑, Bax↑                                            | [33]       |
| Ophiopogonis radix         | Reduces islet OS damage                                                  | NO production↑, ROS activity↑, Ca2+ concentration↑, UCP-2↑                     | [40]       |
|                            |                                                                          | SOD, GSH↑, MDA↓                                                               | [36]       |
| CS                         | Reduces islet OS damage                                                  | DPPH, ABTS↓, NO↓, iNOS, COX-2, IL-1β↓                                       | [43]       |
| TFLB                       |                                                                          | The antioxidant enzyme activity↑, free radicals↑                             | [44]       |
| Anoectochilus roxburghii   | Reduces islet OS damage                                                  | ROS↑[GLUT-2, pyruvate kinase gene], JNK signal transduction pathway↑, FOXO1↑ | [48]       |
| Cinnamaldehyde             |                                                                          | IFN-γ, IL-4↓ inflammatory cell infiltration↑, the polarization of T helper cell | [51]       |
| Mogroside                  |                                                                          | PPARγ, GLP-1↑                                                                | [53]       |
| Polygonatum odoratum       |                                                                          | Slow the rejection and protect the transplanted β cells                       | [55]       |
| Emoidin                    | Promotes GLP-1 secretion                                                | Cell survival rate↑, ROS induced islet cell damage before transplantation↑    | [56]       |
| Trichosanthis              | Cell transplantation protection                                         | Hypothalamic insulin signaling↑, systemic insulin sensitivity↑                 | [58]       |
| Euonymus fortunei          | Improving insulin resistance                                            |                                                                        |            |
| GEB                        |                                                                          |                                                                        |            |
ConflictsofInterest

Theauthorsdeclarethattheyhavenoconflictsofinterest.
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