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Review Article

Research progress on the regulatory effects of Chinese food and medicine homology on type 1 diabetes mellitus

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Abstract: Type 1 diabetes mellitus (T1DM) is an autoimmune disease targeting pancreatic β-cells, where infiltration and attack by T-cells and other immune cells lead to β-cell destruction and subsequent insulin deficiency. The precise etiology of T1DM remains unidentified. Current research has yielded various anti-T1DM drugs for clinical use, such as ultra-long-acting basal insulin and ultra-rapid-acting insulin. However, these medications often cause undesirable side effects, necessitating the exploration of safer alternatives. Notably, Chinese botanicals and medicinal equivalents offer advantages including wide availability, safety, and biological activity, facilitating natural screening for anti-T1DM agents. This study examines select food and medicine homologs known for their anti-T1DM properties—*Astragalus*, *Ganoderma lucidum*, honey, ginger, *Curcuma longa*, mulberry, and *Cornus officinalis*—and reviews their effects on T1DM, focusing on immunomodulation and other pathways.

Keywords: Chinese food and medicine homology; type 1 diabetes mellitus; effects; application

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1 Introduction

Diabetes mellitus (DM) is a complex, chronic systemic disease characterized by metabolic disorders such as hyperglycemia, hyperinsulinemia, and hypertriglyceridemia[1]. It manifests primarily in two forms: T1DM and Type 2 diabetes mellitus (T2DM). Additionally, diabetes can occur during pregnancy and due to various conditions including drug toxicity, genetic disorders, endocrine disorders, insulin receptor abnormalities, and exocrine pancreatic disorders[2]. In 2021, the global prevalence of diabetes was 6.1%, with an estimated 529 million affected individuals worldwide. T2DM accounted for 96.0% of all diabetes cases in 2021, and projections suggest that by 2050, over 1.31 billion people will have diabetes[3]. T1DM constitutes approximately 5-10% of all diabetes cases[4]. Despite differences in diabetes type, individuals with T1DM experience higher healthcare costs and income loss compared to those with T2DM. T1DM (**Table 1**) is characterized by inflammation and autoimmunity, involving infiltration of self-reactive T lymphocytes and subsequent production of pro-inflammatory cytokines and reactive oxygen species[5].

On November 17, 2023, the National Health Commission and State Administration for Market Regulation issued Announcement No. 9 of 2023, titled "Implementation of Traditional Food and Chinese Herbal Medicine Practices for Codonopsis and Other 9 Substances." This announcement prohibits the addition of medications to food products but permits the inclusion of substances traditionally used in both food and Chinese herbal medicine (referred to as food and medicine substances). This regulatory update aims to foster innovation within the food industry. Currently, there is a greater focus on T2DM research compared to T1DM, with many etiological factors of T1DM remaining unclear. Therefore, an overview of the impact of Chinese food and medicine homology on T1DM could serve as a valuable reference for future research in this area.

Currently, injectable therapies for T1DM include ultra-long-acting basal insulin and ultra-rapid-acting bolus insulin formulations[12]. Despite their effectiveness, these medications are associated with adverse side effects and necessitate long-term treatment. Therefore, safer and more effective interventions are

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Table 1 Type 1 diabetes mellitus

	Type 1 diabetes mellitus	Ref.
Interpretation	T1DM also known as juvenile diabetes or insulin-dependent DM, is an autoimmune disease characterized by an abnormal immune response targeting pancreatic β-cells. This results in the loss of their insulin-producing function, leading to hyperglycemia and disturbances in glucose metabolism.	[6]
Standard criteria	The goal for patients with T1DM is to maintain blood glucose levels within a target range of 70-180 mg/dL. Values below 70 mg/dL are categorized as hypoglycemia (i.e., "low"), while values below 54 mg/dL indicate severe, clinically significant hypoglycemia. Conversely, values above 180 mg/dL are classified as hyperglycemia (i.e., "high").	[7]
Features	The classical triad of weight loss, polyuria and polydipsia, to ketoacidosis	[8]
Pathogenesis	Environmental factors, such as viral infections (including enteroviruses, rubella, mumps, rotavirus, parvovirus, and cytomegalovirus), genetic susceptibility (e.g., specific HLA DR/DQ alleles), and immunodeficiency	[9, 10]
Therapies	A new basal long-acting insulin analog, insulin glargine 300 U/mL (Toujeo®), and two new ultra-rapid acting analogs, faster aspart 100 U/mL (Fiasp®) and ultra-rapid lispro (Lyumjev®), have been developed and approved for the pediatric population. Additionally, an inhaled insulin formulation, technosphere insulin (Afrezza®), has been approved for adult use. Adjuvant pharmacotherapy options include pramlintide, Glucagon-like peptide-1 (GLP-1) analogs, and SGLT2 inhibitors.	[11]

needed. Natural medicines offer a promising alternative due to their safer profiles and fewer side effects, making them suitable for widespread use at appropriate doses. Remarkably, Chinese food and medicine homology have demonstrated significant efficacy in treating diabetes, particularly T1DM. For instance, Chen *et al.*[13] discovered that Formononetin binds directly to Keap1, activating the Keap1/Nrf2 signaling pathway. This activation leads to the upregulation of HO-1 and NQO1 expression, mitigating intracellular reactive oxygen species (ROS) overproduction, thereby attenuating ALX-s-induced damage in MIN6 cells and ameliorating ALX-stimulated T1DM. Additionally, Abdulrhman *et al.*[14] proposed honey as a potential therapeutic agent due to its stimulatory effects on diseased β-cells, suggesting it for future trials targeting pancreatic β-cells. Furthermore, Hassan *et al.*[15] demonstrated that aqueous cinnamon bark extracts exhibit strong hypolipidemic activity and contribute to glucose homeostasis in diabetic animals. Lee *et al.*[16] found that mulberry extract protects pancreatic β-cells from H_2O_2-induced oxidative stress and associated apoptotic cell death by reducing DPPH free radicals, lipid peroxidation, and intracellular ROS accumulation, as well as inhibiting H_2O_2-induced DNA condensation or breakage, highlighting its potential in protecting β-cells from oxidative stress. Lastly, Sharp-Tawfik *et al.*[17] showed that *Cornus officinalis* enhances β-cells viability and oxidative capacity, potentially via Nuclear factor of activated T cells, cytoplasmic 2 (NFATC2)-mediated pathways, suggesting its role in enhancing β-cells energy metabolism, proliferation, and endocrine functions (**Fig. 1**).

In recent years, natural polysaccharides, polyphenols, and flavonoids have garnered significant attention for their potential health benefits, including their anti-type 1 diabetes properties. Analysis of publication trends from the Web of Science indicates a notable increase in research on "T1DM and polysaccharides" since 2018, with substantial growth observed over the past five years (2016-2020) (**Fig. 2A**). Similarly, "T1DM and polyphenols" has shown a steady rise in publications (**Fig. 2B**), while "T1DM and flavonoids" has demonstrated a modest increasing trend (**Fig. 2C**). These findings underscore the promising role of natural polysaccharides, polyphenols, and flavonoids in T1DM treatment. Through a systematic search on the Web of Science, this review identifies *Astragalus*, *Ganoderma lucidum*, honey, ginger, *Curcuma longa*, mulberry, and *Cronus officinalis* as the most extensively studied medicinal substances in this context. Building on this foundation, we discuss the therapeutic effects of 20 representative medicinal foods for managing T1DM, aiming to contribute to the development of effective treatment strategies for this condition.

2 Pathogenesis of T1DM

T1DM is a chronic autoimmune disease characterised by the

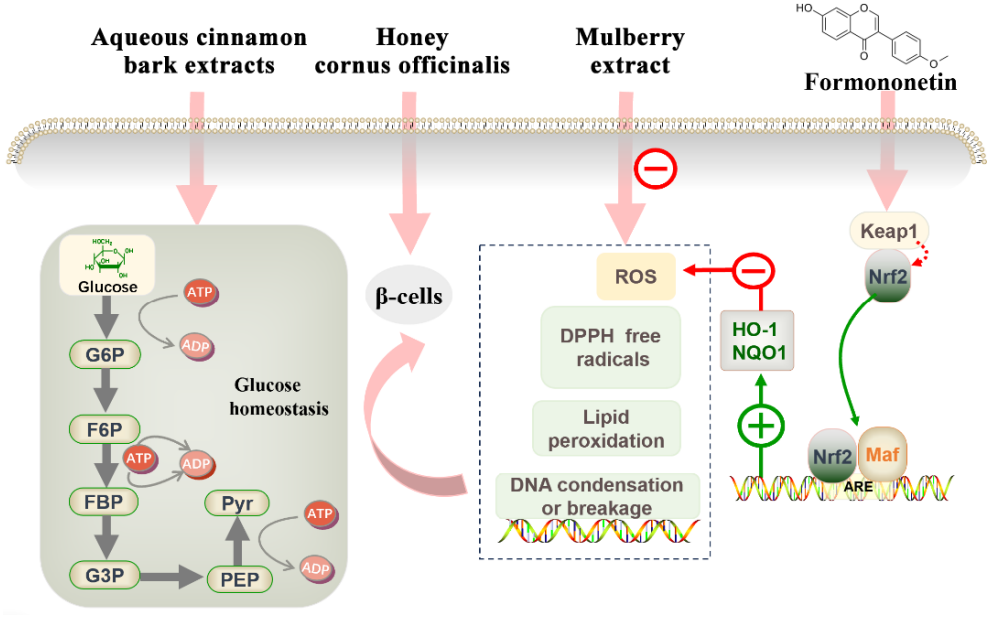


Figure 1 Effects of the five kinds of food and medicine homology on type 1 diabetes mellitus.

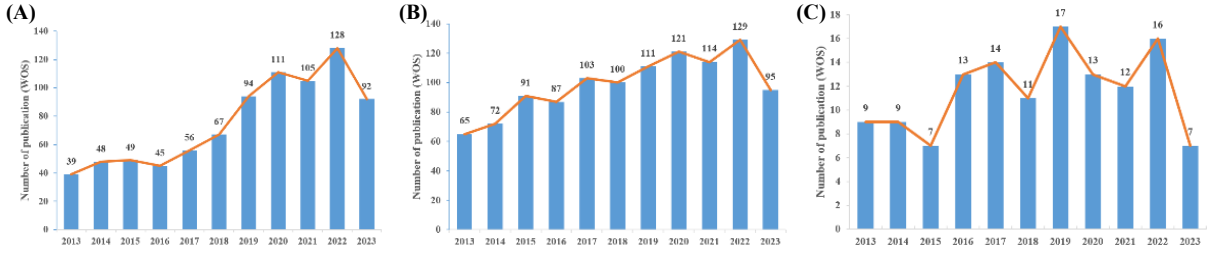


Figure 2 Number of publications on T1DM and active compounds of natural origin (indexed by Web of Science) (A) Number of publications on "T1DM and polysaccharides", 2013-2023 (B) Number of publications on "T1DM and polyphenols", 2013-2023 (C) Number of publications on "T1DM and flavonoids", 2013-2023.

progressive and insidious destruction of β cells. This condition results from a breakdown in the immune system, primarily mediated by T helper 1 (Th1) cells. The process involves the activation and infiltration of immune cells into the islets, which collectively destroy pancreatic β cells and lead to overt hyperglycemia[18]. The discovery of insulin in 1922 marked a significant milestone in diabetes treatment, catalyzing profound advancements in understanding T1DM pathogenesis and the development of sophisticated methods for managing glucose homeostasis in patients[19]. The pathogenesis of T1DM is primarily categorized into two main areas:

2.1 Genetic susceptibility

Polymorphisms in the HLA regions of the major histocompatibility complex (MHC) largely determine the genetic risk of developing T1DM[20]. Alleles at the HLA-DR and HLA-DQ class II loci are the most significant genetic risk factors[21]. The most common HLA haplotypes associated with T1DM are DR3-DQ2 and DR4-DQ8, found in up to 90% of individuals with the condition[22]. The *DRB1*1501-DQA1*0102-DQB1*0602* haplotype, present in approximately 20% of the population but only 1% of patients with T1DM, provides dominant protection against the disease[23]. The most critical genes are located within the MHC HLA class II region on chromosome 6p21, which accounts for about 45% of the genetic susceptibility to T1DM[24]. Hornum and Markholst *et al.*[25] identified eight genes implicated in the etiology of T1DM: Vitamin D receptor (*VDR*), *IL6*, *IL12B*, *AIRE*, *FOXP3*, *B2m*, *Cblb*, and *Lyp/Ian4L1*. The relationship of these genes to the pathogenesis of T1DM is discussed. For instance, the VDR gene, located on chromosome 12q12-14, is associated with immune regulation, prevention of regulatory T cell activation, suppression of autoimmunity, and polymorphisms linked to insulin secretion by β-cells, suggesting VDR's role as a diabetes susceptibility gene. Thus, T1DM is influenced by genetic susceptibility, with different populations and individuals exhibiting varying genetic predispositions, potentially contributing to susceptibility to polygenic diseases under environmental influences.

2.2 Environmental factors

Environmental risk factors may trigger autoimmune processes that lead to β-cells destruction and the onset of T1DM in genetically predisposed individuals. These factors include dietary compounds (e.g., cow's milk, vegetable proteins, nitrates, wheat gluten) and viruses (e.g., coxsackie B viruses, rubella viruses, cytomegaloviruses, and retroviruses)[23]. Human β-cells, particularly those in the coxsackievirus B family, are susceptible to infection, which can result in a dramatic reduction in glucose-induced insulin secretion[26]. Additionally, the consumption of cow's milk, especially through cow's milk-based infant formula, has been suggested as a potential risk factor for the development of insulin-dependent T1DM. Cow's milk contains various components, including α-casein, β-casein, β-lactoglobulin, γ-casein, α-lactalbumin, gammaglobulin, albumin, and hormonal constituents such as insulin, macrophage colony-stimulating factor (M-CSF), and transforming growth factor-β1 (TGF-β). Notably, some studies have found that patients with recent-onset T1DM exhibit a higher degree of humoral and cellular immune responses to milk components compared to controls[27]. Ororan *et al.*[28] reported a case of a patient with late-onset T1DM who initially managed the condition on a very low-carbohydrate diet with complete avoidance of insulin therapy for 18 months, followed by tight glycemic control with minimal insulin doses. This approach resulted in some improvement and temporary alleviation of glycemic status. Moreover, wheat proteins may contribute to enteropathy, where accumulated peptides and proteins on the intestinal surface trigger a primary inflammatory response. Additionally, protein flavor receptors in meat and fish can cause elevated insulin release from β-cells in response to food-derived amino acids and peptides. Exotic fruits, such as pineapple, papaya, bananas, kiwi, mango, and grapes, contain high levels of fructose, which has been linked to increased inflammatory responses[29]. Thus, numerous environmental risk factors influence the mechanisms of T1DM through various pathways, including β-cells destruction and heightened inflammatory responses.

3 Effects of food and medicine homology on type 1 diabetes mellitus

In 2023, the Chinese Health Commission and the General Administration of Market Supervision jointly issued an announcement. Currently, three batches of lists detailing food and medicinal substances have been published, encompassing a total of 102 substances[30]. Using the Web of Science, 20 of these substances were identified as having effects on T1DM, as shown in **Table 2**.

Active ingredients, including polysaccharides, polyphenols, and flavonoids, and others., were extracted from food and medicinal sources (**Fig. 3**)[31-34]. Various animal and cellular models were employed to evaluate how these ingredients impact T1DM through mechanisms such as immunomodulation, enzyme and protein activity, gene expression, and signaling pathways. For example, Astragalus polysaccharides (APS) protect pancreatic cells from autoimmune-induced cell death by modulating several inflammatory and apoptotic cytokines. APS has demonstrated potential to modulate T helper cells 1 and 2, reduce inflammatory responses, enhance antioxidant activity, and protect pancreatic cells from apoptosis (**Table 2**)[31].

Table 2 Modulation of T1DM by food and medicine homology

	Food and medicine homology	Active ingredient	Model	Dosage	Index	Modulating effect	Ref.
1	Clove	Clove essential oil (CEO)	Male Sprague-Dawley (SD) rats	20 mg/kg body weight (BW), 2 months	Blood glucose↓, total cholesterol (TC)↓, xanthine oxidase↓, lipid peroxides↓, thiols groups↓, Inducible nitric oxide synthase (iNOS) expression↓	Enzymatic activity: a potent α-amylase inhibitor gene expression level: prevent iNOS-mediated nitrosative stress	[35]
		Clove flower extract (CFE)	Male adult mature albino rats (Rattus norvegicus)	A 100 g gel (20 mg/mL of either CFE or the antibiotic cefepime), one time every day, 2 weeks	Improved wound size, wound index, mRNA expression of the wound healing markers, growth factor signaling pathways, inflammatory cytokine expression, as well as anti-inflammatory cytokines, as well as an antiapoptotic one.	Inhibit distinctively the P. mirabilis bacterium obtained.	[32]
2	Purslane	Plant-derived oleanolic acid (OA) and maslinic acid (MA)	Male SD rats	OA/MA (80 mg/kg), 5 weeks	Food intake↓, blood glucose↓, gastrointestinal ghrelin expression↓	The reduction of ghrelin expression	[36]
		Oil extracts of purslane seeds	Male SD rats	250 mg/kg/d, 42 consecutive days	Ameliorated the BW loss, fasting blood glucose(FBG), urine volume, serum creatinine, uric acid, blood urea nitrogen; ROS accumulation↓, lipid peroxidation↓	SDF-1/IL10/PPARγ–mediated tuning of keap1/Nrf2 and NF-κB transcription	[37]
		Portulaca oleracea (PO)	Male Wistar rats	100, 300 mg/kg/d, 8 weeks	Malondialdehyde (MDA)↑, TGF-β1↑, tumor necrosis factor-α (TNF-α)↑, the seminiferous tubules diameter↓, sperm count and motility↓, LH↓, testosterone↓, total thiol↓, vascular endothelial growth factor (VEGF)↓, superoxide dismutase (SOD) activity↓	(1)The decreasing of blood glucose level and testicular tissue damage (2)The improvement of inflammatory factors (3)The modulation of sex hormones level and fertility potential	[38]
3	Glycyrrhizic	Glycyrrhizic acid (GA)	Male SD rats	0, 50, 100, 150 mg/kg, 2 weeks	Plasma GLP-1↑	Increase glucagon like peptide-1 secretion via TGR5 activation in type 1-like diabetic rats	[39]
4	Cinnamon	Cinnamon extract (CE)	Male Wistar rats	3, 30, 100 mg/kg/d, 22 days	Uncoupling protein-1 (UCP-1)↑, glucose transporters (GLUT)↑	1) Upregulation of mitochondrial UCP-1 2) Enhance translocation of GLUT4 in the muscle and adipose tissues	[40]
		Cinnamomum zeylanicum aqueous bark extract	Male Wistar rats	200 mg/kg, 15 days	TC ↓, triglyceride (TG)↓, low-density lipoprotein (LDL)↓, very low-density lipoprotein (VLDL)↓, high-density lipoprotein (HDL)↑, tissue glycogen↑ improve differential regulation and expression of glucose homeostatic enzymes, glucokinase (GK), glucose-6-phosphatase (G6Pase), phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphate dehydrogenase (G-6PDH), Ins II	Improve the process of glycogenesis in liver	[15]
		The combinatorial extract of Nigella sativa & cinnamomum cassia's (NSCCe)	Male Wistar rats	100, 200 mg/kg, 28 days	Normalized plasma glucose levels, lipid profile and kidney function parameters	Better Half maximal inhibitory concentration (IC_{50}) values, and better inhibition of α-glucosidase; enhance glucose and lipid control, reverse pancreatic cell damage	[41]
5	Sea Buckthorn	A blueberry and sea buckthorn concentrate with a complex composition	Children ages 8 to 17	3×1 comprimates/day, 2 months	Blood glucose level↓, HbA1C↓, C peptide concentration↑, antioxidant enzymes activities↑	Increase antioxidant activity	[42]

(Continued)

	Food and medicine homology	Active ingredient	Model	Dosage	Index	Modulating effect	Ref.
6	Zingiber	6-shogaol	Male C57BL/6J mice	5, 10 mg/kg BW, 2 weeks	Blood glucose↓, BW↓, alanine aminotransferase (ALT)↓, aspartate transaminase (AST)↓, TNF-α↓, TGF-β1↓, mRNA expression↓	Decrease expression of ki-67, cell proliferation related protein, in addition proapoptotic protein caspase3 expression reverse normal condition level	[43]
		Curcuma longa	Male rabbits	2 g/kg BW, 8 days	Serum glucose↑, serum transaminases↑, antioxidant activity↑,	As antidiabetic, hepatoprotective and antioxidant	[44]
		Zingiber officinale	SD male rats	4 mL/kg, 6 weeks	serum cholesterol↓, serum triglyceride↓, blood pressure↓	Serum cholesterol, serum triglyceride and blood pressure	[45]
7	Mulberry Leaf	Mulberry Leaf Extract	Male Kunming (KM)	300, 600, 1,200 mg/kg/d, 42 days	Blood glucose↓, MDA↓, blood urea nitrogen (BUN)↑, CHO↑, Lactate dehydrogenase (LDH)↓, β2-microglobulin (β-2-MG)↓, MDA↓	Improve glucose and lipid metabolism, enhance scavenging of ROS, and reduce the oxidative damage of free radicals on islet β-cells, promote the repair and proliferation of islet β-cells	[46]
8	Mulberry	Mulberry extract (ME)	The MIN6N pancreatic β-cells	0-500 μg/mL, 0-24 h	1, 1-diphenyl-2-picryl-hydrazyl radical (DPPH) radicals↓, radicals↓, DNA condensation and/or fragmentation↓	Protect pancreatic β-cells against hydrogen peroxide-induced oxidative stress	[16]
		MeOH extracts from mulberries	INS-1 cell line, immortalized rat pancreatic islet beta cells,	0-100 μM, 0-24 h	ROS↓, apoptosis rate↓	Prevent STZ-induced apoptotic pancreatic β-cells death via the inhibition of the caspase signaling pathway and induction of Bcl-2 protein expression	[47]
		mulberry extracts	MIN6N pancreatic β-cells	10-500 μg/ml, 0-48 h	DPPH↓, β-cells death↓, lipid peroxidation↓, DNA fragmentation↓, ROS↓	Protect pancreatic β-cells against oxidate stress induced by Hydrogen peroxide (H_2O_2) by limiting ROS production	[48]
		Resveratrol	Wistar male rats	10, 20 mg/kg, 4 weeks	SOD↑, Catalase (CAT)↑, GPx↑, thoracic outlet syndrome (TOS)↓, TAR↑, TOS/TAR↑, AOPP↑	Antioxidative properties, diminish oxidative stress in lenses of individuals suffering	[49]
9	Inulin	Cichorium glandulosum seeds n-buOH fraction (CGSB)	Male KM mice	100 mg/kg, 2 weeks	Plasma insulin↑, TG↓, free fatty acids in adipose tissue and liver↓	Antioxidant mechanisms repair damaged beta cells, α-glucosidase inhibiting activity, accommodate the mRNA level of PPAR-α to intervene with glucolipid metabolism	[50]
		Inulintype fructans (ITFs)	Female NOD/LtJ mice	5% (wt/wt) ITF(l), ITF(s), 24 weeks	$CD25^+Foxp3^+CD4^+$ regulatory T cells↑, $IL17A^+CD4^+$ Th17 cells↓, cytokine↓, protein 3 caspase-1-p20-IL-1βinflammasome↓, occludin↑, claudin-2↑, antimicrobial peptides -defensin-1↑, cathelicidin-related antimicrobial peptide as well as short-chain fatty acid production↑	ITF(l) but not ITF(s) delays the development of T1D via modulation of gut-pancreatic immunity, barrier function, and microbiota homeostasis.	[51]
10	Lobed Kudzuvine Root	Puerarin	Male SD rats	100 mg/kg/d, 8 weeks	Firmicutes/Bacteroidetes ratio↑ Muscle strength↑, weight↑, skeletal muscle cross-sectional areas↑, expressions of several muscle wasting marker genes↓, Akt/mTOR↑, LC3/p62↓	Akt/mTOR activation and autophagy inhibition	[52]
11	Honey	Bee Honey Extract	Male Swiss albino mice	2 mg/kg BW, 7 days	BW↑, liver glycogen levels↑, MMP-9↓, TIMP-1↑, BGLs↓	Improve the antioxidant activities of pancreatic tissue, completely restored islet cells	[53]
		H-RJ	Male SD rats	100 mg/kg BW, 28 days	VLDL-C↓, TG↓	Phenolic compounds such as flavonoids are potent antioxidants	[54]

(Continued)

	Food and medicine homology	Active ingredient	Model	Dosage	Index	Modulating effect	Ref.
		Honey	Patients	77.3 g sugars /100 g of the honey, 2 h	GI and PII↓, C-peptide↑	Stimulatory effect on diseased beta cells	[14]
		Honey	SD rats	0.3-0.9 mL/kg, 4 weeks	Blood glucose↓, HbA1c↓, total cholesterol↓, LDL↓, VLDL↓, triglycerides↓	Possess cholesterol-reducing activity, vasodilative and hypotensive activities, and activity against tumor formation	[55]
		Honey	Patients	Amount = weight of subject in kg × 1.75 with a maximum of 75 g, 2 h	GI and PII↓, C-peptide↑	Anti-inflammatory, anti-oxidant and anti-microbial effects	[56]
12	Fu-Pen-Zi	Fu-Pen-Zi fruit extracts	C57BL/6 male mice	30 mg/kg BW, 18 days	BW↓, hyperglycemia↓, hyperlipidemia↓, skeletal muscle atrophy↓, liver oxidative stress↓, steatosis↓, Atrogin-1↓, Trim63↓	Glucose tolerance, modulate liver glycogen metabolism, inhibit hepatic gluconeogenesis via activating insulin/Akt/Gsk3β and LKB1/AMPK signaling	[57]
		Raspberry pulp polysaccharide (RPP)	Male SD rats	300, 600 mg/kg, 20 days	Blood glucose↓, CD4↓, CD8↓, TNF-α↓, IFN-γ↓, IL-2↓, IgA↓, IgE↓, IgG↓, IgM↓, SOD↑, GSH-Px↑, MDA↓, improve the damage of islet β-cells	The metabolic function of pancreas is maintained by alleviating immune response and oxidative stress to improve the damage of islet beta cells	[58]
13	*Angelica*	Angelica Injection	Male SD rats	100% and 50% of angelica injection, 4 weeks	TFL↑, Motor nerve conduction velocity (MNCV)↑, morphology of sciatic nerve↑, myelinated nerve fiber density↑, the expressions of NGF and Brain derived neurotrophic factor (BDNF) in soleus and sciatic nerve↑,	Direct increase in NGF expression and direct or indirect increase in BDNF expression	[59]
		Danggui buxue tang (DBT)	Wistar rats	3.6 g/kg/day, 8 weeks	Blood glucose↓, triglycerides↓, cholesterol↓, β_2−microglobulin↑, albumin↑, triglyceride↓, cholesterol↓, high−density lipoprotein−cholesterol↑	Suppress transforming growth factor−β_1 mRNA expression.	[60]
		Curcumin	MIN6 cells	20 μM, 1 h	ROS↓, protein kinase↓, activate Silent information regulator 1 (SIRT1)↓, C/EBP homology protein (CHOP)↓,	Inhibit the PERK-CHOP pathway of ER stress mediated by SIRT1	[61]
		Chotosan	Wistar rats	1 g/kg/day, 3-7 days	Restored spatial working memory and hippocampal LTD; NR2B↑,	Modulate NMDA-receptor subunit expression	[62]
14	*Curcuma Longa*	Curcumin	Male C57BL/6 J mice	1,500 mg/kg/day, 2 weeks	BW↓, skeletal muscle weight↓, cellular cross-sectional area of the skeletal muscle↓, ubiquitination of protein↓, muscle-specific ubiquitin E3 ligase atrogin-1/MAFbx and MuRF1↓, nuclear factor-κB activation↓, concentrations of the inflammatory cytokines tumour necrosis factor-α↓, interleukin-1β↓, oxidative stress↓	Inhibit protein ubiquitination	[63]
		Curcumin analog JM-2	Male C57BL/6 mice	10 mg/kg, 8 weeks	NF-κB↓, the proinflammatory factors and macrophage infiltration↓	Inhibit the NF-κB pathway	[33]
		curcumin	Male Wistar rats	80, 130 mg/kg, 60 days	The values of creatinine↓, uric acid↓, and urea in urine↓, normalized to the normal level, kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) genes↓	Improve oxidative toxic stress in the kidney tissues	[4]

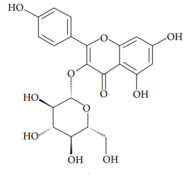
(Continued)

	Food and medicine homology	Active ingredient	Model	Dosage	Index	Modulating effect	Ref.
15	*Cistanche Salsa*	Salidroside (SAL)	Male mice	25, 50, 100 mg/kg, 10 weeks	ROS↓, MDA↓ SOD↑, CAT↑, GSH↑, the fluorescence expressions of p38 MAPK phosphorylation↓, the protein expressions of ZO-1↓, Occludin↑, Claudin-11 and N-cadherin↑	Inhibit oxidative stress mediated blood-testis barrier damage	[64]
16	*Astragalus*	Astragalus polysaccharide	Male C57BL/6 mice	100, 200, 400 mg/kg, 30 days	Islet inflammation↓, Blood insulin autoantibody↓, spleen cell proliferation of Con A↓, Th1 / Th2↓, PPARγ↑	Regulate humoral immunity and cellular immunity	[65]
		Astragalus Polysaccharide	Female NOD mice	2 g/kg, 10 weeks	Serum C-P level↓, $CD4^+/CD8^+$ ratio↓, IL-1β↓, IL-2↓, IL-6↓, IL-12↓, TNF-α↓, INF-γ↓, Fas↓, iNOS↓ IL-4↑, IL-5↑, IL-10↑, TGF-β↑, Bcl-2↑, SOD↑	Correct the imbalance between the Th1 / Th2 cytokines	[66]
		Astragalus polysaccharide	C57BL/6J male mice	100, 400 mg/kg BW/day, 15 days	Expression of galectin-1↑, the percentage of apoptotic $CD8^+$ T cells↓	Up-regulate the expression of galectin-1, resulting in the apoptosis of $CD8^+$ T cells	[67]
		Astragalus Polysaccharide	C57BL/6J male mice	100, 200, 400 mg/kg BW, 30 days	Blood glucose↓, serum insulin↑, β-cells mass↑, apoptotic β-cells percentage↓, Th1/Th2 cytokine ratio↓, PPARγ gene expression↑	Immunoregulatory actions on Th1/Th2 cytokine ratio, strongly associated with PPARg gene expression in spleens	[68]
		Astragalus polysaccharides combined with Crataegus flavonoids	Male NIH Swiss outbred mice	200 mg/kg/day, 4 weeks	The FBG↓, food and water intake↓, serum insulin levels↓, the protein expression levels of pancreatic and duodenal homeobox-1 and phosphorylated adenosine 5'-monophosphate-activated protein kinase in the pancreatic and liver tissue samples↑, the mRNA expression levels of neurogenin 3↑, v-maf musculoaponeurotic fibrosarcoma oncogene family↑, protein A and insulin↑ interleukin 6↓, tumor necrosis factor-α↓, chemokine ligand 2↓	A synergic antidiabetic effect, which may involve improvements in islet function and liver metabolism	[69]
		A *ganoderma atrum* polysaccharide (PSG-1)	Male KM mice	25, 50, 100 mg/kg BW, 4 weeks	Blood glucose↓, apoptosis of islet cells↓, IL-1β↓, TNF-α↓, INF-γ↓, the TLR4-dependent NF-κB signal pathway↓, the activities of anti-oxidant enzymes↑, the amount of MDA↓	Inhibit the mitochondrial apoptotic pathway and activate the PI3K/Akt signal pathway, PSG-1 specifically suppressed TLR4-dependent NF-κB pathway-mediated pancreas dysfunction	[70]
17	*Ganoderma Atrum*	rLZ-8	Male SD rats	0.05, 5 mg/kg, 3 months	Blood glucose↓, blood lipid↓, HbA1c↓, insulin secretion↑, TNF-α↓, IL-1β↓, IL-10↑, the number of regulatory T cells↑, Foxp3↑, restore balance between anti-inflammatory and inflammatory cytokines	Inhibit inflammation and enhance T cells generation	[71]
		Ganoderma lucidum polysaccharide (Gl-PS)	C57BL/6 male mice	10, 50, 250 mg/kg/day, 8 days	Mean perfusion rate↑, MnSOD nitration↓, MnSOD↑, glutathione peroxidase activities↑ the redox enzyme p66Shc expression↓	Suppression of cutaneous MnSOD nitration, p66Shc and mitochondrial oxidative stress.	[72]
		Ling zhi-8 (LZ-8)	Female NOD and DBA/2 mice	10.3-12.6 mg/kg BW, 38 weeks	$L3T4^+/Lyt\text{-}2^+$ ratio↑	Suppressor T cells are generated by the LZ-8 stimulation	[73]
18	*Cornus Officinalis* (CO)	CO extract	Female NOD/ShiLtJ mice	250 mg/mL, a volume of 200 μL, 15 weeks	Incidence and hyperglycemia↓, C-peptide↑, pancreatic insulitis↓	Preserve β-cells function by promoting β-cells viability	[74]

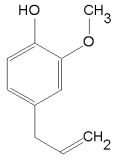
(Continued)

	Food and medicine homology	Active ingredient	Model	Dosage	Index	Modulating effect	Ref.
		CO	Human 1.1B4 pancreatic cells	500, 1,000 μg/mL, 24 h	Sequestosome-1/SQSTM1/p62↑, LC3-II↑, total p62↓	Promote highly protective mechanisms within pancreatic β-cells via both autophagy and the Keap1/Nrf2 pathways via the adaptor molecule of p62	[75]
		Morroniside	Bone marrow mesenchymal stem cell (BMSC)	0, 1, 10, 100, 1,000 μmol/L,	Reverses the Hyperglycaemia (HG)-impaired osteogenic differentiation, advanced glycation endproducts (AGEs)↓, bone loss↓, bone microarchitecture↑, Glyoxalase 1 (Glo1)↑, the receptor of advanced glycation endproducts (RAGE)↓	Attenuate HG-mediated BMSC dysfunction partly through the inhibition of AGE-RAGE signalling and activation of Glo1	[34]
		CO	Human 1.1B4 pancreatic β-cells	25-1,000 μg/mL, 24 h	β-cells death↓, cell viability and oxidative capacity↑, NFATC2↑	Increase the energy metabolism of β-cells while inducing the NFAT pathway to signal for increased proliferation and endocrine function	[17]
19	*Gastrodia Elata*	Fermented-*gastrodia elata* blume (FGE)	Normal male ICR mice	20, 100 mg/kg/day, 3 weeks	Oral glucose tolerance test (OGTT)↓, FBG↓, HbA1c↓, TC↓, TG↓, LDL-C↓, HDL-C↑, plasma insulin↑	The elevation of insulin production	[76]
20	*Eucommia Ulmoides*	Eucommia bark	The male Wistar rats	1 g/kg in a volume of 1.5 mL/kg distilled water, 20 days	The plasma levels of blood urea nitrogen and creatinine but also improved renal fibrosis↓, TGF-β↓, connective tissue growth factor↓, phosphorylation of Smad2/3↓	Inhibit TGF-β/Smad signaling and suppress TGF-β/connective tissue growth factor expression	[77]

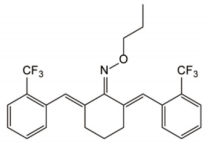
Notes: The symbols "↑" and "↓" are used to denote an increase and decrease, respectively.



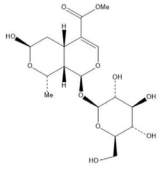
Astragalin (*Astragalus membranaceus*)



Eugenol (*Syzygium aromaticum*)



JM-2 (*Curcuma longa*)



Morroniside (*Cornus officinalis*)

Figure 3 Active ingredients were extracted from food and medicinal sources.

4 Application of food and medicine homology in type 1 diabetes mellitus

Food and medicine homology known for their hypoglycemic effects, enhanced immunomodulation, and antioxidant properties have a broad range of applications for managing T1DM through dietary interventions. These applications are primarily categorized into five areas: dietary supplements, antidiabetic alternative medicines, antidiabetic adjuvant medicines, functional health foods, and adjuvant treatments:

4.1 Dietary supplements: blueberry sea buckthorn concentrate

Polysaccharides exhibit a range of beneficial activities, including antioxidant, immunoregulatory, anticomplementary, anti-inflammatory, antifatigue, and hepatoprotective properties[78]. T1DM may be mitigated by activating the PI3K/Akt survival pathway, a mechanism that has been explored in various other diseases. For instance, polysaccharide-enriched fractions from the root of Radix Angelicae Sinensis has been shown to promote hematopoiesis and thrombopoiesis in mouse models, likely due to its anti-apoptotic effects, which are thought to involve the PI3K/Akt pathway[79]. Similarly, the combination of curcumin (CUR) and berberine (BBR) provided more effective protection against acetaminophen (APAP)-induced drug-induced liver injury (DILI) than did individual treatments. This protective mechanism appears to involve the alleviation of hepatic inflammation through the inhibition of NF-κB activation, potentially mediated by the PI3K/Akt and PPARγ signaling pathways (**Fig. 4**)[80]. In the context of Parkinson's disease (PD), APS protects neurons and stabilizes mitochondrial function by inhibiting ROS production and promoting autophagy via the PI3K/Akt/mTOR pathway[81]. Additionally, polyphenols, known for their anti-inflammatory and antioxidant properties[82], can alleviate T1DM by neutralizing ROS, a mechanism also studied in other diseases. For example, polyphenols exhibit neuroprotective effects in PD by clearing ROS and inhibiting oxidative stress and neuroinflammation[83]. Consequently, it is suggested that both food and medicine homologues may offer potential benefits in alleviating T1DM

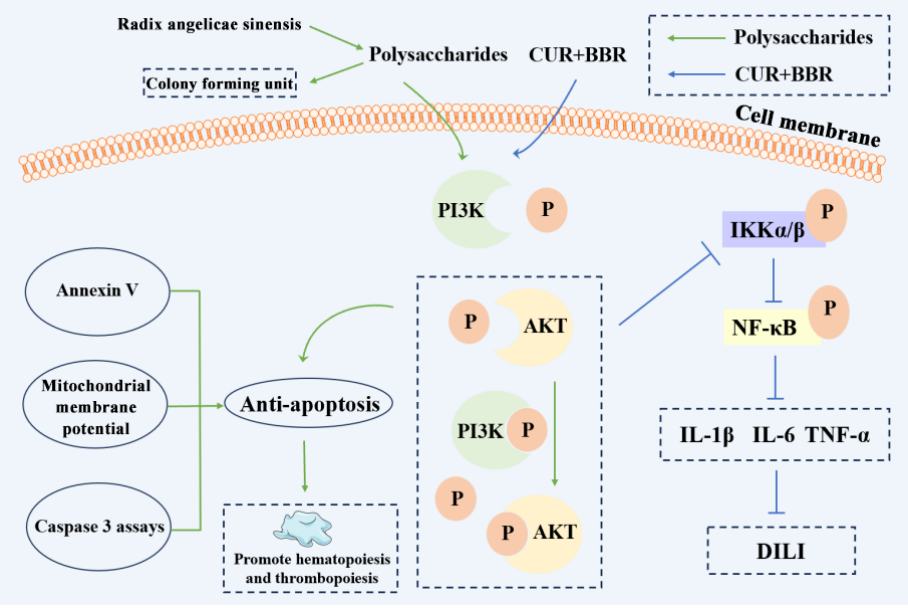


Figure 4 The potential PI3K/Akt signaling pathways involving Radix Angelicae Sinensis polysaccharides, CUR, and BBR.

through these mechanisms.

Concentrates, extracts, or combinations derived from food and medicinal homologues can serve as dietary supplements and effectively modify T1DM. For instance, Nemes-Nagy *et al.*[42] demonstrated that treatment with blueberry sea buckthorn concentrate, a dietary supplement, for two months improved antioxidant activity in children with T1DM. This product is well-tolerated and non-toxic, making it suitable for long-term use in diabetic patients and for precise insulin dose adjustments to manage hypoglycemia. It is considered one of the antidiabetic botanical agents. Li *et al.*[70] reported that PSG-1 significantly reduced apoptosis in pancreatic islet cells by inhibiting the mitochondrial apoptotic pathway and activating the PI3K/Akt survival pathway. Additionally, PSG-1 exhibits anti-inflammatory properties and maintains homeostasis in the redox system, suggesting its potential as an alternative dietary supplement for improving T1DM management. Furthermore, Dzydzan *et al.*[84] found that antioxidants, cyclic enol ether terpenes, and polyphenols in *Cornus officinalis* extracts can neutralize ROS and inhibit lipid peroxidation—factors that damage blood cell structures in DM—indicating their potential as therapeutic agents or dietary supplements.

4.2 Antidiabetic alternative medicines: honey-royal jelly (H-RJ) mixture

Antioxidants address chronic diseases linked to oxidative stress by scavenging free radicals. They play a crucial role in combating inflammation, cancer, diabetes, and aging, while also protecting against cardiovascular disease and obesity[85]. Studies have demonstrated that both food and pharmaceutical compounds can mitigate T1DM through this mechanism.

Homeopathic substances offer advantages such as naturalness, safety, and easy availability, making them a promising alternative to conventional antidiabetic drugs with fewer side effects than injectable medications. For instance, Nohair *et al.*[54] demonstrated that royal jelly-honey effectively controlled blood glucose levels in diabetic rats and also reduced blood lipids, specifically VLDL-C and TG. Royal jelly-honey can be considered both a nephroprotective and antioxidant agent, with the H-RJ mixture emerging as a promising antidiabetic alternative. Additionally, Yun *et al.*[86] found that curcumin induced epigenetic changes by modulating HDAC2 and HAT (p300) activity, which resulted in decreased NF-κB activation and reduced release of inflammatory cytokines. This study also revealed that curcumin affects chromatin remodeling under diabetic conditions. Future research is anticipated to explore curcumin as a potential treatment for chronic inflammation and complications associated with diabetes.

4.3 Antidiabetic adjuvant medicines: recombinant ling zhi-8

Treg cells exert their effects through intracellular and membrane factors, including cytokines. Both cell-to-cell contact, involving membrane molecules, and soluble factors, such as cytokines, are necessary for the inhibitory actions of Treg cells[87]. Research in other diseases has demonstrated that Treg cell immune regulatory mechanisms can alleviate conditions; for example, the Xin-Li formula mitigates heart failure induced by hyperlipidemia and myocardial infarction in rats through Treg cell immunomodulation and NLRP3 inflammasome inhibition[88]. Consequently, it is suggested that similar mechanisms may also alleviate T1DM.

Food and medicine homology are increasingly utilized as adjuvants in antidiabetic therapies to enhance immunomodulatory effects. For instance, Xiao *et al.*[71] demonstrated that recombinant ling zhi-8 (rLZ-8) lowers blood glucose levels and inhibits the secretion of pro-inflammatory cytokines. This effect is likely attributed to its ability to enhance Treg production, suggesting that rLZ-8 could be a valuable adjunct to current antidiabetic treatments. Additionally, Kaur *et al.*[41] found that Nigella sativa and Cinnamomum cassia exhibit significant antihyperglycemic effects and could serve as supplementary therapeutic agents alongside existing hypoglycemic drugs. Unlike other therapies, this combination has shown potential in counteracting immune dysfunction and protecting pancreatic islets. These findings support the consideration of Nigella sativa and Cinnamomum cassia as adjuncts in diabetes treatment regimens.

4.4 Functional health foods: mulberry leaves

The insulin signaling pathway plays a crucial role in maintaining both the number and function of pancreatic beta cells, which are the primary target cells of insulin. Dysregulation of insulin signal transduction in beta cells can result in impaired beta cell number and function[89]. T1DM can potentially be alleviated by promoting normal insulin secretion. For instance, studies have shown that resveratrol enhances glucose-stimulated insulin secretion in INS-1E beta cells and human islets via a SIRT1-dependent mechanism[90]. Consequently, it is suggested that similar food and medicine homologues may also alleviate T1DM through this mechanism.

Functional foods, including substances that are homologous to medicine, are not designed for direct treatment but offer specific nutritional and health benefits. They have the capacity to regulate bodily functions, enhance physical fitness, and potentially prevent T1DM. For instance, Zhang *et al.*[91] demonstrated that the leaves of Morus alba L. (called Sangye in Chinese, ML) are commonly used as functional foods, including beverages, noodles, and herbal teas, due to their biological and nutritional value. Additionally, ML-derived products, such as powders, extracts, and capsules, are widely consumed as dietary supplements for blood glucose and sugar regulation. Ny *et al.*[92] reported that astragalus positively impacts general health by reducing the risk of neurodegenerative diseases, T1DM, and cancer. It also improves disease management and mitigates side effects associated with food intake. Additionally, astragalus possesses acceptable organoleptic qualities and can enhance the overall quality of food products. Zhou *et al.*[93] found that the highest antioxidant and optimal hypoglycemic activities were observed in the CC60 fraction of the aqueous extract of astragalus membranaceus. The most rapid hypoglycemic effect occurred at a dose of 1000 mg/kg, suggesting that polysaccharides from this extract have potential for development as oral hypoglycemic agents.

4.5 Adjuvant treatments: turmeric supplementation

Chronic activation of inflammatory pathways plays a crucial role in the pathogenesis of insulin resistance[94]. This process has been investigated in relation to other diseases; for example, shikonin has been shown to inhibit eosinophilic expression, cytokine production, and regulate the ERK/NF-κB signaling pathway[95]. Consequently, it is suggested that similar food and medicine homologues may also help alleviate T1DM through these mechanisms.

Food and medicine homology can be utilized in the treatment of T1DM, offering notable benefits such as hypoglycemic and antioxidant effects. For instance, Erbas *et al.*[96] discovered that honey and fruit juices are more effective than prescription sugar in managing hypoglycemia and could be prioritized for treating hypoglycemic events in children and adolescents with T1DM. Sena-Júnior's study indicates that turmeric supplementation provides therapeutic benefits by enhancing glycemic and insulin sensitivity control and serving as a protective agent against inflammatory mediators. The combined use of turmeric and physical activity has demonstrated antioxidant, anti-inflammatory, and hypoglycemic effects, suggesting its potential as a treatment to improve the quality of life and survival of diabetic patients[97]. Lien *et al.*[98] observed a 33% reduction in the incidence of diabetic ketoacidosis among all users of Chinese medicine, with a 40% reduction in those who received Chinese medicine treatment for more than 180 days. This implies that combining Chinese and Western medicine treatments may decrease the risk of DKA in T1DM patients, with Traditional Chinese Medicine potentially having a significant positive impact on T1DM management. Additionally, Wang *et al.*[99] showed that glycosaminoglycanss (GAGs) ameliorated autoimmune T1DM by upregulating $CD4^+FoxP3^+$ and $CD8^+CD122^+PD\text{-}1^+$ regulatory T cells. GAG also synergized with cyclosporine A (CsA) to reverse Cyclosporine A-induced $CD4^+FoxP3^+$ Treg decline, further suppressing autoimmunity and T1DM, which underscores the clinical importance of TCM in treating T1DM.

5 Conclusions and prospects

T1DM is a prevalent condition, and researchers worldwide are actively seeking methods to prevent and treat it. Substances derived from Chinese food and medicine, which come from a variety of natural sources, have been reported to offer preventive and therapeutic benefits for T1DM. Notable examples include *Astragalus*, *Ganoderma lucidum*, honey, ginger, *Curcuma longa*, mulberry, mulberry leaves, and cornelian cherry. Potential mechanisms of these substances have been identified, such as the hypoglycemic and anti-apoptotic effects of PSG-1, which are mediated through the inhibition of the mitochondrial apoptotic pathway and activation of the PI3K/Akt signaling pathway. Additionally, PSG-1 specifically inhibits the TLR4-dependent NF-κB pathway, which helps mitigates pancreatic dysfunction and maintains pancreatic redox homeostasis.

Future research should focus on less-studied substances from Chinese medicinal and food sources, exploring the effects and regulatory mechanisms of specific active ingredients on T1DM. This research could significantly contribute to the development of dietary supplements or adjunctive therapies for T1DM by examining the interactions and effects of multiple medicinal and food ingredients.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

Acknowledgments

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