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Review article

The association between circulatory, local pancreatic PCSK9 and type 2 diabetes mellitus: The effects of antidiabetic drugs on PCSK9

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ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a potent modulator of cholesterol metabolism and plays a crucial role in the normal functioning of pancreatic islets and the progression of diabetes. Islet autocrine PCSK9 deficiency can lead to the enrichment of low-density lipoprotein (LDL) receptor (LDLR) and excessive LDL cholesterol (LDL-C) uptake, subsequently impairing the insulin secretion in β-cells. Circulatory PCSK9 levels are primarily attributed to hepatocyte secretion. Notably, anti-PCSK9 strategies proposed for individuals with hypercholesterolemia chiefly target liver-derived PCSK9; however, these anti-PCSK9 strategies have been associated with the risk of new-onset diabetes mellitus (NODM). In the current review, we highlight a new direction in PCSK9 inhibition therapy strategies: screening candidates for anti-PCSK9 from the drugs used in type 2 diabetes mellitus (T2DM) treatment. We explored the association between circulating, local pancreatic PCSK9 and T2DM, as well as the relationship between PCSK9 monoclonal antibodies and NODM. We discussed the emergence of artificial and natural drugs in recent years, exhibiting dual benefits of antidiabetic activity and PCSK9 reduction, confirming that the diverse effects of these drugs may potentially impact the progression of diabetes and associated disorders, thereby introducing novel avenues and methodologies to enhance disease prognosis.

1. Introduction

In humans, proprotein convertase subtilisin/kexin type 9 (PCSK9) is predominantly expressed by hepatocytes, which is the sole source of circulating PCSK9 [1]. The proximal end of the PCSK9 promoter contains a functional sterol regulatory element (SRE) responsible for sensing and responding to changes in intracellular cholesterol concentrations [2]. During transcriptional regulation, SRE binding proteins (SREBP1 and SREBP2) bind to the SRE sequence of PCSK9 and upregulate PCSK9 expression. *In vivo*, PCSK9 is mainly regulated by SREBP2 [3]. Another upstream regulator of PCSK9 is hepatocyte nuclear factor 1α (HNF1-α), located 28bp upstream of SRE [4]. Mammalian target of rapamycin complex 1 (mTROC1) activates protein kinase C α (PKCα), which reduces HNF1-α

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expression and eventually leads to decreased PCSK9 expression [5]. Furthermore, SREBP2 and HNF1-α exert a synergistic role in the transcription of the PCSK9 protein, and mutations in the HNF1-α binding site on the PCSK9 promoter can damage the integrity of the SRE sequence and disrupt its binding with SREBP2 [4]. As a crucial lipid-regulating protein, PCSK9 predominantly binds to the low-density lipoprotein (LDL) receptor (LDLR) and degrades it via the lysosomal pathway, thus increasing plasma levels of LDL cholesterol (LDL-C) [6,7]. Apolipoprotein B (ApoB) is an important component of LDL that participates in the identification and binding of LDL to LDLR [8]. Although PCSK9 interacts with ApoB to separate it from the autophagosome and enter the lysosome for degradation, LDLR does not participate in this process [9]. In addition to LDL-C regulation, PCSK9 has been positively correlated with lipoprotein a (Lp(a)) and triglycerides (TG) [8,10]. Notably, PCSK9 monoclonal antibody-mediated Lp(a) reduction occurs independent of the benefits of LDL-C reduction in cardiovascular events [11]. Lp(a) reportedly participates in lysosomal degradation via the PCSK9-regulated LDLR pathway [12]. PCSK9 may participate in plasma TG-rich lipoprotein metabolism via transcriptional/post-transcriptional regulation of ApoB, a microsomal TG transporter. LDLR has been shown to substantially increase the production of TG-rich ApoB in the small intestine [13,14].

Type 2 diabetes mellitus (T2DM) is frequently associated with abnormal lipid metabolism, accompanied by decreased high-density lipoprotein (HDL) and increased levels of non-HDL, including total cholesterol (TC), TGs, LDL-C, and ApoB upregulation [15]. Given the disordered lipid metabolism in patients with diabetes, PCSK9-targeted treatment could afford cardiovascular benefits in these patients [16]. PCSK9 monoclonal antibodies can reduce LDL-C levels by 60%, which is superior to the lipid-lowering efficacy afforded by combining statins and ezetimibe; hence, PCSK9 monoclonal antibodies have been explored in large-scale clinical trials [17–19]. Notably, a PCSK9 monoclonal antibody was shown to reduce TG and Lp(a) levels [20,21]. Nevertheless, excessive reduction in LDL-C levels has been associated with the risk of new-onset diabetes mellitus (NODM) [22]. Consistently, studies have found that statins, well-known powerful lipid-lowering agents that primarily lower LDL-C, can induce NODM, increase insulin resistance, and lead to an inability to maintain compensatory insulin secretion [23,24]. Owing to the excellent lipid-lowering ability of PCSK9 monoclonal antibodies (alirocumab and evolocumab), their effects on NODM warrant long-term assessment and research. In addition to inhibiting circulating PCSK9 (mainly hepatogenic), the role of pancreatic-secreted PSCK9 and the potentially detrimental effects of PSCK9 inhibition have received growing attention [25].

Given the high price of PCSK9 inhibitors, several antidiabetic drugs that can suppress PCSK9 expression have been explored. The advantages of oral administration and the dual benefits of antidiabetic drugs and PCSK9 reduction may exert potential clinical applications. Herein, the association between diabetes mellitus and PCSK9, present in the circulation and locally in islet cells, was assessed in basic and clinical trials. Furthermore, we reviewed the relationship between PCSK9 monoclonal antibodies and NODM, as well as emerging artificial and natural drugs that exert antidiabetic and PCSK9 reduction activities.

2. Diabetes and dyslipidemia

Dyslipidaemia is closely associated with cardiovascular disease. Previous studies have demonstrated the advantages of lipid-lowering therapy in reducing the risk of cardiovascular diseases [26]. Dyslipidaemia, including abnormalities in LDL, HDL, non-HDL, and TG levels, is an important factor that increases the risk of cardiovascular events in patients with T2DM [27,28]. In an observational study assessing 46,786 patients with T2DM, levels of LDL, HDL, and non-HDL were associated with an increased risk of coronary heart disease [29]. Moreover, the ratio of non-HDL-C to HDL exhibited the highest predictive power for the occurrence of coronary heart disease in patients with diabetes [29]. Given these findings, therapies targeting LDL-C to lower the incidence of cardiovascular events in patients with diabetes may have potential clinical use [30].

In patients with diabetes, lipid-lowering therapy, especially LDL-C reduction, can substantially reduce the incidence of coronary heart disease. Additionally, there is no minimum threshold for LDL-C reduction [31]. Although certain minor adverse effects remain controversial, markedly lowering LDL levels has been deemed safe [31]. Nevertheless, even if lipid-lowering drugs exert beneficial effects on cardiovascular events in patients with diabetes, reduction in LDL-C may contribute to the risk of NODM [32]. In addition, in a study assessing the relationship between genetic variations in serum lipid component levels and T2DM, populations with low hereditary LDL-C levels were considerably associated with the risk of NODM [33]. In a study evaluating the association between the genetic risk score for LDL-C and the risk of developing diabetes in patients not taking lipid-lowering or blood pressure control drugs, the LDL-C concentration was found to be inversely related to the risk of NODM at baseline [22]. This may indicate that markedly low LDL-C levels, attributed to genetic factors or lipid-lowering drugs, can be associated with an increased risk of NODM; however, it remains unclear whether the side effects of lipid-lowering drugs or very low LDL-C levels were responsible for this observation. Prospective studies with a longer follow-up of patients with inherited low LDL-C levels could help clarify whether LDL-C is negatively associated with NODM. In addition, owing to the distinct mechanisms of action of lipid-lowering drugs, more attention should be paid to the category of lipid-lowering drugs when examining the relationship between lipid-lowering drugs and NODM. A meta-analysis found no increase in the incidence of NODM when the target LDL-C level was >2.59 mmol/L [34]. Could this imply that there exists a threshold blood lipid level that leads to NODM? Nevertheless, the risks and benefits should be evaluated clinically, given that the cardiovascular benefits of low LDL-C levels may outweigh the associated diabetes risk.

3. Plasma PCSK9 concentration is closely related to diabetes mellitus

3.1. Diabetes mellitus and PCSK9, Lp(a)

Patients with diabetes reportedly have higher serum PCSK9 levels than those without diabetes [35]. Patients with diabetes exhibit

elevated PCSK9 and Lp(a) levels, showing a substantial positive correlation [36]. Furthermore, the synergistic effects of PCSK9 and Lp (a) may substantially contribute to atherosclerosis in patients [36]. Interestingly, the PCSK9 inhibitor PCSK9 monoclonal antibody markedly reduced Lp(a) levels by 18%–32% over 12 weeks of treatment [16]. Conversely, in a study assessing statin-treated patients, statin treatment increased PCSK9 concentration but decreased Lp(a) levels; the PCSK9 concentration was not significantly associated with Lp(a) [11]. A study conducted among the Han Chinese population found no significant difference in plasma PCSK9 levels in patients with or without diabetes mellitus, as well as no correlation between PCSK9 and Lp(a) levels [37]. Surprisingly, in a FOURIER trial performed among patients diagnosed with atherosclerotic cardiovascular disease, Lp(a) levels were markedly low in patients with a history of diabetes. These variations may indicate racial differences in the relationship between PCSK9 and Lp(a) levels in diabetes. Accordingly, the relationship between PCSK9 and Lp(a) concentrations in patients with diabetes should be comprehensively explored.

3.2. Diabetes mellitus, PCSK9, and metabolic dysfunction

In a cross-sectional study, plasma PCSK9 levels were found to be increased by 14% in patients with metabolic syndrome and by 13% in patients with T2DM ($P < 0.005$) [38]. Muoio et al. examined young female‘‘s aged 15–26 years with obesity or T2DM. The authors found that serum PCSK9 levels were substantially elevated in obese and young females with T2DM and were associated with metabolic disorders [39]. However, no significant differences in PCSK9 levels were observed in young male subjects, and young females had higher PCSK9 levels than males of the same age [39]. In 116 patients with diabetes, circulating PCSK9 concentrations highly correlated with multiple atherogenic lipoproteins, including Apo B100, Apo B48, and Apo C3, and the inflammatory marker PTX3. This finding suggests that PCSK9 may be involved in lipid metabolism disorders and potentially promote inflammatory atherosclerosis in patients with diabetes [40].

3.3. Diabetes mellitus, PCSK9, and race

In studies conducted among African-Americans and Tunisians, serum PCSK9 levels were found to be substantially associated with T2DM [35,36,39]. However, Zhou et al. detected no significant differences in plasma PCSK9 levels in patients with normal glucose metabolism, abnormal glucose metabolism, or T2DM [41]. In studies conducted among Asian [42] and Caucasian [41] subjects, no significant difference in serum PCSK9 levels was observed between patients with diabetes and controls. Accordingly, the association between diabetes and serum PCSK9 concentrations may be influenced by ethnic composition, which should be considered during clinical treatment.

3.4. PCSK9 gene mutation and diabetes risk

According to a large meta-analysis, a reduction of 1 mmol/L in plasma LDL-C was associated with an odds ratio (OR) of 1.19 for T2DM (95% confidence interval [CI]:1.02–1.38; $P = 0.03$) but a reduced risk of coronary artery disease [32]. Ference et al. found that mutations in PCSK9 and HMGCR were associated with reduced LDL-C levels [43]. The risk of NODM was increased only in patients with impaired fasting glucose levels. However, the cardiovascular benefits may override these adverse outcomes [43]. In a Mendelian randomisation study involving four independent PCSK9 mutants, LDL-C levels were inversely correlated with fasting glucose levels and new-onset T2DM [44].

4. Localised PCSK9 deficiency in the islets and homeostasis

The main pathogenesis of T2DM is thought to be related to islet β-cell death, which, in turn, results in impaired insulin secretion [45]. Dyslipidaemia has been associated with β-cell death and impaired islet function in T2DM, leading to cell lipotoxicity [46–48]. Depending on the contribution of LDLR, a high LDL concentration in the culture system reduced islet β glucose-stimulated insulin secretion (GSIS), while HDL afforded protective effects against islet β-cell exhibited dysglycaemia and decreased plasma insulin levels, and staining revealed islet apoptosis, local inflammation of the islets, and abnormal contours [49,50]. Conversely, female mice did not show any notable response, possibly due to the protective effects of oestrogen on β-cells [50–52]. The authors further confirmed that observed effects in PCSK9 knockout mice were related to sex, age, dietary composition, glucose metabolism, impaired GSIS, irregularly shaped islets, and early signs of cytoplasmic apoptosis of eosinophilic and nuclear pyknosis [53]. This led to the postulation that the observed effects could be attributed to abnormal biogenesis of insulin secretion granules [53]. Furthermore, Da Dalt et al. elucidated the mechanism through which islet δ-cell-secreted PCSK9 protects islet β-cells from cytotoxicity induced by lipid accumulation, i.e., via reduced cholesterol uptake by islet β-cells [25]. These mechanisms depend on the hyperactivation of LDLR in pancreatic β-cells owing to reduced PCSK9 levels [25]. After excluding the effects of liver-derived PCSK9, the authors found that circulating PCSK9, the primary target of PCSK9 monoclonal antibodies, did not affect pancreatic β-cell function in a liver-specific PCSK9 knockout mouse model [25]. In pancreatic-specific PCSK9 knockout mice, Da Dalt et al. found that LDLR expression on the β-cell surface was increased, accompanied by insufficient insulin secretion, despite normal serum PCSK9 levels, further confirming that LDLR on the β-cell membrane is regulated by islet localised PCSK9 rather than by hepatogenic PCSK9 [54]. Moreover, the PCSK9 loss-of-function P.R46L variant was found to be associated with an increased risk of glucose levels at 2 h and enhanced risk of diabetes in a meta-analysis of genetic association studies (OR of 1.19; 95% CI:1.02–1.38) [32]. Other Mendelian randomisation studies have mentioned that PCSK9 dysfunction mutations are associated with an increased risk of diabetes, although this increase has only been observed in individuals with impaired fasting glucose levels (LDL-C decreased by 10 mg/dL, OR of 1.11; 95% CI:1.04–1.19) [43].

Conversely, Bonneguilt et al. found no abnormal cholesterol content in the islets of PCSK9 knockout mice, and insulin secretion function did not differ from that of normal mice [55]. Furthermore, the authors constructed a Cox regression model and found that the PCSK9 functional loss mutation, p.R46L type, was not associated with fasting blood glucose or fasting insulin levels. Moreover, no association was observed between the P.R46L mutant and T2DM [56]. Most recently, Peyot et al. established the first unprecedented PCSK9 islet β-cell-specific knockout (KO) mouse model, which showed normal glucose tolerance and insulin sensitivity when compared with those control mice; however, pancreatic secretory function remained unaltered in KO mice [57]. Furthermore, β cells of β-cell KO mice did not exhibit abnormal LDLR expression. Meanwhile, expression levels of LDLR and cholesterol synthesis-related gene HMGCR mRNA were substantially reduced (32 and 29%, respectively), indicating that β cells may undergo transcriptional adaptation to stabilise LDLR levels and intracellular cholesterol content [57]. Another study on human β-cells demonstrated that both endogenous and exogenous PCSK9 regulates LDLR. However, exogenous PCSK9, recombinant PCSK9, and PCSK9 silencing did not change the GSIS of β-cells [58]. In line with the findings of Peyot et al. the authors observed that PCSK9 was mainly expressed by β-cells, as determined by immunofluorescence staining of human donor islets, which contradicted the findings of Da Dalt et al. [58].

Therefore, it is yet to be comprehensively clarified whether PCSK9 deficiency affects glucose homeostasis-related indicators (including fasting insulin, fasting blood glucose, and haemoglobin A1c [HbA1c]) through cholesterol accumulation. One explanation

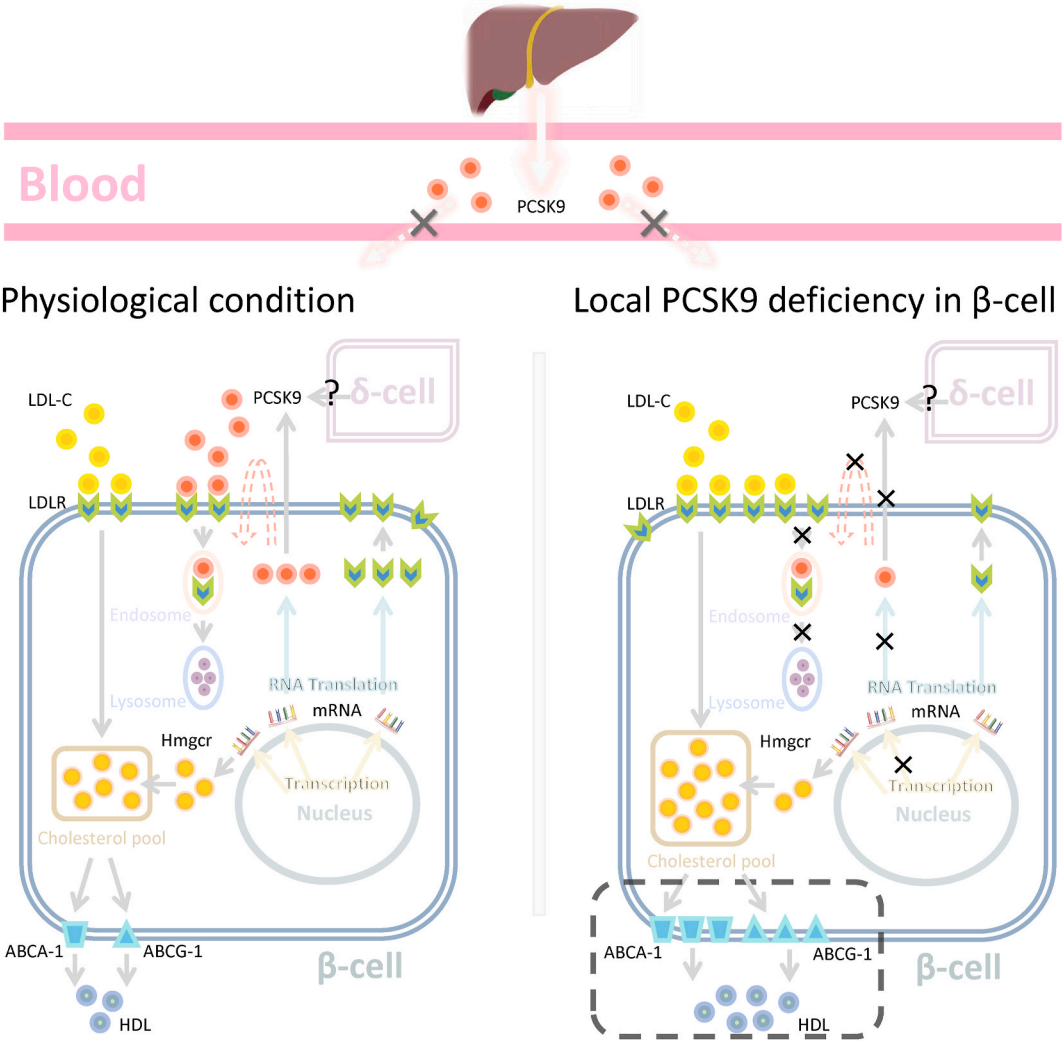

Fig. 1. Suppressed PCSK9 secretion by β-cells leads to compensatory lipid accumulation in β-cells. PCSK9 secreted by islet β-cells can bind to LDLR on the cell membrane and achieve clearance of LDLR via the endosomal-lysosome pathway, thereby maintaining the appropriate LDLR density on the cell membrane. This process prevents excessive lipid uptake by β-cells owing to high LDLR density (Physiological condition). Failure of β-cells to secrete PCSK9 can increase LDLR expression on the membrane, subsequently inducing LDL-C accumulation in the cholesterol pool. Excessive lipid accumulation may lead to "lipid toxicity" and impair islet β-cell function (Local PCSK9 deficiency). Nevertheless, reduced *de novo* cholesterol synthesis and increased protein expression of excreted lipids can compensate for lipid toxicity and thus ensure normal pancreatic islet function. The effects of δ-cell-secreted PCSK9 on LDLR of β-cells remain controversial. Hepatogenic PCSK9 does not impact β-cell LDLR abundance. LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, Proprotein convertase subtilisin/kexin type 9.

may be that, in clinical settings, the PCSK9 concentration in P.R46L mutant subjects was only 15% less than that in normal subjects [59], which is not markedly notable when compared with that of PCSK9 knockout animal models; therefore, PCSK9 deficiency-induced islet damage observed in animal models has not been observed in large-scale clinical studies. Considering another possible reason, even under elevated LDLR expression, the serum LDL-C concentration was inherently low in the P.R46L mutant owing to PCSK9 deficiency, impacting LDL-C uptake of β-cells; hence, lipid toxicity is less likely to occur. Therefore, impaired islet function in P.R46L is reflected in a slight elevation of blood glucose or mild insulin resistance, but it is not sufficiently severe to cause diabetes. Nevertheless, long-term prospective follow-up studies assessing PCSK9-deficient populations are warranted. In addition, the cholesterol pool of β-cells is not only affected by LDLR expression but also by *de novo* synthesis of cholesterol, as well as esterification and excretion of cholesterol [60]. Accumulated evidence suggests that β-cells possess a protective strategy against excess lipid accumulation during PCSK9 absence; for example, increased expression levels of the ATP-binding cassette transporter A1 (ABCA1), ATP-binding cassette transporter G1 (ABCG1), and liver X receptor (LXR), which are responsible for lipid excretion [25,61]. In addition, increased expression of acetyl-coenzyme A acetyltransferase 1 (ACAT1) and fatty acids such as sterol O-acyltransferase 1 (SOAT1) has been documented; these enzymes are responsible for cholesterol esterification [25,54]. We speculate that the expression of genes related to β-cell-mediated cholesterol synthesis is compensatively downregulated during PCSK9 deficiency; however, further research is needed to confirm this hypothesis. Future investigations should explore pathways through which β-cells can compensate for PCSK9 absence to avoid lipotoxicity, which could yield novel concepts for the repair of islet function. In addition, it remains unclear whether PCSK9, which acts on islet β-cells, originates from β- or δ-cells [25,55,57,58]. The discrepant findings could be attributed to the low PCSK9 secretion in the pancreas and the different antibodies and techniques employed. Fig. 1 illustrates the potential mechanism through which restricted secretion of PCSK9 leads to compensatory lipid accumulation in β-cells.

Table 1
Association between PCSK9 monoclonal antibodies and the risk of new-onset diabetes mentioned in the manuscript.

Trail	N	Duration	Target population	Study groups	Change of lipid profile	Change of glucose spectrum	Risk of new-onset diabetes incidence VS placebo
Open-Label OSLER-1 Extension Study [75]	1,324	≥208weeks	–	Evolocumab, 420 mg monthly	LDL-C decreased by 58%	FPG did not change significantly	No significant difference
FOURIER randomized controlled trial [76]	27,564	2.2 years	Patients with ASCVD and LDL-C ≥1.8 mmol/L	Evolocumab, 140 mg fortnightly or 420 mg monthly	LDL-C decreased by 59%, non-HDL decreased by 52% Apo B decreased by 49%	HbA1c and FPG did not change significantly	No significant Difference (HR of 1.05; 95% CI, 0.94 to 1.17)
GLAGOV Randomized Clinical Trial [77]	968	78 weeks	Patients with angiographic coronary disease treating statins	Evolocumab, 420 mg monthly	LDL-C decreased by 60.7%	Glucose and HbA1c did not change significantly	No significant difference
FOURIER randomized controlled trial [78]	2,341	78 weeks	Patients with LDL-C ≥1.8 mmol/L and a maximum tolerated dose of statins at high risk of cardiovascular events	Alirocumab, 150 mg fortnightly	LDL-C decreased by 62%	No information	No significant Difference (P = 0.84)
ODYSSEY FH I and FH II [79]	735	78 weeks	Patients with familial hypercholesterolemia and LDL-C ≥1.8 mmol/L	Alirocumab, 75 mg fortnightly	LDL-C decreased by 57.9% (FH I) and 51.4% (FH II)		No significant difference
Meta-analysis [80]	26,123	–	–	Alirocumab or Evolocumab	No information	FPG and HbA1c did not change significantly	No significant difference(HR of 1.05; 95% CI, (0.95–1.16)
Meta-analysis [81]	65,957	≥12 weeks	–	Alirocumab or Evolocumab	No information		No significant difference (HR of 0.97; 95% CI, 0.91–1.02; P = 0.22)
Meta-analysis [82]	68,123	78 weeks	–	Alirocumab, Evolocumab, or Bococizumab	No information	FPG and HbA1c increased	No significant difference (HR of 1.04; 95% CI, 0.96–1.13; P = 0.427)

5. PCSK9 monoclonal antibodies do not increase the incidence of diabetes

5.1. Statins, PCSK9, and NODM

Statins, a representative class of lipid-lowering drugs, can reduce LDL-C by 30–50% [62] and negatively affect lipid metabolism and glucose homeostasis [63]. However, a substantial proportion of individuals exhibit a poor response to statins, with a <15% reduction in LDL-C levels [64]. The poor lipid-lowering performance of statins could be attributed to elevated PCSK9 levels [63]. In response to reduced cholesterol levels, the expression of SREBPs is enhanced, and SRE in the PCSK9 gene promoter subsequently increases PCSK9 expression [3]. The LDLR promoter also has a highly conserved SRE sequence, which is regulated by statin-induced upregulation of SREBPs [2]. However, as PCSK9 expression is also upregulated, LDLR is generally inhibited after overlap, which profoundly affects LDL-C uptake by hepatocytes, leading to an inability to modulate circulating lipids promptly [2]. Overall, the serious adverse effects of PCSK9 upregulation can impair the lipid-lowering effect of statins. Similarly, patients with high initial plasma levels of mature PCSK9 were less responsive to statins. Accordingly, baseline levels of PCSK9 may predict the lipid-lowering efficacy of statins [65].

The effects of statins on NODM involve metabolic abnormalities in multiple organs and tissues, the mechanisms of which remain unclear. In the liver, statins activate two key enzymes in the gluconeogenesis pathway via the statin/pregnane X receptor (PXR)/serum/glucocorticoid regulated kinase 2 (SGK2) mediated pathway, thereby promoting hepatocyte gluconeogenesis [66]. The activation of hepatic gluconeogenesis leads to hyperglycemia [66]. In pancreatic islets, statins inhibit glucose uptake by pancreatic β-cells via concentration-dependent inhibition of glucose transporter-2 (GLUT-2) receptors, resulting in decreased sensitivity to glucose levels and impaired insulin secretion [67]. In the adipose tissue, myocardium, skeletal muscle, and other tissues, statins reportedly reduce insulin receptor sensitivity and thus inhibit the phosphorylation of insulin receptor substrates, preventing normal insulin signalling and glucose uptake through GLUT-4 [68]. In a clinical follow-up study, statin use was found slightly increase the risk of NODM; however, this increase was more likely to occur in elderly and prediabetic patients [69]. Patients with diabetes showed a 26.6% increase in the risk of statin intolerance [70]. Nevertheless, the benefits of statins on cardiovascular events far outweigh their potential negative effects [69]. Therefore, in patients taking statins for a prolonged period, attention should be paid to the primary prevention of diabetes, and the risk of diabetes should be assessed.

5.2. PCSK9 monoclonal antibodies and NODM

Alirocumab and evolocumab, both PCSK9 monoclonal antibodies, are potent PCSK9 inhibitors that reduce LDL and Lp(a) levels by more than 60 and 30%, respectively [16,71,72]. These agents may reduce the incidence of cardiovascular events [71,73]. Lipid-lowering drugs, such as statins, increase PCSK9 levels and the incidence of NODM. Meanwhile, PCSK9 monoclonal antibodies can achieve extremely low LDL-C levels, along with increased LDLR levels [74]. The association between PCSK9 monoclonal antibodies and NODM has been extensively explored (Table 1).

The open-label extension study (OSLER-1) for the long-term evaluation of LDL-C confirmed the excellent inhibitory effects of evolocumab on LDL-C levels in different ethnic groups. Additionally, the effects were sustained over a prolonged period and did not increase fasting plasma glucose levels or the incidence of diabetes [75]. In the FOURIER randomised controlled trial assessing 27564 patients with atherosclerotic cardiovascular disease, evolocumab substantially reduced the incidence of cardiovascular outcomes, regardless of whether the participants had diabetes [76]. During the three-year observation period, PCSK9 inhibitors did not increase the risk of NODM (hazard ratio [HR] of 1.05; 95% CI: 0.94–1.17) in prediabetic patients and patients with normal blood glucose at baseline [76]. In the GLAGOV randomised clinical trial that used statins as background treatment, evolocumab showed no obvious correlation with blood glucose, HbA1c, and newly diagnosed diabetes when compared with the placebo [77]. Among patients who received statins at the maximum tolerated dose, the monoclonal antibodies had no significant effect on the rate of NODM ($P = 0.84$) [78]. Moreover, there was no significant effect on the incidence of diabetes in patients with a family history of hypercholesterolemia [79]. According to a systematic review and meta-analysis conducted by Cao et al. comprising 18 studies with 26123 subjects, there was no significant heterogeneity in the rate of NODM (HR of 1.05; 95% CI:0.95–1.16) or glucose homeostasis, including HbA1c and fasting plasma glucose, in the group receiving monoclonal antibodies alirocumab and evolocumab when compared with the control group [80]. In a meta-analysis of 23 studies involving 65,957 patients, PCSK9 was not associated with a risk of NODM (HR of 0.97; 95% CI:0.91–1.02; $P = 0.22$). Considering the type, the risk of diabetes was remarkably reduced with alirocumab therapy (relative risk: 0.91; 95% CI: 0.85–0.98; $P = 0.01$) [81]. However, as patients in the control group tended to take higher doses of statins than those in other groups, PCSK9 monoclonal antibodies showed a greater risk of diabetes when the statins were comparable between the control and blank groups. This suggests that unbalanced background lipid regulation may obscure the efficacy of PCSK9 monoclonal antibodies against diabetes [81].

In addition, de Carvalho et al. conducted a meta-analysis of >96,000 patient-years. Alarmingly, the authors observed that 1.5 years of PCSK9 monoclonal antibody treatment resulted in a slight increase in blood glucose (1.88 mg/dL increase) and HbA1c (0.0332% increase) levels. Although these changes are insufficient to induce diabetes, the risk of NODM was found to be positively associated with reduced LDL-C levels and treatment duration [82]. Cao et al. highlighted that the observations could be attributed to the inclusion of participants treated with bococizumab, which is not a fully humanised monoclonal antibody [83,84]. In addition, nearly half of the patients who received bococizumab developed antibiotic-resistant antibodies [83]. In summary, the PCSK9 monoclonal antibody only targets circulating PCSK9 and does not impact the islet microenvironment PCSK9 [25]. As stated in a review by Carugo et al. despite the relative safety of PCSK9 monoclonal antibodies, the occurrence of hyperglycaemic events should be considered during the early application of PCSK9 monoclonal antibody therapy [85]. Combined with the slightly increased risk of diabetes associated with

lipid-lowering drugs, such as statins, and the possible risk of diabetes associated with excessively low LDL-C levels, long-term blood glucose testing cannot be completely ignored in patients taking PCSK9 monoclonal antibodies.

6. Effects of antidiabetic drugs on PCSK9

For inhibiting PCSK9 expression, current strategies include blocking the formation of the PCSK9-LDLR complex using peptides and PCSK9 monoclonal antibodies, reducing PCSK9 expression with antisense oligonucleotides (ASOs) and siRNA, and interfering with PCSK9 secretion [86]. Among them, ASOs are a class of short natural nucleic acid analogues that specifically bind to mRNA to induce its degradation or prevent its translation, which was shown to reduce PCSK9 mRNA by 60% and increase liver LDLR protein levels by 2–3 times in high-fat diet mouse models [86]. However, screening for small oral molecules that inhibit PCSK9 from existing agents used in clinical practice, especially antidiabetic drugs, including marketable synthetic antidiabetic drugs or natural substances, may afford better clinical treatment strategies. These general agents, which stabilise glucose and control lipid levels, may be valuable in clinical practice. Another option involves commercial synthetic oral antidiabetic drugs, such as liraglutide, metformin, and other novel synthetic natural compound analogues. As shown in fig. 2 A and 2 B and Table 2, certain natural and synthetic antidiabetic agents can be used to treat diabetes and reduce PCSK9 expression.

6.1. Natural inhibitors and their artificial derivatives

The discovery of natural drugs or active ingredients that inhibit the expression of PCSK9, followed by the development of oral small molecules with anti-PCSK9 activity, are undoubtedly new pharmacological strategies to inhibit PCSK9 activity. In this section, we summarise the natural PCSK9 inhibitors and their synthesised derivatives exerting dual antidiabetic and PCSK9 inhibitory effects.

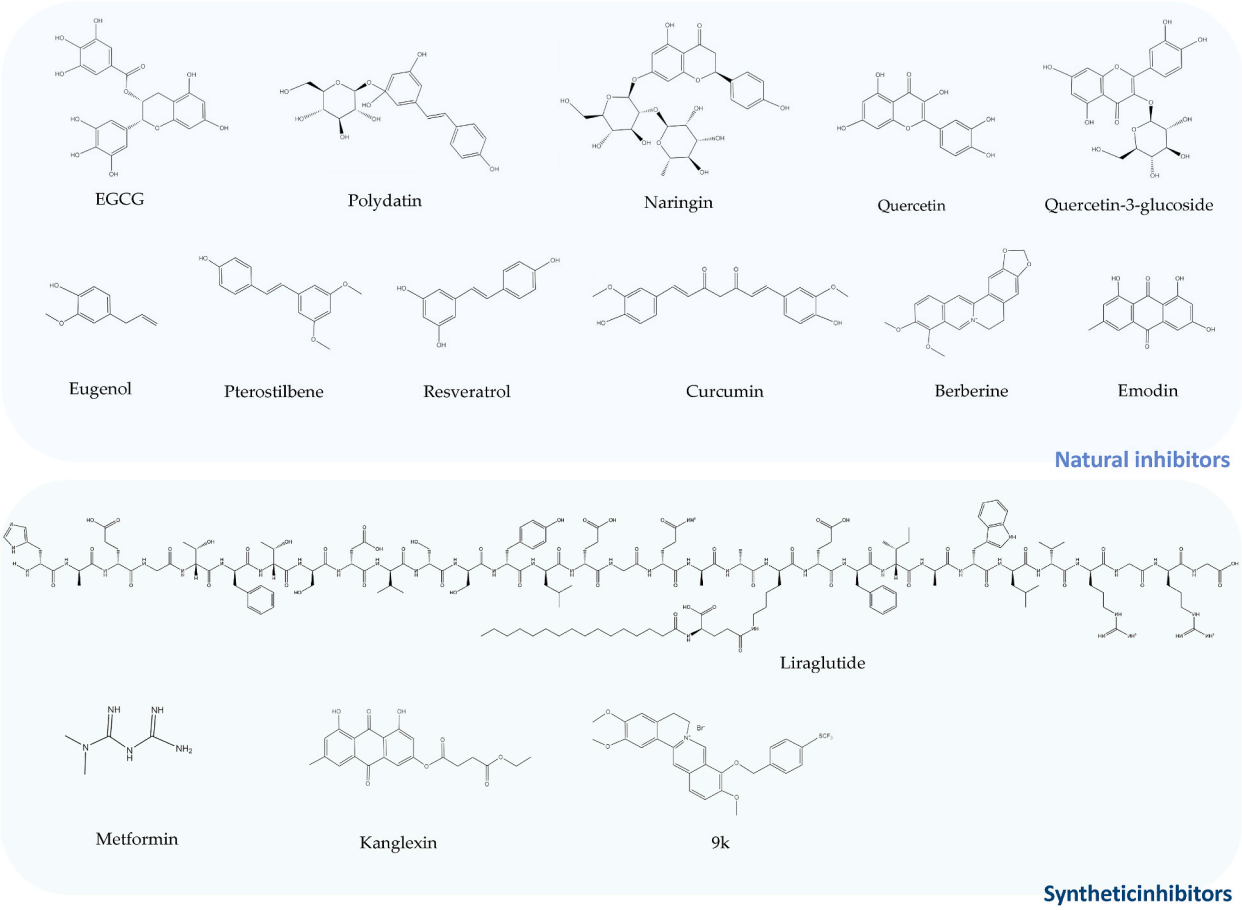

Fig. 2. Synthetic or natural drugs with dual antidiabetic and PCSK9 lowering benefits. A. Chemical structures of natural antidiabetic compounds and synthetic antidiabetic drugs acting on PCSK9; B. (1) Synthetic inhibitors: a, GLP-1 (glucagon-like peptide-1) receptor agonist; b, biguanide; c, anthraquinones; d, isoquinoline alkaloids; (2) Natural inhibitors: I, isoquinoline alkaloids; II, polyphenols; III, sterol/stanols; IV, nutrients; V, anthraquinones; VI, others. PCSK9, Proprotein convertase subtilisin/kexin type 9; (−), negative regulation.

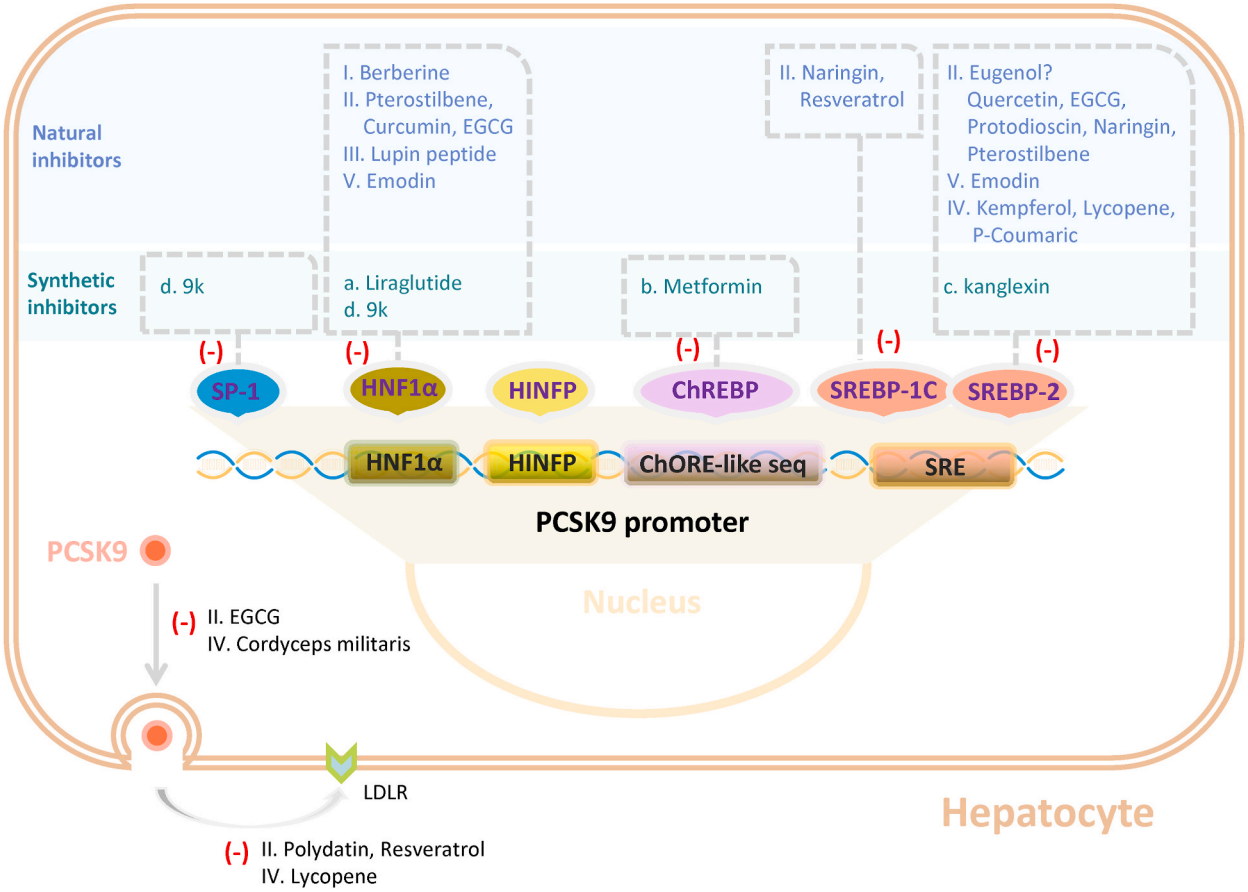

Fig. 2. (*continued*).

6.1.1. Polyphenols

Polyphenols, secondary metabolites of plant-based foods, can be valuable compounds to combat diabetes and diabetic complications such as diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, and diabetic cardiomyopathy [87–90]. This class of compounds includes pterostilbene, curcumin, and epigallocatechin-3-gallate (EGCG). The cardiovascular health benefits of polyphenols are well documented [91]. Moreover, the ability of polyphenols to regulate blood lipid levels and reduce LDL-C levels has been reported.

6.1.1.1. The role of pterostilbene. Pterostilbene, a natural analogue of resveratrol, reportedly exhibits greater bioavailability than resveratrol and has potential clinical value owing to the replacement of two hydroxyl groups of resveratrol with two methyl groups [92]. *In vitro*, pterostilbene reversed palmitic acid-mediated insulin resistance in HepG2 cells by inhibiting NADPH oxidase 3 (NOX3), thereby suppressing oxidative stress [93]. Pterostilbene also inhibited the expression of genes encoding phosphoenolpyruvate carboxykinase, glucose-6-phosphatase, and pyruvate carboxylase, thereby inhibiting glucose production in HepG2 cells [93]. Additionally, pterostilbene reportedly functioned as a natural peroxisome proliferator-activated receptor (PPAR)-α agonist, activating the AMPK pathway to increase the expression of fatty acid oxidation-related genes, thereby exerting antidiabetic effects [94]. *In vivo*, treatment with 20 mg/(kg·d) pterostilbene substantially reduced fasting blood glucose levels and fasting insulin levels (FINS) in high-fat and high-glucose diet/induced diabetic rats [95]. Similar results were obtained in 65% fructose-fed diabetic rats, who demonstrated alleviated metabolic disorders and liver oxidative stress following pterostilbene treatment [96]. Based on western blotting analysis, pterostilbene could activate PPARγ and PI3K/Akt signalling pathways in the adipose tissue of diabetic rats [97]. In addition, treatment with 20 mg/(kg·d) pterostilbene markedly reduced the LDL-C levels in diabetic rats [95]. Lin et al. demonstrated that pterostilbene upregulated LDLR expression on the cell membrane surface and exerted a dose-dependent effect on LDL particle accumulation in cardiomyocytes [98]. The authors also noted pterostilbene-induced downregulation of PCSK9 and PCSK9 mRNA and upregulation of LDLR mRNA expression [98]. Based on miRNA targets predicted using bioinformatic analysis, two miRNAs (hsa-miR-6825 and hsa-miR-335) were enhanced by silencing transcription factors HIF1α, HNF1-α, Nrf2, and SREBP2, thus affecting PCSK9 and LDLR expression [98]. Given the characteristics of pterostilbene, such as the first-pass effect, low water solubility, ease of oxidation, and poor oral utilisation, Zhao et al. synthesised pterostilbene esterified and polymerised with 3-acrylamidophenyl boric acid to generate glucose-responsive nanoparticles exerting rapid and efficient antidiabetic effects [99]. However, whether the new

Table 2
Effects of natural antidiabetic compounds and synthetic antidiabetic drugs on PCSK9.

Medicament Names	Major antidiabetic mechanism	Antidiabetic evidence	Mechanism for PCSK9 inhibition	Evidence for lowering PCSK9	Effects on LDLR	Effects on lipid metabolism	References
Synthetic inhibitors							
Liraglutide	Activate GLP-1 receptor	In vitro, vivo, and clinical trials	Downregulated HNF-1α expression	In vitro, in vivo, and clinical trials	Upregulate LDLR and mRNA	apoB48↓ , TC↓ , TG↓ , LDL-C↓	[153,159, 160,174–177]
Metformin	AMPK-dependent and AMPK-independent mechanisms	In vitro, vivo, and clinical trials	Downregulate ChREBP expression	In vitro, in vivo, and clinical trials	Upregulate LDLR and mRNA	LDL-C↓	[163,167, 168,178]
Kanglexin	Promote FGFR1/ERK signaling	In vitro	Downregulate SREBP2 expression	In vitro and in vivo	Upregulate LDLR	TC↓TG↓	[169–173]
Natural inhibitors							
Polyphenols							
EGCG	Inhibit NLRP3 pathway	In vitro and in vivo	Downregulate HNF-1αexpression	In vitro, in vivo, and clinical trials	Upregulate LDLR and mRNA	LDL-C↓	[111–116]
Polydatin	Promote AMPK and Akt signaling, inhibit NF-kB	In vitro, in vivo, and clinical trails	Form hydrogen bonds with PCSK9	In vitro and in vivo	Upregulate LDLR	LDL-C↓	[100–104, 179]
Eugenol	Promote GLUT4-AMPK signaling	In vitro and in vivo	Unknown	In clinical trials	Unknown	LDL-C↓	[180–184]
Naringin	Upregulate the FoxM1 and PDX-1 transcription factor	In vitro and in vivo	Downregulate SREBP2 expression	In vivo	Upregulate LDLR	TC↓ , TG↓ , LDL-C , HDL-C↑	[185–187]
Quercetin	Promote the MAPK AMPK AGE-RAGE signaling	In vitro and in vivo	Inhibits secretion and SREBP2	In vitro and in vivo	Unknown	TC↓ , TG↓ , LDL-C↓ , HDL-C↑	[188–194]
Quercetin-3-glucoside	Inhibit NF-kB signaling	In vitro and in vivo	Attenuate PCSK9 secretion	In vitro and in vivo	Upregulate LDLR and mRNA	TC↓ , TG↓ , LDL-C↓ , HDL-C↑	[195–200]
Pterostilbene	Promote AMPK, PI3K/ Akt, and Nrf2 signaling	In vitro, in vivo, and clinical trails	Downregulate SREBP2 and HNF1-α expression	In vitro	Upregulate LDLR and mRNA	TC↓ , TG↓ , VLDL-C↓ , LDL-C↓	[93–95, 97–99], [201–204]
Resveratrol	Promote AMPK, PI3K/ Akt/FoxO3a, Nrf2, SIRT/FOXO signaling	In vitro, in vivo, and clinical trails	Downregulate SREBP1-c expression	In vitro	Upregulate LDLR	TC↓ , TG↓	[205–211]
Curcumin	Promote AMPK and MAPK signaling. Inhibit NF-kB	In vitro, in vivo, and clinical trials	Downregulate HNF1-α expression	In vitro	Upregulate LDLR	TC↓ , TG↓ , LDL-C↓ , HDL-C↑	[212–215]
Isoquinoline alkaloids							
Berberine	Promote AMPK and MAPK signaling	In vitro, vivo, and clinical trials	Promote HNF1-α degradation	In vitro, in vivo, and clinical trials	Upregulate LDLR and mRNA	TC↓ , TG↓ , LDL-C↓ , HDL-C↑	[4,122–132, 136,138, 216–218]
9 k	Unknown	Unknown	Downregulate HNF1-α and sp1 expression	In vitro	Upregulate LDLR	LDL-C↓	[138]
Anthraquinones							
Emodin	Downregulate SREBPs expression	In vivo and *in vitro*	Unknown	In vivo	Upregulate LDLR	TC↓ , TG↓ , LDL-C↓ , HDL-C↑	[145, 149–152]

pterostilbene nanoparticles also exert potent PCSK9 lowering effects like pterostilbene warrants further investigation.

6.1.1.2. The role of polydatin. Polydatin (resveratrol-3-*O*-β-mono-D-glucoside), the major component of *Polygonum cuspidatum*, exhibited antidiabetic effects in both in vivo and *in vitro* experiments [100]. The observed antidiabetic effects were mainly achieved through various signalling pathways, including NF-kB, Akt, and AMPK [101–103]. As a novel and promising oral formula, polydatin-loaded chitosan nanoparticles were markedly effective against T2DM [104]. Wang et al. revealed that polydatin could improve lipid and glucose metabolism in T2DM by downregulating PCSK9 [104]. In a hepatocyte study, polydatin upregulated LDLR and GCK levels by inhibiting PCSK9 expression in PA-induced insulin-resistant HepG2 cells [104]. In the db/db C57BL/6 mice, polydatin exerted antidiabetic effects, ameliorated lipid accumulation, and increased glucokinase protein levels in hepatocytes to confer hepatoprotective effects. Meanwhile, polydatin markedly reduced PCSK9 expression, indicating that these improvements were possibly mediated by inhibiting PCSK9 expression [104].

6.1.1.3. The role of EGCG. Catechin is a phenolic active substance extracted from natural plants such as tea, comprising the active molecule epigallocatechin-3-gallate (EGCG) [105]. EGCG possesses anti-cancer, anti-obesity, anti-cardiovascular, neuroprotective,

and other inherent properties [106–110]. Recent studies have suggested that EGCG also exerts effects against diabetes and its numerous complications, including diabetic nephropathy [111], peripheral neuropathy [112], diabetic retinopathy [113], and glucose tolerance [114]. Mechanistically, EGCG has been found to improve glucose tolerance, which may partly depend on blocking the activation of nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) to suppress inflammation [114]. Cui et al. reported that in 224 age- and sex-matched case-control studies, non-green tea drinkers had higher plasma PCSK9 and LDL-C levels than tea drinkers [115]. Similar results were reported in animal studies [115]. In an *in vitro* study, EGCG downregulated PCSK9 expression by activating Foxo3, an inhibitory protein targeting the PCSK9 promoter sequence HNF1-α [115,116].

6.1.2. Plant isoquinoline alkaloids

Secondary metabolites of higher plants comprise a variety of phenols, terpenoids, and alkaloids. Although alkaloids are relatively rare in plants, isoquinoline alkaloids are among the most abundant [117]. Examples of isoquinoline alkaloids include berberine, palmatine, morphine, codeine, sanguinarine, and papaverine [118]. Studies have shown that isoquinoline alkaloids exhibit anti-inflammatory, antioxidant, antidiabetic, and lipid regulation properties [119,120].

6.1.2.1. The role of berberine. Berberine is primarily derived from the genus Berberis, especially the bark and roots [121]. Its biological activity is largely attributed to methylenedioxy, located at C2–C3 [118]. In an *in vitro* study, Yin et al. found that berberine increased glucose utilisation and enhanced insulin-induced glucose uptake. Berberine application for 5 h enhanced AMPK phosphorylation [122]. In cardiomyocytes, berberine increased the translocation of glucose transporters, enhanced myocardial glucose uptake, and improved cellular glucose consumption via the AMPK pathway [123,124]. In adipocytes, berberine reduced lipid accumulation, enhanced adipocyte energy metabolism, and suppressed adipogenesis via the AMPK pathway [125]. *In vivo*, treatment with berberine 150 mg/(kg·d) for 16 weeks increased insulin secretion and the insulin sensitivity index and decreased β-cell regeneration and islet injury [126]. Berberine intervention in diabetic rats reduced FBS, FINS, and homeostatic model assessment of insulin resistance index (HOMA-IR). It also upregulates glucagon-like peptide 1 (GLP-1), an oestrogenic hormone secreted by the intestinal mucosa L cells and expressed by islet α cells [127]. Gene array data analysis revealed that berberine primarily mediates its action via the mitogen-activated protein kinase pathway to improve glucose metabolism in the intestinal tract [127]. Recent in vivo studies have revealed that berberine can reduce blood lipid levels in rats, improve liver lipid accumulation, and reduce aortic atherosclerotic plaque formation [128]. Cameron et al. found that berberine inhibited PCSK9 protein and mRNA expression [129]. Based on the findings of the actinomycin D test, the authors further suggested that berberine does not affect the stability of PCSK9 mRNA but contributes to the reduced activity of the PCSK9 promoter [129]. Subsequently, Li et al. identified the HNF1-α regulatory sequence 28bp upstream of SRE and found that berberine could regulate PCSK9 expression [4]. Thus, berberine does not affect the expression of the HNF1-α gene [130]. In the presence of berberine, a dose-dependent increase in HNF1-α protein was observed using inhibitors of the autophagy-lysosome and ubiquitin-proteasome systems (UPS), suggesting that berberine downregulates HNF1-α protein expression via the UPS pathway [130]. Interestingly, Jia et al. discovered that berberine improved the lipid profile in high-fat diet rats and increased serum PCSK9 concentration by upregulating SREBP2, despite inhibiting HNF1-α expression [131]. Likewise, a new compound synthesised by chemically modifying berberine, i.e., 8-hydroxy dihydroberberine, which did not alter the expression levels of SREBP2, confirming that SREBP2 was not involved in the mechanism through which berberine reduced PCSK9 expression and upregulated LDLR expression [132].

However, owing to the involvement of P-glycoprotein, the intestinal absorption of berberine is limited; therefore, there is an urgent need to resolve the issue of poor bioavailability (F<1%) [133,134]. Accordingly, Ochin et al. synthesised berberine encapsulated nanoparticles (Bc-NPs) that could release released berberine in a time-dependent manner *in vitro* [135]. Owing to the poor oral bioavailability of berberine and the high concentration of its metabolites in vivo, Cao et al. identified demethyleneberberine (M3) among the metabolites and proved that M3 had stronger lipid-lowering effects than berberine and other metabolites [136]. In addition, the authors synthesised hydroxypropyl-berberrubine (A8), an analogue of M3 obtained by structural modification, that markedly increased LDLR expression. In addition, the authors showed that berberine and its analogues mainly mediate their PCSK9 and LDLR regulatory effects via the ERK pathway [136]. As primary components of natural isoquinoline alkaloids, tetrahydroprotoberberine derivatives (THPBs) were modified to obtain new indole-containing derivatives demonstrating stronger PCSK9 regulation and oral availability [137]. Compound 9 K has recently been developed as a berberine derivative; however, its mechanism of action differs from that of berberine. In addition to targeting HNF1-α, 9 K inhibits the sp1 promoter sequence to reduce PCSK9 expression [138].

6.1.3. Anthraquinones

The basic structure of anthraquinone comprises a 9,10 anthracene dione (C14H8O2), which contains three benzene rings as parent nuclei [139]. Several anthraquinones have been identified, including emodin, aloe-emodin, and chrysophanol, extracted from plants, fungi, and lichens. These substances have been shown to prevent hypoxia, apoptosis, high-fat diet, and inflammation-induced myocardial infarction [140–142].

6.1.3.1. The role of emodin. Emodin is primarily extracted from *Polygonum cuspidatum* and *Rheum palmatum*. As a natural anthraquinone compound, emodin can regulate blood lipids, exert antidiabetic effects, and protect the heart, liver, kidney, pulmonary, and nervous system [143–148]. Zhao. et al. reported that emodin upregulated the expression of L-type calcium channels in the heart and pancreas of diabetic rats in a dose-dependent manner [145]. Li et al. found that emodin suppressed the transport of SREBP protein in

huh7 cells *in vitro*, downregulated liver LDL-C and“” TG levels, and improved insulin tolerance in vivo [149]. Mechanistically, emodin decreases SREBP-1 and SREBP-2 mRNA levels in the liver and adipose tissues, which may be one mechanism underlying its antidiabetic effects [149]. In addition, Xue et al. found that emodin treatment substantially improved glucose tolerance and insulin sensitivity in rats and upregulated PPARγ mRNA, suggesting that the activation of PPARγ-related genes may be involved in its antidiabetic mechanism [150]. The lipid-regulating effects of emodin mainly involve the upregulation of AMPKα, ABCA1, ABCG1, and LDLR and the downregulation of SREBP-2, HMGCR, and PCSK9. The mechanisms underlying PCSK9 reduction warrant further elucidation [151]. Similarly, aloe-emodin, another natural anthraquinone derived primarily from aloe vera, was shown to reduce PCSK9 expression and lipid levels by targeting SREBP-2- and HNF1-α-mediated PCSK9 expression [152].

6.2. Synthetic inhibitors

This section summarises certain synthetic hypoglycaemic drugs that can regulate lipid metabolism, along with a recent report revealing their excellent PCSK9 inhibitory activity.

6.2.1. The role of liraglutide

Liraglutide is a glucagon-like peptide-1 receptor agonist (GLP1) that not only reduces blood glucose levels and improves lipid metabolism, but can also decrease the incidence of cardiovascular events and mortality [153–157]. Yang et al. reported that liraglutide downregulated PCSK9 expression in human HepG2 cells in a time- and dose-dependent manner. According to in vivo studies in mice, liraglutide decreased the body weight of wild-type and db/db mice but downregulated blood glucose only in db/db mice [158]. Enzyme-linked immunosorbent assays, haematoxylin-eosin staining, immunohistochemistry, and immunofluorescence revealed that liraglutide treatment substantially decreased serum lipid levels (TG, TC, and LDL-C), as well as markedly reduced PCSK9 levels in the plasma and liver tissues of db/db mice [158]. Conversely, the protein level of LDLR was dramatically upregulated in hepatocytes [158]. The findings could be attributed to liraglutide-mediated actions through an HNF1-α dependent mechanism; HNF1-α is a crucial regulator of PCSK9 gene transcription [4], participating in the regulation of PCSK9 expression. Similarly, Vergès et al. conducted a clinical study on patients with diabetes exhibiting dyslipidaemia. Six-month treatment with liraglutide markedly upregulated the catabolism of ApoB100-containing lipoproteins and the LPL protein content, but effectively reduced the plasma PCSK9 content [159]. Additionally, the authors reported that liraglutide reduced PCSK9 levels in patients with diabetes who were not taking statins; however, this effect was not observed in patients taking statins or with poorly controlled glycaemia [160].

6.2.2. The role of metformin

Metformin, a glucogenic biguanide, is frequently employed as the first-line agent for newly diagnosed T2DM [161]. Metformin mainly inhibits glycogen neogenesis and decomposition and reduces liver glucose output to reduce serum glucose via AMPK-independent mechanisms and AMPK-dependent pathways [162]. Recent studies have found that metformin can effectively reduce serum TG and LDL-C levels while increasing serum HDL-C levels [163,164]. Importantly, metformin has been associated with a reduced risk of cardiovascular events [165] and beneficial effects on cardiac lipid metabolism [166], independent of its glycaemic regulatory effects [165]. Hu et al. proposed that metformin regulates glucose and glucose metabolites in hepatocytes and blocks ChREBP nuclear translocation to reduce ChREBP expression and inhibit its transcriptional activity, thereby reducing the expression and transcriptional activity of PCSK9 [167]. The authors also noted that metformin treatment could substantially reduce serum LDL-C and PCSK9 levels in patients with diabetes [167]. In addition, metformin downregulated PCSK9 expression by inhibiting the SREBP2 and HNF1-α pathways to enhance LDL-C uptake in cultured hepatocytes. In addition, metformin exerted a regulatory effect on genes that regulate cholesterol production and transport, such as AMPK and HMGCR [168].

6.2.3. The role of kanglexin

Kanglexin, a synthetic anthraquinone, was found to possess higher biological activity and solubility but lower toxicity than natural anthraquinone compounds [169]. Kanglexin reportedly affords various cardiovascular benefits, such as preventing myocardial injury and cardiac insufficiency after myocardial infarction through the NLRP3 pathway [170]; inhibiting myocardial fibrosis and cardiac remodelling through TGF-β1/ERK1/2 noncanonical pathway [171]; and reversing myocardial senescence by binding to the ubiquitin-like domain of Parkin, a key regulatory protein of mitochondrial autophagy [169]. A recent study revealed that kanglexin promoted angiogenesis and wound healing by stimulating the FGFR1/ERK signalling pathway, indicating potential therapeutic effects in diabetic foot syndrome [172]. Kanglexin was found to reduce blood lipids, inhibit liver fat accumulation, and reverse the oleic acid-induced accumulation of cellular lipids in vivo by stimulating the AMPK pathway [173]. Additionally, kanglexin downregulated PCSK9 and upregulated LDLR expression by suppressing SREBP-2 expression, thus achieving lipid regulation [173].

7. Discussion

LDLR binds to PCSK9 via the lysosomal degradation pathway. Reduced PCSK9 secretion by pancreatic β-cells leads to impaired LDLR clearance in cell membranes, resulting in excessive LDLR accumulation and, in turn, mediates the β-cell uptake of excessive LDL-C. Excessive lipid accumulation in islet β-cells, either due to dyslipidaemia or abnormally increased LDLR expression in the islet β membrane, depending on the LDLR approach, can induce severe lipid toxicity in β-cells. Ultimately, this results in islet β-cell damage and disorders of insulin secretion. Importantly, LDLR of islet β-cells was degraded only by self-secreted PCSK9 and not by liver-derived, circulating PCSK9. This finding validates the safety of PCSK9 monoclonal antibodies targeting only circulating PCSK9.

Plasma concentrations of PCSK9 and Lp(a) are closely associated with diabetes mellitus. Despite controversial data, the PCSK9 concentration may be positively associated with the rate of NODM. However, the causal relationship between the serum PCSK9 concentration and diabetes needs to be further elucidated in future investigations. In addition, this conclusion is mainly based on clinically observed phenomena. As an inflammatory factor, serum PCSK9 indirectly impacts the function of islet β-cells by activating inflammatory pathways. However, the molecular mechanisms underlying the association between PCSK9 and T2DM warrant further exploration.

In exceptional cases, such as in patients with PCSK9 dysfunctional mutations, markedly low plasma PCSK9 concentrations may be associated with an increased risk of NODM. These findings may be attributed to abnormal lipid accumulation of β-cells caused by excessive LDLR on the β-cell surface in patients with PCSK9 dysfunctional mutations. An increased risk of NODM has also been observed in individuals with inherited low LDL-C levels; however, the underlying cause for low LDL-C levels, i.e., their association with PCSK9 deficiency, is yet to be established. In addition, an increased risk of NODM has been noted in individuals taking lipid-lowering drugs, raising concerns regarding the potential of low LDL-C levels to induce NODM. The available evidence clearly highlights the safety of PCSK9 monoclonal antibodies. As different lipid-lowering drugs act on distinct targets in the body, potentially causing diverse side effects, future studies should focus on differentiating the effects of different drug types on NODM.

Several first-line synthetic antidiabetic agents (e.g., liraglutide and metformin) exhibit the additional benefit of lowering PCSK9 levels. These agents are currently being investigated in clinical studies. Recently, several natural antidiabetic compounds (e.g., anthraquinones, polyphenols, nutrients, and sterols) have emerged, and their benefits in reducing PCSK9 have been explored. Unlike PCSK9 monoclonal antibodies, most antidiabetic agents discussed in the current review inhibit transcription, thereby downregulating PCSK9 expression. This may represent a new direction for developing therapeutic strategies to suppress PCSK9 levels. However, we are still at the inception of developing drugs capable of reducing both glucose and PCSK9. Although a growing number of antidiabetic drugs were found to reduce PCSK9 expression, these results remain mostly limited to *in vitro* studies and obese or diabetic mouse models. Hence, clinical trials assessing these agents are urgently needed to evaluate their clinical benefits, including the effects of PCSK9 reduction and the extent of lipid metabolism improvement, and to assess the risk of potential side effects. To achieve better clinical efficacy, approaches such as synthesising derivatives based on existing natural drugs that allow easier oral administration, extracting bioactive ingredients with potent PCSK9-lowering effects from existing drugs, or encapsulating drugs using nanotechnology to obtain better pharmacokinetic profiles should be considered. The multifarious effects of these drugs may influence the progression of diabetes and associated disorders, thereby introducing novel approaches and methodologies to enhance disease prognosis.

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Declaration of competing interest

All authors declare that they have no competing interests, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

Abbreviations

PCSK9	Proprotein convertase subtilisin/kexin type 9
SRE	sterol regulatory element
HNF1-α	hepatocyte nuclear factor 1α
mTROC1	Mammalian target of rapamycin complex 1
PKCδ	protein kinase C δ
LDLR	low-density lipoprotein receptor
LDL-C	LDL cholesterol
TGRL	TG-rich lipoprotein
HDL	high-density lipoprotein
TC	total cholesterol
Lp(a)	lipoprotein a
T2DM	type 2 diabetes
NODM	new-onset diabetes mellitus
GSIS	β glucose-stimulated insulin secretion
GSIS	glucose-stimulated insulin secretion
PXR	pregnane X receptor

SGK2 serum/glucocorticoid regulated kinase 2
GLUT-2 glucose transporter-2
ASOs antisense oligonucleotide
NOX3 NADPH oxidase 3
FBG fasting blood glucose levels
FINS fasting insulin levels
AAPBA 3-acrylamidophenyl boric acid
polydatin resveratrol-3-*O*-β-mono-D-glucoside
EGCG epigallocatechin-3-gallate
NLRP3 nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3
HOMA-IR homeostatic model assessment insulin resistance index
GLP-1 glucagon-like peptide 1
UPS ubiquitin-proteasome system
Hdber 8-hydroxy dihydroberberine
Bc-NP berberine encapsulated nanoparticles
M3 berberrubin
A8 hydroxypropyl-berberrubine
MI myocardial infarction
THPBs tetrahydroprotoberberine derivatives

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