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REVIEW

Metabolic basis of solute carrier transporters in treatment of type 2 diabetes mellitus

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Abstract Solute carriers (SLCs) constitute the largest superfamily of membrane transporter proteins. These transporters, present in various SLC families, play a vital role in energy metabolism by facilitating the transport of diverse substances, including glucose, fatty acids, amino acids, nucleotides, and ions. They actively participate in the regulation of glucose metabolism at various steps, such as glucose uptake (*e.g.*, SLC2A4/GLUT4), glucose reabsorption (*e.g.*, SLC5A2/SGLT2), thermogenesis (*e.g.*, SLC25A7/UCP-1), and ATP production (*e.g.*, SLC25A4/ANT1 and SLC25A5/ANT2). The activities of these transporters contribute to the pathogenesis of type 2 diabetes mellitus (T2DM). Notably, SLC5A2 has emerged as a valid drug target for T2DM due to its role in renal glucose reabsorption, leading to groundbreaking advancements in diabetes drug discovery. Alongside SLC5A2, multiple families of SLC transporters involved in the regulation of glucose homeostasis hold potential applications for T2DM therapy. SLCs also impact drug metabolism of diabetic medicines through gene polymorphisms, such as rosiglitazone (*SLCO1B1*/*OATP1B1*) and metformin (*SLC22A1−3*/*OCT1−3* and *SLC47A1*, *2*/*MATE1*, *2*). By consolidating insights into the biological activities and clinical relevance of SLC transporters in T2DM, this review offers a comprehensive update on their roles in controlling glucose metabolism as potential drug targets.

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1. Introduction

The prevalence of diabetes in adults aged 20−79 was 10.5% worldwide in 2021, according to the International Diabetes Federation (IDF)[1]. The total number of diabetic patients is estimated at 537 million with a projection to 783 million by 2045 globally[1]. This poses a significant burden on the healthcare systems in many countries. Type 2 diabetes mellitus (T2DM), also known as adult-onset diabetes, is characterized by insulin resistance, which is observed by hyperglycemia accompanied by hyperinsulinemia. Although etiology of T2DM is multifaceted, involving genetic and environmental factors[2], chronic energy excess, such as obesity (absolute energy excess) and aging (relative energy excess), is a prominent risk factor for T2DM[2]. Current strategies for prevention and treatment of T2DM include lifestyle adjustments, medication, and metabolic surgery[2]. However, there is a strong demand for the development of new medicines due to limitations in efficacy and side effects of current drugs. Exploring new drug targets is crucial for improving T2DM care.

Solute carriers (SLCs) represent a class of exciting drug targets in the treatment of diabetes. SLCs belong to a superfamily of membrane transporters, comprising over 60 families with more than 400 members[3]. The primary function of SLCs is to facilitate the transmembrane transport of various substances and xenobiotics, including glucose, fatty acids, amino acids, nucleotides, neurotransmitters, and ions[3]. SLCs are divided into two main classes based on their functions: passive (facilitative) transporters and secondary-active transporters. Passive transporters rely on an electrochemical or chemical gradient to facilitate substance transport across the membrane without consuming active energy. For instance, SLC25A8 (UCP2) spontaneously transports proton (H^+) across the mitochondrial intermembrane into the mitochondrial matrix[3]. Secondary-active transporters transfer substances against electrochemical or chemical gradients by coupling with the movement of a second solute for energy supply. Among these transporters, cotransporters (symporters) transport both the substance and the driving substance in the same direction, while antiporters transport substances in opposite directions. For example, SLC5A1 (SGLT1) and SLC5A2 (SGLT2) are symporters that facilitate the movement of both Na^+ and glucose in the same direction across the membrane of intestinal mucosal epithelial cells for glucose absorption and renal proximal tubular epithelial cells for glucose reabsorption, respectively[4]. These activities play a role in regulating blood glucose levels under physiological conditions. As reviewed in our previous work, SLC16A1 (MCT1) acts as an antiporter, facilitating the exchange of lactate and pyruvate across the cell membrane during glycolysis[5]. This transporter regulates glucose metabolism and the distribution of intermediate metabolites inside and outside cells. Modulating the activities of SLCs can potentially impact blood glucose levels and glucose metabolism at the cellular and organ levels.

SLCs exhibit high expression levels in metabolically active organs such as the liver, kidney, brain, and intestine[6]. They have proven to be successful targets in the treatment of various diseases, including T2DM. Currently, activities of over 80 SLC transporters are known in human diseases, and some of these SLCs have been validated as effective drug targets. One outstanding example is SLC5A2 (SGLT2), which is inhibited by SGLT2 antagonists that are widely used as diabetes medicines worldwide. These antagonists efficiently reduce blood glucose levels by inhibiting glucose reabsorption from urine in the kidney. Furthermore, they also lower the risk of diabetic complications, such as hypertension and diabetic cardiomyopathy[7]. The successful development of SLC-based medicines highlights the potential of SLCs for applications in the treatment of T2DM. However, further investigation is needed to understand the mechanisms by which SLC proteins are regulated by intracellular and extracellular signals in the context of T2DM.

Recently, several comprehensive reviews have discussed the physiological properties of various families of SLC transporters, focusing on drug discovery for diseases such as cancers, cardiovascular diseases, psychiatric disorders, and metabolic diseases[5−9]. However, these reviews lack a specific focus on T2DM due to their broad coverage of diseases, resulting in a limited introduction to the metabolic activities of relevant SLC families. In this review, we aim to provide an extensive details of SLC families involved in the regulation of glucose metabolism, emphasizing their potential applications in the treatment of T2DM. We will also provide an update on the current status of market availability and production pipelines of SGLT1/2 inhibitors. Additionally, we will discuss the impact of SLC polymorphisms on drug metabolism, specifically in relation to T2DM medicines.

2. Solute carrier transporters in glucose metabolism

SLC families play crucial roles in the development of T2DM by influencing energy metabolism. T2DM arises from a state of energy excess, characterized by an imbalance between energy intake and demand in the body, often associated with factors like obesity or aging. These states of energy excess contribute to hyperglycemia in T2DM by inducing insulin resistance, which is further compounded by endocrine disorders characterized by hyperinsulinemia and hyperglucagonemia in affected individuals[10]. Effective treatment strategies for T2DM involve the removal of excess energy, as evidenced by the positive outcomes in patients undergoing weight loss, urinary glucose excretion, and inhibition of mitochondrial respiration[10,11]. In this context, SLCs emerge as excellent drug targets for control of energy surplus by regulating glucose metabolism.

SLC transporters play a crucial role in controlling blood glucose at various steps of energy metabolism. They involve in following events in the regulation of blood glucose levels: glucose absorption from food, glucose reabsorption from urine, glucose uptake by peripheral tissues, and glucose production by the liver, kidney, and intestine. Tissue-specific expression of different families of SLC transporters is responsible for these events.

Notably, the SLC2 family includes glucose transporters (GLUT1, GLUT2, GLUT3, GLUT4, etc.), which facilitate glucose uptake by peripheral tissues and enable glucose sensing by neurons in the brain. The SLC5 family comprises SLC5A1 (SGLT1) and SLC5A2 (SGLT2), which play crucial roles in glucose absorption from food in the intestine (SGLT1) and glucose reabsorption from urine in the kidney (SGLT2 in particular, and to a lesser extent, SGLT1). Inhibiting the activities of SLC5A1 (SGLT1) and SLC5A2 (SGLT2) forms the pharmacological basis for several drugs used in the treatment of T2DM, approved by the United States Food and Drug Administration (FDA). This section focuses on the SLC transporters involved in glucose regulation and their potential roles in the treatment of T2DM (refer to Table 1). Figs. 1 and 2 provide information on their tissue expression, cellular localization, transport substrates, and transport patterns.

2.1. *Solute carrier 2 (SLC2) family*

The SLC2 family, also known as glucose transporter (GLUT) proteins, consists of 14 members responsible for transporting glucose and similar substances (such as fructose, mannose, ascorbate, and urate ions) across the cell membrane in humans. Based on sequence similarity, the 14 transporters are categorized into three classes: Class 1 (SLC2A1−4, 14), Class 2 (SLC2A5, 7, 9, and 11), and Class 3 (SLC2A6, 8, 10, 12, and 13). All members of the SLC2 family function as passive transporters, with the exception of SLC2A13, also known as the H^+/myo-inositol symporter (HMIT)[12]. Currently, four members of this family, namely SLC2A1, SLC2A2, SLC2A3, and SLC2A4, have been reported to be associated with T2DM[12−14].

SLC2A2 (GLUT2) is involved in glucose uptake in various cell types for energy metabolism and glucose sensing. Multiple genetic loci of *SLC2A2* have been found to strongly associate with hyperglycemia, insulin resistance, impaired islet β-cell function, and increased susceptibility to T2DM in several genome-wide association studies (GWASs)[15−17]. SLC2A2 is primarily expressed in the liver, pancreatic islet β cells, intestine, kidney, and brain. In pancreatic β cells, it facilitates the transport of glucose into the cytosol, triggering glucose-stimulated insulin secretion in response to elevated blood glucose levels[14,18]. Inhibiting SLC2A2 activity leads to a suppression of insulin secretion, which is beneficial in controlling hyperinsulinemia in T2DM. In the liver, SLC2A2 is responsible for glucose uptake by hepatocytes in the fed state, but not for glucose output in fasting conditions[14,19]. Inhibiting SLC2A2 function may reduce hepatocyte glucose uptake and control hepatic steatosis by reducing de novo lipogenesis. In the kidney, GLUT2 is essential for the second stage of glucose reabsorption after the initial SGLT2-driven glucose reabsorption, as GLUT2 mediates glucose entry into the bloodstream at the basolateral membrane of epithelial cells[20]. In the intestine, GLUT2 is considered non-essential for glucose absorptionrelative to the primary role of SGLT1[14,20]. In the brain, GLUT2 transports glucose into neuronal cells for energy supply and central glucose sensing, contributing to brain control of thermogenesis and glucagon secretion in response to leptin[21,22]. Additionally, central GLUT2-dependent glucose sensing plays a role in the regulation

Table 1 The role of the typical SLC transporters in glucose and energy metabolism related to T2DM treatment.

SLC family	Substrate category	Gene name	Protein name	Activity/mechanism(s) related to T2DM treatment	Ref.
SLC2	Glucose	*SLC2A2*	GLUT2	Stimulating glucose-stimulated insulin secretion in the pancreatic β cells and glucose uptake in the liver; Influencing glucose reabsorption in kidney; Controlling thermogenesis, glucagon secretion and glucose sensing in the brain	12,14,18−23
		SLC2A4	GLUT4	Improving insulin-stimulated glucose uptake, systemic glucose clearance and muscle glucose utilization	25−27
SLC5	Glucose	*SLC5A1*	SGLT1	Facilitating glucose absorption in intestine	20,32
		SLC5A2	SGLT2	Stimulating glucose reabsorption in the kidney	20,32
		SLC5A9	SGLT4	Facilitating intestinal absorption and renal reabsorption of sugar analogues	36
		SLC5A10	SGLT5	Stimulating renal fructose reabsorption	41,42
SLC7	Amino acid	*SLC7A10*	ASC-1	Facilitating adipocyte serine uptake and total glutathione levels; Inhibiting oxidative stress, lipid accumulation, insulin resistance	45,47
SLC13	Sulfate/carboxylate	*SLC13A5*	NaCT, NaC2, INDY	Stimulating citrate uptake from the sinusoidal blood into hepatocytes for lipid synthesis; Regulating energy expenditure, hepatic glucose production, and insulin sensitivity	50,54−58
SLC16	Monocarboxylate	*SLC16A1*	MCT1	Stimulating pyruvate uptake; Increasing ATP levels; Promoting insulin secretion	59,60
		SLC16A11	MCT11	Regulating lipid accumulation, and insulin resistance	70
		SLC16A13	MCT13	Mediating PPARα activity in the regulation of lipid metabolism	72
SLC25	Miscellaneous (from small ions like H^+ to the larger molecules like ATP)	*SLC25A7*	UCP1	Reducing fasting blood glucose and body weight; Reversing glucose intolerant; Promoting heat generation	78,79
		SLC25A8	UCP2	Regulating insulin sensitivity, and glucolipid metabolism	80
		SLC25A9	UCP3	Regulating insulin sensitivity, glucose tolerance and glucose uptake	81,82
		SLC25A4/5	ANT1/2, AAC1/2	Regulating ATP synthesis, thermogenesis and cell apoptosis	84−87
		SLC25A1	CIC	Stimulating citrate transport from mitochondrial TCA cycle to the cytoplasm for de novo fatty acid synthesis, glucose-stimulated insulin secretion, hepatic gluconeogenesis	89−92
SLC30	Zinc	*SLC30A8*	ZnT8	Regulating glucose tolerance and insulin secretion	98−100

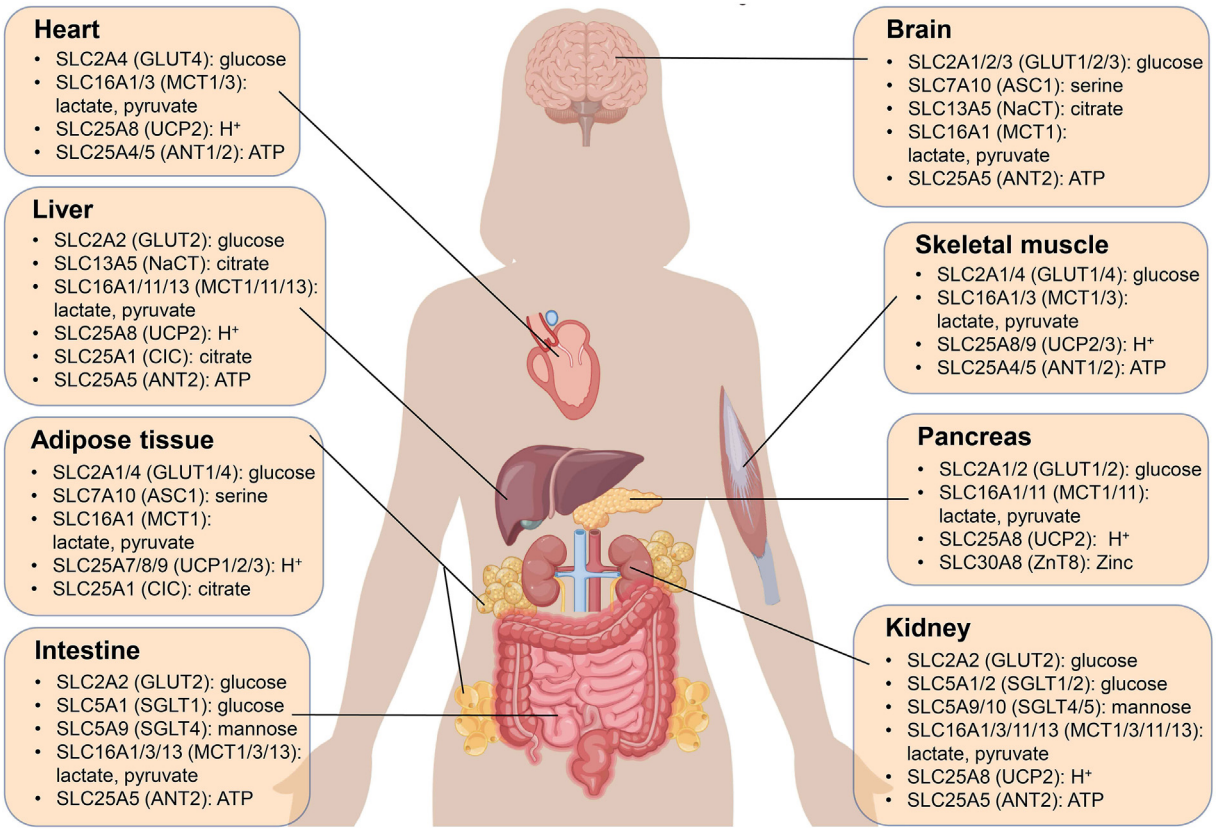

Figure 1 Tissue distribution and substrates of potential SLC targets for treatment of T2DM (By Figdraw). SLC transporters, which hold promise in the context of T2DM therapy, are found across various tissues, with high expression in organs actively engaged in glucose metabolism. These organs encompass the liver, pancreas, kidney, intestine, muscle, and adipose tissue. The pivotal roles of these transporters are facilitating the transmembrane transport of metabolic substrates, including but not limited to glucose, serine, citrate, pyruvate, protons, ATP, and zinc.

of the autonomic nervous system by glucose and is involved in the normal development and function of pancreatic β cells[14,23]. Due to its significant role in glucose sensing in β cells and neuronal cells, SLC2A2 (GLUT2) has emerged as a potential target for treating T2DM to control hyperglycemia.

SLC2A4 (GLUT4) is an insulin-sensitive glucose transporter, which is activated by membrane translocation upon insulin stimulation. *SLC2A4* is highly expressed in the insulin-sensitive tissues, such as adipose tissue, skeletal muscle, and cardiac muscle. *SLC2A4* locates in the cytosol before activation and translocated to the cell surface upon activation by the insulin signal. The translocation disorder is responsible for impaired insulin-stimulated glucose uptake in the mechanism of insulin resistance in T2DM[12,24]. Based on our previous discussion and assessment, SLC2A4 dysfunction in adipose tissues and skeletal muscle may promote glucose uptake and lipid synthesis in the liver[13]. Whole body *SLC2A4* deficiency in the gene knock mice leads to glucose intolerance and fasting hyperglycemia, while *SLC2A4* overactivation in adipose tissue results in insulin sensitization[25]. *SLC2A4* overexpression alleviates insulin resistance by increasing *SLC2A4* density in the cell surface, leading to improvement in insulin-stimulated glucose uptake, systemic glucose clearance and muscle glucose utilization[26,27]. These results indicate that *SLC2A4* activation by drugs may enhance systemic insulin sensitivity to control hyperglycemia in T2DM.

Other members of the SLC2 family, including SLC2A1 (GLUT1) and SLC2A3 (GLUT3), hold potential in the management of T2DM or diabetic complications. GLUT1 is the primary glucose transporter in red blood cells and is expressed in various cell types in different tissues, such as the blood−brain barrier, adipocytes, and kidney cortex mesangial cells. In these cells, GLUT1 mediates glucose uptake under stress conditions like hypoxia. Hypoxia-inducible factor 1 alpha (HIF-1α) induces the expression of GLUT1 in response to hypoxia[28]. Polymorphisms in the *GLUT1* gene (such as rs12407920, rs841847, rs841853, rs3729548) are associated with the risk of diabetic nephropathy[29]. GLUT3, on the other hand, is the primary glucose transporter in the central nervous system and placenta, facilitating glucose uptake in these tissues. Down-regulation of DNA methylation in the *GLUT3* gene promoter increases its expression, leading to increased glucose uptake during placental development. This mechanism may contribute to hyperglycemia in pregnant women with gestational diabetes[30]. It has been observed that *GLUT1* and *GLUT3* expression levels are decreased in T2DM patients, which may contribute to hyperglycemia, as indicated by increased HbA1c levels[31]. However, the potential applications of GLUT1 and GLUT3 in T2DM treatment have not been extensively studied.

2.2. *Solute carrier 5 (SLC5) family*

The SLC5 family consists of 11 transporters and one glucose sensor. Among them, SLC5A1 (SGLT1) and SLC5A2 (SGLT2) are the sodium/glucose cotransporters (SGLTs) that are

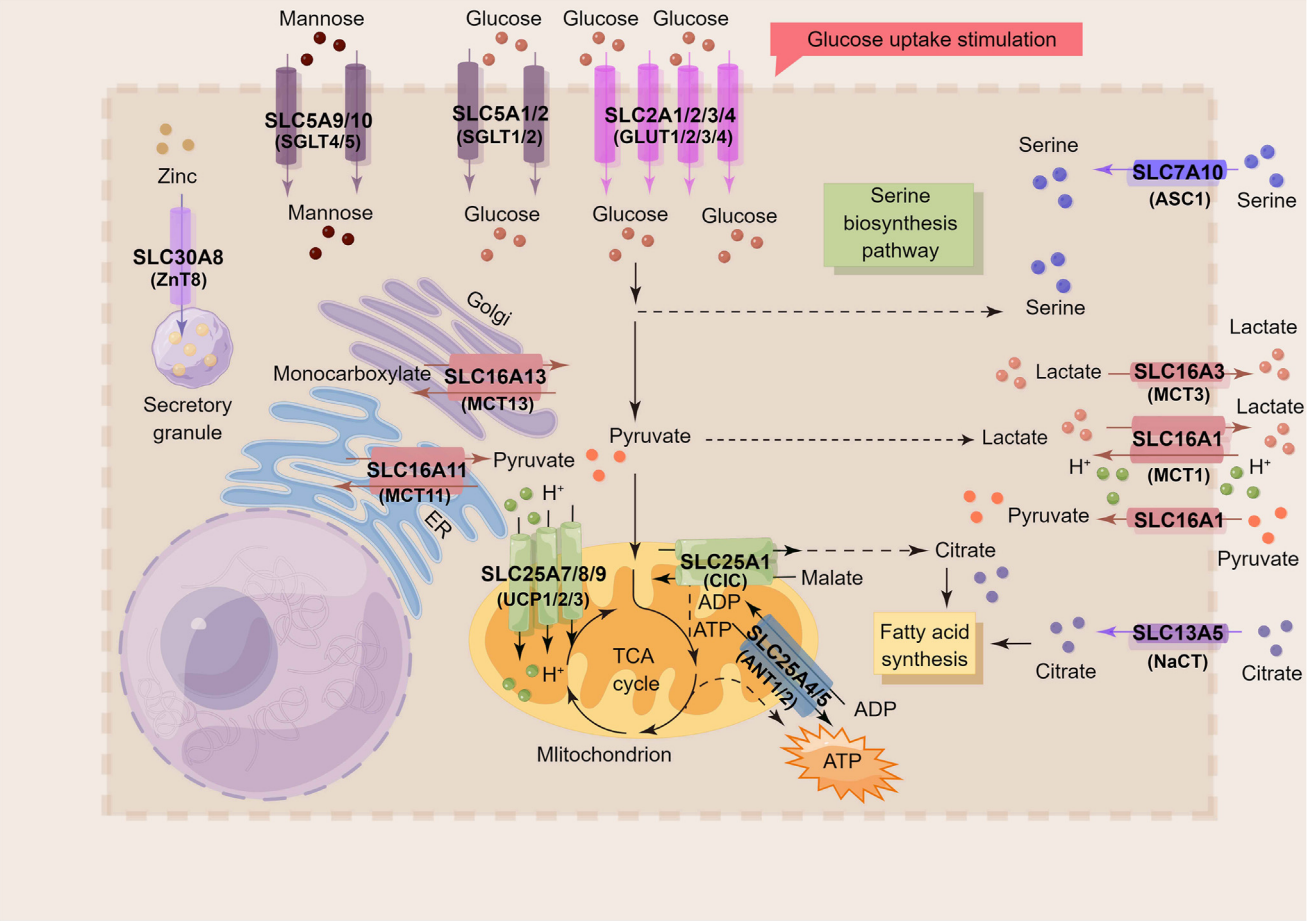

Figure 2 Subcellular localization and transport patterns of potential SLC targets for the treatment of T2DM (By Figdraw). SLC transporters involved in regulating glucose metabolism, a key aspect of T2DM, are expressed in either the plasma membrane or various intracellular membranes, such as the mitochondrial and endoplasmic reticulum membrane. The arrow symbols represent the direction of the transport process. For instance, SLC2A1/2/3/4 and SLC5A1/2 facilitate glucose influx into the cytoplasm, SLC16A1 acts as a lactate/pyruvate exchanger in the plasma membrane, while SLC25A1 operates as a citrate/malate exchanger in the mitochondrial membrane. Additionally, SLC25A7/8/9 transport protons to the mitochondrial matrix, and SLC30A8 transports zinc to secretory granules.

specifically expressed in the intestines and kidneys. SGLT1 and SGLT2 are the most well-known SLC transporters in the context of diabetes therapy. They play a crucial role in glucose reabsorption in the proximal renal tubules and glucose absorption in the intestinal mucosa[20,32,33]. In the kidney, glucose reabsorption occurs through two steps: SGLT2 transports glucose from urine into the cytosol of tubular epithelial cells, while the glucose transporter 2 (encoded by the *SLC2A2* gene) at the basolateral membrane of the cells moves glucose from the cytosol into the bloodstream.

Dysfunction of SGLT2 resulting from a mutation in the *SLC5A2* gene leads to familial glucosuria, an inherited disorder. Patients with this condition can excrete over 100 g of glucose per day in their urine, without experiencing renal tubular dysfunction or hypoglycemia. By blocking the glucose transporter function of SGLT2 through the use of chemical inhibitors, a similar effect of increased glucose excretion can be achieved. This approach has now become a strategy in the treatment of T2DM. Phlorizin, a chalcone derived from the bark of apple tree roots, was the first SGLT2 inhibitor discovered. It was found in the 1930s that phlorizin increased glucose levels in urine (glycosuria)[34]. Dapagliflozin was the first synthetic SGLT2 inhibitor approved for the treatment of T2DM, receiving approval in Europe in 2012 and USA in 2014. Other drugs in the class of SGLT2 inhibitors include canagliflozin and empagliflozin[35]. Additionally, dual inhibitors of SGLT1 and SGLT2, such as sotagliflozin and licogliflozin, have been developed to control blood glucose levels with better efficacy[7].

Furthermore, other members of the SGLT family, such as SLC5A9 and SLC5A10, may be potential drug targets for T2DM or diabetic complications. SLC5A9 (SGLT4) is involved in the intestinal absorption and renal reabsorption of glucose analogues like mannose and 1,5-anhydro-D-glucitol, which have been linked to T2DM through their serum concentrations[36]. A recent study identified three rare variants of *SLC5A9* gene (rs149485404, rs775853981, and rs61997217) associated with proliferative diabetic retinopathy, suggesting that SLC5A9 may play a role in diabetes complications[37]. SLC5A10 (SGLT5) is primarily expressed in the kidney and is responsible for the transport of mannose and fructose, to a lesser extent glucose and galactose[38]. The *SGLT5* variant rs117355297 has been associated with circulating levels of 1,5-anhydroglucitol, a biomarker for diabetic

complications[39,40]. Previous research using *SGLT5* knockout mice indicated that SGLT5 plays a significant role in renal fructose reabsorption[41]. Epidemiological studies have shown an association between fructose intake and the prevalence of diabetes and obesity[42]. However, the specific therapeutic potential of SLC5A9 and SLC5A10 in the treatment of T2DM requires further exploration.

2.3. Solute carrier 7 (SLC7) family

The SLC7 family is responsible for the transportation of amino acids and consists of 15 members in two subgroups. The first subgroup comprises cationic amino acid transporters (CATs), including SLC7A1−4 and SLC7A14. The second subgroup consists of hetero-monomolecular amino acid transporters (HATs), including SLC7A5−13 and SLC7A15[43]. SLC7A10, also known as alanine-serine-cysteine transporter-1 (ASC-1), is a neutral amino acid transporter[44]. It facilitates the uptake of neutral amino acids, playing a role in maintaining total glutathione levels and controlling reactive oxygen species (ROS)[45]. SLC7A10 exhibits high expression in white adipose tissue, contributing to antioxidant activities[45,46]. *SLC7A10* may be a downstream target of a T2DM risk gene known as KLF14 risk allele. This risk allele decreases the mRNA expression of *SLC7A10* in adipose tissue[46]. Reduction in *SLC7A10* expression in adipose tissue is associated with an increased risk of insulin resistance, adipocyte hypertrophy, and metabolic syndrome in multiple human cohorts[46,47]. Conversely, an enhanced SLC7A10 activity in adipocytes through gene overexpression yields opposite effects, including a reduction in oxidative stress, a decrease in lipid accumulation, and improved insulin sensitivity[47]. This suggests that a chemical activator of SLC7A10 may have the potential to improve adipocyte hypertrophy and insulin resistance.

2.4. Solute carrier 13 (SLC13) family

SLC13A5, a member of the SLC13 family (human Na^+-sulfate/carboxylate cotransporters), has shown promise as a drug target for the treatment of carbohydrate and lipid metabolism disorders, such as diabetes, non-alcoholic fatty liver disease, and obesity[48]. The SLC13 family consists of five members in two subgroups. The first subgroup includes three genes encoding sodium-coupled di- and tri-carboxylate transporters (NaDC or NaC), which transport intermediates of the citric acid cycle (TCA cycle). These genes are *SLC13A2* (*NaC1*), *SLC13A3* (*NaC3*), and *SLC13A5* (*NaC2*). The second subgroup comprises two genes encoding sodium-coupled sulfate transporters (NaS) involved in the transport of sulfates, selenite, and thiosulfate. These genes are *SLC13A1* (*NaS1*) and *SLC13A4* (*NaS2*)[49].

SLC13A5 (NaC2/NaCT/INDY), also known as the sodium-coupled citrate transporter, is primarily expressed in the liver and kidney, where it facilitates the uptake of citrate from the blood for glucose and lipid production[50]. In *Drosophila melanogaster*, *SLC13A5* was initially identified as a longevity gene, and mutations in the mammalian homologue Indy gene were found to extend lifespan[51]. Interestingly, mRNA expression of *SLC13A5* was found to be increased in the livers of patients with non-alcoholic fatty liver disease (NAFLD), along with insulin resistance and obesity, suggesting a potential link between SLC13A5 and T2DM[52]. Inhibition of SLC13A5 activity, either through gene deletion or the use of pharmacological blockers, has shown improvements in insulin resistance, T2DM, obesity, and NAFLD in various model organisms[53−56]. These beneficial effects are believed to be related to increased energy expenditure and correction of energy surplus resulting from SLC13A5 inhibition.

Inactivation of the *SLC13A5* gene has been found to promote hepatic mitochondrial biogenesis, fatty acid oxidation, and energy expenditure by decreasing the ATP/ADP ratio, leading to the activation of AMPK. This activation provides protection against high-fat diet (HFD) and aging-induced insulin resistance and obesity in *SLC13A5* knockout mice[54]. In studies involving dietary obese rats and mice, hepatic knockdown of *SLC13A5* using antisense oligonucleotides and shRNA, respectively, demonstrated improved insulin sensitivity, reduced hepatic glucose production, and inhibited hepatic lipid accumulation[55,56]. Moreover, the development of small molecule inhibitors targeting SLC13A5 has shown promising results. One such inhibitor, PF-06649298, was found to completely block citric acid uptake and protect mice from diet-induced glucose intolerance[57]. A more potent inhibitor, PF-06761281, demonstrated dose-dependent reduction in citrate uptake by the liver and kidney, resulting in decreased blood glucose levels in rats[58]. These findings suggest that a chemical inhibitor of SLC13A5 may hold potential as a drug candidate for the treatment of T2DM.

2.5. Solute carrier 16 (SLC16) family

The SLC16 family, which consists of monocarboxylate transporters (MCTs), plays a significant role in various aspects of diabetes. Among the fourteen members of the SLC16 family, four members, namely SLC16A1, SLC16A3, SLC16A11, and SLC16A13, have been identified as being related to diabetes based on current literature[59]. SLC16A1, also known as MCT1, has been recognized as a molecular target for controlling hyperinsulinemia. Hyperinsulinemia is a common endocrine disorder in T2DM characterized by excessive insulin secretion by pancreatic β-cells. SLC16A1 promotes insulin secretion by facilitating the import of glucose metabolites, such as pyruvate or lactic acid, into β-cells[59,60]. This transport of glucose metabolites, particularly pyruvate, from the blood and extracellular matrix into β-cells leads to increased ATP levels, promoting insulin secretion and subsequently raising plasma insulin levels as shown in *SLC16A1* overexpression[60]. Interestingly, studies have shown that disruption of the *SLC16A1* gene can prevent diet-induced obesity, insulin resistance, and hepatic steatosis[61]. These findings suggest that inhibiting SLC16A1 could potentially reduce the risk of hyperinsulinemia and, consequently, prevent obesity and T2DM. However, the effectiveness of chemical inhibitors targeting SLC16A1 needs to be tested.

SLC16A1 (MCT1) and SLC16A3 (MCT4) are highly expressed in various tissues such as the intestine, skeletal muscle, and brain, as reported in the cancer field[62,63]. They play a role in transporting intermediate metabolites of glucose, namely lactic acid and pyruvate, across the cell membrane[59]. In the context of T2DM, the activity of SLC16A3 has been implicated in diabetic nephropathy, which is a common T2DM complication in the kidneys. In a study examining gene expression in ethnic Malays with T2DM, *SLC16A3* was found to be overexpressed in diabetic nephropathy patients[64]. This suggests that SLC16A3 may be associated with susceptibility to diabetic complications, such as

nephropathy. In summary, SLC16A1 and SLC16A3, play roles in hyperinsulinemia and diabetic nephropathy.

The function of SLC16A11 has been linked to T2DM in human genome-wide association studies[65,66]. These studies found that variants of the *SLC16A11* gene were associated with a high susceptibility to T2DM in the Mexican population[65,66]. Individuals carrying variant alleles of *SLC16A11* exhibit increased carbohydrate utilization and reduced rates of lipid oxidation, leading to fat accumulation and an elevated risk of insulin resistance in T2DM[67,68]. A recent study has shown that gene mutations mimicking the *SLC16A11* variants increase the risk of developing T2DM[69]. However, another study challenged this notion by demonstrating that global inactivation of the *SLC16A11* gene in mice did not result in significant metabolic defects[70]. Moreover, reconstitution of mutant SLC16A11 activity specifically in the liver increased the risk of insulin resistance and triglyceride accumulation in the knockout mice[70]. These conflicting results highlight the need for further investigation into the cell type-specific function of SLC16A11 to better understand its role in T2DM.

SLC16A13 (MCT13) is another member of the SLC16 family that has been associated with T2DM in GWASs. In a GWAS analysis of Japanese patients, the *SLC16A13* variant rs312457 was identified as being associated with a high risk of T2DM[71]. A mouse study provided further insights into the role of SLC16A13 in lipid metabolism. It showed that *SLC16A13* gene expression in the small intestine was upregulated by a PPARα agonist in wild-type mice but not in PPARα-null mice. This suggests that SLC16A13 may mediate PPARα activity in the regulation of lipid metabolism[72]. PPARα is a key nuclear receptor involved in stimulating hepatic lipid catabolism. Therefore, downregulation of SLC16A13 activity may lead to lipid accumulation, increasing the risk of hepatic steatosis and insulin resistance. However, the precise mechanisms by which SLC16A13 regulates lipid metabolism in the pathogenesis of human T2DM remain unclear.

2.6. *Solute carrier 25 (SLC25) family*

ATP overproduction resulting from mitochondrial overheating is considered a risk factor for insulin resistance, particularly under conditions of substrate overload in obesity[10]. Mitochondria have two competing processes: ATP production and heat production (thermogenesis), both of which contribute to the dissipation of the mitochondrial potential. Increasing heat production is an attractive strategy to address ATP overproduction. In this regard, members of the SLC25 family represent promising drug targets.

The transporters of the SLC25 family are primarily located in the mitochondrial membranes to function as channels for substance exchange across the membranes, including the outer and inner membranes of mitochondrion. The mitochondrial potential is established by the respiratory chain with a H^+ gradient across the inner membrane[73]. Several members of the SLC25 family have the ability to reduce the mitochondrial potential through proton leak, which is also known as the heat production event. The SLC25 family consists of 53 members, categorized based on their functions, including those of uncoupling proteins (UCPs). UCPs mediate proton leak by transporting protons from the mitochondrial membrane space to the mitochondrial matrix, thereby uncoupling the oxidative phosphorylation and ATP synthesis. Among the six UCP members, three of them have been extensively studied in the context of thermogenesis in brown/beige adipocytes (SLC25A7/UCP1), antioxidant activities in various cell types (SLC25A8/UCP2), and energy metabolism in skeletal muscle (SLC25A9/UCP3) in relation to T2DM or obesity[74,75]. Multiple human studies have established associations of UCPs polymorphisms to obesity and diabetes[76,77].

UCP1 is predominantly expressed in brown and beige adipocytes for thermogenesis. Inducing UCP1 activity through cold stimulation or hormones promotes insulin sensitivity by addressing the energy excess state through heat release. A recent study observed a decreased *UCP1* expression in beige adipocytes derived from adipose-derived stem cells of patients with T2DM. This reduction in *UCP1* expression, along with the accumulation of ROS, may contribute to the thermogenic dysfunction of beige adipocytes[78]. Activation of UCP1 in skeletal muscle has shown beneficial effects, including reducing fasting blood glucose levels, lowering body weight, and reversing glucose intolerance in genetically engineered obese mice[79]. While, *UCP2* deficiency has been implicated in improving insulin sensitivity and glucolipid metabolism in mice on HFD by modulating the PPAR signaling pathway[80]. The role of UCP3 remains controversial in the literature. Loss of UCP3 function in muscle has been reported to enhance glucose uptake, improve glucose tolerance, and increase insulin sensitivity in diet-induced obese (DIO) rats[81]. Conversely, overexpression of *UCP3* in muscle has also been shown to improve insulin sensitivity in HFD-induced obese mice[82]. The physiological roles of UCP2 and UCP3 still require investigation in humans.

Adenine nucleotide translocases (ANT), also known as mitochondrial ADP/ATP carriers (AAC) in yeast, belong to another group of uncoupling proteins within the SLC25 family. Traditionally, they import ADP into the mitochondrial matrix for ATP synthesis and export ATP to the cytosol at the same time[83]. The SLC25A4 (ANT1/AAC1) isoform is highly expressed in the heart and skeletal muscle, while SLC25A5 (ANT2/AAC2) is expressed ubiquitously. Recent studies have revealed that these isoforms also mediate H^+ leak from the intermembrane space into the mitochondrial matrix, contributing to thermogenesis[84]. Increased activity of ANT proteins may reduce the mitochondrial potential, thereby increasing the risk of cell apoptosis. The regulation mechanisms of ANT expression are still largely unknown. However, a recent study demonstrated that NF-κB regulates the protein abundance of ANT2 in mouse brown adipocytes[85]. Inactivation of NF-κB activity in p65-KO mice led to increased ANT2 protein levels in brown adipocytes, which resulted in decreased thermogenesis and increased cell apoptosis in brown fat. Conversely, NF-κB gain-of-function in p65-OE mice led to decreased ANT2 protein levels in brown adipocytes, leading to enhanced thermogenesis[85]. Sodium butyrate treatment at a high dose was shown to induce ANT2 (SLC25A5) activity, leading to the opening of the mitochondrial permeability transition pore and subsequent collapse of the mitochondrial potential, promoting cell apoptosis[86,87]. This effect was accompanied by increased expression and activation of ANT2 proteins.

SLC25A1 is the citrate carrier (CIC) located in mitochondria responsible for exporting citrate from the TCA cycle to the cytosol. The exported citrate serves as a substrate for the production of acetyl-CoA, which is a substrate in de novo fatty acid synthesis, sterol biosynthesis, and protein acetylation[88]. The function of SLC25A1 is essential for de novo fatty acid synthesis from glucose, leading to lipid accumulation during adipocyte hypertrophy. This process is strongly

associated with weight gain and the impairment of systemic insulin resistance in obesity[89,90]. In primary rat islets, inhibiting SLC25A1 function using a substrate analogue (1,2,3-benzenetricarboxylate, BTC) or reducing its mRNA expression with shRNA has been shown to suppress glucose-stimulated insulin secretion[91]. Additionally, inhibiting SLC25A1 with a chemical inhibitor (CTPI-2) or specific gene knockout in the liver has been found to improve insulin sensitivity by inhibiting hepatic gluconeogenesis and lipid synthesis in DIO mice[92]. Therefore, the development of specific inhibitors targeting SLC25A1 may hold promise as potential drug candidates for the treatment of T2DM.

2.7. *Solute carrier 30 (SLC30) family*

The SLC30 family consists of 10 members that facilitate cytoplasmic zinc transport, which is essential for regulating zinc toxicity, as well as the secretion, storage, and supply of zinc-containing proteins[93]. Among these members, SLC30A8, also known as zinc transporter 8 (ZnT8), is highly expressed in the pancreas, where it plays a crucial role in providing zinc for insulin synthesis and influencing the endocrine system[94]. Variants in the *SLC30A8* gene have been associated with susceptibility to T2DM in various ethnic groups, as demonstrated by several GWASs analysis[95–97]. Inactivation of ZnT8 function in pancreatic β-cells has been shown to significantly impair glucose tolerance in *ZnT8*-knockout mice, while overexpression of *ZnT8* in β-cells has the opposite effect, improving glucose tolerance[98]. These findings indicate that ZnT8 plays a role in promoting insulin secretion in β-cells. The favorable response observed with *ZnT8* overexpression strongly suggests that an activator of ZnT8 may reduce blood glucose levels by enhancing insulin secretion, thereby offering a potential therapeutic approach for the control of T2DM.

In contrast to the possibility mentioned above, a recent study utilizing transgenic mice carrying a loss-of-function variant of human *SLC30A8* suggests that inhibiting ZnT8 actually leads to increased insulin secretion[99]. This finding is further supported by another study showing that overexpression of the loss-of-function ZnT8 variant (R325) reduced pancreatic zinc and proinsulin levels but increased insulin levels and glucose tolerance in transgenic mice with diet-induced obesity[100]. Additionally, in human studies involving the sequencing or genotyping of over 150,000 individuals, loss-of-function mutations or variants of *SLC30A8* were found to actually protect individuals from developing T2DM[101]. These studies suggest that inhibiting ZnT8 may decrease the risk of T2DM by promoting up-regulation of insulin secretion. In conclusion, both animal and human studies highlight the importance of ZnT8 in glucose homeostasis. However, due to the complex nature of ZnT8's functions in the onset and progression of T2DM, further investigation is needed to better understand the effects of drug interventions targeting ZnT8.

3. Solute carrier transporters in the metabolism of T2DM medicines

Drug metabolism plays a crucial role in determining the effectiveness and potential toxicity of medicines. It is influenced by the genetic background of individuals. With advancements in sequencing technology and genetic pharmacology, our understanding of how genetic variations impact drug metabolism has significantly progressed. Gene polymorphisms provide new insights into the variations observed in drug metabolism among individuals. Among the potential factors influencing drug absorption, distribution, and excretion, polymorphisms in SLC genes, which encode drug transporters, are of particular importance. In this section, we will explore the role of SLC gene polymorphisms in the regulation of medicines used in the T2DM treatment. Please refer to Table 2 for specific details.

3.1. *Solute carrier 21 (SLC21) family*

The SLC21 family encompasses the organic anion transporting polypeptide superfamily (OATPs), predominantly expressed in the kidney, liver, intestine, and brain, where they play a role in regulating drug absorption and distribution[102]. In the context of diabetes, several members of this family, including SLCO1B1 (OATP1B1), SLCO1B3 (OATP1B3), and SLCO2B1 (OATP2B1), have been implicated in the metabolism of diabetes medicines, such as nateglinide, repaglinide (which induce GLP-1 activity by suppressing the GLP-1 degrading enzyme DPP IV), and rosiglitazone (a PPARγ agonist with insulin sensitizing activity)[103]. Among these members,

Table 2 The SLC transporters polymorphisms associated with T2DM drug response.

SLC family	Gene name	Protein name	Genetic polymophism	Drug (category)	Ref.
SLC21/SLCO	*SLCO1B1*	OATP1B1	*rs4149056, rs2306283, rs4149015*	Repaglinide, nateglinide (Meglitinide derivatives); Rosiglitazone (Tiazolidinediones)	104–108
SLC22	*SLC22A1*	OCT1	*rs12208357, rs34130495, rs72552763, rs34059508, rs34104736, rs36103319, rs34447885, rs628031, rs200684404, rs1867351, rs622342, rs3413095, rs461473, rs4646272*	Metformin (Biguanide)	111–117
	SLC22A2	OCT2	*rs145450955, rs316019, rs201919874*	Metformin (Biguanide)	119–122
	SLC22A3	OCT3	*rs2076828, rs68187715, rs8187725, V423F*	Metformin (Biguanide)	123,124
SLC47	*SLC47A1*	MATE1	*rs2252281, rs2289669, rs8065082, rs77630697, rs77474263, rs35790011, rs76645859, rs35395280, rs149774861, A310V rs35646404*	Metformin (Biguanide)	126–130
	SLC47A2	MATE2	*K64N, G211V, G393R, rs34399035, rs146901447, rs12943590*	Metformin (Biguanide)	115,130,131

the *SLCO1B1* gene polymorphism has been associated with the efficacy of antidiabetic drugs. The single nucleotide polymorphism (SNP) V174A (c.521T > C, rs4149056) in *SLCO1B1* leads to reduced transportation of nateglinide and repaglinide, altering their pharmacokinetics[104−106]. Another SNP, c.-11187G > A (rs4149015), in *SLCO1B1* is associated with an enhanced effect of repaglinide in controlling hyperglycemia[106]. Alongside the c.521T > C SNP, the N130D variant (c.388A > G, rs2306283) in *SLCO1B1* is another common variant associated with decreased plasma concentration of repaglinide and shortened time to maximum concentration of nateglinide[107]. Furthermore, the *SLCO1B1* c.521T > C variant has been linked to enhanced rosiglitazone activity in improving insulin sensitivity[108]. However, these findings have been challenged by another study that observed no impact on the activity of rosiglitazone or pioglitazone at conventional therapeutic doses[109]. Hence, more research is needed to clarify the effect of the *SLCO1B1* c.521T > C polymorphism.

3.2. *Solute carrier 22 (SLC22) family*

The SLC22 family, consisting of 12 members, plays a crucial role in regulating the cellular uptake and renal clearance of metformin, a first-line medicine for the treatment of T2DM with insulin sensitization activity. The family includes organic cation transporters (OCTs/SLC22A1−3), the ergothioneine transporter (OCTN1/SLC22A4), the carnitine transporter (OCTN2/SLC22A5), the organic anion transporters (OATs/SLC22A6-11), and the urate anion-exchanger (URAT1/SLC22A12)[110]. Among these members, SLC22A1 (OCT1), SLC22A2 (OCT2), and SLC22A3 (OCT3) have been found to play essential roles in the pharmacokinetics of metformin[110]. Genetic polymorphisms in *SLC22A1*, including R61C (rs12208357), G401S (rs34130495), M420del (rs72552763), G465R (rs34059508), S189L (rs34104736), G220V (rs36103319), S14F (rs34447885), M408V (rs628031), and P117L (rs200684404), have been associated with decreased cellular uptake and reduced therapeutic effectiveness of metformin[111−116]. Variants, such as R61C, G401S, M420del, G465R, and a promoter-linked synonymous variant (rs1867351) of the *SLC22A1* gene, are thought to increase the renal clearance of metformin[114]. Genetic variations at rs622342, rs3413095, rs461473, and rs4646272 in the *SLC22A1* gene have been linked to HbA1c levels and the insulin sensitization activity of metformin[115−117].

Furthermore, it has been reported that renal SLC22A2 (OCT2) plays a significant role in the renal clearance of metformin[118]. Certain SNPs in the *SLC22A2* gene, such as T201M (rs145450955), A270S (rs316019), and T199I (rs201919874), have been found to influence the renal excretion and clearance of metformin[119−122]. In the case of *SLC22A3*, three variants, namely T44M (rs68187715), T400I (rs8187725), and V423F (c.1267G > T), have been shown to have a significant impact on metformin uptake[123]. Additionally, the genetic variant rs2076828 of *SLC22A3* has been associated with reduced sensitivity to metformin[124]. It is important to note that these genotype/phenotype associations can be controversial in different populations, emphasizing the need for caution when extrapolating data obtained from ethnically diverse populations.

3.3. *Solute carrier 47 (SLC47) family*

The SLC47 family, also known as multi-drug and toxin extrusion (MATE) proteins, are efflux transporters responsible for pumping their substrates out of cells. They are known to regulate the activities of metformin. Among the members of this family, SLC47A1 (MATE1) is primarily expressed in the liver and kidney and plays a significant role in the pharmacokinetics of metformin[125]. Several studies have suggested that specific variants of *SLC47A1*, including rs2252281, rs2289669, and rs8065082, are associated with metformin activities[126,127]. Additionally, during a multiethnic cohort study, five nonsynonymous variants of *SLC47A1*, namely G64D (rs77630697), L125F (rs77474263), V338I (rs35790011), V480M (rs76645859), and C497S (rs35395280), were identified to be closely associated with reduced metformin transporter activity[128−130]. Furthermore, three other genetic polymorphisms, D328A (rs149774861), V159M (rs35646404), and A310V (c.929C/T) of *SLC47A1*, were also shown to be associated with decreased metformin uptake[129,130].

The SLC47A2 (MATE2) transporter is highly expressed in renal epithelial cells and also plays a crucial role in the excretion of metformin[125]. In a study conducted on the Japanese population, two nonsynonymous SNPs of *SLC47A2*, namely K64N (c.192G/T) and G211V (c.632−633 GC/TT), were identified and found to be associated with reduced transport and uptake of metformin[130]. Another SNP, G429R (rs34399035), of *SLC47A2* was reported to apparently impact long-term HbA1c values in European Caucasians[115]. Moreover, several genetic variants of *MATE2* with significant functional effects have been identified. These include G393R (c.1177G > A), P162L (c.485C > T, rs146901447), and g.−130G > A (rs12943590)[131]. Among these variants, c.1177G > A and c.485C > T were associated with significantly reduced metformin uptake and decreased SLC47A2/MATE2 protein expression. The g.−130G > A variant was associated with a significant increase in the gene promoter activities and reduced binding by the transcriptional repressor myeloid zinc finger 1. Additionally, the SNPs P162L and G393R were found to associate with dramatically lower metformin uptake, while rs12943590 was linked to a poorer response to metformin[131].

4. SLC-based T2DM drugs in market and pipeline

Chemical drugs that target SLC transporters have been utilized in the clinical treatment of various diseases. Currently, FDA of the United States has approved 10 classes of SLC-based drugs for the management of conditions, such as T2DM, psychiatric disorders, kidney disease, progressive familial intrahepatic cholestasis, hypertension, edema, tardive dyskinesia, gout, hyperuricemia, osteoporosis, high blood cholesterol, peripheral and coronary arterial disease. These medicines target 10 families of SLC transporters, including SLC5, SLC6, SLC9, SLC10, SLC12, SLC18, SLC22, SLC25, SLC29, and SLC65[132,133]. In addition, there are eight more classes of SLC-targeted drugs currently in the pipeline, undergoing clinical trials for the treatment of various diseases. These conditions include type 1 diabetes (T1DM), T2DM, NAFLD, obesity, postoperative pain, schizophrenia, Duchenne muscular dystrophy, hepatitis B/D infection, constipation, gout, hyperuricemia, cancers, and anemia. These potential medicines target proteins belonging to eight SLC families, namely SLC5, SLC6, SLC7, SLC9, SLC10, SLC16, SLC22, and SLC40[132,133]. These studies highlight the growing importance of SLC transporters in the field of drug discovery.

In the field of T2DM treatment, SLC5A1 (SGLT1) and SLC5A2 (SGLT2) are the major cellular targets for drug development. Specifically, for SGLT2, there are currently 11 selective inhibitors approved worldwide for the clinical treatment of T2DM (Table 3). Four of these inhibitors, namely canagliflozin,

Table 3 Approved drugs or drugs in the pipeline targeting SLC5A1/2 (SGLT1/2) for T2DM treatment.

Drug status	Gene (protein)	Drug/compound	Research and development units	Country/ region	Approval number/ clinical trial ID	Time	Ref.
Approved	*SLC5A2* (SGLT2)	Canagliflozin	Janssen Pharmaceuticals Inc.	United States	NDA204042	2013/03/29	134–136
			Jassen-Cilag International Nv	European Union	EMEA/H/C/002649	2013/11/15	
				China	H20170375; H20170374	2017/09/29	
			Mitsubishi Tanabe Pharma	Japan	22600AMX00744	2014/07/04	
		Dapagliflozin	AstraZeneca	European Union	EMEA/H/C/002322	2012/11/11	134,137
				United States	NDA202293	2014/01/08	
				China	H20170120; H20170118; H20170205; H20170119; J20170039; H20170117; H20170206; J20170040	2017/03/10	
				Japan	22600AMX00528; 22600AMX00529	2014/03/24	
		Empagliflozin	Boehringer Ingelheim	European Union	EMEA/H/C/002677	2014/05/22	134,138
				United States	NDA204629	2014/08/01	
				China	H20170351	2017/09/20	
			Boehringer Ingelheim and Eli Lilly	Japan	22600AMX01387000; 22600AMX01386000	2014/12/26	
		Ertugliflozin	Merck Sharp & Dohme	United States	NDA209803	2017/12/19	134,139–141
				European Union	EMEA/H/C/004315	2018/03/21	
			Pfizer Manufacturing Deutschland Gmbh	China	HJ20200023	2020/07/29	
		Bexagliflozin	TheracosBio	United States	NDA214373	2023/01/20	142,143
		Enavogliflozin	Daewoong Pharmaceutical	Korea	*N/A*	2022/11/30	144
		Henagliflozin	Jiangsu Hengrui Medicine	China	H20210052; H20210053	2021/12/31	145,146
		Remogliflozin	Glenmark Pharmaceutical	India	*N/A*	2019/04/30	147,148
		Ipragliflozin	Astellas Pharma and Kotobuki Pharmaceutical	Japan	22600AMX00009; 22600AMX00010	2018/12/21	149–151
		Tofogliflozin	Chugai Pharmaceutical	Japan	22600AMX00548; 22600AMX00549	2014/03/24	152,153
		Luseogliflozin	Taisho Pharmaceutical	Japan	22600AMX00540000; 22600AMX00541000	2014/03/24	154,155
New-drug application	*SLC5A1/2* (SGLT1/2)	Sotagliflozin	Lexicon Pharmaceuticals	United States	*N/A*	2021/12/30	158,159
	SLC5A2 (SGLT2)	Janagliflozin	Sihuan Pharmaceutical Holdings Group Ltd.	China	CXHS2200014; CXHS2200013; CXHS2200015; CXHS2200012	2022/02/28	160,161
Clinical trial	*SLC5A1/2* (SGLT1/2)	Licogliflozin	Novartis Pharmaceuticals	United States	Phase II (NCT03152552)	2017/07/25	162,163
		LX-2761	Lexicon Pharmaceuticals Inc.	United States	Phase I (N/A)	2018/12/20	164
	SLC5A1 (SGLT1)	SY-008	Suzhou Yabao Pharmaceutical R&D Co., Ltd.	United States	Phase I (NCT03462589)	2018/08/02	165,166
				China	Phase I (CTR20180242; CTR20180803; CTR20200654)	2018/03/20	

Table 3 (*continued*)

Drug status	Gene (protein)	Drug/compound	Research and development units	Country/ region	Approval number/ clinical trial ID	Time	Ref.
		SY-009	Suzhou Yabao Pharmaceutical R&D Co., Ltd.	United States	Phase II (NCT05426018)	2022/07/01	167,168
				China	Phase II (CTR20220144)	2022/08/11	
	SLC5A2 (SGLT2)	Rongliflozin	Sunshine Lake Pharma Co., Ltd.	United States	Phase I (NCT05427682; NCT05497674)	2022/02/21	169−171
			Guangdong HEC pharm Co., Ltd.	China	Phase III (CTR20201620; CTR20201770)	2021/02/20	
		Tianagliflozin	TIPR Pharmaceutical Co., Ltd.	China	Phase II (CTR20201558)	2020-08-10	172
		LH-1801	Jiangsu Lianhuan Pharmaceutical Co., Ltd.	China	Phase I (CTR20230259; CTR20230260)	2023-01-31	173
		DWC202213	Daewoong Pharmaceutical Co., Ltd.	Korea	Phase I (NCT05737771)	2023-01-25	174
		DA-2811	Dong-A ST Co., Ltd.	Korea	Phase I (NCT04938752)	2021-07-08	175

N/A: not available.

dapagliflozin, empagliflozin, and ertugliflozin, have been approved by regulatory agencies, such as the United States FDA, European Medicines Agency (EMA), and National Medical Products Administration (NMPA) of China[134−141]. Bexagliflozin, approved in the United States in January 2023, is indicated as an adjunct to diet and exercise to improve blood glucose control in adults with T2DM[142,143]. Enavogliflozin[144], henagliflozin[145,146] and remogliflozin[147,148] have recently received approvals in Korea, China, and India, respectively, for the treatment of T2DM. Additionally, in the Japanese market, there are three more drugs approved for T2DM treatment by the Pharmaceuticals and Medical Devices Agency (PMDA), including ipragliflozin[149−151],

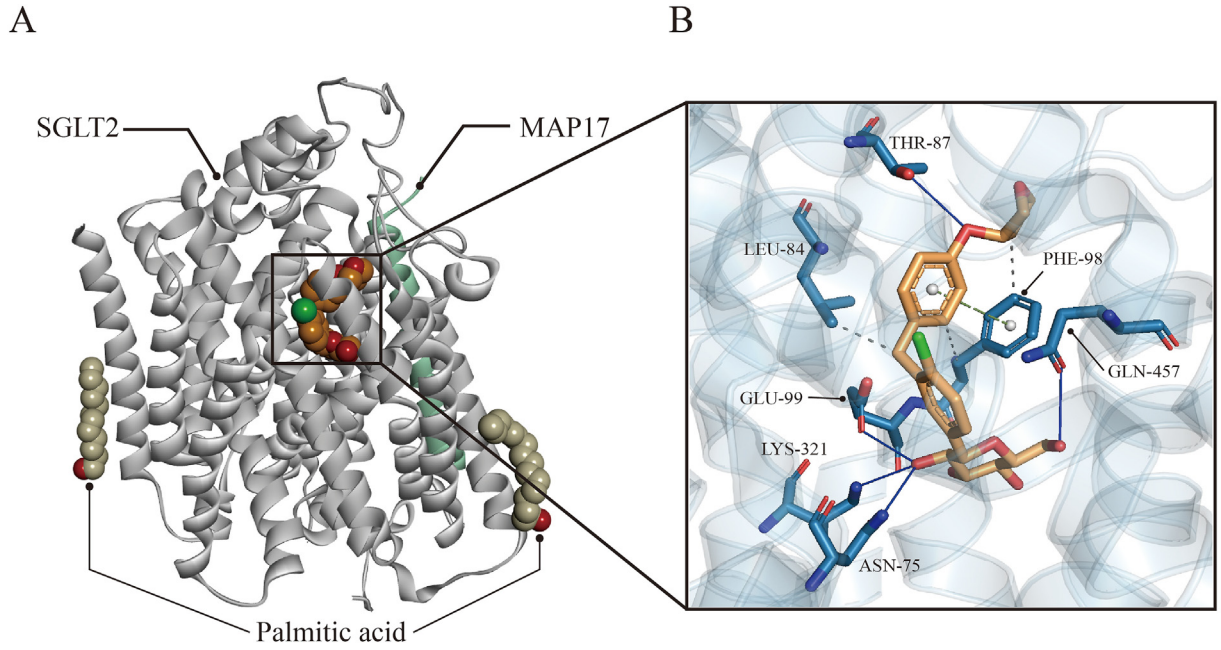

Figure 3 The configuration of the human SGLT2−MAP17 complex bound to empagliflozin. (A) The cryo-electron microscopy (cryoEM) structure of the human SGLT2 (hSGLT2) protein (depicted in gray) in complex with the membrane protein MAP17 (shown in green) and the drug empagliflozin (represented in brown) [Protein Data Bank (PDB) entry 7VSI]. (B) A closer view highlighting the interactions between empagliflozin and hSGLT2. Potential hydrogen bonds are indicated by solid blue lines, hydrophobic interactions by dashed black lines, and pi-stacking interactions by dashed green lines. The figures were generated using PyMOL and PLIP (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index).

tofogliflozin[152,153] and luseogliflozin[154,155]. Notably, there are currently no medicines available on the market that exclusively target SGLT1 for the treatment of diabetes.

The field of SLC-based drug development has shown significant activity in the treatment of diabetes. One notable example is the dual inhibitor sotagliflozin, which was approved by the EMA in 2019 for the treatment of patients with T1DM. However, it was rejected by the United States FDA and subsequently withdrawn from the market[156,157]. Nevertheless, the development of sotagliflozin for the treatment of T2DM has recently reentered the phase of new drug application and clinical trials[158,159]. Another promising candidate, janagliflozin, a selective SGLT2 inhibitor for the treatment of T2DM, is currently in the phase of new drug application and clinical trials[160,161]. While the clinical studies of the dual SGLT1/2 inhibitor licogliflozin for T2DM have been terminated, its clinical studies for the treatment of obesity and NAFLD are ongoing[162,163]. Additionally, several other SLC-based drugs targeting SGLT1, SGLT2, or both are in the pipeline under clinical trials for the treatment of T2DM, including LX-2761 (a dual SGLT1/2 inhibitor)[164], SY-008[165,166] and SY-009[167,168] (SGLT1-specific inhibitors), and five SGLT2-specific inhibitors (rongliflozin[169−171], tianagliflozin[172], LH-1801[173], DWC202213[174], DA-2811[175]). However, sergliflozin, developed by GlaxoSmithKline, was discontinued after Phase II trials (NCT00291356)[176]. These studies highlight the active pursuit of SLC-based drug development in the treatment of diabetes and other metabolic diseases.

The structure of the hSGLT2-MAP17 complex in the presence of empagliflozin has been determined using cryogenic electron microscopy, with an overall resolution of 2.95 Å[177]. Human SGLT2 (hSGLT2) interacts with the cell membrane protein MAP17, primarily through the transmembrane helix 13 domain of hSGLT2, to form a functional transporter complex. Empagliflozin, a drug used in the treatment of diabetes, binds to both the sugar-substrate-binding site and the external vestibule of hSGLT2, resulting in the inhibition of glucose import by locking hSGLT2 in an outward-open conformation (Fig. 3). The antagonistic activity of SGLT1 and SGLT2 inhibitors is not dependent on insulin secretion, which reduces the risk of hypoglycemia, a major side effect associated with some diabetes medicines[178]. Additionally, apart from lowering hyperglycemia and glycosylated hemoglobin levels, these inhibitors offer several advantages. They exhibit cardio-reno-protective properties and contribute to reductions in body weight, blood pressure, and triglyceride levels. The adverse effects, such as urogenital infections and polyuria, associated with these medicines are predictable and controllable[7]. The introduction of SGLT2 inhibitors has brought about a significant shift in the treatment strategies for T2DM, focusing on increasing glucose excretion in the urine instead of the traditional approach of reducing urine glucose levels through the use of insulin or insulin mimetics.

5. Conclusions

In this review, we provide evidence to support the current understanding of SLC activities in regulating glucose metabolism and their potential applications in the treatment of T2DM. One of the validated drug targets for T2DM medicines is SLC5A5 (SGLT2). SGLT2 inhibitors have demonstrated efficacy in reducing hyperglycemia and have shown additional benefits including body weight correction, blood pressure normalization, and fatty liver improvement in clinical settings[179−183]. Furthermore, SGLT2 inhibitors have shown protective effects on cardiovascular and renal functions in the clinical trials[184−186]. To date, 11 medicines targeting SGLT2 have been approved for T2DM therapy worldwide. Additionally, there are 11 other drugs based on single or dual inhibitors of SGLT2 and SGLT1 in the pipeline, currently being considered for new applications or undergoing clinical trials for T2DM therapy.

Other families of SLC proteins, including SLC2, SLC7, SLC13, SLC16, SLC25, and SLC30, also hold potential as drug targets for T2DM or metabolic diseases due to their involvement in the regulation of energy metabolism. These proteins play crucial roles in various aspects of glucose metabolism, such as glucose reabsorption, insulin sensitivity, glucose production, energy expenditure, lipid oxidation, regulation of glutathione levels, mitochondrial respiration, and mitochondrial accumulation of ROS, among others.

From a pharmacological perspective, SLC transporters play two important roles in relation to T2DM. First, they contribute to the control of glucose metabolism, and second, they regulate drug metabolism. In terms of glucose metabolism, two families of SLCs are involved in glucose uptake (*e.g.*, SLC2A4/GLUT4) and glucose reabsorption (*e.g.*, SLC5A2/SGLT2), directly influencing blood glucose levels. Other families of SLCs regulate glucose utilization in metabolic processes, such as thermogenesis (*e.g.*, SLC25A7/UCP-1), ATP production (*e.g.*, SLC25A4/ANT1 and SLC25A5/ANT2), and synthesis of lipids and glucose (*e.g.*, SLC13A5/NaCT and SLC25A1/CIC).

Additionally, SLCs play a significant role in the metabolism of T2DM medicines. Genetic polymorphisms in SLC genes can influence the effectiveness of T2DM drugs. For example, SNPs in genes such as *SLCO1B1* (*OATP1B1*), *SLC22A1-3* (*OCT1-3*), *SLC47A1* (*MATE1*), and *SLC47A2* (*MATE2*) can impact the disposition and metabolism of drugs like repaglinide, rosiglitazone, and metformin. Moreover, the expression of certain SLC genes in the liver of obese mice was found to be altered and restored by metformin treatment. This observation provides new insights into the mechanism of metformin in insulin sensitization and obesity[187].

Indeed, the exact transport mechanisms and regulatory pathways of those SLCs remain largely unknown. There is ongoing debate regarding the applicability of certain SLC members in drug discovery. Furthermore, SLC-based medicines currently on the market may have side effects that need to be carefully controlled or eliminated, such as issues with low blood volume and electrolyte imbalances[188]. Other reported side effects include polyuria, urinary and reproductive tract infections, lower limb amputation, acute kidney injury, diabetic ketoacidosis, hyperkalemia, and more[188−191]. Research on the application of SLCs in the treatment of T2DM is still in its early stages, and our understanding of most SLCs is limited in terms of genetics, pharmacology, and toxicology. This review presents various families of SLCs involved in the regulation of energy metabolism and drug metabolism relevant to T2DM. However, more studies in both humans and animals are needed to explore the potential applications of SLCs and enhance our understanding of their roles in T2DM therapy.

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Author contributions

Jiamei Le wrote and revised the manuscript, prepared the tables and drew the figures. Jiamei Le, Yilong Chen, and Wei Yang searched databases for information on the solute carrier transporters in T2DM. Jianping Ye and Ligong Chen provided the idea, guided the manuscript writing and revised the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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