Advances in SGLT2 Inhibitors for Type 2 Diabetes Management

Mohd. Javed Naim [1*]

Abstract

Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors have emerged as a significant class of medications for the management of type 2 diabetes mellitus, offering improved glycemic control and cardiovascular benefits. This review focuses on the development of various SGLT2 inhibitors, highlighting their chemical structures, pharmacological properties, and therapeutic potential. Methods: A comprehensive literature review was conducted, summarizing the synthesis and biological evaluation of multiple SGLT2 inhibitors, including novel compounds derived from C-aryl glucoside scaffolds, C-glucosides, and 5α-carba-β-D-glucopyranose derivatives. Studies utilized various techniques, such as click chemistry, Friedel-Crafts alkylation, and pharmacokinetic assessments, to evaluate the efficacy and selectivity of these inhibitors. Results: Several promising compounds were identified, including compound 1 (GCC5694A) with an IC50 of 0.460 nM against SGLT2 and strong selectivity for SGLT1, and compound 26, which exhibited an IC50 of 4.47 nM, surpassing dapagliflozin. Novel derivatives, such as compound 22 (IC50 = 47 nM) and compound 27, demonstrated significant inhibitory effects and selectivity profiles. Pharmacokinetic studies revealed compounds like compound 28 had enhanced half-lives compared to established drugs like sergliflozin. Additionally, compounds such as the nitric oxide-releasing dapagliflozin derivative exhibited dual anti-diabetic and anti-thrombotic properties. Conclusion: The ongoing development of SGLT2 inhibitors demonstrates substantial advancements in therapeutic options for type 2 diabetes. The structural modifications and novel compounds explored in this review highlight the potential for improved efficacy and safety profiles, suggesting that these new agents could play a vital role in diabetes management and warrant further clinical investigation.

Keywords: SGLT2 inhibitors, pharmacokinetics, glucose metabolism, drug development, diabetes therapy.

Significance | This review highlights novel SGLT2 inhibitors, emphasizing their potential in enhancing therapeutic options for type 2 diabetes management.

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1. Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a unique class of antidiabetic drugs that have transformed the management of type 2 diabetes mellitus (T2DM) through an insulin-independent mechanism. Unlike traditional therapies that rely on enhancing insulin sensitivity or stimulating insulin release, SGLT2 inhibitors work by targeting the sodium-glucose co-transporter-2 in the proximal renal tubules. This transporter is responsible for reabsorbing the majority of filtered glucose in the kidneys. By inhibiting SGLT2, these drugs prevent glucose reabsorption, promoting its excretion through urine, thereby reducing blood glucose levels. This distinct mode of action provides a therapeutic advantage, especially in advanced stages of T2DM, where insulin resistance and declining β-cell function often limit the effectiveness of insulin-based therapies (Ferrannini & Solini, 2012; Inzucchi et al., 2015; White, 2015).

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The historical development of SGLT2 inhibitors dates back to the discovery of phlorizin, a naturally occurring O-glycoside found in the bark of apple trees and other plants. Initially identified by French chemists in 1835, phlorizin was recognized for its ability to induce glycosuria by inhibiting both SGLT1 and SGLT2, albeit non-selectively (Ehrenkranz et al., 2005). Subsequent studies in the 1950s and 1960s revealed that phlorizin could block glucose transport in the kidney and small intestine, limiting its passage into erythrocytes and reducing blood glucose levels in diabetic animal models (Keller & Lotspeich, 1959; Alvarado & Crane, 1962). However, the non-selective inhibition of SGLT1 resulted in significant gastrointestinal side effects, such as dehydration and diarrhea, and its rapid metabolism in the intestinal tract limited its clinical applicability (Rossetti et al., 1987; Katsuno et al., 2007; Abdul-Ghani & DeFronzo, 2008).

Despite these challenges, phlorizin laid the groundwork for the development of more selective and metabolically stable SGLT2 inhibitors. Early attempts to refine phlorizin's structure, such as with T-1095, faced similar limitations due to non-selective inhibition of SGLT1 and SGLT2 (Oku et al., 1999). However, further advances led to the successful development of selective SGLT2 inhibitors, such as dapagliflozin, canagliflozin, empagliflozin, and others, which overcame the limitations of phlorizin and T-1095 (Bhattacharya et al., 2020; Haider et al., 2019). The objective of this review is to provide a comprehensive overview of the pharmacological properties, clinical benefits, and potential risks associated with SGLT2 inhibitors. This includes a detailed exploration of their mechanism of action, pharmacokinetics, therapeutic indications, and adverse effects, along with an examination of their role in improving glycemic control, cardiovascular outcomes, and renal protection in patients with T2DM. Additionally, this review will highlight ongoing challenges and future research directions to optimize the use of SGLT2 inhibitors in clinical practice.

1.1 SGLT2 inhibitors in clinical practice

SGLT2 inhibitors have emerged as a pivotal class of medications for managing diabetes mellitus. Their mechanism of action involves the inhibition of the sodium-glucose co-transporter 2 (SGLT2) protein in the kidneys, which is primarily responsible for reabsorbing glucose back into the bloodstream. By blocking this transporter, SGLT2 inhibitors promote the excretion of excess glucose through urine, effectively lowering blood glucose levels. This innovative approach not only aids in glycemic control but also offers additional benefits, making these drugs integral to contemporary diabetes management strategies. In clinical practice, SGLT2 inhibitors play a vital role in the comprehensive management of type 2 diabetes. One of their primary benefits is effective blood sugar control. These inhibitors work by promoting the excretion of glucose through the urine, thereby reducing blood sugar levels. They can be used as a monotherapy for glycemic control or in combination with other antidiabetic medications such as insulin, sulfonylureas, or metformin, depending on the patient's needs (Bhosle et al., 2022). This versatility makes SGLT2 inhibitors a valuable option in personalized diabetes treatment plans.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors, such as canagliflozin and empagliflozin, have demonstrated significant cardiovascular benefits in patients with type 2 diabetes mellitus (T2DM). Research indicates that these medications lower the risk of cardiovascular events, including heart failure and stroke, in diabetic patients, enhancing their overall cardiovascular health (Vallon & Verma, 2021). In addition to their cardiovascular effects, SGLT2 inhibitors have also shown renoprotective properties, making them particularly beneficial for individuals with both diabetes and chronic kidney disease (CKD). Studies have confirmed that these drugs slow the progression of diabetic kidney disease, offering a dual benefit in managing T2DM and preventing renal complications (Bailey et al., 2022).

A notable advantage of SGLT2 inhibitors is their association with weight loss, an important factor for overweight or obese individuals with T2DM. By promoting urinary glucose excretion, these drugs contribute to calorie loss, aiding in weight reduction (Pinto et al., 2015). Additionally, SGLT2 inhibitors have been linked to modest reductions in blood pressure, a beneficial effect for patients with hypertension, a common comorbidity in T2DM (Thomas & Cherney, 2018).

Despite their benefits, SGLT2 inhibitors are not without risks. They are generally well tolerated, but some adverse effects have been reported. The most common side effects include an increased risk of urinary tract infections and genital infections. Moreover, although rare, euglycemic diabetic ketoacidosis (DKA) can occur, particularly during periods of illness or surgery, and requires careful monitoring (Singh & Kumar, 2018).

When prescribing SGLT2 inhibitors, healthcare professionals must consider the individual needs, preferences, and comorbidities of each patient. Factors such as cardiovascular risk, renal function, and the potential for adverse effects play a crucial role in determining the appropriateness of these medications in clinical practice. Regular evaluation and monitoring are essential to ensure optimal treatment outcomes. The role of SGLT2 inhibitors in diabetes management, including their cardiovascular and renal benefits, as well as potential risks, is summarized in Figure 1.

1.1.1 SGLT2 Inhibitors Overview

Canagliflozin

Canagliflozin, a member of the SGLT2 inhibitor class, enhances glucose excretion in urine, thereby reducing blood glucose levels without the reliance on insulin. Clinical studies indicate that it effectively lowers blood pressure, reduces body weight, and improves glycemic control while posing a minimal risk of

hypoglycemia. Additionally, canagliflozin positively influences cardiovascular risk factors, including arterial stiffness, serum uric acid levels, and blood pressure. Ongoing research aims to further elucidate its effects on renal and cardiovascular health. Common side effects include increased urination and genitourinary infections. Cost-utility evaluations suggest that canagliflozin may be more economical than other antihyperglycemic agents. While generally well tolerated, patients prone to volume depletion may experience adverse effects. The U.S. FDA approved canagliflozin in March 2013 as the first SGLT2 inhibitor for managing type 2 diabetes mellitus (T2DM) under the brand name Invokana® (Janssen Pharmaceuticals, Johnson & Johnson, New Brunswick, NJ, USA) (Jakher et al., 2019; Neal et al., 2017).

Dapagliflozin

Dapagliflozin is effective in lowering blood pressure, body weight, fasting plasma glucose levels, and HbA1c in individuals with T2DM. However, it can increase the risk of hypoglycemia, urinary tract infections (UTIs), and vaginal infections when combined with other medications. Dapagliflozin has shown promise in reducing diabetes-related complications, including diabetic retinopathy, foot amputations, and end-stage renal disease. Research indicates that its efficacy is consistent across diverse populations, including Chinese and Japanese individuals. In patients with type 1 diabetes, the combination of dapagliflozin with insulin therapy can lead to reduced glycemic levels and insulin requirements, albeit with an increased risk of hypoglycemia. It is advised to avoid co-administration with loop diuretics to prevent dehydration and hypotension (Saeed & Narendran, 2014; Imran et al., 2020).

Empagliflozin

Empagliflozin, an antidiabetic medication approved by the FDA in 2014, is indicated for adult patients with T2DM. It can be used as monotherapy or in combination with other diabetes medications. Notably, the FDA has also approved empagliflozin for reducing the risk of cardiovascular mortality (Zinman et al., 2015; Neeland et al., 2016; Schwaiger et al., 2019).

Ertugliflozin

Ertugliflozin, another specific SGLT2 inhibitor, is utilized for treating individuals with T2DM. Marketed as Steglatro, it is indicated as an adjunct to diet and exercise to manage hyperglycemia in adults aged 18 and older. Clinical studies have shown that ertugliflozin effectively reduces HbA1c levels in patients with T2DM. It may also offer benefits for individuals with hypertension or obesity. Its mechanism involves increasing sodium excretion through osmotic diuresis, resulting in a slight reduction in blood pressure. Moreover, glucose excretion promotes weight loss due to lower caloric intake (Kovacich & Chavez, 2018).

Ipragliflozin

Ipragliflozin, also classified as an SGLT2 inhibitor, is prescribed for managing T2DM. It functions by inhibiting the SGLT2 protein in the kidneys, thereby promoting increased glucose excretion and lowering blood glucose levels. This medication not only aids in glycemic control but also provides cardiovascular benefits and renal protection (Komatsu et al., 2020).

Luseogliflozin

Luseogliflozin, another SGLT2 inhibitor, reduces blood glucose levels through increased glucose excretion in urine and decreased glucose reabsorption by the kidneys. It is indicated for the treatment of T2DM and is associated with side effects that may impact lipid profiles, potentially influencing arteriosclerosis and liver function (Yabe et al., 2017).

SGLT2 inhibitors represent a significant advancement in diabetes management, offering various therapeutic benefits alongside their primary role in glucose regulation.

1.2 Indications of SGLT-2 Inhibitors

SGLT-2 inhibitors are a class of antihyperglycemic medications that specifically target the SGLT-2 proteins expressed in the proximal convoluted tubules of the kidneys (Nespoux & Vallon, 2020). Recent research has highlighted the significance of SGLT-2 inhibitors, leading to their approval as effective glucose-lowering agents for the treatment of diabetes (Bonora et al., 2020). These medications have been the subject of extensive reviews, which assess their pharmacological mechanisms, biological interactions, and clinical efficacy, including safety data from clinical trials (Handlon, 2005; Aylsworth et al., 2014).

By selectively inhibiting SGLT-2 proteins, these medications promote increased glucose excretion in urine while simultaneously reducing blood glucose levels (Scheen, 2019; Kanwal & Banerjee, 2013). SGLT-2 inhibitors represent a novel therapeutic approach to managing diabetes, particularly beneficial in situations where β-cell function declines and insulin resistance increases (Chao & Henry, 2010). They primarily act on the kidneys through an insulin-independent mechanism, inhibiting the reabsorption of filtered glucose by approximately 30-50%. This action leads to reduced glucotoxicity and a partial correction of hyperglycemia, as noted by Scheen and Paquot (2014).

SGLT-2 inhibitors are increasingly recognized as preferred glucose-lowering agents for patients with type 2 diabetes mellitus (T2DM), especially when metformin monotherapy does not adequately control blood glucose levels. Their use is particularly recommended in patients with a history of atherosclerotic cardiovascular disease (CVD), heart failure, and/or chronic kidney disease, provided their estimated glomerular filtration rate (eGFR) is sufficient (Davies et al., 2018). It is worth noting that hyperglycemia itself can enhance the expression of SGLT-2 and lead to increased renal glucose reabsorption, resulting in inadequate glycemic control. Therefore, the inhibition of SGLT-2 not only lowers blood glucose levels but also induces glycosuria, thereby improving overall diabetes management (Rieg et al., 2014; Vallon, 2015).

In summary, SGLT-2 inhibitors represent a valuable addition to diabetes management, effectively addressing hyperglycemia and providing ancillary benefits in patients with cardiovascular and renal complications.

Mechanism of action of SGLT2 Inhibitors

SGLT2 inhibitors primarily target the SGLT2 proteins expressed in the proximal convoluted tubules of the kidneys, where they facilitate the reabsorption of filtered glucose from the tubular lumen. The use of SGLT2 inhibitors lowers the renal threshold for glucose (RTG), leading to increased glucose excretion in urine and a decrease in the reabsorption of filtered glucose. Clinical studies have demonstrated that SGLT2 inhibitors can reduce HbA1c levels by approximately 0.7% (Plosker, 2014).

By blocking SGLT2-mediated glucose reabsorption, these inhibitors increase the distal tubular sodium load. This effect subsequently inhibits the renin-angiotensin-aldosterone system (RAAS), resulting in a decrease in both preload and afterload, which contributes to their cardioprotective properties (Lytvyn et al., 2017). Figure 3 illustrates the mode of action of SGLT2 inhibitors on the kidneys.

In addition to their glycemic effects, SGLT2 inhibitors lower uric acid levels through mechanisms that include natriuresis and diuresis, along with arterial vasodilation. These drugs also modify cardiac metabolism by favoring ketogenesis over carbohydrate utilization. The beneficial outcomes observed in patients with heart failure may be attributed to these favorable hemodynamic effects and a reduction in cardiac disease biomarkers (Januzzi et al., 2017). According to the "thrifty substrate" concept, during SGLT2 inhibitor therapy and mild, chronic hyperketonemia, β-hydroxybutyrate is actively transported into the heart via specific transporters, such as the monocarboxylate transporter (MCT) system. Consequently, glucose and fatty acids are less oxidized, enhancing the heart's efficiency by utilizing β-hydroxybutyrate as an alternative cardiac fuel source (Yang et al., 2020).

The nephroprotective effects of SGLT2 inhibitors arise from the increase in distal sodium (Na^+) concentrations and the inhibition of tubuloglomerular feedback. This results in afferent vasoconstriction and a reduction in intraglomerular pressure, ultimately leading to decreased albuminuria. The disruption of proximal sodium and glucose reabsorption processes causes natriuresis, while also altering renal mitochondrial metabolism, reducing renal hypoxia, and modifying pathways that promote inflammation and fibrosis (Yau et al., 2022; Larmour & Levin, 2021).

SGLT2 inhibitors offer a multifaceted approach to managing diabetes and its complications by enhancing renal glucose excretion, improving cardiac metabolism, and providing nephroprotective benefits.

2. Pharmacodynamic properties

In the kidneys, glucose is filtered through the glomerulus and reabsorbed in the proximal convoluted tubule (PCT). The maximum reabsorption rate of glucose in humans is approximately 375 mg/min. In individuals with normal glucose tolerance, the rate of glucose filtration is typically lower than the tubular maximum glucose reabsorption capacity (TmG), ensuring complete reabsorption of filtered glucose and the absence of glycosuria. This balance is maintained as the average daily plasma glucose level remains around 100 mg/dL, with an estimated glomerular filtration rate (eGFR) of 180 L/day. However, in individuals with poorly managed type 1 or type 2 diabetes, glycosuria can occur when the filtered glucose load exceeds TmG. As noted by DeFronzo et al. (2017), healthy individuals do not exhibit glycosuria until their blood glucose levels exceed approximately 180 mg/dL.

Glucose transport is crucial for reabsorption, as glucose is a polar molecule that cannot passively diffuse through the PCT walls. The sodium-glucose co-transporter 2 (SGLT2) is located on the S2 and S3 segments of the PCT, where it plays a pivotal role in glucose reabsorption. SGLT2 exhibits a high affinity but low capacity for glucose, accounting for approximately 90% of glucose reabsorption in the S1 segment of the PCT. The Na/K ATPase pump on the basolateral membrane establishes a sodium gradient by extruding three sodium ions into the bloodstream while bringing two potassium ions into the tubule lumen. This gradient enables the SGLT proteins to harness energy from sodium's downward gradient to transport glucose against its concentration gradient across the PCT's apical membrane. This mechanism exemplifies secondary active transport, where SGLT2 mediates a 1:1 cotransport of sodium and glucose (DeFronzo et al., 2017). Once inside the cell, glucose is transported into the bloodstream by the GLUT1 and GLUT2 transporters located on the basolateral membrane (Sattar et al., 2016).

Pharmacodynamically, SGLT2 inhibitors lead to a reduction in TmG and the glucose resorption threshold, resulting in increased glycosuria. For instance, in well-controlled patients with type 2 diabetes, dapagliflozin has been shown to decrease TmG by 56%, dropping from 420 mg/min to 184 mg/min (DeFronzo et al., 2012). Interestingly, glycosuria can also occur in non-diabetic individuals with normal glycemia, as the glucose resorption threshold may decline from 180 mg/dL to a range of 40–80 mg/dL, as reported by DeFronzo et al. (2013) and Polidori et al. (2014).

While SGLT2 is responsible for reabsorbing approximately 90% of filtered glucose (around 160 g/day in healthy individuals), inhibitors of SGLT2 typically increase urinary glucose excretion by approximately 80 g/day, which is less than half of the total filtered glucose load. In this context, SGLT1 also plays a role in glucose reabsorption. Although SGLT2 reabsorbs the majority of glucose, SGLT1, located distally in the S2/S3 segments, has a maximum

transport capacity of around 80 g/day. When SGLT2 is inhibited, SGLT1 can operate at its maximum resorptive capacity, leading to increased glucose delivery to SGLT1, which further contributes to glycemic control. Therefore, while the urine glucose output may be substantial, it remains less than 50% of the filtered glucose load. Overall, Abdul-Ghani et al. (2015) report that SGLT2 reabsorbs 90% of the filtered glucose, while SGLT1 reabsorbs up to 40%, highlighting the importance of both transporters in glucose homeostasis.

3. Pharmacokinetics

The pharmacokinetics of SGLT2 inhibitors, which play a key role in managing type 2 diabetes, involve several important processes. In terms of absorption, these inhibitors are efficiently absorbed through the gastrointestinal system. The intake of food has no significant effect on their pharmacokinetics, allowing drugs such as ertugliflozin, dapagliflozin, and empagliflozin to be administered with or without meals. However, it is recommended that these medications be taken before meals to reduce postprandial plasma glucose spikes, which occur due to delayed intestinal glucose absorption (Garcia-Ropero et al., 2018).

Once absorbed, SGLT2 inhibitors are distributed throughout the body via the bloodstream. They exhibit high plasma protein binding (PPB), with dapagliflozin at 91%, empagliflozin at 86%, and ertugliflozin at 93%. Canagliflozin has the highest PPB, binding at 99%. Importantly, plasma protein binding does not show significant alterations in patients with hepatic or renal impairment. These inhibitors also demonstrate substantial tissue distribution, with volumes of distribution for canagliflozin (83.5L), dapagliflozin (118L), ertugliflozin (85.5L), and empagliflozin (74L), particularly targeting the kidney's renal tubules where they exert their pharmacological effects (Scheen, 2015).

Regarding metabolism, SGLT2 inhibitors undergo biotransformation primarily through glucuronidation, mediated by uridine 5'-diphosphate-glucuronosyltransferases (UGTs), with minimal involvement of the cytochrome P450 system. UGT1A9 plays a central role in the metabolism of these drugs. For example, canagliflozin is metabolized by UGT1A9 and UGT2B4, ertugliflozin by UGT1A9 and UGT2B, dapagliflozin by UGT1A9, and empagliflozin by multiple UGTs, including UGT2B7, UGT1A3, UGT8, and UGT1A9 (Scheen, 2015).

Excretion primarily occurs via the kidneys. SGLT2 inhibitors are filtered through the glomerulus and bind to the luminal membrane of the proximal convoluted tubule. By binding to SGLT2 receptors in the nephron's early segments, they inhibit up to 60% of glucose reabsorption. Due to their long elimination half-lives, SGLT2 inhibitors require only once-daily dosing for effective glycemic control (Wright, 2021).

3.1 Administration

SGLT2 inhibitors are available in oral formulations, with dosing tailored to specific clinical indications. Prior to initiating treatment with dapagliflozin, it is crucial to assess renal function, as impaired kidney function can impact the drug's efficacy. Additionally, any volume depletion in patients should be corrected before starting therapy with SGLT2 inhibitors. These medications are generally contraindicated before surgeries, during prolonged fasting, or in patients with severe medical conditions due to an increased risk of ketoacidosis (Scheen & Deeks, 2017).

Most SGLT2 inhibitors can be taken with or without food. However, canagliflozin is specifically recommended to be taken before the morning meal. Canagliflozin is available in 100 mg and 300 mg doses (Dhillon, 2019). Dapagliflozin is available in 5 mg and 10 mg tablets, while empagliflozin comes in 10 mg and 25 mg tablets, both taken once daily in the morning (Frampton, 2018). Ertugliflozin, offered in 5 mg and 15 mg doses, is also administered once daily in the morning (Marrs & Anderson, 2020).

In addition to their standalone formulations, several SGLT2 inhibitors are available as fixed-dose combinations (FDCs). These combinations include ertugliflozin with metformin, dapagliflozin with saxagliptin, linagliptin with empagliflozin, dapagliflozin with metformin, ertugliflozin with sitagliptin, and metformin with empagliflozin extended-release (ER) (Marrs & Anderson, 2020; Jakher et al., 2019). These FDCs provide flexible treatment options for patients with type 2 diabetes, allowing for a more tailored approach to managing blood glucose levels.

4. Adverse effect

SGLT2 inhibitors are associated with several adverse effects, including mycotic genital infections, urinary tract infections (UTIs), bladder cancer, bone fractures, diabetic ketoacidosis, hypoglycemia, hypotension, and dehydration. Mycotic genital infections such as candidiasis, vulvovaginitis, vulvar abscess, and bacterial vaginitis are among the common side effects of SGLT2 inhibitors. Female sex and a history of recurrent genital infections (three or more per year) are significant risk factors. Preventive measures include maintaining personal hygiene and optimizing diabetic care. Most infections are mild and can be managed with appropriate hygiene, without the need to discontinue the medication (Engelhardt et al., 2021). Urinary tract infections are more likely with SGLT2 inhibitors due to the increased excretion of glucose in the urine, which creates an environment conducive to bacterial growth. All SGLT2 inhibitors, including dapagliflozin, empagliflozin, and canagliflozin, are associated with an elevated risk of genitourinary infections (Jabbour et al., 2014; Haering et al., 2015). Bladder cancer has been linked to dapagliflozin based on a meta-analysis of 22 randomized controlled trials (RCTs). As a result, dapagliflozin is not recommended for patients with active bladder cancer (Yang et al., 2013; Lin & Tseng, 2014). Bone

fractures have also been reported, particularly with canagliflozin, which has been associated with an increased risk of fractures that typically occur 12 weeks after starting the medication (Watts et al., 2016). Diabetic ketoacidosis (DKA) is another concern, with the risk being about three times higher in individuals on SGLT2 inhibitors. Canagliflozin carries the highest risk, followed by dapagliflozin and empagliflozin (Douros et al., 2020). While hypoglycemia is not typically induced by SGLT2 inhibitors when used alone, the risk increases when these drugs are combined with insulin or sulfonylureas. Continuous use of these combinations can significantly enhance the likelihood of hypoglycemia (Zhao et al., 2022).

SGLT2 inhibitors may cause hypotension and dehydration due to their osmotic diuretic effects, leading to increased urination. Dehydration can contribute to hypotension or low blood pressure (Mazidi et al., 2017). Monitoring and managing these side effects are crucial for ensuring patient safety during SGLT2 inhibitor therapy.

4.1 Toxicity

Toxicity associated with SGLT2 inhibitors lacks a known antidote, and these drugs are not effectively removed via dialysis. A retrospective analysis of SGLT2 inhibitor overdoses reported to 13 US poison control centers found that most cases, except those involving young patients, did not result in hypoglycemia. Instead, the most common symptoms included nausea, vomiting, and lightheadedness. However, intentional overdoses have been associated with more severe symptoms such as hypoglycemia, tachycardia, vomiting, disorientation, hypertension, and urinary incontinence (Schaeffer et al., 2018).

Evidence from individuals with familial renal glycosuria suggests that long-term renal glycosuria does not negatively impact kidney function. Nevertheless, it remains unclear whether increased urine glucose concentrations due to SGLT2 inhibitors will lead to a higher risk of urinary tract infections (UTIs). A prospective study involving over 600 diabetic women found that glycosuria did not increase the likelihood of developing UTIs. This finding is supported by phase I and II clinical trials of SGLT2 inhibitors, which demonstrated no significant difference in UTI incidence between patients receiving active medication and those on placebo (Geerlings et al., 2014).

Additionally, protein-bound uremic toxins may affect the pharmacokinetics and pharmacodynamics of SGLT2 inhibitors by interfering with their protein-binding capacity and secretion from renal tubules. A decline in renal function is associated with a reduction in the pharmacodynamic response to SGLT2 inhibitors, as indicated by lower levels of urinary glucose excretion in patients with impaired kidney function (Geerlings et al., 2014). Monitoring kidney function and adjusting dosages in patients with renal impairment is essential for the safe use of SGLT2 inhibitors.

5. Synthesized potential SGLT2 inhibitors

A series of compounds developed by Kong et al. (2022) featured a C-aryl glucoside scaffold for biological testing, focusing on their activity against SGLT2. Among these compounds, compound 1 (GCC5694A), which includes a dihydrobenzofuran moiety, exhibited the most promising in vitro activity against SGLT2, with an IC50 value of 0.460 nM. This compound demonstrated strong selectivity for SGLT1 and good metabolic stability compared to the reference drug, dapagliflozin. Following oral administration, compound 1 was rapidly absorbed, reaching its maximum plasma concentration (Cmax) within 1 hour. It exhibited a terminal half-life of 4.9 hours and an oral bioavailability of 77.4%. Notably, the pharmacokinetic profiles of compound 1 and dapagliflozin were found to be quite similar.

Additionally, Mukkamala et al. (2020) synthesized benzyl C-analogues of dapagliflozin and evaluated their potential as SGLT1 and SGLT2 inhibitors using a cell-based, non-radioactive fluorescence glucose uptake test. Among the tested compounds, compound 2 demonstrated the highest potency as an SGLT2 inhibitor, with an IC50 value of 0.64 nM, significantly outperforming dapagliflozin, which had an IC50 value of 500 nM for SGLT2 inhibition compared to its weaker activity against SGLT1.

In the context of dapagliflozin's pharmacokinetics, Karumanchi et al. (2020) investigated its metabolites, which are critical for the treatment of type 2 diabetes. The study identified three primary metabolites: benzylic hydroxy dapagliflozin (3), oxo dapagliflozin (4), and desethyl dapagliflozin (5). Utilizing high-resolution mass spectrometry (HRMS) with a Xevo G2 QTOF mass spectrometer and electrospray ionization (ESI) method, alongside purification via column chromatography, the study emphasized the significant role that these pharmacologically active metabolites play in drug development and discovery. The therapeutic effects and pharmacological actions of these metabolites can enhance or mitigate the effects of the parent drug.

Furthermore, Wang et al. (2019) introduced a novel class of SGLT2 inhibitors, termed 6-deoxy O-spiroketal C-arylglucosides, aimed at treating type 2 diabetes mellitus. This innovation involves modifying the interaction with the glucose binding site of hSGLT by removing the hydroxy group at C-6 from the sugar moiety of traditional SGLT-2 inhibitors, thereby altering their physicochemical properties and target identification methods. Among the compounds evaluated, compound 6 exhibited the most potent suppression of hSGLT-2, with an IC50 value of 4.5 nM, outperforming the established standard dapagliflozin, which showed an IC50 value of 8.3 nM.

The SGLT2 inhibitor tofogliflozin was developed by Murakata et al. (2019) through the intramolecular cycloaddition of dihydroisobenzofuran. The synthesis of the dihydroisobenzofuran

moiety (7) involved several key steps, including intramolecular [4 + 2] cycloaddition of a dienone-yne intermediate, followed by aerobic aromatization and anomeric equilibration. The desired derivative of tofogliflozin (7) was isolated after extensive hydrogenolysis and global deprotection. Under aerobic conditions, the dienone-yne molecule underwent intramolecular cycloaddition, yielding the dihydroisobenzofuran moiety integral to its structure.

Kuo et al. (2018) synthesized benzocyclobutane-C-glucosides that act as potent oral dual inhibitors of SGLT1 and SGLT2, utilizing a rodent model for evaluation. Among the compounds tested, Compound 8 exhibited remarkable potency, with IC50 values of 1 nM for SGLT2 and 45 nM for SGLT1. Additionally, it demonstrated excellent pharmacokinetic profiles, with bioavailability (F) ranging from 78% to 107% in dogs, monkeys, rats, and mice. Treatment with Compound 8 significantly and dose-dependently reduced blood glucose levels in Sprague-Dawley (SD) rats and maintained an anti-hyperglycemic effect in Zucker Diabetic Fatty (ZDF) rats for up to 24 hours. These results suggest that Compound 8 holds potential as an effective pharmacological tool for managing metabolic syndrome.

Ng et al. (2018) developed novel carbasugars (pseudo-sugars) as potential SGLT2 inhibitors, synthesizing them from inexpensive D-gluconolactone, which features a biologically stable "pseudo-glycosidic" C-O bond. Various cross-coupling processes catalyzed by transition metals were employed in the synthesis. The β-pseudo-C-glycosides demonstrated greater activity compared to their α-counterparts, indicating that the β-configuration at C-1 is critical for SGLT2 inhibition. Among these, allylic analogue 9 exhibited an IC50 of 24 nM and over 400-fold selectivity for SGLT2 compared to SGLT1, while dapagliflozin had an IC50 of 0.9 nM for SGLT2. The researchers developed a clear, stereodivergent synthesis pathway for these pseudo-C-glycosides, highlighting a chemo-selective diamide reduction followed by a regioselective and stereoselective Pd-catalyzed allyl-aryl coupling reaction. Notably, allylic carbasugar 9 demonstrated significant potency and selectivity toward SGLT2 while maintaining physiological stability.

Chu et al. (2019) synthesized and biologically assessed a series of N-glucosyl indole derivatives as SGLT2 inhibitors, building on their prior research involving various sugar moieties. They prepared 16 novel N-glucosyl indole compounds, testing their efficacy against hSGLT2. The most effective inhibitor identified was compound 10, which contained acethydrazide and demonstrated an EC50 value of 33 nM. This compound significantly enhanced urinary glucose excretion in rats at a dose of 50 mg/kg compared to the vehicle control.

Li et al. (2018) synthesized nitric oxide-releasing dapagliflozin derivatives, evaluating them as potential anti-diabetic and anti-thrombotic agents. These novel NO donor/SGLT2 inhibitor hybrids were designed to mitigate both hyperglycemia and thrombosis. Among these, Compound 11 exhibited superior efficacy as an SGLT2 inhibitor, with an IC50 of 125.7 nM and anti-platelet aggregation effects of 14.43%. Its NO-mediated anti-platelet action was confirmed in the presence of a NO scavenger. In subsequent in vivo trials, Compound 11 demonstrated significant reductions in urinary glucose excretion and glucose-lowering effects, even at doses ten times higher than dapagliflozin. This versatile hybrid compound is anticipated to serve as a promising therapeutic option for managing cardiovascular complications associated with type 2 diabetes.

The SGLT2 inhibitor tofogliflozin was developed by Murakata et al. (2019) through the intramolecular cycloaddition of dihydroisobenzofuran. The synthesis of the dihydroisobenzofuran moiety (7) involved several key steps, including intramolecular [4 + 2] cycloaddition of a dienone-yne intermediate, followed by aerobic aromatization and anomeric equilibration. The desired derivative of tofogliflozin (7) was isolated after extensive hydrogenolysis and global deprotection. Under aerobic conditions, the dienone-yne molecule underwent intramolecular cycloaddition, yielding the dihydroisobenzofuran moiety integral to its structure.

Kuo et al. (2018) synthesized benzocyclobutane-C-glucosides that act as potent oral dual inhibitors of SGLT1 and SGLT2, utilizing a rodent model for evaluation. Among the compounds tested, Compound 8 exhibited remarkable potency, with IC50 values of 1 nM for SGLT2 and 45 nM for SGLT1. Additionally, it demonstrated excellent pharmacokinetic profiles, with bioavailability (F) ranging from 78% to 107% in dogs, monkeys, rats, and mice. Treatment with Compound 8 significantly and dose-dependently reduced blood glucose levels in Sprague-Dawley (SD) rats and maintained an anti-hyperglycemic effect in Zucker Diabetic Fatty (ZDF) rats for up to 24 hours. These results suggest that Compound 8 holds potential as an effective pharmacological tool for managing metabolic syndrome.

Ng et al. (2018) developed novel carbasugars (pseudo-sugars) as potential SGLT2 inhibitors, synthesizing them from inexpensive D-gluconolactone, which features a biologically stable "pseudo-glycosidic" C-O bond. Various cross-coupling processes catalyzed by transition metals were employed in the synthesis. The β-pseudo-C-glycosides demonstrated greater activity compared to their α-counterparts, indicating that the β-configuration at C-1 is critical for SGLT2 inhibition. Among these, allylic analogue 9 exhibited an IC50 of 24 nM and over 400-fold selectivity for SGLT2 compared to SGLT1, while dapagliflozin had an IC50 of 0.9 nM for SGLT2. The researchers developed a clear, stereodivergent synthesis pathway for these pseudo-C-glycosides, highlighting a chemo-selective diamide reduction followed by a regioselective and stereoselective Pd-catalyzed allyl-aryl coupling reaction. Notably, allylic carbasugar 9 demonstrated significant potency and selectivity toward SGLT2 while maintaining physiological stability.

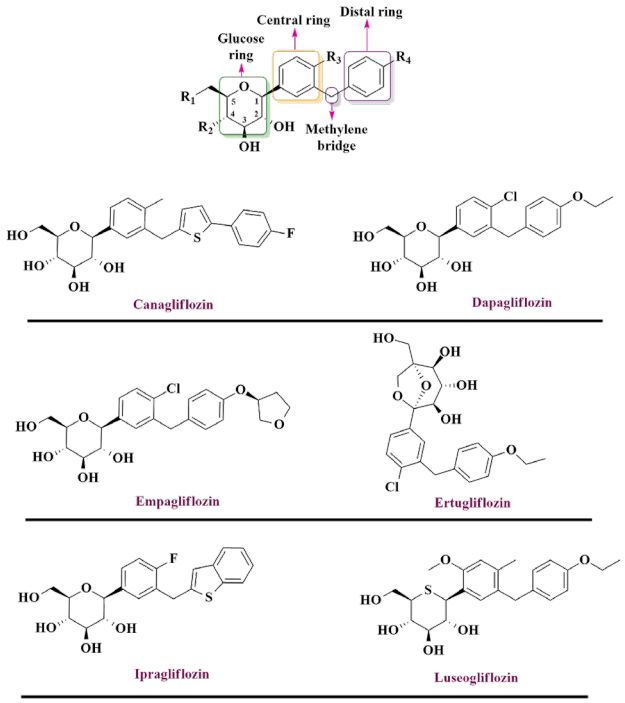

Figure 1. Chemical structures of various SGLT2 inhibitors and their prototype framework (Maksud et al., 2024).

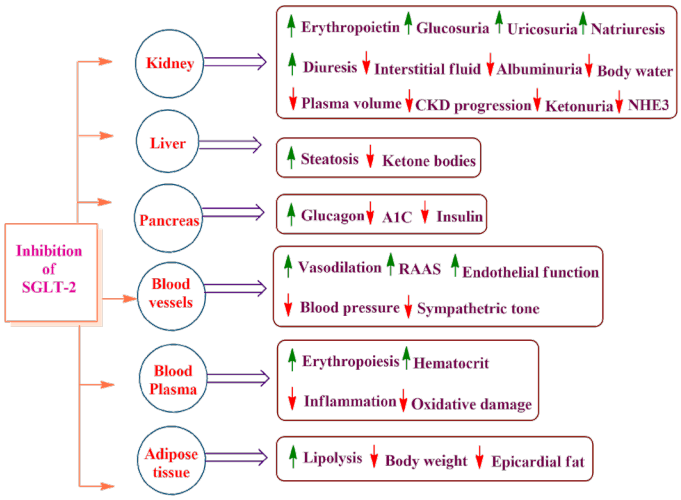

Figure 2. A schematic representation of the different mechanisms implicated in SGLT2 inhibition.

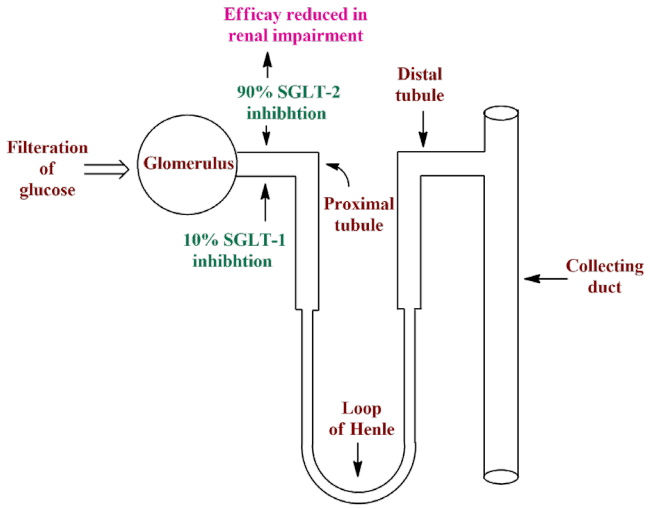

Figure 3. Mechanism of action of SGLT2 inhibitors on the kidney (Scheen AJ, 2014; Maksud et al., 2024).

Chu et al. (2019) synthesized and biologically assessed a series of N-glucosyl indole derivatives as SGLT2 inhibitors, building on their prior research involving various sugar moieties. They prepared 16 novel N-glucosyl indole compounds, testing their efficacy against hSGLT2. The most effective inhibitor identified was compound 10, which contained acethydrazide and demonstrated an EC50 value of 33 nM. This compound significantly enhanced urinary glucose excretion in rats at a dose of 50 mg/kg compared to the vehicle control.

Li et al. (2018) synthesized nitric oxide-releasing dapagliflozin derivatives, evaluating them as potential anti-diabetic and anti-thrombotic agents. These novel NO donor/SGLT2 inhibitor hybrids were designed to mitigate both hyperglycemia and thrombosis. Among these, Compound 11 exhibited superior efficacy as an SGLT2 inhibitor, with an IC50 of 125.7 nM and anti-platelet aggregation effects of 14.43%. Its NO-mediated anti-platelet action was confirmed in the presence of a NO scavenger. In subsequent in vivo trials, Compound 11 demonstrated significant reductions in urinary glucose excretion and glucose-lowering effects, even at doses ten times higher than dapagliflozin. This versatile hybrid compound is anticipated to serve as a promising therapeutic option for managing cardiovascular complications associated with type 2 diabetes.

Lin et al. (2013) developed and evaluated a series of C-aryl D-glucofuranosides as SGLT2 inhibitors. Among these compounds, Compound 19 demonstrated the highest in vitro inhibitory effect against SGLT2, with an EC50 of 0.62 μM and a selectivity that was 47 times higher against SGLT1 compared to dapagliflozin. The presence of an OCH_3 group adjacent to the sugar moiety was critical for SGLT2 selectivity, although substituents such as Cl or CH_3 also enhanced SGLT2 potency.

Ikegai et al. (2013) synthesized C-glucosides featuring azulene rings to investigate their potential for treating diabetes through selective SGLT2 inhibition. Their most effective SGLT2 inhibitor, Compound 20, was created by introducing a phenolic hydroxyl group to the core benzene ring. When administered orally, it exhibited a significant and prolonged antihyperglycemic effect in diabetic rats and mice. The addition of hydroxyl groups to the glucoside at the ortho position enhanced its inhibitory potency against SGLT2 (IC50 = 8.9 nM) while maintaining a remarkable selectivity of 280-fold against SGLT1. Based on these promising preclinical results, a mono-choline salt of Compound 20 (YM543) was identified as a potential therapeutic candidate.

Li et al. (2012) synthesized 1,2,3-triazole analogs of SGLT2 inhibitors using a "click chemistry" approach, specifically the copper-catalyzed azide-alkyne cycloaddition (CuAAC) method. This facilitated the straightforward production of C-glucosides utilizing triazole aglycone derivatives. Substituted 1,2,3-triazoles are key components in complex bioactive molecules, including tazobactam, as well as antiviral, anti-HIV, antibacterial, and antiallergic agents. Although all synthesized compounds exhibited lower efficacy than dapagliflozin, Compound 21 showed the best urinary glucose excretion (UGE) rate of 300 mg/200 g body weight/24 hours.

Yao et al. (2012) developed and assessed novel C-indolylxylosides as SGLT2 inhibitors. Structure-activity relationship (SAR) studies indicated that substituents at the 7-position of the indole moiety, combined with a p-cyclopropylphenyl group in the distal position, resulted in optimal SGLT2 inhibition. Compound 22 emerged as the most effective inhibitor, exhibiting an EC50 of 47 nM, which positioned it as a promising candidate for type 2 diabetes (T2DM) treatment. Subsequent pharmacokinetic and animal studies revealed that Compound 22 was metabolically stable and significantly effective in reducing blood glucose levels in streptozotocin (STZ)-induced diabetic rats.

In 2012, Chen et al. utilized the Mitsunobu reaction to synthesize and evaluate gem-difluoromethylated analogs of dapagliflozin as SGLT2 inhibitors. The biological assessment indicated that these analogs were more potent SGLT2 inhibitors than dapagliflozin. Notably, Compound 23 exhibited exceptional efficacy, with an IC50 of 0.35 nM, significantly outperforming dapagliflozin, which had an IC50 of 1.98 nM.

Kim et al. (2011) synthesized novel macrocyclic C-aryl glucosides as potential SGLT2 inhibitors for antidiabetic applications. Macrocycles were introduced into dapagliflozin by modifying the ortho-position of the proximal ring and the C-6 position of the carbohydrate. Two distinct synthetic macrocyclization pathways were employed to generate new ansa SGLT2 inhibitors. Among the synthesized compounds, Compound 24, featuring a dioxacyclopentadecine macrocycle with a methylthiophenyl group at the distal ring, demonstrated an IC50 of 0.778 nM. Meanwhile, Compound 25, with an ethoxyphenyl group at the distal ring, exhibited an IC50 of 0.899 nM. Both compounds showed superior in vitro inhibitory efficacy compared to the standard dapagliflozin.

Lee et al. (2011) synthesized novel thiophenyl C-aryl glucoside SGLT2 inhibitors, which were designed as potential antidiabetic agents by substituting a phenyl surrogate for the proximal ring of dapagliflozin. Among the compounds evaluated, Compound 26 exhibited the strongest inhibitory effect against SGLT2 in vitro, with an IC50 value of 4.47 nM, surpassing that of the reference drug dapagliflozin.

Ohtake et al. (2011) developed 5α-carba-β-D-glucopyranose derivatives as potential novel inhibitors of sodium-dependent glucose cotransporter 2 (SGLT2) aimed at treating type 2 diabetes. When compared to sergliflozin, Compound 27 demonstrated the highest inhibition of hSGLT2 and significant selectivity over hSGLT1. Pharmacokinetic studies revealed that Compound 28 exhibited a terminal half-life (T1/2) three times longer than that of

sergliflozin in db/db mice, indicating promising pharmacokinetic properties.

Zhao et al. (2011) employed anhydrous aluminium chloride-mediated Friedel-Crafts alkylation to synthesize gem-dimethyl-bearing C-glucosides for use as SGLT2 inhibitors. These compounds achieved an optimal inhibition rate of 79%. The efficacy of these compounds in preventing hyperglycemia was assessed using the oral glucose tolerance test (OGTT) in mice. Consistent with structure-activity relationship (SAR) data from similar compounds, the para-position of the benzene ring adjacent to the glucose moiety was identified as the most favorable site, followed by the 6-position and 2-position. Although all derivatives exhibited notable anti-hyperglycemic effects, they were less effective than dapagliflozin, the positive control. The most potent derivative, Compound 29, demonstrated an inhibition rate of 72%.

Song et al. (2011) introduced a novel class of C-aryl glucoside SGLT2 inhibitors featuring a thiazole motif. The synthesized thiazolylmethylphenyl glucosides were evaluated using a cell-based SGLT2 inhibition assay with methyl-R-D-glucopyranoside (AMG). The most potent SGLT2 inhibitors identified in vitro were Compounds 30 and 31, containing furanyl and thiophenyl moieties, respectively, with IC50 values of 0.720 nM and 0.772 nM.

Kang et al. (2010) investigated pyridazine and thiazole analogs for SGLT2 inhibition through in vitro testing. The most effective compound in the thiazole series, Compound 32, exhibited an IC50 of 121 nM and contained a 4-ethylbenzyl group at the 5-position of the thiazole, highlighting its potential as an SGLT2 inhibitor.

Lansdell et al. (2008) were the first to synthesize fluorophore-conjugated SGLT2 inhibitors aimed at treating diabetes mellitus and obesity. This development was intended to facilitate high-throughput binding assays using fluorescence polarization. Despite the incorporation of a fluorophore, TAMRA-labeled Compound 33 demonstrated significantly higher potency than its alkyl-chain-linked counterpart, showing over tenfold greater efficacy than phlorizin, with an IC50 of 45 nM. This finding underscored the necessity of coupling the fluorophore to the SGLT2 pharmacophore to achieve optimal potency.

6. Conclusion

SGLT2 inhibitors represent a promising and innovative class of medications for the management of type 2 diabetes. By inhibiting glucose reabsorption in the kidneys, these drugs not only reduce blood glucose levels but also offer additional benefits such as promoting weight loss, lowering blood pressure, and providing cardiovascular protection. Clinical trials and real-world evidence have demonstrated their efficacy in improving glycemic control, reducing cardiovascular events, and slowing the progression of diabetic kidney disease. Moreover, SGLT2 inhibitors show significant promise in treating heart failure and decreasing the likelihood of hospitalization, even in patients without diabetes.

While SGLT2 inhibitors are generally well-tolerated, potential side effects, including urinary tract infections, genital mycotic infections, and euglycemic diabetic ketoacidosis, should be carefully monitored. It is crucial that healthcare providers are vigilant in managing these risks and educating patients to ensure optimal outcomes.

In conclusion, SGLT2 inhibitors offer a valuable and multifaceted approach to diabetes management, with potential benefits extending beyond glycemic control. As ongoing research continues to shed light on the long-term effects and broader applications of these medications, clinicians should consider incorporating them into individualized treatment plans for patients with type 2 diabetes, while remaining attentive to potential adverse effects and monitoring patient safety.

Author contributions

M.J.N. developed the research concept, designed the study, drafted the manuscript, and conducted a comprehensive review.

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Competing financial interests

The authors have no conflict of interest.

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