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Review

The Development of SGLT Inhibitors: From Phlorizin to Modern Therapeutics

Sai Zhao [1,*,#], Xiaoyu Li [2,#], Yuxuan Wu [3], Yuanzhen Cai [4], Nian Tong [5], Zhijing Zhang [6,7,8,9], Hui Cai [2], Xue-Wei Liu [10], Feiqing Ding [1,2,*]

[1] Department of Chemistry, Sinco Pharmachem (Shenzhen) R&D Co., Ltd., Shenzhen 518000, China
[2] School of Pharmaceutical Sciences, Sun Yat-sen University Shenzhen Campus, Shenzhen 518107, China; lixy939@mail2.sysu.edu.cn (X.L.); caihui5@mail.sysu.edu.cn (H.C.)
[3] International College of Pharmaceutical Innovation, Soochow University, Suzhou 215021, China; 2553401045@stu.suda.edu.cn
[4] Department of Analytics & Data Science, School of Analytics & Computational Sciences, Harrisburg University of Science & Technology, Harrisburg, PA 17101, USA; YCai2@my.harrisburgu.edu
[5] Department of Pharmacy, University at Buffalo, Buffalo, NY 14260, USA; niantong@buffalo.edu
[6] State Key Laboratory of Bioactive Molecules and Druggability Assessment, Jinan University, Guangzhou 510632, China; zhijing0815@126.com
[7] MOE Key Laboratory of Tumor Molecular Biology, Jinan University, Guangzhou 510632, China
[8] Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, College of Pharmacology, Jinan University, Guangzhou 511436, China
[9] Department of General Surgery, The First Affiliated Hospital of Jinan University, Guangzhou 510632, China
[10] School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore; xuewei@ntu.edu.sg
* Correspondence: g.manager@sincopharmachem.com (S.Z.); dingfq3@mail.sysu.edu.cn (F.D.)
# These authors contributed equally to this work and share first authorship.

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Abstract: Diabetes mellitus poses a significant and escalating burden on global public health. As a major breakthrough in glycemic control, sodium-glucose transporters (SGLT) inhibitors are now established as indispensable agents for managing type 2 diabetes. This status is evidenced by the continuously increasing market share in the antidiabetic agent market worldwide. The development of these inhibitors shows how leads from natural products ultimately evolved into clinically useful agents via structure-based drug design. Specifically, structural modifications to overcome the metabolic instability of phlorizin have yielded orally administrable SGLT inhibitors with improved pharmacokinetic profiles. This modification represents a shift towards more resource-efficient and sustainable molecular design. In recent years, these inhibitors have been found to have cardiorenal protective effects independent of glycemic status in clinical trials, thereby fundamentally altering their therapeutic positioning towards heart failure and chronic kidney disease. This article reviews the current market landscape and the evolutionary trajectory of SGLT inhibitors. Additionally, we discuss emerging R&D strategies, highlighting the role of computational drug design and structural biology in accelerating the identification of novel scaffolds. By leveraging these advanced methodologies, researchers can overcome current limitations in potency and selectivity. These approaches offer promising avenues for optimizing lead compounds and developing next-generation therapies with improved pharmacological profiles.

Keywords: type 2 diabetes; SGLT2 inhibitors; phlorizin; *C*-glycosides; cardiorenal protection; dual SGLT1/2 inhibition; structure-based drug design; artificial intelligence; machine learning; sustainable pharmaceutical synthesis; resource-efficient drug design

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1. Introduction

Diabetes was first described more than 3500 years ago in the ancient Egyptian *Ebers Papyrus* (1552 BC), where persistent polyuria was recorded as its hallmark symptom.[1] To date, reports[2–5] and extensive global burden studies[6–8] show that diabetes remains one of the world's four leading diseases. As documented in the 2025 IDF Diabetes Atlas, around 11.1% of adults worldwide live with diabetes, corresponding to approximately 589 million people. If current trends persist, the global patient population is projected to reach 853 million by 2050.[9]

Lifestyle interventions, including dietary adjustments and regular physical exercise, remain vital to diabetes management.[10] In addition to these supplemental measures, glycemic control is the cornerstone of corresponding treatment. The latter is crucial for long-term complication prevention.[11] Various hypoglycemic agents have thus been developed to lower glycemic levels, each targeting different physiological pathways. For example, metformin mainly acts on the liver to inhibit glucose production,[12] while Dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin increase the level of endogenous incretin hormones.[13] Glucagon-Like Peptide-1 (GLP-1) receptor agonists like semaglutide demonstrate a multi-faceted effect by inhibiting glucagon release, stimulating insulin secretion, and slowing down digestion.[14] Sulfonylurea drugs like gliclazide directly promote insulin secretion in the pancreas.[15] Despite the availability of so many treatment options, a class of drugs known as SGLT inhibitors has emerged as particularly prominent since the early 2010s.[16] They have a distinct mechanism of action compared to their predecessors. In fact, they promote the excretion of sugar in the urine by effectively removing excessive glucose from the body, rather than targeting the insulin pathway.[17] The chemical structure of SGLT inhibitors is also quite different compared to other classes. They are glucose mimetics that structurally mimic the endogenous substrate of SGLTs.[18] Interestingly, this carbohydrate-based framework not only proves to be clinically transformative but also redefines the treatment paradigm.[19] Given the distinctive origin and clinical importance of SGLT inhibitors, it is worthwhile to provide an overview of this series of agents.

Carbohydrate-derived SGLT inhibitors launched between 2010 and 2025 have reshaped type 2 diabetes management. While several reviews have already addressed the pharmacology, medicinal chemistry, or clinical outcomes of SGLT inhibitors, few have attempted to integrate these perspectives within a single framework. This review integrates innovation vectors including structural biology, AI/ML design, market intelligence, and clinical data. By doing so, it uniquely bridges molecular insights from cryo-EM with their real-world therapeutic impact. Specifically, we begin with a market analysis based on proprietary Cortellis data. We present regional sales distributions and 2024–2025 year-over-year trends, which are rarely compiled together in existing reviews. We then track the structural trajectory from phlorizin to *C*-glycosides and discuss how recently resolved cryo-EM structures have rationalized the selectivity profiles of marketed gliflozins. These structural insights further guide the development of next-generation selective/dual SGLT inhibitors. Next, we survey machine learning applications in SGLT inhibitor discovery, from hit identification to scaffold prioritization, a topic barely covered in older SAR reviews. Finally, we overview the cardiorenal protective trials. Together, these perspectives complement and extend existing reviews.

2. Methods for literature retrieval and screening

This review is based on targeted searches in PubMed, Web of Science Core Collection, and the Cortellis commercial intelligence database, with a cut-off date of August 9, 2026. Search strategies combined terms for medicinal chemistry (e.g., phlorizin, SGLT inhibitor, *C*-glycoside, cryo-EM, artificial intelligence), major cardiovascular and renal outcome trials (EMPA-REG, CANVAS, DECLARE, CREDENCE, DAPA-CKD, EMPA-KIDNEY, DAPA-HF, EMPEROR-Preserved,

EMPEROR-Reduced, DELIVER, SCORED, SOLOIST-WHF), and market analytics (global sales, regional shares, 2024–2025 trends). We included full-text English publications reporting phase III trial results, structure-activity relationship studies, cryo-EM structural analyses, peer-reviewed reviews, regulatory approval documents, and validated Cortellis sales datasets. Conference abstracts, duplicate reports, and non-clinical studies lacking translational relevance were excluded. For each of the four thematic sections: market performance, structural evolution, and cardiorenal protection, data were extracted separately. Where trial interpretations diverged, we relied on the primary New England Journal of Medicine reports. Market data were taken exclusively from Cortellis trailing-twelve-month (TTM) figures to ensure consistency. All commercial data were extracted from Clarivate Cortellis Product Intelligence (TTM sales to June 30, 2025), with regional grouping (USA, EU Top 5, Rest of Europe, Latin America, Rest of World) as defined in the database. Gross distributor-level turnover was converted to USD using database exchange rates. Full extraction details for market data are provided in Supplementary Table S1.

3. Global market evolution of SGLT inhibitors

The outstanding clinical efficacy of SGLT inhibitors has been reflected in their significant commercial success in the global pharmaceutical market. This success has ushered in a new era in diabetes management. Figure 1a illustrates the regional sales distributions for dapagliflozin, canagliflozin, empagliflozin, and the aggregated group of other SGLT2 inhibitors. It also displays their combined worldwide market share in 2025. The global market is highly concentrated: empagliflozin accounts for 61.4% of total SGLT2 sales, followed by dapagliflozin at

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35.4%, while canagliflozin contributes only 1.8%. The remaining 1.4% is collectively attributed to nine emerging or regionally focused SGLT2 inhibitors, reaffirming the dominance of the Big Three. Across the Big Three products, the United States remains the largest commercial market, though their regional patterns differ. Empagliflozin's sales are heavily concentrated in the U.S. (80%), consistent with its competitive positioning, broad clinical indications, and widespread adoption. Dapagliflozin demonstrates a more diversified international footprint, with sales distributed across the United States (61%), EU Top 5 (14%), and Rest of World (14%). Canagliflozin shows a more balanced regional distribution, but its overall volume is markedly lower than the other two leaders. In contrast, the combined 'other SGLT2 inhibitors' group is driven primarily by the Rest of World region (67%), reflecting the presence of several region-specific or newly launched products outside major Western markets. According to Cortellis data[20] (see Supplementary Table S1) and Figure 1b, empagliflozin remains the global leader with worldwide sales exceeding USD 30 billion and 21% YoY (year-over-year) growth, followed by dapagliflozin at USD 17.3 billion with 16.1% growth. All sales data were extracted from Clarivate Cortellis over the TTM window ending June 30, 2025, representing gross distributor-level turnover standardized to US dollars. It is important to distinguish this metric from manufacturer-reported net revenue. The Cortellis data captures the total volume moving through wholesale channels. This metric typically exceeds the net sales figures reported directly by manufacturers in their financial statements. Full raw segmented datasets and extraction parameters are supplied in Supplementary Table S1. Today, the SGLT2 inhibitor class holds a 10–15% share of the global type 2 diabetes market. As a leading oral therapy alongside DPP-4 inhibitors, the SGLT2 inhibitor class represents a critical and high-growth category in diabetes management.[20]

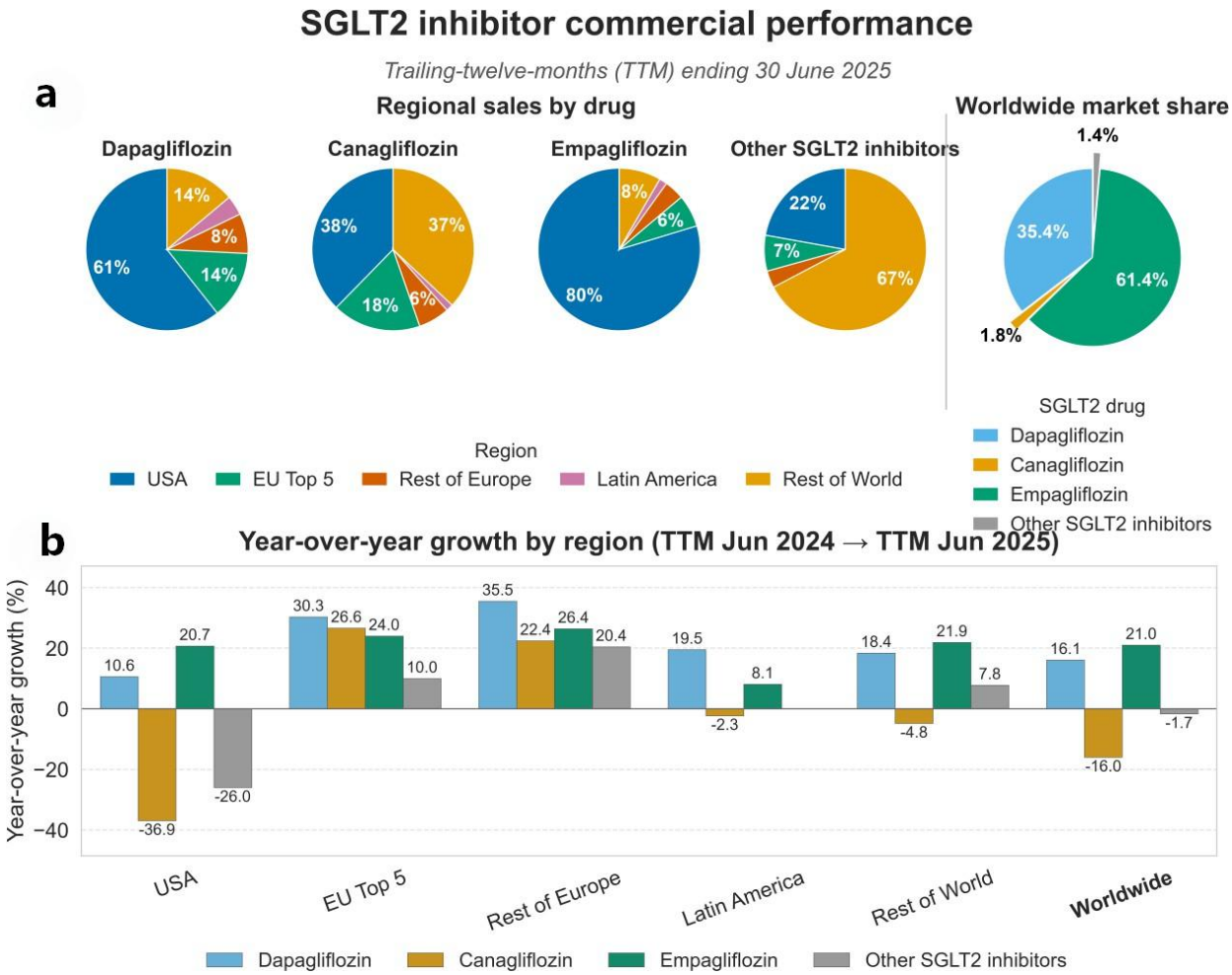

Figure 1. Commercial performance of SGLT2-inhibitor products, analyzed using Clarivate Cortellis trailing-twelve-month (TTM) sales dataset ending 30 June 2025. (**a**) Pie-chart plots of regional sales by drug and the worldwide market-share distribution. Regional grouping is defined according to the Cortellis database classification: USA, EU Top 5 (Germany, France, UK, Italy, Spain), Rest of Europe, Latin America, and Rest of World. (**b**) Bar-chart illustration for year-over-year growth by region (TTM June 2024 to TTM June 2025). Note on Data Metrics: All sales metrics represent gross distributor-level turnover converted into US dollars. This metric reflects the total wholesale channel volume and should be distinguished from manufacturer-reported net revenue (direct factory sales), as the latter typically excludes distributor margins and rebates. Complete segmented raw-sales information is supplied within Supplementary Table S1.

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As viewed from the table in Section 5, the period from 2010 to 2025 can be roughly divided into three phases. The historical development of SGLT inhibitors, herein, is categorized into distinct phases based primarily on their regulatory approval dates by major agencies such as the FDA and EMA. It is important to note that the initial discovery of a compound, its subsequent regulatory approval for clinical use, and its commercial launch in specific markets are discrete stages that can occur years apart. Our analysis focuses on regulatory approvals as the key milestone. In the first phase, the period from 2012 to 2014 marked the first wave of SGLT2 inhibitor approvals, establishing the class as a major treatment option. During this time, dapagliflozin (2012), canagliflozin (2013), and empagliflozin (2014) rapidly gained widespread adoption in both North American and European markets.[21–25] In parallel, Japan's PMDA approved a trio of domestically developed agents in 2014 (i.e., ipragliflozin, luseogliflozin, and tofogliflozin), signaling the realistic globalization of this drug class.[25]

A subsequent phase of innovation (2017–2023) was defined by agents with refined structures, exemplified by ertugliflozin (2017)[25] and bexagliflozin (2023).[26] These compounds have prolonged half-life and reduced risk of ketoacidosis. This progression signals the maturity of the field, as focus moves beyond foundational efficacy toward refining safety profiles and long-term durability.

Then, the period around 2019 saw regional pharmaceutical companies emerging as significant new players. In India, China, South Korea, and other markets, locally developed SGLT2 inhibitors were successively launched, such as remogliflozin (India, 2019),[25] henagliflozin (China, 2021),[25] and enavogliflozin (South Korea, 2022).[27] This strategic shift towards local research and production is expected to reshape the global market landscape: it may not only intensify price competition but also further enhance the accessibility of such drugs in the Global South countries. Thus, the current SGLT inhibitor market is entering a new stage of regional diversification. Based on the commercial success of several blockbuster drugs, this field is expected to form a more competitive and extensive global treatment pattern in the future.

4. Phlorizin as the lead compound

As previously discussed, the market performance of SGLT inhibitors has been exceptional, and their developmental trajectory in medicinal chemistry is equally noteworthy, meriting a more detailed examination. Natural products, ranging from small molecules to macromolecules like polysaccharides, have long been recognized as prime examples of bioprospecting and valuable sources of pharmacologically active agents. Consequently, they have garnered extensive research interest across multiple therapeutic areas.[28–31] A notable example is phlorizin (Figure 2), a natural compound found in the bark of fruit trees, particularly apple trees.[32] The evolution from plant-derived phlorizin to synthetic gliflozins illustrates a transition from extract-dependent sourcing to resource-efficient synthetic mimicry. This transition is a key narrative in sustainable pharmaceutical innovation. Researchers in the 19th century showed great interest in this compound due to its potential antidiabetic properties, as they noticed that glucosuria occurred when animals were administered phlorizin.[33] However, not until the 1980s and 1990s did researchers understand the real mechanism behind this physiological phenomenon. In fact, phlorizin exerts its antidiabetic effects by inhibiting one type of transporter, known as SGLTs.[34–36] Among disclosed isoforms of SGLTs (i.e., SGLT1-6), SGLT1 and SGLT2 are the most studied ones owing to their importance in glucose regulation, but they are located in different parts of the body and have different functions.[37,38] SGLT1 is primarily expressed in the small intestine and kidney, where it facilitates glucose and galactose absorption from food in the intestine and reabsorption of glucose in the proximal kidney tubule, accounting for about 10% of glucose reabsorption in the kidney. It has a high affinity for glucose but low capacity. In contrast, SGLT2, predominantly located in the kidney, mediates most glucose re-absorption in the proximal tubule, accounting for about 90% of renal glucose re-absorption and characterized by lower affinity but higher capacity.[39] To facilitate a systematic comparison, Table 1 summarizes the key distinctions between SGLT1 and SGLT2 in terms of tissue distribution, physiological function, therapeutic rationale, representative inhibitors, and clinical status. Research further showed that phlorizin acts as a dual inhibitor of both SGLT1 and SGLT2.[40] While SGLT2 inhibition in the renal proximal tubules promotes glucose excretion, the simultaneous inhibition of SGLT1 in the gastrointestinal tract was believed to lead to undesirable side effects, resulting in malabsorption, and causing gastrointestinal issues such as diarrhea, bloating, and abdominal discomfort.[41] Additionally, the oral bioavailability of phlorizin is low due to its labile β-glycosidic bond, which is readily hydrolyzed by intestinal β-glucosidases. This enzymatic cleavage converts phlorizin into its aglycone form, phloretin, and glucose, preventing substantial absorption of intact phlorizin.[42]

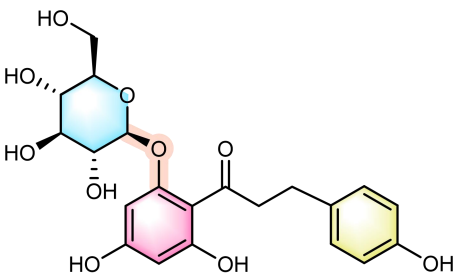

Figure 2. Structure of phlorizin.

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Table 1. Comparison between SGLT1 and SGLT2.

Features	SGLT1	SGLT2
Tissue distribution	Small intestine (brush border); kidney proximal tubule S3 segment (minor renal expression)	Kidney proximal convoluted tubule S1/S2 segments (almost exclusively renal)
Transport characteristics	High-affinity, low-capacity; $2Na^+$:1 glucose stoichiometry	Low-affinity, high-capacity; $1Na^+$:1 glucose stoichiometry
Physiological function	Mediates intestinal glucose/galactose absorption; reabsorbs residual ~10% of filtered glucose in distal proximal tubule	Reabsorbs ~90% of filtered glucose in early proximal tubule
Therapeutic rationale for inhibition	Delay intestinal glucose absorption → reduce postprandial glucose spikes; stimulate GLP-1 release; potential cardioprotective effects	Promote urinary glucose excretion → lower blood glucose; activate tubuloglomerular feedback → reduce hyperfiltration; cardio-renal protection
Representative inhibitors	Mizagliflozin; LX2761	Dapagliflozin, empagliflozin, ertugliflozin
Clinical status	Selective SGLT1 inhibitors: under clinical investigation	Multiple agents approved for T2DM, HF, and CKD

Consequently, its dual inhibitory role together with extensive first-pass metabolism limits phlorizin's clinical utility as an oral antihyperglycemic drug.[43] Given these drawbacks, it was then the task of medicinal chemists to structurally modify phlorizin, the lead compound, to yield drug candidates that are devoid of its shortcomings and possess both enhanced target specificity and suitable bioavailability.

5. A macro-perspective on SGLT inhibitor development

Efforts on structural modification of phlorizin via rational drug design have already yielded twelve SGLT inhibitor drugs (mainly SGLT2 inhibitors) approved to date (see Table 2). This class now stands as a pillar in the field of diabetes treatment on par with the DPP-4 inhibitors in clinical importance.[44] Since aspects such as the structural evolution, SAR studies, and specific profiles of various SGLT inhibitors are already well-elucidated in previous reviews[45–48] and other literature,[49–51] a detailed account is not within our scope. The contribution herein, therefore, will offer a more macro-level and succinct overview, presenting our perspective on key developments in this field.

5.1. From O-glycosides to C-glycosides

Early structure-activity relationship (SAR) studies were centered on the phloretin portion of phlorizin to investigate the roles of those phenolic hydroxyl groups.[49] Nevertheless, the *O*-glycosidic linkage susceptible to enzymatic cleavage remains unmodified, and therefore the oral bioavailability remains poor for these compounds such as sergliflozin (Figure 3; $t_{1/2}$ = 1–1.5 h)[52] and T-1095 (Figure 3; $t_{1/2}$ = 1.3 h).[53] The short half-life precluded their further development as viable clinical candidates.[54] Therefore, replacement of *O*-glycosides with other stable scaffolds, for instance, *C*-aryl glycosides, was ultimately proven to be a determinant step in pursuit of orally bioavailable SGLT2 inhibitors. This innovation ushered in the first generation of "gliflozins" with dapagliflozin, canagliflozin, and empagliflozin (see Table 2) emerging as the pioneering clinical agents in this area. In contrast to the former class such as sergliflozin, the sugar moiety is now directly linked to the aglycone. The structural feature renders gliflozins stable towards hydrolysis by digestive enzymes and hepatic metabolizing systems,[49] and the metabolic stability translates into high oral bioavailability and prolonged half-lives suitable for once-daily dosing. For instance, dapagliflozin exhibits an oral bioavailability of ~78% and a half-life of ~12.9 h, a stark contrast to *O*-glycoside predecessors.[55] Beyond metabolic stability, the *C*-aryl glycoside scaffold is also compatible with modern catalytic *C*-glycosylation methods. Such process improvements have reduced reliance on protecting groups and heavy metals in gliflozin manufacturing.

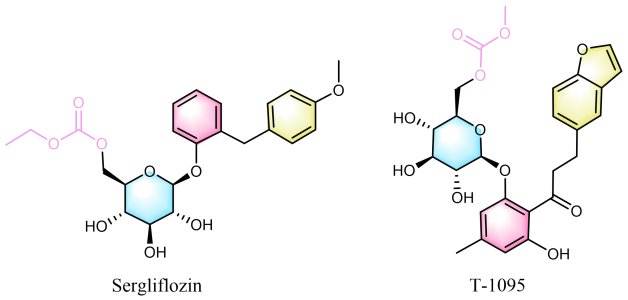


Figure 3. Structures of sergliflozin and T-1095.

Table 2. SGLT inhibitors launched during 2010–2025.[56,57]

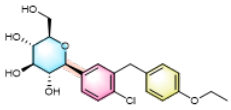
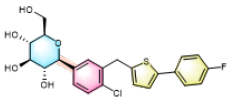
No.	Generic name	Brand name	Structure	SGLT1/2 targeting	Regulator	Approval year	Approved indication	Current status
1	Dapagliflozin	Forxiga/Farxiga		SGLT2	EMA, FDA, NMPA, PMDA	EU: 2012; US: 2014; China: 2017; Japan: 2014	T2DM, HFrEF, CKD, HFpEF	Globally launched
2	Canagliflozin	Invokana		SGLT2	FDA, EMA, PMDA, NMPA	US: 2013; EU: 2013; Japan: 2014; China: 2017	T2DM, CKD	Globally launched

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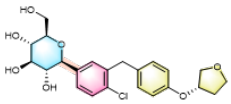
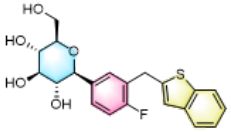
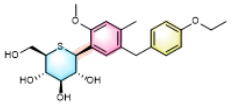
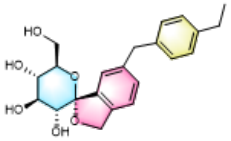
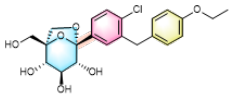
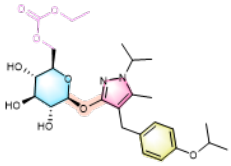
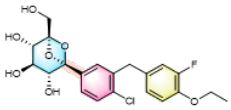
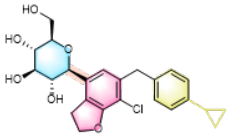
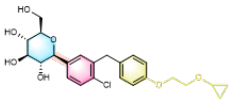
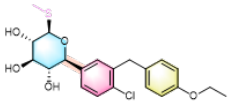
Table 2. *Cont.*

No.	Generic name	Brand name	Structure	SGLT1/2 targeting	Regulator	Approval year	Approved indication	Current status
3	Empagliflozin	Jardiance		SGLT2	EMA, FDA, NMPA, PMDA	EU: 2014; US: 2014; China: 2017; Japan: 2014	T2DM, HFrEF & HFpEF, CKD	Globally launched, global market-leading SGLT2 inhibitor by sales volume
4	Ipragliflozin	Suglat		SGLT2	PMDA	Japan: 2014	T2DM	Launched in Japan
5	Luseogliflozin	Lusefi		SGLT2	PMDA	Japan: 2014	T2DM	Launched in Japan
6	Tofogliflozin	Apleway/ Deberza		SGLT2	PMDA	Japan: 2014	T2DM	Japan-only launch
7	Ertugliflozin	Steglatro		SGLT2	FDA, EMA, NMPA	US: 2017; EU: 2018; China: 2020	T2DM	Globally launched
8	Remogliflozin etabonat	Remo/Remozen		SGLT2	CDSCO (India)	India: 2019	T2DM	Launched in India
9	Henagliflozin	Ruiqin		SGLT2	NMPA	China: 2021	T2DM	China-only launch
10	Enavogliflozin	Envlo		SGLT2	MFDS (South Korea)	South Korea: 2022	T2DM	South Korea-only launch; Latin America export expansion later
11	Bexagliflozin	Brenzavvy		SGLT2	FDA	US: 2023	T2DM	US-only launch
12	Sotagliflozin	Inpefa		SGLT1/2	FDA	US: 2023	HF or T2D with CKD and other CV risk factors	Launched in US

Note: Abbreviations: T2DM = Type 2 diabetes mellitus; T1DM = Type 1 diabetes mellitus; SGLT1 = Sodium-glucose cotransporter 1; SGLT2 = Sodium-glucose cotransporter 2; EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; NMPA = National Medical Products Administration (China); PMDA = Pharmaceuticals and Medical Devices Agency (Japan); MFDS = Ministry of Food and Drug Safety (South Korea); CDSCO = Central Drugs Standard Control Organization (India); HF = Heart failure; HFrEF = Heart failure with reduced ejection fraction; HFpEF = Heart failure with preserved ejection fraction. For specific IC_{50} values of representative compounds, please refer to Section 5.2.2.

5.2. Structural diversification and subtype selectivity optimization

In the next stage, structural optimization of SGLT inhibitors further enhances SGLT2 potency and selectivity over SGLT1. Cryo-EM and mutagenesis studies have suggested that this selectivity is determined by a delicate "multi-point fit" involving sugar C6 substitution, aglycone conformation, and the interaction of distal aromatic rings with a hydrophobic vestibule unique to SGLT2.[58,59] The following section summarizes the key SAR insights for each major structural segment and also points out the shift from empirical optimization to structure-based drug design (Figure 4).

5.2.1. C6 position and the glucopyranose core in the sugar portion

The sugar-binding pockets of human SGLT1 and SGLT2 differ by only three residues around C6-OH (SGLT1: T460/L286/M283 vs. SGLT2: S460/V286/L283), generating a larger

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sub-pocket in SGLT2.[58] Early SAR showed that replacing C6-OH (Figure 4) with hydrophobic substituents such as -CH_3 and -CHF2 (compounds 2 and 3), decreased SGLT2 inhibitory activity (Figure 5a). In the meantime, introducing a polar oxime group at C-6 also resulted in less potent hSGLT2 inhibitors (compound 4, Figure 5a) than the parent drug.[49] Researchers subsequently showed interest in the D-glucopyranose moiety, replacing it with an L-xylopyranose ring, a pentose that lacks the side chain. As noted above, dapagliflozin, with a C6-OH group, exhibits high selectivity for SGLT2 over SGLT1 (~1,000-fold, Figure 5a), whereas sotagliflozin (compound 6, Figure 5a), which carries a more hydrophobic C6-SCH_3 group, shows markedly reduced selectivity (~20 fold), enabling dual SGLT1/2 inhibition. Compared with compound 5 (Figure 5a), sotagliflozin retains a level of SGLT2 inhibitory activity comparable to that of dapagliflozin.[49] Niu and coworkers' cryo-EM structural data have provided initial views of the architecture of an LX2761 binding site on hSGLT1 (PDB: 7WMV, Figure 5c).[60] As LX2761 and its mimetics share the same sugar ring scaffold with sotagliflozin and act as dual SGLT1/2 inhibitors, their sugar moiety is expected to bind to hSGLT1 in the same manner as sotagliflozin. The study indicates that replacing the C6-OH with SCH3 breaks the hydrogen bond to Q457 in hSGLT1, but makes new hydrophobic contacts with T460, L286, and M283 (Figure 5c).[60] This modification markedly enhances hSGLT1 inhibitory potency from 1400 nM to 36 nM.[60,61] In contrast, the corresponding residues in SGLT2 (S460/V286/L283) provide less favorable steric accommodation for this substituent, maintaining inhibitory potency against SGLT2 comparable to dapagliflozin. This molecular mechanism of "enhancing SGLT1 inhibition rather than weakening SGLT2 inhibition" confers its dual SGLT1/2 inhibitory profile.[60] Interestingly, installation of a methoxy group at this identical position (compound 5, Figure 5a) failed to reproduce the trend observed for sotagliflozin.[49] This can likely be attributed to the diminished hydrophobic contacts between the smaller, less polarizable methoxy group and the surrounding residues, compared to the methylthio moiety in sotagliflozin.

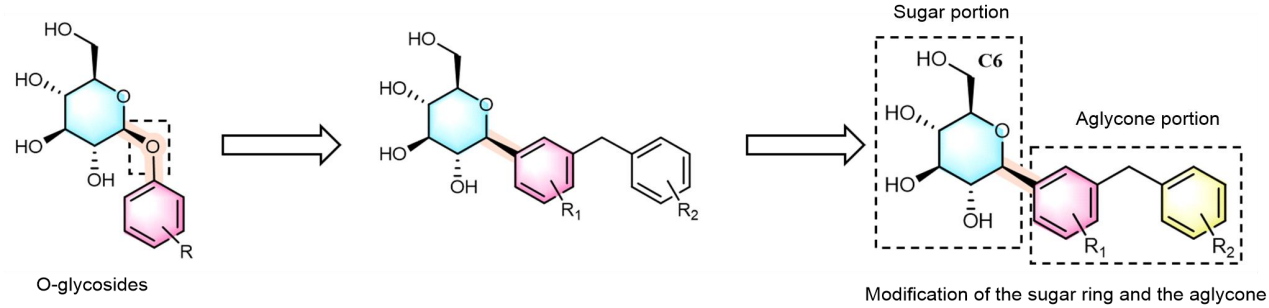

Figure 4. Pathway of structure modification.

5.2.2. Aglycone portion optimization

The aglycone portion of most SGLT2 inhibitors consists of two segments, i.e., a central aryl ring and a distal aryl ring (Figure 4). The central aryl ring controls the orientation of the whole molecule, whereas the distal ring docks into an extracellular vestibule that is wider in SGLT2 than in SGLT1.[59]

Structural and SAR analyses have elucidated the binding features of marketed SGLT2 inhibitors. For instance, dapagliflozin (Figure 6) has a chlorophenyl core and an ethoxyphenyl tail. It forms a hydrogen bond with Gln457 via a water bridge, achieving potent inhibition and high selectivity for SGLT2 over SGLT1.[59] Canagliflozin with a central thiophene ring (Figure 6) presents a distal fluorophenyl that forms T-shaped π-π stacking with Phe98 ($IC_{50} \approx$ 2–6 nM range across studies).[59] Empagliflozin (Figure 6) comprises a central 4-chlorophenyl ring connected through a methylene bridge to a distal phenyl bearing an (*S*)-tetrahydrofuran-3-yloxy group. Its distal aromatic tail occupies the Leu84/Val95 hydrophobic pocket within SGLT2 and exhibits low-nanomolar inhibitory potency (IC50 = 3.1 nM) and >2,500-fold subtype selectivity versus SGLT1.[58]

Collective SAR data suggest that electron-rich five-membered heterocycles such as thiophene and dihydrobenzofuran offer comparable or even superior SGLT2 potency and selectivity compared to benzene counterparts. This trend is well exemplified by clinically approved agents including canagliflozin and tofogliflozin (Figure 6).[49] Molecular dynamics simulations would be required to verify whether this superiority stems from enhanced scaffold flexibility that enables deeper insertion of the distal ring into the binding pocket. All aforementioned SAR conclusions[49] regarding the aglycone skeleton are summarized in the upper panel of Figure 6. In general, the aromatic ring frameworks and substituent patterns on aglycone moieties jointly govern the inhibitory potency and subtype selectivity of these compounds.

Apart from the findings above, the *para*-position substituent on the distal aryl ring serves as another vital factor for fine-tuning SGLT2 inhibitory activity and subtype selectivity. Empagliflozin exemplifies this through its binding profile. Lipophilic *para*-substituents ranging from strong electron-withdrawing halogens to weak electron-donating alkoxy groups can sustain high SGLT2 inhibitory potency. Nev-

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ertheless, a delicate physicochemical balance must be maintained. Generally, increasing the steric bulk or alkyl chain length of para-substituents elevates SGLT2 affinity. However, this modification drastically diminishes selectivity over SGLT1.[49,62]

Accordingly, clinically successful SGLT2 inhibitors such as empagliflozin and bexagliflozin adopt compact, rigid small lipophilic groups at this para site. Such tailored substituents appear to fit well into the unique hydrophobic outer vestibule of SGLT2, potentially engaging characteristic amino acid residues including His268 but showing limited interaction with the corresponding binding pocket of SGLT1. This rational design strategy can achieve an optimal balance between high inhibitory potency and excellent SGLT1/2 selectivity.[62]

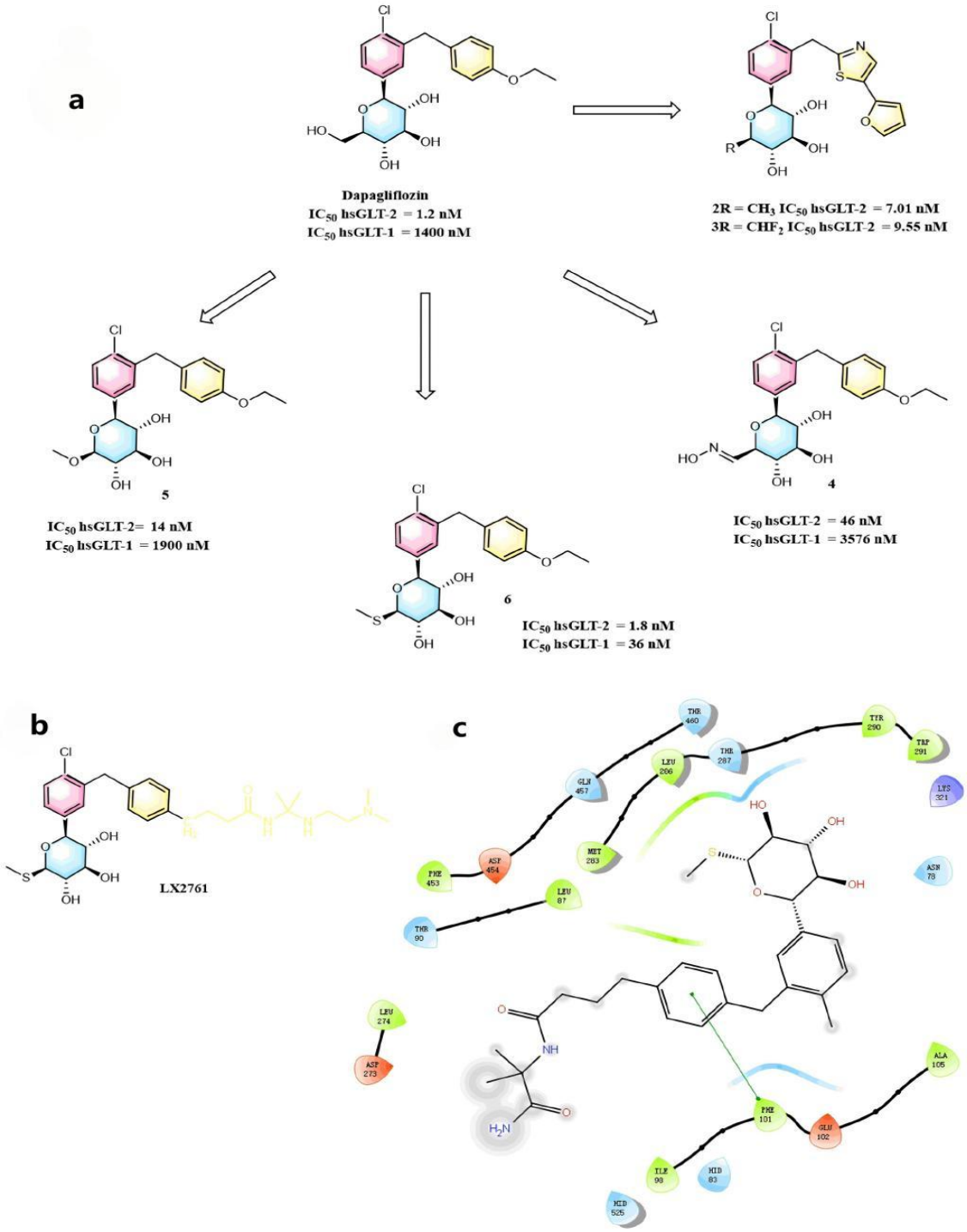

Figure 5. (**a**) Representative examples of structural modification at C6 position and the glucopyranose core; (**b**) Structure of LX2761; (**c**) 2D ligand interaction diagram between an LX2761 mimetic and hSGLT1 (PDB: 7WMV).[60]

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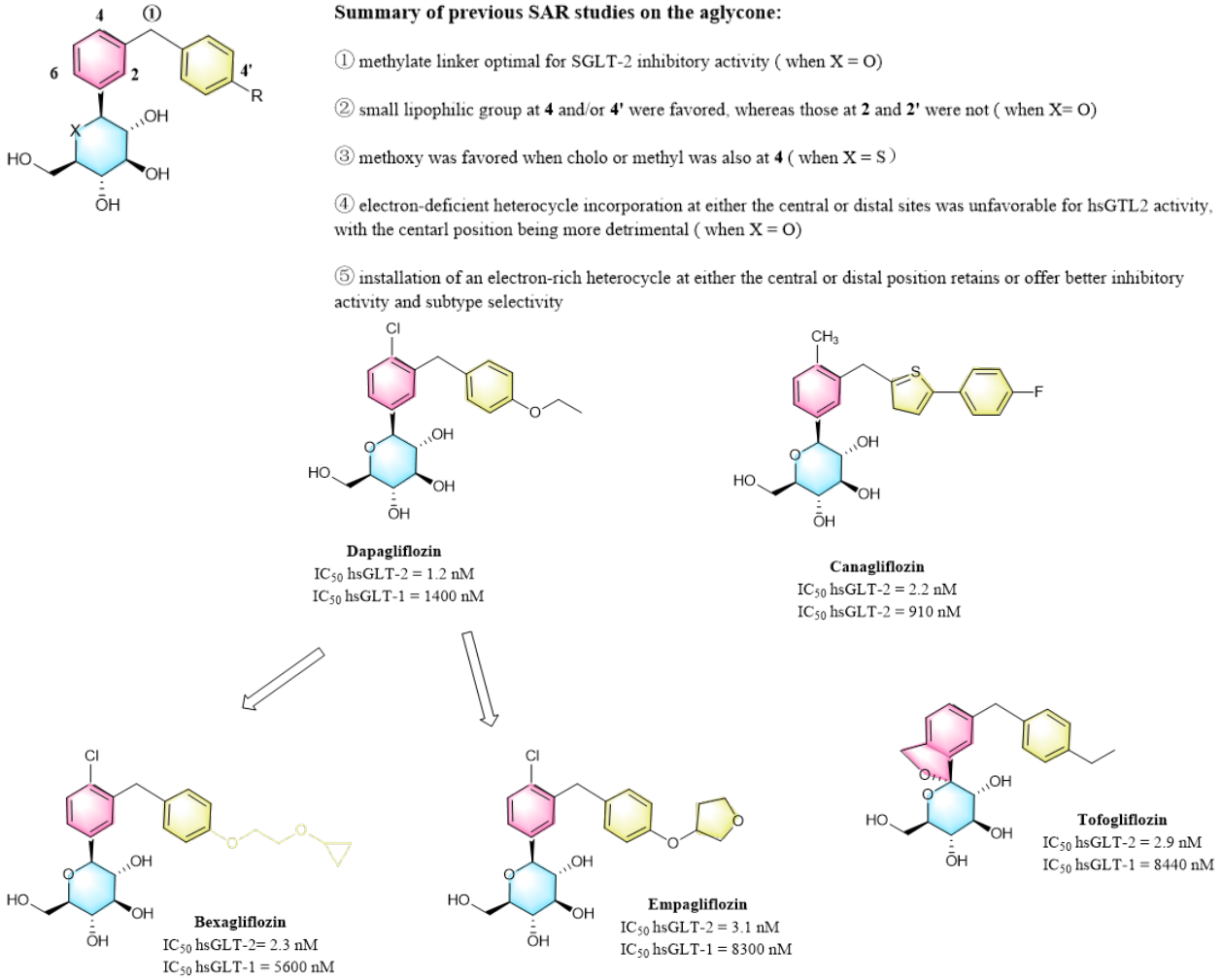

Figure 6. Summary and representative examples regarding SAR findings of the aglycone scaffold.

5.2.3. Structure- and mechanism-based design of next-generation SGLT1/2 inhibitors

The compounds and design strategies discussed in this section span different developmental stages. For clarity, we note that sotagliflozin and mizagliflozin have reached clinical development, while the structural optimization strategies discussed below represent rational design hypotheses that have not yet been clinically validated. Owing to recent disclosure of cryo-EM structures of the human SGLT2-MAP17 complex and SGLT1 inhibitors with SGLT1, we now have a better understanding of the mechanism of these transporters. This creates a foundation for the rational design and optimization of new compounds which aim at these transporters. As discussed earlier, SCH3 in sotagliflozin forms more hydrophobic interactions with neighboring amino acids in a smaller cavity of SGLT1 than SGLT2, which is also consistent with the cryo-EM structures (PDB: 8HG7, Figure 7a).[59] Therefore, smaller moieties of hydrophobic nature would be expected to favor the inhibitory activity against SGLT1. In addition, the cryo-EM analysis showed that other parts of the glucoside binding pockets are conserved between hSGLT1 and hSGLT2, so no significant difference can be seen in SGLT1 or SGLT2 inhibitors regarding their sugar portion.[59] These studies also found that the distal aromatic rings of gliflozins determine SGLT1/2 selectivity. This is due to differential hydrophobic contacts in the extracellular vestibule. In hSGLT2, residues such as V95 and L283 interact with the aglycone tail, whereas their bulkier counterparts, I98 and M283 in hSGLT1 alter pocket geometry.[59] Additionally, differences in the central binding region, i.e., A160 in hSGLT1 vs. the bulkier V157 in hSGLT2, further contribute to selectivity.[60] This may explain why SGLT1-specific inhibitors, such as mizagliflozin (Figure 7b), are predicted to clash with V157, whereas SGLT2-selective gliflozins favor the hSGLT2 pocket.[60]

The structural analyses also demonstrated that different classes of SGLT2 inhibitors stabilize distinct conformational states of the transporter. Gliflozins, such as canagliflozin and dapagliflozin, have all been shown to bind to the outward-facing conformation of hSGLT2.[59] They occupy both the glucose-binding site and the extracellular vestibule, which locks the transporter in an outward-open state and prevents substrate access from the extracellular side.[58,59] In contrast, phlorizin has been shown to have a distinct binding mode.

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It stabilizes the inward-open conformation of hSGLT2, with its binding site located near the intracellular side of the Na^+-binding pocket. Notably, further study has demonstrated that phlorizin exhibits biphasic binding kinetics, suggesting the existence of two distinct binding sites on hSGLT2.[59]

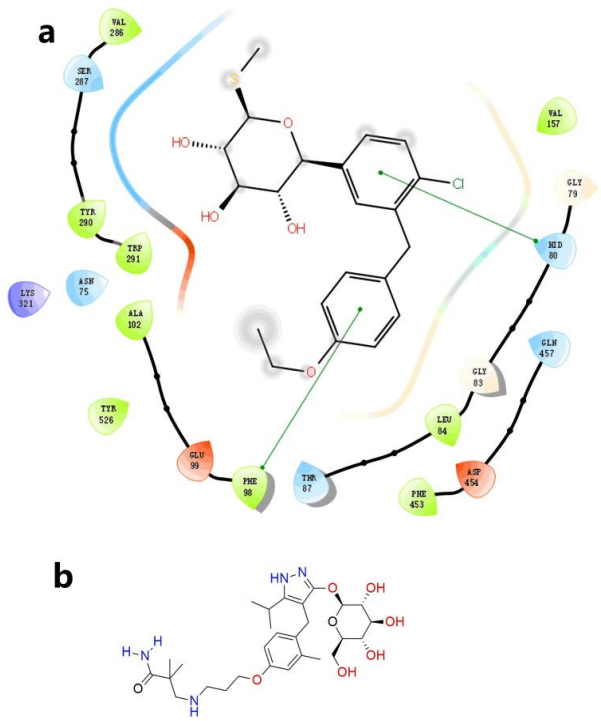

Figure 7. (**a**) Sotagliflozin and its interactions with hSGLT2; (**b**) Structure of mizagliflozin.

From a drug design point of view, these findings offer two strategic insights. First, the outward-facing conformation stabilized by gliflozins represents a promising target for developing high-affinity, metabolically stable SGLT2 inhibitors. This approach has already yielded several clinically successful drugs. Second, the distinct binding modes of phlorizin suggest a potential avenue for designing conformation-selective inhibitors that could trap SGLT2 in the inward-open state. Moreover, the extracellular high-affinity site for phlorizin remains structurally uncharacterized. However, its existence suggests that optimizing the phloretin aglycone moiety to enhance interactions with this site could improve potency. This may provide a conceptual strategy for developing novel chemotypes that target SGLT2 via a conformational mechanism distinct from those already known.[60,62]

5.2.4. SGLT inhibitor discovery and repurposing using artificial intelligence and machine learning

The integration of artificial intelligence (AI), particularly machine learning (ML) methods, now serves as a critical innovation vector in modern SGLT inhibitor discovery (Figure 8). Aligning with the scope of sustainable science, these data-driven approaches accelerate hit identification and reduce the reliance on trial-and-error approaches across the drug discovery pipeline. They provide a practical way to dissect the intricate structure-activity relationships governing the activity of SGLT-targeted compounds. Using large-scale bioactivity datasets, ML models can efficiently prioritize novel scaffolds, estimate binding affinity, and highlight structural features relevant to potency and pharmacokinetic performance. When combined with structural biology techniques such as cryo-electron microscopy and molecular dynamics simulations, ML approaches further support atomic-level interpretations of SGLT1 and SGLT2 conformational behavior, supporting the development of more selective and better-tolerated inhibitors. Recent representative studies illustrate these advances clearly.

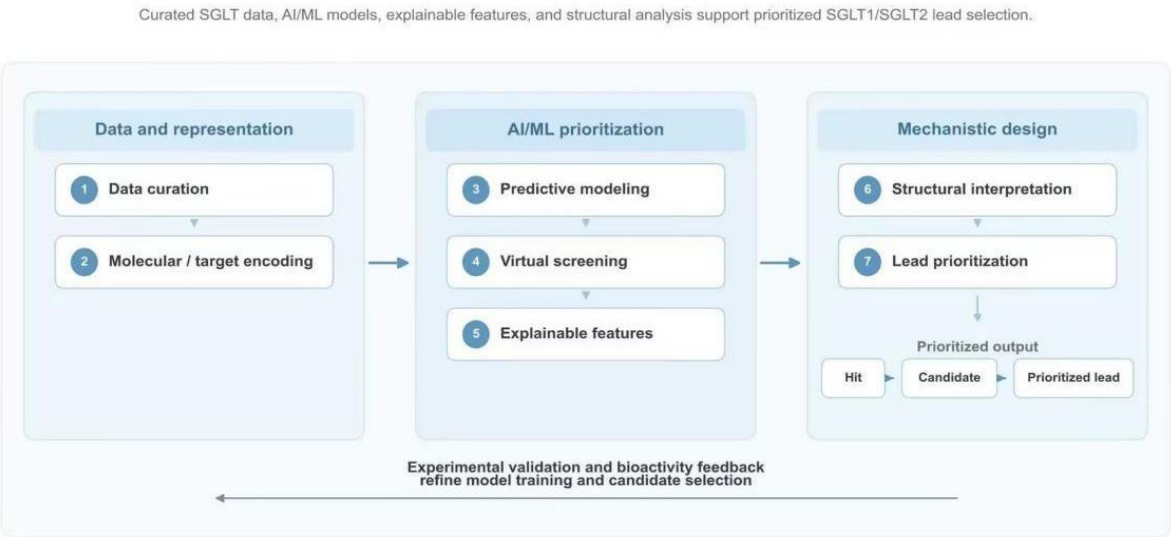

Figure 8. Artificial Intelligence-aided Drug Development (AIDD) workflow for SGLT inhibitor development.

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Burggraaff et al. constructed a proteochemometric random forest model to screen for SGLT1 inhibitors, since no human SGLT1 crystal structure was available.[63] The model was trained on merged ChEMBL public data and a chemically diverse in-house library containing 3,686 unique molecules. It achieved a five-fold cross-validation MCC of 0.48, with sensitivity and specificity of 0.64 and 0.93, respectively. After virtual screening of over 1.8 million Enamine compounds, 77 representative candidates underwent cellular *in vitro* testing. Among them, 30 molecules exhibited low-micromolar SGLT1 inhibitory activity, yielding a 39% hit rate. The hits included structurally novel scaffolds (average Tanimoto 0.33 for the diverse set) and analogues of four non-glycosidic leads including bepridil, bupivacaine, cloperastine, and trihexyphenidyl (Figure 9). The varied structures of active hits suggest multiple potential binding pockets on SGLT1. More importantly, this work demonstrates that proteochemometrics can be productively applied to solute carriers, a target class where structural information remains scarce.

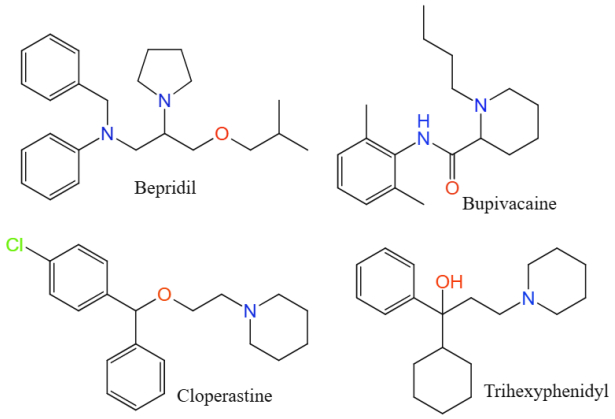

Figure 9. Chemical structures of four identified novel hSGLT1 inhibitors: bepridil, bupivacaine, cloperastine, and trihexyphenidyl.

Zhao and coworkers reviewed applications of machine learning across antidiabetic drug classes, including SGLT2 inhibitors.[64] They summarized how widely used ML workflows, including 3D-QSAR visual analysis using genetic algorithms and partial least squares and QSAR models based on multilayer perceptron neural networks, SVM and projection pursuit regression, have been applied to characterize *C*-aryl glucoside analogs and other inhibitor series. Their overview emphasizes that ML not only improves activity prediction but also pinpoints actionable structural determinants, such as the beneficial role of electron-withdrawing substituents on aromatic rings for enhancing SGLT2 inhibition.

Moinul et al. applied a multi-model QSAR strategy to identify structural fingerprints responsible for SGLT2 inhibition.[65] This 2022 study built multiple ligand-based machine learning models to seek SGLT2 inhibitors, given the absence of resolved human SGLT2 crystal structures. A dataset of 224 diverse SGLT2 agents was classified by an IC50 threshold of 21.1 nM. Bayesian and recursive partitioning models were adopted to extract structural fingerprints. The favorable Bayesian fingerprints share highly similar *C*-aryl glucoside scaffolds, while unfavorable ones converge on indole *O*-glucosides and nitrogen-rich heterocycles. This internal similarity within each fingerprint group is largely explained by skewed scaffold distribution in the training set, with ECFP6's local-fragment sensitivity further reinforcing this pattern. Nine ML classifiers were also constructed. Random Forest, Decision Tree, AdaBoost, and Gradient Boosting achieved perfect training AUC (1.00). Among them, Random Forest delivered the best predictive accuracy in both the split-test (85.71%) and 10-fold cross-validation (74.11%) settings. Finally, 669 FDA-approved drugs were virtually screened via multi-model consensus filtering, retaining 14 candidates unanimously predicted active by the four top-performing models. The 2D structures of some active compounds were illustrated in Figure 10 as repurposing hits, and further wet-lab assays are warranted to validate these computational findings.

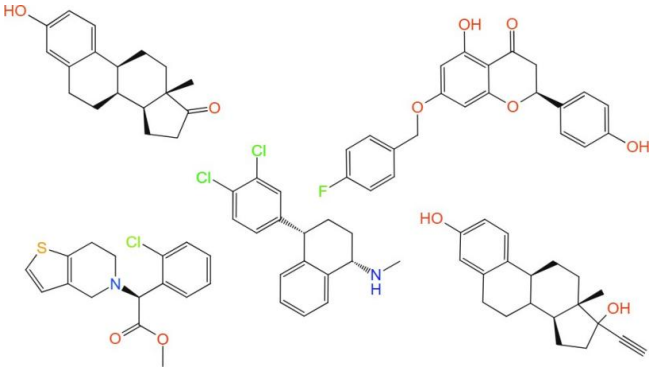

Figure 10. 2D structures of some actives as predicted by Random Forest (RF), Decision Tree (DT), AdaBoost (ABC) and Gradient Boosting (GBC) models.

Yu and colleagues combined machine learning and molecular dynamics simulations to deepen mechanistic understanding of SGLT2 inhibition.[66] They built classification models on a dataset of 240 SGLT2 inhibitors and adopted the resolved cryo-EM SGLT2 structure (PDB: 7VSI) to identify activity-driving substructures. Six molecular fingerprints and six machine learning algorithms, including RF and XGBoost, were compared, and ECFP-derived models achieved the best predictive power, which was further verified via Y-scrambling tests. Meanwhile, SHAP analysis identified ten potency-boosting Morgan fragments dominated by conjugated aromatic moieties, alongside six unfavorable substructures. The authors further performed 100 ns transmembrane MD simulations and MM-PBSA free energy calculations on six representative SGLT2 ligands (i.e., ENV, EMG, IPG, TG, SG, and DG). The calculated binding free energies correlated strongly with experimental values (R^2 = 0.90 for the six inhibitors, and 0.92 for residue mutants), indicating that the simulation system reliably recapitulates target-inhibitor binding behavior. Overall, this

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integrated ML-simulation workflow may provide structural guidance for designing novel SGLT2 lead skeletons.

Illahi et al. built QSAR classification and regression models for SGLT2 inhibitor activity prediction using the KNIME platform.[67] They curated 899 valid compounds filtered from 1,049 ChEMBL entries and adopted a 21.1 nM IC50 threshold to distinguish actives from inactives. Among tested algorithms, SVM reached the best classification accuracy of 81.66%, while XGBoost performed best in regression tasks with an external R^2 of 0.69 and MAE of 0.47. MoSS (Christian Borgelt's Molecular Substructure Miner) mining retrieved 113 activity-associated fragments with high structural similarity, almost all originating from standard *C*-glucoside skeletons. The pronounced scaffold bias in the training dataset may create the same limitation seen in Moinul's prior work, compromising the models' generalization toward structurally distinct novel leads.

Kaijage and Kraszewski's 2025 review critically reassessed progress and challenges in developing selective SGLT1 inhibitors.[68] The authors pointed out major flaws in early mechanistic work using low-similarity bacterial vSGLT templates and emphasized that recent cryo-EM data have uncovered critical structural differences between SGLT1 and SGLT2. SGLT1 has a unique Na3 pocket, and the EL5 loop of SGLT2 forms an aromatic cage that drives the inherent SGLT2 selectivity of approved gliflozins. The paper demonstrated the utility of molecular dynamics, MM-GBSA and mutagenesis as effective approaches to analyse ligand-pocket interactions. However, even with putative anti-cancer effects suggested by preclinical data, the application of SGLT2 inhibitors is hampered by systemic side effects. The authors also outlined unresolved mechanistic gaps, such as unknown Na3 occupancy and proposed lead design strategies targeting SGLT1's characteristic pockets, polar EL5 interactions and allosteric regulation to address existing therapeutic limitations.

Table 3 summarizes the profiles of the aforementioned AI/ML studies. Notably, Burggraaff's study has a massive screening dataset (million-level) and experimentally validates the identified hits. This comprehensive approach provides high confidence in the model's ability to predict promising molecules. In contrast, the other studies use relatively small training sets (hundreds to thousands of molecules) with high structural similarity, leading to significant multicollinearity. Moreover, none of these studies incorporate ADMET properties during early screening, likely due to data scarcity, which further compromises the reliability of their predictions.

Table 3. Summary of representative AI/ML studies in SGLT inhibitor research.

Study	Dataset size	Algorithm	Best metric	Validated hit rate
Burggraaff et al. (2019)[63]	Training set: 1,683 (public) + 2,007 (in-house) molecules; Screening library: 1.8 million molecules	RF	MCC: 0.48	39%
Moinul et al. (2022)[65]	224 molecules	KNN, SVC, RF, etc. (9 algorithms)	Accuracy: 85.71%, Precision: 85.93%, Recall: 85.38%, F1-score: 85.54% (Random Forest: Split-test approach)	NA
Yu et al. (2024)[66]	1,240 molecules	KNN, SVC, RF, etc. (6 algorithms)	MCC: 0.782 (RF-ECFPs)	NA
Illahi et al. (2025)[67]	899 molecules	MLP, NB, RF, SVM, etc. (6 algorithms)	Accuracy: 81.66% (SVM, for QSAR classifier); R^2: 0.69, MAE: 0.47 (XGB, for QSAR regression)	NA

Note: Abbreviations: MCC, Matthews Correlation Coefficient; KNN, K-Nearest Neighbors; SVC, Support Vector Classifier; RF-ECFPs, Random Forest-Extended-Connectivity Fingerprints; SVM, Support Vector Machine; XGB, eXtreme Gradient Boosting; MAE, Mean Absolute Error.

6. Mechanistic deepening and paradigm shift in clinical benefit

6.1. From "glucose lowering" to "cardio-renal-metabolic protection"

6.1.1. Clinical trials conducted to study the cardiorenal protective effects of SGLT inhibitors

The first-in-class SGLT2 inhibitors were originally positioned as "glucuretics". By obstructing the low-affinity glucose transporter localized to the S1 segment of the renal proximal tubule, these agents induce urinary glucose loss of 40–80 g per day and produce a concomitant 0.5–0.7% reduction in glycated haemoglobin.[69] Yet subsequent investigations have shown that the osmotic diuretic effects play only a limited role in the broader spectrum of cardiorenal protective actions afforded by this drug class. Consistent with the integrated cardiovascular-kidney-metabolic (CKM) disease continuum proposed by the AHA and summarized in two landmark contemporary reviews,[70,71] SGLT inhibitors exert cardioprotective benefits, primarily reductions in HHF and, in select populations, cardiovascular mortality. They also confer renoprotective benefits, including slowing of eGFR decline and reduction in progression to kidney failure. These effects are thought to be mediated, at least in part, by anti-inflammatory, antifibrotic, and hemodynamic mechanisms that operate across multiple organ systems. In discussing these benefits, it is important to note that the evidence is derived from different levels of evidence. Wherever possible, we prioritize findings from randomized controlled trials (RCTs), including the landmark cardiovascular outcome trials (CVOTs) such as SOLOIST-WHF, SCORED, and others. However, some mechanistic insights and subgroup findings are based on post hoc analyses or preclinical studies, which should be interpreted as exploratory rather

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than confirmatory.

To dissect the cardiorenal protective mechanisms of SGLT inhibitors, a series of industry-sponsored phase III placebo-controlled trials have been conducted over the past decade to confirm their clinical efficacy, and 12 relevant trials are categorized and summarized in Table 4 according to four core clinical phenotypes: T2D/ASCVD,[72–75] HFrEF,[76–79] HFmrEF/HFpEF,[80,81] and CKD with or without type 2 diabetes.[82,83] The guideline class and level of evidence in the last column are based on the ESC 2023 Heart Failure Update (for HF trials),[84] the KDIGO 2024 CKD Guideline (for renal trials),[85] and the ADA Standards of Care 2026 (for diabetes trials).[86]

For the T2D/ASCVD phenotype aligned with ADA Standards 2026 guidance, three landmark phase III trials of selective SGLT2 inhibitors recruited participants with type 2 diabetes and established atherosclerotic cardiovascular disease or elevated atherosclerotic risk. In EMPA-REG OUTCOME (n = 7,020 T2D), empagliflozin lowered MACE risk by 14%, cut cardiovascular mortality by 38%, and reduced heart failure hospitalizations by 35%.[72] The CANVAS Program (n = 10,142 T2D) yielded a 33% fall in heart failure admissions and a 40% reduction in the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77).[73] DECLARE-TIMI 58 (n = 17,160 T2D) showed neutral MACE outcomes but still delivered a 27% reduction in heart failure hospitalization and 24% lower renal composite risk.[74] All three trials were primarily designed to evaluate atherosclerotic cardiovascular endpoints, with renal protection only assessed as secondary analyses. Two trials targeted the HFrEF phenotype (LVEF ≤ 40%). This aligns with the phenotype definitions later adopted in the 2023 ESC guidelines. DAPA-HF (n = 4,744) reduced composite cardiovascular death or worsening heart failure by 26%, accompanied by a 17% drop in all-cause mortality.[78] EMPEROR-Reduced (n = 3,730) produced a 25% risk reduction for the same primary composite and cut first and recurrent heart failure admissions by 30%.[79] Both trials enrolled mixed cohorts of diabetic and non-diabetic participants with consistent therapeutic effects across subgroups.

Table 4. Landmark randomized controlled trials of SGLT inhibitors for cardiorenal outcomes in type 2 diabetes, atherosclerotic cardiovascular disease, chronic kidney disease and heart failure. Data presented as Hazard Ratio (Relative Risk Reduction).

Phenotype category	Trial	Drug vs. placebo	Inclusion criteria	Sample size (T2D %)	eGFR Range	Primary outcome (HR, 95% CI)	Key secondary findings	Guideline recommendation
T2D/ASCVD	EMPA-REG OUTCOME	Empagliflozin	T2D + high CV risk	7,020 (100%)	≥30	MACE: HR 0.86	HHF ↓35%; CV death ↓38%; all-cause death ↓32%	ADA 2026: I,A
T2D/ASCVD	CANVAS Program	Canagliflozin	T2D + high CV risk	10,142 (100%)	≥30	MACE: HR 0.86	HHF ↓33%; renal composite HR 0.60	ADA 2026: I,A
T2D/ASCVD	DECLARE-TIMI 58	Dapagliflozin	T2D + ASCVD/risk	17,160 (100%)	≥60	MACE: HR 0.93 (NS)	HHF ↓27%; renal composite ↓24%	ADA 2026: I,A
HFrEF	DAPA-HF	Dapagliflozin	LVEF ≤ 40%, ±T2D	4,744 (42%)	≥30	Worsening HF/CV death: HR 0.74	All-cause death ↓17%	ESC 2023: I,A
HFrEF	EMPEROR-Reduced	Empagliflozin	LVEF ≤ 40%, ±T2D	3,730 (50%)	≥20	CV death/HHF: HR 0.75	Total HHF ↓30%	ESC 2023: I,A
HFmrEF/HFpEF	EMPEROR-Preserved	Empagliflozin	LVEF > 40%, ±T2D	5,988 (49%)	≥20	CV death/HHF: HR 0.79 (21% RRR)	HHF ↓27%	ESC 2023: I,A
HFmrEF/HFpEF	DELIVER	Dapagliflozin	LVEF > 40%, ±T2D	6,263 (45%)	≥25	Worsening HF/CV death: HR 0.82	LVEF> or less than 60% consistent	ESC 2023: I,A
T2D+Recent HF	SOLOIST-WHF	Sotagliflozin	T2D + recent worsening HF	1,222 (100%)	≥30	CV death/HHF/urgent: HR 0.67	No determined benefit for HFrEF	Terminated early
CKD (±T2D)	DAPA-CKD	Dapagliflozin	CKD (UACR 200–5,000)	4,304 (67.5%)	25–75	eGFR↓50%/ESKD/CV death: HR 0.61	Renal-specific 0.56; all-cause death 0.69	KDIGO 2024: I,A
CKD (±T2D)	EMPA-KIDNEY	Empagliflozin	Broad CKD (eGFR 20–90)	6,609 (46%)	20–90	Kidney progression/CV death: HR 0.72	All-cause hosp. ↓14%	KDIGO 2024: I,A
CKD + T2D	CREDENCE	Canagliflozin	T2D + CKD (UACR 300–5,000)	4,401 (100%)	30–90	Renal/CV death: HR 0.70	HHF ↓39%; ESKD ↓32%	KDIGO/ADA: I,A
CKD + T2D	SCORED	Sotagliflozin	T2D + CKD (any UACR)	10,584 (100%)	25–60	CV death/HHF/urgent: HR 0.74	First MACE HR 0.84	Terminated early

Note: Abbreviations: T2D, type 2 diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; HFrEF, heart failure with reduced ejection fraction (LVEF ≤ 40%); HFmrEF, heart failure with mildly reduced ejection fraction (LVEF 41%–60%); HFpEF, heart failure with preserved ejection fraction (LVEF ≥ 40%); CKD, chronic kidney disease (±T2D means patients with or without type 2 diabetes); LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; MACE, major adverse cardiovascular events (covering cardiovascular death, non-fatal myocardial infarction and non-fatal stroke); CV, cardiovascular; HHF, hospitalization for heart failure; ESKD, end-stage kidney disease; HR, hazard ratio; NS, non-significant; I,A, Class I, Level A recommendation; Terminated early refers to trials that were prematurely stopped due to sponsor funding shortage, with pre-defined primary endpoints adjusted during the trial period.

Per the 2023 ESC focused update on heart failure, two dedicated trials assessed patients with stable HFmrEF and HFpEF (LVEF >40%), alongside SOLOIST-WHF, which enrolled people with type 2 diabetes after recent decompensated heart failure. EMPEROR-Preserved (n = 5,988) demonstrated a 21% relative risk reduction in the composite outcome of cardiovascular death and heart failure hospitalization, and a 27% relative risk reduction in heart failure admissions.[80] DELIVER (n = 6,263) achieved an 18% primary outcome reduction, with uniform benefit observed even in patients with LVEF above or below 60%. Equivalent efficacy was seen regardless of concurrent type 2 diabetes status in both studies.[81] SOLOIST-WHF (n = 1,222, all T2D patients with recent worsening HF) achieved a 33% relative reduction in cardiovascular death, heart failure hospitalization or urgent HF visits (HR = 0.67). Of note, this trial was prematurely terminated due to funding constraints. Its pre-specified primary endpoints were revised mid-study.[77] Although sotagliflozin demonstrated promising cardiorenal outcomes in SOLOIST-WHF, whether SGLT1 inhibition contributes independently to these benefits has not been established. No adequately powered head-to-head trial comparing sotagliflozin with a selective SGLT2 inhibitor has been

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conducted, and the observed effects may simply reflect the combined action of both targets. Therefore, claims regarding additional cardiorenal advantages of dual inhibition should be regarded as preliminary and require confirmation in future prospective trials.

Under the KDIGO 2024 CKD guideline framework, four pivotal trials evaluated SGLT inhibitor efficacy in patients with chronic kidney disease with or without type 2 diabetes. CREDENCE (n = 4,401 albuminuric T2D CKD) reduced combined renal and cardiovascular events by 30%. DAPA-CKD (n = 4,304 mixed diabetic/non-diabetic CKD) produced a 39% reduction in primary outcome,[75] while EMPA-KIDNEY (n = 6,609 wide-spectrum CKD) confirmed renoprotection down to eGFR 20 mL/min/1.73 m^2 and cut all-cause hospitalizations by 14%.[83] The SCORED trial evaluated sotagliflozin in adults with type 2 diabetes and moderate kidney impairment (eGFR 25–60), covering all albuminuria grades. It cut the composite risk of cardiovascular death, heart failure admission and urgent HF visits by 26% (HR = 0.74), with a nominal 16% reduction in MACE. However, this trial was halted early for funding reasons, and its primary endpoints were modified mid-study.[76] Similarly, the SCORED trial demonstrated cardiorenal benefits with sotagliflozin. However, the contribution of SGLT1 inhibition cannot be isolated from SGLT2 effects without a direct comparison with a highly selective SGLT2 inhibitor.

Overall, these 12 trials demonstrate cardiorenal protection across all four predefined phenotypes. The most consistent benefit is the reduction in HHF, observed across T2D/ASCVD, HFrEF, HFmrEF/HFpEF, and CKD populations regardless of baseline diabetes status. Composite renal outcomes were consistently reduced in dedicated CKD trials and as secondary endpoints in the CVOTs. Cardiovascular mortality reduction was most prominent in T2D/ASCVD (EMPA-REG OUTCOME) and HFrEF (DAPA-HF). Nevertheless, no significant effect on stroke has been observed. The magnitude of benefit may vary across patient populations and clinical endpoints, underscoring the importance of interpreting these findings within the context of each specific trial population.

6.1.2. Proposed mechanisms of cardiorenal protection

As summarized in Table 5, researchers have conducted relevant studies to explain how SGLT inhibitors exert certain cardiorenal protective effects. To date, there are four types of mechanisms that are proposed regarding these effects. Among these putative SGLT2 inhibitor mechanisms, haemodynamic regulation carries the strongest clinical validation. SGLT blockade alleviates glomerular hypertension and curbs albuminuria, a finding replicated uniformly across landmark kidney outcome trials.[75,82,83] Anti-inflammatory, antifibrotic and antioxidant signals are only supported by preclinical models and observational human biomarker data, and to date, no trial data has confirmed that these pathways directly reduce clinical events.[78,87] Meanwhile, ketone-driven myocardial metabolism remains an unvalidated preclinical hypothesis lacking human interventional proof.[88,89] Finally, the SGLT1-mediated GLP-1/incretin pathway remains a plausible but less validated mechanism. Although dual inhibition enhances GLP-1 and PYY secretion and the SCORED trial showed clinical signals, evidence is still largely limited to surrogate biomarkers rather than hard outcomes.[90,91] Overall, haemodynamic remodeling so far best accounts for SGLT2i clinical benefits, while other pathways remain largely speculative.

Table 5. Stratification of SGLT inhibitor cardiorenal mechanisms by evidence tier.

Mechanism	Evidence tier	Core trial/study basis
Haemodynamic regulation	High (hard endpoint randomized controlled trials)	CREDENCE,[75] DAPA-CKD,[82] EMPA-KIDNEY[83]
Anti-inflammatory/antifibrotic effects	Low (biomarker only, no event proof)	DAPA-HF,[78] CREDENCE biomarker subanalysis[87]
Ketone myocardial metabolism	Very low (preclinical hypothesis)	Isolated heart, rodent and large-animal preclinical metabolic HF studies[88,89]
SGLT1-mediated GLP-1/incretin pathway	Low to moderate (biomarker and surrogate endpoint evidence)	SCORED trial,[76] mechanistic studies on GLP-1[90]/PYY secretion[91]

6.2. Dual SGLT1/2 inhibition

Dual SGLT1/2 inhibition acts at two distinct sites, i.e., intestinal SGLT1 and renal SGLT2. Blocking intestinal SGLT1 slows glucose absorption, dampens postprandial glucose spikes, and promotes GLP-1 (and PYY) secretion, of which GLP-1 has documented cardiometabolic effects. As discussed earlier, concurrent renal SGLT2 inhibition confers established glucosuric and haemodynamic benefits observed with selective SGLT2 inhibitors.[92] Sotagliflozin is the only clinically approved dual inhibitor, showing a 20-fold selectivity for the renal transporter. This moderate selectivity window allows simultaneous inhibition of both transporters. Although highly selective SGLT2 inhibitors have been shown to affect intestinal SGLT1 and incretin release, these effects are less pronounced and more transient than those of sotagliflozin, which sustains SGLT1 inhibition into the distal small intestine and produces more widespread and durable incretin augmentation.[93] Based on positive SCORED trial outcomes versus placebo, sotagliflozin has secured US regulatory approval for adults with heart failure or type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors. While the SGLT2-selective agents studied in outcome trials with dapagliflozin,

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empagliflozin, and canagliflozin demonstrate consistent cardiorenal protection across landmark heart and kidney outcome trials, sotagliflozin's dual intestinal-renal glucose blockade confers a unique pharmacological profile via SGLT1-mediated incretin augmentation. However, direct head-to-head randomized comparisons against pure SGLT2-selective agents remain absent, so incremental clinical benefits attributable to gut SGLT1 inhibition cannot be definitively established from existing trial data.[76,77,92]

7. Conclusion

The story from phlorizin to gliflozins teaches us a lesson in drug design: it is often more efficient to refine a natural product than to start from scratch. Here, structure-guided design provides the tools to address the limitations of early compounds. More importantly, these drugs have proven to do far more than lower blood glucose. Their unexpected benefits in heart failure and kidney disease have reshaped our understanding of the connections among metabolism, the heart, and the kidneys.

Looking forward, the mechanistic understanding we have gained opens several paths. Dual SGLT1/2 inhibitors, for example, promise better overall metabolic control, but will require careful handling of gut-related side effects. AI and computational chemistry are accelerating the search for new leads, though we must recognize that these tools cannot replace solid experimental validation. We are also intrigued by the potential of these agents in the treatment of neurodegenerative diseases. Further translational studies are needed to validate these promising preclinical findings for liver[94] and neurodegenerative[95] diseases. Only then can SGLT inhibitors be broadly adopted in precision medicine practice.[96] Ultimately, the gliflozin experience reminds us that the most impactful drugs are those that not only treat disease but also deepen our understanding of human physiology.

Supplementary Materials

The supporting information can be downloaded at https://ssi.ukscip.com/uploads/7/asset-file/2026/09/asset-file_b4878d719efea9ef9d2c5236bb10e5b3.pdf.

Author Contributions

Conceptualization, S.Z. and F.D.; methodology, S.Z.; software, Y.C. and Y.W.; validation, N.T. and Z.Z.; formal analysis, H.C. and X.-W.L.; investigation, X.L. and X.-W.L.; resources, X.L. and X.-W.L.; data curation, Y.C.; writing—original draft preparation, S.Z.; writing—review and editing, S.Z., X.L. and F.D.; visualization, Y.C. and N.T.; supervision, F.D.; project administration, Z.Z.; funding acquisition, F.D. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

The data underlying this study are available in the published article and its supplementary material.

AI Use Statement

During the preparation of this work, the authors used Qwen (Tongyi Qianwen, Alibaba Cloud) for language organization and manuscript polishing. The authors subsequently reviewed and edited the content as necessary and take full responsibility for the final content of the published article.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Loriaux, D.L. Diabetes and the Ebers Papyrus: 1552 BC. *Endocrinologist* **2006**, *16*, 55–56. [CrossRef]
2. World Health Organization. *World Health Statistics 2025: Monitoring Health for the SDGs, Sustainable Development Goals*; World Health Organization: Geneva, Switzerland, 2025.
3. Huang, Q.; Li, Y.; Yu, M.; Lv, Z.; Lu, F.; Xu, N.; Zhang, Q.; Shen, J.; Zhu, J.; Jiang, H. Global burden and risk factors of type 2 diabetes mellitus from 1990 to 2021, and forecasts to 2050. *Front. Endocrinol.* **2025**, *16*, 1538143. [CrossRef]
4. Forray, A.-I.; Gavrilaș, L.; Crăciun, A.-E.; Borzan, C.M. The global burden of disease: A focus on type II diabetes. In *Handbook of Public Health Nutrition: International, National, and Regional Perspectives*; Springer: Cham, Switzerland, 2025; pp. 1–25. [CrossRef]
5. Vaduganathan, M.; Mensah, G.A.; Turco, J.V.; Fuster, V.; Roth, G.A. The global burden of cardiovascular diseases and risk: A compass for future health. *J. Am. Coll. Cardiol.* **2022**, *80*, 2361–2371. [CrossRef]
6. Wang, R. Global burden of Alzheimer's disease and other dementias during 1990–2021: A Global Burden of Disease and Risk Factors Study 2021-based study. *Neuroepidemiology* **2025**, *60*, 16–27. [CrossRef]
7. Force, L.M.; Kocarnik, J.M.; May, M.L.; Bhangdia, K.; Crist, A.; Penberthy, L.; Pritchett, N.; Acheson, A.; Deitesfeld, L.; Aalruz, H. The global, regional, and national burden of cancer, 1990–2023, with forecasts to 2050: A systematic analysis for the Global Burden of Disease Study 2023. *Lancet* **2025**, *406*, 1565–1586. [CrossRef]

8. Hacker, K. The burden of chronic disease. *Mayo Clin. Proc. Innov. Qual. Outcomes* **2024**, *8*, 112–119. [CrossRef]
9. International Diabetes Federation (IDF). *IDF Diabetes Atlas*, 11th ed.; International Diabetes Federation (IDF): Brussels, Belgium, 2025.
10. Kim, H.J.; Kwon, O. Nutrition and exercise: Cornerstones of health with emphasis on obesity and type 2 diabetes management—A narrative review. *Obes. Rev.* **2024**, *25*, e13762. [CrossRef]
11. Skyler, J.S. Effects of glycemic control on diabetes complications and on the prevention of diabetes. *Clin. Diabetes* **2004**, *22*, 162–166. [CrossRef]
12. Bailey, C.J. Metformin: Historical overview. *Diabetologia* **2017**, *60*, 1566–1576. [CrossRef]
13. Gallwitz, B. Clinical use of DPP-4 inhibitors. *Front. Endocrinol.* **2019**, *10*, 389. [CrossRef]
14. Nauck, M.A.; Quast, D.R.; Wefers, J.; Meier, J.J. GLP-1 receptor agonists in the treatment of type 2 diabetes—State-of-the-art. *Mol. Metab.* **2021**, *46*, 101102. [CrossRef]
15. Tomlinson, B.; Patil, N.G.; Fok, M.; Chan, P.; Lam, C.W.K. The role of sulfonylureas in the treatment of type 2 diabetes. *Expert Opin. Pharmacother.* **2022**, *23*, 387–403. [CrossRef]
16. Dahlén, A.D.; Dashi, G.; Maslov, I.; Attwood, M.M.; Jonsson, J.; Trukhan, V.; Schiöth, H.B. Trends in antidiabetic drug discovery: FDA approved drugs, new drugs in clinical trials and global sales. *Front. Pharmacol.* **2022**, *12*, 807548. [CrossRef]
17. Agarwal, S.; Lingvay, I. SGLT inhibitors: A serendipitous glycaemic tale. *Nat. Rev. Endocrinol.* **2024**, *20*, 65. [CrossRef]
18. Lalhmangaihzuala, S.; Vanlaldinpuia, K.; Khiangte, V.; Laldinpuii, Z.; Liana, T.; Lalhriatpuia, C.; Pachuau, Z. Therapeutic applications of carbohydrate-based compounds: A sweet solution for medical advancement. *Mol. Divers.* **2024**, *28*, 4553–4579. [CrossRef]
19. Mishra, S.; Upadhaya, K.; Mishra, K.B.; Shukla, A.K.; Tripathi, R.P.; Tiwari, V.K. Carbohydrate-based therapeutics: A frontier in drug discovery and development. *Stud. Nat. Prod. Chem.* **2016**, *49*, 307–361. [CrossRef]
20. Clarivate Analytics. *Cortellis*; Clarivate Analytics: London, UK, 2025.
21. FDA Drug Safety Communication. *FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)*; Food and Drug Administration: Silver Spring, MD, USA, 2017. Available online: https://web.archive.org/web/20251208135825/https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-confirms-increased-risk-leg-and-foot-amputations-diabetes-medicine (accessed on 14 December 2025).
22. FDA Drug Safety Communication. *FDA Removes Boxed Warning about Risk of Leg and Foot Amputations for Canagliflozin (Invokana, Invokamet, Invokamet XR)*; Food and Drug Administration: Silver Spring, MD, USA, 2020. Available online: https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin (accessed on 14 December 2025).
23. Bonnesen, K.; Heide-Jørgensen, U.; Christensen, D.H.; Lash, T.L.; Hennessy, S.; Matthews, A.; Pedersen, L.; Thomsen, R.W.; Schmidt, M. Comparative cardiovascular effectiveness of empagliflozin versus dapagliflozin in adults with treated type 2 diabetes: A target trial emulation. *Circulation* **2024**, *150*, 1401–1411. [CrossRef]
24. Modzelewski, K.L.; Pipilas, A.; Bosch, N.A. Comparative outcomes of empagliflozin to dapagliflozin in patients with heart failure. *JAMA Netw. Open* **2024**, *7*, e249305. [CrossRef]
25. Cao, X.; Du, X.; Jiao, H.; An, Q.; Chen, R.; Fang, P.; Wang, J.; Yu, B. Carbohydrate-based drugs launched during 2000–2021. *Acta Pharm. Sin. B* **2022**, *12*, 3783–3821. [CrossRef]
26. Hoy, S.M. Bexagliflozin: First approval. *Drugs* **2023**, *83*, 447–453. [CrossRef]
27. Demirkiran, C.; Demiryürek, Ş.; Demiryürek, A.T. Recent progress and perspectives in sodium-glucose cotransporter 1/2 inhibitors. *Mini-Rev. Med. Chem.* **2025**, *25*, 354–364. [CrossRef]
28. Cui, Y.-L.; Li, B. Hypoglycemic effects of edible fungus polysaccharides: A mini review. *Food Med. Homol.* **2025**, *2*, 9420046. [CrossRef]
29. Fu, G.-Q.; Li, Y.-X.; He, Y.; Zhang, H.; Ma, X. Extraction, structure and bioactivity of *Tremella fuciformis* polysaccharides: A review. *Food Med. Homol.* **2025**, *2*, 9420038. [CrossRef]
30. Yu, Y.-Y.; Duan, Y.-N.; Ma, S.; Hu, Q.-H.; Ma, G.-X. Research progress on the mechanism of functional activity of edible fungi polysaccharides—Focusing intestinal mucus as a key and entry point. *Food Med. Homol.* **2025**, *2*, 9420042. [CrossRef]
31. Zhang, H.-N.; Liu, Y.; Zhang, H.-L.; Wan, Q.-Z.; Wang, Y.-Q. Effect of different drying and grinding techniques on the physicochemical properties and biological activities of fungal polysaccharides. *Food Med. Homol.* **2025**, *2*, 9420045. [CrossRef]
32. Helvacı, Ö.; Helvacı, B. A story of serendipities: From phlorizin to gliflozins. *Exp. Clin. Transplant.* **2023**, *21*, 105–108. [CrossRef]
33. McKee, F.; Hawkins, W. Phlorhizin glucosuria. *Physiol. Rev.* **1945**, *25*, 255–280. [CrossRef]
34. Lin, J.; Hahn, K.-D.; Kinne, R. Synthesis of phlorizin derivatives and their inhibitory effect on the renal sodium/D-glucose cotransport system. *Biochim. Biophys. Acta Biomembr.* **1982**, *693*, 379–388. [CrossRef]
35. Alavi, N.; Spangler, R.A.; Jung, C.Y. Sodium-dependent glucose transport by cultured proximal tubule cells. *Biochim. Biophys. Acta Biomembr.* **1987**, *899*, 9–16. [CrossRef]
36. Hoffman, B.B.; Ziyadeh, F.N. Facilitative glucose transport proteins and sodium-glucose co-transporters in the kidney. *Curr. Opin. Nephrol. Hypertens.* **1995**, *4*, 406–412. [CrossRef]
37. Wright, E.M.; Turk, E. The sodium/glucose cotransport family SLC5. *Pflügers Arch.* **2004**, *447*, 510–518. [CrossRef]
38. Sano, R.; Shinozaki, Y.; Ohta, T. Sodium-glucose cotransporters: Functional properties and pharmaceutical potential. *J. Diabetes Investig.* **2020**, *11*, 770–782. [CrossRef]
39. Zhao, M.; Li, N.; Zhou, H. SGLT1: A potential drug target for cardiovascular disease. *Drug Des. Dev. Ther.* **2023**, 2011–2023. [CrossRef]
40. Blaschek, W. Natural products as lead compounds for sodium glucose cotransporter (SGLT) inhibitors. *Planta Med.* **2017**, *83*, 985–993. [CrossRef]

41. Lehmann, A.; Hornby, P.J. Intestinal SGLT1 in metabolic health and disease. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2016**, *310*, G887–G898. [CrossRef]
42. Crespy, V.; Aprikian, O.; Morand, C.; Besson, C.; Manach, C.; Demigné, C.; Rémésy, C. Bioavailability of phloretin and phloridzin in rats. *J. Nutr.* **2001**, *131*, 3227–3230. [CrossRef]
43. Meng, W.; Ellsworth, B.A.; Nirschl, A.A.; McCann, P.J.; Patel, M.; Girotra, R.N.; Wu, G.; Sher, P.M.; Morrison, E.P.; Biller, S.A. Discovery of dapagliflozin: A potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. *J. Med. Chem.* **2008**, *51*, 1145–1149.
44. Khan, F.; Hussain, T.; Chaudhry, T.Z.; Payal, F.; Shehryar, A.; Rehman, A.; Ramadhan, A.; Hayat, M.T.; Dabas, M.M.; Khan, M. Comparing the efficacy and long-term outcomes of sodium-glucose cotransporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, metformin, and insulin in the management of type 2 diabetes mellitus. *Cureus* **2024**, *16*, e74400. [CrossRef]
45. Niu, Y.; Ye, X. Antidiabetic drugs based on sodium-glucose cotransporter 2 inhibitors. In *Medicinal Chemistry and Drug Development*; Elsevier: Amsterdam, The Netherlands, 2025; pp. 55–70. [CrossRef]
46. Anderson, S.L. Dapagliflozin efficacy and safety: A perspective review. *Ther. Adv. Drug Saf.* **2014**, *5*, 242–254. [CrossRef]
47. Kshirsagar, R.P.; Kulkarni, A.A.; Chouthe, R.S.; Pathan, S.K.; Une, H.D.; Reddy, G.B.; Diwan, P.V.; Ansari, S.A.; Sangshetti, J.N. SGLT inhibitors as antidiabetic agents: A comprehensive review. *RSC Adv.* **2020**, *10*, 1733–1756. [CrossRef]
48. Wright, E.M. SGLT2 inhibitors: Physiology and pharmacology. *Kidney360* **2021**, *2*, 2027–2037. [CrossRef]
49. Maccari, R.; Ottanà, R. Sodium-glucose cotransporter inhibitors as antidiabetic drugs: Current development and future perspectives. *J. Med. Chem.* **2022**, *65*, 10848–10881.
50. Plosker, G.L. Canagliflozin: A review of its use in patients with type 2 diabetes mellitus. *Drugs* **2014**, *74*, 807–824. [CrossRef]
51. Scott, L.J. Empagliflozin: A review of its use in patients with type 2 diabetes mellitus. *Drugs* **2014**, *74*, 1769–1784. [CrossRef]
52. Hussey, E.K.; Clark, R.V.; Amin, D.M.; Kipnes, M.S.; O'Connor-Semmes, R.L.; O'Driscoll, E.C.; Leong, J.; Murray, S.C.; Dobbins, R.L.; Layko, D. Single-dose pharmacokinetics and pharmacodynamics of sergliflozin etabonate, a novel inhibitor of glucose reabsorption, in healthy volunteers and patients with type 2 diabetes mellitus. *J. Clin. Pharmacol.* **2010**, *50*, 623–635. [CrossRef]
53. Yamaguchi, K.; Kato, M.; Ozawa, K.; Kawai, T.; Yata, T.; Aso, Y.; Ishigai, M.; Ikeda, S. Pharmacokinetic and pharmacodynamic modeling for the effect of sodium-glucose cotransporter inhibitors on blood glucose level and renal glucose excretion in db/db mice. *J. Pharm. Sci.* **2012**, *101*, 4347–4356. [CrossRef]
54. Isaji, M. SGLT2 inhibitors: Molecular design and potential differences in effect. *Kidney Int.* **2011**, *79*, S14–S19. [CrossRef]
55. Maranghi, M.; Carnovale, A.; Durante, C.; Tarquini, G.; Tiseo, G.; Filetti, S. Pharmacokinetics, pharmacodynamics and clinical efficacy of dapagliflozin for the treatment of type 2 diabetes. *Expert Opin. Drug Metab. Toxicol.* **2015**, *11*, 125–137. [CrossRef]
56. Knox, C.; Wilson, M.; Klinger, C.M.; Franklin, M.; Oler, E.; Wilson, A.; Pon, A.; Cox, J.; Chin, N.E.; Strawbridge, S.A. DrugBank 6.0: The DrugBank knowledgebase for 2024. *Nucleic Acids Res.* **2024**, *52*, D1265–D1275. [CrossRef]
57. MedChemExpress. Available online: https://www.medchemexpress.com/ (accessed on 11 November 2025).
58. Niu, Y.; Liu, R.; Guan, C.; Zhang, Y.; Chen, Z.; Hoerer, S.; Nar, H.; Chen, L. Structural basis of inhibition of the human SGLT2-MAP17 glucose transporter. *Nature* **2022**, *601*, 280–284. [CrossRef]
59. Hiraizumi, M.; Akashi, T.; Murasaki, K.; Kishida, H.; Kumanomidou, T.; Torimoto, N.; Nureki, O.; Miyaguchi, I. Transport and inhibition mechanism of the human SGLT2-MAP17 glucose transporter. *Nat. Struct. Mol. Biol.* **2024**, *31*, 159–169. [CrossRef]
60. Niu, Y.; Cui, W.; Liu, R.; Wang, S.; Ke, H.; Lei, X.; Chen, L. Structural mechanism of SGLT1 inhibitors. *Nat. Commun.* **2022**, *13*, 6440. [CrossRef]
61. Rendell, M.S. The journey from gene knockout to clinical medicine: Telotristat and sotagliflozin. *Drug Des. Dev. Ther.* **2019**, 817–824. [CrossRef]
62. Bassett, R.L.; Gallo, G.; Le, K.-P.N.; Volino, L.R. Bexagliflozin: A comprehensive review of a recently approved SGLT2 inhibitor for the treatment of type 2 diabetes mellitus. *Med. Chem. Res.* **2024**, *33*, 1354–1367. [CrossRef]
63. Burggraaff, L.; Oranje, P.; Gouka, R.; van der Pijl, P.; Geldof, M.; van Vlijmen, H.W.; IJzerman, A.P.; van Westen, G.J. Identification of novel small molecule inhibitors for solute carrier SGLT1 using proteochemometric modeling. *J. Cheminform.* **2019**, *11*, 15. [CrossRef]
64. Zhao, J.; Xu, P.; Liu, X.; Ji, X.; Li, M.; Sooranna, D.; Qu, X.; Lu, W.; Niu, B. Application of machine learning methods for the development of antidiabetic drugs. *Curr. Pharm. Des.* **2022**, *28*, 260–271. [CrossRef]
65. Moinul, M.; Amin, S.A.; Kumar, P.; Patil, U.K.; Gajbhiye, A.; Jha, T.; Gayen, S. Exploring sodium glucose cotransporter (SGLT2) inhibitors with machine learning approach: A novel hope in anti-diabetes drug discovery. *J. Mol. Graph. Model.* **2022**, *111*, 108106. [CrossRef]
66. Yu, Y.; Xia, Y.; Liang, G. Exploring novel lead scaffolds for SGLT2 inhibitors: Insights from machine learning and molecular dynamics simulations. *Int. J. Biol. Macromol.* **2024**, *263*, 130375. [CrossRef]
67. Illahi, A.D.; Hertono, G.F.; Yanuar, A. Computational QSAR-based machine learning approach for predicting activity of SGLT2 inhibitors using the KNIME platform. *Int. J. Appl. Pharm.* **2025**, *17*, 328–333. [CrossRef]
68. Kaijage, N.; Kraszewski, S. Molecular mechanisms and computational insights into human SGLTs: Advancing toward selective SGLT1 inhibition. *Front. Mol. Biosci.* **2025**, *12*, 1668400. [CrossRef]
69. Vallon, V. Glucose transporters in the kidney in health and disease. *Pflügers Arch.* **2020**, *472*, 1345–1370. [CrossRef]
70. Stefanakis, K.; Karakasis, P.; Vasdeki, D.; Popovic, D.S.; Patoulias, D.; Rizzo, M.; Mantzoros, C.S. Newer and novel antidiabetic drug classes across the cardiovascular-kidney-metabolic continuum. *Endocr. Rev.* **2026**, bnag022. [CrossRef]

71. Grigoriou, K.; Karakasis, P.; Nasoufidou, A.; Stachteas, P.; Klisic, A.; Karagiannidis, E.; Fyntanidou, B.; Popovic, D.S.; Patoulias, D.; Antoniadis, A.P. SGLT2 inhibitors in the management of cardio-renal-metabolic syndrome: A new therapeutic era. *Medicina* **2025**, *61*, 1903. [CrossRef]
72. Zinman, B.; Wanner, C.; Lachin, J.M.; Fitchett, D.; Bluhmki, E.; Hantel, S.; Mattheus, M.; Devins, T.; Johansen, O.E.; Woerle, H.J. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N. Engl. J. Med.* **2015**, *373*, 2117–2128. [CrossRef]
73. Neal, B.; Perkovic, V.; Mahaffey, K.W.; De Zeeuw, D.; Fulcher, G.; Erondu, N.; Shaw, W.; Law, G.; Desai, M.; Matthews, D.R. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N. Engl. J. Med.* **2017**, *377*, 644–657. [CrossRef]
74. Wiviott, S.D.; Raz, I.; Bonaca, M.P.; Mosenzon, O.; Kato, E.T.; Cahn, A.; Silverman, M.G.; Zelniker, T.A.; Kuder, J.F.; Murphy, S.A. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **2019**, *380*, 347–357. [CrossRef]
75. Perkovic, V.; Jardine, M.J.; Neal, B.; Bompoint, S.; Heerspink, H.J.; Charytan, D.M.; Edwards, R.; Agarwal, R.; Bakris, G.; Bull, S. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N. Engl. J. Med.* **2019**, *380*, 2295–2306. [CrossRef]
76. Bhatt, D.L.; Szarek, M.; Pitt, B.; Cannon, C.P.; Leiter, L.A.; McGuire, D.K.; Lewis, J.B.; Riddle, M.C.; Inzucchi, S.E.; Kosiborod, M.N. Sotagliflozin in patients with diabetes and chronic kidney disease. *N. Engl. J. Med.* **2021**, *384*, 129–139. [CrossRef]
77. Bhatt, D.L.; Szarek, M.; Steg, P.G.; Cannon, C.P.; Leiter, L.A.; McGuire, D.K.; Lewis, J.B.; Riddle, M.C.; Voors, A.A.; Metra, M. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N. Engl. J. Med.* **2021**, *384*, 117–128. [CrossRef]
78. McMurray, J.J.; Solomon, S.D.; Inzucchi, S.E.; Køber, L.; Kosiborod, M.N.; Martinez, F.A.; Ponikowski, P.; Sabatine, M.S.; Anand, I.S.; Bělohlávek, J. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.* **2019**, *381*, 1995–2008. [CrossRef]
79. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Pocock, S.J.; Carson, P.; Januzzi, J.; Verma, S.; Tsutsui, H.; Brueckmann, M. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N. Engl. J. Med.* **2020**, *383*, 1413–1424. [CrossRef]
80. Anker, S.D.; Butler, J.; Filippatos, G.; Ferreira, J.P.; Bocchi, E.; Böhm, M.; Brunner-La Rocca, H.-P.; Choi, D.-J.; Chopra, V.; Chuquiure-Valenzuela, E. Empagliflozin in heart failure with a preserved ejection fraction. *N. Engl. J. Med.* **2021**, *385*, 1451–1461. [CrossRef]
81. Solomon, S.D.; McMurray, J.J.; Claggett, B.; de Boer, R.A.; DeMets, D.; Hernandez, A.F.; Inzucchi, S.E.; Kosiborod, M.N.; Lam, C.S.; Martinez, F. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N. Engl. J. Med.* **2022**, *387*, 1089–1098. [CrossRef]
82. Heerspink, H.J.; Stefánsson, B.V.; Correa-Rotter, R.; Chertow, G.M.; Greene, T.; Hou, F.-F.; Mann, J.F.; McMurray, J.J.; Lindberg, M.; Rossing, P. Dapagliflozin in patients with chronic kidney disease. *N. Engl. J. Med.* **2020**, *383*, 1436–1446. [CrossRef]
83. EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N. Engl. J. Med.* **2023**, *388*, 117–127. [CrossRef]
84. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* **2023**, *44*, 3627–3639. [CrossRef]
85. Stevens, P.E.; Ahmed, S.B.; Carrero, J.J.; Foster, B.; Francis, A.; Hall, R.K.; Herrington, W.G.; Hill, G.; Inker, L.A.; Kazancıoğlu, R. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int.* **2024**, *105*, S117–S314. [CrossRef]
86. American Diabetes Association Professional Practice Committee. Cardiovascular disease and risk management: Standards of Care in Diabetes—2026. *Diabetes Care* **2026**, *49*, S216. [CrossRef]
87. Januzzi, J.L.; Mohebi, R.; Liu, Y.; Sattar, N.; Heerspink, H.J.L.; Tefera, E.; Vaduganathan, M.; Butler, J.; Yavin, Y.; Li, J.; et al. Cardiorenal biomarkers, canagliflozin, and outcomes in diabetic kidney disease: The CREDENCE trial. *Circulation* **2023**, *148*, 651–660. [CrossRef]
88. Chase, D.; Eykyn, T.R.; Shattock, M.J.; Chung, Y.J. Empagliflozin improves cardiac energetics during ischaemia/reperfusion by directly increasing cardiac ketone utilization. *Cardiovasc. Res.* **2023**, *119*, 2672–2680. [CrossRef]
89. Goedeke, L.; Ma, Y.; Gaspar, R.C.; Nasiri, A.; Lee, J.; Zhang, D.; Galsgaard, K.D.; Hu, X.; Zhang, J.; Guerrera, N. SGLT2 inhibition alters substrate utilization and mitochondrial redox in healthy and failing rat hearts. *J. Clin. Investig.* **2024**, *134*, e176708. [CrossRef]
90. Gorboulev, V.; Schürmann, A.; Vallon, V.; Kipp, H.; Jaschke, A.; Klessen, D.; Friedrich, A.; Scherneck, S.; Rieg, T.; Cunard, R. Na+-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. *Diabetes* **2012**, *61*, 187–196. [CrossRef]
91. Powell, D.R.; Smith, M.; Greer, J.; Harris, A.; Zhao, S.; DaCosta, C.; Mseeh, F.; Shadoan, M.K.; Sands, A.; Zambrowicz, B. LX4211 increases serum glucagon-like peptide 1 and peptide YY levels by reducing sodium/glucose cotransporter 1 (SGLT1)-mediated absorption of intestinal glucose. *J. Pharmacol. Exp. Ther.* **2013**, *345*, 250–259. [CrossRef]
92. Azizogli, A.R.; Vitti, M.R.; Mishra, R.; Osorno, L.; Heffernan, C.; Kumar, V.A. Comparison of SGLT1, SGLT2, and dual inhibitor biological activity in treating type 2 diabetes mellitus. *Adv. Ther.* **2023**, *6*, 2300143. [CrossRef]
93. Powell, D.R.; Zambrowicz, B.; Morrow, L.; Beysen, C.; Hompesch, M.; Turner, S.; Hellerstein, M.; Banks, P.; Strumph, P.; Lapuerta, P. Sotagliflozin decreases postprandial glucose and insulin concentrations by delaying intestinal glucose absorption. *J. Clin. Endocrinol. Metab.* **2020**, *105*, e1235–e1249. [CrossRef]
94. Ahmed, H.; Gomaa, S.; Abdulrazzak, E.; Razzak, I.A.; Kovalovich, K.K. Therapeutic potential of sodium-glucose

cotransporter 2 (SGLT2) inhibitors in liver disease: Focus on cirrhosis. *Cureus* **2025**, *17*, e84768.
95. Kostrzewska, P.; Kuca, P.; Witek, P.; Małyszko, J.; Madetko Alster, N.; Alster, P. SGLT-2 inhibitors in the prevention and progression of neurodegenerative diseases: A narrative review. *Neurol. Ther.* **2025**, *14*, 2295–2312. [CrossRef]
96. McLean, P.; Bennett, J.; Woods, E.T.; Chandrasekhar, S.; Newman, N.; Mohammad, Y.; Khawaja, M.; Rizwan, A.; Siddiqui, R.; Birnbaum, Y. SGLT2 inhibitors across various patient populations in the era of precision medicine: The multidisciplinary team approach. *NPJ Metab. Health Dis.* **2025**, *3*, 29. [CrossRef]

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