Title: An emerging protagonist: Sodium Glucose Co-transporters (SGLTs) as a burgeoning target for the treatment of diabetes mellitus

Running Title: Sodium Glucose Co-transporters (SGLTs) inhibitors targeting type 2 diabetes mellitus

[1] Danish Ahmed, Manju Sharma, Vikas Kumar, Yadav Pankajkumar Subhashchandra.

Keywords: SGLT2, Diabetes, Kidney, Hyperglycemia, Type 2 Diabetes Mellitus.

[1] Address correspondence to this author at Department of Pharmaceutical Sciences, Faculty of Health, Medical Sciences, Indigenous & Alternative Systems of Medicine, Sam Higginbottom Institute of Agriculture, Technology and Sciences (SHIATS)-Deemed University, Allahabad, Uttar Pradesh, INDIA. Tel: +919369589923. Email: danish.ahmed@shiats.edu.in, danishjhamdard@gmail.com .

An emerging protagonist: Sodium Glucose Co-transporters (SGLTs) as a burgeoning target for the treatment of diabetes mellitus

Danish Ahmed[1*], Manju Sharma[2], Vikas Kumar[1], Yadav Pankajkumar Subhashchandra[1]

1Department of Pharmaceutical Sciences, Faculty of Health, Medical Sciences, Indigenous & Alternative Systems of Medicine, Sam Higginbottom Institute of Agriculture, Technology and Sciences (SHIATS)-Deemed University, Allahabad, Uttar Pradesh, INDIA
Email: danish.ahmed@shiats.edu.in, danishjhamdard@gmail.com
Tel: +919369589923, Fax: +91 532 2684394

[2] Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard University, Hamdard Nagar, New Delhi, INDIA
Email: manju_sharma72@yahoo.com
Tel: +919810786730

Abstract

Contemporary therapies to rationalize the hyperglycaemia in type 2 diabetes mellitus (T2DM) generally involve insulin-dependent mechanisms and lose their effectiveness as pancreatic b-cell function decreases to a greater extent. Kidney emerges out as a novel and potential target to trim down the T2DM. The filtered glucose is reabsorbed principally through the sodium glucose co-transporter-2 (SGLT2), a low affinity transport system, which are present at the luminal surface cells that covers the first segment of proximal tubules. Competitive inhibition of SGLT2 therefore represents an innovative therapeutic strategy for the treatment of hyperglycaemia and/or obesity in patients with type 1 or type 2 diabetes by enhancing glucose and energy loss through the urine. Selective inhibitors of SGLT2 reduce glucose reabsorption, causing excess glucose to be eliminated in the urine; this decreases plasma glucose. SGLT2 inhibitors are coupled with osmotic dieresis and loss of weight which aid in reducing the blood pressure. The observation that individuals with familial renal glycosuria maintain normal long-term kidney function provides some encouragement that this mode of action will not adversely affect renal function. This novel mechanism of targeting kidney for the treatment of T2DM is reasonably valuable and is independent of insulin and clutch with the low risk of hypoglycemia.

Introduction:

Diabetes has become an engorgement apprehension worldwide. More or less 285 million people all over the world will be suffering from diabetes by the end of 2010. WHO estimates that more than 346 million people worldwide have diabetes [1]. This number is likely to more than double by 2030 without intervention. Almost 80% of diabetes deaths occur in low- and middle-income countries. The most common disorder of glucose homeostasis is type2 diabetes mellitus (T2DM). It accounts for 90-96% of all cases of diabetes [**2]**. Sodium-dependent glucose cotransporters (SGLTs) facilitate the transport of glucose against a concentration gradient with synchronized transport of sodium down a concentration gradient [**3]**. The anticipation is there is about 90% of total renal glucose reabsorption is aided by SGLT2. Thus a new therapeutic approach without dependence on insulin and appropriate for use in amalgamation with other agents would be preeminent choice for treatment of hyperglycemia in type 2 diabetes mellitus (T2DM). Sodium Glucose co-transporter inhibitors create a center of attention as there is a need of potential therapy for diabetes mellitus with lesser side effects.[**5**]. This review scrutinize the niceties of various SGLT2 inhibitors

The role of SGLT is fundamental in the mutual transfer of sugar and sodium across the epithelial membrane. The transport of sugar takes place in the small intestine and the renal tubule through active transport. It necessitates the coupling of cellular energy metabolism to the transepithelial transfer. It is SGLT where the coupling takes place. There is no hydrolysis of ATP is engaged as compared to the primary active transport episodes for instance those intervened by ion translocating ATPases. As an alternative the SGLT exploit the energy accumulated in an ion gradient for the translocation of sugars against the concentration gradient. Sodium is the major ion present in the mammals whose gradient across the cell membrane has been used as thrust. The secondary active transport of sugars, carboxylic acid and the aminoacids rivet the synchronized movement of sodium ions by and large in the same direction as the substrate. [6] (Kinne 1991). (**Figure No.1)**

Kidney is the main organ where active transport of sugar takes place in the early part of the proximal tubule. Research work on the transport of sugar in the early and late segments of proximal tubule and vesicles demonstrate that the kidney contains two D-glucose cotransporters with the difference in their stoichiometry for sodium in the early proximal tubule. There is a mutual translocation of one sugar and one sodium molecule in the luminal membrane while two sodium ions are transferred with one sugar molecule in the late part of proximal tubule. There is a divergence in the affinity for D-glucose for the two transporters. [7] (Burckhardt and Kinne 1992). **(Figure No.2)**

The transporter in the early part has been identified as SGLT1 at the same time the transporter found in the early proximal tubule as SGLT2.

The sodium gluocose cotransporter (SGLT2) is a high capacity, low affinity proximal tubular cell transporter that reabsorbs filtered glucose. Mutations in this transporter lead to renal glycosuria. In diabeteic animal models, there appears to be upregulation of the SGLT2 receptors and GLUT2mRNA. SGLT2 antagonism provides an interesting therapeutic option to decrease glucose loads in diabetes. Nonspecific SGLT2 inhibitors like phlorizin have disturbing gastrointestinal side effects. More specific inhibitors like dapagliflozin and sergiflozin are being tested in small clinical trials. The effect on the progression of diabetic kidney disease remains to be studied. [8] (Wright et al. 2007)

Sodium-D-Gluocse transportation: Molecular Aspect

Discovery of human intestinal SGLT1 by Ernie Wright and his acquaintances pave the way for the identification of an identical gene in the kidney [9] (Morrison et al. 1991). This further allowed the researchers to do mutagenesis studies, structural elucidation and the discovery of substrate binding sites as well as inhibitor binding sites [8] (Wright et al. 2007).

The extensive research on the membrane topology of the transporter which was possible only after the acquaintance of the sequence was done. The research showed that the N-terminus of

thee transporter is pointing outside of the cell with 14 transmembrane segments. The position of the loop 13-14 is essential after pholrizin binding site requires the loop 13-14. The C-terminus also plays a vital role in the recognition and translocation of the sugar. [8] (Wright et al. 2007). The N-terminal segments IV-V are implicated in the recognition of sodium as well as glucose binding. **(Table No.1)**

SGLT: Binding situate

After exhaustive research it has been established that sugars in the hexose and D-configuration are transferred while sugars with L-configuration are unable to be transferred. The hydroxyl group at C2 position must be present in the equilateral manner in order to transport the sugars. Consequently the presence of hydroxyl group at C3 position is also plays a vital role. The hydroxyl group at C6 is of not much importance. SGLT2 have one hydrophobic binding site at C6 position therefore the alkyl residues present at C6 have higher affinity than SGLT1. [10] (Kipp et al. 1997).

Table No. 1: Pharmacodynamic parameters of SGLT2 inhibitors currently in development

Compound	Selectivity for SGLT2 vs. SGLT1 (Fold)	UGE in humans at highest dose; mean value ±SD[a] (g/day)	Reduction in HbA1c (%)
ASP1941	255 (ref. 28)	90.8 ± 16.0 (ref. 29) 58.9 ± 14.6 (ref. 31) 50 (ref. 30)	−0.8 (ref. 30)
BI 10773	>2,500 (ref. 32)	72.6 ± 35.9 (ref. 33) 88 ± 20.3 (ref. 34) 90.8 (ref. 35)	NR
Canagliflozin	414 (ref. 36)	129.2 ± 20.8 SE (ref. 37) 113 (ref. 38)	−0.92 (ref. 37)
Dapagliflozin	1,200 (ref. 39)	70 (ref. 22)	−0.61 to −0.89 (refs. 16–19)
LX4211	20 (ref. 40)	80 (ref. 40)	−1.25 (ref. 40)

[a]SD unless otherwise indicated; SD/SE was not reported in some studies.

HbA1c, hemoglobin A1c; NR, not reported; SD, standard deviation; SE, standard error;

UGE, urinary glucose excretion.

Novel SGLT2 inhibitors:

1. Phlorizin:

It is beta glucoside obtained from the bark of apple roots. Phlorizin normalized plasma glucose and corrected glucotoxicity induced decline in insulin sensitivity and pancreatic β-cell function in animal models of diabetes mellitus [11-13].

Phlorizin has proved useful as a physiological research tool and has been used in this capacity for more than 150 years. But there are several limitation of this SGLT inhibitor is that it is non-selective SGLT inhibitor, inhibiting SGLT2 and SGLT1 inhibitor. [14,15,]

Another limitation of phlorizin embrace the poor oral bioavailability and susceptibility of O-linkage to be cleave by the β-glucosidase in the gastrointestinal tract. [16,17]. For this reason phlorizin has to be given by parentral route in order to be effective. In order to improve the shortcomings of the phlorizin, another compounds or derivatives of phlorizin came into existences which are discussed later in the article.

2. T-1095:

It is improved derivative of phlorizin that can be administered orally as prodrug. [18]. T-1095 is another O-glucoside with greater metabolic firmness as compared to the phlorizin. Though it is a non-selective SGLT inhibitor. [16, 18, 19]. It was discontinued in the Phase-II clinical trial. [16].

3. Sergiflozin Etabonate:

Sergliflozin is highly specific inhibitor of SGLT2 in its glycated form [20, 21]. Sergliflozin is found to be very potent and and selective for rat SGLT2 with a selectivity ration of 41. Based on Ki value (**Table No.2)** the selectivity of sergliflozin towards human SGLT2 was also found to be far above the ground. Sergliflozin etabonate (Active form of Sergliflozin) encouraged excretion of glucose depending on blood glucose level. Upon chronic administration of sergliflozin etabonate to Zuker fatty rats there is no alteration in body weight (622.6 ± 12.4, 614.7 ± 23.2, and 615.8 ± 15.6g for vehicle, 10mg/kg and 30 mg/kg group respectively) as well as the food intake (30.6 ± 2.0, 29.5 ± 2.5, and 32.1 ± 1.3g for vehicle 10mg/kg and 30 mg/kg group respectively) but it reduces both the glycated heamoglobin (**Figure No.3A, 3B**) and fasting plasma glucose (**Figure No.4) [22]**

Sergliflozin was discontinued for various unfavorable effects such as non-desired pharmaceutical properties, non-selectivity and development of new SGLT2 inhibitors. [23-25]

Table No.2: Ki values of sergliflozin etabonate, sergliflozin, and phlorizin for rat SGLTs

	Ki Value (nM)	
	Rat SGLT1	Rat SGLT2
Sergliflozin etabonate	3350 ± 110	651 ± 149
Sergliflozin	704 ± 254	17.1 ± 2.6
Phlorizin	275 ± 153	41.8 ± 11.4

Data are presented as means±S.E.M. from 3 experiments. An AMG uptake experiment was performed with COS-7 cells transiently transfected with rat SGLT1 or SGLT2, and the Ki values for each SGLT were calculated. *(Copyright 2009, Elsevier, Data adapted with permission from Fujimori et al, (Yoshikazu Fujimori, Kenji Katsuno, Kazuma Ojima, Ikumi Nakashima, Shigeru Nakano, Yukiko Ishikawa-Takemura, Hiroshi Kusama, Masayuki Isaji, Sergliflozin etabonate, a selective SGLT2 inhibitor, improves glycemic control in streptozotocin-induced diabetic rats and Zucker fatty rats, European Journal of Pharmacology, Volume 609, Issues 1–3, 1 May 2009, Pages 148-154)*

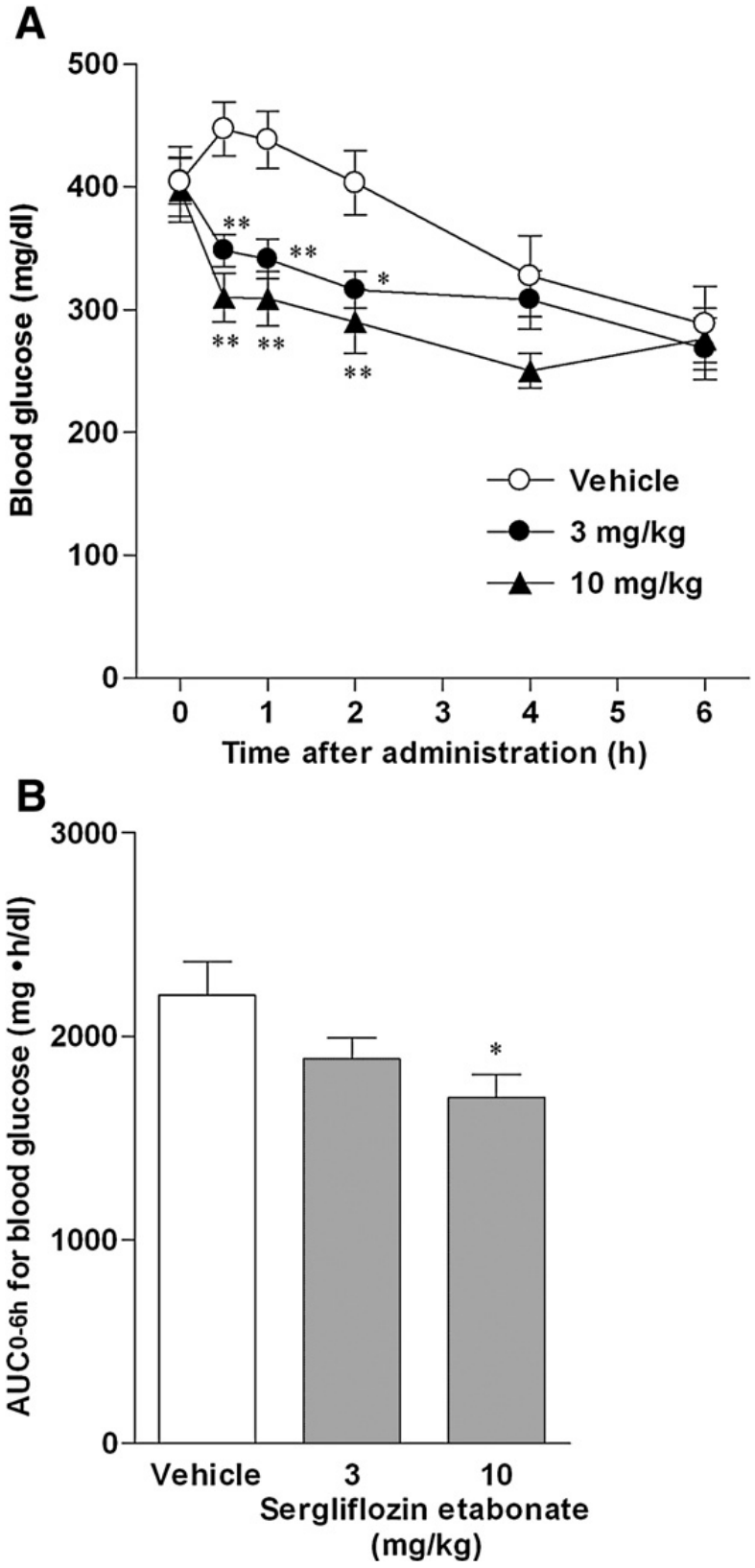

Figure No. 3: Acute effects of sergliflozin etabonate in Zucker fatty rats. Sergliflozin etabonate was orally administered to fed Zucker fatty rats. Blood glucose concentrations (A) were measured, and the AUC0–6 h for blood glucose (B) was calculated. Data are presented as means±S.E.M. (n=7–8). *Pb0.05, **Pb0.01 vs. vehicle group. *(Adapted with permission from Fujimori et al, Yoshikazu Fujimori, Kenji Katsuno, Kazuma Ojima, Ikumi Nakashima, Shigeru Nakano, Yukiko Ishikawa-Takemura, Hiroshi Kusama, Masayuki Isaji, Sergliflozin etabonate, a selective SGLT2 inhibitor, improves glycemic control in streptozotocin-induced diabetic rats and Zucker fatty rats, European Journal of Pharmacology, Volume 609, Issues 1–3, 1 May 2009, Pages 148-154*

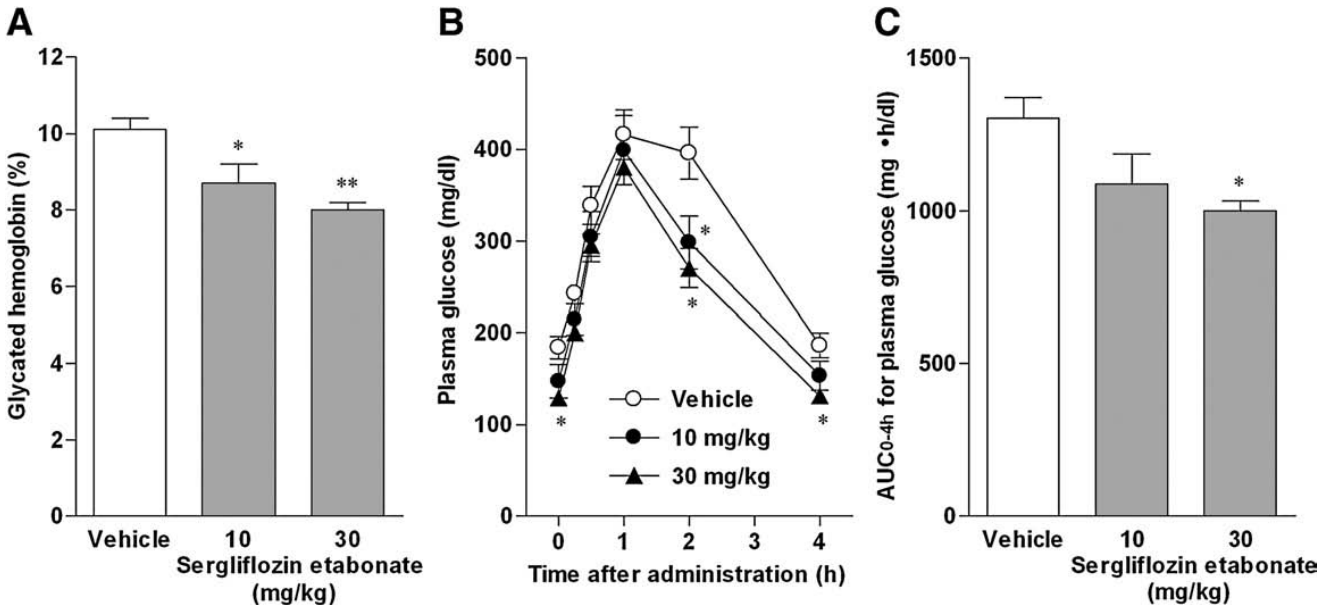

Figure No. 4: Chronic effects of sergliflozin etabonate in Zucker fatty rats. Sergliflozin etabonate was orally administered to Zucker fatty rats twice daily for 2 weeks. At the end of the administration period, glycated hemoglobin (A) was determined; and the oral glucose tolerance test (2 g/kg) was performed. Plasma glucose concentrations (B) were measured, and the AUC0–4 h for plasma glucose (C) was calculated from the plasma glucose concentration during the oral glucose tolerance test. Data are presented as means±S.E.M. (n=4–5). *Pb0.05, **Pb0.01 vs. vehicle group. (*Adapted with permission from Fujimori et al, Yoshikazu Fujimori, Kenji Katsuno, Kazuma Ojima, Ikumi Nakashima, Shigeru Nakano, Yukiko Ishikawa-Takemura, Hiroshi Kusama, Masayuki Isaji, Sergliflozin etabonate, a selective SGLT2 inhibitor, improves glycemic control in streptozotocin-induced diabetic rats and Zucker fatty rats, European Journal of Pharmacology, Volume 609, Issues 1–3, 1 May 2009, Pages 148-154)*

4. Dapagliflozin:

Dapagliflizon is potent inhibitor of human SGLT2 and has EC_{50} of 1.1 nM with 1200 fold selectivity for human SGLT2 over SGLT1 and contain C-glucoside in lieu of O-glycoside linkage which makes it β-glucosidase resistant.[26] It is under clinical trial. Earlier clinical trials showed the efficacy of dapagliflozin versus placebo in the patients of type 2 diabetes mellitus and metformin [27] and sulfonylurea glimepiride [28].

A randomized noninferiority clinical trial conducted by Nauck etal [29] of dapagliflozin versus gliplizide. The trial showed that dapagliflozin reduces the plasma glucose level in the same manner as of glipizide with lesser episodes of hypoglycemia. It also reduces the systolic as well as diastolic blood pressure in the type 2 diabetes mellitus patients. Consequently the patients treated with dapagliflozin experiences the weight loss while patients receiving the glipizide sustained weight gain.

Dapagliflozin has marked effect on blood glucose level. Some excellent investigations [3-33], in the treatment naïve patients for 12 weeks, in patients on metformin monotherapy for 24 weeks and in poorly controlled patients receiving insulin and oral antidiabetic drug for 12 weeks shows that dapagliflozin has dose dependent effect on the PPG (Post prandial glucose) levels in poorly controlled patients while dose dependency is lesser in case of treatment-naïve patients. The above study clarifies that higher filtered load of glucose in poorly controlled patients in responsible for higher excretion of glucose from the kidney which results in the better HbA1c values. [34] **(Table No 2).**

Table No.2: Effect of dapagliflozin on blood glucose parameters

Blood glucose Measure	Dapagliflozin monotherapy in 389 treatment-naïve patients in a 12-week study						Dapagliflozin as an add-on to metformin in 546 patients inadequately controlled by metformin alone in a 24-week study				Dapagliflozin combination therapy in 71 patients inadequately controlled by insulin plus OADs in a 12-week study		
	2.5mg	5mg	10mg	20mg	50mg	Placebo	2.5 mg	5mg	10mg	Placebo	10mg	20mg	Placebo
Mean change from baseline in FPG (mg/dl)	-16	-19	-21	-24	-31	-6	-17.8	-21.5	-23.5	-6.0	-2.4	-9.6	17.8
Change from baseline in PPG	-9382[a]	-8478[a]	-10149[a]	-7053[a]	-10,093[a]	-3182[a]					-34.3[b]	-41.9[b]	18.7[b]
Mean absolute change from baseline in HbA1c (%)	-0.71	-0.72	-0.85	-0.55	-0.90	-0.18	-0.67	-0.70	-0.84	-0.30	-0.61	-0.69	0.09

AUC, area under the curve; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; OAD, oral antidiabetic drug; PPG, postprandial plasma glucose. [a] Mean change in AUC ((mg/dL)*min). [b]Plasma glucose levels measured after 120 min during a 75 g oral glucose tolerance test.

(Adapted with permission from List et al (List JF, Whaley JM. Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans. Kidney Int 2011; 79 (Suppl 120): S20–S27.)

5. Remigliflozin:

Remigliflozin is an O-glycoside SGLT2 inhibitor. It was developed as a consequential candidate for SGLT2 inhibition with better selectivity and pharmacokinetic profile.[35]. Its selectivity towards human SGLT2 was higher as compared to human SGLT1. (Ki values: 12.4 and 4520 nmol/l towards human SGLT2 and human SGLT1 respectively). While remigliflozin etabonate inhibit SGLT2 more potently in vivo as compared to the Phlorizin ,Sergliflozin and T-1095. Remigliflozin is an O-glycoside which is susceptible to β-glucosidase.[36]. Moreover, it causes reduction of blood glucose and body weight as well as the blood pressure in type2 diabetes mellitus patients. [23].

6. Canagliflozin:

Canagliflozin is another C-glucoside and has ~200-fold selectivity for SGLT2 (IC_{50} 2.2 nM) as compared to SGLT1 (IC_{50} 0.44μM) (**Table No. 3)** [37]. One recent research has shown the potency and selectivity of Canagliflozin towards SGLT2 inhibition. There was noteworthy diminution in the blood glucose level receiving the Canagliflozin at 3mg/kg without any alteration in the food intake in hyperglycemic high-fat diet fed KK (HG-KK) mice (**Figure No.5**). On the contrary there is only slight reduction in the blood glucose levels in normoglycemic mice (Figure). Consequently, it can be said that there will be less hypoglycemic episodes with Canagliflozin. Furthermore, Canagliflozin remarkably increases the urinary glucose excretion [38] (Table). At this moment in time Canagliflozin is under Phase-III clinical trial.

	IC50 (nM)			
Compound	**hSGLT1**	**hSGLT2**	**GLUT1**	**UGE[a] (mg/day)**
Canagliflozin	910	2.2	>10000	3696

Table No. 3: hSGLT1, hSGLT2, Facilitated Glucose Transporter 1 (GLUT1) Inhibitory Activity, and Rat Urinary Glucose Excretion (UGE) Data for Canagliflozin. (. (*Adapted with permission from Sumihiro Nomura et al , (Discovery of Canagliflozin, a Novel C-Glucoside with Thiophene Ring, as Sodium-Dependent Glucose Cotransporter 2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus Sumihiro Nomura, Shigeki Sakamaki, Mitsuya Hongu, Eiji Kawanishi, Yuichi Koga, Toshiaki Sakamoto, Yasuo Yamamoto, Kiichiro Ueta, Hirotaka Kimata, Keiko Nakayama, and Minoru Tsuda-Tsukimoto Journal of Medicinal Chemistry 2010 53 (17), 6355-6360, Copyright 2010 @American Chemical Society)*

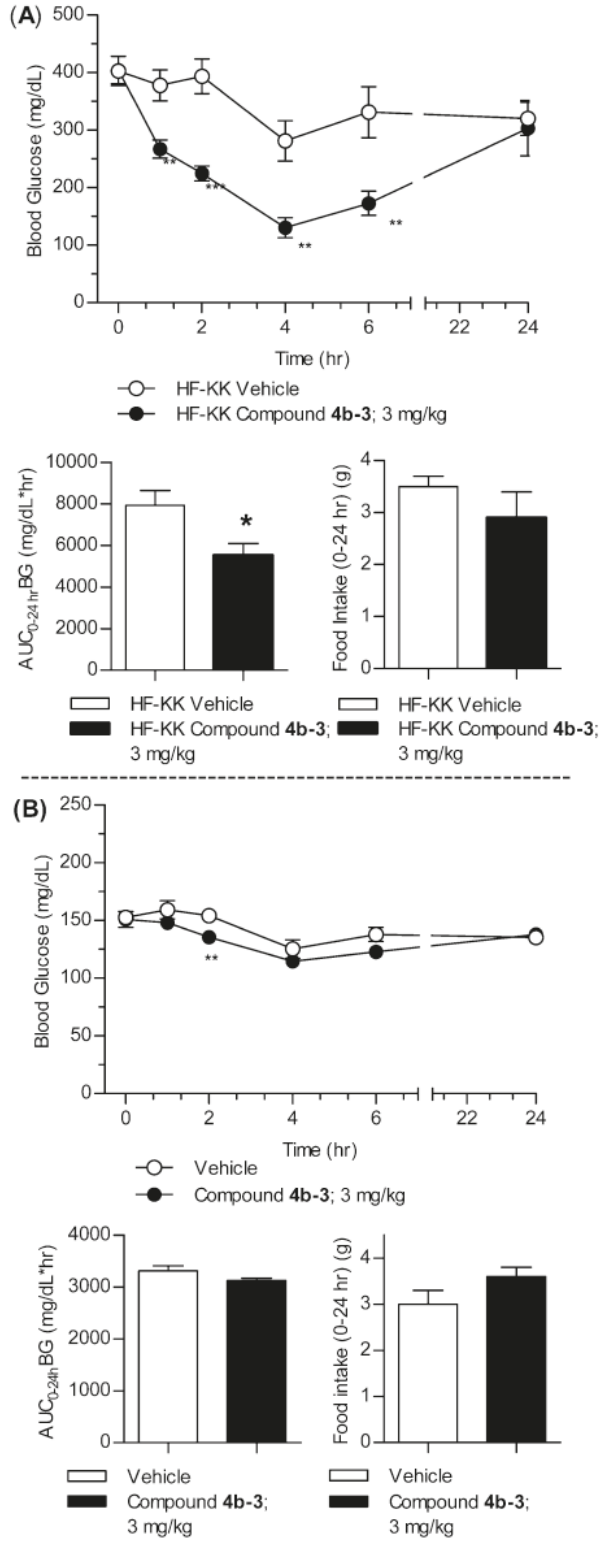

Figure No.5. Effects of single oral dosing of Canagliflozin on blood glucose levels and food intake in high-fat diet fed KK (HF-KK) (A) and normal (B) mice. Data are expressed as the mean (SEM (n = 5): * P < 0.05, ** P < 0.01 vs vehicle. (*Adapted with permission from Sumihiro Nomura et al , (Discovery of Canagliflozin, a Novel C-Glucoside with Thiophene Ring, as Sodium-Dependent Glucose Cotransporter 2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus Sumihiro Nomura, Shigeki Sakamaki, Mitsuya*

Hongu, Eiji Kawanishi, Yuichi Koga, Toshiaki Sakamoto, Yasuo Yamamoto, Kiichiro Ueta, Hirotaka Kimata, Keiko Nakayama, and Minoru Tsuda-Tsukimoto Journal of Medicinal Chemistry 2010 53 (17), 6355-6360, Copyright 2010 @American Chemical Society)

Table No. 4: Clinical progress of some important SGLT2 inhibitors for the treatment of type 2 diabetes mellitus

Compound	Manufacturing Company	Development Phase
T-1095	Tanabe	Discontinued
TS-033	Taisho	Discontinued
AVE2268	Sanofi-Aventis	Discontinued
YM-543	Astellas/Kotobuki	Discontinued
Remogliflozin	GlaxoSmithKline	Discontinued
Sergliflozin	GlaxoSmithKline/Kissei	Discontinued
Dapagliflozin	Bristol-Myers Squibb/AstraZeneca	Phase III
Canagliflozin	JNJ/Mitsubishi Tanabe	Phase III
BI 10773	Boehringer Ingelheim	Phase II
BI 44847	Boehringer Ingelheim/Ajinomoto	Phase II
R-7201	Roche/Chugai	Phase II
TS-071	Taisho	Phase II
LX4211	Lexicon	Phase II

Contemporary view and prospective advantages of the SGLT2 inhibitors:

Many new SGLT2 inhibitors have been developed as result of modification in the prototype Phlorizin. After withdrawal of non-selective SGLT2 inhibitors viz. Phlorizin, T-1095 etc, newer SGLT2-selective inhibitors such as sergliflozin, remogliflozin, AVE—2268 and YM-543 have also been taken off. Though new selective SGLT2 inhibitors curtail the adverse effects resulted from SGLT1 inhibition such as gastrointestinal disturbances which is associated with the non-selective SGLT2 inhibitors.

Sergliflozin and Dapagliflozin reduces the blood pressure probably by their osmotic diuretic and tuboglomerular reflex. As far as the Pharmacokinetic profile is concerned C-glycosides are longer acting as compared to O-glycosides. Consequently, C-glycosides suppress the postprandial hyperglycemia and fasting hyperglycemia more prominently than short acting O-glycosides. Controlling the postprandial hyperglycemia is vital for thwarting cardiovascular adverse effects.[39].

The important gain from SGLT2 inhibitors is the co-transportation of the sodium as well as glucose which reduces the reabsorption of both the glucose and sodium which results in diuretic action of SGLT2 inhibitors. Another benefit of SGLT2 inhibitor is the reduction of blood glucose without any change in the body weight which is the adverse effect associated with most of the Oral Antidiabetic drugs (OADs) such as sulfonylureas, insulin and thiazolidinediones (TZDs).

Limitations of the SGLT2 inhibitors:

Although the mechanism of action of SGLT2 inhibitors may resides potential benefits in it, nevertheless they are associated with an assortment of precincts as well such as polyuria and polydipsia which results in hypovolemia particularly in the dehydrated patients. Urinary excretion of glucose also results in an increased risk of urinary tract infections (UTIs) and genitourinary infections. Furthermore, most of the Oral Antidiabetic Drugs (OADs) either improve insulin resistance or insulin secretion whereas SGLT2 inhibitors are thought to increase the glycemic control through urinary excretion of the same, irrespective of how the glucose level increased. Consequently diminution of glucotoxicity might improve the insulin resistance as well as the insulin secretion.

Conclusion:

Currently overabundances of therapies are available to target the diabetes mellitus. Nevertheless, targeting the glucose level remain on top priority in sizeable percentage of type 2 diabetes mellitus patients. Increased blood glucose level contributes to the succession and development of type 2 diabetes mellitus. Reducing the blood glucose level through increased urinary excretion of sugar put forward impending advantages of better glycemic control, minimum risk of hypoglycemia and sympathetic effect on the body weight. At present many companies are developing potential SGLT2 inhibitors with different selectivity, pharmacokinetic profiles, potency and efficacy. SGLT2 inhibitors are expected to improve the glycemic control, insulin resistance as well as the conservation of pancreatic β-cells. The insulin independent mechanism of action of SGLT2 inhibitors might provide better treatment for the type 2 diabetes mellitus patients. These are expected to provide better synergistic results when used as combinatorial therapy with other antidiabetic drugs despite predictable adverse effects for instance polyuria, urinogenital infections, and UTIs.

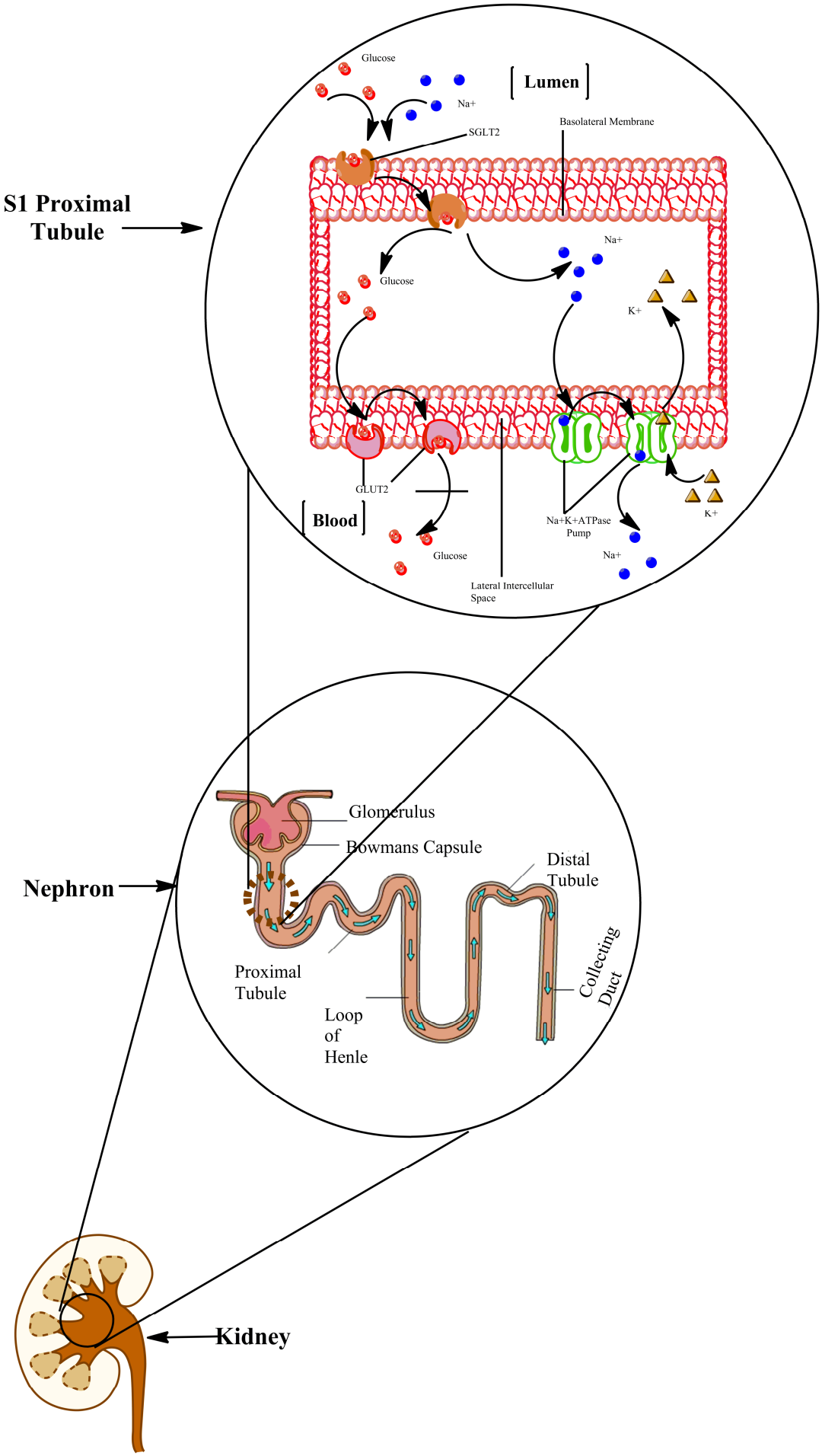

Figure No.1 , Reabsorption of glucose from the renal proximal tubules by the sodium glucose cotransporters SGLT2 . Almost all of the glucose entering glomeruli in the afferent glomerular arterioles is filtered into the nephron fluid of the proximal renal tubules. Most (up to ┐ 90%) of this filtered glucose is reabsorbed in the initial proximal convoluted segment (S1) by SGLT2 located at the luminal surface of proximal tubular cells. Remaining glucose is reabsorbed from the filtrate in themore distal convoluted and straight segments by SGLT1. Glucose within the proximal tubular cells is then transported back to the interstitial compartment and thence to the plasma by the facilitative glucose transporters GLUT2 in the S1 segment, respectively. In normal individuals with an average plasma glucose concentration of 5–5.5 mmol/L (90–100mg/dL), approximately 160–180 g of glucose is filtered daily, with less than 0.5 g/day of glucose appearing in the urine. Based on Bakris et al. and Bays

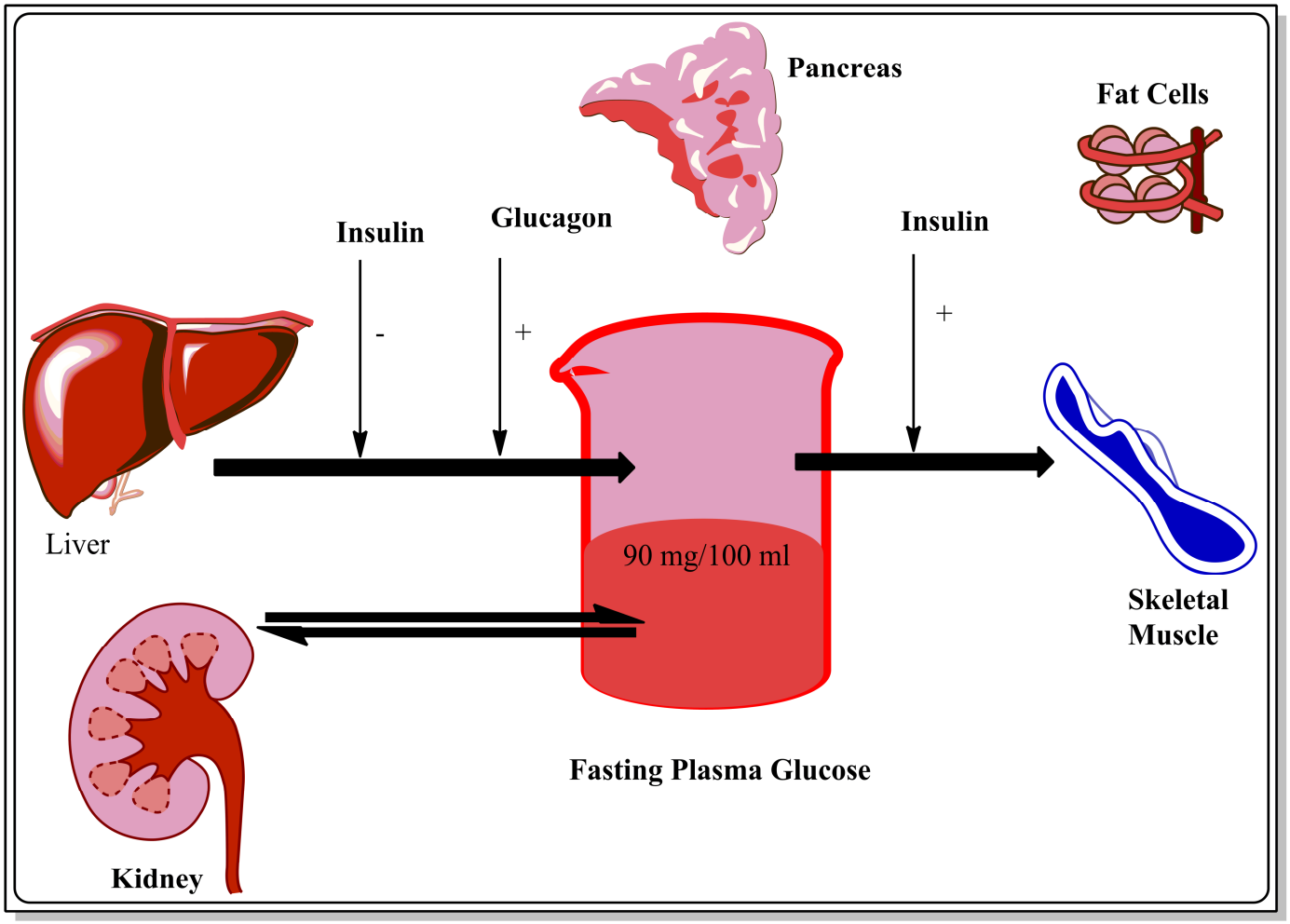

Figure No. 2. **Normal glucose homeostasis.** This outlines the hormonal interactions that are important in regulating normal glucose homeostasis. Normal fasting glucose homeostasis involves the hormonal regulation of glucose utilization and production, as well as the filtration and reabsorption of glucose by the kidney10. Under basa conditions, glucose uptake by the tissues is matched by glucose production from the liver; this enables fine regulation of glucose at a fixed level. Gluconeogenesis in the liver helps prevent hypoglycaemia. *(Reproduced with permission from Edward C. Chao, Copyright @2010, Macmilan Publishers Limited.)*

Conflict of Interest: Authors declares no conflict of interest.

References:

1. International Diabetes Federation. Diabetes Atlas, 4th ed.; International Diabetes Federation: Montreal, Canada, 2009.

2. Dwarakanathan, A. Diabetes update. J. Insur. Med. 2006, 38; 20–30.

3. Mackenzie, B.; Loo, D. D.; Panayotova-Heiermann, M.; Wright, E. M. Biophysical characteristics of the pig kidney Naþ/glucose cotransporter SGLT2 reveal a common mechanism for SGLT1 and SGLT2. J. Biol. Chem. 1996; 271: 32678–32683.

4. Moe, O. W.; Berry, C. A.; Rector, F. C. The Kidney, 5th ed.; Brenner, B. M.,Rector, F. C., Eds.;WBSaunders Co.: Philadelphia, PA, 2000; 375-415.

5. Washburn, W. Evolution of sodium glucose co-transporter 2 inhibitors as anti-diabetic agents. Expert Opin. Ther. Patents 2009, 25, 1485–1499.

6. Kinne RKH (1991) Selectivity and direction – plasma-membranes in renal transport. Am J Physiol 260:F153–F162

7. Burckhardt G, Kinne RKH (1992) Transport proteins. Cotransporters and countertransporters. In: Seldin DW, Giebisch G (eds) The kidney: physiology and pathophysiology. New York, Raven, pp 537–586.

8. Wright EM, Hirayama BA, Loo DF (2007) Active sugar transport in health and disease. J Intern Med 261:32–43.

9. Morrison AI, Panayotova-Heiermann M, Feigl G, Scholermann B, Kinne RKH (1991) Sequence comparison of the sodium-D-glucose cotransport systems in rabbit renal and intestinal epithelia. Biochim Biophys Acta 1089:121–123

10. Kipp H, Kinne-Saffran E, Bevan C, Kinne RK (1997) Characteristics of renal Na+-D-glucose cotransport in the skate (Raja erinacea) and shark (Squalus acanthias). Am J Physiol 273: R134–R142.

11. Ehrenkranz JRL, Lewis NG, Kahn CR, Ross J. Phlorizin: a review. Diabetes Metab Res Rev. 2005;21:31 – 8.

12. Rossetti L, Shulman GI, Papachristou D, DeFronzo RA. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest. 1987; 79:1510 – 5.

13. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. Diabetes Care. 1990;13:610 – 30.)

14. Kanai Y, Lee WS, You G, Brown D, Hediger MA: The human kidney low affinity Na_/glucose cotransporter SGLT2. Delineation of the major renal reabsorptive mechanism for D-glucose. J Clin Invest 93:397-404, 1994

15. Panayotova-Heiermann M, Loo DD, Wright EM: Kinetics of steady-state currents and charge movements associated with the rat Na_/glucose cotransporter. J Biol Chem 270:27099-27105, 1995

16. Isaji M: Sodium-glucose cotransporter inhibitors for diabetes. Curr Opin Investig Drugs 8:285-292, 2007

17. Ehrenkranz JR, Lewis NG, Kahn CR, Roth J: Phlorizin: A review. Diabetes Metab Res Rev 21:31-38, 2005

18. (MengW, Ellsworth BA, Nirschl AA, et al: Discovery of dapagliflozin: A potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. J Med Chem 51:1145-1149, 2008)

19. Oku A, Ueta K, Arakawa K, et al: T-1095, an inhibitor of renal Na_-glucose cotransporters, may provide a novel approach to treating diabetes. Diabetes 48:1794 1800, 1999.

20. Katsuno, K., Fujimori, Y., Takemura, Y., Hiratochi, M., Itoh, F., Komatsu, Y., et al. (2007)

21. Sergliflozin, a novel selective inhibitor of low-affinity sodium glucose cotransporter (SGLT2), validates the critical role of SGLT2 in renal glucose reabsorption and modulates plasma glucose level. J Pharmacol Exp Ther 320, 323−330.)

22. Yoshikazu Fujimori, Kenji Katsuno, Kazuma Ojima, Ikumi Nakashima, Shigeru Nakano, Yukiko Ishikawa-Takemura, Hiroshi Kusama, Masayuki Isaji, Sergliflozin etabonate, a selective SGLT2 inhibitor, improves glycemic control in streptozotocin-induced diabetic rats and Zucker fatty rats, European Journal of Pharmacology, Volume 609, Issues 1–3, 1 May 2009, Pages 148-154.

23. (Dobbins R, Kapur A, Kapitza C, O'Connor-Semmes R, Tao W, Hussey EK. Remogliflozin etabonate, a selective inhibitor of the sodium-glucose transporter 2 (SGLT2) reduces serum glucose in type 2 diabetes mellitus (T2DM) patients. Diabetes. 2009;58(suppl. 1). Abstract

24. Hussey EK, Kapur A, O'Connor-Semmes R, Tao W, Poo J, Dobbins R. Safety, pharmacokinetics and pharmacodynamics of remogliflozin etabonate (SGLT2 inhibitor) and metformin when coadministered in type 2 diabetes mellitus (T2DM) patients. Diabetes. 2009;58(suppl. 1). Abstract

25. Hussey E, Clark RV, Amin DM, et al. Early clinical studies to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of single doses of sergliflozin, a novel inhibitor or renal glucose reabsorption, in healthy volunteers and subjects with type 2 diabetes mellitus. Diabetes. 2007;56:A49. Abstract

26. Dapagliflozin: a sodium glucose cotransporter 2 inhibitor in development for type 2 diabetes Diabetes Therapy, Abd A. Tahrani · Anthony H. Barnett , 2010, 1(2):45-56.)

27. Bailey, C. J., Gross, J. L., Pieters, A., Bastien, A. & List, J. F. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a andomized, double-blind, placebo-controlled trial. Lancet. 375, 2223–2233 (2010).

28. Strojek, K. et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a andomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes. Metab. 13, 928–938 (2011)

29. (Nauck, M. A. et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin. Diabetes Care 34, 2015–2022 (2011)

30. List JF, Woo V, Morales E et al. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 2009; 32: 650–657.

31. Wilding JP Norwood P, T'Joen C et al. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. Diabetes Care 2009; 32: 1656–1662

32. Bailey CJ, Gross JL, Pieters A et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a andomized, double-blind, placebo-controlled trial. Lancet 2010; 375: 2223–2233

33. Bailey CJ, Gross JL, Bastone L et al. Dapagliflozin as an add-on to metformin lowers hyperglycaemia in type 2 diabetes patients inadequately controlled with metformin alone. Diabetologia 2009; 52 (Suppl 1): S76

34. List JF, Whaley JM. Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans. Kidney Int 2011; 79 (Suppl 120): S20–S27.

35. Fujimori Y, Katsuno K, Nakashima I et al. Remogliflozin etabonate, in a novel category of selective low-affinity sodium glucose cotransporter (SGLT2) inhibitors, exhibits antidiabetic efficacy in rodent models. J Pharmacol Exp Ther 2008; 327: 268–276.

36. Masayuki Isaji, SGLT2 inhibitors: molecular design and potential differences in effect, Kidney International (2011) 79 (Suppl 120), S14–S19.

37. Liang, Y. et al. (2009) JNJ-28431754/TA-7284, an SGLT inhibitor, lowers blood glucose and reduces body weight in obese and type 2 diabetic animal models. Diabetes 58 (Suppl 1), Abstract 534-P.

38. Discovery of Canagliflozin, a Novel C-Glucoside with Thiophene Ring, as Sodium-Dependent Glucose Cotransporter 2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus Sumihiro Nomura, Shigeki Sakamaki, Mitsuya Hongu, Eiji Kawanishi, Yuichi Koga, Toshiaki Sakamoto, Yasuo Yamamoto, Kiichiro Ueta, Hirotaka Kimata, Keiko Nakayama, and Minoru Tsuda-Tsukimoto Journal of Medicinal Chemistry 2010 53 (17), 6355-6360)

39. Leiter LA, Ceriello A, Davidson JA et al. Postprandial glucose regulation: new data and new implications. Clin Ther 2005; 27(Suppl B): S42–S46.