*Ağrı Tıp Fakültesi Dergisi 2025 3(3):99-101*
*e-ISSN: 2980-0978*

***Editorial/ Editöryal***
***DOI:10.61845/agrimedical.1811202***

# Beyond glycemic control: The pleiotropic potential of SGLT-2 inhibitors

## Glisemik kontrolün ötesinde: SGLT-2 inhibitörlerinin pleiotropik potansiyeli

Selma Sezen[1]*

[1] *Department of Medical Pharmacology, Faculty of Medicine, Agri Ibrahim Cecen University, Agri, Turkey*

*0000-0001-6575-6149*
*Sorumlu Yazar: Selma Sezen*
*e-mail: selma-sezen@hotmail.com*
*ssezen@agri.edu.tr*

Gönderilme Tarihi: 26/10/2025
Kabul Tarihi: 27/10/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:** Sezen S. Beyond glycemic control: The pleiotropic potential of SGLT-2 inhibitors. Ağrı Med J. 2025; 3(3): 99-101.

SGLT inhibitors (SGLTi), used by a large number of patients worldwide, are now regarded by researchers as having pharmacological potential beyond glycemic control due to their pleiotropic effects. In humans, cellular transport of glucose is mediated by glucose transporters (GLUTs). These are divided into two groups: Sodium-glucose co-transporters (SGLT), which actively transport sodium-dependent glucose, and GLUTs, which operate on the principle of facilitated diffusion. GLUTs, which are divided into three subfamilies, are present in all body cells to facilitate the transport of glucose into cells (1, 2). SGLTs, on the other hand, have been identified in many different tissues, including the kidneys, human umbilical cord cells, coronary arteries and vascular smooth muscle cells, brain, thyroid, and uterus. Although many isoforms of SGLTs have been identified, the most commonly known isoforms are SGLT-1 and SGLT-2 (3). Selecting a receptor group present in numerous tissues as a therapeutic target may seem concerning; however, fortunately, the distribution of these receptors varies across tissues.

When the historical development of SGLTi is examined, this time the story begins not with the apple, but with the bark of the apple tree. Although phlorizin, isolated from the bark of apple trees by French chemists, was proposed for the treatment of malaria, fever, and certain infectious diseases, experiments revealed that it caused glucosuria. Strikingly, it was proposed as an experimental animal model of diabetes because symptoms characteristic of diabetic patients, such as glucosuria, polyuria, and weight loss, were observed (4). In the 1900s, phlorizin, which was used to induce diabetes in animals, was later understood through concomitant studies following the characterization of SGLTs to be able to regulate fasting and postprandial glucose levels (5-7). So what happened to phlorizin? After a series of experiments, it was determined to be a potent inhibitor of both SGLT-1 and SGLT-2. Administration of 15–20 g of phlorizin to individuals with diabetes has been reported to cause glucosuria. However, subsequent studies showed that phlorizin's low oral bioavailability, its causing gastrointestinal complaints, and its being an SGLT-1i prevented it from becoming a drug candidate (8). Nevertheless, important data had been recorded, and phlorizin-based analogs began to be synthesized. First, O-glucoside analogs of phlorizin were synthesized, but none were successful. Subsequently, C-glucoside derivatives of phlorizin began to be investigated, and finally, in 2008, dapagliflozin was developed. The first gliflozin to enter clinical use is dapagliflozin. Dapagliflozin received its first approval for clinical use from the EMA in 2012 and from the FDA in 2014. This approval was for achieving glycemic control, in conjunction with diet and exercise, in adult patients diagnosed with Type 2 Diabetes Mellitus (however, this would not be the only approval obtained from the FDA). Shortly thereafter, empagliflozin and canagliflozin also took their place among the gliflozins (8-10).

It was recognized during the testing of phlorizin that SGLT-2i act through the kidney (4). In subsequent studies, their glucose-lowering effects in the kidneys were demonstrated (11). One of the most important clinical risks of developing a drug that aims to reduce blood glucose is hypoglycemia. However, the risk of hypoglycemia associated with SGLT-2i is low. In the kidney of a healthy individual, glucose filtered from the glomerulus enters the tubules and is reabsorbed by SGLT-1 and SGLT-2. SGLT-2 is more densely expressed in the S1 and S2 segments of the renal proximal tubule. It is responsible for a substantial portion of sodium and glucose reabsorption in the renal tubules. By contrast, SGLT-1 is a low-capacity glucose transporter and is present in tissues other than the kidney as well. Thus, even when SGLT-2 is inhibited, it enables a small amount of glucose to be reabsorbed from the renal tubules, thereby reducing the risk of hypoglycemia (12). Several hypotheses have been proposed regarding the renoprotective effects of SGLT-2i. The most notable include activation of tubuloglomerular feedback, reduction of proximal tubular metabolic stress, reduction of hypoxia, reduction of mitochondrial injury, reduction of hyperglycemia-driven inflammation, and reduction of oxidative stress (13). Numerous clinical reports indicate that SGLT-2i reduces the risk of kidney failure and other major renal outcomes by 30–40% not only in patients with diabetes but also in individuals with chronic kidney disease (CKD) without diabetes (14). In a randomized, multicenter clinical trial with 4,289 participants, it was reported that, compared with placebo, those receiving

dapagliflozin had a lower risk of death due to kidney disease or cardiovascular causes. In this study centered on patients with CKD, lower risks of hospitalization related to cardiovascular causes and lower mortality rates were reported in those treated with dapagliflozin (15). The effects of SGLT-2i in combination with other drugs or in individuals with multiple chronic conditions also remain a subject of interest. In a study investigating the effects of 12-week empagliflozin therapy, in addition to angiotensin-converting enzyme inhibitors, on the molecular dynamics of the renin angiotensin system, it was determined that it induced activation of the alternative renin angiotensin system axis in patients with CKD and diabetes (16). In another study involving 507 intensive care patients with acute organ dysfunction, the hypothesis was proposed that dapagliflozin therapy might reduce composite outcomes such as in-hospital mortality, initiation of renal replacement therapy, and length of stay in the intensive care unit. However, the investigators reported that dapagliflozin did not improve clinical outcomes in critically ill patients (17).

Since SGLT-2i has found a place in clinical use, research has focused, in addition to diabetic control, on their protective effects on both the kidney and the cardiovascular system. What actually enabled this to take shape rapidly was the FDA's 2008 guidance, "Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" (18). Because SGLT-2i were in the development phase, cardiovascular risks were also evaluated during the studies, and a substantial amount of data was recorded. After they began to be used in the treatment of type 2 diabetes, the diversity of data increased. Zinman and colleagues, in a randomized, double-blind study involving 7,028 patients with type 2 diabetes and lasting approximately three years, reported that once-daily empagliflozin (10 mg or 25 mg) significantly reduced the primary composite cardiovascular endpoint and all-cause mortality compared with placebo (19). In a study including 309,056 patients across six countries, treatment with SGLT-2i in patients with type 2 diabetes and atherosclerotic cardiovascular disease was associated with a lower risk of cardiovascular death and hospitalization for heart failure compared with other glucose-lowering drugs (20). In a study involving 10,142 patients with type 2 diabetes and high cardiovascular risk, canagliflozin therapy was observed to provide a significant reduction in rates of cardiovascular death or hospitalization for heart failure. In this study, regarding the provision of effective outcomes by 100 mg or 300 mg canagliflozin therapy versus placebo, the extent to which treatment duration had an effect is quite striking, debatable, yet inspiring, because the patients were followed for approximately 188 weeks (21).

Owing to its success and mechanism in diabetes treatment, its effects on obesity and metabolic syndrome have also been investigated. In a randomized clinical study involving 24 individuals diagnosed with prediabetes who were not receiving pharmacological therapy, it was determined that after 12 weeks of 10 mg dapagliflozin treatment, patients' body weight, body mass index, waist circumference, fasting blood glucose, and uric acid decreased (22). In overweight and obese women with polycystic ovary syndrome, it was recorded that combination therapy with canagliflozin and metformin, compared with the group receiving metformin monotherapy, resulted in significantly lower total testosterone, area under the curve for glucose, and area under the curve for insulin. On the other hand, they reported that no significant difference was found between the two groups in improving menstrual frequency, weight control, hyperandrogenemia, and alleviating insulin resistance. At the end of this 12-week study, the emphasis in the article is quite valuable: we do not yet fully know the long-term outcomes of SGLT-2 inhibition (23). It has long been known that metabolic alterations affect cellular genomic stability. It has been proposed that the regulation of cellular energy by antidiabetic drugs may, in relation to this, modify the direct and indirect epigenetic effects caused by oncometabolites (24). Indeed, it has been reported that SGLT-2 expression is increased in various cancer types such as prostate, pancreatic, lung, and cervical cancer. In a preclinical study, canagliflozin was shown to significantly suppress the growth of pancreatic cancer cells in vitro and in vivo (25). The results of a meta-analysis suggested that SGLT-2i may reduce the likelihood of anthracycline-induced cardiac problems (26). Meta-analyses report that they are an effective and safe tool for improving the prognosis of patients with cancer and diabetes, and they are in agreement that further research is needed (27,28). The number and diversity of studies on SGLT-2i are increasing by the day. In addition to their beneficial effects in patients, SGLT-2i, which are generally considered safe, are closely monitored for adverse events. We know that SGLT isoforms are present at varying levels across different tissues in the body and that SGLT-2i such as dapagliflozin can cross the blood–brain barrier. In this context, a comprehensive network meta-analysis has proposed that dapagliflozin exerts a novel and specific prophylactic effect against Parkinson's disease (29). In conclusion, this story that began with the bark of the apple tree speaks volumes about the discovery of new drug molecules and the potential to expand the indications of established drugs, and it continues to be rewritten every day.

**Ethical Approval**
Ethics committee approval is not required for this article.

**Conflict of Interest**
The author is the Editor-in-Chief of this journal and was not involved in the peer review or decision-making process for this editorial.

**Financial Disclosure**
No financial support was received for the study.

**Authors' Contributions**
SS: Conceptualization, literature review, Writing-original draft, Writing-review & editing

**Data Sharing Statement**
Not available

## REFERENCES


1. Sano R, Shinozaki Y, Ohta T. Sodium-glucose cotransporters: functional properties and pharmaceutical potential. J Diabetes Investig. 2020;11(4):770–82.
2. Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet. 2021;398(10296):262–76.
3. Bendotti G, Montefusco L, Pastore I, Lazzaroni E, Lunati ME, Fiorina P. The anti-inflammatory and immunological properties of SGLT-2 inhibitors. J Endocrinol Invest. 2023;46(12):2445–52.
4. White JR. Apple trees to sodium glucose co-transporter inhibitors: a review of SGLT2 inhibition. Clin Diabetes. 2010;28(1):5–10.
5. Rossetti L, Smith D, Shulman GI, Papachristou D, DeFronzo RA. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest. 1987;79(5):1510–5.
6. Blondel O, Bailbe D, Portha B. Insulin resistance in rats with non-insulin-dependent diabetes induced by neonatal (5 days) streptozotocin: evidence for reversal following phlorizin treatment. Metabolism. 1990;39(8):787–93.
7. Brichard SM, Henquin JC, Girard J. Phlorizin treatment of diabetic rats partially reverses the abnormal expression of genes involved in hepatic glucose metabolism. Diabetologia. 1993;36:292–8.
8. Helvacı Ö, Helvacı B. A story of serendipities: from phlorizin to gliflozins. Exp Clin Transplant. 2023;21(Suppl 2):105–8.
9. Balakumar P, Sundram K, Dhanaraj SA. Dapagliflozin: glucuretic action and beyond. Pharmacol Res. 2014;82:34–9.
10. Moradi-Marjaneh R, Paseban M, Sahebkar A. Natural products with SGLT2 inhibitory activity: possibilities of application for the treatment of diabetes. Phytother Res. 2019;33(10):2518–30.
11. Chen X, Wang J, Lin Y, Liu Y, Zhou T. Signaling pathways of podocyte injury in diabetic kidney disease and the effect of sodium-glucose cotransporter 2 inhibitors. Cells. 2022;11(23):3913.
12. Dai ZC, Chen JX, Zou R, Liang XB, Tang JX, Yao CW. Role and mechanisms of SGLT-2 inhibitors in the treatment of diabetic kidney disease. Front Immunol. 2023;14:1213473.
13. Wanner C, Nangaku M, Kraus BJ, Zinman B, Mattheus M, Hantel S, et al. How do SGLT2 inhibitors protect the kidney? A mediation analysis of the EMPA-REG OUTCOME trial. Nephrol Dial Transplant. 2024;39(9):1504–13.
14. Upadhyay A. SGLT2 inhibitors and kidney protection: mechanisms beyond tubuloglomerular feedback. Kidney360. 2024;5(5):771–82.
15. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46.
16. Antlanger M, Domenig O, Kaltenecker CC, et al. Combined sodium glucose co-transporter-2 inhibitor and angiotensin-converting enzyme inhibition upregulates the renin-angiotensin system in chronic kidney disease with type 2 diabetes: results of a randomized, double-blind, placebo-controlled exploratory trial. Diabetes Obes Metab. 2022;24(5):816–26.
17. Tavares CAM, Azevedo LCP, Rea-Neto Á, et al. Dapagliflozin for critically ill patients with acute organ dysfunction: the DEFENDER randomized clinical trial. JAMA. 2024;332(5):401–11.
18. U.S. Food and Drug Administration. Guidance for industry on diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes; availability. Fed Regist. 2008;73.
19. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.
20. Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study. Circulation. 2017;136(3):249–59.
21. Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS Program. Circulation. 2018;138(5):458–68.
22. Ramírez-Rodríguez AM, González-Ortiz M, Martínez-Abundis E. Effect of dapagliflozin on insulin secretion and insulin sensitivity in patients with prediabetes. Exp Clin Endocrinol Diabetes. 2020;128(8):506–11.
23. Zhang J, Xing C, Cheng X, He B. Canagliflozin combined with metformin versus metformin monotherapy for endocrine and metabolic profiles in overweight and obese women with polycystic ovary syndrome: a randomized controlled trial. Front Endocrinol (Lausanne). 2022;13:1003238.
24. Benedetti R, Benincasa G, Glass K, et al. Effects of novel SGLT2 inhibitors on cancer incidence in hyperglycemic patients: a meta-analysis of randomized clinical trials. Pharmacol Res. 2022;175:106039.
25. Ren D, Sun Y, Zhang D, et al. SGLT2 promotes pancreatic cancer progression by activating the Hippo signaling pathway via the hnRNPK-YAP1 axis. Cancer Lett. 2021;519:277–88.
26. Mohsin S, Hasan M, Sheikh ZM, et al. Efficacy of SGLT2 inhibitors for anthracycline-induced cardiotoxicity: a meta-analysis in cancer patients. Future Cardiol. 2024;20(7–8):395–407.
27. Fan G, Zuo H, Lin L, Xu C, Yan R. The efficacy and safety of sodium glucose cotransporter 2 inhibitors for patients with anticancer therapy: a meta-analysis of cohort studies. Glob Heart. 2025;20(1):53.
28. Copur S, Yildiz AB, Covic A, Kanbay M. Is there any robust evidence showing that SGLT2 inhibitor predisposes to cancer? Eur J Clin Invest. 2024;54(2):e14131.
29. Tseng PT, Zeng BY, Hsu CW, et al. The pharmacodynamics-based prophylactic benefits of GLP-1 receptor agonists and SGLT2 inhibitors on neurodegenerative diseases: evidence from a network meta-analysis. BMC Med. 2025;23(1):197.