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The role of flozins in managing cardiovascular risk in patients with type 2 diabetes - narrative review

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Abstract

Introduction. Cardiovascular disease is a leading cause of morbidity and mortality among patients with type 2 diabetes mellitus. The emergence of flozins, a class of sodium-glucose co-transporter-2 inhibitors, has introduced a novel therapeutic avenue with potential cardiovascular benefits beyond glycemic control.

Objective. This review aims to synthesize current evidence on the role of flozins in managing cardiovascular risk among patients with T2DM, examining their efficacy, safety profile, and mechanisms of action.

Review methods. A comprehensive literature search was conducted using databases, covering studies published between 2015 and 2024. Clinical trials, meta-analyses, and observational

studies evaluating the cardiovascular outcomes associated with flozins in T2DM patients were included.

Brief description of the state of knowledge. Research shows that flozins improve glycemic control and provide significant cardiovascular protection, reducing major adverse cardiovascular events, heart failure hospitalizations, and cardiovascular mortality in T2DM patients. These benefits are likely due to hemodynamic changes, enhanced cardiac function, and reduced inflammation and oxidative stress.

Summary. Flozins represent a promising therapeutic option for reducing cardiovascular risk in T2DM patients. Their dual benefits on both metabolic and cardiovascular health position them as a cornerstone in the management of T2DM. Further research is needed to fully elucidate their long-term benefits and safety in diverse patient populations.

Key words: flozins, SGLT2 inhibitors, type 2 diabetes, cardiovascular risk

Introduction and objective

Sodium glucose co-transporter 2 receptor (SGLT-2) inhibitors called flozines are one of the newest drugs used in type 2 diabetes mellitus (T2DM) patients. Flozines are also recommended for nondiabetic patients, to improve their cardiovascular and metabolic outcomes. The positive impact on cardiovascular risk has been described with kidney-protective effects, regardless of the presence of diabetes. [1-2]

Flozins have been used in the treatment of diabetes since 2012. Originally these medications were intended for the treatment of type 2 diabetes in combination with other oral medications or insulin if the therapy was intensified or as monotherapy [3]. Currently, there are approximately 530 million people suffering from diabetes globally, and according to forecasts, in 2050 as many as 1.3 billion people may suffer from diabetes in the world. Patients with type 2 diabetes (T2D) account for 90-95% of diagnoses [4]. According to the guidelines of the Polish Diabetes Association from 2024, SGLT-2 inhibitors, GLP-1 RA and metformin should be considered first-line drugs when starting pharmacological treatment of type 2 diabetes. [5]

Diabetes is associated with numerous complications, the most serious of which concern the cardiovascular system. Patients with T2DM have a significantly increased risk of cardiovascular diseases, including heart attack, stroke, and heart failure, which is the leading cause of death in this population. Flozins have emerged and show promising results in the management of both hyperglycemia and cardiovascular risk. [6-8]

Since the beginning of use of the SGLT-2 inhibitors, it has been noticed that they slightly, but statistically significantly, reduce both systolic and diastolic blood pressure. The antidiabetic effect of these drugs consists in inhibiting the reabsorption of glucose and partially sodium in the renal tubules, which leads to an increase in the amount of urine excreted. Most likely, increased diuresis is responsible for the drop in blood pressure. [9].

These drugs are also contributing to positive clinical outcomes in people suffering from heart failure with reduced ejection fraction (HFrEF) with or without diabetes, thus reducing mortality associated with cardiovascular disease. This is the first class of medication that can be used in every patient with symptomatic heart failure due to type 2 diabetes. That therapy also improves the prognosis of patients with HFpEF. [10]

This review aims to comprehensively examine the literature and latest scientific reports to evaluate the cardiovascular outcomes associated with flozin use in T2DM patients, thereby offering insights into their role in reducing cardiovascular risk.

Review and methods

The literature review was conducted using the PubMed, Google Scholar, Web of Science, and NCBI databases, focusing on research articles published from 2012 to 2024. Keywords used included "SGLT2 inhibitors," "flozins," "cardiovascular risk," "type 2 diabetes," "empagliflozin," "canagliflozin," "dapagliflozin,", “heart failure”, “hypertension”. Inclusion criteria were peer-reviewed articles reporting on clinical trials, meta-analyses, and observational studies examining the cardiovascular effects of flozins in T2DM patients. Exclusion criteria included studies on type 1 diabetes.

Description of the state of knowledge

Glucose is transported to tissues via various glucose transporters, mainly by 2 families the sodium-glucose-linked transporters SGLT and facilitated diffusion glucose transporters GLUT which consist of more subclasses [11]. The distribution varies in tissues with SGLT2 mainly distributed in kidney proximal tubular cells [12]. They are responsible for roughly 90% of the reabsorption of filtered glucose, which prevents energy loss through glycosuria [13, 14].

Flozins work by blocking these channels, resulting in glucose excretion via urine and consequently reduced serum glucose levels, enhancing systolic blood pressure (SBP) and glycated hemoglobin (HBA1c) levels, mitigating the macrovascular and microvascular complications linked to T2DM [14,15]. Additionally, these inhibitors instigate natriuresis, leading to negative water and salt balance, which reduces blood pressure and prevents tubuloglomerular feedback stimulation [14].

SGLT2 inhibitors play a role in promoting caloric loss associated with diabetes enhancing the release of hypoxia-inducible factors (HIF1 and 2) from juxtaglomerular apparatus and alleviating anemia through EPO (erythropoietin) release [13]. Regardless of the occurrence of diabetes, clinical studies have also noted a substantial reduction in albuminuria levels [15].

Currently, there are three SGLT2 selective inhibitors approved for the treatment of diabetes type 2 and are following canagliflozin, dapagliflozin and empagliflozin [14, 16].

Scheme of Diabetes Type 2 Treatment

In Poland, the scheme of diabetes type 2 treatment according to A Position of Diabetes Poland includes:

I. initiation of therapy: modification of the lifestyle (less calorie intake and increased physical activity (At least 30-45 minutes per day) to reduce the body weight

II. pharmacotherapy might be started with monotherapy or combined treatment. At first metformin, SGLT-2 inhibitors or GLP1 receptor agonists should be taken into consideration.

In the case of diabetes de novo flozins and/or GLP-1 receptor agonists should be the first line of treatment if patient meets at least one of the following criteria:

- documented atherosclerotic cardiovascular disease
- heart failure
- chronic kidney disease
- numerous cardiovascular risk factors
- severe hyperglycemia (HbA1C > 8,5%)

Under the same circumstances, flozins can be added to the treatment of patients with pre-existing diabetes [5].

Desired Effects

SGLT2 inhibitors, through their mechanism of action, have several desired effects beyond just lowering blood glucose levels in patients with type 2 diabetes. The more important effects of these drugs include:

1) Reduction in Glycated Hemoglobin (HbA1c): All SGLT2 inhibitors have been shown to significantly reduce HbA1c levels, contributing to better long-term glycemic control [17].

2) Improvement in Lipid Metabolism: Studies have shown that the use of SGLT2 inhibitors positively affects lipid metabolism on several different levels. They decrease lipid accumulation in visceral fat, regulate the serum lipoprotein levels, beneficially change the ratio of LDL particles, reduce lipid oxidation, and shift substrate utilization towards the usage of ketone bodies, which are more efficient in myocardial metabolism, and less reactive oxygen species are created through their oxidation, affect the β-oxidation and the transportation of lipid molecules in the cells [18].

3) Reduction in Blood Pressure: The use of SGLT2 inhibitors is associated with a modest but statistically significant reduction in both SBP, and DBP. The exact mechanisms are not entirely understood, but it is believed to be multifactorial, with the diuretic effect being the most significant contributing factor [19]. In a meta-analysis conducted by Georgianos and

Agarwal, the decrease in SBP after SGLT2 inhibitors was 3.62 mm Hg, and the reduction in DBP was 1.7 mm Hg in 24-hour recordings [20].

4) Reduction in Obstructive Sleep Apnea: There is emerging evidence that SGLT2 inhibitors may reduce the incidence or severity of obstructive sleep apnea in patients with type 2 diabetes, the coexistence of these two factors is estimated at up to 86% in patients with type 2 diabetes [21].

5) Weight Loss: SGLT2 inhibitors, including dapagliflozin, canagliflozin, and empagliflozin, have been shown to reduce body weight and waist circumference [18,22]. This weight loss is thought to result from increased lipolysis in visceral fat tissue and increased lipid metabolism [23]. Furthermore, the effects of SGLT2 inhibition on weight loss are moderate and diminish with time, due in part to counter-regulatory mechanisms (such as increased energy intake) being activated to attempt to maintain weight [24].

6) Improvement in Beta-Cell Function and Insulin Sensitivity: Canagliflozin has been shown to improve beta-cell function as measured by HOMA 2 - %B [22]. Empagliflozin, on the other hand, has been associated with improved insulin sensitivity, increased endogenous glucose production, increased concentration of GLP-1, and reduced insulin secretion contributing to better glucose homeostasis [25].

7) Reduction in inflammation: SGLT2 inhibitors, including empagliflozin, canagliflozin, and dapagliflozin, have been shown to reduce inflammatory markers in patients with diabetes. Although the precise mechanisms by which SGLT2 inhibitors modulate inflammation are not fully understood, one hypothesis is that the reduction in glucose levels leads to a decreased inflammatory response in macrophages. This is because macrophages, which play a key role in inflammation, predominantly rely on glucose from glycolysis as their primary energy source [24].

8) Improving vascular function: SGLT2 inhibition has been shown to improve vascular function by attenuating endothelial cell activation, inducing direct vasorelaxation, reducing endothelial cell dysfunction and molecular changes associated with early atherogenesis decreasing arterial wall stiffness, and decreasing vascular resistance [24]. These effects are particularly important in reducing the risk of hypertension and atherosclerosis in patients with diabetes.

Cardiovascular and Renal Effects of SGLT2 Inhibitors

SGLT2 inhibitors are initiated through a broad range of indications, many of them aiming for cardiovascular benefits or nefroprotective means or overall better outcomes. Major mechanisms of these benefits include better hemodynamic work of the heart, including lower preload from diuretic effect, lower afterload by lowering blood pressure, partially from diuretic mechanism and from natriuretic effect. Worth mentioning is that flozins lower blood pressure without changing heart rate (significantly), which is the contribution of SGLT2 inhibitors blocking the sympathetic activity, but only in patients with higher sympathetic tone present already [26-29]. Flozins reduce blood pressure following the circadian rhythm, with the best effect during daytime [30]. Notably, the medications present with low risk of hypotension in patients with normal blood pressure levels.

Wide mechanisms of metabolic action, including reduction of endogenous insulin secretion, improved production of glucagon (inhibition of SGLT2 on α-cells), greater glucagon:insulin ratio promotes lipolysis and ketogenesis, and greater consumption of β-hydroxybutyrate contributes for lower production of reactive oxygen species (ROS), leading to many positive outcomes including lower risk for developing and reducing the progression of atherosclerosis [26,27,31]. Other effects of SGLT2 blockade include alteration of cytokines and adipokines synthesis and excretion to favor balance between proinflammatory molecules (such as leptin) and anti-inflammatory (e.g. adiponectin) [26,31,32]. Adipokines play an important role in HF pathogenesis. SGLT2 inhibitors act both molecularly on restoring the balance between the substances as well as reducing epicardial adipose tissue, responsible for adipokines release [26,31]. The effect can depend on the duration of treatment, or on adipose tissue cells differentiation in other phenotypes which is assumed to have a beneficial impact [33].

It has been proven that flozins hypotensive effects partially come from reduction of arterial stiffness [26,29,33]. Arterial stiffness as a solitary effect is influenced by many factors, including proper synthesis and levels of vasodilatory NO, which SGLT2 inhibitors stimulate to be produced locally in endothelial cells, additionally flozins reduce oxidative stress by suppressing inflammation and profibrotic cytokines, mainly NF-κB and collagen type IV [33]. In other studies, physiological impact of SGLT2 inhibition did not present with the same outcomes, leaving potential impact on arterial stiffness as unclear. For example EMPA-HEART CardioLink-6 trial showed that empagliflozin was improving the oxidative stress

state by lowering and stabilization of superoxide generating enzyme NOX1 and enhanced production of antioxidant catalase [26]. Some authors did not show any benefit of flozins on arterial stiffness, others suggested the impact of uricosuria as a potential factor contributing to improved vascular stiffness.

In several studies SGLT2 inhibitors markedly reduced risk of stroke [34-36]. The mechanism behind the effect is not entirely clear, it is suggested however, that flozins can mediate cardiac action potentials and have antiarrhythmic properties, affecting atrial fibrillation and atrial flutter [36-39].

Some authors propose that SGLT2 inhibitors cardiovascular and renal benefits come from direct inhibition of sodium-hydrogen exchangers, mainly NHE1 in the heart, NHE3 located in kidneys, and NHE9 in inflammatory cells [11,12,26,31,40]. NHE1 is linked with cardiomyocyte loss and systemic inflammatory state, and NHE3 blockade favors natriuretic and uricosuric mechanisms of flozins.

SGLT2 inhibitors have been shown to reduce the levels of uric acid, which contributes to many cardiovascular complications, atherosclerosis, congestive heart failure and gait. The effect of uricosuria, which flozins have, is probably due to activation of GLUT9, an urate-glucose transporter, or URAT1 inhibition [26,27].

In EMPULSE study patients receiving 10mg of empagliflozin presented with acute HF, the empagliflozin arm showed significant reduction in NT-proBNP concentration levels compared to placebo [40,41]. In contrast with earlier trials, NT-proBNP remained at the same levels as control groups [42]. This can be explained by the small impact of SGLT2 inhibitors on NT-proBNP levels – in EMPULSE reduction was observed in AUC under the curve, not just with a single measurement of peptide concentration in 12 weeks follow-up. Important fact to state, that positive outcomes in EMPULSE study remained consistent with patients in both acute de novo HF and decompensated chronic HF, both with and without diabetes. In EMPULSE trial the diuretic response was also a consideration, showing greater weight loss in patients receiving empagliflozin rather than placebo, suggesting positive effect of diuretic mechanism on hemodynamic state, leading to reduced preload and therefore, associated cardiovascular events and overall mortality [40]. Due to the strong diuretic mechanism there was concerns raised, that flozins may provoke AKI in acute HF patients, but neither many trials showing reduction in kidney-related deaths in chronic HF, nor recent studies in acute HF

nor EMPULSE study showed increased risk for AKI in patients receiving empagliflozin [26,36,40,43,44]. AKI risk markers were low due to kidney tubular-glomerular feedback with GFR reduction as an empagliflozin effect. SGLT2 inhibitors show overall nephroprotective abilities.

Either in patients with chronic HF with preserved LVEF (HFpEF) or with chronic HF with reduced LVEF (HFrEF), SGLT2 inhibitors, notably empagliflozin, performed with consistent outcomes [45-47,48,49]. This means with flozin usage, cardiovascular and renal health do not vary with the phenotype of heart failure. In addition, dapagliflozin in the DELIVER trial showed that SGLT2 inhibitors have consistent effect throughout the full range of LVEF, including HF with mildly reduced LVEF (HFmrEF) [50,51]. In this case, the effect remained with no heterogenicity with a similar study, DAPA-HF [46,48,50].

Dapagliflozin (10mg p.o.) showed clear benefit of exercise capacity. In the PRESERVED-HF trial, patients with HFpEF performed better in 6MWT, getting approximately 20 meters more than the placebo group. This outcome represents [42], as well as big overall improvement in KCCQ-CS and KCCQ-OS questionnaires comparing with placebo, the effect of notably improving the health status, making it less likely to worsen, showing clear benefit with exercise capacity.

The outcome can be explained by several mechanisms: SGLT2 inhibitors significantly reduce pulmonary artery pressure (both systolic and diastolic), leading to decongestion and can improve symptoms of HF as well as aid with exercise capacity [42,52]; due to metabolic effects, SGLT2 inhibitors provide better myocardial energy production and provoke better energetic supplies gathering – reduction of oxidative stress and favoring glucooxidation and fatty acid oxidation as an ATP source for cardiac muscle [29,31,53,54] – this effect is not only limited to myocardium, but for microvascular endothelium as well, by inhibition of TNF-α and nitrous oxide (NO) synthesis, SGLT2 inhibitors can alleviate inflammation response present in HFpEF, and can positively impact NO production and promote better LV diastolic function [26,54,55]; flozins have been shown to impact diastolic function of heart trabeculae by titin phosphorylation. This impact accounts for improved patients' symptoms, physical limitations and reflects improvement in clinical scales such as KCCQ-CS and KCCQ-OS and 6MWT.

In SOLOIST-WHF study [54], evaluating the sotagliflozin use in patients with diabetes and acute HF episode, showed similar benefits to DELIVER and EMPEROR-Preserved. Sotagliflozin is however, SGLT1 and SGLT2 inhibitor. The results were similar to aforementioned studies [51,54], and it remains not clear whether SGLT1 inhibition does come with any further benefit.

Empagliflozin showed clinical benefit in acute HF both with normal LVEF (HFpEF) and reduced LVEF (HFrEF), which is consistent with the results of the EMPEROR-Reduced, EMPEROR-Preserved and EMPULSE trials [43,45,57]. In acute HF SGLT2 inhibitors were shown to aid conventional diuretic therapy, lowering the doses of loop diuretics, while providing higher daily urinary output. The effect can be explained by negative effect of loop diuretics (sodium retention by activation of RAA system and sympathetic tone in tubular sites) and flozins overcoming diuretic resistance, by increasing natriuretic effect; SGLT2 inhibitors are also responsible for fluid elimination from interstitial space which helps with overall decongestion [26,40,41,56-59]. Worth mentioning is the effect of glucosuria caused by flozins, which promotes osmotic diuresis.

Large meta-analysis of several big RCTs (DECLARE-TIMI 58, CANVAS Program, VERTIS CV, EMPA-REG OUTCOME, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, CREDENCE, SOLOIST-WHF, SCORED, DAPA-CKD, EMPA-KIDNEY) showed that kidney disease progression can be slowed (by 37%) either in patients with or without diabetes when SGLT2 inhibitors are introduced 60[60]. Similarly, AKI risk is significantly lower in group featuring flozins by 23% (both with and without diabetic patients). Flozins were reported to be safe at lower eGFRs of at least 20ml/min/1,73m2 with patients without diabetes. A careful suggestion has been made that SGLT2 inhibitors can be used in patients below that level of glomerular filtration in order to prevent from chronic kidney disease progression, as patients with eGFR<20ml/min/1,73m2 had the most benefits in slowing down the CKD course [28,36,60].

The effects responsible for these outcomes were also suggested by the CANVAS Program, mainly lowering of blood pressure, as the mechanism of hypertensive nephropathy, decrease in intraglomerular pressure, albuminuria reduction and improvement of hemodynamic state, mainly reduction of volume overload, all contribute to being protective factors [26,28,61,62]. In contrast, DIAMOND trial which measured proteinuria in non-diabetic patients with CKD showed no significant decrease in proteinuria in patients, inducing

acute and reversible dip in GFR and body weight reduction which can be linked to prompt fluid depletion with osmotic diuresis and interstitial fluid disposal [40,63]. Reduction of GFR by SGLT2 inhibitors helps to relieve destructive factors on glomeruli, and at the same time limits the filtration of toxic products to the nephrons themselves (e.g. albumin, growth hormones, advanced glycation end products) [26]. These nephrotoxins provoke regional hypoxia, trigger reactive oxygen species formation, promote inflammation and fibrosis [26,64]. Flozins aid with slowing down the process of diabetic kidney disease progression and limit the fibrosis. Furthermore [26], lower oxygen pressure in the renal medulla and deep cortex caused by SGLT2 inhibitors is proposed to activate hypoxia-inducible factors HIF-1 and HIF-2. These, however, enhance erythropoietin production and as a result, increases hematocrit, improving oxygen delivery either to kidneys or the heart. It has been proposed that beneficial impact of higher EPO production is the main factor in cardiovascular events reduction performed by SGLT2 inhibitors usage [26,29,41,64].

Adverse Effects of Flozins

The use of flozins (SGLT2 inhibitors) in managing type 2 diabetes mellitus (T2DM) has been associated with a range of adverse effects, which must be considered alongside their cardiovascular benefits.

One of the most commonly reported adverse effects of SGLT2 inhibitors is an increased risk of genitourinary infections [65,66]. This includes both urinary tract infections (UTIs) and genital mycotic infections.According to the studies, the incidence is higher in women compared to men [65]. The mechanism behind this is the increased glucose excretion in urine, which creates a favorable environment for bacterial and fungal growth [67]. In the EMPA-REG OUTCOME trial, the incidence of genital infections was significantly higher in the empagliflozin group compared to the placebo group [68]. Similarly, the CANVAS Program reported that 11.6% of patients treated with canagliflozin experienced genital infections compared to 3.2% in the placebo group [69].

Research also indicates that patients with type 2 diabetes (DM2) who use SGLT2 inhibitors may face a heightened risk of acute kidney injury (AKI), particularly when these medications are combined with non-steroidal anti-inflammatory drugs (NSAIDs), anti-RAS therapies, or diuretics [65]. Dapagliflozin, in particular, has been associated with worsening renal function [70]. In the CANVAS Program, the incidence of AKI was not significantly

different between the canagliflozin and placebo groups [69]. In contrast, the DECLARE-TIMI 58 trial reported a lower incidence of AKI in the dapagliflozin group compared to placebo, suggesting a potential protective effect on the kidneys [71]. Additionally, kidney transplant recipients (KTRs) are more susceptible to urinary tract infections (UTIs) due to physiological changes in the genitourinary system and an increased risk of euglycemic ketoacidosis related to SGLT2 inhibition [72].

Diabetic ketoacidosis (DKA) is a serious but rare adverse effect associated with SGLT2 inhibitors. Although the overall incidence is low, it is higher compared to patients not using these drugs. In a review of multiple trials, the incidence of DKA was reported to be approximately 0.1-0.4% among patients taking SGLT2 inhibitors, with a significant difference compared to the placebo group [73]. The DECLARE-TIMI 58 trial found an incidence of DKA of 0.3% in the dapagliflozin group versus 0.1% in the placebo group [71].

The potential link between SGLT2 inhibitors and an increased risk of lower limb amputation remains uncertain [66]. The CANVAS Program identified an increased risk of lower limb amputations with canagliflozin use. The incidence was 6.3 per 1,000 patient-years in the canagliflozin group compared to 3.4 per 1,000 patient-years in the placebo group [69]. In contrast, the EMPAREG and DECLARE studies did not indicate any increased risk of amputation [68,71].Additionally, no evidence of heightened amputation risk was found among a substantial cohort of new SGLT2-i users compared to new users of other oral antidiabetic agents [74]. The potential mechanisms through which SGLT2 inhibitors might influence amputation risk remain speculative.

SGLT2 inhibitors can cause volume depletion due to their diuretic effect, leading to symptoms such as hypotension and dizziness, dehydration [65,75]. The incidence of volume depletion-related adverse events was higher in the empagliflozin group (2.5%) compared to the placebo group (1.8%) in the EMPA-REG OUTCOME trial [64]. Similarly, in the DECLARE-TIMI 58 trial, the incidence of volume depletion events was 7.0% with dapagliflozin versus 5.1% with placebo [71].

While SGLT2 inhibitors provide significant cardiovascular benefits in patients with T2DM, they are associated with several adverse effects that need to be managed carefully. These include an increased risk of genitourinary infections, diabetic ketoacidosis, lower limb amputations, volume depletion, and, in some cases, acute kidney injury. Clinicians should

weigh these risks against the benefits when prescribing these medications and monitor patients closely for these adverse effects.

Pricing and Reimbursement of Flozins in Poland

In Poland, the pricing and reimbursement policies for flozins (empagliflozin, canagliflozin, and dapagliflozin) significantly affect their use in type 2 diabetes mellitus (T2DM). The National Health Fund (NFZ) includes these drugs in the reimbursement list for qualifying T2DM patients. Studies suggest that reimbursement improves medication adherence and clinical outcomes, ultimately reducing long-term diabetes-related healthcare costs [76].

Conclusions

The use of flozins, a class of SGLT2 inhibitors, represents a significant advancement in the management of cardiovascular risk among patients with type 2 diabetes. This review has highlighted the growing body of evidence supporting their efficacy not only in glycemic control but also in reducing the incidence of major cardiovascular events, heart failure, and renal complications. The pleiotropic effects of flozins, including their impact on blood pressure, body weight, and arterial stiffness, contribute to their cardioprotective properties. As more clinical trials continue to validate these findings, flozins are increasingly being integrated into treatment guidelines, offering a dual benefit of metabolic control and cardiovascular protection. However, careful patient selection and monitoring are essential to optimize outcomes and minimize potential risks associated with their use. Future research should aim to further elucidate the long-term benefits and mechanisms by which flozins exert their protective effects, thereby solidifying their role in the comprehensive management of type 2 diabetes and its associated cardiovascular risks.

Authors' Contributions:

Conceptualization was done by Paulina Bednarczyk and Izabella Chodak ; methodology by Weronika Chodak; software by Sebastian Lechowski; checking by Martyna Klimek; formal analysis by Magdalena Czyczerska; investigation by Martyna Klimek; resources by Izabella Chodak; data curation by Weronika Chodak; writing - rough preparation by Paulina Bednarczyk; writing - review and editing by Sebastian Lechowski; visualization by Magdalena Czyczerska; supervision by Izabella Chodak; project administration by Martyna

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