

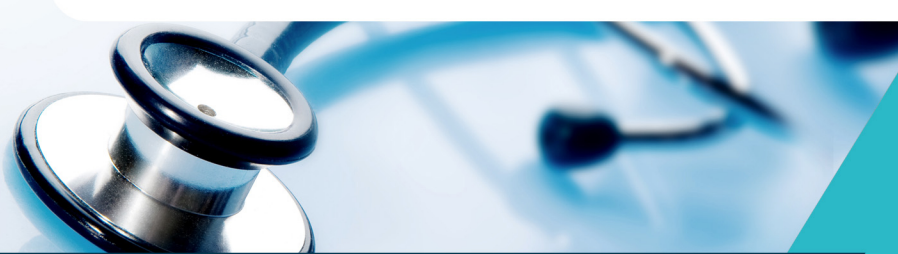


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A Review of the Novel Antidiabetic Medications: Efficacy, Safety and Innovation

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REVIEW ARTICLE

A Review of the Novel Antidiabetic Medications: Efficacy, Safety and Innovation

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Abstract:

Introduction:

Type 2 diabetes is a chronic health condition affecting hundreds of millions of people. Type 2 diabetes has traditionally been combated with a combination of lifestyle modification, insulin therapy and pharmacological agents, including sulfonylureas, biguanides, thiazolidinediones and alpha-glucosidase inhibitors. Type 2 diabetes is associated with an increased risk of cardiovascular disease and the development of diabetic kidney disease. Although sulfonylureas are low-cost drugs and widely prescribed, they have been shown in recent cardiovascular outcome trials to present a high risk of hypoglycemia, which in turn increases the risk of negative cardiovascular outcomes. Metformin, a biguanide that is the most commonly-prescribed antidiabetic agent worldwide, is contraindicated in patients with risk factors for lactic acidosis, including heart failure and chronic kidney disease.

Objectives:

The last decade has seen significant advances in the development of novel antidiabetic agents shown to possess both reno- and cardioprotective qualities. This article aims to review the available literature and recent studies demonstrating the efficacy and safety of these agents individually, as well as exploring areas of future development in the field.

Methods:

The reporting of this review is based on the 2020 PRISMA statement. A literature search for all papers related to antidiabetic medication was conducted using reliable sources such PubMed and Google Scholar Databases, including a recent meta-analysis of renal and cardiovascular outcome trials.

Conclusion:

A critical analysis of clinical trials on type 2 diabetes and the two most severe comorbidities in cardiovascular and chronic kidney diseases may help cardiologists, urologists and diabetes specialists to adapt their therapeutic approaches to individual patients. Data related to antidiabetic effects of agents of natural origin accompanied by their Cardioprotective and renoprotective capacity testify benefits of these compounds as novel therapeutic agents.

Keywords: Antidiabetic agents, Cardioprotective, Renoprotective, Bioactive compounds, Efficacy, Safety.

Article History

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1. INTRODUCTION

Type 2 diabetes (T2D) is a chronic health condition affecting hundreds of millions of people. It is a disease that, in the preceding decades, is increasing exponentially in prevalence, imposing significant economic burdens on health systems around the world [1] and representing the ninth lead-

ing cause of mortality [2] in spite of global preventative efforts. T2D has traditionally been combated with a combination of lifestyle modification, insulin therapy and pharmacological agents, including sulfonylureas (SU), biguanides, thiazolidinediones and alpha-glucosidase inhibitors. SU are low-cost drugs and widely prescribed, but have been shown in recent cardiovascular outcome trials (CVOTs) to present a high risk of hypoglycemia [3], which in turn increases the risk of negative cardiovascular (CV) outcomes. Metformin, a biguanide which is the most commonly-prescribed antidiabetic

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agent worldwide, is contraindicated in patients with risk factors for lactic acidosis including heart failure, and chronic kidney disease (CKD) [4]. T2D is associated with an increased risk of cardiovascular disease (CVD) and the development of diabetic kidney disease (DKD) [5], and so there is a clear need to develop medications which complement existing therapies with superior safety profiles and more favorable outcomes in these patients. This need has begun to be addressed in the last decade, which has seen significant advances in the development of novel antidiabetic agents shown to possess both reno- and cardioprotective qualities, including sodium-glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide 1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase-4 inhibitors (DPP-4i). This article aims to review the available literature and recent studies demonstrating the efficacy and safety of these agents individually, as well as exploring areas of future development in the field.

2. METHODOLOGY

The reporting of this review is based on the 2020 PRISMA statement [6]. Available checklist items are listed below:

2.1. Eligibility Criteria

Randomized controlled trials (RCTs) of male or female children and adolescents with T2D, assessing both reno- and cardioprotective properties of SGLT2i, GLP-1 RA and DPP-4i analogues vs. placebo or any other antidiabetic agents, Bioactive compounds (Ginseng, Flavonoids) were included.

2.2. Information Sources

A literature search for all papers related to antidiabetic medication was conducted using reliable sources such PubMed and Google Scholar Databases, including a recent meta-analysis of renal and cardiovascular outcome trials.

2.3. Search Strategy, Selection Process, Data Collection Process

Manual searches by the independent reviewers were performed using the search terms 'novel antidiabetic', 'targeting SGLT2i or GLP-1 RA or DPP-4i', 'treatment' 'outcomes' and 'natural therapy or phytotherapy in type 2 diabetes mellitus'. Studies published from 2018 to 2022 were selected as recent advances in the field. In order to provide a scientific background for the review and for the discussion of results, older scientific studies and reviews were considered as well. Original papers, high quality recent research articles, English language, and focus on novel antidiabetic agents were the main inclusion eligible criteria.

2.4. Data Items, Outcome Assessment

The efficacy of SGLT2i or GLP-1 RA or DPP-4i analogues and bioactive compounds was assessed by hemoglobin A1c (HbA1c) and fasting plasma glucose concentrations (FPG). Assessment of the safety of SGLT2i or GLP-1 RA or DPP-4i analogues and bioactive compounds was performed by the reporting of adverse events (hypoglycemia, renal function by assessing urine albumin-creatinine ratio (uACR) and estimated

glomerular filtration rate (eGFR), major adverse cardiovascular events (MACE), cardiac inflammation, vascular function).

2.5. Study Risk of Bias Assessment

The quality of studies was evaluated by assessing the parameters such as blinding of participants and personnel, blinding of outcome assessment and incomplete outcome data for every single study.

2.6. Study Selection

Search strategy yielded 526 articles, 420 unique records were screened. 212 articles were recorded for eligibility, after excluding 204 studies during the full-text review, 8 studies were included in the final analysis (Fig. 1).

2.7. Study Characteristics

Meta-analysis of 166,371 participants from 170 randomized controlled trials assessing cardiovascular safety of antidiabetic agents, Zhuang *et al.* [7], meta-analysis of randomized trials assessing cardiovascular and kidney outcomes of GLP-1 receptor, Sattar *et al.* [8], meta-analysis of eight CVOTs, 60,080 patients, Giugliano *et al.* [9], meta-analysis of 286 children, Chadda *et al.* [10], a double-blind, randomized, phase 3 trial, 705 individuals, Rosenstock *et al.* [11], a double-blind, placebo-controlled, 64 individuals, assessing the effect of American ginseng on arterial stiffness in subjects with T2D, Mucalo *et al.* [12], a double-blind, randomized, crossover design, 23 individuals, Jovanovski *et al.* [13], a randomized, double-blind, placebo-controlled clinical trial, 23 participants, Park *et al.* [14].

2.8. Results of Individual Studies and Discussion

The findings of the studies examining novel antidiabetic agents and bioactive compounds implications are discussed separately. The implications of results for future research are discussed in section 8 and the conclusion.

3. SGLT2i

Inhibition of the sodium-glucose cotransporter 2 (SGLT2) in the proximal tubule induces urinary glucose excretion by preventing reuptake, thereby reducing the overall glucose burden. An investigation reviewing the safety of SGLT2i was carried out by Filippas-Ntekouan and co-authors [15], in which they assessed the risk of adverse effects, finding that SGLT2i do not increase the risk of hypoglycemia even when combined with insulin therapy; that the risk of euglycemic DKA (diabetic ketoacidosis) is low; that urogenital infections are the most common reported adverse event and are easily manageable in most patients; and that, in view of their positive CV and renal effects, SGLT2i could be considered first-line treatment for T2D. Vallon and Verma [16], in their review of the effects of SGLT2i on renal and CV function, found that drugs in this class can modulate cardiac inflammation, promote erythropoietin (EPO) production, and improve vascular function, but noted the need for further research into the mechanisms contributing to these effects. A comprehensive investigation of the structure-activity relationship between the

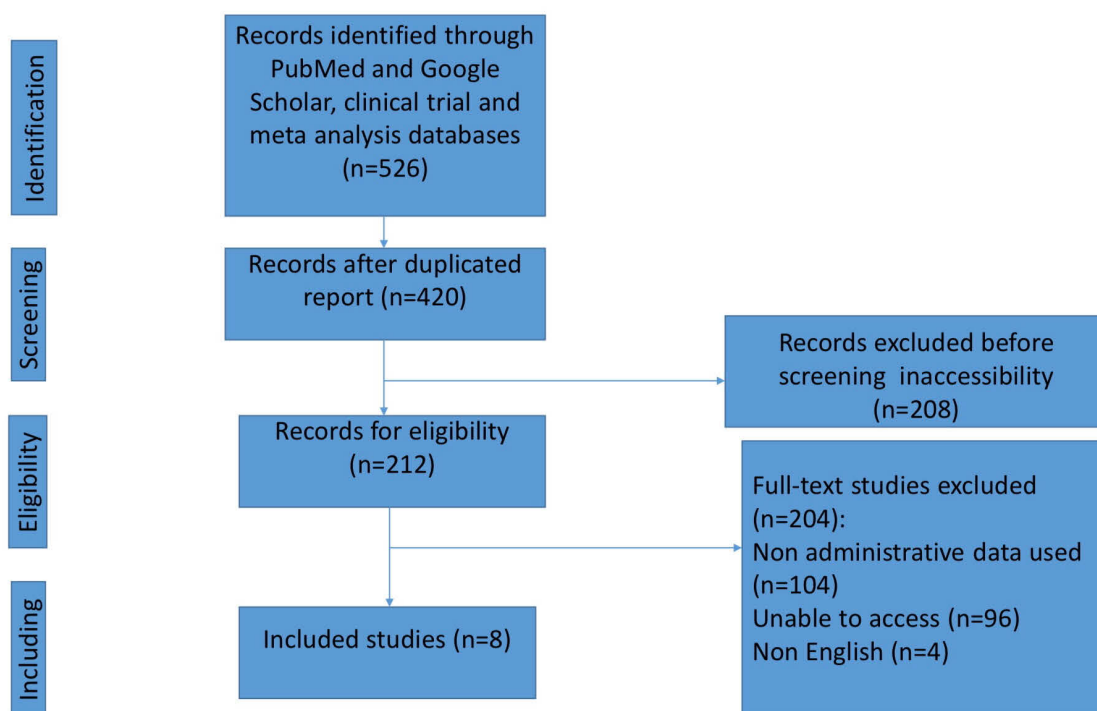


Fig. (1). PRISMA flow diagram for included studies.

SGLT2 and the SGLT2i dapagliflozin, along with its various analogues, was conducted by Bhattacharya and colleagues [17], which found that the incorporation of the di-fluoro group by replacing the OH group in the sugar nucleus potentiates the SGLT2 inhibitory activity showing that designs for future SGLT2i could yield drugs with even more improved efficacy and safety than those available in practice today.

4. GLP-1 RA

Glucagon-like peptide-1 (GLP-1) is a powerful endogenous insulinotropic incretin hormone secreted by intestinal L-cells. The development of synthetic agents targeting its receptors in order to treat T2D signified a major step in the search for novel antidiabetic agents. GLP-1 RA includes a variety of medications used in clinical practice globally, such as exenatide, lixisenatide, liraglutide, albiglutide and semaglutide, whose clinically relevant differences have been ably described by Nauck and Meier [18]. MACE remains one of the strongest adverse outcomes among patients with cardiovascular disease. Although the component of MACE is not fully defined, Five-point MACE outcomes, including acute myocardial infarction, stroke, cardiovascular mortality, hospitalization for unstable angina or revascularization procedures and heart failure are considered in observational studies [19]. Sattar and colleagues [8] conducted a meta-analysis of eight trials comprising 60,080 T2D patients and found GLP-1 RA reduced major adverse cardiovascular events (MACE) and all-cause mortality by 14% and 12%, respectively, as well as benefiting kidney function. Another meta-analysis inclusive of all GLP-1 RA CVOTs published

until June 2021 conducted by Giugliano and colleagues [9] found that the data shows a favorable profile for GLP-1 RA, particularly oral semaglutide which had the highest probability to be ranked first (>90%) in reducing all-cause mortality and CV death. Furthermore, in what is possibly the first meta-analysis considering primary outcomes of glycemic control in children, Chadda *et al.* [10] found GLP-1 RA has similar efficacy as in adults for the treatment of obesity and T2D, which should be seen as encouraging despite limitations resulting from the relatively few controlled trials available. Novel approaches to therapy in this drug class are still being developed; Rosenstock and colleagues [11] carried out a double-blind randomized phase 3 trial (SURPASS-1) across 52 medical research centers using the dual GLP-1/GIP (glucose dependent insulinotropic polypeptide) agonist tirzepatide for T2D patients, finding drug once a week, at doses of 5, 10 and 15 mg as monotherapy for type 2 diabetes showed robust reductions compared with placebo in glycemic control. During the trial, tirzepatide showed a comparable safety profile to that of selective GLP-1 RA, indicating its suitability for use in practice.

5. DPP-4i

Dipeptidyl peptidase-4 (DPP-4) is an enzyme that plays a major role in glucose metabolism by breaking down the incretins GLP-1 and GIP. Agents inhibiting DPP-4 therefore increase the postprandial glucose-dependent pancreatic secretion of insulin and suppress the release of glucagon [20]. A review conducted by Sesti and colleagues [21] assessing the impact of DPP-4i in clinical practice over the last decade in

Italy and evaluating post-marketing surveillance generally suggests DPP-4i are indicated even in patients who are at higher risk of hypoglycemia, including those with impaired renal function. In his review of the therapeutic utility of DPP-4i, Makrilakis [22] cites a systematic meta-analysis of 189 trials showing no difference in all-cause mortality between any incretin drug versus control, but notes that sitagliptin, vildagliptin and saxagliptin (with dose adjustment); as well as linagliptin (without the need for dose adjustment) were well-tolerated in patients with kidney impairments ranging from moderate renal insufficiency to end-stage renal disease (ESRD), concluding DPP-4i may perform well as a reasonable second-line therapy in conjunction with metformin. Renal /cardiovascular effects and possible side effects of SGLT2i, GLP-1 RA, DPP-4i are summarized in Fig. (1).

6. BIOACTIVE COMPOUNDS

Extracts of plants have been playing an important role in prevention and treatment of diseases even in modern time. In the last few decades, several human trials, have revealed that ginseng (which contains ginsenoside) may exert antidiabetic effect, regulating insulin and glucose metabolism path ways through different mechanisms [23]. Reduction of Hb A1c and fasting blood glucose levels in diabetic patients receiving ginseng has been proved in conducted human trial by Yoon *et al.* [24]. Park and group [14] believe that hydrolyzed ginseng extract cut the absorption of glucose in the intestinal lumen, decreasing fasting plasma glucose. In order to explore antidiabetic mechanism of ginseng in vitro cell and in vivo animal experiments are conducted. It has been reported that ginseng improves beta cells function, intensifying insulin sensitivity. Moreover, Protoginsenoside (PPT)- type ginsenoside Rg1 not only affects insulin resistance but improves liver function and lipid profile, testifying therapeutic use of Rg1 in type 2 diabetic patients with fatty liver [25]. Furthermore, ginseng has been considered in CVD treatment. Hypotensive effect of ginseng is mediated by increasing nitric oxide (NO) and cGMP, vasorelaxation and angiotensin converting enzyme (ACE) inhibition. Anti-inflammatory and antioxidant properties of ginseng may play an important role in the prevention of CVDs and atherosclerosis through the regulation of hypertension and diabetes as common CVDs risk factors [26, 27]. Cardioprotective effects of ginseng are under investigation by numerous clinical trials. For instance, antihypertensive and antidiabetic effects of Asian ginseng (AG) were observed by Mucalo and coauthors in subjects with type 2 diabetes and concomitant hypertension [12]. Results of double-blind, randomized, crossover study by Jovanovski *et al.* [13] revealed that ginsenoside Rg3-enriched Korean red ginseng extract significantly reduces central and peripheral blood pressure in healthy adults. Tamer and colleagues [28] observed that ginseng fractions improve renal function in nitroarginine (L-NAME)-induced kidney injury in rats. Also, ginseng is shown to have antimicrobial property against

microorganisms which cause kidney injuries.

Flavonoids are the most common naturally occurring polyphenol compounds. Although the link between polyphenols and the risk of diabetes is still a controversy, various recorded evidences of investigations in cell, animal and clinical trial have proved antidiabetic activity of polyphenols [29]. Antidiabetic action of flavonoid Kaempferol is achieved by enhancing glucose metabolism in skeletal muscle and impeding gluconeogenesis in the liver [30]. Luteolin mediates its hypoglycemic potential *via* improving insulin sensitivity of body cells [31]. Additionally, in vivo and in vitro studies have shown that flavonoids are involved in preventing cardiovascular disease. Flavonoids reduce platelet aggregation, modulate antioxidant defense system, play a role in regulation of inflammation, exert anti-hypertensive, anti-hyperlipidemic and antiatherogenic properties [32]. Also, flavonoids are suggested to prevent renal injury, and possess antitumor activity suppressing renal carcinoma cell proliferation [33]. Antidiabetic and renal/ cardiovascular properties of ginseng and flavonoids are demonstrated in Fig. (2).

As a matter of fact, concomitant use of natural products and synthetic drugs may be suggested in patients with diabetes mellitus (Fig. 3).

7. OVERVIEW OF NOVEL AGENTS

In their extensive 2018 network meta-analysis of 170 randomized controlled trials comprising 166, 371 T2D patients, Zhuang *et al.* [7] compared CV outcomes in order to establish an evidence-based hierarchy of CV safety profiles in all current antidiabetic agents. Their research found that SGLT2i ranked first in the reduction of MACE, with SU in last place; that SU is associated with the highest risks of MACE, severe hypoglycemia and all-cause mortality; that the DPP-4i vildagliptin possesses the best CV safety profile of any novel antidiabetic agent in any class; and that SGLT2i, GLP-1 RA and DPP-4i display favorable safety profiles in general. Focusing on renoprotective effects specifically, Leite and co-authors [34] examined evidence concerning novel therapeutic agents for T2D and demonstrated SGLT2i and GLP-1 RA are indicated for maintaining renal function in patients at risk of progressive renal function impairment, including those with structural kidney damage, albuminuria, and a family history of kidney disease. Brown and colleagues [35] reviewed cardiorenal outcomes in patients with T2D treated with SGLT2i and GLP-1 RA using results from four randomised controlled CVOTs, as well as data from health insurance databases and health services in multiple countries, finding a reduction in body weight, glycated haemoglobin (HbA1c), blood pressure, uACR and eGFR. In their consensus article investigating CV, renal and liver protection in novel antidiabetic agents, Kotsis and co-authors [36] reviewed the available evidence and corroborated the above findings, suggesting SGLT2i and GLP-1 RA promote weight loss, prevent heart failure and improve renal disease endpoints.

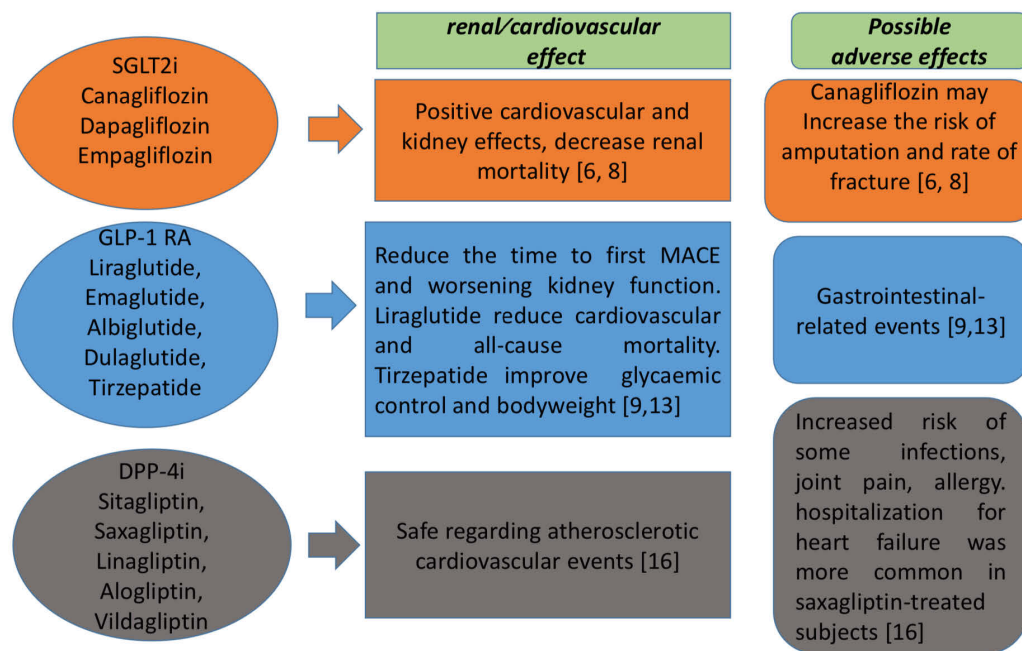


Fig. (2). Overview of the different classes of novel antidiabetic drugs (SGLT2i, GLP-1 RA, DPP-4i) used in current approved T2D treatments, in ongoing clinical trials and under investigation.

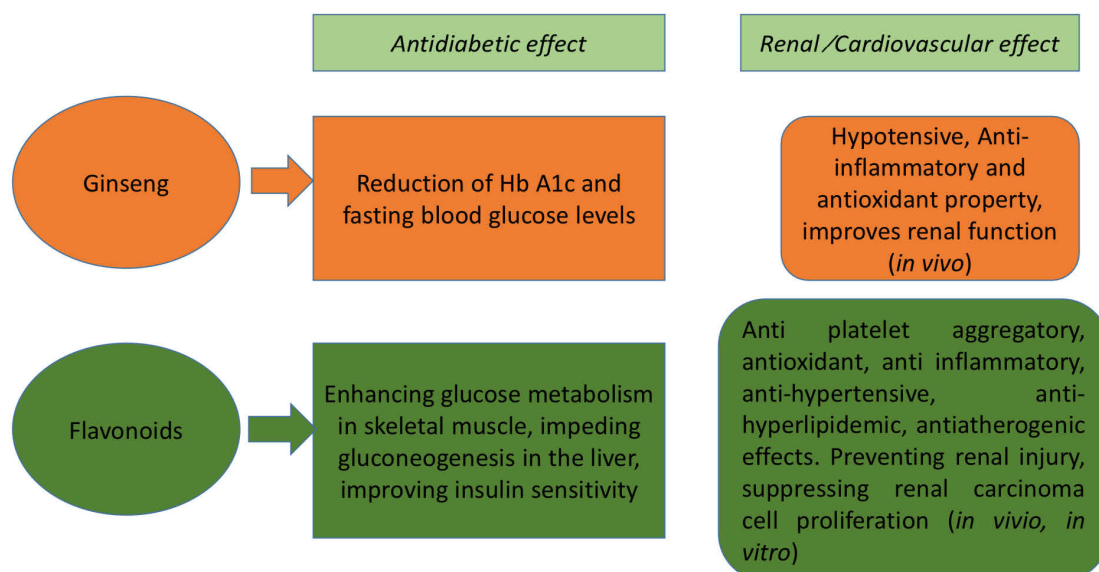


Fig. (3). Overview of the antidiabetic and renal/ cardiovascular effects of natural compounds (Ginseng, Flavonoids).

8. FUTURE PERSPECTIVES

Nascent research into drugs targeting beta-cell M_3 muscarinic receptors (M3Rs) using positive allosteric moderators (PAMs) to promote endogenous insulin release [37, 38] and continuing research into the role of fungal metabolites [39] and dietary polyphenols [40, 41] in the treatment of T2D present exciting opportunities to further develop ways to

combat one of the most challenging global healthcare burdens today. However, it is clear from the increasing interest in, research on, and use of novel antidiabetic agents in the classes SGLT2i, GLP-1 RA and DPP-4i, that the ‘revolution’ in T2D therapy is already underway. In recent years, multiple CVOT and other clinical trial results have shown vastly improved safety and efficacy in treatment when these agents are used in

monotherapy or in combined therapy with existing medications, particularly in the former, newer classes. Considering the proven cardioprotective, renoprotective and limited adverse effects of many of these drugs, it is striking that therapy is still relatively infrequently initiated in eligible patients worldwide - a phenomenon that has prompted diabetologists Scherthaner and colleagues [42] to offer a “manifesto for change” urging positive change in practice at a local level. Highlighting the importance of cardiorenal protection in the treatment of T2D, their research proposes several ways to surmount the “clinical inertia” in the prescription of SGLT2i and GLP-1 RA, including advocating for refined post-CVOT treatment pathways, focusing interdisciplinary care, educating reimbursement authorities, and working on an individual level with clinicians through personal feedback to incentivize change. A 2020 statement released by the American Heart Association echoes the sentiment, asserting that the well-established, positive CVD and CKD effects of these drugs impel the need to incorporate multidisciplinary care to identify at-risk patient populations who may benefit from their use, as well as urging legislative support to promote equitable access [43].

Positive effects of SGLT2i, GLP-1 RA and DPP-4i on various aspects of cardiovascular and kidney function will be incredibly helpful in the further development of T2D therapy in patients with a high risk of cardiovascular and kidney diseases. This review provides a summary of studies examining the antidiabetic effects of ginseng and flavonoids as natural medicine. However, some limitations have to be acknowledged. The small number of included studies in the present review may affect the quality of evidence. Additionally, more reliable data will be required to assess the effect of these novel antidiabetic agents on some physiological and biochemical parameters as indicators of cardiovascular and renal function. Lack of high quality researches and limited number of participants might not support the safety and efficacy outcomes of bioactive compounds. Hence, safety and efficacy of natural products should be evaluated cautiously.

CONCLUSION

Since the increased incidence of T2D worldwide is associated with the development of cardiovascular complications and renal events, convenient control and treatment of diabetes mellitus, along with management and CV outcomes in diabetic patients seem important. A critical analysis of clinical trials on T2D and the two most severe comorbidities in CVD and CKD may help cardiologists, urologists and diabetes specialists to adapt their therapeutic approaches to individual patients. Data related to antidiabetic effects of agents of natural origin accompanied by their Cardioprotective and renoprotective capacity testify benefits of these compounds as novel therapeutic agents. We now need to encourage and facilitate their use in clinical practice globally.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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LIST OF ABBREVIATIONS

CKD	=	Chronic Kidney Disease
CVD	=	Cardiovascular Disease
DKD	=	Diabetic Kidney Disease

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