



Phytochemicals with sodium-glucose co-transporter inhibitory effects for the management of diabetes; a narrative review on recent findings

Mehrnaz Salehi^{1*}, Najmeh Rayatpisheh¹, Mahsa Salehi², Hossein Mardanparvar³

Abstract

Diabetes mellitus is a chronic condition suffering millions of people worldwide. According to the International Diabetes Federation (IDF), it is estimated that by 2045 about 783 million people will be affected by this disease. Diabetes can be treated today with various hypoglycemic drugs, including metformin and sulfonylureas. However, it has unwanted side effects, such as nausea, diarrhea, hypothyroidism, weight gain, liver failure, tachycardia, and lactic acidosis. A newer group of oral diabetes drugs, such as the sodium-glucose co-transporter inhibitors (SGLTi), are recognized as useful in treating blood sugar levels in diabetic patients. Natural phytochemicals derived from plants have long been used to treat chronic diseases such as diabetes, and traditional phytotherapy for diabetes has been recommended by the world health organization. Herbal medicines are believed to have fewer side effects, so nearly 80% of the drugs are derived directly from plants or modified plants. Given the importance of these results, we were inspired to investigate the impact of phytochemicals with his SGLT2 inhibitory effects on diabetes in order to develop the next generation of safer therapeutic strategies for diabetic patients.

Keywords: Diabetes mellitus, Herbal products, Metformin, Sodium-glucose co-transporter inhibitors, SGLT2 inhibitor, AMP-activated protein kinase

Citation: Salehi M, Rayatpisheh N, Salehi M, Mardanparvar H. Phytochemicals with sodium-glucose co-transporter inhibitory effects for the management of diabetes; a narrative review on recent findings. J Ren Endocrinol. 2023;9:e25095. doi: 10.34172/jre.2023.25095.

Copyright © 2023 The Author(s); Published by Nickan Research Institute. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Millions of people around the world suffer from diabetes mellitus (DM) which is a prevalent condition. According to the International Diabetes Federation (IDF), it is estimated that diabetes will affect 783 million people worldwide by 2045 (1). Despite several hypoglycemic agents currently in clinical practice, they have unfavorable side effects, and the known complications associated with diabetes continue to affect the quality of life.

Hyperglycemia can now be treated with a variety of anti-diabetic drugs since the majority of these drugs act by boosting insulin secretion, increasing insulin sensitivity, supplementing insulin, and promoting glucose absorption. However, these drugs, including sulfonylureas and metformin, have several undesirable side effects, such as tachycardia, hypothyroidism (for sulfonylureas) and lactic acidosis, and diarrhea (for metformin). Natural products, on the other hand, are cheaper and have a better safety record (2). It is an undeniable fact that in modern and ancient Chinese medicine local fruits are widely used to treat diabetics. For example, various locally grown fruits are used in Ayurvedic treatments throughout the

Indian subcontinent, including Bangladesh (3).

In the same way, herbal products such as bark, fruits, seeds, fruit peels, and leaves are always thought to be good sources of bioactive phytochemicals that can help to treat various diseases, such as diabetes, hypertension, cancer, fever, pain, and other diseases (4,5).

Nearly 80% of drugs are either directly extracted from plants or modified forms of plants because phytomedicines are thought to have fewer side effects (6).

Fruits are one of the most well-known natural sources of dietary minerals, vitamins, fiber, and a wide range of other vital nutrients. Saponins, carotenoids, flavonoids, isothiocyanates, polyphenols, and several other bioactive phytochemicals are all abundant in fruits (5,7).

Therefore, it is true to say that diabetes, obesity, cancer, and other diseases, including cardiovascular problems, can all benefit from fruit consumption (3,5).

Antidiabetic drugs for treating hyperglycemia are widely available on the market today. Among these man-made substances, sodium-glucose cotransporter inhibitors (SGLT2i) have been approved to treat diabetic patients to lower blood sugar levels. Originally discovered

Received: 11 April 2023, Accepted: 5 June 2023, ePublished: 11 June 2023

¹School of Medicine, Shahrekord University of Medical Science, Shahrekord, Iran. ²Anatomical and Clinical Pathologist, Mazandaran University of Medical Science, Mazandaran, Iran. ³Department of Nursing, Faculty of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

*Corresponding Author: Mehrnaz Salehi, Email: mehrnazsalehimd@gmail.com

■ Implication for health policy/practice/research/medical education

Inhibition of sodium-glucose cotransporter 2 has been considered a promising therapeutic target in the treatment of type 2 diabetes.

as antidiabetic drugs, these drugs were brought to market after numerous clinical studies showed their magical ability to effectively control diabetes. By preventing the reabsorption of filtered glucose and increasing glycosuria, this class of diabetes medications may lower blood glucose levels.

As the first SGLT2 inhibitor, canagliflozin received FDA approval in March 2013, and empagliflozin and dapagliflozin were then approved by the FDA in 2014 (8). Researchers have become interested in using natural drugs to treat human illnesses. Accordingly, a promising approach to treat diabetes is the use of natural substances with SGLT2 inhibitory effect. Some recent studies have demonstrated that some herbal-based medications may have ant hyperglycemic effects similar to SGLT2i. Considering the importance of these results, we aimed to review the impacts of some phytochemicals with SGLT2 inhibitory effects on diabetes to reach a better knowledge.

Phytochemicals

Since ancient times, east Asia has used natural phytochemicals derived from plants as treatments to prevent chronic illnesses like diabetes. A considerable amount of these phytochemicals have been identified to have few side effects, while several scientific research has increasingly gathered evidence of their effectiveness (9). These compounds act through important intracellular signaling pathways. As pharmaceuticals and dietary supplements, natural compounds have been widely used to regulate normal physiological states and treat various chronic conditions.

Several studies have shown that active phytochemicals found in natural compound extracts have a variety of antidiabetic effects, including AMP-activated protein kinase (AMPK) pathway activation, glucose transporter 4 (GLUT4) expression/translocation, insulinotropic effect, protein tyrosine phosphatase 1B inhibition, with lower side effects, peroxisome proliferator-activated receptor γ (PPAR γ) activation and α -glucosidase inhibition (10).

In diabetes and metabolic disease, phytochemicals, dihydrochalcones in particular, and their related substances have been shown to target several crucial pathways that are connected to energy and glucose metabolism (11).

SGLT2 inhibitory effects on diabetes

The kidney has recently been identified as a target for diabetes treatment due to its crucial role in maintaining glucose homeostasis, and SGLT2, a transporter protein, is responsible for the most of glucose reabsorption from the

glomerular filtrate (12).

A low-capacity, high-affinity glucose transporter known as the SGLT1 protein is expressed in both the renal tubules and small intestine; Inhibition of this protein can lead to gastrointestinal disorders such as severe diarrhea. The high capacity, low-affinity transporters of glucose known as SGLT1 proteins are expressed in kidney's proximal tubule. These transporters are accountable for roughly 90% of filtered glucose reabsorption; therefore, they are ideal for diabetes treatment. The main co-transporter, SGLT2, actually reabsorbs the filtered glucose in the kidney's tubular nephron. Hyperglycemia in people with diabetes may lead to an increase in kidney glucose reabsorption levels above normal (13). SGLT2i, the newest class of oral antidiabetic agents, offers renal and cardiovascular benefits (14) (Figure 1).

Phytochemicals with SGLT2 inhibitory effects

Acer nikoense a native plant in Japan

Acer nikoense is a plant, originated in Japan, is now being widely cultivated and its stem bark extractions are used in traditional Japanese medicine. *A. nikoense* (Aceraceae) bark contains a number of acerogenins and acerosides (15) with a various biological activities, including anti-inflammatory, anti-cancer, anti-bacterial and anti-fungal effects, and is administered as a Japanese medicine for hepatic disorders and eye diseases. Morita et al in 2010, investigated *A. nikoense* for its inhibitory activity against SGLT. As mentioned, it contains several acerogenins and acerosides. Acerogenins A and B had a strong inhibitory effect on SGLT1; however, this herb has a weaker effect on SGLT2 (16).

Alstonia macrophylla a native tree in Southeast Asia

The Apocynaceae family includes the tree *Alstonia macrophylla*, as a well-known source of phytochemicals, is primarily found in Southeast Asia and tropical areas of Asia and Africa. Various active chemicals and extracts from *A. macrophylla* have been used to exhibit a number

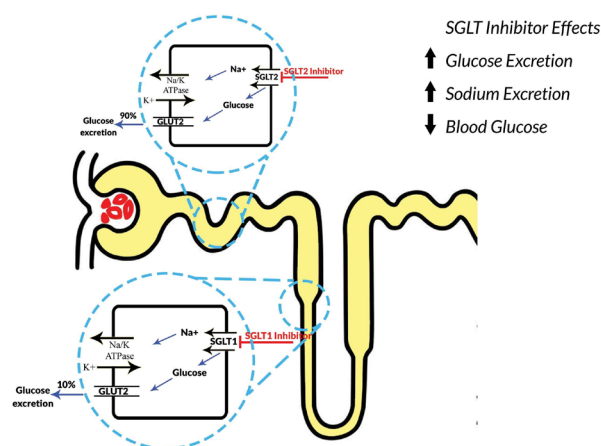


Figure 1. SGLT2 and SGLT1 inhibitory effects on diabetes.

of biological activities, such as antidiabetic, antipyretic, antimicrobial, antimalarial, antiprotozoal, antioxidant, anti-inflammatory, antifertility, and antipsychotic effects (17). Arai et al isolated a new ajmaline-type alkaloid, alstiphyllanine H (18) and alstiphyllanines E–G (1–3) from *A. macrophylla* leaves. Following two-dimensional nuclear magnetic resonance spectroscopy analysis, their structures were completely studied. The pipeline-type alkaloid with an ester side chain at position C-17 might be crucial to demonstrate inhibitory activity, according to the structure-activity relationship investigation of these synthesized and alkaloid analogs against SGLT1 and SGLT2 (18).

Aspalathin a native plant in South Africa

An indigenous plant to South Africa called *Aspalathus linearis*, also known as rooibos, contains flavonoid and C-glucosyl dihydrochalcone, is administered to treat type 2 diabetes and other conditions related to diabetes. The effect of aspalathin hypoglycemia is linked to AMPK activation and increased GLUT4 translocation to the plasma membrane. Aspalathin also lowers the gene expression of hepatic enzymes involved in lipogenesis and glucose synthesis. These findings greatly imply that aspalathin has a potential anti-diabetic effect (19). Treatment with aspalathin proved successful outcomes in reducing the negative effects of mitochondrial dysfunction and insulin resistance by lowering the levels of well-known pro-inflammatory markers like protein kinase C-theta (PKC- θ), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) (20). Previously, Muller et al showed the anti-diabetic effect of aspalathin and this substance's ability to modify the insulin receptor substrate one and the insulin receptor through the inhibition of protein tyrosine phosphatases to decrease hyperuricemia and induce glucosuria through the inhibition of SGLT2 (11).

Gnetum gnemonoides a native liana in Southeast Asia-Pacific region

The tropical liana *Gnetum gnemonoides* is widespread throughout the Southeast Asia-Pacific region, particularly New Guinea, Bismarck Archipelago, Indonesia, Malaysia and Philippines. The medical efficacy of *G. gnemonoides* has not yet been the subject of a scientific study, but it is known that stilbenes extracted from the *Gnetum* species have biological characteristics like antioxidant, hepatoprotective, enzyme inhibitory activities and antimicrobial (21).

In an investigation by Shimokawa et al, the SGLT inhibitory activity of *G. gnemonoides* was examined. The oxyresveratrol component units of stilbene trimmers, gneyulins A and B which were isolated from the bark of *G. gnemonoides*, showed modest inhibitory activity against SGLT1 and SGLT2, while dihydro flavonol-C-glycosides, noidesols A and B, had no SGLT impact (22).

Phlorizin-derived synthetic compounds

Phlorizin, a photochemical molecule, is a natural glycoside belonging to the polyphenol family, which was discovered to increase glucose excretion in the urine. It belongs to the group of organic compounds known as chalcones and can be found in several plants, particularly plentiful in apples. In clinical studies, the apple bark's phlorizin was applied as a small-dose antipyretic (23). Subsequently, it was demonstrated that high doses of phlorizin could excrete glucose through the urine. In the late 20th century, it was discovered that SGLTs were present in the proximal tubules of the kidney and the small intestine. SGLT-2 was subsequently detected in the kidney and SGLT-1 in the small intestine (24).

Several phlorizin analogs have been synthesized, despite the fact that phlorizin was not developed as a diabetes medication. There are two main classifications of these synthetic compounds; Analogues of C-glucoside and analogs of O-glucoside. Initially, a selective SGLT2 inhibitor that could be taken orally was first developed using O-glucoside analogs. This inhibitor had strong inhibitory and high selectivity activities compared to phlorizin (25). And, dapagliflozin showed over 1200-fold higher potency for human SGLT2 compared to SGLT1 in C-glucoside analogs, which were developed similarly (26). In a study, conducted by Osorio et al, both hypertension and hyperglycemia were prevented by SGLT2 inhibition in diabetic rats, pointing to the possibility of a hypertensive mechanism linked to SGLT2 activity as well as the possibility that elevated SGLT2 expression may be linked to the development of diabetic renal problems. Phlorizin has been shown in most research to have an anti-diabetic impact (27), and some studies have also noted its antioxidant and anti-inflammatory properties (28).

Phyllanthus emblica a native tree in Bangladesh and central India

In Bangladesh, *Phyllanthus emblica* L (also known as *Emblica officinalis* Gaertn), a well-known tree belonging to the Euphorbiaceae family, is popularly known as "Amla" or "Amlaki". This type of deciduous tree of average size, which is native to Bangladesh and central India in southeast Asia, grows to a height of 8 to 18 meters. According to reports, *P. emblica* contains saponins, phenolic compounds, tannins, flavonoids glycosides, alkaloids, amino acids, and proteins. They contain a variety of therapeutic benefits, including antioxidative, cytotoxic properties, anti-inflammatory, antiatherogenic, antidiabetic and hypolipidemic (29).

Even though *P. emblica* L. is used medicinally, the fruits, known as Phyllanthi Fructus (PF), are more frequently employed in traditional Chinese medicine (TCM) to treat a variety of infections and non-infectious disorders. China's Ministry of Health recognized PF as a dual-purpose therapeutic substance in 1998 (30). In a research study by Sharma et al, investigated the anti-

diabetic effects of *P. emblica* substances and conducted molecular docking against T2D therapy targets. Eleven phytochemicals were initially evaluated for their high binding affinities to three T2D receptors. These three T2D receptors were Sodium-glucose co-transporter type 2 inhibitors (SGLT2), PPAR- γ and glucagon-like peptide receptor agonists (GLP-1 agonists). Their research demonstrates that *P. emblica*'s compounds are excellent promising antidiabetic options. Additionally, Sharma et al performed molecular docking on 60 phytochemicals by using AutoDock Vina (a molecular modeling simulation software), of *P. emblica* against targets such as SGLT2, GLP-1 agonists and PPAR- γ . This was followed by toxicity prediction and drug-likeness prediction, which produced a large number of phytochemicals against T2D that could then be synthesized and optimized in the future to develop potential medications for more efficiently management and treatment of Diabetes (31).

Polyherbal mixture

The concept of polyherbal or polypharmacy, which could be considered as one of the comprehensive strategies to deal with diabetes and its new complications, confers maximum effectiveness and fewer adverse effects according to the synergistic action of several herbs to achieve greater potentiality than a single herb. Additionally, Aimil Pharmaceuticals, which received approval from the Indian government's AYUSH ministry launched a number of polyherbal formulations such as BGR-34 (blood glucose regulator) (32, 33).

Suvarna et al in a systematic review and meta-analysis demonstrate that polyherbal preparations have a glucose-lowering effect on people with type 2 diabetes (34).

In a recent study by Kumar et al, by mixing up 7 herbs, they made a polyherbal formulation (PHF), containing (*R. cinerea*, *A. roxburghiana*, *C. pareira*, *C. longa*, *D. indica*, *T. sinensis*, and *S. glabra*) which, by inhibiting the SGLT2 protein, had a significant effect on the reduction of glucose. PHF-fed rats had significantly lower levels of cholesterol, triglycerides, bilirubin, SGOT, and SGPT. Both histopathological analysis and toxicological testing showed the formulation to be safe. Therefore, PHF can be used as a potential antihyperglycemic agent for antidiabetic drugs in animal models (35).

Quercetin a novel flavonoid

Quercetin is the main flavonoid and is predominantly present in foods like onions, cabbage, cauliflower, apples, almonds, tea, berries and many others. It indicates a variety of biological processes, such as anti-inflammatory, anti-carcinogenic and antiviral properties; also Inhibiting aggregation of platelet, permeability of capillary and peroxidation of lipid. There are reports that flavonoids can help with diabetes. The majority of quercetin is found in plants as hydrophilic glycosides, which cannot be directly absorbed. It is believed that up to 65-81% of

quercetin aglycone is absorbed when the glycosides are hydrolyzed (36). In a study, Ader et al examined the effects of quercetin-4-glucoside (spiraeoside) and quercetin-3-glucoside (isoquercitrin) on the mucosal uptake of the non-metabolizable glucose analogue methyl-D-glucopyranoside (MDG) using an in vitro mucosal uptake technique. They discovered that SGLT-1-mediated MDG absorption was considerably decreased by both glucosides, but was not affected by quercetin-3-rhamnoglucoside (rutin) or aglycon quercetin. Therefore, based on the current findings, it is not possible to directly infer the quercetin glucosides' transport across the intestinal brush-border membrane (37). Scientists investigate that additional research on Quercetin might help us find new quercetin glucosides that have SGLT2i properties.

Schisandra chinensis a native plant in Northern China

In China's northeast mountain region, *Schisandra chinensis* is a well-known traditional plant. It has five distinct therapeutic flavors, including hot, sweet, sour, salty, and bitter, with sour being the most significant. Regarding TCM philosophy, it strengthens internal organs and is one of the best diabetes herbal remedies (38). Wang et al found that in vivo and in vitro models of DN (diabetic nephropathy), schisandrin A reduced the TXNIP/NLRP3 signaling pathway and activated the AdipoR1/AMPK signaling pathway, as a result, schisandrin A is a potential treatment for DN or other types of diabetes (39). Gu et al conducted a study in which demonstrated that in a [¹⁴C]-methyl-d-glucopyranoside ([¹⁴C]-AMG) uptake assay, the ethanol extract of SCF (*Schisandra Chinensis Fructus*) at 1 mg/mL concentration strongly inhibited 73% of SGLT2 and 89 percent of SGLT1 activities. The ethanol extract was fractionated into nine fractions, of these, F8, at a concentration of 1 mg/mL, inhibited SGLT 2 specifically ($P < 0.001$, 42% inhibition) without inhibiting SGLT 1. Three substances—schisandrin B (γ -schisandrin), schisandrin and deoxyschisandrin—were discovered in F8 by using LC/MS-MS tool, and their concentrations were determined. The [¹⁴C]-AMG uptake assay examination, however, revealed that these three substances did not decrease SGLT 2 activity, demonstrating that the active SGLT component(s) from SCF have not yet been discovered (40).

Sophora flavescens a traditional Chinese remedy

Undoubtedly one of the most well-known and significant traditional Chinese remedies is *Sophora flavescens*. Many illnesses, including leukorrhea, dysentery, jaundice, scabies, fever, pyogenic skin infection, swelling, and discomfort are treated with this species' (also known as "Kushen") root. In a study by Sato et al, the potential SGLT inhibition properties of nine compounds that were extracted from the dried root of *S. flavescens* were investigated. It is interesting to note that the isoflavonoid-based compounds maackiain and formononetin only

showed selective inhibitory efficacy against SGLT2 and not SGLT1. According to the structure-activity relationship (SAR) analysis study, an isoflavonoid's hydroxyl functional group is essential for its ability to inhibit SGLT2. Additionally, the two sophoraflavanone G and (-)-kurarinone, the two most potent compounds, showed good selectivity with IC₅₀ values of 4.1 and 1.7 M for SGLT2 and 18.7 and 10.4 M for SGLT1, respectively (41). Sato and co-workers also, discovered seven flavonoids from *S. flavescens* (1, 3-8), as well as a 5-lavandulyl chalcone (9) that effectively inhibited SGLT1 and SGLT2. Compared to SGLT1, these flavonoids more effectively inhibited SGLT2. Additionally, the lavandulyl group of C-8 or C-5 (chalcone) is a functional group that is shared by the chalcone of 5 and the SGLT1-inhibitory flavanones (5, 6, and 8). According to these findings, SGLT1-inhibitory activity is significantly mediated by the lavandulyl group in the flavanone skeleton. Furthermore, a dihydroxy group of C-3 needed for lavandulyl flavanones and also hydroxyl group needed for SGLT2-inhibitory isoflavonoids. Additionally, methoxy groups may strengthen the inhibitory effects against SGLTs in the flavanone skeleton of C-5. As a result, it might be beneficial to research these substances in order to develop new SGLT inhibitors as anti-diabetic drugs (41). In another study by Yang and colleagues in 2015, several flavonoids that may inhibit SGLT2 were isolated. From the *S. flavescens* active methanol fraction, they found a number of isoflavonoid glycosides with possible SGLT2 inhibitory activity (42). As a result, investigating these molecules may be helpful for creation of novel SGLT inhibitors as diabetic medications.

Vitexin an active ingredient of traditional Chinese medications

Many traditional Chinese medications contain the active ingredients vitexin and isovitexin, which were isolated

in a variety of medicinal herbs. Due to its numerous pharmacological benefits, such as anti-hyperalgesic, neuroprotective, anti-cancer, anti-oxidant, and anti-inflammatory activities, vitexin (apigenin-8-C-glucoside) has recently attracted more attention. An isomer of vitexin known as isovitexin (apigenin-6-C-glucoside), which is typically isolated along with vitexin, also shows a variety of biological functions (43). Several plants produce vitexin, which has a hypoglycemic effect and can be utilized as an anti-diabetic agent. Vitexin and isovitexin, when given orally, dramatically decreased postprandial blood glucose in both sucrose-induced diabetic rats and sucrose-loaded normoglycemic mice, indicating a potential role in diabetes (44).

A study in 2018 by Rezwendy et al revealed that vitexin's antidiabetic action is mediated through SGLT2 inhibition, which improved blood glucose levels. The goal of this work was to develop a pharmacophore-based screening method to identify drugs from an Indonesian botanical database that have the potential to be used as SGLT2 inhibitors. These findings demonstrated the potential SGLT2 inhibitory activity of cucumern A, cucumern B and Vitexin (45).

Phytochemical acceptance and as a potential treatment for diabetes

Traditional plant therapies for diabetes have been advised by WHO, because they are non-toxic, effective, have few to no side effects, and are thought to be great candidates for oral medications (46) (Table 1).

Additionally, numerous phytochemicals with anti-diabetic activities have been extracted from plants in recent years. Further discussion has been conducted on a number of phytoconstituents, including flavonoids, alkaloids, peptidoglycans, amino acids, glycosides, glycolipids, polysaccharides, saponins, dietary fibers, and

Table 1. Phytochemicals

Phytochemical name	Effect	Model	Region	Reference
<i>Acer nikoense</i>	SGLT1i, SGLT2i	Molecular modeling based on NMR analysis	Japan	(16)
<i>Alstonia macrophylla</i>	SGLT1i, SGLT2i	In vitro	Asia and Africa	(18)
Aspalathin	SGLT2i, PTPi Lowering inflammatory markers PKC- θ , IL-6, TNF- α	-	South Africa	(11,20)
<i>Gnetum gnemonoides</i>	SGLT1i, SGLT2i, antioxidant, hepatoprotective enzyme inhibitory activities, and antimicrobial	In vitro	New Guinea, Bismarck Archipelago, Indonesia, Malaysia Philippines	(21,22)
Phlorizin	SGLT1i, SGLT2i, antioxidant, and anti-inflammatory	In vivo	-	(26-28)
<i>Phyllanthus emblica</i>	SGLT2i, GLP-1 agonists, and PPAR- γ	Molecular docking	Bangladesh Central India	(31)
Polyherbal mixture	SGLT2i	In vivo	-	(35)
Quercetin	SGLT1i	In vitro	-	(37)
<i>Schisandra chinensis</i>	Reduction of the TXNIP/NLRP3 and activation of the AdipoR1/AMPK signaling pathways	In vivo	China's northeast mountain	(39)
<i>Sophora flavescens</i>	SGLT2i	In vitro	China	(41)

others derived from various medicinal herbs that have been found to be effective hypoglycemic agents (47). Ahmadi et al studied Iranians between 15 and 64 for diabetes in accordance with the WHO's Stepwise guidelines (from 2005 to 2016). The results show the adult population of Iran increased its use of traditional herbal remedies. They concluded that, patients with diabetes are increasingly turning to traditional herbal remedies, either on their own or in conjunction with other forms of treatments. Due to the widespread use of traditional herbal remedies for the treatment of diabetes and the potential for herb-drug interactions, Policymakers need to take necessary actions to control herb supplies and raise people's awareness of using herbs (48).

Conclusion

In light of the increasing incidence of diabetes mellitus, this review highlighted scientific research on the anti-hyperglycemic potential of phytochemicals. Inhibition of SGLT2 has been considered a promising therapeutic target in the treatment of type 2 diabetes; This is because SGLT2 plays an important role in renal glucose reabsorption and whole-body glucose homeostasis in the human body. In this review, various phytochemicals with different chemical and biological characteristics were summarized; further investigations are needed to discover new phytochemicals for the development of next-generation SGLT2 inhibitors which are safer and more efficient than traditional medications.

Acknowledgments

The authors are thankful to the "Research Center of nephropathology, Isfahan University of Medical Sciences, Iran" for providing technical supports.

Authors' contribution

Conceptualization: MehS.

Validation: MehS

Investigation: MehS.

Resources: MehS.

Data curation: MehS.

Writing-original draft preparation: MehS.

Writing-reviewing and editing: NR, MahS, HM.

Visualization: MehS.

Supervision: MehS.

Project management: MehS.

Conflicts of interest

The author declares no conflict of interest.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/ Support

Nil.

References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional

- and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract.* 2022;183:109119. doi: 10.1016/j.diabres.2021.109119.
2. Li GQ, Kam A, Wong KH, Zhou X, Omar EA, Alqahtani A, et al. Herbal medicines for the management of diabetes. *Adv Exp Med Biol.* 2012;771:396-413.
3. Devalaraja S, Jain S, Yadav H. Exotic Fruits as Therapeutic Complements for Diabetes, Obesity and Metabolic Syndrome. *Food Res Int.* 2011;44:1856-65.
4. Emon NU, Alam S, Rudra S, Haidar IKA, Farhad M, Rana MEH, et al. Antipyretic activity of *Caesalpinia digyna* (Rottl.) leaves extract along with phytoconstituent's binding affinity to COX-1, COX-2, and mPGES-1 receptors: In vivo and in silico approaches. *Saudi J Biol Sci.* 2021;28:5302-5309. doi: 10.1016/j.sjbs.2021.05.050.
5. Zamljen T, Medič A, Veberič R, Hudina M, Štampar F, Slatnar A. Apple Fruit (*Malus domestica* Borkh.) Metabolic Response to Infestation by Invasive Brown Marmorated Stink Bug (*Halyomorpha halys* Stal.). *Horticulturae.* 2021;7:212.
6. Ashrafi S, Alam S, Emon NU, Ahsan M. Isolation, Characterization and Pharmacological Investigations of a New Phenolic Compound along with Four Others Firstly Reported Phytochemicals from *Glycosmis cyanocarpa* (Blume) Spreng. *Molecules.* 2022 4;27:5972. doi: 10.3390/molecules27185972.
7. Asif M. The role of fruits, vegetables, and spices in diabetes. *Intern J Nutrit, Pharmacol, Neurolog Dis.* 2011;1:27.
8. Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. *Drug Des Devel Ther.* 2014;8:1335-80. doi: 10.2147/DDDT.S50773.
9. Chung MY, Choi HK, Hwang JT. AMPK activity: a primary target for diabetes prevention with therapeutic phytochemicals. *Nutrients.* 2021;13:4050. doi: 10.3390/nu13114050.
10. Hung HY, Qian K, Morris-Natschke SL, Hsu CS, Lee KH. Recent discovery of plant-derived anti-diabetic natural products. *Nat Prod Rep.* 2012;29:580-606.
11. Muller CJF, Joubert E, Chellan N, Miura Y, Yagasaki K. New Insights into the Efficacy of Aspalathin and Other Related Phytochemicals in Type 2 Diabetes-A Review. *Int J Mol Sci.* 2021;23:356. doi: 10.3390/ijms23010356.
12. Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. *Diabet Med.* 2010;27:136-42.
13. Shubrook JH, Bokaie BB, Adkins SE. Empagliflozin in the treatment of type 2 diabetes: evidence to date. *Drug Des Devel Ther.* 2015;9:5793-803.
14. Singhal R, Hechanova LA. SGLT2 inhibitors: benefits for CKD and cardiovascular disease in type 2 diabetes. *Curr Cardiol Rep.* 2022;24:183-9. doi: 10.1007/s11886-022-01637-0.
15. Nagai M, Kubo M, Fujita M, Inoue T, Matsuo M. Studies on the constituents of aceraceae plants. II. Structure of aceroside I, a glucoside of a novel cyclic diarylheptanoid from *Acer nikoense* Maxim. *Chemical and Pharmaceutical Bulletin.* 1978;26:2805-10.
16. Morita H, Deguchi J, Motegi Y, Sato S, Aoyama C, Takeo J, et al. Cyclic diarylheptanoids as Na⁺-glucose cotransporter (SGLT) inhibitors from *Acer nikoense*. *Bioorg Med Chem Lett.* 2010;20:1070-4.
17. Khyade MS, Kasote DM, Vaikos NP. *Alstonia scholaris* (L.) R. Br. and *Alstonia macrophylla* Wall. ex G. Don: A comparative review on traditional uses, phytochemistry and pharmacology. *J Ethnopharmacol.* 2014;153:1-18. doi: 10.1016/j.jep.2014.01.025.
18. Arai H, Hirasawa Y, Rahman A, Kusumawati I, Zaini NC, Sato S, et al. Alstiphyllanines E-H, picraline and ajmaline-type alkaloids from *Alstonia macrophylla* inhibiting sodium

- glucose cotransporter. *Bioorg Med Chem*. 2010;18:2152-8.
19. Son MJ, Minakawa M, Miura Y, Yagasaki K. Aspalathin improves hyperglycemia and glucose intolerance in obese diabetic ob/ob mice. *Eur J Nutr*. 2013;52:1607-19.
 20. Mazibuko-Mbeje SE, Mthembu SX, Muller CJ, Ziqubu K, Muvhulawa N, Modibedi RV, et al. Aspalathin alleviates skeletal muscle insulin resistance and mitochondrial dysfunction. *Physiol Res*. 2022 Nov 28;71:643-656. doi: 10.33549/physiolres.934844.
 21. Choi CI. Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors from Natural Products: Discovery of Next-Generation Antihyperglycemic Agents. *Molecules*. 2016;21:1136. doi: 10.3390/molecules21091136.
 22. Shimokawa Y, Akao Y, Hirasawa Y, Awang K, Hadi AH, Sato S, et al. Gneyulins A and B, stilbene trimers, and noidesols A and B, dihydroflavonol-C-glucosides, from the bark of *Gnetum gneumonoides*. *J Nat Prod*. 2010;73:763-7.
 23. Gosch C, Halbwirth H, Stich K. Phloridzin: biosynthesis, distribution and physiological relevance in plants. *Phytochemistry*. 2010;71:838-43.
 24. Danne T, Biester T, Kordonouri O. Combined SGLT1 and SGLT2 Inhibitors and Their Role in Diabetes Care. *Diabetes Technol Ther*. 2018;20:S269-s77.
 25. Oku A, Ueta K, Arakawa K, Ishihara T, Nawano M, Kuronuma Y, et al. T-1095, an inhibitor of renal Na⁺-glucose cotransporters, may provide a novel approach to treating diabetes. *Diabetes*. 1999;48:1794-800.
 26. Meng W, Ellsworth BA, Nirschl AA, McCann PJ, Patel M, Girotra RN, 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*. 2008;51:1145-9.
 27. Osorio H, Bautista R, Rios A, Franco M, Arellano A, Vargas-Robles H, et al. Effect of phlorizin on SGLT2 expression in the kidney of diabetic rats. *J Nephrol*. 2010;23:541-6.
 28. Rezk BM, Haenen GR, van der Vijgh WJ, Bast A. The antioxidant activity of phloretin: the disclosure of a new antioxidant pharmacophore in flavonoids. *Biochem Biophys Res Commun*. 2002;295:9-13.
 29. Hasan MR, Islam MN, Islam MR. Phytochemistry, pharmacological activities and traditional uses of *Emblica officinalis*: A review. *Intern Current Pharma J*. 2016;5:14-21.
 30. Yan X, Li Q, Jing L, Wu S, Duan W, Chen Y, et al. Current advances on the phytochemical composition, pharmacologic effects, toxicology, and product development of *Phyllanthus Fructus*. *Front Pharmacol*. 2022;13:1017268. doi: 10.3389/fphar.2022.1017268.
 31. Sharma P, Joshi T, Joshi T, Chandra S, Tamta S. In silico screening of potential antidiabetic phytochemicals from *Phyllanthus emblica* against therapeutic targets of type 2 diabetes. *J Ethnopharmacol*. 2020;248:112268.
 32. Gajarmal D, Kumar Rath D. Review on promotions of ayurveda product, bgr-34 through multimedia. *J Drug Res*. 2016;5:16-29.
 33. Karole S, Shrivastava S, Thomas S, Soni B, Khan S, Dubey J, et al. Polyherbal formulation concept for synergic action: a review. *J Drug Delivery and Therapeutics*. 2019;9:453-66.
 34. Suvarna R, Shenoy RP, Hadapad BS, Nayak AV. Effectiveness of polyherbal formulations for the treatment of type 2 Diabetes mellitus - A systematic review and meta-analysis. *J Ayurveda Integr Med*. 2021;12:213-22.
 35. Kumar A, Negi AS, Chauhan A, Semwal R, Kumar R, Semwal RB, et al. Formulation and evaluation of SGLT2 inhibitory effect of a polyherbal mixture inspired from Ayurvedic system of medicine. *J Tradit Complement Med*. 2022;12:477-487. doi: 10.1016/j.jtcme.2022.03.003.
 36. Aguirre L, Arias N, Teresa Macarulla M, Gracia A, P Portillo M. Beneficial effects of quercetin on obesity and diabetes. *The Open Nutraceuticals Journal*. 2011;4:189-198.
 37. Ader P, Blöck M, Pietzsch S, Wolffram S. Interaction of quercetin glucosides with the intestinal sodium/glucose cotransporter (SGLT-1). *Cancer Lett*. 2001;162:175-80.
 38. Qiao Z, Du X, Zhuang W, Yang S, Li H, Sun J, et al. Schisandra Chinensis acidic polysaccharide improves the insulin resistance in type 2 diabetic rats by inhibiting inflammation. *J Med Food*. 2020;23:358-66. doi: 10.1089/jmf.2019.4469.
 39. Wang X, Li Q, Sui B, Xu M, Pu Z, Qiu T. Schisandrin A from *Schisandra chinensis* Attenuates Ferroptosis and NLRP3 Inflammasome-Mediated Pyroptosis in Diabetic Nephropathy through Mitochondrial Damage by AdipoR1 Ubiquitination. *Oxid Med Cell Longev*. 2022;2022:5411462.
 40. Qu Y, Chan JY, Wong CW, Cheng L, Xu C, Leung AW, et al. Antidiabetic Effect of *Schisandrae Chinensis Fructus* Involves Inhibition of the Sodium Glucose Cotransporter. *Drug Dev Res*. 2015;76:1-8. doi: 10.1002/ddr.21233.
 41. Sato S, Takeo J, Aoyama C, Kawahara H. Na⁺-glucose cotransporter (SGLT) inhibitory flavonoids from the roots of *Sophora flavescens*. *Bioorg Med Chem*. 2007;15:3445-9.
 42. Yang J, Yang X, Wang C, Lin Q, Mei Z, Zhao P. Sodium-glucose-linked transporter 2 inhibitors from *Sophora flavescens*. *Med Chem Res*. 2015;24:1265-71.
 43. He M, Min JW, Kong WL, He XH, Li JX, Peng BW. A review on the pharmacological effects of vitexin and isovitexin. *Fitoterapia*. 2016;115:74-85. doi: 10.1016/j.fitote.2016.09.011.
 44. Choo CY, Sulong NY, Man F, Wong TW. Vitexin and isovitexin from the Leaves of *Ficus deltoidea* with in-vivo α -glucosidase inhibition. *J Ethnopharmacol*. 2012;142:776-81.
 45. Rezwendy R, Syahdi RR, Yanuar A. Indonesian herbal SGLT2 inhibitor discovery through pharmacophore-based virtual screening. *Pharmacog J*. 2018;10:803-807.
 46. Shokeen P, Anand P, Murali YK, Tandon V. Antidiabetic activity of 50% ethanolic extract of *Ricinus communis* and its purified fractions. *Food Chem Toxicol*. 2008;46:3458-66. doi: 10.1016/j.fct.2008.08.020.
 47. B Gaikwad S, Krishna Mohan G, Sandhya Rani M. Phytochemicals for diabetes management. *Pharmaceutical Crops*. 2014;5:11-28.
 48. Ahmadi S, Rafiey H, Sajjadi H, Nosrati Nejad F, Ahmadi N, Yoosefi M, et al. Trend and pattern of using herbal medicines among people who are aware of their diabetes mellitus: results from National STEPs Surveys in 2005 to 2011 in Iran. *J Diabetes Metab Disord*. 2021;20:1319-1325. doi: 10.1007/s40200-021-00859-3.