



The fabulous story of glyphozines.

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Abstract


Received: June 12, 2022
Accepted: July 30, 2023
Published: Agosto 15, 2023
Editor: Dr. Franklin Mora Bravo.

Cite:

Valdés-Socin H, Vanoni M. The fabulous story of glyphozines. REV SEN 2023;11(2):91-97.

DOI: <http://doi.org/10.56867/53>
SOCIEDAD ECUATORIANA DE NEFROLOGÍA DIÁLISIS Y TRASPLANTE.

ISSN-L: 2953-6448

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Introduction: The surprising history of gliflozins begins with the phlorizin-induced renal diabetes model and culminates with synthesizing the C glycosides derived from phloridzin: gliflozins. These drugs, specifically SGLT-2 inhibitors, constitute a new class of oral antidiabetics with unsuspected beneficial effects at cardiovascular and renal levels.

Objective of the review: The aim of the present historical narrative review of the events related to developing glyphozins from phlorizin.

Essential points of the review:

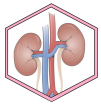
- Phloridzin or phlorizin, a natural O-glucoside, was discovered in 1835 by two Belgian chemists: Laurent-Guillaume de Koninck (1809-1887) and Jean Servais Stas (1813-1891).
- Joseph von Mering described in 1883 the glucosuric effects of phlorizin, first in dogs, then in humans, which will lead to a model of nephrogenic diabetes.
- In the 1950s, phlorizin was observed to block glucose transport in different epithelia, including the kidney and intestine.
- Today, phlorizin is known to be a nonspecific antagonist of glucose (GLUT) receptors. We also owe a lot to patients with congenital glycosuria, in whom inactivating mutations of GLUT receptors were identified.

Conclusion: The fabulous fate of gliflozins illustrates the relevance of the history of medicine and translational research that allowed significant therapeutic advances for many diabetic, renal, and cardiac patients.

Keywords:

MeSH: Diabetes mellitus; History; Sodium-Glucose Transporter 2 Inhibitors; Heart Failure; Renal Insufficiency, Chronic.

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Phlorizin was discovered in 1835 by two Belgian chemists: Laurent-Guillaume de Koninck (1809-1887) and Jean Servais Stas (1813-1891) [1]. De Koninck was a doctor and studied in Leuven and then became an assistant in the chemistry laboratory of Jean-Baptiste Van Mons (1765-1842) [1, 2].

Jean Servais Stas, a doctor, was born in Leuven and assisted his former chemistry teacher, Van Mons. Prof. Van Mons was an expert in fruit trees and the owner of an apple nursery [1, 2]. These chemists have a large number of apple tree roots to analyze. They isolate a crystalline glucoside from the bark of these roots, which they call phloridzin [1- 4]. Later, its name will be simplified: phlorizin [1- 2].

The phlorizin molecule is composed of a glucose molecule linked to a polyphenolic dihydrochalcone, or phloretin, by an O-Osodic bond. Its chemical structure is similar to that of other dihydrochalcones known for their intense sweetening power [1- 4]. It is naturally present in fruit trees such as apples and pears [1- 4]. At that time, antipyretic properties were attributed to phlorizin, which were never confirmed later [5]. Phlorizin will disappear from the medical literature for 50 years. At the end of the 19th century, physiologist Joseph Von Mering began investigating its effects on dogs [6]. What he discovers will, unexpectedly, lead to significant advances in diabetes over the next two centuries.

Phlorizin: A reversible experimental model of nephrogenic diabetes

Joseph Friedrich Freiherr, Baron Von Mering (1849-1908), was born in Cologne, Germany, to a noble family [1, 2]. In 1885, in Strasbourg, Von Mering studied the physiological effects of phlorizin in dogs [7- 9]. Von Mering discovered a glucosuric effect after oral administration but also by injection of phlorizin [7- 9]. In 1886, von Mering also reported that phlorizin administration reduced blood sugar in dogs [7- 9]. He speculates that “the substance can induce glycosuria by changing something in the kidney.” Von Mering then administered phlorizin to humans at a dose of 2 g per day for a month. He obtained a daily glycosuria of 91 g [1- 2]. Glucosuria stops with the suppression of phlorizin. Von Mering then reported that the administration of phlorizin at doses of 15 to 20 g daily to normal subjects induces daily glycosuria of 6 to 8 g/100 ml without affecting their general condition [1- 2].

From nephrogenic diabetes to pancreatic diabetes

The mechanism of diabetes of pancreatic origin was discovered thanks to Von Mering's collaboration with Oskar Minkowski (1809-1887), a physiologist born in Alexoten (Kowno), in Tsarist Russia [10]. The Argentine Nobel Prize winner Bernardo Houssay [11- 12], who in turn contributed to the description of diabetes of pituitary origin in 1947, narrated in another article [13] the details of this discovery favored by the happy role of chance, which we summarize below.

Von Mering researched the digestion of the pancreas in 1889. He met Dr. Minkowski in the institute's library, who suggested helping him perform a pancreatectomy on his dogs, an operation that was considered unfeasible. The dog operated on by Minkowski survived the process but later developed polyuria [13]. Minkowski realized that dog urine contains 12 g/100 ml of glucose. Believing he could have operated on a dog previously treated with phlorizin by von Mering, Minkowski proceeded alone, without assistance, to a total pancreatectomy on three new dogs. Two of them developed glycosuria before dying quickly from duodenal necrosis. The third dog survived but with permanent diabetes [13]. A true gentleman, Minkowski, granted Von Mering the position of first author of the publication on pancreatic diabetes. Minkowski later showed that the hypoglycemic action of phlorizin is mainly renal [14, 15]. Russian physiologists observed that phlorizin lost its hypoglycemic effect in dogs nephrectomized and rendered diabetic by pancreatectomy [13, 15, 16].

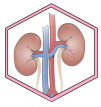
Phlorizin and diabetes: a missed therapeutic opportunity

The idea of using phlorizin or a derivative for hypoglycemic and therapeutic purposes in diabetes was not yet mature in the 20th century. However, in 1980, Di Fronzo's team developed a diabetic rat model to demonstrate that a normalization of plasma glucose accompanies glycosuria induced by phlorizin without observing hypoglycemia [17]. Phlorizin normalized insulin sensitivity in partially pancreatectomized rats but did not affect insulin action in controls [17].

Figure 1. Laurent Guillaume de Koninck.



Laurent-Guillaume de Koninck (1809-1887)

**Figure 2.** Jean Servais Stas.**Jean Servais Stas (1813-1891).**

However, phlorizin was also not used to treat diabetes in the 1990s due to its low oral bioavailability and adverse effects. Indeed, phlorizin is metabolized to phloretin by intestinal glucosidase [1, 2, 17]. Therefore, it must be administered parenterally to be sufficiently active [1, 2, 17]. Furthermore, phloretin is also a potent inhibitor of SGLT-1 (sodium-glucose linked transporter), which can lead to reduced glucose transport to other tissues, such as the central nervous system, an effect then considered potentially harmful [17].

Phlorizin: its glucosuric effect elucidated

SGLT cotransporters (sodium-glucose cotransporters) [18] are membrane proteins involved in sodium-dependent glucose transport and are of two types: SGLT-1 and SGLT-2. They are related to glucose absorption in the small intestine (SGLT-1) and at the kidney level (SGLT-2 and, to a lesser extent, SGLT-1). SGLT-2 is also present in the sinusoidal membrane of hepatocytes, where it participates in glucose uptake and glucose release into the blood and pancreatic β cells [18].

Phlorizin competitively inhibits SGLT-1 and SGLT-2 [16]. Therefore, it promotes urinary loss of glucose in the renal tubule and reduces intestinal absorption. The intestinal glucose load is accompanied by digestive side effects, such as diarrhea [2, 16]. The tubulo-glomerular feedback hypothesis to explain the mechanism of glomerular hyperfiltration in diabetic patients allows us to postulate that inhibitors of the SGLT-2 cotransporter, by ensuring a more significant influx of

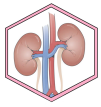
sodium at the level of the macula densa, can reduce secondary hyperfiltration. to vasodilation of the afferent arteriole [2]. This, combined with its diuretic effect, recently explained by Verma and Mc Murray [19], selectively extracts more fluid from the interstitial space than from the vascular area, which would explain why the administration of gliflozins contributes to reducing cardiovascular mortality.

SGLT-2 receptors: mutations in humans and animal models

In humans, inactivating mutations affecting the SGLT-2 gene (locus on chromosome 3q26.2-q27) determine Fanconi-Bickel syndrome, described in 1949 [20]. This rare autosomal recessive disorder is characterized early by hepatorenal glycogen accumulation with hepatomegaly, tubular nephropathy, fasting hypoglycemia, glucose and galactose intolerance, and growth deficits in affected children [20].

In mice, knockout of the SGLT-2 gene results in early diabetes [21]. This is due to impaired glucose-stimulated insulin secretion and abnormal development of pancreatic islets in the postnatal period [21]. The premature death of the animals is due to suppression of glucose-stimulated insulin secretion [21].

Figure 3. Joseph Friedrich, Baron von Mering (1849-1908)

**Figure 4.** Bernard Houssay (1887-1971).

From phlorizin to glyphozins

In the late 1990s, an O-glucoside derivative of phlorizin was developed in Japan under the name T-1095 [22]. This substance, tested in diabetic rats and mice, was influential in treating diabetes. In this animal model, T-1095 decreased glycated hemoglobin, delaying the appearance of microalbuminuria. Like phlorizin, this substance is nonspecific, inhibiting SGLT-1 and SGLT-2. Due to the presence of SGLT-1 in the heart and brain, its development was halted, citing its lack of selectivity and a safety profile considered insufficient [18, 19].

During the 21st century, American and European laboratories successively developed specific SGLT2 antagonists: canagliflozin, empagliflozin, dapagliflozin, and ertugliflozin [2, 19, 23]. Recent, randomized, double-blind trials carried out in many patients have provided significant added benefits in patients with diabetes mellitus, preventing and treating chronic renal failure, proteinuria, and heart failure with reduced and slightly reduced ejection fraction. These new molecules changed the international guidelines for managing type 2 diabetes, heart failure, and chronic kidney disease [19].

Conclusions

Phloridzin or phlorizin, a natural O-glucoside present in apple and pear trees, was discovered by Belgian researchers at the end of the 19th century, and its therapeutic possibilities went unnoticed for a long time. Von Mering discovered "nephrogenic diabetes" by

demonstrating the glucosuric effects of phlorizin. In the early 20th century, efforts were made to look for points of similarity between "pancreatic diabetes" and phlorizin-induced "nephrogenic diabetes." Although the hypoglycemic effects of phlorizin were also demonstrated early by von Mering, the "pancreatic diabetes" paradigm (which von Mering himself and Minkowski helped discover) prevailed during the 20th century. As a result, the treatment of diabetic patients was carried out mainly with insulin, secretagogues, and insulin sensitizers.

The identification of SGLT-2 at the renal level, in turn, contributes to revealing the glucosuric mechanism of phlorizin while providing an answer to the etiology of familial glycosuria or Fanconi-Bickel syndrome. These discoveries gave new impetus to the search for phlorizin derivatives: C-glycosides or gliflozins. Today, gliflozins have become one of the cornerstones in the treatment of diabetes, allowing researchers to look away from the pancreas to redirect it to the intestine and kidney as new actors in diabetes. Finally, gliflozins are also emerging as new players in chronic kidney and heart failure, with or without diabetes. However, this, dear reader, is another story...

Abbreviations

iSGLT2: sodium-glucose cotransporter two inhibitors.

DRD: diabetic kidney disease.

DM: diabetes mellitus.

Supplementary information

Supplementary materials have not been declared.

Acknowledgments

Does not apply.

Author contributions

Hernán Valdés-Socin: conception, writing of the article, analysis of conclusions.

Miguel Vanonil: bibliographic search, article writing and graph review.

Both authors read and approved the final version of the article.

Financing

The source of the funding for this article was our resources.

Availability of data or materials

Does not apply.

Statements

Ethics committee approval and consent to participate

Does not apply.

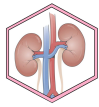
Consent for publication

Does not apply when images or photographs of the physical examination or X-rays/CT scans/MRI of patients are not published.

Conflicts of interest

HVS declares that it has no conflict of interest in this article.

MV declares that he is a speaker for AstraZeneca and Novo Nordisk.



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