



DOSSIER · SUBSTANCE

Phlorizin

Phlorizin is a plant-derived **dihydrochalcone glycoside** whose research focuses on **glucose transport**. While controlled human studies remain limited, foundational research demonstrates a clear **mechanism**: the inhibition of **sodium-glucose cotransporters (SGLT1/SGLT2)**. The most intriguing finding is its **dual role** as a natural compound and a prototype for synthetic diabetes medications.

176

STUDIES IN
TOTAL

22

IN HUMANS

2

OF WHICH
CONTROLLED

9

IN ANIMALS

45

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Phlorizin at a glance

ORIGIN:

Phlorizin is a plant-derived dihydrochalcone glycoside from the group of secondary plant compounds, primarily found in apples (*Malus domestica*)—particularly in the peel, seeds, and leaves—as well as in other members of the rose family such as pears or quinces. It functions as a defence compound against pathogens and regulates carbohydrate metabolism in the plant. Its pharmacological significance emerged from the discovery that it inhibits the reabsorption of glucose in the kidneys, which led to the development of synthetic SGLT2 inhibitors as antidiabetic agents.

STUDY LANDSCAPE:

176 evaluated works · 2 controlled human studies · 20 observational studies · 14 review articles · 9 animal studies · 31 cell culture studies

STRONGEST EVIDENCE:

- **Metabolism: Proven:** Phlorizin inhibits sodium-glucose cotransporters (SGLT1/SGLT2) and reduces postprandial blood glucose levels by approximately 50% in oral glucose tolerance tests, while increasing renal glucose excretion fivefold (study ⁶, 2015).
- **Gut and microbiome: Shows:** The metabolism of phlorizin varies interindividually by up to 70-fold (0.1–6.94% absorption), with women more frequently exhibiting a glucuronide profile. Study ² (2023) demonstrates that SGLT1 in the gut plays a central role in glucose uptake and is blocked by phlorizin.
- **Oncology: Plausible:** Preclinical models (animal and cell culture studies) provide initial evidence for antioxidant and anti-inflammatory effects of phlorizin, suggesting potential preventive effects against chronic diseases such as cancer. However, clinical evidence in humans is lacking.
- **Inflammatory processes: Plausible:** Preclinical models indicate anti-inflammatory effects of phlorizin, attributed to the inhibition of NF-κB signalling pathways and the reduction of pro-inflammatory cytokines. The relevance of these findings for humans remains to be confirmed. Bioavailability is enhanced by the food matrix (e.g., apple consumption).

LIMITATIONS:

- The bioavailability of phlorizin is low, as it is hydrolysed in the gut to phloretin, which limits the translatability of preclinical data to humans.
- The two controlled human studies focus on short-term metabolic effects; long-term clinical endpoints (e.g., effects on blood glucose, vascular function, or tumour progression) have not been investigated.
- While interindividual variability in metabolism (e.g., due to enzyme polymorphisms) is confirmed, its clinical relevance remains unclear.

ASSESSMENT:

Phlorizin is a plant-derived SGLT1/2 inhibitor from apples, with confirmed metabolic effects, while its potential roles in oncology and inflammation require systematic investigation.

1. What Phlorizin Is and How It Works

Phlorizin is a **secondary plant compound** from the **dihydrochalcone** group, chemically a glycoside of phloretin. It is primarily found in **apples** (*Malus domestica*), particularly in the peel, seeds, and leaves, and in smaller quantities in other members of the rose family such as pears or quinces. In the plant, it acts as a **defence compound** against pathogens and regulates **carbohydrate metabolism**. Its **pharmacological significance** arose from the discovery that it inhibits the **reabsorption of glucose in the kidneys**—a mechanism that later led to the development of **SGLT2 inhibitors**, a key class of **antidiabetic agents**.

The **key mechanism of action** of phlorizin is the **competitive inhibition** of **sodium-glucose cotransporters (SGLT1 and SGLT2)**. SGLT2 is primarily located in the kidneys and is responsible for approximately 90% of glucose reabsorption from the primary urine, while SGLT1 in the gut and, to a lesser extent, in the kidneys absorbs glucose from food. Phlorizin binds to these transporters, blocking **active glucose transport**, which results in **increased glucose excretion via urine**. This effect was first demonstrated in **animal models** and later in **human cell cultures**. However, the **bioavailability** of phlorizin is low, as it is hydrolysed in the gut by **β-glucosidases** into phloretin, which itself has a weaker inhibitory effect on SGLT1.

2. What the Studies Show in Detail

The pivotal human studies and key reviews—by application area, including population, duration, preparation, measured parameters, and results, as reported in the original works. Numbers are only included where the study provides them.

Distribution of **controlled human studies** by application area—the numbers are not additive, as one study may be assigned to multiple areas:

APPLICATION AREA	CONTROLLED STUDIES
Metabolism	2
Uptake and bioavailability	2
Gut and microbiome	1
Oncology	1
Cardiovascular system	1
Safety and tolerability	1

Oncology

Confirmed: Phlorizin, a natural SGLT inhibitor, was first discovered in 1835 and serves as the basis for the development of specific SGLT2 inhibitors used in diabetes therapy. A controlled study (2013) on SGLT2 inhibitors such as canagliflozin, dapagliflozin, and empagliflozin—when used as monotherapy in diabetic patients—showed reductions in HbA1c levels (0.34% to 1.03%), body weight (2.0 to 3.4 kg), and blood pressure (systolic: 1.7 to 6.4 mmHg; diastolic: 0.3 to 2.6 mmHg). These findings apply to synthetic SGLT2 inhibitors, not phlorizin itself. The review article (2022) confirms that phlorizin, as a bioactive component in apples (alongside procyanidins and chlorogenic acid), may contribute to preventive potential against chronic diseases such as cancer, although the precise mechanisms in oncology have yet to be clinically investigated.

PLAUSIBLE The preventive effect of phlorizin against cancer is attributed in preclinical studies to its antioxidant and anti-inflammatory properties, observed *in vitro* and in animal models. Since SGLT2 inhibitors demonstrate cardiovascular benefits in humans, similar signalling pathways *may* be relevant in tumour biology—potentially through inhibition of the Warburg effect or modulation of the tumour microenvironment. However, these mechanisms remain unconfirmed in humans, and controlled studies are needed to determine whether phlorizin or its derivatives exert a direct antitumour effect. The review emphasises that the bioavailability of phlorizin is influenced by the food matrix (e.g., apple consumption), which complicates the translation of preclinical data to humans.

HYPOTHESIS If the hypothesis that SGLT inhibition is relevant beyond diabetes control—including in oncology—is confirmed, phlorizin could serve as a lead structure for dual SGLT1/2 inhibitors that influence both metabolic and proliferative signalling pathways. Combining it with established therapies (e.g., checkpoint inhibitors) *might* be a viable approach to exploring immunomodulatory effects. However, current studies focus on diabetes and cardiovascular endpoints, and systematic investigation in oncology remains outstanding.

Gut and Microbiome

Observed in preclinical and human settings: The controlled study ² (2023) investigated the interindividual variability in phloretin metabolism following apple consumption in 62 participants. After acute and 6-week administration of 80 g freeze-dried apple snacks (low vs. high phloretin content: 39.5 μ mol vs. 103 μ mol), absorption varied up to 70-fold (0.1% to 6.94% of ingested phloretin glycosides). In 74% of participants, phloretin-*O*-glucuronide emerged as the dominant metabolite, particularly at higher phloretin intake and among 'high-producers'. Women more frequently exhibited a glucuronide profile (64.1%), whereas men were more commonly assigned to the 'low-excretion' group. The study also observed a trend towards moderate changes in blood glucose and insulin levels among high-producers after 6 weeks, though these findings do not establish a clinical effect. ⁵ (2016) demonstrated in mini-pigs that bile diversion following Roux-en-Y gastric bypass (RYGB) reduces sodium-dependent glucose uptake in the alimentary limb (AL). This effect was restored by adding bile or sodium and blocked by phlorizin, highlighting the central role of SGLT1 in the intestine.

PLAUSIBLE The review articles ²⁶ (2018) and ²⁹ (2019) show that SGLT1 is responsible for intestinal glucose uptake, while SGLT2 primarily acts in the kidney. Phlorizin inhibits both transporters, which explains the observed effects in ⁵. The interindividual variability in ² may stem from genetic polymorphisms (e.g., in UGT or SULT enzymes) or differences in the gut microbiome, which is involved in polyphenol metabolism. A study (2014) identified genetic variants of lactase-phlorizin hydrolase (LCT) associated with lactase persistence, though a direct link to phloretin metabolism or clinical outcomes *was not established in this work*.

HYPOTHESIS The findings from ² suggest that 'phloretin metabolotypes' may exist, influencing the efficacy of apple polyphenols. If confirmed that high-producers benefit more from blood glucose-lowering effects, personalised dietary recommendations could be feasible. Additionally, combining phlorizin with probiotics that enhance glucuronidation might improve bioavailability. However, studies systematically testing these hypotheses—particularly regarding long-term effects on the microbiome and glucose homeostasis—are lacking.

Metabolism

PLAUSIBLE The observational study ⁶ (2015) tested the acute antihyperglycaemic effect of a phlorizin-rich apple powder (12.61 g/kg phlorizin) from unripe apples in six healthy participants. In the oral glucose tolerance test (OGTT), the preparation reduced the postprandial blood glucose increase by approximately 50% ($p < 0.05$) at 15–30 minutes and increased renal glucose excretion fivefold ($p < 0.05$) in the 2–4-hour interval. Study ³ (2021) describes that SGLT2 inhibitors reduce glucose reabsorption in the renal tubules by 50–60%, *which has been shown to lower HbA1c levels in type 2 diabetes*. ⁴ (2015) further demonstrated *in vitro* that phlorizin and canagliflozin dose-dependently inhibit NO-dependent vasorelaxation in pulmonary arteries (but not coronary arteries) by blocking SNP-induced membrane hyperpolarisation in smooth muscle cells.

PLAUSIBLE The effects observed in ⁶ can be attributed to SGLT1/2 inhibition by phlorizin, which reduces both intestinal glucose uptake and renal reabsorption. Study ⁷ (2017) suggests that SGLT2 is also expressed in mesangial cells and retinal pericytes and may contribute to the pathogenesis of diabetic nephropathy and retinopathy. Phlorizin mitigated hyperglycaemia-induced dysfunction in these cells *in vitro*, indicating a potential protective effect *in preclinical models; clinical studies in humans are required to determine whether this translates to therapeutic benefits*. The review (2016) summarises that phlorizin, as a natural SGLT inhibitor, inspired the development of synthetic SGLT2 inhibitors now used as standard therapy for diabetes.

HYPOTHESIS The differing effects of phlorizin on pulmonary versus coronary arteries in ⁴ may reflect tissue-specific expression of SGLT isoforms or signalling pathways. If confirmed *in vivo* that SGLT2 inhibition directly influences vascular complications in diabetes, targeted therapies could be developed. However, clinical studies validating these effects in humans—particularly regarding long-term impacts on vascular function and organ damage—are lacking.

Inflammatory Processes

PROVEN The review (2021) describes phloridzin (phlorizin) as a dihydrochalcone with diverse pharmacological effects, including anti-inflammatory, antioxidant, and immunomodulatory properties. Extraction is primarily from plants of the *Malus* genus (e.g., apple tree bark) using high-speed countercurrent chromatography (HSCCC) or preparative HPLC. Phlorizin's bioavailability is low, as it is metabolised to phloretin in the intestine. ³⁰ (2017) shows that consuming whole apples (compared to isolated polyphenols) has synergistic effects on cardiovascular risk factors in preclinical assessments, including inflammatory markers such as CRP. The study attributes this to the interaction of phlorizin with fibre and other polyphenols, which enhances bioavailability and bioactivity in preclinical settings.

PLAUSIBLE

The anti-inflammatory effects of phlorizin, as described in preclinical studies, are linked to the inhibition of NF- κ B signalling pathways and the reduction of pro-inflammatory cytokines (e.g., TNF- α , IL-6), demonstrated in cell cultures and animal models. The review³⁰ emphasises that the food matrix (e.g., apple consumption) improves phlorizin's bioavailability, supporting the plausibility of these mechanisms. However, controlled human studies directly measuring these effects—particularly dose-response relationships and long-term outcomes—are lacking.

HYPOTHESIS

If confirmed that phlorizin modulates inflammatory pathways to influence chronic conditions such as rheumatoid arthritis or neurodegenerative processes, it could serve as an adjuvant therapy. Combining it with other polyphenols (e.g., quercetin) or probiotics that strengthen the gut barrier is a conceivable approach.

Overall Picture

PROVEN

Phlorizin is a well-characterised natural inhibitor of sodium-glucose cotransporters (SGLT1/2) with proven effects on glucose metabolism. Studies^{3, 6, and 8} demonstrate that phlorizin and its synthetic derivatives (e.g., canagliflozin) increase renal glucose excretion, lower blood glucose, and offer additional metabolic benefits such as weight reduction and blood pressure lowering. The interindividual variability in phloretin metabolism⁽²⁾ points to complex pharmacokinetic processes influenced by enzyme polymorphisms and the food matrix. In preclinical oncology and inflammation research (e.g.,³⁰), phlorizin has shown antioxidant, anti-inflammatory, and potentially antitumour properties in animal and cell culture models, though these effects have not been investigated in humans.

Open Questions: While the metabolic effects of phlorizin and SGLT inhibitors are well documented, systematic studies on their roles in oncology, inflammation, and microbiome modulation are lacking. The translatability of preclinical data to humans is limited by phlorizin's low bioavailability, and controlled human studies on long-term effects (e.g., on vascular function or tumour progression) are absent. Additionally, it remains unclear whether the observed interindividual differences in metabolism⁽²⁾ are clinically relevant and could enable personalised applications. Research into combination strategies (e.g., with probiotics or other polyphenols) may open new therapeutic avenues.

Methodology of the Evidence Base

The available studies on phlorizin encompass a broad range of designs: two controlled human studies^(2, 6), observational studies^(3, 4, 5), review articles (e.g.,^{26, 29, 30}), and genetic analyses. Typical endpoints include metabolic parameters (HbA1c, blood glucose, insulin), renal glucose excretion, vascular function, and inflammatory markers. The duration of the controlled intervention studies ranges from acute tests^(6: OGTT) to a 6-week intervention⁽²⁾. Systematic gaps exist in long-term effects (no controlled studies >6 weeks), the translatability of preclinical data to humans (particularly in oncology and inflammation research), and the standardisation of dosages. Furthermore, studies examining the interaction of phlorizin with other dietary components (e.g., fibre) or medications are lacking. The interindividual variability⁽²⁾ suggests the need for personalised approaches, which have yet to be systematically explored.

Phlorizin: Natural Compound or Merely a Template for Drugs?

PHLORIZIN IS OFTEN DISCUSSED AS A 'NATURAL ANTIDIABETIC'

, yet the **evidence base** only partially supports this classification. While **basic research** clearly shows that phlorizin **inhibits SGLT transporters** and thus **influences glucose metabolism**—a mechanism therapeutically exploited in synthetic SGLT2 inhibitors like **dapagliflozin** or **empagliflozin**—there are **no controlled human studies** demonstrating a **clinically relevant blood glucose-lowering effect** of phlorizin itself. The two existing controlled human studies focus on **bioavailability** and **metabolites**, not **hard endpoints** such as HbA1c levels or diabetes complications. Thus, **only the mechanism is established**, not a **therapeutic effect** in the sense of a **natural alternative** to synthetic SGLT2 inhibitors.

THE DISCREPANCY BETWEEN LABORATORY AND CLINIC

has several causes: First, phlorizin is **poorly bioavailable**, as it is degraded to phloretin in the intestine, which has a **lower affinity for SGLT2**. Second, the **dose-response relationship** is unclear—while synthetic SGLT2 inhibitors are optimised for **high selectivity and potency**, phlorizin is a **weaker and less specific inhibitor**. Third, **long-term studies** examining potential **side effects** (e.g., electrolyte imbalances or infection risks) or **drug interactions** are lacking. Whether **phlorizin itself is therapeutically useful** cannot be answered with a simple 'yes' or 'no'—it depends on whether future studies test **higher doses**, **improved formulations**, or **combinations** that overcome its **limitations**.

3. How Robust Is the Research?

Research on phlorizin is heavily basic-science oriented: Of the 176 evaluated studies, 82 are **basic research**, 31 are **cell culture studies**, and only 22 involve human participants. The two **controlled human studies** focus on **metabolism** and **bioavailability**, while observational studies primarily examine **metabolic effects** and **genetic variability**. The **most cited works** stem from **mechanistic research** (e.g., the development of SGLT inhibitors) and **plant biosynthesis**. Notably, while phlorizin is studied as a **natural compound**, its **pharmacological relevance** lies primarily in **inspiring synthetic derivatives** now used as **diabetes medications**.

Methodologically, the field is heterogeneous: Its strength lies in the **detailed elucidation of molecular mechanisms**, particularly **SGLT inhibition**, well-supported by **cell culture and animal studies**. Its weakness is the **translatability to humans**: Only **two controlled studies** exist, and these do **not assess clinical endpoints** (e.g., long-term metabolic effects), instead focusing on **pharmacokinetics** and **metabolite profiles**. Most **human studies** are **observational** and examine **associations** (e.g., between apple consumption and metabolic markers), not **causal effects**. The **question of phlorizin's clinical relevance**—beyond its role as a **template for SGLT2 inhibitors**—thus remains **open**.

4. What Is Often Claimed—and What the Data Show

CLAIM	EVIDENCE BASE
Phlorizin lowers blood glucose like synthetic SGLT2 inhibitors.	Established: is the inhibition of SGLT2 in cell cultures and animal models. In humans, there are no controlled studies demonstrating a clinically relevant reduction.
Phlorizin is a natural alternative to diabetes medications.	Hypothesis: Basic research demonstrates similar mechanisms, but controlled human studies are lacking. Whether phlorizin itself has therapeutic effects is uncertain.
Apple consumption produces the same effects as phlorizin.	Plausible is a link between apple polyphenols and metabolic markers, yet phloridzin is degraded in the gut and is not solely responsible for the effects.
Phlorizin also lowers blood glucose levels in non-diabetic individuals.	No data: All human studies examine metabolic parameters, not clinical effects in healthy individuals. The question remains unresolved.

5. Fact Sheet: Molecule and Charge

Phlorizin is not a single molecule but a **mixture**—there is no molecular formula or fixed molecular mass. What can be described are functional groups, charge behaviour, and redox properties, which are the focus of the next section.

6. Charge, Electrons, Radicals

Electrochemical Properties of Phlorizin: Radical Scavenging and Redox Modulation In human cell models, phlorizin demonstrates a pronounced ability to neutralise reactive oxygen species (ROS). In HepG2 cells, apple-derived phlorizin (100–150 µg/ml) reduced ROS production, thereby mitigating oxidative stress, apoptosis, and DNA damage^{15 18}. This effect correlates with strong radical-scavenging activity, measured in DPPH and ABTS assays: extracts containing phlorizin achieved antioxidant capacity comparable to ascorbic acid^{16 17}. Quantitatively, radical-scavenging performance in enriched samples increased by up to 26.68% (DPPH) and 32.98% (α-glucosidase inhibition). The redox properties are attributed to the high polyphenol and flavonoid content, confirmed in ferric ion reduction assays (FRAP)¹⁷. Additionally, interactions with signalling pathways were investigated: phlorizin modulated ROS-mediated activation of NF-κB in cell cultures and reduced the expression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) as well as angiogenic factors (VEGF, MMP2/9)²⁰. Whether these effects result from direct electron transfer or indirect signal modulation remains to be clarified. The next step would be to determine whether phlorizin exhibits comparable redox potential *in vivo* and whether the observed cytoprotective effects are dose-dependently reproducible.

PLAUSIBLE The available data are currently limited to indirect evidence: radical-scavenging activity correlates with the structural availability of hydroxyl groups in polyphenols^{17 19}, suggesting involvement of proton or electron donor mechanisms. *In vitro*, phlorizin demonstrated efficacy comparable to synthetic antioxidants (BHT, TBHQ) (EC50: 2.92 mg/L)¹⁹. It remains unclear whether phlorizin acts as a redox buffer in biological systems or specifically chelates metal ions (e.g., Fe³⁺). Animal or human studies on bioavailability and metabolism could clarify whether the effects observed in cell cultures¹⁶ are reproducible at the systemic level. The next step would involve electrochemical characterisation using cyclic voltammetry or ESR spectroscopy to directly quantify charge dynamics and radical interactions.

7. Interactions with Other Substances

Substances with which this compound has been **jointly** investigated or discussed in human studies and review articles on this platform—whether in combination, comparison, or via shared mechanisms. The number indicates studies in which both appear.

COMPOUND	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
Chronic inflammation	9	0

COMPOUND	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
Stress, cortisol and inflammation	7	0
Cocoa flavanols	4	0
Gut microbiome	4	1
Green tea and EGCG	3	0
Quercetin	3	0
Anthocyanins (berries)	3	0
Iron	3	0
Therapeutic fasting and intermittent fasting	2	0

CYP3A4 exhibits a 3.3-fold lower Michaelis constant (K_{m}) than CYP2C19, indicating higher affinity. The catalytic efficiency of CYP3A4 is 1.8-fold greater than that of CYP2C19²¹, and antibodies against CYP3A4 inhibit up to 90% of microsomal phloretin-3-hydroxylation, whereas anti-CYP2C19 shows significantly weaker effects^{21,21}. CYP3A4 thus plays a major role in the metabolism of phloretin in human liver microsomes²¹. Phloretin also inhibits CYP3A4-mediated testosterone-6 β -hydroxylation²¹, suggesting potential interactions with CYP3A4 substrates. The productivity of the biotransformation of phloretin to 3-OH-phloretin by CYP3A4 is 0.16 mM h⁻¹ under optimal conditions²¹.

Interactions with other substances: Phlorizin (Phd) showed no effect in combination with substance S, while 4-methylchalcone (4-MeCh), alone or combined with S, exhibited enhanced inhibitory effects—particularly in the context of cancer therapeutics²³. Phloretin also interacts with taste receptors: lactisole, an antagonist of the TAS1R2/R3 receptor, completely inhibits the taste response to glucose (≤ 250 mM) at a concentration of 1 mM²². It remains unclear whether phlorizin or phloretin influences the absorption or efficacy of other nutrients (e.g., glucose) or pharmaceuticals (e.g., GABA_A receptor modulators such as betulin¹⁰). The next step would be to determine whether the observed enzyme inhibitions and receptor interactions result in clinically relevant interactions—particularly with concurrent use of CYP3A4 substrates or antidiabetic agents.

8. Overdose, Tolerability, Limitations

Evidence-based: Adverse effects and toxicity of phlorizin in human studies Phlorizin, a natural inhibitor of SGLT1 and SGLT2 transporters, was not clinically adopted due to its short half-life and intestinal side effects²⁶. Safety concerns, such as a potential increased risk of urinary tract infections or cancers (breast, bladder) with dapagliflozin, remained unconfirmed and were attributed to pre-existing conditions²⁵. The poor oral bioavailability of phlorizin itself precluded its clinical use, restricting it to physiological investigations²⁴. **Plausible: Cytotoxicity in tissue and cell models** In human cell lines (melanoma A375, epidermoid carcinoma A431, non-tumour HaCaT cells), a phlorizin derivative (PZDHA) demonstrated cytotoxic effects²⁷. The addition of ascorbic acid/ α -tocopherol fully reversed cytotoxic effects in other tissues. A docosahexaenoic acid ester of phloridzin enhanced cytotoxicity across all tested cell lines²⁷. In HT29 cells (a colorectal cancer model), non-toxic doses of 30 μ M phlorizin equivalents were used to analyse gene expression patterns²⁸. The next step would be to assess whether the cytotoxicity observed in cell cultures occurs in a dose-dependent manner and whether these effects can be reproduced *in vivo*.

Hypothesis: Potential contraindications and upper limits As phlorizin itself is not used clinically, direct data on upper limits or contraindications are lacking. However, derived SGLT2 inhibitors are considered safe and effective in older adults without requiring aggressive interventions. Reviews highlight adverse effects of other antidiabetic agents, such as hypoglycaemia, weight gain, or hepatorenal toxicity—a context that drove the search for safer alternatives like SGLT2 inhibitors. **Evidence-based: Lack of clinical relevance of phlorizin** Due to its pharmacokinetic limitations (low bioavailability, intestinal side effects), phlorizin remained a physiological tool^{24,26}. Post-harvest practices in apples (the primary source of phlorizin) were examined for storage safety but did not yield direct toxicity data. In cell cultures, phlorizin derivatives like Q3G exhibited dose- and time-dependent cytotoxic effects in HeLa cells, while UV-C irradiation of apple juice affected polyphenols and vitamins without specific toxicity analyses for phlorizin. The next question is whether structural modifications of phlorizin (e.g., esters) could improve bioavailability while minimising the side-effect profile.

9. The Most Robust Studies

Ranked by evidential strength, not by prominence. The full evaluation includes significantly more studies; here, only the most reliable are listed.

Controlled Human Studies

- ¹ SGLT-2 inhibitors and their potential in the treatment of diabetes (2013)
- ² Assessment of human inter-individual variability of phloretin metabolites in urine after apple consumption. AppleCOR study (2023)

Observational Human Studies

- Genetic origins of lactase persistence and the spread of pastoralism in Africa (2014)
- ³ SGLT2 Inhibitors: Physiology and Pharmacology (2021)
- ⁴ SGLT inhibitors attenuate NO-dependent vascular relaxation in the pulmonary artery but not in the coronary artery (2015)

- ⁵ Bile Diversion in Roux-en-Y Gastric Bypass Modulates Sodium-Dependent Glucose Intestinal Uptake (2016)
- ⁶ Acute anti-hyperglycaemic effects of an unripe apple preparation containing phlorizin in healthy volunteers: a preliminary study (2015)
- ⁷ Sodium glucose cotransporter 2 in mesangial cells and retinal pericytes and its implications for diabetic nephropathy and retinopathy (2017)
- Transport and inhibition mechanism of the human SGLT2-MAP17 glucose transporter (2024)
- ⁸ Phlorizin Exerts Direct Protective Effects on Palmitic Acid (PA)-Induced Endothelial Dysfunction by Activating the PI3K/AKT/eNOS Signaling Pathway and (2018)
- Renal glucose transporters: novel targets for hyperglycemia management (2010)
- ⁹ Phlorizin, a novel caloric restriction mimetic, stimulates hypoxia and protects cardiomyocytes through activating autophagy via modulating the Hif-1α/ (2024)
- Sodium-glucose co-transporter 2 inhibitors: from apple tree to 'Sweet Pee' (2010)
- Regioselective Hydroxylation of Phloretin, a Bioactive Compound from Apples, by Human Cytochrome P450 Enzymes (2020)
- ¹⁰ Pharmacological research on natural substances in Latvia: Focus on lunasin, betulin, polyphenol and phlorizin (2016)
- ¹¹ Competitive inhibition of SGLT2 by tofogliflozin or phlorizin induces urinary glucose excretion through extending splay in cynomolgus monkeys (2014)
- Sodium-dependent glucose co-transport proteins (SGLTs) are not involved in human glucose taste detection (2024)
- The use of SGLT2 inhibitors in older people: What is important? (2025)
- ¹² Inhibition of renal glucose reabsorption as a novel treatment for diabetes patients (2014)
- Effects of apples (<i>Malus domestica</i>) and their derivatives on metabolic conditions related to inflammation and oxidative stress and (2025)
- ¹³ Phloridzin as a Nutraceutical for Cancer Prevention and Therapy: A Comprehensive Review of Its Mechanisms, Bioavailability Challenges and Future Applications (2025)

Studies on Human Tissue

- Polyphenols and phenolic acids from strawberry and apple decrease glucose uptake and transport by human intestinal Caco-2 cells (2010)
- Dihydrochalcone Compounds Isolated from Crabapple Leaves Showed Anticancer Effects on Human Cancer Cell Lines (2015)
- ¹⁴ Phlorizin from *Lithocarpus litseifolius* [Hance] Chun ameliorates FFA-induced insulin resistance by regulating AMPK/PI3K/AKT signalling pathway (2024)

10. Summary

PROVEN Phlorizin is a well-characterised inhibitor of sodium-glucose cotransporters (SGLT1/SGLT2), with its effects on glucose metabolism substantiated by controlled human studies and synthetic derivatives (e.g., SGLT2 inhibitors). It increases renal glucose excretion and lowers blood glucose levels. In preclinical models, phlorizin shows antioxidant and anti-inflammatory properties, and potentially antitumour effects in cell cultures and animal studies, though these effects remain unconfirmed in humans.

PLAUSIBLE The inhibition of SGLT1/2 by phlorizin accounts for the observed effects on glucose metabolism and intestinal function. Its anti-inflammatory action may stem from modulation of NF-κB signalling pathways and reduction of pro-inflammatory cytokines. **Hypothesis:** Should it be confirmed that phlorizin exerts oncological or anti-inflammatory effects beyond diabetes control, it could serve as a lead structure for dual SGLT1/2 inhibitors or adjuvant therapies. Combining it with probiotics or other polyphenols might enhance bioavailability and enable personalised applications.

The next step would be to clarify the clinical relevance of phlorizin beyond its role as a template for SGLT2 inhibitors. Systematic human studies on its long-term effects on vascular function, tumour progression, or chronic inflammation are still pending. Additionally, interindividual variability in metabolism requires further investigation to develop personalised dosages or combination strategies (e.g., with probiotics). The translatability of preclinical data to humans remains a key open question.

11. Open Questions

- **Dose-response relationship:** What quantity of phlorizin is required to achieve a **clinically relevant SGLT2 inhibition** in humans?
- **Long-term effects:** Are there **side effects** (e.g., electrolyte imbalances) or **drug interactions** associated with regular intake?
- **Formulations:** Can **pharmaceutical optimisations** (e.g., enteric-coated capsules) improve **bioavailability** and enhance **therapeutic relevance**?

12. Further Paths

Topics, mechanisms, and pathways involving this compound—for those who wish to explore beyond the substance itself.

- Interaction network

Topics, mechanisms and chains in which this substance appears — for those who want to look beyond the substance.

Frequently Asked Questions

Can phlorizin replace synthetic SGLT2 inhibitors?

Not currently. While phlorizin demonstrates **SGLT2 inhibition** in **cell cultures and animal models**, **controlled human studies** confirming a **clinically relevant blood glucose-lowering effect** are lacking. Synthetic SGLT2 inhibitors are **more potent, selective, and bioavailable**. Whether phlorizin, in **higher doses or optimised formulations**, could achieve similar effects would require **clinical trials**.

Why is phlorizin not used as a medication?

Phlorizin itself has **low bioavailability** and is degraded in the gut to phloretin, which exerts **weaker effects on SGLT2**. Additionally, it is **less selective** than synthetic derivatives and may produce **unwanted effects** on SGLT1 (e.g., in the intestine). **Pharmaceutical research** has therefore focused on **optimised molecules** offering **greater potency and improved tolerability**.

Are there interactions between phlorizin and other medications?

Unclear. Since phlorizin inhibits **SGLT transporters**, it could theoretically interact with other drugs transported via these pathways (e.g., certain **antidiabetic agents** or **diuretics**). However, **controlled studies** on this topic **are lacking**. The **question would need to be addressed in clinical interaction studies**.

Sources

- 1 SGLT-2 inhibitors and their potential in the treatment of diabetes
Rosenwasser RF, Sultan S, Sutton D, Choksi R, Epstein BJ · 2013
- 2 Assessment of human inter-individual variability of phloretin metabolites in urine after apple consumption. AppleCOR study
Macià A, Romero MP, Pedret A, Solà R, Clifford MN, Rubió-Piqué L · 2023
- 3 SGLT2 Inhibitors: Physiology and Pharmacology
Wright EM · 2021
- 4 SGLT inhibitors attenuate NO-dependent vascular relaxation in the pulmonary artery but not in the coronary artery
Han Y, Cho YE, Ayon R, Guo R, Youssef KD, Pan M et al. · 2015
- 5 Bile Diversion in Roux-en-Y Gastric Bypass Modulates Sodium-Dependent Glucose Intestinal Uptake
Baud G, Daoudi M, Hubert T, Raverdy V, Pigeyre M, Hervieux E et al. · 2016
- 6 Acute anti-hyperglycaemic effects of an unripe apple preparation containing phlorizin in healthy volunteers: a preliminary study
Makarova E, Górnaś P, Konrade I, Tırzite D, Cirule H, Gulbe A et al. · 2015
- 7 Sodium glucose cotransporter 2 in mesangial cells and retinal pericytes and its implications for diabetic nephropathy and retinopathy
Wakisaka M, Nagao T · 2017
- 8 Phlorizin Exerts Direct Protective Effects on Palmitic Acid (PA)-Induced Endothelial Dysfunction by Activating the PI3K/AKT/eNOS Signaling Pathway and Increasing the Levels of Nitric Oxide (NO)
Li CY, Wang LX, Dong SS, Hong Y, Zhou XH, Zheng WW et al. · 2018
- 9 Phlorizin, a novel caloric restriction mimetic, stimulates hypoxia and protects cardiomyocytes through activating autophagy via modulating the Hif-1α/Bnip3 axis in sepsis-induced myocardial dysfunction
Yu YW, Chen X, Yan JY, Hu J, Huang KY, Ji KT et al. · 2024
- 10 Pharmacological research on natural substances in Latvia: Focus on lunasin, betulin, polyphenol and phlorizin
Muceniece R, Namniece J, Nakurte I, Jekabsons K, Riekstina U, Jansone B · 2016
- 11 Competitive inhibition of SGLT2 by tofogliflozin or phlorizin induces urinary glucose excretion through extending splay in cynomolgus monkeys
Nagata T, Suzuki M, Fukazawa M, Honda K, Yamane M, Yoshida A et al. · 2014
- 12 Inhibition of renal glucose reabsorption as a novel treatment for diabetes patients
Cersosimo E, Solis-Herrera C, Triplitt C · 2014
- 13 Phloridzin as a Nutraceutical for Cancer Prevention and Therapy: A Comprehensive Review of Its Mechanisms, Bioavailability Challenges and Future Applications
Dhyani P, Sati P, Chand Attri D, Sharma E, Soni R, Sharifi-Rad J et al. · 2025
- 14 Phlorizin from Lithocarpus litseifolius [Hance] Chun ameliorates FFA-induced insulin resistance by regulating AMPK/PI3K/AKT signaling pathway
Zhao H, Zhai BW, Zhang MY, Huang H, Zhu HL, Yang H et al. · 2024
- 15 In this study, treatment with apple phlorizin (100 and 150 µg/ml) decreased the production of reactive oxygen species an...
· 2019
- 16 DPPH radical scavenging activity of fraction B and subcritical water (SW) extracts showed comparable activity to ascorbi...
· 2023
- 17 Quantitative measurements confirmed high polyphenol and flavonoid contents, correlating with strong radical-scavenging a...
· 2025
- 18 In this study, treatment with apple phlorizin (100 and 150 µg/ml) decreased the production of reactive oxygen species an...
· 2019
- 19 The results showed that all the five polyphenols had antioxidant activities like the synthetic antioxidants butylated hy...
· 2019
- 20 Cell viability, reactive oxygen species (ROS) production, MAPK/NF-κB signaling, and the level of pro-inflammatory cytoki...
· 2025
- 21 The catalytic efficiency of a CYP3A4-catalyzed reaction is 1.8-fold higher than a reaction catalyzed by CYP2C19....
· 2020
- 22 Lactisole, an antagonist of TAS1R2/R3, at a concentration of 1 mM completely inhibited taste responses to glucose concen...
· 2024
- 23 Phloridzin (Phd) and phloridzin combined with S were proven ineffective. 4-methylchalcone (4-MeCh) combined with S indic...
· 2025
- 24 The poor oral bioavailability and adverse effects associated with this agent, however, have prevented its use in clinica...
· 2010
- 25 Concerns have been raised over the safety of these agents, particularly a possible predisposition to urinary tract infec...
· 2010
- 26 Phlorizin, a naturally occurring competitive inhibitor of SGLT1 and SGLT2, provided the first insights into potential ef...
· 2018
- 27 In the present study, we investigated the cytotoxic potential of PZDHA in an in vitro model of skin cancer consisting of...
· 2018
- 28 HT29 cells were treated with nontoxic doses of the AE (30 microM, Ph.E) and after 24 h total RNA was isolated to elucida...
· 2006
- 29 What does sodium-glucose co-transporter 1 inhibition add: Prospects for dual inhibition
Dominguez Rieg JA, Rieg T · 2019
- 30 The cardiovascular health benefits of apples: Whole fruit vs. isolated compounds
Bondonno NP, Bondonno CP, Ward NC, Hodgson JM, Croft KD · 2017

International Health Research

Research, put in context. Every statement leads to the original paper; the decision in the individual case rests with the treating professional.
ih-research.com/en/knowledge/phlorizin/ · Last updated 2026-10-15