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Therapeutic indication of Phloridzin: A new Gleam for metabolic disorders

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1. Abstract

Phloridizin is a phenolic phytoconstituent and glucoside derivative of phloretin, a dihydrochalcone from the bicyclic flavonoid family. It was initially isolated from the apple tree's bark. Phloridzin (PZ or phloretin-2′-O-glucoside) is a key flavonoid glycoside derivative found primarily in apple peels.

2. Introduction:

PIn today's context, a balanced diet usually includes fruits and vegetables that are rich in phytochemicals, such as flavonoids and phenols. These metabolites demonstrate biological activity and have immunostimulant properties (Khalid et al., 2018). One particularly active phytochemical is phloridzin. Further molecular modifications could enhance its pharmacological effectiveness. Phloridzin and its derivatives possess various beneficial properties, including anticancer, anti-obesity, anti-diabetic, antioxidant, anti-aging, antibacterial, and melanogenic effects (Khalid et al., 2018). Phloridzin (also known as PZ or phloretin-2′-O-glucoside) is a flavonoid glycoside found in all parts of the apple tree, with the highest concentration typically present in the fruit.Reg bioflavonoids are classified into two categories: major and minor flavonoids. The primary flavonoids include flavones, anthocyanidins, and isoflavones, while the minor flavonoids consist primarily of dihydrochalcones. Phloretin and its glycoside, phloretin-2'-glucose, are key members of this minor group. Most studies have concentrated on the effects of phloretin on controlling hyperglycemia by altering glucose absorption and excretion in diabetes. As a result, phloretin has led to the development of a new family of anti-diabetic medications known as SGLT2 (sodium-glucose co-transporter 2) inhibitors. However, there is limited research regarding phloretin's effects on the skeletal system, particularly its impact on skeletal muscle under experimental conditions.Several studies have investigated the anti-inflammatory effects of Phloridzin in preventing inflammation in the lungs and liver (Zielinska et al., 2019). A novel derivative of Phloridzin, known as Phloridzin myristic acid (PZM), is created through the enzymatic acylation of myristic acid. This derivative has demonstrated strong antioxidant capacity in vitro, as well as hepatoprotective benefits in vivo, showing greater bioactivity compared to natural Phloridzin. Additionally, significant hepatoprotective efficacy of the Phloridzin derivative against CCl4-induced hepatotoxicity has been reported.For decades, researchers have conducted numerous investigations on the physiological impacts, pharmacological activities, production, and distribution of Phloridzin and its derivatives. This review will provide a detailed summary of Phloridzin's biomedical applications in metabolic disorders, as well as its patents. This study also discusses the clinical limits and potential strategies for their application in different areas of the therapeutic goal.

3.Natural Source of Phloridzin

Other families that contain phloridizin include Fagaceae, Rosaceae, and Cucurbitaceae. It is primarily found in malus species uncooked apples, specifically Malus domestica. It is the primary phenolic-glucoside in apple trees and can also be found in the roots, bark, shoots, and leaves. Apple peel has 12–418 mg/kg, but apple pulp contains 4–20 mg/kg. Golden Delicious has the lowest concentration, while Reineta Green and Glycine max seed coats contain a high amount of Phloridzin. hloridzin can also be obtained from various plants, including sweet tea leaves, Jaeschke's barberry, strawberries, and chayote, as well as lingonberries, lettuce, Chinese broccoli, and European plums (Tian et al., 2021). In nature, it exists alongside other phytocomponents, such as polyphenols including quercetin, epicatechin, catechin, rutin, and procyanidins. Researchers have found that the concentration of phloridzin in sweet tea is 100 times greater than that found in apples, indicating that sweet tea is an excellent natural source of this compound.

4.Extraction methods

Researchers (Alberti et al.) reported a variety of extraction techniques, including ultrasound-assisted aqueous two-phase extraction (Paudel et al.), semi-preparative analytical HPLC technique (Liang et al.), HSCCC-HPLC-diode array detector-mass spectrometric methods (HSCCC-HPLC-DAD-MS),

response surface methodology (Zhang et al.), magnetic molecularly imprinted polymers (MMIPs) (Gao et al.), X-5 resin and polyamide resin purification.

5. Pharmacokinetic

Phlorizin, also known as phlorrhizin or phlorizoside, is a compound that belongs to the bicyclic flavonoid family. It appears as a weakly basic, white to yellow crystalline solid with a harsh flavor. The molecular weight of phlorizin is 436.4 g/mol, and its chemical formula is C21H24O10. Its IUPAC name is 1-[2,4-dihydroxy-6-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyphenyl]-3-(4-hydroxyphenyl)propan-1-one.
Phlorizin's structure can be found in Figure 2 (PubChem 2000). It is freely soluble in solvents like hot water, ethanol, dimethyl sulfoxide (DMSO), and dimethyl formamide (DMF), but it has poor solubility in ether and cold water. The melting point of phlorizin ranges from 110 to 200°C, above which it decomposes. According to in vivo studies, phlorizin enhances the fractional elimination of glucose by up to 60%, while there is no observed change in the rate of glomerular filtration and renal plasma flow.It has been claimed that Phloridzin has a reduced binding constant with HSA due to competition between common ions and drug binding to the target protein, even though sites for Phloridzin and metal ions for HSA were not discovered in the same location. Divalent and trivalent metal ions would not modify Phloridzin's k value, but they would reduce the drug's binding strength to HSA. As a result, more Phloridzin could be released into the blood plasma, increasing the drug's maximal effectiveness and producing hazardous effects.

6. Effect on CNS

Another study found that Phloridzin has anti-parkinsonian effects through mechanisms such as reducing dopaminergic neuron loss and depletion, suppressing apoptosis (via the reduction of caspase-3,8 and 9, Bax/Bcl-2, and a-synuclein accumulation), modulating nuclear and cellular inflammatory signalling, reducing the expression of pro-inflammatory cytokines (IL-6, IL-1b, and NF-B), and increasing the expression of neurotrophic factors.

7. In vivo Findings

HFD and STZ-induced Hyperglycemia: It was observed that L. polystachyu Rehd. extract (Sweet tea) containing Phloridzin tends to exert remedial and preventive effects on hyperlipidemia and hyperglycemia caused by the high-fat diet (HFD) and Streptozocin (STZ) in rats, by improving polyphagia, polydipsia, polyurea, reducing weight, Fasting blood glucose (FBG), serum cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) levels, while increasing high-density lipoprotein cholesterol Phloridzin at 20mg/kg to rats raised the risk of osteoporosis and muscle mass in High-fat diet (HFD) and Streptozocin (STZ) induced diabetic female rats, and the serum biochemical parameters confirm the unfavorable.

8. Antioxidant action.

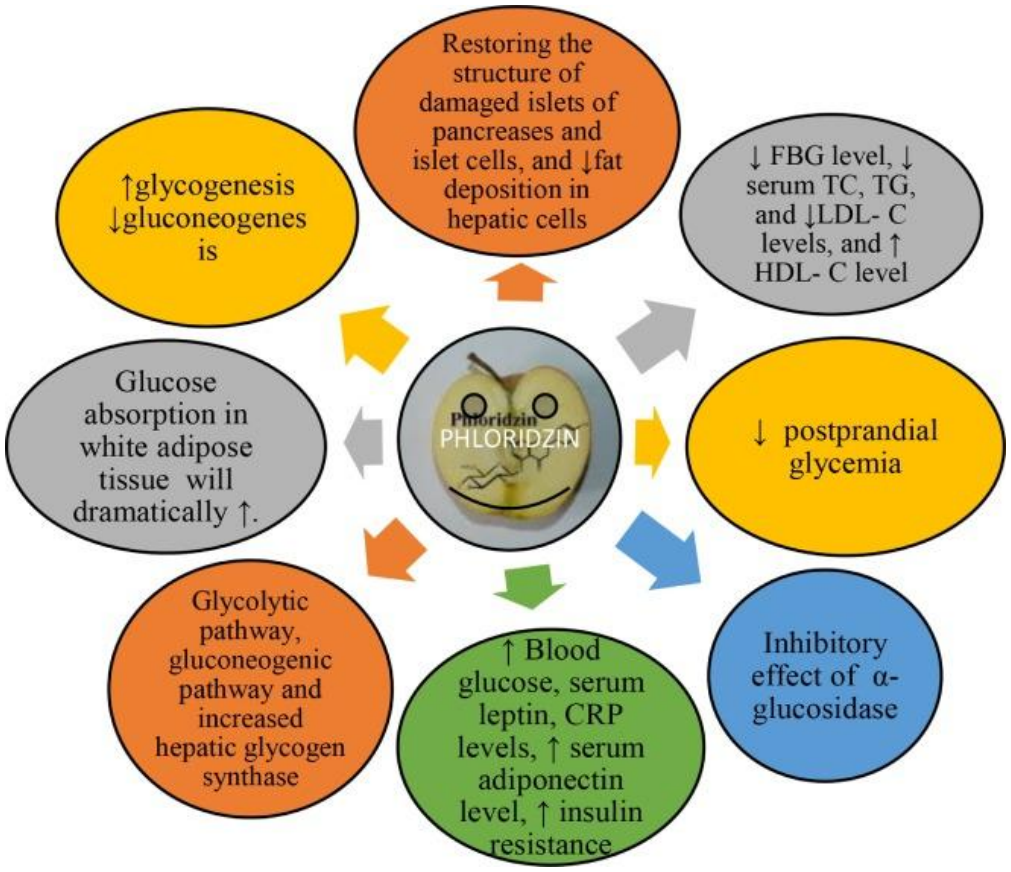
Phloridzin has the highest peroxyl radical scavenging activity, making it suitable for application as a natural antioxidant in the food industry, particularly to eliminate free peroxyl radicals produced by food (Khalid et al., 2018). In another study, it was discovered that Phloridzin at a dose of 2.0mg/ml improves the life span of drosophila in the Drosophila melanogaster fly model by enhancing various antioxidant enzymes (SOD, catalase) and by reducing the expression of stress defense enzymes like cap-n-collar (a homolog of mammalian Nrf2), deacetylase .

9. Anti-inflammatory action.

In vitro studies show that Phloridzin reduces/prevents intestinal inflammatory problems by decreasing the formation of AGEs; this is supported by the bovine serum albumin (BSA)/glucose and BSA/(MGO) methylglyoxal assays (Zielinska et al., 2019). It has been shown that Phloridzin metabolites have an anti-inflammatory action. Three Phloridzin metabolites isolated from rat urine were found to lower Lipopolysaccharide (LPS)-stimulated NO levels and iNOS expression in RAW 264.7 macrophage cells of mouse plasma (Zhao et al., 2017).

10. Hepatoprotective effect.

In the NAFLD (non-alcoholic fatty liver disease) model: Finding from the mixing of aqueous phloridizin-rich fruit extracts in Monosodium glutamate (MSG) and HFD. Induced T2D animals had higher levels of hepatic glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase, and glutathione (GSH) (Tian et al., 2021). The current findings indicate that pharmacological inhibition of SGLTs in T2D patients with Phloridzin at a dose of 0.4 g/kg may be an effective strategy for improving glycemic control and preventing the development and progression of NAFLD (David-Silva et al., 2020). The supporting mechanism confirms that phloridizin modulates hepatic lipid-regulating enzymes while decreasing collagen buildup in liver tissues. Overall, these findings suggest that Phloridzin could be effective in avoiding obesity and inflammation.



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11. Cardioprotective effect.

Ex vivo Methods: Phloridzin was tested for its ability to inhibit Electrically-Induced Ventricular Tachyarrhythmia (VT) in Langendroff-perfused guinea-pig hearts at a dose of 100 µM. The supported mechanism was confirmed: by limiting intracellular Ca2+ excess and inhibiting impulse conduction, VT will be slowed. As a result, Phloridzin has demonstrated to possess a cardioprotective effect against inflammation.

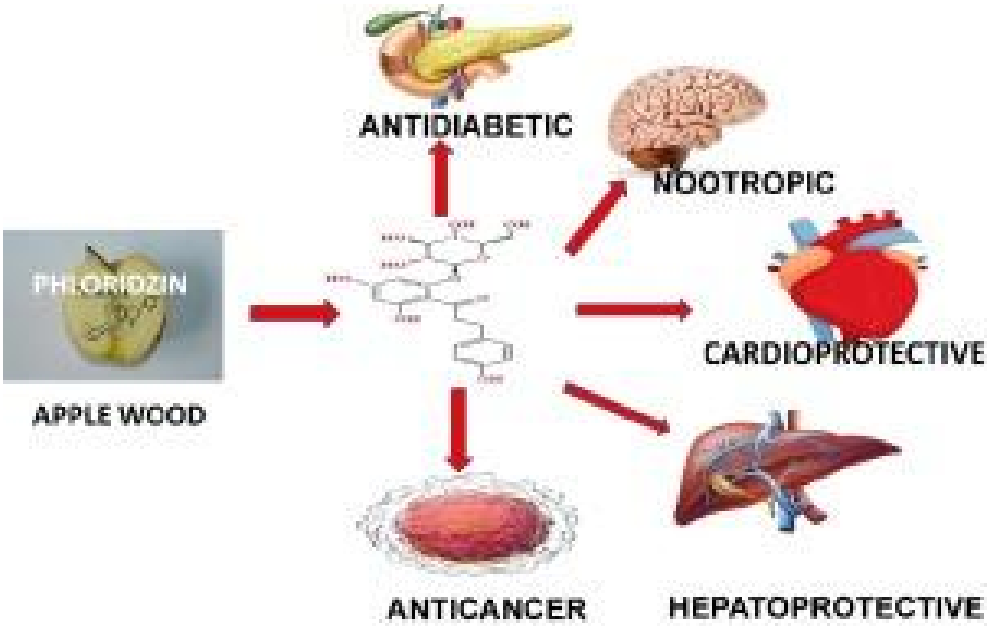
12. Anticancer action

Phloridzin is believed to have anti-proliferative properties in a variety of cancer cell lines and has been shown to inhibit tumor growth in a few animal models (Roleira et al., 2015).

In vitro cytotoxicity studies: Phloridzin-rich methanolic fruit extract of Sechium edule var. Nigrum spinosum was found to reduce cell damage. Its derivative was also discovered to be protective against tumor cell lines, showing that Phloridzin

In vivo cytotoxicity testing: Sub-cytotoxic Phloridzin docosahexaenoate (PZ-DHA) at a dose of 100mg/kg was observed to possess anti-metastatic effect in BALB/c and NOD-SCID female mice model by inhibiting various metastatic actions (migration, invasion, EMT) and metastasis-associated signalling pathways (TGFß, Akt/PI3K, MAPK) in Triple-Negative Breast Cancer (TNBC cells).

Graphical Abstract



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13. Future Prospect

Some of the drawbacks identified regarding Phloridzin included its nonselective target towards the GLUT receptor, which could lead to other undesired situations; thus, in the future, its derivatives could be adjusted for selective binding to the target receptor while lowering the unwanted effects. Phloridzin is a potential biomarker for food additives and intake. As a result, more research is needed to explicate the toxicological information of Phloridzin and its derivatives, as well as to give information for large-scale manufacture and packaging that is easily accessible and effective for consumption. Phloridzin or its equivalents remain unaffected. So, novel drug delivery systems or procedures could be devised for the safe and targeted distribution of Phloridzin.

14. Conclusion

According to reported shards of evidence from probable preclinical discoveries, plant extract, or Phloridzin, has several biological benefits, particularly as an antioxidant and protectant against cytotoxic and other illnesses. This review discusses the findings of recent publications, with an emphasis on the special role in metabolic illnesses that differs from the usual therapeutic role, as well as in conditions where less traditional medications are available for treatment. It also discusses the process underlying their use in diabetic and related diseases. Phloridzin has recently been the subject of clinical research and patent applications. Metabolic disorders encompass a wide range of illnesses, including antihypoglycemic, hepatoprotective, nootropic in cognitive impairment, antiinflammatory, and cytoprotective in cancer.

15. Reported Patents on Phloridzin

The literature indicates that Phloridzin patents can be categorized into two types: those containing Phloridzin derivatives and those that combine Phloridzin with other compositions. One notable patent, US 9,248,082 B2, outlines an anti-aging composition that includes a derivative of Phloridzin. This invention revealed that by combining at least one first active ingredient—either phloretin or its derivatives—with at least one second active ingredient from a selection including cinnamic acid, resveratrol, retinol, ascorbic acid, tocopherol, and their derivatives, an effective treatment for radical-induced skin damage can be achieved (Pinnell et al., 20).

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