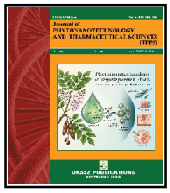
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Phlorizin: Insight into its antidiabetic mechanism and pharmacological applications

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Abstract

The dihydrochalcone phlorizin, which is present in the bark of apple trees, has important pharmacological and antidiabetic qualities. Insulin resistance or deficiency causes hyperglycaemia, the hallmark of diabetes mellitus, a metabolic disease. The principal mechanism of phlorizin is the inhibition of sodium-glucose transporters (SGLT1 and SGLT2), which results in decreased blood glucose levels and increased excretion of glucose in the urine. It reduces the risk of diabetes complications such neuropathy, retinopathy, and cardiovascular illnesses by regulating lipid metabolism and improving insulin sensitivity. Phlorizin has antitumor, antioxidant, antibacterial, antiviral, and hepatoprotective properties in addition to its antidiabetic benefits. Its capacity to control inflammatory reactions, oxidative stress, and cell division highlights its promise as a versatile therapeutic agent.

1. Introduction

Hyperglycaemia is a group of physiological dysfunctions together referred to as diabetes mellitus. It is a direct result of either excessive or inadequate glucagon or insulin production. The pancreatic beta cells are damaged by type 1 diabetes (T1D), an autoimmune disease. This high blood sugar causes the classic symptoms of polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased eating). Three categories have historically been used to categorize diabetes: Insulin-dependent diabetes mellitus (IDDM), also known as type 1 diabetes, is typified by the body's incapacity to produce insulin, requiring the utilization of an insulin pump or injection. This is also referred to as "juvenile diabetes" (Blair, 2016). Insulin resistance, a condition in which cells misuse insulin, whether or not there is a complete lack of insulin, is the root cause of non-insulin-dependent diabetic mellitus, or type 2 diabetes (NIDDM). This kind of diabetes was first referred to as "adult-onset diabetes". The third basic kind of diabetes, known as gestational diabetes, is caused by high blood glucose levels in pregnant women without a history of diabetes. It could happen prior to the onset of type 2 DM (Deshmukh *et al*., 2015).

1.1 Pathophysiology of diabetes mellitus

There is a clear correlation between hyperglycaemia and behavioural and physiological responses. When hyperglycaemia is detected, the brain communicates with the pancreas and other organs *via* nerve impulses in an attempt to mitigate its consequences.

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1.1.1 Type 1 diabetes mellitus

The autoimmune destruction of insulin-producing cells in the pancreas by macrophages and CD^{4+} and CD^{8+} T lymphocytes that enter Langerhans islets is the defining feature of type 1 diabetes. Numerous factors make type 1 diabetes mellitus an autoimmune disease (Al Homsi and Lukic, 1992). the presence of autoantibodies specific to islets, changes in T cell-mediated immunoregulation, particularly in the CD^{4+} T cell compartment, the role of TH1 cells and monoclines in producing interleukins in the disease process, the response to immunotherapy, and the frequency of other organ-specific auto-immune diseases in affected individuals or their relatives were among the factors. These included the presence of accessory and immunocompetent cells in infiltrated pancreatic islets and the relationship between the class II (immune response) genes of the major histocompatibility complex (MHC; human leucocyte antigens HLA) and disease susceptibility. Before starting insulin therapy, 85% of patients had circulating islet cell antibodies and most had detectable anti-insulin antibodies. Most islet cell antibodies specifically target glutamic acid decarboxylase (GAD) on pancreatic B cells (Holt, 2004).

The lack of insulin secretion resulting from the autoimmune destruction of pancreatic β-cells leads to the metabolic disorders associated with type 1 diabetes. Along with reduced insulin production, patients with type 1 diabetes also have increased glucagon release and abnormal pancreatic α-cell activity. hyperglycaemia typically causes a reduction in glucagon production; however, in people with type 1 diabetes, hyperglycaemia does not prevent glucagon release. The ensuing unnecessarily high amounts of glucagon worsen the metabolic abnormalities brought on by insufficient insulin.Insulin insufficiency is the primary aberration in type 1 diabetes; nonetheless, there is a problem with the way insulin is given. Unchecked lipolysis and elevated free fatty acid levels in

plasma are caused by a lack of insulin, and both conditions hinder glucose metabolism of glucose in peripheral tissues such as skeletal muscle. It was clarified that poor glucose, lipid, and protein metabolism are the primary metabolic abnormalities brought on by insulin insufficiency in type 1 diabetes. Additionally, this reduces the expression of many genes required for target tissues to respond appropriately to insulin, including glucokinase in the liver and the GLUT 4 class of glucose transporters in adipose tissue. It also worsens glucose consumption and insulin insufficiency (Cryer, 2012).

1.1.2 Type 2 diabetes mellitus

When these processes malfunction Reduced insulin production as a consequence of pancreatic β-cell malfunction and reduced insulin action as a result of insulin resistance are the outcomes of type 2 diabetes. These are the two primary pathophysiological flaws in diabetes type 2. When resistance to insulin is the norm, the bulk of β-cells changes to become more capable of increasing insulin supply and offsetting the unusual and unreasonable demand. Although, plasma insulin is usually high (during fasting and after meals), it is not enough to maintain normal glucose homeostasis "relative" to the level of insulin resistance. It is nearly hard to isolate the role of each in the etiopathogenesis of DM2, given the close connection between insulin secretion and the delicate balance of glucose homeostasis, which is sensitive to hormone activity (Bearse *et al*., 2004).

Insulin resistance and hyperinsulinemia eventually lead to impaired glucose tolerance. Except for maturity-onset diabetes of the young (MODY), the mode of inheritance for type 2 diabetes mellitus remains uncertain. An autosomal dominant trait called MODY may result from mutations in the glucokinase gene on chromosome 7p. MODY is characterized by hyperglycaemia diagnosed before age twenty-five in situations where islet cell antibodies (ICA) are negative, is manageable for more than 5 years without the use of insulin (Dong *et al*., 2007).

2. Phlorizin

Phlorizin is the precursor of phlorizin, a glycoside that is included in the dihydrochalcone group of flavonoids. Dihydrochalcones, which have been used for a long time to cure liver disorders, are abundant in tea pear leaves. They might be used as a substitute hepatoprotective treatment to stop and treat liver damage brought on by acetaminophen (APAP). Dihydrochalcones from Lithops polystachyus induce apoptosis *via* the mitogen-activated protein kinase pathway, protecting mice's kidneys against cisplatin-induced renal injury. Young leaves, apple fruits, and rhizomes of apples, together with various tissues and sweet tea, are the main sources of phlorizin. Additionally, phlorizin has several positive health effects, especially in the areas of cardiovascular protection, antioxidant, antiviral, and antidiabetic activities (Petersen, 1835).

Numerous studies have demonstrated that phlorizin increases glucose uptake and insulin sensitivity. This, in turn, inhibits the sodium-glucose transporter system (SGLT1) in the mucosa of the small intestine, preventing the absorption of glucose into the bloodstream. Phlorizin has a potent tyrosinase inhibitory action and can help treat a few skin disorders. Therefore, by looking at the sources, extraction techniques, and biological activities of phlorizin, this study aims to give a theoretical foundation for further research on the compound (de Koninck, 1836).

2.1 Chemistry

beta-D-glucopyranosyloxy-glucose, 1-[2-]-4,6-dihydroxyphenyl phlorizin A member of the chalcone class of chemical compounds, -3-(4-hydroxyphenyl)-1-propanone is made up of two aromatic rings connected by an alkyl spacer and a glucose moiety (Figure 1). French scientists extracted phlorizin from apple tree bark in 1835. Based on the antipyretic properties of willow and cinchona tree extracts and the observation that phlorizin's bitter taste was similar to other remedies used in the treatment of malaria, it was assumed that phlorizin had antipyretic properties and could be useful in the treatment of fevers and infectious diseases, especially malaria. In the 1887 Merck Index, phlorizin is classified as a 'Glycosidaus der Wurzelrinde des Apfelbaumes', or 'glycoside from the bark of apple trees (Petersen, 1835). Phlorizin caused glycosuria at dosages higher than 1.0 g, as reported by von Mering in 1886 and later recorded in Merck Index editions (de Koninck, 1836).

At the same time as it was discovered that consuming phlorizin caused glycosuria, diabetes mellitus was recognized as a kidney illness with structural abnormalities, characterized by continuous sugar excretion in the urine and polyuria. Based on the finding that the urine of people with diabetes mellitus and those of phlorizin-treated dogs exhibited similarities, researchers observed that phlorizin diabetes in dogs resulted in weight loss, polyuria, and glycosuria, all of which were indicative of the symptoms of the disease that occur naturally in humans (Merck, 1885).

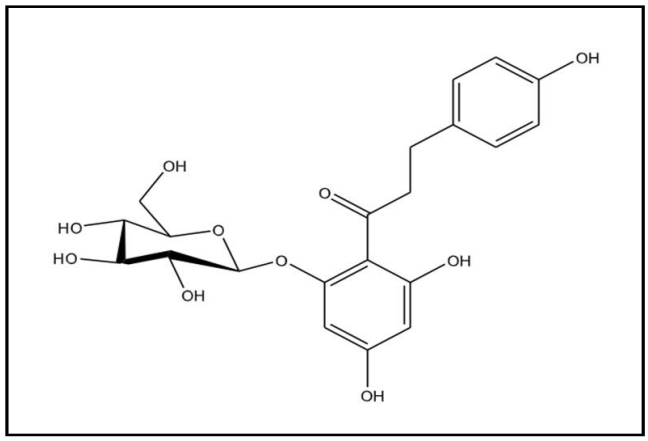


Figure 1: Chemical structure of Phlorizin.

Phlorizin is used as a research instrument to examine renal function in humans because it can cause glycosuria, which indicates the presence of "sound kidneys." This is based on von Mering's observations regarding the effects of phlorizin on the kidneys and the fact that "the production of artificial nephritis in rabbits with cantharidin or chromate may partially or completely abolish the susceptibility to phlorizin." In the 1930s, Homer Smith created non-invasive clearance techniques to assess glomerular filtration rate and renal blood flow in healthy individuals by injecting phlorizin intravenously to cause glycosuria (von Mering, 1886).

Fundamental ideas in renal hemodynamic and tubule-mediated metabolic transport were developed as a result of Smith's investigations on the kidney's excretion of glucose using phlorizin. His research also shown that individuals may safely receive phlorizin intravenously. When, Laveen used phlorizin in an experimental

manner to try to prevent tumor cells from absorbing glucose, he was able to demonstrate the safety of phlorizin administered intravenously to patients in the 1970s. Research into phlorizin's mode of action started to concentrate on its effects on cells and molecules in the 1950s. Phlorizin was first found to inhibit aerobic metabolism and cause mitochondrial swelling at large amounts **(10–4 to 10–3 M). Conversely, concentrations of 10–4 to 10–6 M** prevented glucose from being facilitated transported entered erythrocytes and prevented the kidney and small intestine from transporting sugar. Subsequent investigation into phlorizin's effects on the kidneys revealed that the active transport system causing the kidneys to reabsorb glucose is situated on the brush edge, or luminal membrane, of proximal tubular cells. Phlorizin was discovered to have a 1000-3000 times higher binding affinity than glucose for the renal glucose transporter (Stiles and Lusk, 2012).

2.2 Pharmacokinetics

SGLT2 and SGLT1 are two essential glucose transporters that play a major role in glucose reabsorption in renal tubules. The majority of the glucose that passes through the glomerulus is taken up again by the bloodstream by the SGLT2 glucose transporter, which is low-affinity and high-capacity and expressed in the proximal renal tubules (Zhang *et al*., 2022). The high-affinity, low-capacity transporter SGLT1 is primarily responsible for the absorption of glucose from the gastrointestinal tract. Additionally, the kidney, lungs, and liver all express it (Wang *et al*., 2023).

Blood glucose is entirely reabsorbed by sodium-coupled transporters in the brush boundary membrane from the proximal tubules after being freely filtered by the glomeruli. Almost all of the 144 g of glucose that the glomeruli filter in a 24 h period is reabsorbed in the renal tubules. Glucosuria begins to appear when blood glucose rise to the renal threshold for re-absorption is 180 mg/dl, or 8 to 10 mmol/liter. Based on cell morphologies, the proximal tubule has been divided into S1, S2, and S3 segments. However, more recent ultra-structural analyses of computer-assisted three-dimensional reconstruction of mouse proximal tubules revealed no obvious morphological segmentation of the proximal tubule. There is evidence of variation in sodium-dependent glucose transport along the proximal tubule. For glucose dependent on sodium absorption, the S1 and S2 segments exhibit low affinity and high capacity, while the far portions exhibit increased affinities and poor ability (Bai *et al*., 2022). The S1 and S2 segments, where SGL T2 is present, absorb the majority of the filtered glucose, while the S3 segments, where SGL T1 is present, reabsorb the remaining glucose. Renal glucose transport in individuals with diabetes. Uncontrolled diabetes is known to cause modifications in renal tubular reabsorption; of particular the up-regulation of renal glucose transporters (GLUTs) is significant in this regard. Diabetes causes a decrease in the outwardly directed gradient of extracellular glucose from tubular cells into the interstitial. In order to preserve renal tubular glucose reabsorption in diabetes, up-regulation of SGLT2 is a crucial adaptation1. In the kidneys of diabetic rats, there is an up-regulation of SGLT2 mRNA expression, which may be counteracted by reducing blood glucose levels. Compared to cells from healthy persons, SGLT2 and GLUT2 expression in human exfoliated proximal tubular epithelial cells from fresh urine of diabetic patients is much greater (Z. Wang *et al*., 2019).

Additionally, there is proof that in diabetic rat models, In the renal proximal tubules, the GLUT2 gene is expressed at an elevated level. Given that higher plasma glucose levels are expected to result in greater degrees of glucosuria caused by the inhibitors, uncontrolled diabetes that results in increased expression of SGLT2 has practical implications. Preclinical research using T-109522-24, a nonspecific SGLT inhibitor, has demonstrated this. Interestingly, renovascular hypertensive rat models also exhibit this up-regulation of SGLT2 receptors. The authors conjectured that over-expression of SGLT2 generated by angiotensin II likely plays a role in enhanced Na+ absorption, which in turn causes or maintains hypertension. Rats given either Losartan or Ramipril had significantly lower levels of SGLT2 protein and mRNA as well as immunostaining intensity. Given the high rate of hypertension associated with diabetes, this may be relevant in that condition. First report of SLGTs' therapeutic potential to cause glucosuria. The glucoside phlorizin is composed of a glucose moiety and two aromatic rings (a glycone moiety) joined by an alkyl spacer (Zhang *et al.,* 2017).

French chemists extracted it till apple tree-bark in the 19th century for use as a fever and infectious illness remedy, especially for malaria. For almost 150 years, physiologists have employed phlorizin-which causes glucosuria - as a tool in physiological study since Von Mering noted in 1886. 1975 research found that while glomerular filtration rate and renal plasma flow did not alter, a 60% rise in fractional excretion of glucose was seen in dogs given a phenolizing infusion. In intestinal and renal epithelia, phorizin is a competitive high-affinity inhibitor of glucose transport that is reliant on salt. Consequently, it results in malabsorption from the renal tubules of glucose and galactose and glucose from the small intestine (Turner *et al.,* 2005). In normal rats, phlorizin inhibits the small intestine's ability to absorb glucose during enteric perfusion and results in severe glucosuria. Additionally, it dramatically decreases blood glucose in rats with streptozotocin-induced diabetes and in mice tested orally for glucose tolerance. In animal studies, it enhances counterregulatory responses and lowers the risk of hypoglycaemia (Tian *et al.,* 2021).

In dogs with insulin-deprived alloxan-induced diabetes, Unger's group reported in 1986 that intravenous glucose did not effectively suppress the pronounced hyperglucagonemia. Nevertheless, the hyperglucagonemia was easily suppressible when phlorizin was used to rectify hyperglycaemia. Treatment with phlorizin restored insulin sensitivity to normal in all partly pancreatectomized rats, but it has nil impact on insulin-action inside controls. This suggests that glucotoxicity was reversed, rather than insulin sensitivity being directly affected. By modifying the ambient glucose level irrespective of insulin levels, phlorizin can up-regulate the glucose transport response to insulin in adipose cells according to research on animals. This action may be caused by modifications in GLUT functional activity (Ehrenkranz *et al.,* 2005).

Due to its limited oral bioavailability and lack of selectivity, phlorizin is not a good candidate for betterment as medication for the diabetic cure. These findings give crucial proof of concept evidence. T-1095 is a synthetic derivative of phenylalanine that, in contrast to phenylalanine, enters the bloodstream by oral ingestion and converted to its activated form, (T-1095A). It decreases blood-glucose amount in diabetic mice by increasing urine glucose excretion and inhibiting the action of SGLT1 and SGLT2 in the kidney. Long-term T-1095 therapy resulted in lower blood glucose and glycosylated haemoglobin (HbA1c) levels in obese insulin-resistant yellow KK rat models and diabetic rats caused by streptozotocin. In the diabetic insulin-resistant GK rat-models, severe (T-1095) therapy reduced

blood glucose and HbA1c levels, prevented the development of diabetic neuropathy, and somewhat improved insulin resistance and glucose intolerance. At study's conclusion, no negative side effects were noted. Nevertheless, this medication was never developed to the point of clinical trial, most likely due to its inhibition of SGLT1 (Chen *et al.,* 2022).

The study by Yamaguchi *et al*. (2011) investigates the pharmacokinetic and pharmacodynamic effects of the sodium-glucose cotransporter inhibitor, Phlorizin, on renal glucose transport in rats. The study found that phlorizin exhibits biphasic elimination and fits a two-compartment model. After administration, glucose levels in plasma decreased but normalized within 4 h. Renal glucose clearance (CLR, Glc) increased significantly post-injection and decreased with time. The relationship between CLR,Glc and phlorizin concentration showed that inhibition of renal glucose reabsorption is concentration-dependent, equating to the glomerular filtration rate (GFR). No hysteresis was observed, indicating a direct relationship between phlorizin concentration and its effect on glucose clearance (Yamaguchi *et al.,* 2011).

3. Pharmacological properties

3.1 Antioxidant effect

Phlorizin's pharmacological action had been the interest of much investigation in current years, with a keen eye on examining its possible pharmacological mechanism through the effects of antioxidants. Phlorizin's antioxidant action has been extensively researched and is regarded as a significant factor. Currently, one of the hot research topics is the screening of naturally occurring bioactive compounds with anti-aging qualities (H. Wang *et al.,* 2019). found that phlorizin considerably decreased the amount of malondialdehyde and enhanced the activity of antioxidant enzymes. Phlorizin's antioxidant properties enable it to suppress apoptosis by regulating proteins related to it, improve the biochemical markers of aging animals, and modify the NF-KB/IKB-α/IL-1β signalling pathway NF-KB / IKB- / IL-1. showed that by controlling the Nrf2 protein's expression and genes related to Apoptosis, phlorizin, at least in part, reduced oxidative stress, DNA deterioration and death in (HepG2) cells caused by H_2O_2. Additionally, it has been proposed that phlorizin's cooperation with the body's own stress defence system may act as a partial mediating factor for its antioxidant and anti-aging properties (Liu *et al.,* 2021).

Numerous illnesses, such as diabetes, cancer, and cardiovascular disease, are frequently accompanied by oxidative stress. According to studies, phlorizin can boost the body's production of antioxidant enzymes, including glutathione reductase (GR), catalase (CAT), glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and glutathione Glypeptide peroxidase. As a result, oxidative stress brought on by d-galactose and malondialdehyde (MDA) is reduced in PC12 cells, delaying the aging process (Silva *et al.,* 2020). These enzymes help the body eliminate dangerous free radicals that have accumulated, preserving intracellular redox equilibrium and lessening oxidative stress-induced cell damage. Additionally, phlorizin has been discovered to inhibit several signalling pathways linked to oxidative stress, such as NF-κB, PPARγ, and NADPH oxidase (NOX). By blocking these pathways, phlorizin can prevent inflammatory reactions and Apoptosis, shielding cell from damaging effects of oxidative stress (Zhao *et al.,* 2022).

3.2 Antibacterial effect

Prior research of phlorizin's bacterial inhibition action has been published. *Salmonella typhimurium*, *Listeria monocytogenes*, and *Staphylococcus aureus* are just a few of the Gram positive and Gram-negative that phlorizin has been shown to be able to suppress. Phlorizin's precise mode of inhibition against bacteria is yet unknown, though. According to their research, phlorizin has the capacity to stop *L. monocytogenes* from growing. This implies that phlorizin may be highly effective against *L. monocytogenes* as an antibacterial agent. The decreased energy and protein within cells, the disturbance of the metabolism within cells, and intracellular DNA agglutination are believed to be the mechanisms by which phlorizin inhibits microorganisms (Peterhans and Schweizer, 2013).

Electro spun wound dressings provide antimicrobial, anti-inflammatory, and therapeutic roles in the management of skin wounds. Phlorizin can successfully suppress previous studies have shown that *S. aureus* RN4220 biofilm formation can be reduced by as much as 70% (Sun *et al.,* 2022). Interestingly, bacterial colonization is more likely to occur when CuS nanoparticles are applied to wounds while simultaneously encouraging collagen deposition and re-epithelialization, which aid in wound healing. Phlorizin is thought to have tremendous promise for wound healing, potentially by promoting autophagy and blocking the activation of the mTOR signalling pathway (Slavov *et al.,* 2016).

3.3 Antiviral effect

There is evidence that phlorizin possesses antiviral properties. The impact and mode of action on BVDV infections (Bovine Viral Diarrhoea Viruses) infections were discovered through experimental research. The worldwide cattle sector is greatly impacted by BVDV, a very important virus that causes animals to display distinct strains of B and T cells immunological tolerance (Zhang *et al.,* 2022). Phlorizin limits the pace at which CP BVDV induces beclin-1 levels and LC3B-I to LC3B-II, according to the study's investigation of the underlying mechanism. Studies conducted *in vitro* and *in vivo* showed that phlorizin successfully prevent NCP infection with BVDV. This finding emphasizes the potential as a novel dietary approach to the management of BVDV infection (Lin *et al.,* 2019).

Phlorizin interferes with cellular glucose to prevent Zika Virus infection. Zika Virus (ZIKV) is a resurgent flavivirus linked to neurological conditions including microcephaly. The findings demonstrated that the African genotype (MR766) and the Puerto Rican genotype (PRVABC59) of the ZIKV Virus, had much lower infection titers when exposed to phlorizin. The reduction in the amount of virus was ascribed to host-targeted suppression, which included decreased Akt/mTOR pathway phosphorylation and apoptotic caspase-3 and -7 activity. The study findings showed that phlorizin inhibits the spread of ZIKV, and its ability to block glucose absorption suggests that phlorizin could be a useful starting point for the creation of antiviral medications targeting ZIKV (de Oliveira, 2016).

3.4 Antitumor effect

Phlorizin has been shown to have anti-tumor properties. It is a commonly used medication for a number of disorders. According to 2018 global cancer data (Borggreve *et al.,* 2021), among all malignant tumors globally, oesophageal cancer ranks sixth in terms of death and seventh in terms of morbidity. It is a common tumor of the

digestive system. In recent years, oesophageal cancer survival rates have increased because to neoadjuvant treatment (Liu *et al.,* 2015), less invasive surgery, and current precision radiotherapy; however, overall effectiveness has not increased. Many investigations have shown how important. The JAK/STAT signalling pathway is involved in the onset, progression, and demise of oesophageal cancer (Wang *et al.,* 2014).

Phlorizin has been shown in several studies to prevent proliferation of multiple cancer cells, including HL60 human leukaemia cells, rat mammary adenocarcinoma, human leukaemia, bladder cancer, and B16 Mouse Melanoma. Phlorizin's anticancer effects have been well studied, however despite this, It is distinguished by low solubility in water and lipids, an uncertain mechanism of action, and limited potency. in an effort to overcome these restrictions (Perumal *et al.,* 2023). created a series of derivatives of phlorizin that showed moderate cytotoxicity against a number of cancer cell lines, Including human adenocarcinoma MCF-7, human oesophageal cancer EC109, human lung cancer A549, human non-small cell lung cancer SPC-A1, and human breast cancer MDA-MB-231. These findings show that phlorizin and its derivatives have the potential to be effective inhibitors of cancer cells. Phlorizin's promise *in vivo* anticancer efficacy is further demonstrated by the finding that it dramatically decreased cancerous tumours in mice with liver disease generated by diethyl nitrosamine and $CC1_4$, while also restoring blood biochemical markers (Shin *et al.,* 2012).

Studies reveal that p53 is upregulated and pro-apoptotic JNK and p38 protein kinases are activated, which results in the releasing of Smac/DIABLO and Cytochrome C from mitochondria into the cytosol. By attaching to apoptotic bodies in the Cytoplasm, Cytochrome C triggers Caspase-9, which then triggers Caspase-3. DNA repair enzyme Caspases 3 cleaves DNA disintegration, PARP a characteristic of apoptosis, shows that phlorizin can cause cell death by activating intrinsic pro-apoptotic pathways. Phlorizin's antitumor actions are mostly due to the suppression of pathways that aid in survival, such as AKT and Erk1/2. To summarize, phlorizin inhibits the growth of tumor cells *via* controlling the processes of cell proliferation and death. Moreover, it controls the production of proteins linked to the cell cycle, preventing the cycle's advancement and preventing tumor cells from proliferating and dividing. Additionally, by controlling signalling pathways linked to apoptosis, phlorizin encourages tumor cells to undergo apoptosis and prevents their survival and growth. The key of phlorizin's antitumor activity is its capacity to control cell division and proliferation (Tevar *et al.,* 2010).

3.5 Protecting the liver

Apple peel component phlorizin has been used for more than a century because of its many biological functions, such as liver protection and antioxidant capabilities. In Western nations, One prevalent chronic liver disorder is non-alcoholic fatty liver disease (NAFLD) (Safaei *et al.,* 2016). NAFLD is a broad term that includes a variety of pathophysiological disorders. One such condition is non-alcoholic steatohepatitis (NASH), a condition that may end in hepatocellular carcinoma and cirrhosis. One of the hallmarks of NASH is inflammation (Firneisz, 2014). NAFLD B is regarded as the hepatic a part of the metabolic syndrome associated with obesity and type 2 diabetes (T2D), which is characterized by poor glucose metabolism (Medhat *et al.,* 2020). Research has indicated that improvements in glucose metabolism are correlated with improvements in non-alcoholic fatty liver disease (NAFLD), which reverses the effects of Steatosis and Cytosis and lowers the lipogenic enzymes' activation in the liver. Phlorizin, a dual SGLT1/2 inhibitor, when taken for a brief period of time can improve (NASH) and encourage adjustments to the liver's processing of glucose linked to non-alcoholic fatty liver disease (NAFLD) caused by diabetes mellitus by restoring glycaemic control and hepatic glucose metabolism. Phlorizin has been shown to improve memory and cognitive function in D-galactose-induced mice, reduce oxidative stress, and sustain the activity of natural antioxidant enzymes. It can also maintain the normal shape of nerve cells. Additionally, research on PC12 cells has indicated that phlorizin's interaction with the Nrf2 pathway may be responsible for its liver-protective and antiageing properties(Lee *et al.,* 2013).

3.6 Other pharmacological properties

According to reports, phlorizin significantly reduces the erythema, epidermal thickness, and skin shedding that result from ultraviolet B (UVB) irradiation in nude mice. Additionally, it lessens the HaCaT cells' apoptosis brought on by UVB radiation. The apoptotic signalling pathway of MAPK/NF-κB is thought to be activated as the mechanism underlying these effects (Antika *et al.,* 2017). Moreover, phlorizin has been shown to improve normal human keratinocytes' and fibroblasts' capacity for self-healing. Vascular endothelial cell growth factors are expressed more often and the control of the mTOR signalling pathway are assumed to be linked to this improvement (Yamazaki *et al.,* 2016). Phlorizin dramatically increases the survival rate of cerebral cortical neurons or human neuroblastoma cells (SH-SY5Y) *in vitro* when they are subjected to hydrogen peroxide (H_2O_2) or increased glucose levels (glucose>17.6 mmol·L1). The suppression of SGLT-mediated Na+ and glucose inflow is responsible for this action. Research conducted in living mice has demonstrated that phlorizin administered to the ventricle that is lateral considerably lower the amount of stroke to the brain caused *via* blockage of the middle cerebral artery (MCAO). The working mechanism underlying it decrease is linked to phlorizin's anti-apoptotic signalling and SGLT inhibition (Hirose *et al.,* 2014).

In guinea pigs, phlorizin has been found to significantly inhibit ischemic contracture caused by myocardial ischemia caused by Langendorff cardiac perfusion. It also contributes to the prevention and management of arrhythmias brought on by acute global ischemia. The suppression of Ca^{2+} influx and the control of calcium ion dependence on voltage (Ca^{2+}) channel are thought to be involved in the mechanism of action (Ehrenkranz *et al.,* 2005). Furthermore, phlorizin has shown the capacity to prevent symptoms such as diarrhoea, weight loss, and haemolytic anaemia in mice suffering from acute colitis induced by dextran sulphate sodium. Additionally, it enhances intestinal brush border integrity and colon cell morphology (Najafian *et al.,* 2012). Moreover, it has been discovered that an intraperitoneal injection of phlorizin dramatically reduces the impairment of learning and memory in male ddY mice by preventing cell death in the hippocampus CA3 region caused by bilateral carotid artery occlusion (BCAO). The suppression of SGLT family genes might be the cause of this improvement. All things considered, the results of this study demonstrate the advantages of phlorizin for resistance against memory loss, colitis, heart ischemia, skin loss, and Cerebral-Ischemia improvement. Nevertheless, further research is required to completely comprehend the underlying processes at work (Kashiwagi *et al.,* 2015).

Phlorizin, a sodium-glucose cotransporter (SGLT) inhibitor, has been shown to reduce acute renal toxicity in certain contexts. Specifically, in a mouse model for diabetic nephropathy, phlorizin pretreatment was found to reduce the uptake of streptozotocin (STZ) in the kidneys. This reduction in STZ uptake consequently decreased the direct toxic effects on the kidneys without interfering with the intended â-cell toxicity. This finding is significant because it suggests that phlorizin can mitigate the nephrotoxic effects of STZ, which is commonly used as a diabetogenic agent in experimental models. By reducing STZ-induced kidney damage, researchers can better study diabetic nephropathy without the confounding factor of direct renal toxicity (Brouwers *et al.,* 2013).

Phlorizin, a novel caloric restriction mimetic, has been shown to protect cardiomyocytes in sepsis-induced myocardial dysfunction by activating autophagy through the modulation of the Hif-1α/Bnip3 axis. It works by activating AMP-activated protein kinase (AMPK), which is crucial for cellular energy homeostasis and promotes autophagy (Tian *et al.,* 2022). Phlorizin induces a hypoxic condition, stabilizing hypoxia-inducible factor 1-alpha (Hif-1α), a transcription factor that responds to low oxygen levels. Under these conditions, Hif-1α upregulates Bnip3, a protein that plays a significant role in autophagy by interacting with Beclin-1, promoting the formation and degradation of autophagosomes. This process reduces oxidative stress and apoptosis in cardiomyocytes, improving cardiac function and survival rates in sepsis-induced myocardial dysfunction. Thus, phlorizin enhances autophagy through the Hif-1α/Bnip3 axis, protecting cardiomyocytes from the detrimental effects of sepsis-induced myocardial dysfunction (Yu *et al.,* 2024).

Phlorizin has been studied for its effects on the lungs, particularly in the context of sepsis-induced pulmonary inflammation. It inhibits the sodium-glucose cotransporter 1 (SGLT1) in the lungs, leading to increased glucose concentration in the airway surface liquid, which may exacerbate respiratory infections. In sepsis-induced lung injury, phlorizin treatment was associated with increased bronchial inflammation and atelectasis (collapse of lung tissue) due to SGLT1 inhibition, which affects glucose transport and cellular energy balance. Additionally, phlorizin reduced catalase activity, an important antioxidant enzyme, resulting in increased oxidative stress in the lungs and significantly decreased survival rates in septic rats. While phlorizin has beneficial effects in other contexts, its impact on the lungs, particularly in sepsis, appears to be detrimental due to increased inflammation, oxidative stress, and reduced survival rates (Diamant, 1962).

Phlorizin has been shown to have significant effects on neuroinflammation, particularly through its influence on macrophages and the activation of specific signalling pathways. It reduces the inflammatory phenotype of macrophages, which are key players in neuroinflammatory disorders such as multiple sclerosis (MS). Phlorizin achieves this by activating the nuclear factor erythroid 2–related factor 2 (Nrf2) signalling pathway. This activation is mediated by autophagy, a process where cells degrade and recycle their components, which in turn leads to the degradation of Kelch-like ECH-associated protein 1 (Keap1) and subsequent activation of Nrf2. By promoting Nrf2 activation, phlorizin helps reduce the production of pro-inflammatory mediators and enhances the production of anti-inflammatory mediators and growth factors. This shift in macrophage phenotype from pro-inflammatory to anti-inflammatory contributes to the suppression of neuroinflammation and supports the repair of damaged central nervous system (CNS) tissue (Tian *et al.,* 2018).

4. Phlorizin's antidiabetic mechanism

The world's first SGLT antagonist, SGLT1 and SGLT2 are both specifically and competitively inhibited., resulting in lower blood-glucose levels and higher occurrence of glucose through the Urine. Phlorizin has been demonstrated in studies to considerably enhance lipid metabolism and blood sugar levels in diabetic mice (O'Neill *et al.,* 2015). In diabetic animal models, it improves dyslipidaemia, reduces blood sugar, bringing levels back to normal sensitivity to insulin, promotes insulin sensitivity, and controls renal glucose absorption and intestine microbiota. A typical diabetogenic medication used within animal models (DN) is streptozotocin (STZ) (Greally and Ilson, 2018).

It functions similarly to phlorizin, acting on HMG-CoA Reductase directly to lower Cholesterol production and producing an insulin-like action. In addition, it has been associated with inhibition of phosphodiesterase, decreased secretion of degradation of cAMP, and decreased triacylglycerol [28]. Research has shown that the pharmacokinetic behaviour of phlorizin inside rats with Type II diabetes (T2D) produced by STZ differs significantly from that of normal rats. In comparison to normal rats, the (AUC) and C-max values of (T2D) rates are greater, while the Tl/2 value is less. Moreover, T2D rats have a higher bioavailability than that of normal rats for phlorizin and its metabolites (Zhang *et al.,* 2021).

Phlorizin has proven to have a major effect in reducing the problems related to diabetes. Kidney damage, neuropathy, and cardiovascular and cerebrovascular disorders are frequently among these consequences. Phlorizin can efficiently lessen the danger brought on by this issue through a variety of ways (Lu *et al.,* 2012). carried out research in which rats were given a high-fatty diet to cause diabetes, and they were then given Intraperitoneal Injections of STZ. The outcomes demonstrated that treating diabetic symptoms with phlorizin was beneficial. Phlorizin also demonstrated the capacity to lower blood sugar while fasting, raise blood lipid levels, shield Pancreatic islets from harm, and lessen the buildup of fat in liver cells. Additionally, it was shown that phlorizin protected the eyesight of C57 BLKS/J db/db mice by obstructing Apoptosis and vascular proliferation in response to oxidative stress, and retinal neuropathy. Phlorizin's suppression of glycogen synthase kinase-3, pathway activation, ubiquitin-proteasome pathway modulation, and decreased generation of high-end Glycation End-Products (AGEs) may all be connected to this protective mechanism (Lu *et al.,* 2022).

According to the previously mentioned studies, phlorizin has the ability for successfully reduce blood sugar levels and lessen insulin dependence; both are critical for the management of diabetes. Phlorizin also shows promise in preventing and treating problems associated with diabetes, as well as improving diabetes control by regulating energy metabolism and weight control. Phlorizin's clinical use will be advanced, a thorough knowledge of the processes behind its action will be facilitated, and more effective therapies for diabetic patients will be provided by doing more study (Patlak, 2002).

5. Conclusion

Phlorizin is a potential option for the treatment of diabetes because of its suppression of SGLT1 and SGLT2, which greatly enhances insulin sensitivity and glycaemic control. Its diverse range of pharmacological characteristics, including as antitumor, antibacterial, antioxidant, and viral actions, augment its potential as a therapeutic

agent. Phlorizin has advantages, however its non-selectivity and limited oral bioavailability present problems for clinical use. To fully realize its medicinal potential, future research should concentrate on increasing its bioavailability and investigating synthetic compounds. Phlorizin's potential for the development of innovative therapies for diabetes and its associated problems underscores the necessity of further research into its processes and uses.

Conflict of interest

The authors declare no conflict of interest relevant to this article.

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