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"THERAPEUTIC PROMISE AND CHALLENGE OF PHLORIDZIN: A REVIEW EVIDENCE ON GLUCOSE REGULATION ANTICANCER AND NEUROPROTECTIVE EFFECTS"

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ABSTRACT

Phloridzin is a flavonoid that comes from a variety of sources and is rapidly gaining recognition for its biological action. By controlling the IL-1β/IKB-α/NF-KB signalling pathway, phloridzin can have antioxidant benefits. It simultaneously reduces intracellular DNA agglutination, decreases intracellular protein and energy synthesis, and destroys intracellular metabolism to produce its antimicrobial action. Furthermore, phloridzin has a number of pharmacological actions, including hepatoprotective, antiviral, ant diabetic, and anticancer properties. This article examines phloridzin's plant sources, extraction, and biological activities based on both domestic and international research findings, offering a resource for enhancing phloridzin's therapeutic use.

Phloridzin is a glycoside derivative of Phloretin, a dihydrochalcone that is a member of the bicyclic flavonoid family and a phenolic phytoconstituent. It was initially separated from the apple tree's bark. Phloridzin, also known as phloretin-2′-O-glucoside or PZ, is a significant flavonoid glycoside derivative that is mostly present in apple peels. Other families like as

Fagaceae, Rosacea, and Cucurbitaceous include phloridzin. It is mostly present in raw apples of the Malus species, such as Malus domestica. It is present in the roots, bark, shoots, and leaves of apple trees and is the main phenolic-glucoside. Apple pulp has 4–20 mg/kg of it, whereas an apple peel has 12–418 mg/kg.

Phloridzin is well known for being highly soluble in organic solvents but poorly soluble in water. These days, a variety of techniques are frequently used, such as microwave-assisted extraction, ultrasonic-assisted extraction, and others. Traditional methods mostly depend on organic solvent extraction. The literature now in publication proposes a number of methods for Phloridzin separation, including macro porous resin adsorption. It has been discovered that Phloridzin possesses antiviral properties. The impact and mechanism of Phloridzin on bovine viral diarrhoea virus (BVDV) infection were examined experimentally in a study by Zhang et al. Animals infected with BVDV show strain-specific B and T cell immunological tolerance, making it a highly significant disease that impacts the global cattle sector.

This review offers a thorough synthesis of their taxonomy, chemistry, dietary sources, and bioavailability. With an emphasis on the regulation of vital cellular pathways such PI3K/Akt/mTOR, NF-κB, and AMPK, mechanistic developments pertaining to antioxidant, anti-inflammatory, antibacterial, anti-obesity, neuroprotective, cardio-protective, and anticancer properties are discussed.

KEYWORDS: - Phloridzin, cardio-protective, glycoside derivative, bovine viral diarrhoea virus (BVDV), etc.

INTRODUCTION

Phloridzin, a member of the dihydrochalcone class of flavonoids, is Phloridzin's glucoside. Dihydrochalcone, which are abundant in tea pear leaves, have long been used to treat liver disorders. Acetaminophen-induced liver damage can be prevented and treated with them as a substitute hepatoprotective drug (APAP). Lithops polystachyon dihydrochalcone inhibit cisplatin-induced nephrotoxicity in mice by inducing apoptosis through the mitogen-activated protein kinase pathway. The early leaves, rhizomes, and fruits of apples, sweet tea, and other tissues are the primary sources of Phloridzin. Furthermore, Phloridzin contains several health-promoting properties, such as antiviral, ant diabetic, cardiovascular protection, and antioxidant active.(1)

According to additional research, phloridzin may help lessen Parkinson's disease symptoms by limiting the loss of dopaminergic neuronal cells and the neurotransmitter dopamine,

suppressing apoptosis (by reducing caspase-3,8, and 9, Bax/Bcl-2, and α-synuclein accumulation), regulating nuclear and cellular inflammatory signalling, lowering the expression of pro-inflammatory cytokines (IL-6, IL-1β, and NTFs), and boosting antioxidant activities. Numerous investigations on the physiological impacts, pharmacological actions, production, and distribution of phloridzin and its derivatives have been conducted for decades. The purpose of this review is to provide a detailed summary of Phloridzin's patents and biological uses in metabolic diseases. The clinical limits and potential interventions for their use in different regions of the therapeutic goal are also included in this review.(2)

In guinea pigs, Phloridzin has been shown to significantly reduce ischemic contracture brought on by Langendorff cardiac perfusion-induced myocardial ischemia. Additionally, it helps prevent and treat arrhythmias brought on by acute global ischemia. The suppression of Ca2+ inflow and the control of voltage-dependent calcium ion (Ca2+) channels are thought to be connected to the mechanism of action. Phloridzin has demonstrated the capacity to prevent symptoms including hematochezia, diarrhea, and weight loss in mice suffering from acute colitis brought on by dextran sulfate sodium. Additionally, it enhances the integrity of the intestinal brush border and colon cell shape. Additionally, it has been discovered that intraperitoneal injection of Phloridzin considerably reduces cell death caused by bilateral carotid artery occlusion (BCAO) in the hippocampal CA3 region of male ddY mice, consequently reducing learning and memory deficit in mice. The suppression of SGLT family genes may be responsible for this improvement.(1)

As complementary methods to traditional pharmacotherapy, nutraceuticals have become increasingly popular as preventive and therapeutic agents for the management of chronic diseases. (3) Esculetin (ESC), a naturally occurring coumarin derivative often referred to as 6, 7-dihydroxycoumarin, stands out among these due to its wide range of biological functions. The anti-inflammatory, antioxidant, anticoagulant, and anticancer effects of ESC have been thoroughly studied, and new molecular evidence supports a variety of clinical uses.

New ESC variants with enhanced pharmacokinetic and safety characteristics have been produced by modern synthetic methods, increasing their therapeutic value in pharmaceutical and nutritional contexts. This study supports the incorporation of ESC into comprehensive health management strategies and establishes its diverse functions in disease pathogenesis. (4)

1.1 OVERVIEW OF NATURAL BIOACTIVE COMPOUNDS

Bioactive substances derived from plants, fungus, lichens, and other natural sources have multiple pharmacological significance and greater chemodiversity. Phenolics, alkaloids, tannins, saponins, lignin, glycosides, and terpenoids are some of the main classes of bioactive substances. Numerous scholarly groups have been motivated to investigate the potential uses of these unusual molecules in a variety of sectors, including biomedicine and agriculture. For example, plant metabolites are used as medication sources in medicine and to make environmentally beneficial biopesticides. These phytocompounds have been widely employed by humans as a source of medication since ancient times due to their many health-promoting qualities. Many medication leads have recently been found as a result of the evaluation of natural bioactive compounds for their broad medicinal potential. In order to comprehend the chemistry, analytical techniques, biosynthesis mechanisms, and pharmacological activities of many natural compounds, scientists have come to trust the field of natural products research. Natural product-based treatment is now thought to be the safest and most appropriate alternative medicine. In this sense, meeting the growing demand for natural metabolites from the food, pharmaceutical, and flavour and fragrance industries is an unprecedented challenge. In order to meet the demand for naturally occurring bioactive chemicals, numerous natural resources are being investigated.(5)

According to bioactive compounds are compounds that have a range of effects on cells, including the potential to enhance human health by supporting bodily biological processes. Numerous biological peptide actions have been reported, including antimicrobial, antioxidant, anti-thrombotic, anti-hypertensive, and immunomodulatory. These advantages led to an increase in the commercialization of peptide medicines from 14.1 million dollars in 2011 to 25.4 million dollars in 2018, and they continue to motivate scientists to do extensive research in this area. There are already about 60 peptide-based medications known, which suggests that the number of peptides created will increase dramatically in the near future. (6)

A wide range of structures and functions found in natural bioactive compounds make them a great source of molecules for the creation of food additives, functional foods, and nutraceuticals. Some of those molecules, like polyphenols, are present in nature at large concentrations, but others are only found at very low levels, necessitating massive harvesting to collect sufficient amounts. Additionally, the structural complexity and diversity of these compounds make chemical synthesis unprofitable. Advanced technologies have been developed as a result of the inherent challenges in generating and screening these chemicals. Conventional liquid-liquid or solid-liquid extraction techniques are frequently employed for

their extraction, while more sophisticated techniques include pressurized-liquid extraction, subcritical and supercritical extractions, and extractions aided by microwaves and ultrasounds.(7)

1.2 HISTORICAL BACKGROUND OF PHLORIDZIN

The primary phenolic chemical in apples (Malus x domestica) is the dihydrochalcone phloridzin, which is abundant in the bark, roots, and leaves. Only apples contain large concentrations of phloridzin, while other genera have relatively modest amounts of dihydrochalcones. An unidentified carbon double bond reductase (CDBR) is thought to be the primary branch point enzyme in the phloridzin route, which is a branch of the phenylpropanoid pathway. Finding the CDBR enzyme and comprehending why large levels of this dihydrochalcone are exclusive to apples were the main goals of this thesis.(8)

There are less reports of PT and PZ's anticancer properties. DNA fragmentation indicates that PT inhibits protein kinase C activity and induces death in B16 melanoma 4A5 cells. When extracellular glucose is added, PT-induced death of B16 melanoma 4A5 cells is reversed, indicating that PT is involved in the suppression of glucose transmembrane transport. On Fischer 344 male rats subcutaneously transplanted with FBC cells (methylcholanthrene caused stage 3 transitional cell bladder cancer), significant in vivo antiproliferative effectiveness of PT and PZ was demonstrated. The Fischer bladder carcinoma in vivo tumor model is the name given to this model. Additionally, subcutaneous transplants of mammary cancer (also called mammary adenocarcinoma in vivo tumor model) into Fischer 344 female rats are inhibited by PT and PZ. Both in vitro and in vivo, PT and PZ prevent glucose transfer into viable tumor cells, as determined by the uptake of 2-deoxy-D-glucose by the brain, liver, spleen, and tumor tissue.(9)

Researchers have been using phloridzin as a medicinal product and physiological research tool for more than 150 years. Phloridzin's function in mammalian physiology was the subject of most of the early research on the drug. Only in the latter half of the 20th century was its function in plants examined. French scientists first separated phloridzin from apple tree bark in 1835. Since apple bark accounts for more than 10% of the tissue's dry weight, it is a rich source of phloridzin. Early researchers hypothesized that phloridzin would have comparable antipyretic qualities since they compared its bitter taste to the anti-malarial chemicals obtained from cinchona bark. In a prior work, the phenylpropanoid components of tt5 seeds were profiled using liquid chromatography in conjunction with electrospray ionization quadrupole time of flight mass spectrometry (LC/ESI-QTOF-MS). Compared to wild type Lansberg erecta (Ler) seeds, tt5 seeds accumulated increased amounts of several metabolites,

including three substances that were purportedly identified as dihydronaringenin chalcone hexosides. According to Sumner's (2007) reporting guidelines for chemical analysis, these dihydrochalcones were assigned an annotation level of 2. Based on physicochemical characteristics or spectral resemblance to commercial and public spectrum libraries, putatively identified substances are assigned Level 2. ESI-LC/MS/MS analysis of tt5 seed extracts and commercially available phloridzin and Phloretin standards was carried out by high resolution accurate mass MS to further demonstrate that the dihydronaringenin chalcone hexosides are phloridzin. Spectral data at lower mass accuracy for the parent ion as well as MS2 and MS3 daughter ions that matched phloridzin and phloretin standards were obtained by performing three consecutive rounds of MS fragmentation in the linear quadropole ion trap.(8)

1.3 IMPORTANCE IN MODERN THERAPEUTICS

Consuming a nutritious diet on a regular basis lowers the chance of developing a chronic illness. These days, fruit and vegetable products high in vital phytochemicals like flavonoids and phenols are frequently included in a balanced diet. According to these metabolites have immunostimulant qualities and are physiologically active. One extremely potent phytochemical is phloridzin. Its pharmacological activity may be expanded by additional molecular changes. According to phenolidzin and its derivatives have anti-cancer, anti-obesity, anti-diabetic, antioxidant, anti-aging, anti-microbial, and melanogenic properties. Phloridzin, also known as phloretin-2′-O-glucoside or PZ, is a flavonoid glycoside that is mostly found throughout the apple tree, although it is most prevalent in fruits. Major and minor flavonoids are additional classifications for bioflavonoids. Distinct Flavones, anthocyanidins, and isoflavones are examples of large flavonoids; dihydrochalcones are examples of minor flavonoids. The main components of this final group are phloretin and its glycoside, phloretin-2′-glucose. These substances are mostly present in apples, which are eaten by many people. Phloridzin increased tyrosinase activity and melanin levels in tumor cells by blocking the activity of Protein Kinase C (PKC), according to in vitro research.Phloridzin also enhanced the synthesis of cAMP and phosphorylated cAMP-response element-binding protein (CREB). Overall, the results of this study demonstrate that phloridzin stimulates melanogenesis by increasing tyrosinase gene expression via the cAMP signaling pathway.(10)

A diet rich in fruits and vegetables is believed to lower the chance of developing chronic illnesses. Carotenoids, phenolics, flavonoids, and isoflavonoids are examples of phytochemicals that have been linked to the majority of the beneficial effects of fruits and

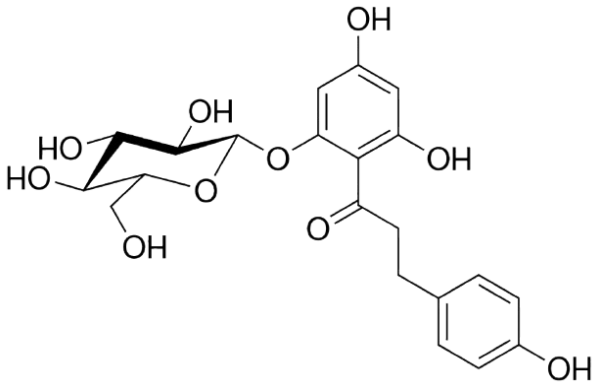
vegetables. We were drawn to the purported photo-genoprotective activity of phloridzin-rich polyphenolic fractions since phenylpropanoids are highly intriguing phenolic components, but their dermo-cosmetic applications are hardly documented in literature. Plasmid DNA was used to assess the phloridzin-rich polyphenolic fractions' anti-ultraviolet protective function mediated by free radical scavenging. Given the growing interest of dermatologists in solar DNA damage.(11)

Phloridzin's primary pharmacological activity is to inhibit the sodium-dependent glucose linked transporters (SGLT1 and SGLT2), which prevents intestinal glucose absorption and causes renal glycosuria. Phloridzin's biological actions include preventing bone loss in rats, improving memory in mice, and inhibiting lipid peroxidation in addition to its antidiabetic properties. Phloridzin increases the expression of the tyrosinase gene via the cAMP signaling pathway, which promotes melanogenesis. It has been found that phloretin, the aglycone of phloridzin, exhibits strong antioxidant action in lipid peroxidation inhibition and peroxynitrite scavenging. Compared to phloretin, glycosylation at 2-OH reduced phloridzin's antioxidant activity by eighteen times.(12)

2.1 CHEMICAL STRUCTURE AND CLASSIFICATION

Natural products have been crucial to human health and wellbeing, particularly those derived from medical plants or herbs. They are typically categorized as alkaloids, sterols, terpenoids, polysaccharides, and polyphenols (such as flavonoids, lignans, stilbenes, and phenolic acids) based on their chemical structures. These varied phytochemical groups are significant sources of beneficial bioactive chemicals and show a wide range of health advantages for humans. Indeed, several of them have been developed into contemporary medicinal medications or used as lead compounds for structural alterations. Additionally, a significant amount of our daily meals consist of plant-based foods including fruits, vegetables, legumes, grains, and nuts that give us vital nutrients. Phloridzin, sometimes referred to as phlorizoside or phlorrhizin, is a member of the class of chemical compounds called flavonoid O-glycosides. Compounds with a carbohydrate moiety that is O-glycosidically bonded to the 2-phenylchromen-4-one flavonoid backbone are known as flavonoid O-glycosides. Phloretin-2 is the chemical name for phloridzin, often known as Phloridzin.-O-β-D-glucopyranoside) is a glucoside of phloretin, a monosaccharide derivative and a member of the dihydrochalcone family of bicyclic flavonoids [6], which is a subgroup in the various plant phenyl-propanoid production pathway. Phloridzin With a molecular weight of 436.4 g/mol and the chemical formula C21H24O10 (Figure 1: 1-Propanone, 1-[2-(β-D-glucopyranosyloxy)-4,6-

dihydroxyphenyl]-3-(4-hydroxyphenyl)-), phenolidzin is a very weak basic (basically neutral) and bitter-tasting molecule. (13)



STRUCTURE OF PHLORIDZIN

Classification of phloridzin

1. FLAVONOID GLYCOSIDE

The Myrtaceae tree Eugenia jumbos L. is primarily found in central and western Guatemala. The leaves' anti-inflammatory and digestive qualities make them popular in traditional medicine. It was discovered that the crude extract has potent anti-inflammatory properties. Flavonoids were identified as the main constituents of leaves during preliminary phytochemical study, which prompted us to look at them further. The isolation and characterisation of two new flavonol diglycosides are described in this work.

2. DIHYDROCHALCONE DERIVATIVE

Dihydrochalcones are a class of flavonoids that lack a heterocyclic C ring and have a simple C6-C3-C6 backbone structure. In the production of flavonoids, dihydrochalcones are regarded as the main precursors and significant intermediates. In plant tissues, dihydrochalcones-primarily phloridzin, sieboldin, trilobatin, and phloretin—represent the predominant flavonoid class. They are found throughout apple trees, particularly in the leaves and young fruits. Because of their bioactivities, dihydrochalcones have recently garnered more attention. For instance, the most prevalent phenolic chemical in Malus plants is phloridzin. controls apoptosis and modifies gene expression to stop cancer cells from proliferating. When normal BALB/c mice are fed a diet containing phloridzin, it lowers their blood glucose levels. (14)

3. PHENOLIC COMPOUND

Phytochemicals, also known as phenolic compounds, are present in a variety of fruits, meals, and drinks. Due to their positive impacts on human health, apples are the focus of the expanding scientific interest in these chemicals. There are, however, few publications on the specific phenolic chemicals found in apple trees. Flavonoids and non-flavonoids are two categories of phenolic chemicals, which are secondary metabolites found naturally in plants. Benzoic and cinnamic acids are examples of phenolic acids, which are subclasses of non-flavonoids. Flavonols, flavones, flavan-3-ols, flavanones, isoflavones, anthocyanidins, and chalcones are subgroups of flavonoids. The health benefits of phenolic chemicals are diverse. They can serve as antioxidants, lower inflammation, prevent cancer and heart disease, and prevent obesity and excessive cholesterol. It is well known that phloridzin has an antihyperglycemic effect. Phloridzin-containing apple leaves were shown to have an antihyperglycemic effect in healthy volunteers and to significantly inhibit the postprandial rise in blood glucose levels in mice. According to a recent review by Tian et al., this impact is achieved via the inhibition of sodium-dependent glucose transporters (SGLTs), primarily SGLT1 in the intestinal epithelial cells. (15)

4. NATURAL POLYPHENOL

Two cytotoxic lipid-derived R,?-unsaturated aldehydes that have been linked to the emergence of diseases linked to carbonyl stress are acrolein (ACR) and 4-hydroxy-trans-2-nonenal (HNE). In order to find efficient ACR and/or HNE scavenging agents under physiologically simulated conditions, 21 natural polyphenols were evaluated. It was discovered that by acting as sacrificial nucleophiles, flavan-3-ols, theaflavins, cyanomaclurin, and dihydrochalcones successfully captured ACR and HNE. Phloretin was the most successful, quenching up to 90.1% HNE in 24 hours and 99.6% ACR in 90 minutes. These useful polyphenols created adducts with ACR and HNE, according to further LC-MS/MS research. Phloretin with ACR produced a significant adduct that was isolated and identified as diACR-conjugated phloretin by LC-MS and NMR spectroscopy. Polyphenols have historically been used to prevent lipid peroxidation by using their antioxidant activity to combat pro-oxidation variables that may cause or speed up lipid peroxidation (18). However, the potential negative consequences of secondary products, particularly RCS produced by oxidative stress, were not taken into account in this strategy to stop lipid peroxidation. (16)

2.2 NATURAL SOURCES AND DISTRIBUTION

2.2.1 Natural sources

An essential phytochemical called phloridzin was initially identified in apple tree bark. One of the most popular fruits consumed worldwide, apples are a significant source of polyphenols and belong to the dihydrochalcone family, which is primarily found in plants of the Malus species. Phloridzin is one of the many beneficial biological activities of polyphenols found in apples, and there is ample evidence that regular apple eating improves human health. (13)

A member of the Rosaceae family, hawthorn (Crataegus) is produced all over the world as a culinary and medicinal plant. Because of its abundance of bioactive compounds, it is referred to as the "nutritious fruit." Its preparations are used to make pharmaceuticals, functional foods, and nutritional supplements. Hawthorn has a great medicinal and health value since it is rich in amino acids, minerals, pectin, vitamin C, chlorogenic acid, epicatechol, and choline. Hawthorn has been demonstrated in numerous studies to have antioxidant, anti-inflammatory, anticancer, anti-cardiovascular disease, and digestive-improving qualities. This is associated with its bioactive constituents, which include polyphenols (chlorogenic acid, proanthocyanidin B2, epicatechin), flavonoids (proanthocyanidins, mucoxanthin, quercetin, rutin), and pentacyclic triterpenoids (ursolic acid, hawthornic acid, oleanolic acid). (17)

2.2.2 Distribution

Phloridzin belongs to the chalcone class of chemical compounds and is mostly found in plants belonging to the genus Malus, while it has been shown to be present in other plant species. Phloridzin plays a role in the breakdown of lactose in humans. Furthermore, phloridzin is typically present in lower concentrations in pomegranates and apricots but in higher concentrations in select foods, such as Mexican oregano, European plums, and apples. Additionally, phloridzin has been detected in a number of different foods. (13)

3. PHYSICOCHEMICAL PROPERTIES

Phloridzin, a phloretin 2′-β-D-glucoside, is a dihydrochalcone that is mostly found in the fruits of Malus pumila Mill., Lithocarpus polystachyus REHD, and the root skins, stems, tender leaves, and fruits of Malus hupehensis. It has numerous pharmacological effects, including controlling blood pressure and blood sugar, shielding the heart, scavenging oxygen free radicals, and preventing oxidative damage. As a result, the market for phloridzin-containing products is growing annually. The findings of our study showed that phloridzin has the ability to alter both estrogenic and antiestrogenic actions in both directions. In the

absence of estrogen, it had a notable impact on the growth of estrogen-sensitive estrogen receptor (ER) (+)MCF-7 cells. Phloridzin had antagonistic effects on estradiol-induced MCF-7 cell proliferation when combined with 17β-estradiol, but it had no discernible effect on the proliferation of estrogen-insensitive ER (−)MDA-MB-231 cells. β-galactosidase activity was induced by phenolidzin in a two-hybrid yeast experiment. When the glucoside was given orally for seven days, there was a little rise in the mouse's uterus weight and serum estradiol concentration. Phloridzin was mostly detected in the blood following oral dosing, with a tiny amount being converted to phloretin. Our study demonstrated that phloridzin functioned as a phytoestrogen and was distributed at the target organ. (18)

4. PHARMACOKINETICS AND METABOLISM

The conjugated metabolites that are eliminated in bile and the portion of flavonoids that are not absorbed by the small intestine will be exposed to the microbiota in the large intestine. From heterocyclic and A-ring fission to breakdown into phenolic acids and lactones, these bacteria can produce a wide range of metabolites. The primary metabolites include hydroxylated derivatives of phenylvaleric, phenylpropionic, phenylacetic, and benzoic acids as well as hydroxylated phenylvalerolactones. Glycine and benzoic acids are conjugated to produce hippuric acid and its hydroxylated derivatives. Similar to flavonoids, these substances are often eliminated in urine and may exist as conjugates as a result of Phase II metabolism.The first substance identified as a sodium-glucose cotransporter (SGLT) inhibitor was Phloridzin (PHZ), a kind of dihydrochalcone that is commonly found in Rosaceae, including apples. It has been shown to successfully alleviate diabetes symptoms and consequences. Similar to other flavonoids, PHZ's broad phase I and II metabolism in the digestive tract poses a bioavailability difficulty. In this investigation, we examined the pharmacokinetics and role of phase II metabolism following oral and intravenous PHZ treatment in both normal and type 2 diabetic rats. By applying β-glucuronidase/sulfatase to plasma samples, the phase II metabolic properties of PHZ were examined. Following intravenous injection of three dosages of PHZ in normal rats, the contribution ratio of phase II metabolism of PHZ varied from 41.9% to 69.0%. AUC0−t and Cmax of PHZ were substantially higher in T2D rats than in normal rats, but T1/2 of PHZ was much lower. An enzyme-catalyzed hydrolysis reaction changed PHZ into phloretin (PHT), which was then further turned into conjugates with glycose following intravenous and oral administration. Additionally, it was discovered that T2D rats had a bioavailability of PHZ of roughly 5%, which was much higher than that of normal rats (0%). In conclusion, oral and intravenous

PHZ administration considerably altered the pharmacokinetic properties of the drug in T2D rats when compared to the findings for normal rats.

5. ABSORPTION AND BIOAVAILABILITY

Dietary flavonoids must be liberated from plant meals by chewing, the action of digestive juices in the gastrointestinal tract, and ultimately the microbes of the colon before they can be absorbed from the gut. The type of plant food, the conditions under which it is processed, and the presence of other dietary components can all influence this release from the plant tissues, the so-called food matrix. Its physico-chemical characteristics, including molecule size and configuration, lipophilicity, solubility, and pKa, will determine how well the flavo-noid released from the food is absorbed. The impact of the plant food matrix on absorption is currently only partially understood. There are no reports of well-designed studies that tackled this problem. (19)

In humans, the absorption of dietary flavonol glycosides ranged from extremely fast to extremely slow. Peak concentration times (Tmax) ranged from less than 0.5 to nine hours (Table 1). Onion-derived quercetin glucosides had better bioavailability. The bioavailability of pure quercetin rutinoside and other quercetin glycosides (b-galactosides and b-xylosides) from apples was only 30% of that from onions (Hollman et al., 1997). Therefore, when pure quercetin-b-glucoside or pure quercetin-b-rutinoside were given to healthy human volunteers, the sugar moiety of quercetin glycosides appeared to be a significant glucoside predictor of their bioavailability (Hollman et al., 1999). After consuming the rather than the rutinoside, the peak concentration of quercetin (Cmax) in plasma was 20 times greater and reached (Tmax) more than 10 times faster. (19)

6. EXCRETION

Phloridzin has a melting point of 110 °C and breaks down beyond 200 °C. It is solid at room temperature, poorly soluble in ether and cold water, but soluble in ethanol and hot water. The extraction process for phenolidzin is comparable to that of other phenolic compounds. According to Alberti et al., phloridzin had greater yields (48.4%) in extractions using methanol, and response surface methodology is a suitable strategy for phloridzin extraction from apples. Zhang et al. discovered that compared to the conventional solvent extraction with 35% and 80% ethanol, an ultrasound-assisted aqueous two-phase extraction strategy had several advantages, including lower ethanol consumption, lower impurity of sugar and protein, and higher extraction efficiency of phlo-ridzin. According to Paudel et al., phloridzin

from black raspberry (Rubus occidentalis L.) fruits was extracted in ethyl acetate, separated using semipreparative analytical HPLC, and examined using nuclear magnetic resonance (NMR), HPLC–electrospray ionization mass spectrometry (ESI-MS), and ESI-MS/MS.

Phloridzin is currently separated and purified primarily using chemical extraction, high-speed countercurrent chromatography (HSCCC), resin adsorption technology, and preparative HPLC techniques. Dong et al. used thin layer chromatography (TLC) and HPLC-ESI-MS to isolate, analyze, and identify 99.87% pure phloridzin from the crude extract of Lithocarpus polystachyus. According to Fromm et al., phloridzin from apple seeds can be selectively enriched and further purified using resin adsorption technique. Liang et al. discovered that the HSCCC–HPLC–diode array detector–mass spectrometry (HSCCC-HPLC-DAD-MS) approach was a quick, easy, and efficient way to obtain phloridzin from Malus doumeri leaves with a high purity (above 99%). The produced magnetic molecularly imprinted polymers (MMIPs) were shown by Gao et al. to be appropriate for the selective adsorption of phloridzin from complex substances, including biological samples and natural medicine plant extracts. According to Li et al., phloridzin was purified from apple leaves using macroporous resin and a preparative HPLC process; following additional recrystallization, the phloridzin purity exceeded 98% with a recovery yield of 75.8%. (13)

7. MECHANISMS OF ACTION

7.1 INHIBITION OF SODIUM-GLUCOSE COTRANSPORTERS (SGLTS)

Clinicians treat type 2 diabetes with SGLT2 inhibitors, an insulin-independent class of oral antihyperglycemic drugs. SGLT2 inhibitors are successful at lowering blood glucose levels, according to several key clinical trials, but it's crucial to know when to use them. For individuals with a history of cardiovascular or renal disease who require additional hemoglobin A1c reduction, SGLT2 inhibitors are the most advantageous adjunct medicine to metformin.

We are discovering SGLT2 inhibitors. Serum alanine aminotransferase levels are clinically much lower in diabetic patients with non-alcoholic fatty liver disease, who are more likely to develop cirrhosis and hepatocellular carcinoma. SGLT2 inhibitors are also useful in lowering systolic blood pressure and body weight in obese people. Currently under investigation, dual SGLT1/SGLT2 inhibitors may be the first oral treatment for type 1 diabetes. (20)

Results from DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events), the biggest SGLT2 inhibitor study to date, have recently been examined and released.29 This study evaluated the safety and cardiovascular effects of 10 mg once daily dapagliflozin in

individuals with type 2 diabetes. This study examined secondary prevention (diabetes and established cardiovascular disease) and primary prevention (diabetes and several risk factors, including dyslipidemia, hypertension, and current tobacco use). Crucially, almost 10,000 diabetic patients without atherosclerotic cardiovascular disease were included in this investigation. (20)

7.2 EFFECTS ON BLOOD GLUCOSE LEVELS

Using Caco-2 intestinal cell monolayers, the impact of polyphenols, phenolic acids, and tannins (PPTs) from apples and strawberries on glucose absorption and apical to basolateral transport was examined. Apple and strawberry extracts were found to significantly limit both absorption and transport. We demonstrate that the inhibition of GLUT2 was higher than that of SGLT1 under sodium-containing (glucose transporters SGLT1 and GLUT2 both active) and sodium-free (only GLUT2 active) circumstances. A few of the component PPTs were evaluated in addition to the extracts' analysis. While pelargonidin-3-O-glucoside (IC505802 mM) contributed 26% of the total inhibition by the strawberry extract, quercetin-3-O-rhamnoside (IC50531 mM), phloridzin (IC505146 mM), and 5-caffeoylquinic acid (IC5052570 mM) contributed 26, 52, and 12% of the inhibitory activity of the apple extract. (21)

Although the industrial worth of fruits has long been acknowledged, the enormous and mostly unrealized potential of fruit tree leaves has only recently come to light. The current study investigated the physiological effects of apple leaf extract in mice. We also looked at the potential applications of the active principle or principles and tried to clarify them. When compared to control animals, apple leaf extract increased the quantity of residual glucose in the small intestine and inhibited postprandial rising of the blood glucose level in glucose-loaded mice. An examination of its spectrum data revealed that the active component obtained from bioassay-guided fractionation was phloridzin, a recognized SGLT inhibitor. Ethanol extraction from apple tree leaves produced the best results in terms of an anti-hyperglycemic impact. As the extraction process heated up, these impacts diminished. The extract did not cause hypoglycemia at a normally effective dose, and the inhibitory effects on glucose absorption were not thought to be associated with unspecific gastrointestinal impairment because bolus ingestion of the extract did not affect blood glucose levels in normal mice with or without an overnight fast. As a result, apple tree leaf portions could be a good industrial resource for preserving health in the future. (22)

7.3 IMPACT ON INSULIN SENSITIVITY

Diabetes is characterized by insulin resistance. We investigated the impact of Phloridzin therapy on tissue sensitivity to insulin in partly pancreatectomized rats in order to determine the function of hyperglycemia in the development of insulin resistance. Group I comprised sham-operated controls; group II comprised partially pancreatectomized diabetic rats with moderate glucose intolerance; group III comprised diabetic rats treated with Phloridzin to restore glucose tolerance; group IV comprised Phloridzin-treated controls; and group V comprised Phloridzin-treated diabetic rats reexamined following Phloridzin discontinuation. The euglyemic hyperinsulinemic clamp technique was used to measure insulin sensitivity in awake, stress-free rats. In diabetic rats, insulin-mediated glucose metabolism decreased by roughly 30% ($P < 0.001$). Insulin action in controls was unaffected by Phloridzin administration, whereas insulin sensitivity in diabetic rats was fully restored. Insulin resistance reappeared in Phloridzin-treated diabetic rats when the drug was stopped. These findings show that (a) insulin resistance develops when f-cell mass is reduced, and (b) insulin sensitivity is restored when hyperglycemia is corrected with Phloridzin without affecting insulin levels. (23)

The body's capacity to react to a physiologic increase in the plasma insulin concentration is improved but not normalized by intensified insulin therapy, according to the results of such studies (22–27). This suggests that at least some of the insulin resistance is acquired. However, since treatment simultaneously corrects both the insulin deficiency and its resulting metabolic disturbances, these observations do not determine whether the development of insulin resistance is caused by some metabolic derangement that occurs secondary to the insulin deficiency or insulin deficiency per se. (23)

7.4 EXPERIMENTAL AND CLINICAL EVIDENCE OF PHLORIDZIN

Diabetes is a metabolic disorder marked by either an acquired (type II non-insulin-dependent diabetes mellitus) or congenital (type I insulin-dependent diabetes mellitus) incapacity to carry glucose from the blood to the cells. Insulin resistance or insufficient insulin secretion cause hyperglycemia. Type II diabetes affects around 90% of diabetic individuals, and during the next 25 years, the prevalence of diabetes will increase globally. The goal of diabetes treatment is to slow the disease's progression, which causes consequences such retinopathy, nephropathy, and neuropathy.

Digestive enzymes hydrolyze dietary carbohydrates. Monosaccharides are produced when α-glucosidase breaks the α-glucoside linkages in disaccharides like maltose. The Na+/glucose cotransporter (SGLT1), which is found on the mucosal side of epithelial cells, then

aggressively absorbs the resultant monosaccharides from the small intestine. The SGLT1 is reported to have a high level of substrate specificity. Disaccharides are not substrates for the SGLT1 transporter, which is responsible for the absorption of glucose and galactose from the small intestine. Since SGLT1's identification of glucose represents the initial stage of glucose absorption, inhibiting it may be one of the best ways to prevent blood glucose levels from rising after a meal.

7.5 COMPARISON WITH SYNTHETIC SGLT INHIBITORS

O-glucoside Phloridzin is the source of SGLT2 inhibitors, which reduce blood glucose by preventing renal glucose reabsorption. Additionally, their method modulates sodium-hydrogen exchange in the kidneys and heart while encouraging osmotic diuresis and urine salt excretion. Together, these actions lower cardiac preload, plasma volume, blood pressure, and body weight. Erload et al., thereby aiding in the management of heart failure. The objective of this study was to improve the gastrointestinal absorption and pharmacological efficacy of O-glucoside derivatives for the treatment of heart failure, as well as to increase the inhibition of the SGLT2 protein. Heart failure is very difficult to treat, and there are currently no effective medications for heart failure with preserved ejection fraction (HFpEF). Two antidiabetic sodium-glucose cotransporter 2 (SGLT2) inhibitors, dapagliozin (DAPA) and empapagliozin (EMPA), have been shown to significantly lower mortality in HFpEF patients with and without diabetes. Nowadays, C-glucoside derivatives make up the majority of SGLT2 inhibitors utilized in clinical practice. Long-term use of these substances may put a significant strain on the kidneys, especially in individuals who already have renal insufficiency.

7.6 MECHANISMS OF ANTICANCER ACTIVITY

Phloretin's anticancer effects on several cell lines, including prostrate, lung, oral, breast, and liver, have been well investigated and reported. Numerous researchers have documented phloretin's anticancer effect by apoptosis induction, cell growth inhibition, and cell cycle regulation; additional study has documented phloretin's role in causing mitochondrial-mediated apoptosis in cancer cell lines . Phloretin and phloretin nanoparticles (PhNPs) have been shown to cause apoptosis in cancer cell lines by downregulating the expression of Bcl-2 and upregulating BAX, cytochrome c, PARP, caspases 3 and 9, and apoptotic activating factor (APAF). In their study, Mariadoss et al. showed that positively charged PhNPs caused the outer membrane of the mitochondria to become permeable, which in turn caused proapoptotic proteins to be released and mitochondrial-derived caspases to be activated, resulting in apoptotic cell death. According to Xu et al.'s study, phloretin has a positive

impact on human gastric cancer by encouraging apoptosis through G2/M cell cycle arrest and by reducing JNK activity, which suppresses cell invasion. In a different study, a ruthenium phloretin complex caused breast cancer cells to undergo apoptosis by modifying p53 activity and p53-mediated stimulation of apoptotic events exhibited by p21, Cyt-C, caspase 9, cleaved caspase 3, Bax signaling, and downregulating Bcl-2 mediated signaling. This study sheds insight on the ruthenium phloretin complex's advantageous qualities in stopping the spread of breast cancer, making it a viable option for next cancer chemotherapeutics. Numerous studies have emphasized how phloretin inhibits the type 2 glucose transporter (GLUT2) in cancer cells and induces apoptosis, which stops the metastasis process. Researchers have demonstrated that phloretin-induced glucose deprivation, which results in ATP depletion and the triggering of the mitochondrial death pathway cascade, is responsible for the G0/G1 cell cycle stop in cancer cells produced by GLUT2 inhibition. Phloretin caused a G0/G1 arrest in human glioblastoma cells and enhanced the expression of p27, which further lowered the levels of CDK-2,4,6, and cyclin D and E, leading to apoptosis and decreased cell proliferation Additionally, phloretin's potential benefits as a phytochemical in cancer have been demonstrated by numerous isolated investigations that have validated its involvement in causing apoptosis and cell cycle arrest . In the current situation, thorough in vivo investigations are required to clarify the pathways and mechanisms involved and to transfer the research from the bench to the patient's bedside while bearing in mind phloretin, a powerful therapeutic anticancer agent.

7.7 EFFECTS ON CELL PROLIFERATION AND APOPTOSIS

Skin cancer is one of the most prevalent cancers among Caucasians, and its incidence rates are constantly rising globally. It is divided into two categories: melanoma (MM) and non-melanoma skin carcinomas (NMSCs). MM is one of the most aggressive and deadly solid tumor kinds. Numerous reports have linked UV light exposure to a higher incidence of the mutations that cause MM. Conversely, NMSC includes squamous (SCC) and basal (BCC) cell carcinomas, which are the most prevalent cancers among Caucasians and are distinct forms of keratinocyte carcinomas. Increased exposure to ultraviolet radiation (UVR) has also been associated with an increased incidence of NMSC; nevertheless, compared to MM, its metastatic potential and fatality rates are still comparatively modest. Numerous studies have demonstrated the anti-microbial, anti-oxidant, anti-inflammatory, anti-cancer, and anti-mutagenic characteristics of flavonoids, a significant class of polyphenols. Phloridzin (Phloridzin or phloretin 2′-O-glucoside), one of the main flavonoids in apples, has been shown to have anti-cancer activities against lung, liver, and colon cancer cell lines together

with a number of other hydrochalcone chemicals. Furthermore, it was demonstrated that cryptocaryone and other dihydrochalcone chemicals cause human prostate cancer cells to undergo apoptosis caused by tumor necrosis factor alpha-related apoptosis-inducing ligand (TRAIL). Chalcone derivatives have also been shown to exhibit anti-proliferative properties and to reduce invasiveness in breast cancer cells. According to a recent study, acylation of flavonoid glucosides (containing long chain fatty acids) and their esterification by Lipase B produce fatty acid esters of phloridzin that can cause cytotoxicity in blood, breast, and liver cancer cells as well as induce cell cycle arrest, suppress DNA topoisomerase IIa, and trigger apoptosis. Interestingly, among the other ester molecules, decosahexaenoic acid ester of phloridzin (PZDHA) was determined to be the most promising; hence, its effects were further investigated in later investigations. More precisely, after being exposed to lipopolysaccharide (LPS), PZDHA was demonstrated to have anti-inflammatory qualities in THP-1 differentiated macrophages. Furthermore, it was shown that PZDHA specifically killed breast cancer cell lines while having no effect on non-malignant breast cells. Further studies using breast cancer cell lines and breast cancer Xenograft models demonstrated activation of apoptosis, induction of cell cycle growth arrest (at G2/M phase), and general inhibition of tumor growth.

Nevertheless, no research has yet been done on how PZDHA affects skin cancer experimental models. In order to do this, we used two distinct skin cancer cell lines, A375 (MM) and A431 (NMSC), along with a non-tumorigenic immortalized keratinocyte (HaCaT) cell line, in our in vitro model of skin cancer. The latter was employed as a control, a non-cancerous cell type that is mostly found in the epidermis and the skin's basal layer (basal keratinocytes). Our hypothesis is that, in comparison to the non-tumorigenic cell line, the cancer skin cell lines would be selectively more susceptible to PZDHA-induced cytotoxicity. (24)

7.8 EVIDENCE FROM IN VITRO AND IN VIVO STUDIES

Provided proof that phloridzin exhibited antiaging effects on yeast via boosting SIRT1 and superoxide dismutase (SOD) activity. Phloridzin decreased the progression of polycystic kidney disease in a rat model through the MAPK signaling pathway, according to Wang et al., According to Pei et al., phloridzin may protect the kidneys by controlling differentially expressed proteins that have an impact on tubular transport, glomerular dysfunction, oxidative stress, and lipid metabolism. Wang and associates. (13)

7.9 MECHANISMS OF NEUROPROTECTION

Phloretin (PH) and its glucoside derivative, phloridzin (PZ), belong to the class of phenyl propanoids known as dihydrochalcones. High levels of PH and PZ are found in the apple tree (Malus sp.), and it is believed that PH and PZ are responsible for the antidiabetic effect of

apples. Chalcone derivatives have demonstrated numerous protective effects. Previous studies have reported that PH has anti-inflammatory, anti-oxidant, and neuroprotective effects. Additionally, PZ has been shown to have cytoprotective and neuroprotective properties. PH and PZ shown anti-cancer activities in addition to their cytoprotective and antioxidant properties. Additionally, it has been demonstrated that PH and other chalcone derivatives shield liver cells from damage caused by toxicants. Because of their anti-inflammatory and antioxidant properties, PH and PZ shield cells against toxins. Numerous research on the preventive effects of PH and PZ have been published in the literature; however, there is no evidence regarding how PH and PZ affect neurotoxicity brought on by cancer treatment.

We sought to treat chemotherapy-induced neuronal damage by combining PH and PZ treatment with chemotherapeutics due to their neuroprotective and anti-cancer properties. (25)

7.10 ANTI-OXIDATIVE STRESS AND ANTI-INFLAMMATORY ACTIONS

Natural substances that belong to the class of bicyclic flavonoids include phloretin and its glycosylated counterpart, phloridzin, a dihydrochalcone. The primary sources of these natural chemicals are unripe apples, apple tree roots, and trace amounts of strawberries. Natural sources can contain these dihydrochalcones together with other polyphenols such quercetin, catechin, epicatechin, procyanidins, and routine. Scientists have recently become interested in the bioactivity of dihydrochalcones, an uncommon class of natural antioxidants. For instance, the anti-inflammatory and hepatoprotective properties of a common dihydrocolic phloretin have been studied in mouse models. Additionally, phloridzin (phloretin 2′-β-d-glucoside) has been proposed to have cytoprotective and neuroprotective properties18. These bioactivities can be linked to these substances' antioxidant capability from the perspective of medicine and free radical biology. The presence of the 2,-OH group in phloretin and phloridzin flavonoids has actually been shown to have an antioxidant effect; in fact, these molecules have been shown to be greater antioxidants than the well-known flavonoids. The preventive effects of these natural compounds on indomethacin-induced peptic ulcer in mice will be examined in this study based on the biological activations of phloretin and phloridzin, as well as the existence of inflammatory response and oxidative damage in peptic ulcer injury. (26)

7.11 PRECLINICAL AND CLINICAL EVIDENCE

Historically, the development of compounds that increase endogenous insulin production and/or improve insulin sensitivity has been the main focus of therapeutic approaches to reduce hyperglycemia. On the other hand, substances that improve glucose excretion through the kidneys have long been recognized. Since its initial isolation from the bark of an apple tree in 1835, phenolizin, a naturally occurring phenol glycoside, has proven to be a valuable tool for studying the mechanisms of glucose and electrolyte transport in renal tubules. Early research on animals revealed that oral Phloridzin consumption resulted in renal glycosuria and weight loss without hyperglycemia; similar results were later verified in humans. Investigating the mechanics of glucose and electrolyte transport in renal tubules has been made easier by the discovery of an apple tree in 1835. Early research on animals revealed that oral Phloridzin consumption resulted in weight loss and renal glycosuria without hyperglycemia; these results were subsequently verified in humans. Phloridzin was known to block glucose transport into erythrocytes and to inhibit glucose transport in the kidney and small intestine by the early 1950s. However, the mechanisms and possible significance of Phloridzin-induced renal glycosuria did not come to light until the sodium–glucose co-transporter-2 (SGLT2) was fully characterized in the early 1990s. We now know that Phloridzin's non-selective, competitive inhibition of both SGLT1 and SGLT2 is believed to be a key mechanism for improving glucose and energy disposal in diabetic individuals. Insulin sensitivity significantly improved after administration to partly pancreatectomized rats, as measured by the euglycaemic hyperinsulinaemic clamp letters. (27)

8. OTHER PHARMACOLOGICAL ACTIVITIES

8.1 CARDIOPROTECTIVE EFFECTS

It is now commonly acknowledged that diabetes mellitus is a serious health risk. Diabetic cardiomyopathy (DCM), one of the most common circulatory consequences of diabetes, directly damages heart tissue. DCM can potentially cause cardiac failure when it reaches its ultimate stage. Abnormal activation of cardiomyocytes linked to aberrant cellular metabolism, persistent inflammation, and fibrosis constitute the underlying pathophysiological mechanism. Abnormalities in vascular dynamics and cardiac function could result from these changes. The development of medications that can successfully postpone myocardial remodeling and cure diabetic heart disease is crucial due to the morbidity and mortality linked to these conditions. DCM and inflammation are intimately associated, according to recent data. In vivo DCM formation and progression are facilitated

by hyperglycemia, which triggers the inflammatory cascade. In summary, there is growing recognition of the mechanism behind DCM. (28)

Several natural flavonoid compounds with anti-inflammatory properties have been investigated to see if they could be safe and effective treatments for DCM. Apple and pear trees contain a chemical called phloretin, which has been shown to have strong anti-inflammatory properties. Numerous studies have demonstrated that it can have several positive effects. impacts on cardiovascular function, such as reducing sepsis in rats, boosting adipocyte lipolysis, controlling glucose transporter activity, and preventing macrophages and dendritic cells from releasing inflammatory cytokines in response to lipopolysaccharide (LPS). (29)

8.2 ANTI-OBESITY POTENTIAL

Clinically significant, obesity is a common but treatable illness. It is frequently regarded as a risk factor for the emergence of many illnesses and disabilities. Every age group and practically every location of the world has a high prevalence of obesity. The health care system is heavily burdened by the rising incidence of obesity. Significant health advantages are linked to weight loss during obesity. Diet treatment, exercise, and lifestyle changes are all effective methods for losing weight**.** (30)

In high-fat diet-induced obese mice, phloridzin suppresses visceral and subcutaneous fat formation and prevents adipocyte hypertrophy. Metabolic diseases are caused by both subcutaneous and visceral fat. Additionally, the phloridzin decreased the weight of all white adipose tissue. Impaired insulin resistance and secretion, diabetes, hypertension, inflammation, and dyslipidemia are among the metabolic disorders associated with obesity. Phloridzin supplementation reduced the levels of lipids and free fatty acids in the liver in people with high-fat diet-induced obesity. Phloridzin also raised apo A-I lipoprotein and plasma HDL cholesterol. The metabolic syndrome, which encompasses abdominal obesity, obesity-associated hepatic steatosis, insulin resistance, high fasting glucose, and pro-inflammatory states, may be caused by low levels of HDL cholesterol and apo A-I. The reduction in hepatic fatty acid activity is another way that phloridzin altered the activities of hepatic enzymes and the reduction in white adipose tissue weight. Basic enzymes involved in the control of de novo fatty acid and triglyceride synthesis are synthase and phosphatidate phosphatase. The regulation of hepatic enzymes involved in lipogenesis and cholesterol synthesis may be the cause of phloridzin's reduction in hepatic lipid levels. (31)

8.3 ANTI-MICROBIAL AND ANTI-INFLAMMATORY ACTIVITIES

The body's immune system uses inflammation as a defense mechanism to combat foreign stimuli, ward off infection, or repair injured cells or tissues. Depending on the duration of the inflammation, the type of stimuli, and the body's capacity to heal and overcome the inflammatory damage, inflammation is primarily divided into acute and chronic varieties. Chronic inflammation, which typically lasts for several months to years, causes more negative effects on the body and health conditions like autoimmune disorders, auto-inflammatory disorders, mitochondrial dysfunction, and oxidative stress conditions, such as the overproduction of free radicals, oxidized lipoproteins, advanced glycation end products (AGEs), and so on. Unwanted chronic inflammatory diseases result from this, including cancer, diabetes, obesity, heart problems, stroke, chronic respiratory conditions, and many more. Research is being done to determine the pharmacological actions and medical advantages of groups of natural bioactive molecules, such as flavonoids and other polyphenols, which are among the most intriguing options for the treatment and/or prevention of inflammation and its linked disorders. (32)

Plants are a rich source of phytochemicals with a wide range of biological functions, which has piqued the curiosity of many scientists. Among the phytochemical categories that have inhibitory actions against microorganisms are flavonoids and polyphenolics. Human health is at risk from pathogenic microorganisms, which include viruses, fungi, yeasts, and particularly bacteria. Flavonoids and other polyphenols have lately been shown to have antibacterial properties in a number of research investigations, which is not surprising. As is well known, humans can contract germs by physical contact, airborne transmission, foodborne transmission, and droplet transmission. Potential disease vectors in the food sector include spoiling and exposure to harmful bacteria on the production line. Numerous bacteria, including Campylobacter jejuni, Escherichia coli 0157:H7, Listeria monocytogenes, Salmonella spp., and Staphylococcus aureus, are responsible for foodborne diseases. (33)

As antibacterial agents, flavonoids and polyphenolics likely combat bacteria through a variety of mechanisms, including the breakdown of the bacterial cell wall and cell membrane, the inhibition of biofilm formation, the inhibition of bacterial enzymes and substrate deprivation deprivation of metal iron, and protein regulation. (34)

8.4 POOR BIOAVAILABILITY

A significant precursor of flavanoid glucoside, which is mostly present in apple peels, is phloridzin (PZ), often referred to as Phloridzin or phlor-etin-2'-O-glucoside. In mice subcutaneously transplanted with bladder cancer and mammary adenocarcinoma, prior

research demonstrated that PZ dramatically inhibited tumor cell proliferation. However, problems with low bioavailability prevented further investigation of PZ as a cytotoxic agent. In an attempt to solve this issue, phlo-ridzin docosahexaenoate (PZ-DHA), a new fatty acid ester of PZ, was created by conjugating PZ with docosahexanoic acid (DHA) via a lipase B enzyme-catalyzed acylation. (35)

The penetrability of flavonoids into cells has been enhanced via enzymatic acylation with long chain polyunsaturated fatty acids (PUFAs). PUFAs provide substantial health advantages in addition to offering acyl groups for esterification. DHA, an omega-3 (ω-3) PUFA found abundantly in fish oil, was found to be the primary tumor-suppressing fatty acid in athy- mic mice bearing human colon carcinoma. Additionally, DHA works well as an adjuvant since it increases the effectiveness of certain chemotherapeutics both in vivo and in vitro. Despite the potential health benefits, PUFAs' low stability and high susceptibility to oxidation limit their usefulness as a functional dietary ingredient. Consequently, the enzymatic conjugation of PZ with DHA is advantageous to both parties since it increases the stability of the unsaturated fatty acid and enhances the bioavailability of flavonoids. (36)

8.5 STABILITY ISSUES

To assess the stability of phloridzin and F2 based on time, pH, and storage conditions, we performed a stability analysis. Phloridzin was examined in different solvents including methanol, ethanol, a solution of ethanol-water (80:20, v/v), and phosphate buffer solutions at pH levels of 7, 6, and 5. All solutions were kept at room temperature in the dark and were also subjected to accelerated aging in an oven at 40 °C. We noted that phloridzin gradually precipitates from the buffered solution at pH 5 over a two-week period, while after 60 days in the oven, where it is fully soluble, the recovery rate is approximately 85.7%. This observation rendered it impossible to monitor the stability at room temperature. A similar behavior was noted at pH 6. In the remaining solutions, phloridzin was found to be soluble and stable, with only minimal variations between samples stored at room temperature and those kept in the oven. We noted the highest percentage of recovery for phloridzin over time (94%) in the dark-stored sample with ethanol . (11)

9. TOXICOLOGICAL CONCERNS

Considering a published 4-week study using trans-resveratrol in rats via gavage, where the kidneys were identified as a target organ at a high dosage of 3,000 mg/kg bw/day, a NOAEL of 300 mg/kg bw/day was established. DSM conducted a 4-week preliminary dietary study in rats with resVida R? at dietary concentrations that resulted in an intake of up to 500 mg/kg

bw/day, which was determined to be the NOAEL. In a follow-up 13-week dietary (sub-chronic) study in rats, a high dose of 750 mg/kg bw/day was chosen, which was classified as the NOAEL since the minor effects observed were deemed not adverse. DSM conducted a dietary 4-week preliminary rat study with resVida R? at dietary concentration that resulted in an intake of up to 500 mg/kg bw/day, which was determined to be the NOAEL, taking into consideration a published 4-week study with trans-resveratrol in the rat by gavage12 in which the kidney was identified as a target organ at the high dosage of 3,000 mg/kg bw/day. A high dosage of 750 mg/kg bw/day was used for a later dietary 13-week (sub-chronic) rat trial. Since the modest side effects were deemed not to be harmful, this dose was classified as NOAEL. (37)

10. Limitations in Clinical Translation

When taking into account the expected products, there was no significant difference in the final distribution between men and women ($\chi 2$ = 2, 29, P>0, 05). For every characteristic taken into consideration at baseline, the two research groups were well matched (P>0.05 every time) (Table 1). The active medication was just as well tolerated as the placebo, and no patient had any subjective or laboratory adverse effects. The enrolled subjects maintained comparable eating habits from the randomization visit until the study's conclusion. Following the first four weeks of treatment, the active treated group's FPG dropped (-6.1%, P<0.05), but neither of the treatment groups' anthropometric traits, blood pressure readings, or other hematochemistry parameters showed any discernible changes (P>0.05 consistently). The FPG improved for the active-treated patients at the conclusion of the eighth week of therapy as compared to the baseline (-10,3%, P<0,001) and the placebo group (P<0,001) (Table 3). Additionally, SUA considerably improved (-14.0%, P<0.05 versus baseline; P<0.05 against placebo).(38)

11. FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

In conclusion, despite their wide range of potent pharmacological characteristics, flavonoids are found in small quantities in a variety of dietary sources; the majority of them are poorly soluble in water; some of them are unstable under specific circumstances; they have poor intestinal absorption and bioavailability; and they may require high doses to be effective in human trials. To illustrate the intended efficacy and route of action, the majority of published in vitro studies have utilized metabolically impractical high doses of flavonoids; nevertheless, these results must be verified using standardized in vivo experimental paradigms. Research

utilizing prospective human trials to show the therapeutic effectiveness of standardized flavonoid compounds derived from plant sources is currently missing. For the production of affordable flavonoid-based natural health products, scalable, environmentally and consumer-friendly green technologies are needed. Supplementing cancer patients with flavonoids should be done carefully since they may interact with radiation and other chemotherapies. To overcome bioavailability constraints, provide targeted administration, and increase the therapeutic efficiency of certain flavonoids, multidisciplinary research partnerships are necessary to investigate improved and safe delivery methods of flavonoids. Stage. For the majority of the main flavonoids, phase 2 metabolism and pharmacokinetics have been documented. It is still necessary to comprehend how unabsorbed flavonoids interact with the colon microbiota and the metabolites that occur, as well as their function in illness prevention and therapy. Therefore, the fields of flavonoid nanotechnology, flavonoid-microbiome pharmacology, and flavonoid-inspired treatments are still in their infancy. Such innovative studies are invited to be included in the MDPI Molecules special issue Flavonoids and Their Disease Prevention and treatment in 2021.

12. CLINICAL TRIALS AND REGULATORY STATUS

The use of phytoconstituents for neuro-protection or to prevent neurodegenerative illnesses has attracted a lot of attention from the public and scientific community. Many polyphenols are thought to reduce the onset and progression of neurodegenerative diseases like Parkinson's disease (PD) by suppressing lipid peroxidation, inhibiting neuro-inflammation by lowering pro-inflammatory and pro-apoptotic mediators, and modulating changes in gene expression, including mitochondrial directed flavonoid therapy.

It has been demonstrated that certain polyphenols have neuro-protective effects on both in vitro and in vivo models of neurological diseases. Through direct contact with receptors or enzymes that play important roles in signal transduction, polyphenols and their metabolites are known to have modulatory effects on proteins and enzymes. Those engaged in the protein kinase and lipid kinase signalling pathways are a few instances of these. The inhibition of neuro-pathological processes, iron chelating properties, modulation of signalling pathways related to neuronal survival and differentiation, and regulation of mitochondrial function are the main neuro-chemical mechanisms explaining the protective effects of plant polyphenols.

Phloridzin and other phytochemicals have been thought to exert anti-parkinsonian effects via a number of similar pathways. The mechanisms of action include decreasing the loss of dopaminergic neuronal cells and the depletion of the neurotransmitter dopamine, suppressing

apoptosis (by decreasing caspase-3,8, and 9, Bax/Bcl-2, and α-synuclein accumulation), regulating nuclear and cellular inflammatory signalling, decreasing the expression of pro-inflammatory cytokines (IL-6, IL-1β, and NF-κB), and boosting the expression of neurotropic factors (NTFs) and antioxidant activities. Flavonoids can also be neuro-protective by improving peripheral and cerebrovascular blood flow, which benefits synaptic plasticity processes and cognition.

Dietary polyphenols like phloridzin can activate Nrf2/HO1 antioxidant pathways and down regulate PPAR, NFκB, HIF-1, MMPs, and STAT pathways, according to experimental and epidemiological research. By blocking pro-inflammatory biomarkers such as CXCL (9, 10, 11), CCR1, CCR2, CCL22, CCL17, IL (1β, 6, 17A,22), MIP1α, MIP 1β, IFN-γ, and TNF-α, they can also function as immune response modulators .The primary pathogenic processes in neurodegenerative disorders—oxidative damage, neural inflammation, and mitochondrial damage leading to apoptosis and neuronal death—are countered by all of these mechanisms.

The largest risk factor for idiopathic Parkinson's disease (PD) is still aging.(39) Research has demonstrated the anti-aging properties of yeast's phloridzin.(40) Phloridzin extends life span in yeast through the SIR2 signalling pathways, SOD gene, and an increase in SIRT1 activity, according to mechanism studies. This finding supports further research on phloridzin's anti-aging effects on mammalian cells and experimental animals.(41)

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