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Exploring the chemotherapeutic potential and therapeutic insight of phloretin against human malignancies: a systematic review

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Abstract The search of alternative therapeutic agents for the use of cancer patients has dramatically expanded. Natural products are especially in focus since their structures already function in nature and are more likely to be potent with fewer side effects. Phloretin is a natural product that has been studied for a wide variety of pharmacological actions against human malignancies. This systematic review aims to present up-to-date critical and comprehensive information on the anti-cancer ability of Phloretin with all associated molecular and cellular mechanisms in various forms of cancers. Data retrieved according to PRISMA guidelines from Science Direct, PubMed, and Scopus searching servers by using keywords including Phloretin, cancer name, synergistic, resistance and Pharmacokinetics property was analyzed via some in silico tools. This systematic review comprised 127 articles from different types of study, where Phloretin is hypothesized to be effective against 20 various forms of cancer. Phloretin has been found to inhibit cancer initiation and progression by modulating many imbalanced signalling pathways, including apoptosis, autophagy, necrosis, metastasis, angiogenesis, cell proliferation, glucose absorption, oxidative stress, inflammation, DNA damage, and many other pathways. This wide range of activity may be due to the structural targeting of numerous proteins including, Bcl-2, Bax, Bak, Bad, caspase, cyclins (B1, D1, E) and CDKs (4, 6,7) p18, p21, p27, p53, MMP-2, MMP-8, MMP-9, Wnt/-catenin, PARP, TNF-α, NF-κB, IκB kinase, IL-1β, TNF-α, phospho-Akt, phosphor-p65, NF-κB, PI3K/Akt, MAPK/ERK, p-mTOR. The introduction of nano-technology-based strategies can improve the efficacy of Phloretin for cancer treatment. Existing evidence shows that Phloretin has synergistic

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effects with other natural compounds and conventional drugs, and this mechanism assists in reversing the resistance of anticancer drugs by regulating resistance-related proteins. However, Phloretin possesses favorable pharmacokinetic properties with low toxicity in the human body by in silico methods. Therefore, Phloretin could be a potential anti-cancer drug against numerous cancer treatment by mitigating it's toxic effect and enhancing efficacy using nano-technology-based strategies.

Keywords Phloretin · SAR · Anti-cancer perspective · Nano-formulation · Synergistic · Pharmacokinetics

Abbreviations

Bcl-2	B-cell leukemia 2
Bax	Bcl-2-Associated X protein
PI3K	Phosphoinositide 3-kinase
Akt	Ak strain transforming
mTOR	Mammalian target of rapamycin
MMP9	Matrix metalloproteinase 9
GLUT	Glucose transporters
ULK1	Unc-51 like autophagy activating kinase
ERK1/2	Extracellular signal-regulated kinase 1/2
TPA	Tissue plasminogen activator
LC3B	Light chain 3B
BCL-XL	B-cell lymphoma-extra large
XIAP	X-linked inhibitor of apoptosis protein
VEGF	Vascular endothelial growth factor
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
CAT	Chloramphenicol acetyltransferase
SOD	Superoxide dismutase
NF-B	Nuclear factor-B
Mac-1	Macrophage 1 antigen
PEP	Phosphoenolpyruvate
GraB	Granzyme B
c-Myc	Cellular Myc
ROS	Reactive oxygen species
HCC	Hepatocellular carcinoma
SHP-1	Src homology region 2 domain-containing phosphatase-1
STAT3	Signal transducer and activator of transcription 3
pERK	Protein kinase RNA-like endoplasmic reticulum kinase
VEGFR	Vascular endothelial growth factor receptor
MAPK	Mitogen-activated protein kinase
CXCL12	C-X-C motif chemokine ligand 12
CXCR4	C-X-C motif chemokine receptor 4
TLR1	Toll-like receptor 1
TLR2	Toll-like receptor 2
TNF-α	Tumor necrosis factor-alpha
NOD	Nucleotide-binding oligomerization domain
NLRP3	Nucleotide-binding domain (NOD)-like receptor protein 3
CDK4	Cyclin-dependent kinase 4
CDK6	Cyclin-dependent kinase 6
BAK	Bcl-2 homologous antagonist/killer
PARP	Poly-ADP ribose polymerase
HIF1	Hypoxia-inducible factor-1
HKII	Hexokinase 2
PFKFB3	6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase isozyme 3
PDHK1	Pyruvate dehydrogenase kinase 1
LDH	Lactate dehydrogenase
Pink1	PTEN-induced kinase 1
GSH	Glutathione
NSCLC	Non-small cell lung cancer
JNK	C-Jun N-terminal kinase
TRX	Thioredoxin
TXNIP	Thioredoxin interacting protein
2-NBDLG	2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino]-2-deoxy-D-glucose
PKC	Protein kinase C
Myt1	Myelin transcription factor 1
cdc2	Cyclin-dependent kinase 2
HSP70	70 Kilodalton heat shock protein
IL-6	Interleukin-6
MRP	Multi-drug resistance associated protein 1
BCRP	Breast cancer resistance protein
MDR	Multi-drug resistance

Introduction

Cancer is a common disease as well as a significant global health issue (Siegel et al. 2023). Although the coronavirus disease 2019 (COVID-19) pandemic created delays in cancer patient detection, new cancer

cases and deaths have gradually increased in the last two years(Siegel et al. 2023). The causative agent of cancer is known to all, but therapeutic options are still limited. Some conventional therapies effectively treat numerous cancer patients (Debela et al. 2021; Karpuz et al. 2018; Nobili et al. 2009). Nevertheless, a few of these therapeutic approaches have several drawbacks and restrictions, including several side effects; anaemia, alopecia, poor efficacies, drug resistance, and also the high cost, and unavailability. Therefore, using newly discovered compounds derived from plant sources can provide an innovative and trustworthy therapeutic element for healing a wide variety of human cancers (Shrihastini et al. 2021). Using natural products for cancer treatment is not a new approach. Kurupp et al. reported that a total of 3000 species have anti-cancer characteristics, with plants accounting for more than 60% of presently utilized anti-cancer medicines. (Kuruppu et al. 2019). This is because natural compounds are safe, non-toxic, cost-effective, and readily available from villages to cities and underdeveloped to developed countries (Rodriguez et al. 2015). Our latest study reviewed that natural products regulate cancer progression by targeting apoptosis cell cycle and proliferation, metastasis, angiogenesis, oxidative markers, mammosphere formation, inflammation, regulation enzymatic functions, cell signalling, epigenetics control, and activating immune system (Sohel et al. 2022a, b, c, d; Biswas et al. 2022; Paul et al. 2021; Morshed et al. 2023; Sohel et al. 2023).

Phloretin, chemically known as 3-(4-hydroxyphenyl)-1-(2,4,6-tri hydroxyphenyl) propane-1-one, is a naturally occurring functional phytoestrogen and to the isoflavone category, that is generally found in Rosaceae plants("Phloretin | C15H14O5—PubChem,".; C. Wu et al. 2009a, b; Nakhate et al. 2022; Picinelli, Dapena, and Mangas 1995). This compound has several pharmacological activities, including antioxidative(Rezk et al. 2002), anti-inflammatory(Chang et al. 2012), anti-microbial(Barreca et al. 2014), anti-allergic(Huang et al. 2017), anti-thrombotic (Mariadoss et al. 2019a, b), neuroprotective(Barreca et al. 2017), and hepatoprotective(Lu et al. 2017) due to strong interaction with multiple receptors(Mariadoss et al. 2019a, b). Medicinal chemists can modify its chemical structure and develop analogs with improved pharmacological properties, potentially leading to the development of more potent and selective anticancer drugs. Regarding cancer, previous studies have shown that consumption of Phloretin as a dietary food reduces the risk of certain cancers, such as lung(Min et al. 2015), oral (Yang et al. 2020), esophageal(Duan et al. 2017), gastric, colon(Kim et al. 2022), liver(Min et al. 2015), breast (He et al. 2020.),pancreartic(Brij B Patel et al. 2016), kidney (J. Kim et al. 2018), glioblastoma(Liu et al. 2016), ovarian(Xintaropoulou et al. 2015) cervical(Hsiao et al. 2019), bladder (Hui 2020), myeloma (McBrayer et al. 2012), skin(Casarini et al. 2020), melanoma(KoBoRI et al. 1999) leukemia(KoBoRI et al. 1999), thyroid(Ma et al. 2022), osteosarcoma(Ogawa et al. 2021), oesophagal (Duan et al. 2017) and prostate cancer (Yang et al. 2022). This wide range of anti-cancer activities is mediated by the interaction of Phloretin with some regulatory molecules and modulators. Phloretin is typically thought of as an antioxidant, its impacts on cancer cells can be complicated. Through selective cytotoxicity, pro-oxidant action, and signaling pathway modification, but it can cause oxidative damage to cancer cells. Due to increased metabolic activity and mitochondrial malfunction, cancer cells frequently have greater ROS level than normal cells. Phloretin can take advantage of this vulnerability by raising ROS levels in cancer cells to levels that exceed their antioxidant tolerance and result in oxidative damage. Phloretin also has the ability to interfere with various signaling pathways and cause oxidative damage by affecting the redox balance within cancer cells. Although some experimental studies of Phloretin, with numerous cancer types, have been in various in vitro and pre-clinical trials, the overall anti-cancer profile against numerous types of human malignancies has not been reviewed yet.

Thus, in different study models, authors emphasized Phloretin's total anti-cancer impact with cellular and molecular mechanisms against numerous cancers. Moreover, we targeted unravelling synergistic profiles with other natural products, proteins, and traditional drugs currently used and reversed the efficacy of existing drugs by alleviating multi-drug resistance. Additionally, this article focused on an up-to-date overview of developing nano-strategies for better efficacies, with some additional information, including a pharmacokinetics study and toxicity profile. So, in general, the information covered here will encourage potent scholars to design novel and potentially

clinically proven drugs to fight against cancerous neoplasm.

Methodology

Literature research on phloretin and malignancies

According to PRISMA guidelines, the current systematic review was carried out by using several databases, including Science Direct, PubMed, Scopus, and Google scholar (Dewanjee et al. 2023).

Inclusion criteria

We used different study models, including in silico, in vitro and in vivo, where only the English language was considered for evaluating the anticancer activity of phloretin.

Exclusion criteria

The following exclusion criteria were applied " (I) conference paper, unpublished paper, dissertation, and thesis book (II) Non-English paper (III) Review article, systematic review, meta-analysis, letter (IV) Original studies without the use of tumour cell lines or animal tumor models."

Data extraction

At first, 5161 articles were searched by searching protocol, 2900 articles were excluded due to initial selection, 28 review articles were omitted, 852 articles were excluded due to non-relevance and 39 non-English articles were disqualified. Out of 393 selected, 97 were excluded due to whole plant extract testing, and 41 more were removed due to discussion of other biological activities rather than cancer. Finally, data was retrieved from 137 papers, and the literature search and selection method is shown in a flowchart (Fig. 1).

Pharmacokinetics study analysis

In-silico approaches conducted pharmacokinetics or ADME/Tox prediction through computational tools such as Schrodinger's QuickPro modules, online accessible server admetSAR, and SwissADME were used (Sohel, Sultana, Sultana, Al Amin, et al. 2022).

Result

Sources of phloretin

Phloretin is a natural compound found in various plant sources, particularly in apples and apple-related products like apple juice, apple cider, and apple peel extracts (Szabo et al. 2022). Apple contains up to 2 g of total phenolic content (TPC) per kilogram of wet weight or approximately 400 mg of total phenols per apple (FAO 2013; Choi 2019). Although apples are the most well-known source, small amounts of phloretin can also be found in other fruits like cherries, strawberries, and raspberries, although at much lower levels (Hilt et al. 2003) (Wu et al. 2009a, b; Nakhate et al. 2022; Picinelli, Dapena, and Mangas 1995). Phloretin can be found in a few different plant species, but its concentration tends to be lower than in apples. *Malus doumeri*, *M. domestica Populus candicans* are the common plant species for Phloretin("Phloretin | C15H14O5—PubChem"). Additionally, the *manchurian apricot*, a fruit in the genus *Prunus*, contains Phloretin in a small amount ("*Manchurian Apricot* facts and health benefits,"). Moreover, as a natural sweetener, Phloretin can be found in *Lithocarpus Polystachyus* and *Rehd.* (Shang et al. 2022). Moreover, its derivatives, including Phloretin 3′,5′-di-C-glc, phloretin-2'-glucoside, Phloretin 2′-O-xyloglucoside, Phloretin 2′-O-glucuronide are found in various plant sources (Slimestad et al. 2008) (Hagl et al. 2011). Furthermore, some derivatives, food supplements, topical creams, and Dietary Sources contain a small amount of Phloretin. Unlocking the secret source of Phloretin is tabulated in Table 1.

Chemistry of phloretin

The chemical structure of phloretin consists of three main components: a dihydrochalcone core, a bicyclic ring system commonly referred to as A and B and two phenolic hydroxyl groups at positions 2, 4, and 6 (Minsat et al. 2021). Other functional groups, including the carbonyl group (C = O) and ether linkage (C–O–C), contribute to its overall structure. The chemical formula of phloretin is $C_{15}H_{14}O_5$, where IUPAC name

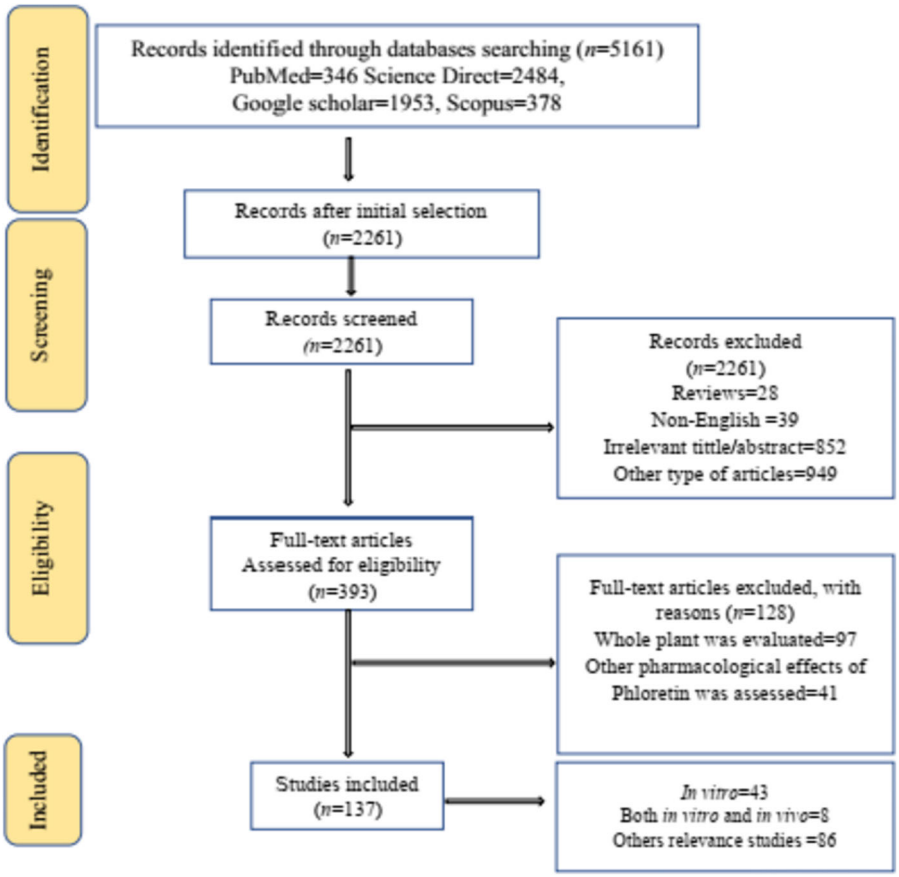

Fig. 1 The PRISMA flow chart showing the method used to choose the studies that were included

is 3-(4-hydroxyphenyl)-1-(2,4,6-tri hydroxyphenyl) propane-1-one and systematic name is 2',4,6'-trihydroxy-3-(4-hydroxyphenyl) propiophenone. It has 20 heavy atom counts, four donor and rotatable hydrogen bond counts, five acceptor hydrogen bond counts, and one covalently bonded unit quantity. There is no formal charge, and the topological polar surface area is 98 $Å^2$. Phloretin has a molecular weight of 274.27 g/mol, while its exact mass is 274.084 g/mol ("Phloretin | C15H14O5—PubChem"). Phloretin has two aromatic phenol rings (rings A and B), hydroxyl groups, and a carbonyl group (Tuli et al. 2022a). Figure 2 portrays the chemical structure of Phloretin.

Structure–activity relationship (SAR) of Phloretin linked with anti-cancer activity

The biological activities of a natural product are attributed to having hydroxyl or phenolic structures as a functional group surrounding its core structures. For example, Phloretin is a potent flavanone with significant health advantages because of its polyphenolic group (Tuli et al. 2022a). The total number and arrangement of functional hydroxyl groups considerably affect Phloretin's antioxidant activity, which can scavenge free radicals or chelate metals. Phloretin has four hydroxyl groups at different position of ring A and B. Due to its pharmacophore and 2,6-dihydroxyacetone region, phloretin can eliminate peroxynitrite radicals with IC_{50} of 3.1 µM (Rezk et al. 2002). This scavenging capacity of Phloretin protects DNA from oxidative damage by raising levels of the antioxidant glutathione (GSH) in human colon cancer Caco-2 and HT-29 cells (Schaefer et al. 2006). The existence of a pair of bonds within phloretin's C2 and C3 atoms has a significant impact on cell proliferation (Jacob et al. 2011). In addition, phloretin's di-OH3',4', double bond at C2–C3, and carbonyl group at C-4 mediate a

Table 1 Exploring natural the source of phloretin

Source	Description	References
Apples	Abundant in apple peels, particularly in red apples. It is often extracted from apple pomace, a byproduct of apple processing	Grigoras et al. (2013; Ulaszewska et al. (2018)
Pears	Pears, especially red-skinned varieties, contain phloretin in their peels, similar to apples	Ulaszewska et al. (2018)
Cherries	Cherries, particularly tart cherries contain phloretin in their skin	
Root Bark of Apple Trees	Phloretin can be extracted from the root bark of apple trees, although this source is less common and less sustainable	Ulaszewska et al. (2018)
Medicinal Plants	Some medicinal plants, such *Malus doumeri*, *M. domestica Populus candicans* contain phloretin in their bark and leaves	"Phloretin | C15H14O5—PubChem (Accessed 22 Sept 2023)
Derivatives	Phloretin derivatives, such as phloretin-2'-glucoside, Phloretin	Hagl et al. (2011)
	2′-O-xyloglucoside, Phloretin 2′-O-glucuronide found in various plant sources	
Supplements	Phloretin supplements are available in the form of capsules or tablets, typically derived from apple extracts	"PHLORETIN 98% Apple Extract Capsules Skin Care Cosmetic Ingredient Polyphenols – Herbadiet)("Phloretin CF | Topical Vitamin C | Vitamin C Gel | SkinCeuticals (Accessed 15 Augt 2023)
Topical Creams	Phloretin is used in topical creams and serums for its antioxidant and skin-brightening properties, often derived from plant sources	"Phloretin CF | Topical Vitamin C | Vitamin C Gel | SkinCeuticals
Dietary Sources	In addition to fruits, small amounts of phloretin can be found in vegetables like Manchurian apricots	Tuli et al. (2022b)

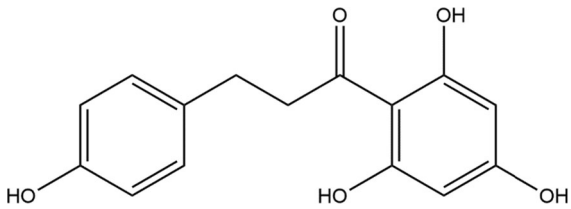

Fig. 2 Chemical structure of Phloretin

selective attack on cyclin-dependent kinase 2 (CDK-2), leading to arrest at cell cycle at G1 phase (Mintie et al. 2020). The structural organization of phloretin facilitates the formation of interaction with metal, including Ruthenium. In MCF-7 and MDA-MB-231 breast cancer cell lines, the combination of Ruthenium-phloretin modifies both natural apoptosis and the anti-angiogenic pathway by modulating p53, Bcl-2, and Bax and lowering the PI3K/Akt/mTOR and MMP9-regulated tumour invasive pathways (Roy et al. 2022). Phloretin has a topological polar surface area (TPSA) of approximately 97.99 $Å^2$. There is a strong connection between this TPSA and anti-cancer activity. Prasanna S, Doerksen RJ concluded that natural compound anticancer properties are correlated with normal TPSA through inhibition of the telomerase and aromatase enzymes in cancer cells (Prasanna and Doerksen 2008). Overall, a brief diagram for SAR studies of Phloretin is summarized at the Fig. 3.

Anti-cancer perspectives of phloretin

In silico anti-cancer activity

In silico analysis can predict or analyze a molecule's biological activity without conducting experiments in a laboratory against diseases, including cancer. In silico analysis can provide valuable insights into its potential effects when assessing the anti-cancer activity of a compound like phloretin. It induced fit molecular docking prediction shows that phloretin

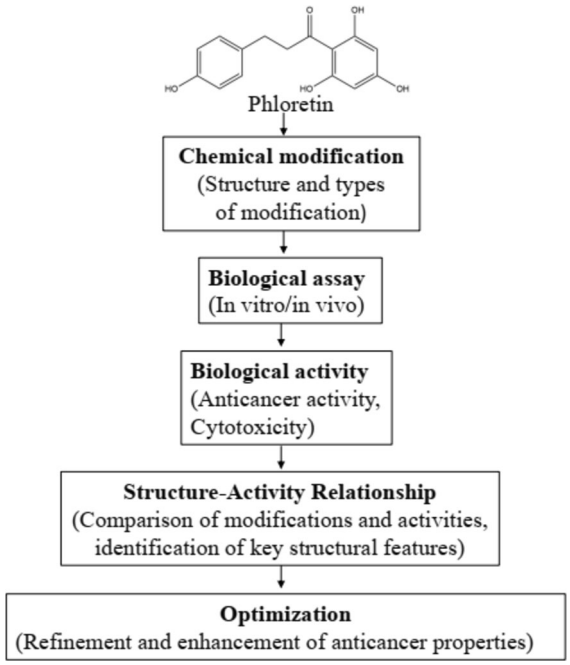

Fig. 3 Diagram for Structure–Activity Relationship (SAR) studies of Phloretin

showed notable binding affinity, especially with carbonic anhydrase I, ENOS, and INOS with variable binding energy. Additionally, Phloretin showcased significant potential against Caspase 3 and NF Kappa, thereby showing its potential as an effective against several anti-cancer therapeutics (Ranjanamala et al. 2021). Anand Mariadoss et al. showed in their study phloretin exhibited a significant binding interaction pattern with several receptors, including EGFR, Bcl-2, NF-ĸB, c-Kit receptor protein-tyrosine kinase, Farnesyl transferase, PDGFs and VEGFR2 proteins (Anand Mariadoss et al. 2018). However, other types of study, including data mining and system pharmacology, are preliminary steps in drug discovery and development against cancer treatment before starting clinical trials.

In vitro and in vivo anti-cancer perspectives

Existing evidence shows that Phloretin is effective against numerous human malignancies at both in vitro and in vivo (animal) (Figs. 4, 5, 6, 7) through several mechanisms. These specific mechanisms might lead to a potential remedy after the study of this leads in further phases of pharmaceutical development. In the sections, phloretin's antitumor properties and related processes in various malignancies are discussed briefly.

Breast cancer

Typically, breast cancer travels to other organs, including bone, liver, brain, and lung, making it a leading cause of death in women, and several factors may contribute to the development of breast cancer (Sun et al. 2017). According to previous research, natural flavonoids such as phloretin can be used to treat breast cancer. Phloretin (60–120 μM) can induce DNA damage and apoptosis while inhibiting cancer cell proliferation, viability, migration, invasion, and development of colonies in MCF-7 and MDA-MB-231 by activating p53, regulating the Bcl2/Bax ratio, and suppressing the PI3K/Akt/mTOR pathway coupled with MMP-9 downregulation (He et al.2020.). Wu et al. described that Phloretin (10–50 mg/kg) inhibits cell cycle progression and cell proliferation by inhibiting paxillin/FAK, Src, and alpha-smooth muscle actin (a-sMA), and the activation of E-cadherin, p53, p21 with decreasing vimentin and N-cadherin levels in MDA-MB-231 tumour xenografts mice(Wu et al. 2018). Phloretin, a GLUT inhibitor, reduced GLUT1 and GLUT12 expression in MCF-7 and MDA-MB-231 cells (Matsui et al. 2017). Phloretin inhibited the mTOR/ULK1, LCB-II pathways in MCF-7 and MDA-MB-231 cell lines, resulting in the control of cell proliferation and activation of autophagy in a separate study (Chen et al. 2021). Phloretin inhibits cell growth in immunocompromised NODS-CID mice model while regulating reactive oxygen species (ROS) level control growth of in vitro MDA-MB-231 breast cancer cells (Brij B Patel et al. 2016) (Patel et al. 2017). JNK and p38 MAP kinase activation have been associated with phloretin-induced caspase-3 cleavage in H-ras-transformed human mammary epithelial cells (H-ras-MCF-10A). Additionally, these researchers found that phloretin increased p53 and Bax while lowering Bcl-xl, leading to apoptosis, and decreased H-ras proliferation at MCF-10A cells in a concentration-dependent way (Kim et al. 2009).

Prostate cancer

Prostate cancer develops when abnormal cells form and grow in the prostate gland. According to a

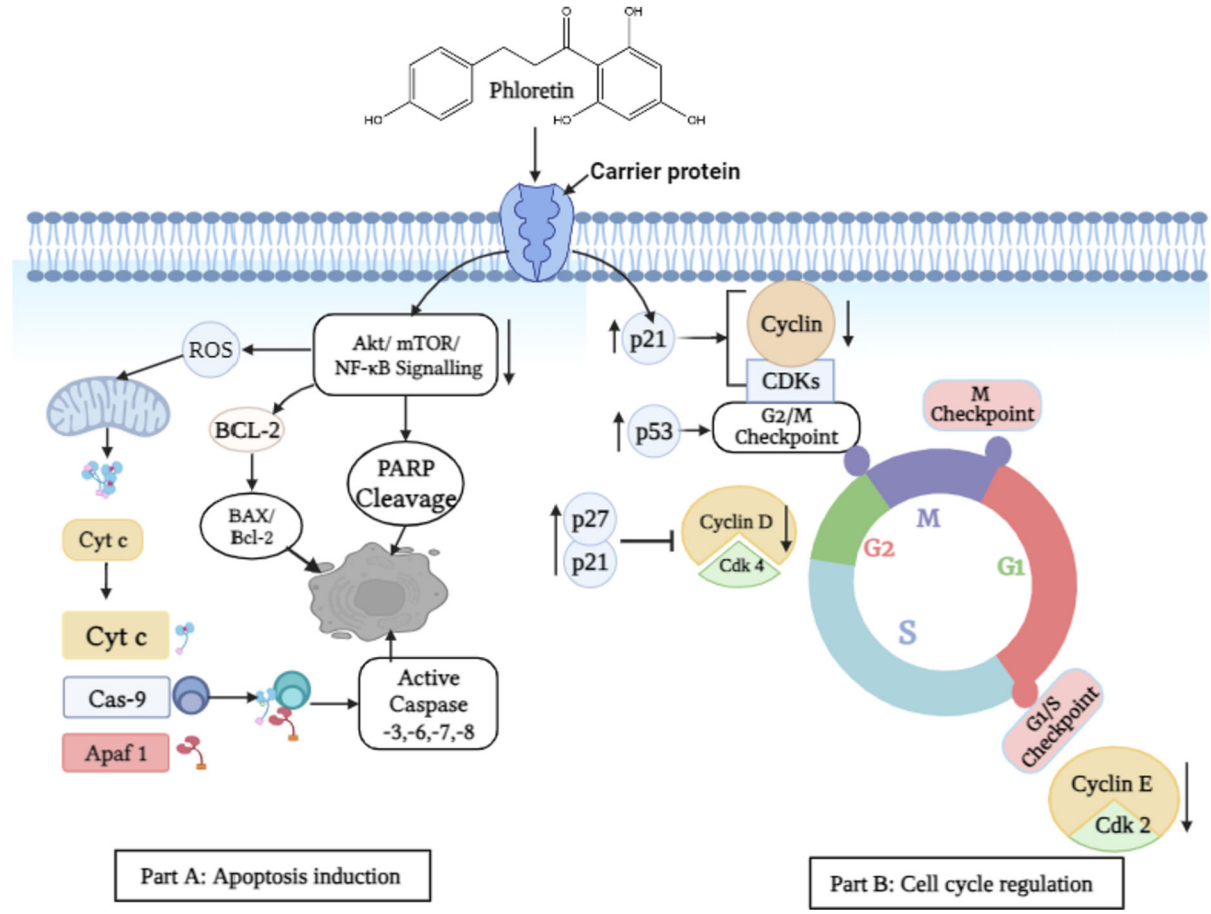

Fig. 4 Regulation of apoptosis and cell proliferation by Phloretin. Phloretin must first cross the cellular membrane, which consists of a lipid bilayer embedded with various proteins. Carrier protein is an example of facilitated transporter, which might be used by Phloretin to entry into the cell before mediate function. Section and B denotes induction of apoptosis and cell cycle regulation, respectively

previous study, Phloretin activates the apoptosis pathway by suppressing Bcl-xL, XIAP, and surviving, while increasing Bax's expression and reducing cell proliferation by decreasing VEGF, CCND1, and CCNB expression in prostate cancer LNCaP, CWR22Rv1, PC-3 cell line (Yang et al. 2022). Kang et al. reported that Phloretin (0–100 μM) inhibited cyclin B1, XIAP, and Bcl-2 in LNCaP cell line culture to arrest the G2/M phase cell cycle and trigger apoptosis (Kang et al. 2020). Furthermore, phloretin (50–100 μM) was associated with increased MTT cytotoxicity and cell death induction at LNCaP prostate cancer cells (Szliszka et al. 2010). In a different study, phloretin was used to examine how some GLUTs (GLUT1 and GLUT4) are regulated inside of androgen-sensitive (LNCaP) as well as insensitive (PC-3) prostate cancer cell lines, where phloretin (25–39.4 μM) showed anti-proliferative properties by modifying the expression of the glucose transporter (GLUT) or by changing glucose binding while also regulating cell growth (Gonzalez-Menendez et al. 2014).

Colon cancer

Colon cancer is a prominent cancer type around the world (Jin et al. 2020). Phloretin has anti-inflammatory, antioxidant, and anticancer properties (Kim et al. 2022). Jin et al. showed that Phloretin induces apoptosis and DNA fragmentation and decreases cell proliferation via upregulating CAT, SOD, glutathione, and Caspase-3, while Bcl-2, NF-B, MMP-9 and Akt/

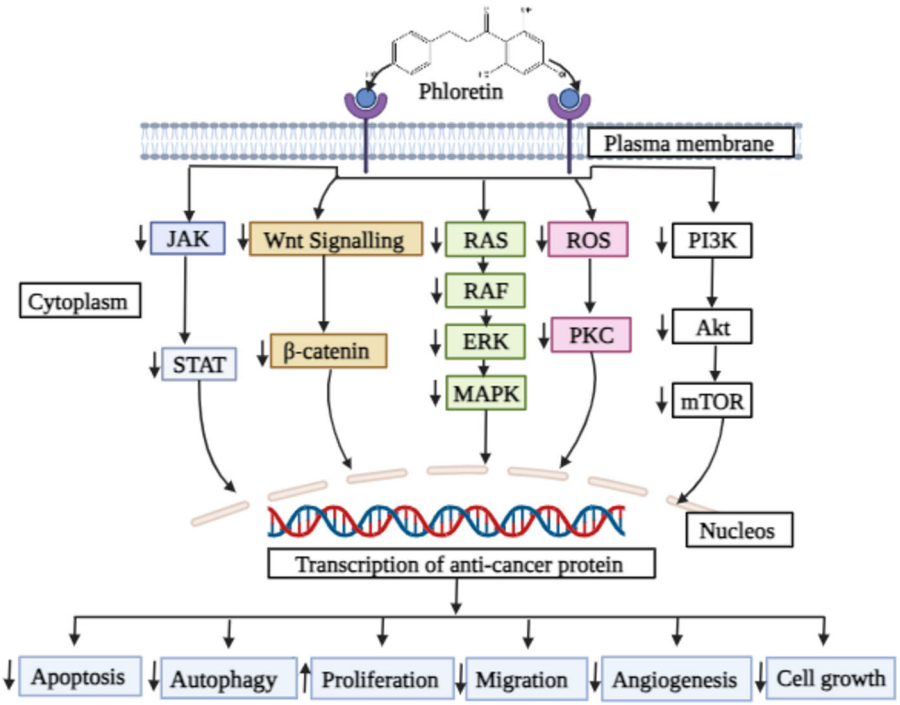

Fig. 5 Control of signaling molecules by Phloretin in cancer treatment

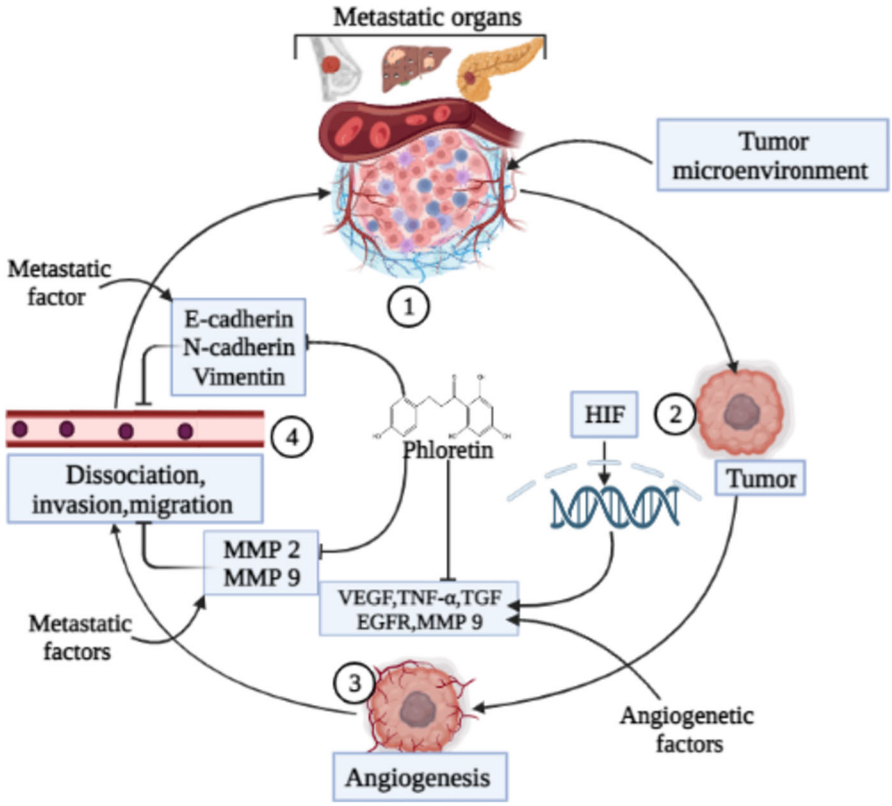

Fig. 6 Phloretin suppress metastasis and angiogenesis

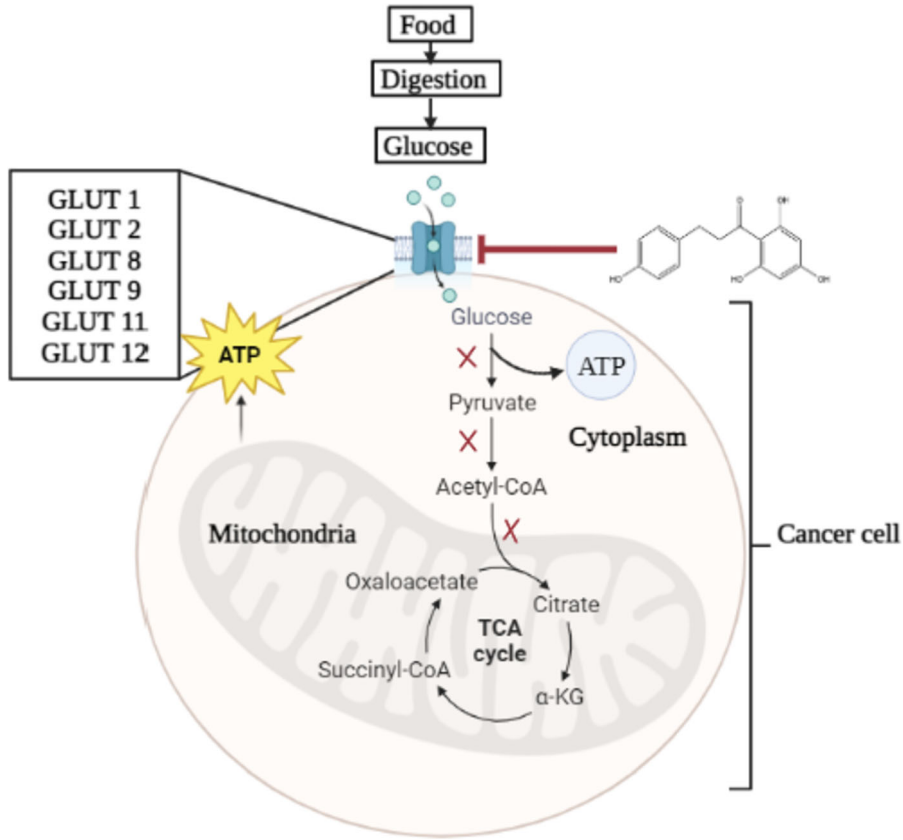

Fig. 7 Effect of Pholretin on glucose absorption by cancer cells via imbibition of GLUTs transporter

mTOR signal were downregulated in HT-29 cells(Jin et al. 2020). Phloretin treatment boosted apoptosis in HT-29 Luc cells by raising cleaved poly(ADP ribose) polymerase, Mac-1, caspase-3, and caspase-8 in a dose-dependent manner (J. L. Kim et al. 2022). Phloretin (2.35–18.75 g/ml) boosts the killing effect of γδ T lymphocytes and the production of PFP and GraB in a human SW-1116 cancer cell line by inhibiting the Wnt signalling pathway(Zhu et al. 2013a, b). Park et al. reported that Phloretin (0-100 mol/L) led to apoptosis in HT-29 cells by increasing the levels of Bax, cytochrome c, caspase-8, -9, -7, and -3, Smac/Diablo, and poly(ADP-ribose) polymerase(Park et al. 2007). Phloretin (100 μM) induced apoptosis and arrested the G2/M checkpoint in human carcinoma SW620 and HCT116 cells via elevating phosphor-cdc2 and Myt1 and decreasing cyclin B and cdc2 (Zhou et al. 2018). Phloretin inhibits cell growth and cell invasiveness in both in vivo and in vitro models by causing a cell cycle arrest at the G0/G1phase, which increases the actions of the p21/Cip1 and p27/Kip1 proteins (p53-mediated proteins) and decreases GLUT2 expression(Lin et al. 2016). Phloretin (25–300 μM) causes programmed cell death (apoptosis) as well as reduced cell proliferation, colony formation, and cell migration at HCT-116 and SW-480 colon cancer cells by inhibiting Wnt/β-catenin signaling, which results in the downregulation of cyclinD1, c-Myc, and survivin and the upregulation of ROS and bax expression(Kapoor and Padwad 2023).

Liver cancer

One of the most prevalent and deadly types of cancer is hepatocellular carcinoma (HCC), also known as liver cancer (Wu et al. 2009a, b). Despite significant advancements regarding treatment strategies in recent years, there are no possibilities for curative therapy, and patients with HCC still have few therapeutic options and poorer prognosis (Pope et al. 2019). However, Phloretin has therapeutic effects against

HCC. Phloretin (200 μM), inhibits glucose transporter (GLUT) and triggers apoptosis in HepG2 cells by suppressing the Akt and Bcl-2 signalling pathways (Wu et al. 2009a, b). Phloretin might increase the expression of SHP-1 and decrease STAT3 as well as inhibit pAKT/pERK signalling in HCC cells leading to reducing angiogenesis, cell proliferation, and inducing apoptosis (Saraswati et al. 2019). Phloretin (1–200 μM) inhibits the iodothyronine-5'-deiodinase and the mammalian glucose transporter in Hep G2 cell line (Movius et al. 1989). Phloretin (50–150 mM), either alone or in combination, has the power to fight liver cancer by inhibiting the glucose transporter GLUT, Bcl-2, NF-κB, T4 5'-deiodinase, STAT3 expression, SHP-1 expression, pAKT/pERK, Akt/VEGFR2 pathway and activating, caspase-3 and -9 in Hep G2 cells (Yang et al. 2009).

Pancreatic cancer

Pancreatic cancer typically develops in advanced stages and has a limited chance of survival (Rawla, Sunkara, and Gaduputi 2019). Phloretin has recently been shown to be effective in treating pancreatic cancer. Phloretin act as a ROS inhibitor to lessen MAPK signalling and SOD activity and reverse treatment resistance in Panc1 and HTB147 pancreatic cancer cells. In addition, in the tumour xenograft model, by inhibiting CXCL12/CXCR4-dependent MAPK signalling and ROS pathways, phloretin and gemcitabine combined inhibit cell proliferation and migration, reversing the drug susceptibility of Panc-1 lines (Patel et al. 2016).

Kidney cancer

Kidney cancer is also known as renal cancer, in which kidney cells develop into malignant tumours. Appropriate treatment is needed to prevent kidney cancer; phloretin has recently proven helpful. According to Funari et al. Phloretin (20–40μM) can prevent ROS formation and inhibit cell growth in HEK-293 cells (Funari et al. 2011). In human embryonic kidney (HEK) 293-hTLR2 cells, phloretin inhibits TLR1 and TLR2 receptors substantially, decreasing TNF-α and interleukin-8 inflammatory cytokines (Kim et al. 2018). Phloretin (50 μM) markedly decreased the renal ECM deposition level and the α -SMA in renal tubules, which cells indirectly influenced cancer and reduced the release of cytokines, including NOD-like receptor family domain 3 (NLRP3) and interleukin-1β (IL-1β), mitochondrial reactive oxygen species (ROS), and morphological lesions in the kidneys of HUA mice (Cui et al. 2020).

Oral cancer

Oral cancer, which is caused due to several factors, makes up 2–4% of all malignancies in the United States(Suhail et al. 2016). Phloretin inhibits the proliferation of human oral cancer cells, making it a potential therapy for oral carcinoma. Phloretin (12.5 μM) promotes necrosis and reduces cell proliferation with migration by inducing cell cycle arrest at the G0/G1 phase in the SCC-1 cell line in which CDK4, CDK6, and cyclin D1 expression are downregulated (Yang et al. 2020). Phloretin (15.3 g/mL) inhibits glucose transporters (GLUTs), induces apoptosis, and reduces cell proliferation in YD-9 cells by elevating the levels of p53 and Bax (Nam et al. 2017). Above research's results indicate that phloretin, a secondary plant metabolite with tremendous pharmacological potential, might have the capacity to be a therapeutic agent for oral cancer by inducing apoptosis, cell cycle arrest, reactive oxygen species (ROS), and inhibiting cell proliferation, migration, and glucose uptake via associated signaling pathways.

Glioblastoma

Glioblastoma (GBM) is one of the deadliest and most resistant solid malignant tumors(Davis 2016)(Nahar Metu et al.,2023). Phloretin has a chemopreventive effect on glioblastoma cells in humans. Phloretin (0–300 μM) suppresses cell proliferation and induces apoptosis in U87 and U251 glioblastoma cells by decreasing Bcl-2, cyclin D, cyclin E and CDK2, CDK4, CDK6, and increasing Bax, Bak, c-PARP (Liu et al. 2016). Furthermore, Phloretin suppressed specific signalling molecules, including PI3K/AKT/mTOR cascades, resulting in G0-G1 cell cycle arrest (Liu et al. 2016). In SH-SY5Y cells, Phloretin (200 μM) lowered cell viability through the JNK-Beclin-1 pathway and triggered autophagy by downregulating p-AKT and p-mTOR (Fan et al. 2022).

Ovarian Cancer

Ovarian cancer is the growth of cells that form in the ovaries. Phloretin (0.6–300 μM) induced apoptosis through activating caspase-3 and suppressed metastasis by reducing the MMP ovarian cancer cell line. Moreover, it stops some cancerous properties, including lowering glycolysis by decreasing the function of HIF1-inducible glycolytic enzymes (GLUT1, HKII, PFKFB3, PDHK1, LDH) (Xintaropoulou et al. 2015).

Bladder cancer

A prevalent form of cancer that starts in the bladder's cells is bladder cancer. Phloretin might be effective in bladder cancer treatment. Hui et al. reported that Phloretin (20 uM) helped to accumulate H_2O_2, leading to cytotoxicity and preventing migration of AQP9 cell lines (Hui 2020).

Myeloma cancer

A plasma cell cancer called myeloma occurs when the blood cells proliferate uncontrollably. Phloretin (100 μM) inhibits GLUT transporters, including GLUT8 and GLUT11, which reduces cellular proliferation and glycolysis in MM.1S, RPMI 8226 and U266 cell (McBrayer et al. 2012). Friday at el. showed that Phloretin (200 μM) enhanced ROS, elevated TRX activity, and lowered TXNIP activity to enhance apoptosis and inhibit cell growth (Friday et al. 2011).

Melanoma cancer

Melanocytes are the cells that produce melanoma, the most dangerous form of skin cancer. In skin cancer melanoma 4A5 cells, phloretin (25 μM) inhibits elastase, MMP-1, decreases cellular tyrosinase activity and melanin concentration, leads to promotes apoptosis and inhibits metastasis via an unknown mechanism (Casarini et al. 2020). In addition, KoBoRI et al. showed how Phloretin led to apoptosis in HL60 and B16 cells by increasing the expression of BAX protein without affecting p53, Bcl-XL, and Bcl-2, and by inhibiting the activity of protein kinase C (KoBoRI et al. 1999). In addition, in SK MEL28 cell lines, Phloretin induces apoptosis and reduces metastasis, suppressing MMPs in a dose-dependent manner (Casarini et al. 2021).

Thyroid cancer

Malignant cells can develop in the tissues of the thyroid gland, resulting in thyroid cancer. Phloretin exerted its anti-cancer activities in thyroid cancer by controlling the pathway of PI3K-Akt and regulating apoptosis-related proteins, including the downregulation of Bcl-2 and Bcl-xL, while the increased expression of Bax, caspase-3, -8, and -9 in thyroid cancer SW579 cell lines (Ma et al. 2022).

Osteosarcoma

The most prevalent form of cancer that originates in the bones is known as osteosarcoma. Phloretin inhibited the uptake of 2-NBDLG, an inhibitor of the sodium-glucose co-transporter (SGLT) and prevented the absorption of 2-NBDLG in osteosarcoma U2OS cell lines in a dose-dependent manner (Ogawa et al. 2021).

Esophageal carcinoma

Cancer of the oesophagus, also known as oesophagal cancer, is a disease that develops in the esophagus, a tube extending from the throat to the stomach. Phloretin (60–100 μg/ml, 6–48 h) prevents cell proliferation and induces apoptosis, a mitochondria-dependent route with proper regulation of bcl-2 and p53 in EC-109 cell (Duan et al. 2017).

Cervical cancer

Cancer that originates in the cells of the cervix is referred to as cervical cancer. In human SiHa cervical cancer cells, phloretin (60 μM) demonstrated substantial inhibition of invasion and migration by downregulation of matrix metalloproteinase (MMP)-2, MMP-3, cathepsin S and mesenchymal markers such fibronectin, vimentin, and RhoA as well as the epithelial-mesenchymal transition brought on by transforming growth factor-1(Hsiao et al. 2019). Another study showed that phloretin increases BAX, activates caspases to induce apoptosis and decreases Bcl2 and MMPs by stopping cell growth (Tuli et al. 2022a). Phloretin also causes cytotoxic activity to be induced in human HeLa cell lines and suppresses the viability of the cells (Abu-Azzam et al. 2022).

Lung carcinoma

The lungs are the primary site of origin for lung cancer, although the disease can also extend to lymph nodes and other organs. Phloretin had an anti-cancer activity in lung cancer A549 cell lines at a 20 mg/kg dose by inducing apoptosis via the P38 MAPK and JNK1/2 pathways in vivo, while increasing the expression levels of BAX, cleaved caspase-3 and -9, and the degraded form of PARP at a 200 μM dosage in A549 cell line (Min et al. 2015). NSCLC starts at the cellular level and causes aberrant lung cells to proliferate quickly and uncontrollably. Phloretin dramatically increased P38 MAPK and JNK1/2 phosphorylation, which inhibited cell proliferation and increased BAX expression, caspase-3, caspase-9, and the degraded form of PARP, while decreasing Bcl-2 in an in vitro model of NSCLC cell line A549. Furthermore, in A549 xenografts, Phloretin at 20 mg/kg exhibited an increasingly substantial tumour growth-inhibiting effect (Min et al. 2015).

Leukemia

Cancer that affects the blood-forming tissues of the body, including the bone marrow and the lymphatic system, is referred to as leukemia. Phloretin (0.1–0.2 mM) increases the Caspase3 activity in human leukemia HL60 cell lines by stopping PKC activity, leading to inducing apoptosis (KoBoRI et al. 1999). A summary of the chemotherapeutic action of Phloretin against human malignancies is tabulated in Table 2.

Combination of phloretin with other agents in cancer treatment

Although future studies are necessary for strong evidence, according to the previous literature review, phloretin might have therapeutic efficacies against a wide range of cancers. However, a combination of Phloretin with other phytochemical or conventional drugs can show more effectiveness because of their synergistic activities at single or several target sites connected to the regulation of cancer. For example, Phloretin has a synergistic anti-tumour effect when taken with radiation, possibly via inducing apoptosis, reducing cell proliferation and cell growth rate at the same time glucose transport in lung cancer in Lewis lung cancer (LLC) xenograft model (Tang and Gong 2021). Phloretin with atorvastatin combination synergistically effective in colon cancer, induced apoptosis and G2/M phase cell cycle arrest through reducing cyclin B expression and upregulating of phospho-cdc2 and Myt1 at SW620 and HCT116 cancer cells (Zhou et al. 2018). Recent research indicates that the combination of Phloretin and cisplatin enhances the therapeutic efficacy of cisplatin by promoting the inhibition of MMP-2, Bcl-2, and MMP-9 with increased levels of cleaved-caspases in A549 cells (Ma et al. 2016). Abkin and colleagues investigated the anti-tumour activity of recombinant HSP70 Chaperone in combination with Phloretin. They discovered that the penetration of HSP70 into K562 cells increased its anticancer effect at in vitro and in vivo melanoma model (Abkin et al. 2016). Phloretin, in combination with daunorubicin, overcomes hypoxia-induced drug resistance by sensitizing daunorubicin-resistant SW620 and K562 cancer cells to its anti-tumor effects and apoptosis (Cao et al. 2007). Berbamine with phloretin efficiently demonstrated anti-tumor effects in two SORA-resistant hepatocellular carcinoma cell lines by augmenting SHP-1, basal, and IL-6-induced the inactivation of STAT3 (W. Zhao et al. 2020). Phloretin substantially induced cytoprotective autophagy in breast cancer cell lines by modulating the mTOR/ULK1 pathway with chemotherapeutic agents such as tamoxifen and doxorubicin (Chen et al. 2021). Phloretin has been observed to be a good combination with other natural products. For example, Payne et al. showed that Phloretin and phloridzin act as anti-neoplastic agents in the HeLa cell line, indicating a better treatment option for cervical cancer (Badwaik, Tockstein, and Thompson 2018). Ruthenium is an inorganic compound. Ruthenium-phloretin chemotherapy is an effective treatment because it modifies intrinsic apoptosis and the anti-angiogenic pathway by modulating p53, Bcl2, and Bax and reducing the PI3K/Akt/mTOR and MMP9-regulated tumour invasive pathways in MCF-7 and MDA-MB-231 breast cancer cell lines (Roy et al. 2022). Phloretin and gemcitabine inhibit cell proliferation, migration, and reverse drug susceptibility in Panc-1 cells in a tumour xenograft model by involving CXCL12/CXCR4-dependent MAPK signaling and ROS pathways (Brij B Patel et al. 2016). An overview of the synergistic activity of Phloretin with

Table 2 Summary of chemotherapeutic activity of Phloretin against human malignancies

Cancer type	Dose	Type of Study (In vitro *and* In vivo)	Molecular Mechanism	Molecular Target	References
Breast	60–120 μM	In vitro MCF-7,MDA-MB-231 In vivo DMBA rat	↑Apoptosis ↓Proliferation ↑Invasion ↓Cell viability	↓Bcl2,PI3K/Akt/mTOR/ EGFR/VEGF, MMP-9 ↑Caspase-3,Bax, p^{53}	(He et al., 2020)
	10–150 μM	In vitro MDA-MB-231 In vivo BALB/c (nude mice bearing MDA-MB231 tumor xenografts)	↓Cell growth ↑Arrested cell cycle ↑Apoptosis ↓Migratory activity	↓Paxillin/FAK, Src,(α-sMA) ↑E-cadherin ↓N-cadherin, vimentin ↑P^{53}, P^{21}	(K. H. Wu et al. 2018)
	100 μM	In vitro MCF-7 MDA-MB-231	↓Cell Migration	↓GLUT1, GLUT12 expression	(Matsui et al. 2017)
	200 μM	In vivo *and* In vitro MCF-7 Balb/c (mice with MDA-MB-231 cell)	↓Autophagy flux ↓Cell proliferation ↑Cellular protective autophagy ↓Tumor cell growth	↓mTOR/ULK1 ↓LCB-II	(Chen et al. 2021)
	100 μM	In vitro MDA-MB-231	↓Cell proliferation ↑Apoptosis	↑Caspase-3	(Nair, Ziaullah, and Vasantha Rupasinghe 2014)
	100 μM	In vitro MDA-MB-231	↓Cell growth	↑ROS ↓Cell transport	(Brijesh B. Patel et al. 2017)
	N/A	in vitro MCF-7 MDA-MB-231	↓Cell proliferation ↑Apoptosis	↑Arrest G2/M phase ↓TPA-induced ERK1/2 phosphorylation ↑LC3B, ↑p21 ↓TPA-induced tumorigenesis of JB6 P + cells	(Schiavano et al. 2015)
	100 μM	in vitro H-Ras MCF10A	↓Cell proliferation ↑Apoptosis	↑Caspase-3,Bax, p^{53} ↑P38 MAPK,JNK ↓Bcl-xl	(M. Kim et al. 2009)
Prostate	100 μM	In vitro PC3, DU145 and LNCaP	↓Cell proliferation ↑Oxidative stress ↓Cell viability	↓VEGF,CCND1,CCNB1 ↑Caspase3/9,Bax ↓ Bcl2,XIAP, Survivin	(C.-H. Yang et al. 2022)
	0,20,50,100 μM	In vitro LNCaP,CWR22Rv1, PC-3, and DU145	↑Cell cycle arrest ↑Apoptosis	↑Arrest G2/M phase ↓Cyclin B1, XIAP, and Bcl-2 ↑Caspase 3	(Kang et al. 2020)
	100 μM	In vitro LNCaP	↓Cell growth ↑Apoptosis	↑BAX/Bcl-2	(Kang et al. 2020)
	50,100 μM	In Vitro LNCaP	↑ Cell death	↑MTT cytotoxicity, C1-C5	(Szliszka et al. 2010)
	25 μM	In vitro LNCaP	↓Proliferation ↓Cell growth	↓GLUT1,GLUT14 expression	(Gonzalez-Menendez et al. 2014)
	39.4 μM	In vitro PC-3	↓Proliferation ↓Cell growth	↓GLUT1,GLUT14 expression	(Gonzalez-Menendez et al. 2014)

Table 2 continued

Cancer type	Dose	Type of Study (In vitro *and* In vivo)	Molecular Mechanism	Molecular Target	References
Colon	5 μM	In vitro HT-29-Luc	↑Apoptosis	↑Caspase-3,-8,-9 ↑Mac-1	(J.-L. Kim et al. 2022a, b)
	1.86 × 10^4 μM	In vitro HT-29 cell line	↑Apoptosis ↑Fragmentation of DNA ↓Cell proliferation	↑Caspase-3, Bax,p^{53} ↓VEGF,mTOR ↓Bcl-2,NF-κB,MMP-9	(Jin et al. 2020)
	NA	In vitro SW-1116	↑Killing effect of γδ T cells	↑PFP and GraB, ↑IFN-γ, ↓Wnt signaling pathway	(S.-P. Zhu et al. 2013a, b)
	0–100 μM	In vitro HT-29	↑Apoptosis ↓Viable cell number	↑Caspase-8,-9,-7,-3, poly(ADP-ribose) polymerase ↑Cytochrome c and Smac/Diablo	(Park et al. 2007)
	100 μM	In vitro SW620 and HCT116	↓Cell survival ↓Cell viability ↑Apoptosis	↑Arrest at the G2/M ↓Cyclin B,cdc2 ↑Phospho-cdc2 and Myt1	(Zhou et al. 2018)
	0-100 μM and 25 mg/kg	In vitro COLO 205 and HT-29 In vivo BALB/c nude mice bearing COLO 205 tumor xenografts	↓Cell growth ↓Tumor cell invasiveness	↓GLUT2 expression ↑G0/G1 phase cell cycle arrest ↑p21/Cip1 and p27/Kip1	(S. Lin et al. 2016)
	25-300 μM	In vitro HCT-116 and SW-480	↓Cell proliferation, ↓Colony formation ↓Migration ↑Apoptosis	↑G2/M phase cell cycle arrest ↑ROS,Bax ↓Bcl-2, CyclinD1, c-Myc, and *Survivin* ↓Wnt/β-catenin signaling	(Kapoor and Padwad 2023)
Liver	200 μM	In vitro HepG2	↑Apoptosis	↓GLUT2 expression	(C. H. Wu et al. 2009a, b)
		In vitro HCC In vivo Hep G2, SK-Hep1	↑ Apoptosis ↓Cell Growth	↑SHP-1 Expression ↓STAT3 expression ↓pAKT/pERK, Akt/VEGFR2 pathway	(Saraswati et al. 2019)
	1–200 μM	In vitro HepG2	↓Cellular Uptake ↓Nuclear Receptor binding of T3	↓TSH ↓T4 5'-deiodinase	(Movius et al. 1989)
	50–150 μM 10 mg/kg	In vitro HepG2 cell, Hep 3B In vivo SCID Mice	↑ Apoptosis ↓Cell Proliferation	↓Caspase-3 and -9, PARP ↑G0/G1, G2/M arrest	(K. C. Yang et al. 2009)
	N\A	In Vitro SMMC-7721	↑Apoptosis ↓Cell proliferation ↓DNA synthesis	↑G1 Phase arrest	(Hui Wang 2012)
	50 μM	In vivo Male C57BL/6 J mice In vitro HepG2 cells	↑Hepatic steatosis ↑Mitochondrial biosynthesis ↓Mitochondrial swelling	↑Fatty acid β-oxidation ↑SIRT1/PGC-1α ↑SIRT3/CypD	(Han et al. 2021)

Table 2 continued

Cancer type	Dose	Type of Study (In vitro *and* In vivo)	Molecular Mechanism	Molecular Target	References
Pancreatic	100 µM	In vitro Panc-1 (CAF-exposed)	↓Cell growth, Migration ↑Apoptosis ↑Antitumor effects, ↓Cell growth	↓MAPK signaling, SOD activity ↓ERK, MEK, Akt Phosphorylation ↑ROS ↓Superoxide dismutase ↓CXCL2/CXCR4	(Brij B Patel et al. 2016)
Kidney	20–40 µM	In vitro HEK- 293	↑Apoptosis ↓Cell growth	↑ (t-BOOH) ↑ROS	(Funari et al. 2011)
	10 µM	In vitro HEK293-hTLR2, HEK293-nul	↓Cell survival ↓Inflammation	↓TLR2, TNF-α, IL-8 ↓ Pam3CSK4	(J. Kim et al. 2018)
	50 µM	In vivo HUA mice In vitro HK-2	↓Inflammation ↓Renal dysfunction ↓Renal fibrosis ↓Glucose transport	↓IL-1β ↓ ROS ↑PGC-1α ↓ECM,α-SMA,BUN/UCAR ↓ GLUT9	(Cui et al. 2020)
Oral	12.5 µM	In vitro SCC-1 cell	↓Cell proliferation ↑Reactive oxygen species (ROS) ↓Cell migration ↑Necrosis ↑Cell cycle arrest	↑G0/G1 Phase ↓Cyclin D1, CDK4 and CDK6 expression	(G. Yang et al. 2020)
	NA	In vitro YD-9 cells	↑ Apoptosis ↑Cell cycle arrest ↓Glucose uptake ↓Cell proliferation	↓GLUTs ↑p53, Bax	(Nam et al. 2017)
	40 µM	In vitro B16 melanoma 4A5 cell	↑Apoptosis	↓Protein kinase C	(Anand and Suresh 2014)
Glioblastoma	0–300 µM	In vitro U87 and U251 cell line	↓Cell proliferation ↑Apoptosis ↑Mitochondrial apoptosis and ROS	↑Arrest G0-G1 phase ↓cdk2, cdk4, cdk6, cyclin D and cyclin E ↓PI3K/AKT/mTOR signaling cascades ↑Bax, Bak and c-PARP, P^{27} ↓Bcl-2	(Liu et al. 2016)
	200 µM	In vitro SH-SY5Y cell	↑Autophagy ↓Cell viability	↑JNK activation ↓p-AKT and p-mTOR levels ↑JNK-Beclin-1 pathway	(Fan et al. 2022)
Ovarian	0.6–300 µM	In vitro OVCAR5 TOV112D OVCAR3 CAOV3	↑Apoptosis ↓Glycolysis	↓GLUT1, HKII,PFKFB3 ↓PDHK1,LDH	(Xintaropoulou et al. 2015)

Table 2 continued

Cancer type	Dose	Type of Study (In vitro *and* In vivo)	Molecular Mechanism	Molecular Target	References
Cervical	60 µM	In vitro	↓Metastasis	↓MMP-2	(Hsiao et al. 2019)
		SiHa	↓Angiogenesis	↓MMP-3	
				↓Cathepsin S	
	N/A		↓Proliferation	↑BAX, Caspases	(Tuli et al. 2022a)
			↓Metastasis	↓Bcl-2	
			↓Angiogenesis	↓MMPs	
			↑Apoptosis	↑Cytokines	
	N/A	In vitro	↑Cytotoxic Activity	N/A	(Abu-Azzam et al. 2022)
		HeLa	↓Cell viability		
Bladder	20 µM	In vitro	↑Apoptosis	↑ROS	(Hui 2020)
		RT112	↓Migration		
		AQP9	↓Proliferation		
Lung	20 mg/kg	In vivo	↑Apoptosis	↑P38 MAPK,JNK1/2	(Min et al. 2015)
		A549 xenografts model	↓Migration	↓Bcl-2	
	200 µM	In vitro		↑PARP,Caspase-3,9, BAX	
		A549			
Myeloma	100 µM		↓Proliferation	↓GLUT4	(McBrayer et al. 2012)
			↓Glycolysis	↓GLUT8	
				↓GLUT11	
	200 µM	In vitro	↓Proliferation	↓TXNIP	(Friday et al. 2011)
		ARH77	↑Apoptosis	↑ROS	
				↑TRX Activity	
Skin	25 µM	In vitro	↑Apoptosis	↓COX-2.Elastase,MMP1	(Casarini et al. 2020)
		Melanoma 4A5 cells	↓Metastasis		
	NA	In vitro	↑Apoptosis	↓MMP9	(Casarini et al. 2021)
		SK MEL28	↓Metastasis		
Melanoma	0.1–0.2 mM	In vitro	↑Apoptosis	↑ Actinomycin D	(KoBoRI et al. 1999)
		4A5		↑Caspase1	
				↑Caspase3	
				↑BAX	
Leukemia	0.1–0.2 mM	In vitro	↑Apoptosis	↓ PKC	(KoBoRI et al. 1999)
		HL60		↓ Caspase3	
Thyroid	N/A	In vitro	↓Proliferation	↑BAX,Caspase-3,8,9	(P. Ma et al. 2022)
		SW579	↑Apoptosis	↓Bcl-2	
				↓PI3K, Akt	
Osteosarcoma	N/A	In vitro	↓Glycolysis	↓ GLUT	(Ogawa et al. 2021)
		U2OS		↑ 2-NBDG	
				↑ 2-NBDLG	
				↓SGLT	
Esophageal	60–100 µM	In vitro	↑Apoptosis	↑p53	(Duan et al. 2017)
		EC-109		↑Apoptotic protease activating factor-1	
				↓Bcl-2	

other phytochemicals and conventional chemotherapeutic agents is tabulated in Table 3.

Power of phloretin in alleviating multi-drug resistance of existing chemotherapeutics drugs in numerous cancer types

Due to numerous serious issues, such as multi-drug resistance, treating cancer patients is becoming difficult (So et al. 2009). This resistance mechanism may result from a variety of potential protective mechanisms, including drug efflux (Po and Pc 2012), drug inactivation (Akhdar et al. 2012), drug detoxification (Akhdar et al. 2012), drug target modification (Lynch et al. 2004), involvement of cancer stem cells (Costea et al. 2020), miRNA dysregulation (Si et al. 2019), epigenetic alteration (Mansoori et al. 2017), and other numerous irregular DNA damage/repair mechanisms, tumour microenvironment, and ROS modulation (Si et al. 2019; Costea et al. 2020; Mansoori et al. 2017). Drug resistance is linked to several proteins, including P glycoprotein (P-GP), MRP 1, MRP 1–9, BCRP, and changes in beta-tubulin (Xue and Liang 2012). However, previous research on natural phytochemical-based selective inhibitors of multi-drug resistance protein might improve the effectiveness of cancer chemotherapy(Molnár et al. 2010). However, most had numerous adverse effects and were ineffective at their intended location. The effectiveness of cancer treatment may potentially be improved by blocking MDR-efflux proteins. In human Panc-1 pancreatic cancer cells, co-treatment with phloretin and daunomycin significantly increased the accumulation of daunomycin and vinblastine by inhibiting drug transport via MRP1 (Nguyen et al. 2003). Zhao et al. describe that phloretin is an effective substrate of P-gp, MRP2, and BCRP and works with active transport, efflux protein transport and cell bypass (Zhao et al. 2020). Molnár et al. described that phloretin is an effective modulator to overcome the resistance of anticancer drugs, where phloretin identified as a potent P-gp inhibitor in mouse lymphoma cells (L1210) and human breast cancer cells MDA-MB-231 cell line (Molnár et al. 2010). Furthermore, phloretin inhibited P-gp-mediated cellular efflux in MCF-7 and MDA435/LCC6 breast cancer cell lines (Zhang and Morris 2003). Phloretin suppresses STAT3 expression in sorafenib-sensitive and resistant HCCs via SHP-1-mediated inhibition of STAT3 and AKT/mTOR/JAK2/VEGFR2 pathway, suggesting that Phloretin could potentially become an anticancer agent for hepatocellular carcinoma by overcoming sorafenib resistance (Saraswati et al. 2019). Phloretin inhibited active efflux and reduced steady-state accumulation of VCR in PC-V40 subline in vincristine (VCR)-selected murine erythroleukemia (MEL) PC4 cell lines. In doxorubicin-resistant SNU-1 gastric cancer cells, Phloretin inhibited proliferation by inducing cell cycle arrest at G0/G1 phase by depleting cyclin D1 and D2 expression, activating autophagy by increasing LC3B II and Beclin-1 expression, and blocking the ERK1/2/MAPK signaling pathway (You et al. 2020). Figure 8 describes the synergetic and overcoming resistance mechanism of Phloretin.

Nano formulation strategies of phloretin with the aim of better bioavailability

According to the literature review, Phloretin has many therapeutic functions, including antioxidant, anti-inflammatory, anti-diabetic and anti-tumour (Crespy et al. 2001; Tuli et al. 2022a). However, its low bioavailability limits its efficacy as a cancer treatment. Nanoformulation strategies can help improve the bioavailability of phloretin and enhance its therapeutic potential in cancer treatment. Phloretin's bioavailability is increased when combined with nanomaterials, a novel method of treating cancer cells. In cancer treatment, the choice of nanoformulation method depends on various factors such as the desired route of administration, therapeutic goals, and the physicochemical properties of Phloretin. Some possible strategies include nanoparticles, nano-emulsions, solid lipid nanoparticles (SLNS), nano-suspensions, self-emulsifying drug delivery systems (SEDDS), co-crystals, nanoparticles with targeting ligands, inclusion complexes, surface modifications and quality control and characterization can ensure the safety and efficacy of the nano-formulation before it can be used for clinical applications. In vitro, phloretin in NLC had a sustained release pattern more suited for absorption than phloretin ethanol solution. Phloretin-loaded chitosan nanoparticles (PhCsNPs) were used to demonstrate PhCsNPs' anticancer effectiveness through the measurement of cytotoxicity, intracellular ROS, mitochondrial dysfunction, lipid peroxidation, antioxidant status, apoptotic-associated gene expression profile, and cell cycle analysis in human oral cancer cell lines

Table 3 Overview of synergistic activity of Phloretin with other phytochemicals and conventional chemotherapeutic agents

Cancer type	Combined agents (pharmaceutically authorized)	Dose (Phloretin + Std drugs)	Cell line	Combined target	References
Colon cancer	Atorvastatin (Yes)	(0–200 μM + 0–20 μM) 10:1	SW620 and HCT116 cell	↑G2/M phase cell cycle arrest ↓Cyclin B ↑Phospho-cdc2 and Myt1	(Zhou et al. 2018)
Lung cancer	Cisplatin (Yes)	5–50 μg/ml + 5–50 μg/ml 1:1	A549 cell	↓Bcl-2, MMP-2, and MMP-9 ↑Cleaved-caspases	(L. Ma et al. 2016)
Melanoma	HSP70 chaperone (Not available)	(20 μM + 50 μg/ml)	B16 and K562 cells	↑IFN-γ production	(Abkin et al. 2016)
Hepatocellular carcinoma	Berbamine (Yes)	Dose dependent	PRF-PLC-5 and HCC-Lm3 cells	↑SHP-1, basal and IL-6-induced STAT3 inactivation	(W. Zhao et al. 2020)
Breast cancer	Doxorubicin (Yes)	100–200 μM + 0.5-1 μM	MCF7 and MDA-MB-231 cells	↓mTOR/ULK1 pathway	(Chen et al. 2021)
	Ruthenium(Yes)	Dose dependent	MCF-7 and MDA-MB-231	↑p53, Bcl2 and Bax ↓PI3K/Akt/mTOR pathway ↓MMP9	(Roy et al. 2022)
Cervical cancer	Phloridzin (Not available)	Not available	HeLa cell line	↓SGLT2 inhibition	(Payne et al. 2018)
Pancreatic cancer	Gemcitabine (Yes)	100 μM + 80 μM	Panc-1 cell	↑CXCL12/CXCR4-dependent MAPK signalling ↑ROS pathways	(Alsanani et al. 2015)

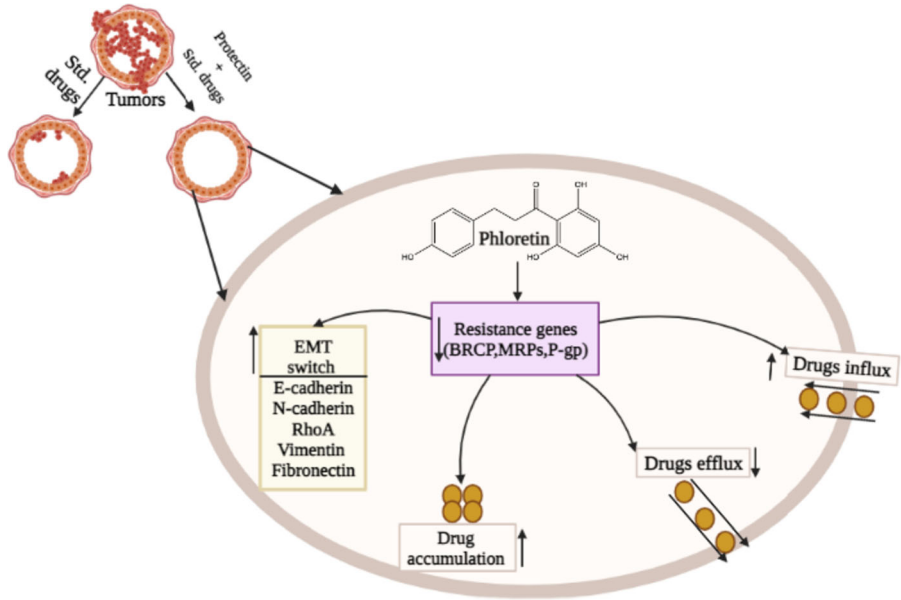

Fig. 8 Graphical presentation of synergistic and alleviating multidrug resistance by Phloretin

(YD-9, CA9-22) by releasing Bax, cytochrome-c, and caspases-3 -9 (Arokia Vijaya Anand Mariadoss et al. 2019a, b; Arokia Vijaya Anand et al. 2019). Phloretin was delivered locally to oral malignancies (YD-9 cell lines) using a fast-dissolving nanofiber (NF) made of poly(vinyl alcohol) (PVA) and D-a-tocopheryl polyethene glycol succinate (TPGS), which also boosted the phloretin's anti-proliferation effectiveness (Nam et al. 2017). In MDA-MB-231 cells (human breast adenocarcinoma cells that express the GLUT1 and CD44 receptors), HACE-d/phloretin NPs showed improved cellular accumulation efficiency, anti-proliferation, and spheroid growth-inhibitory impact at 279 μM concentration. The optical imaging test revealed that the MDA-MB-231 tumour-xenografted mice HACEd/phloretin NPs group had improved anticancer efficacies compared to the other experimental groups (Lee et al. 2017). Flow cytometry was monitored to evaluate the anti-neoplastic effectiveness of the phloretin-attached AuNPs against cervical malignant cell lines (HeLa) (Badwaik, Tockstein, and Thompson 2018). Phloretin-loaded NC-Phl, a novel semi-solid formulation (HG-NCPhl), increased skin penetration and adherence while having a cytotoxic impact on Sk-Mel-28 cells (Casarini et al. 2021). In research, chitosan-coated nanoparticles with phloretin (CS-PLGA/Phl) were examined in vivo using monolayer-growing mouse melanoma cells (B16F10) (Lee et al. 2019). A recent study shows that polymerization-induced self-assembly creates microscopes of cross-linked poly (cyclotriphosphazene-co-phloretin) (PCTPPT). The regulated release of the anti-cancer model medication (CPT) is effectively explored in various pH media (Mehmood et al. 2022). These results imply that phloretin can be introduced into nanoparticles to increase their stability and enhance biological capabilities.

Toxicity of phloretin

Phloretin provides hundreds of therapeutic benefits, however, it may also address several adverse implications or toxic reactions. There may be risks when phloretin is administered to mammalian cells at high dosages, according to a recent study on the substance's related toxicity (de Oliveira 2016). In a corroboration analysis of toxicity, they observed that Phloretin was given at APAP models alone at the maximum dose rate (2.4 mmol/kg), ultimately caused total lethality within 24 h & lower doses were not harmful, while the most significant oral dose alone generated 64% lethality(Geohagen et al. 2018). Despite having cytoprotective properties, Phloretin tended to be toxic in our APAP models (Geohagen et al. 2018). Exposure to 0.1 Mm of phloretin for one hour in primary cultured rat hepatocytes significantly inhibited GSH content and MMP activity, leading to severe cytotoxicity (Frerichs and Ball 1964). Another experiment showed that phloretin could simulate PINK1 knockdown in primary astrocytes at high concentrations, reducing cellular function, viability, and proliferation(Choi et al. 2013). Moreover, Phloretin (30 μM for 60 min before exposure to Amyloid-β) also decreased the toxicity that Aβ peptides induced in cultured PC12 cells. But it's interesting to note that PC12 cells were cytotoxic to phloretin at 300 μM (de Oliveira 2016). One more controversy surrounding Phloretin is its safe consumption levels. The safety of Phloretin consumption remains a topic of discussion. Most people obtain Phloretin from dietary sources like soy and red clover. Consuming moderate amounts of Phloretin from these sources is considered safe for the general population. However, high-dose supplements or concentrated forms of Phloretin may pose risks, particularly if taken by individuals with a history of hormone-related cancers or hormonal imbalances. Additionally, the effects of Phloretin may vary from person to person. Genetic factors, diet, and hormonal status can influence how Phloretin interacts with the body. More investigations on the parent phloretin's safety are needed before human clinical trials can evaluate the bioactive compound's anticancer potential (Fig. 9)

Pharmacokinetics of Phloretin and future perspective in drug development

Lipinski's "Rule of Five" was employed for the "drug-likeness" test, and compounds met the requirements. More precisely, it was revealed that Phloretin's molecular weight, QPlogPo/w, HBD, and HBA were 274.080 g/mol, 2.1, 4, and 5, respectively, indicating that the compounds had good drug-like properties. The ADMETLAB 2.0 server was used to determine the physicochemical properties of phloretin, including molecular weight (MW), volume, density, nHA, nHD, nRot, nRing, MaxRing, nHet, fChar, nRig, flexibility, stereo centres, TPSA, logS, logP, and logD. These results are illustrated in Fig. 10.

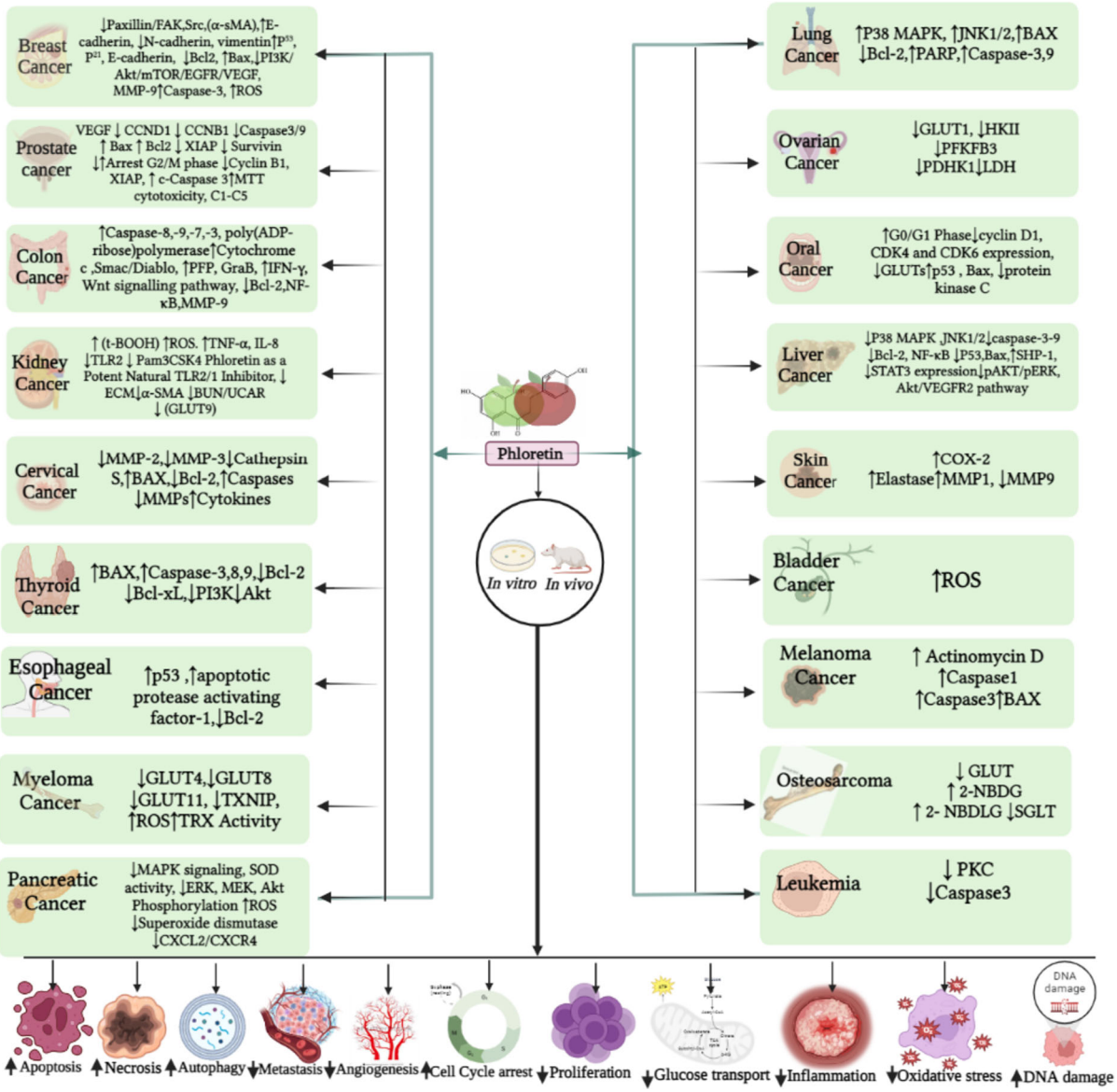

Fig. 9 Overview of anti-cancer profile of Phloretin against human malignancies

In assessing whether or not to advance a molecule to the clinical stage, the assessment of drug absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction may assist in minimizing the risk, time, and expenditure entailed (Wu et al. 2020; Lin et al. 2005; Sohel, Sultana, Sultana, Al Amin, et al. 2022). Table 4 depicts the pharmacokinetics profile of phloretin using in-silico techniques like Schrodinger's QuickPro modules and the publicly available server admetSAR, which gives credible information on absorption, distribution, metabolism, excretion, and toxicity.

Drugs must be absorbed to reach the bloodstream and be used daily. In accordance with what we had anticipated, phloretin could be readily absorbed when taken orally and may pass via skin, gut, and kidney cells. Drug movement within the body is referred to as a distribution, and it depends on several variables, along with the permeability of the blood–brain barrier, the permeability of the central nervous system, the drug's capacity to attach to plasma proteins, and the

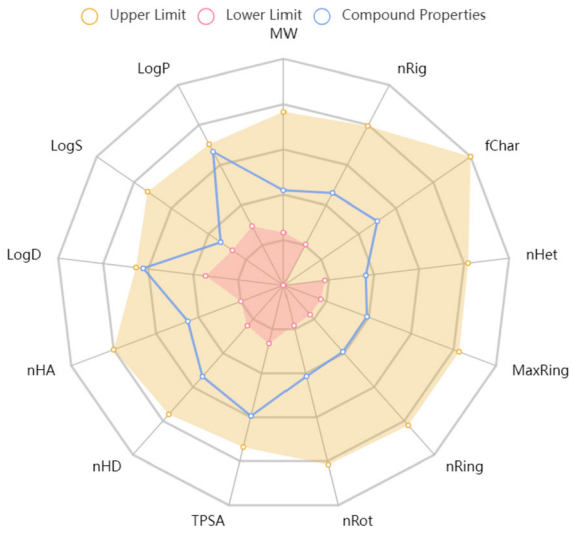

Fig. 10 In silico pharmacokinetics evaluation of Phloretin. Note: MW(Molecular weight), Volume(Vander Waals Volume), Density, nHA (The number of hydrogen bond acceptors), nHD (The number of hydrogen bond donors), nRot (Number of ratable bond), nRing (Number of ring), MaxRing (Number of atom in the biggest ring), nHet (Number of hetero atoms), fChar (Formal charge), nRig (number of rigid bond), flexibility, stereo centres, TPSA(Topological polar surface area), logS (Water solubility), logP (Partition coefficient), logD (Distribution coefficient)

cumulative volume of distribution. Drug concentrations in the bloodstream are reduced dramatically when they bind to plasma proteins such as human serum albumin, lipoprotein, glycoprotein, and globulins. The fact that our intended compounds fall within the recommended range indicating they have a good chance of reaching the target spot and moving freely through the bloodstream. The quantity of bodily fluid necessary for blood plasma to dissolve is known as the volume of distribution. Thankfully, phloretin is highly likely to spread evenly throughout blood and tissue. The central nervous system and blood–brain barrier (QPlogBB) are also critical for medications that address brain disease. However, Phloretin's ability to penetrate the central nervous system and a brain-blood barrier is low.

More than 80% of medications go through the CYP450 enzyme's detoxification process in the liver during first-pass metabolism, and blocking this enzyme increases drug toxicity and causes several side effects. According to the expected metabolic outcome, phloretin is a substrate for many CYP450 subunits, including CYP2C9 and CYP2D6. Phloretin's in silico toxicity profile was predicted using data on hepatotoxicity, cardiotoxicity, skin sensitization, kidney toxicity, eye irritation, and AMES toxicity. Phloretin has demonstrated toxicity against these effects and toxicity against the eye, skin and AMES. Using the total clearance (CLtot) and T 12, we estimated the clearance profile based on the renal clearance property of the compounds. As anticipated, the findings showed that phloretin can be easily eliminated from the human body after performing its therapeutic function. In silico drug-likeness and pharmacokinetics properties profile of Phloretin is summarized at Table 3.

Given that there are fewer toxicity hazards, the pharmacokinetics profile of phloretin predicts good lead and efficiency. So, in the context of cancer treatment and drug discovery, phloretin can serve as an excellent starting point for drug design techniques like docking and pharmacophore-based virtual screening.

Concluding remark and future recommendation

Treating human disorders, including cancer patients, has significantly benefited from using natural products. Due to its inexpensive cost, wide availability, and extended usage history, phloretin may be a promising drug for treating cancer like other plant-based anticancer drugs. We believe that our review is the first of its kind to systematically review the remarkable anticancer potential of phloretin. across a diverse spectrum of cancer types, diverse mechanisms, combinational effect with conventional drugs, reversing antineoplastic activity of resistance drugs, safety profile.Our systematic review showed that phloretin has an anticancer effect against numerous malignancies, including lung, oral, oesophagal, gastric, colon, liver, breast, pancreatic, kidney, glioblastoma, ovarian, cervical, bladder, myeloma, skin, melanoma, leukaemia, thyroid, osteosarcoma, oesophagal and prostate cancer. It can be seen that phloretin employs multiple mechanisms to halt cancer progressions, such as modulation of the signalling cascade associated with apoptosis, autophagy, necrosis, metastasis, angiogenesis, cell proliferation, glucose absorption, oxidative stress, inflammation and DNA damage (Fig. 9). Phloretin's ability to prevent cancer has been connected in particular to the control of several

Table 4 In silico drug-likeness and pharmacokinetics properties profile of Phloretin

Descriptors		Predicted remarks		Comments
		Predicted value	Recommended rage	
Drug likeness	Molecular weight	274.080 g/mol	130.0–500	Good
	QPlogPo/w	–2.1	–2.0–6.5	Soluble
	donorHB	4	0.0–6.0	Good Donor
	accptHB	5	2.0–20.0	Good Acceptor
Absorption	PercentHuman OralAbsorption	73.48	> 80% is high	Highly absorbed
	Skin Permeability	–3.91	–8.0 to –1.0	Highly permeable
	Caco2 permeability	80.19	25–500	Permeable
	MDCK permeability	1e-05	NA	Effective
	P-glycoprotein substrate	Yes	NA	Effective
Distribution	BBB permeability	–1.985	–3.0–1.2	Poorly permeable
	CNS permeability		–2 to + 2	Poorly permeable
	Human serum albumin	93.963%	60%	High binding affinity
	VDs	0.563	NA	Good distribution
Metabolism	CYP1A2 substrate	No	NA/YES	Non-effective
	CYP2C19 substrate	No	NA/YES	Non-effective
	CYP2C9 substrate	Yes	NA/YES	Effective
	CYP2D6 substrate	Yes	NA/YES	Effective
	CYP3A4 substrate	No	NA/YES	Non-effective
Toxicity	Eye irritation	Yes	NA/YES	Toxic
	Hepa-toxicity	No	NA/YES	Non-toxic
	AMES toxicity	Yes	NA/YES	Toxic
	hERG I inhibitors	No	NA/YES	Non -toxic
	Kidney toxicity	No	NA/YES	Non-toxic
	Skin sensitization	Yes	NA/YES	Toxic
Excretion	CL	15.737		Clearable
	T 1/2	0.923		Clearable

proteins Bcl-2, Bax, Bak, Bad, caspase, cyclins (B1, D1, E) and CDKs (4, 6,7) p18, p21, p27, p53, MMP-2, MMP- 8, MMP-9, Wnt/-catenin, PARP, TNF-α, NF-κB, IκB kinase, IL-1β, TNF-α, phospho-Akt, phosphor-p65, NF-κB, PI3K/Akt, MAPK/ERK, p-mTOR. Phloretin may have more potent anticancer effects when coupled with other phytochemicals or conventional drugs than when taken alone. Such synergistic mechanisms aid in alleviating resistance to conventional drugs used in cancer treatment. Phloretin has a good combination with some nano-particles, which adds an extra advantage to improve the bioavailability of phloretin in cancer treatments. Moreover, phloretin has a good structure–activity relationship, positively impacting cancer biology therapeutics. Phloretin possesses favourable in silico pharmacokinetic properties such as absorption, distribution, metabolism, excretion, and less toxicity. However, like many potential cancer treatment strategies, Phloretin has limitations, including limited clinical evidence, low bioavailability, specificity of action, side effects, interaction with other drugs, and optimum doses. Therefore, more research on well-designed clinical trials to evaluate the long-term actual safety and efficacy, improving bioavailability, combination with other cancer therapies, such as chemotherapy, radiation, or immunotherapy, and strategies to prevent or overcome resistance should be explored before recognizing phloretin as a standard cancer biology drug.

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