BioChem

MDPI

Review

An Overview of the Therapeutic Potential of Dimeric Flavonoids for Targeting Cancer Hallmarks

Inês Lopes [1,2,3,†], Isabel Meireles [1,3,†], Rafaela Rocha [1,3], Rui Medeiros [1,4,5] and Fátima Cerqueira [1,4,5,*]

1 Molecular Oncology and Viral Pathology Group, Research Center of IPO Porto (CI-IPOP)/RISE@CI-IPOP (Health Research Network), Portuguese Oncology Institute of Porto (IPO Porto)/Porto Comprehensive Cancer Center (Porto. CCC), Rua Dr. António Bernardino de Almeida, 351, 4200-072 Porto, Portugal; mil@ess.ipp.pt (I.L.); isabel.meireles@ipoporto.min-saude.pt (I.M.); rafaela_soares_rocha@hotmail.com (R.R.); ruimedei@ipoporto.min-saude.pt (R.M.)
2 Technical-Scientific Area of Clinical Analysis and Public Health, School of Health of the Polytechnic Institute of Porto, Rua Dr. António Bernardino de Almeida 400, 4200-072 Porto, Portugal
3 Department of Biomedicine, Faculty of Medicine of the University of Porto 4200-319 Porto, Portugal
4 FP-I3ID, FP-BHS, University Fernando Pessoa, Praça 9 de Abril 349, 4249-004 Porto, Portugal
5 Faculty of Health Sciences, University Fernando Pessoa, Rua Carlos da Maia 296, 4200-150 Porto, Portugal
* Correspondence: fatimaf@ufp.edu.pt
† These authors contributed equally to this work.

Abstract: Evidence found in the literature indicates that dimeric flavonoids constitute important therapeutic options against cancer. Using these molecules to prevent cancer progression might be a novel and promising therapeutic approach with advantages like fewer side effects, easy access in nature, overall health benefits and overcoming drug resistance. Cancer is a complex disease and still not understood, but there are some common mechanisms and biological characteristics underlying tumor progression that have been scrutinized over the years. This information was summarized in a conceptual framework designated as hallmarks of cancer. Dimeric flavonoids exert biological effects in several pathways involved in cancer hallmarks including cell growth, cell cycle, apoptosis, metastasis and metabolism.

Keywords: cancer; drug resistance; dimeric flavonoids; hallmarks

Academic Editor: Chol-Hee Jung

Received: 1 November 2024
Revised: 27 December 2024
Accepted: 6 January 2025
Published: 14 January 2025

Citation: Lopes, I.; Meireles, I.; Rocha, R.; Medeiros, R.; Cerqueira, F. An Overview of the Therapeutic Potential of Dimeric Flavonoids for Targeting Cancer Hallmarks. *BioChem* **2025**, *5*, 2. https://doi.org/10.3390/biochem5010002

1. Cancer and Therapeutic Natural Products

Cancer is a huge problem of public health that involves a group of diseases characterized by the uncontrolled growth and proliferation of abnormal cells, and if the spread of those cells is not controlled, it can result in the death of the patient [1]. Cancers are still a leading cause of death worldwide, and each year, in the European Union, 2.6 million people are diagnosed with cancer and more than 1.2 million deaths occur due to this disease [2].

According to the World Health Organization (WHO), in 2022, the most common cancers worldwide were breast, lung, colorectal and prostate cancers. In the same year, the cancers that caused the highest number of deaths were lung, colon and rectum, liver, stomach and breast [3].

The choice of cancer treatment depends on several factors associated with the stage of the cancer and the patient himself. The most conventional treatments for cancer therapy around the world include chemotherapy, radiotherapy and surgery. Recently, more targeted therapies are being applied, especially immunotherapy [4–6]. The primary goal of these treatments is to eliminate cancer cells while sparing normal cells. However, these conventional cancer treatments have several limitations: moderate to high toxicity to normal

cells, tissues and organs; lack of specificity for multiple subtypes of the same cancer or non-available options; side effects for the patient (like depression, fatigue, vomiting and hemorrhages) and drug resistance [6–9].

Therefore, there is an ongoing need to develop more effective treatments that target cancer cells more effectively but cause fewer side effects [8].

The role of plants in healthcare is prehistoric and has already been documented in various cultures. In fact, the WHO recognizes that 65% of the world's population primarily resorts to traditional medicine using plants as primary healthcare [9].

Natural products extracted from plants have a long history of being used to treat cancer by directly or indirectly altering signal pathways that affect the phenotypes of cancer cells, inducing apoptosis and inhibiting cell proliferation and angiogenesis [10,11].

For example, components of *Ginkgo biloba*, a plant traditionally used in Chinese medicine, can significantly inhibit the growth and proliferation of liver and gastric cancer cells, among other cancers [12]. For example, bilobetin triggers apoptosis, cell cycle arrest, ROS production, and DNA damage, while also inhibiting CYP2J2 activity [13]. In gastric cancer, ginkgolic acid inhibited cancer cells' proliferation, migration and epithelial–mesenchymal transition and promoted apoptosis and oxidative stress [14,15] The study of Kim et al. emphasized Ginkgo biloba extract's role in regulating tumor suppressors such as p53 and pro- and anti-apoptotic proteins like Bax and Bcl-2 [16].

In a study of seaweeds' potential anticancer activity, natural products extracted from the brown seaweed *Sargassum vulgare* have shown that algal polysaccharides inhibit cell proliferation and angiogenesis [2]. Curcumin, a bioactive compound extracted from *Curcuma longa*, showed anticancer activity against lung cancer by acting on the Wnt/β-catenin-dependent pathway and inhibiting the expression of vascular endothelial growth factor [17]. Foumani et al.'s study showed the capacity of colchicine from *Colchicum autumnale* to inhibit cell growth at a low concentration and promote apoptosis (by inducing Bax and p53 expression and decreasing Bcl2 expression) in MCF-7 and 4T1 breast cancer lines [18].

Flavonoids, a group of natural substances with variable phenolic structures, whether in monomeric or dimeric form, show selectivity for tumor cells and have a radio- and chemoprotective effect on healthy cells, but are radio- and chemosensitizers for cancer cells [19,20]. A study in an in vivo murine model of Ehrlich carcinoma showed that apigenin had a radiosensitizing effect marked by inducing apoptosis and downregulation of angiogenic and lymphangiogenic regulators [21]. Li et al. demonstrated that quercetin in combination with a low dose of radiation markedly inhibited HT-29 and DLD-1 colon cancer cells' proliferation by inhibiting Notch-1 signaling [22]. Ichrak et al. demonstrated that kaempferol, in combination with 5-Fluorouracil chemotherapy, had a synergistic inhibitory effect on cell viability, induced cell cycle arrest and apoptosis, and decreased reactive oxygen species in chemo-resistant LS174 colon cancer [23].

Amentoflavone sensitizes oral squamous cells to cisplatin [24] and lung cancer cells to carboplatin [25,26]. This compound also potentiates the effect of sorafenib in osteosarcoma [27] and hepatoma cancer cells [28].

While chemotherapy drugs were demonstrated to be effective against cancer growth during the primary stages of treatment, many patients develop resistance as the therapy time progresses, remaining the major challenge of conventional therapies [6,7]. In those cases, cancer cells evolve or adapt in ways that make them less susceptible or completely resistant to the effects of the drugs meant to kill or inhibit their growth [29]. This phenomenon can be developed by cancer cells through different mechanisms like genetic mutations, drug efflux pumps, DNA damage and repair, and epigenetic regulation [29]. Overall, it is a complex process because resistance to one drug can lead to cross-resistance

to other drugs with similar mechanisms of action and, consequently, result in treatment failure, relapse or limited therapeutic options [5].

Additionally, flavonoids also reduce chemotherapy resistance by having a synergic effect with chemotherapeutic drugs. In sorafenib treatments, for example, rhamentin decreased the metabolic clearance and also sensitized hepatocellular cancer cells to the drug [30], and apigenin increased the cytotoxic effect of that drug in HEpG2 cells by promoting apoptosis and decreasing cell migration and invasion [31]. Apigenin also had a synergic effect with abivertinib, promoting the inhibition of diffuse large B-cell lymphoma in vitro and in vivo in a mouse model by inhibiting p-GSK-3β and its downstream targets [32]. Wang et al. showed that cancer cells' chemoresistance to bortezomib can be overcome by using the flavone scutellarin, which increased apoptosis in an in vivo murine model of multiple myeloma [33].

Similar results from other studies have increased interest in finding active compounds in plant extracts, considered by the scientific community an important source of anticancer drug discoveries [13,34–36].

2. Flavonoids

2.1. Flavonoids

Flavonoids are a group of low-molecular-weight polyphenols found in plant-based products like fruits, vegetables and beverages like wine, juices, and tea [37,38]. This group of compounds can be classified into flavones, isoflavones, flavanones, flavonols, anthocyanidins and flavans depending on the oxidation state of the central carbon in the chemical structure [39,40]. In plants, flavonoids have a role in allowing cell growth and protecting against biotic and abiotic stress, UV light, freezing, heat and drought. Additionally, they protect plants against harmful microorganisms [38,41]. These properties offer numerous health benefits, making them essential in various applications. Their significance lies in their antioxidative, anti-inflammatory, antimicrobial, and anticarcinogenic properties, along with their ability to regulate key cellular enzyme functions [39].

Rutin has shown the ability to induce apoptosis, modulate angiogenesis and oxidative stress and inhibit cell growth in colorectal, gastric, breast, prostate and other cancers [42]. Silibin activates cellular checkpoints and cyclin-dependent kinase inhibitors (CDKIs) and, consequently, promotes cell cycle arrest in prostate, lung, colon, breast and cancers. This compound also showed anti-angiogenic activity by targeting VEGF and VEGF receptors [43]. Quercetin, besides its antioxidant and anti-inflammatory effects, also has anticancer activity that relies on cell cycle inhibition and influences apoptosis by regulating p53, Bcl2 and SOD-mediated apoptotic signaling pathways in breast, prostate, colon, ovarian and lung cancer cells. In vivo, it showed no toxicity after prolonged oral administration in mice [38,44]. Apigenin is able to interact with various miRNA inhibitors and miRNA mimics to suppress cancer cell growth and proliferation [45], induces apoptosis via activation of pentose phosphate pathway-mediated NADPH generation in HepG2 cells [46] and has effectively enhanced the action of cetuximab, significantly reducing p-STAT3 levels in HONE1 and CNE2 nasopharyngeal carcinoma cells [47].

Interest in the anticarcinogenic effects of flavonoids has grown due to in vitro and in vivo experimental evidence showing that they interfere with cancer processes such as cell proliferation, apoptotic and autophagic cell death, cell cycle arrest, angiogenesis, invasion and metastasis [40–42].

There are some clinical trials already completed or in progress for studying the efficacy and safety of flavonoids [42]. Catechins are in phase I and II trials for prostate, breast and cervical cancer; apigenin in phase II for colorectal cancer; quercetin in phase I for prostate cancer; cyanidin for colorectal adenocarcinoma; and genistein in phase II for

bladder, prostate and breast cancer. All these trials were approved by the Food and Drug Administration (FDA) [41].

2.2. Dimeric Flavonoids

A newly identified subclass of two-flavone structures, called dimeric flavonoids, like agathisflavone, amentoflavone and robustaflavone, has sparked scientific interest due to its revealed pharmacological effects like analgesic, anti-inflammatory, antimicrobial, antioxidant and anticancer activity [48,49]. Dimeric flavonoids are a type of flavonoids composed of identical or different flavonoid units linked by C-C or C-O-C bonds, which are connected symmetrically or asymmetrically through an alkyl- or alkoxy-based linker of varying lengths. Typically, dimeric compounds consist of pairs of flavone–flavone, flavone–flavanone, and flavanone–flavanone subunits, as well as dimers of chalcones and isoflavones [22,50].

There are few studies of dimers compared to monomeric flavonoids, which leads to less data about their distribution and role among plants. However, according to the existing literature, most dimeric flavonoids are extracted from the leaves and roots of plants, therefore, they are compounds easily obtained through the diet [51,52].

The dimer structure of the flavonoids can improve drug–receptor interactions, resulting in more effective and stronger biological responses. Moreover, flavonoid dimers have a slightly increased bioavailability and metabolic bioactivity, resulting in an increased effect with a longer duration. The broader range of metabolites produced also contributes to their enhanced action [52].

Considering the significance of natural products as sources for new medications and due to the high incidence of several cancers and resistance to available therapies, it is crucial to research the anticancer properties of biflavonoids for these specific cancers [13,53].

A comparison of the anticancer activity of monomeric versus dimeric forms of flavonoids is often made [54–56].

Dimeric flavonoids' biological activity affects the molecular mechanisms cancer cells need to undergo to succumb to the multistep process of tumorigenesis, known as hallmarks of cancer [57,58].

3. Dimeric Flavonoids and the Hallmarks of Cancer

In 2000, Hanahan and Weinberg published a review outlining the state of the art of knowledge that recapitulated the complexity of cancer [59]. They conceptualized the core set of six traits common to almost all cancer types: "*self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis and tissue invasion and metastasis*". Additionally, they introduced the concept of enabler capabilities, as characteristics that normal cells need to acquire to form a malignant tumor: genome instability [59]. A decade after the first publication, the panorama of cancer research had changed significantly, and the constantly emerging evidence has allowed the refinement of hallmarks of cancer, leading to a revised update where the authors added two more fundamental functional properties acquired in the tumorigenic process: reprogramming of energy metabolism and evading immune destruction. Moreover, they also added tumor-promoting inflammation as a new enabling characteristic [60]. In 2022, in the latest update of the iconic saga, the authors added the last two emerging hallmarks, namely unlocking phenotypic plasticity and non-mutational epigenetic reprogramming, and two more enabling characteristics involving polymorphic microbiomes and senescent cells [61].

New therapeutic strategies with the ability to disrupt the characteristics and acquired capabilities of tumor cells began to emerge [60,61]. Several studies marked the potential

anticancer activity of dimeric flavonoids as compounds that disrupt the hallmark features (Figure 1) [22,53,62–64].

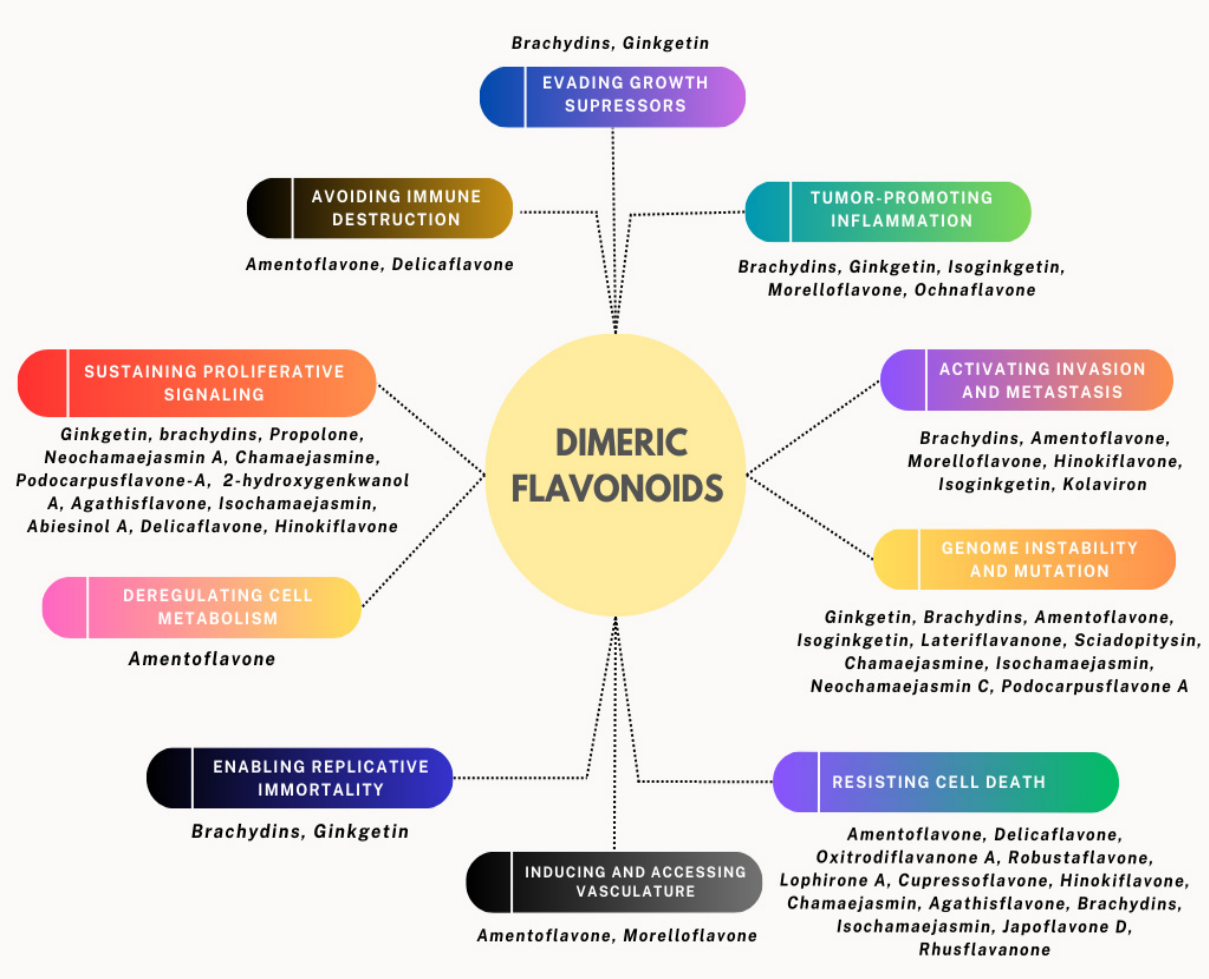

Figure 1. Main hallmarks of cancer targeted by dimeric flavonoids.

3.1. Dimeric Flavonoids and Self-Sufficiency in Growth Signals

Self-sufficiency in growth factors was the first recognized hallmark of cancer and perhaps the most fundamental trait [57]. Normal cells are unable to proliferate in the absence of mitogenic growth signals produced by other cells. In opposition, cancer cells obliviate the need for stimulation from their neighbor cells [57]. In cancer cells, proliferation is powered by their ability to autonomously secrete mediators such as growth factors or cytokines, to which they are responsive, in a process designated autocrine stimulation [63]. An example of a molecule secreted in an autocrine way is TGF-β (Transforming Growth Factor β), one of the most important molecules implicated in several tumorigenic processes including tumor growth [64]. Also, Platelet-Derived Growth Factors (PDGFs) and their receptors can be secreted by cells from glioblastoma [65], sarcoma [66], gastric [67] and lung cancers [68] to modulate the tumor microenvironment and induce tumor growth, angiogenesis and metastasis [69,70]. Ginkgetin is capable of disrupting the hormonal pathway of the estrogen receptor (ER), downregulating the expression of ER-α in breast cancer cells and inducing apoptosis [71,72].

Around 70–90% of cancers express the EGFR (Epidermal Growth Factor Receptor), which has been associated with poor prognosis in breast [72] and cervical cancers [73]. The activation of the receptor results from an autocrine loop [72].

Additionally, the activation of intricate signaling networks induces a proliferative outcome in cancer cells. The major pathways accounting for cell proliferation are PI3K/AKT/mTOR and Ras/Raf/MEK/ERK [74]. Both are highly conserved and well-characterized intracellular signaling transducers, responsible for transmitting extracellular cues to the intracellular targets responsible for the activation of proliferative genes [75].

3.2. Dimeric Flavonoids and Evasion of Growth Suppressors

The sustainment of proliferative signaling is complementary to cancer cells' capacity to evade growth suppressors [57]. In normal cells, proliferative signals are counteracted by mechanisms operating to maintain cellular quiescence and tissue homeostasis. Cancer cells overrule inhibitory signals that halt their growth [57]. The cell cycle contains multiple pathways and checkpoints that inhibit cellular proliferation and growth, but the most prominent mechanisms are related to retinoblastoma protein RB (pRB) [76]. The RB1 gene was the first tumor suppressor to be identified; mutations affecting this gene increase the predisposition to retinoblastomas [77] and osteosarcomas [78]. RB forms a complex with the E2F transcription factor; when RB is phosphorylated, the repression of target genes that regulate cell cycle progression from the G1 to the S phase is released [76]. The dimeric flavonoid Ginkgetin triggered cell cycle arrest by decreasing the expression levels of RB protein in hepatocellular carcinoma cell lines [79].

Growth factors, such as TGF-β and Smad4, can also impact the cell cycle. In the early stages of tumorigenesis, TGF-β exhibits a suppressive role, promoting the blockage of the cell cycle. As the tumor progresses, the cells become insensitive to it, and Smad4 plays a determinant role in this switch of function [59,80,81]. TGF-β is inhibited in breast cancer cells by chamaejasmenin B [82] and in bladder cancer cells by proanthocyanidins [81].

3.3. Dimeric Flavonoids and Evading Programmed Cell Death

Cancer cells have an increased resistance to death. In response to external signals, the cell undergoes a genetically programmed process of suicide called apoptosis. Although apoptosis is a vital occurrence for maintaining tissue homeostasis, in cancer, aberrant cellular multiplication is an essential trait for sustaining tumorigenesis [83–85]. To evade apoptosis, cells can engage in two major pathways: the intrinsic or mitochondrial pathway and the extrinsic or death receptor pathway, regulated by intracellular and extracellular signals, respectively [85]. The extrinsic pathway is activated when cell ligands interact with their receptors on the cell surface such as Fas ligand connecting to Fas ligand and TNF-α connecting to the TNFR1 receptor, triggering a cascade of caspase activation. Neochamaejasmin B induced apoptosis through the activation of caspase-3 and caspase-10 in insect neuronal cells [86]. Other ligands may trigger a different signaling pathway, namely the NF-κB pathway [87]. The transcription factor complex NF-κB has pro-survival functions by promoting the transcription of several anti-apoptotic genes, including Bcl-2 family members (for example, Bcl-XL and A1/Bfl-1) that can impair death dependent on mitochondrial mechanisms [57]. Amentoflavone suppresses tumor progression in bladder cancer by interfering in intrinsic and extrinsic apoptosis pathways, increasing the expression of apoptotic proteins (BAX, FAS, FAS-L) and diminishing the expression of anti-apoptotic proteins and metastasis-associated proteins in bladder cancer cells [88].

3.4. Dimeric Flavonoids and Angiogenesis

In order to grow, the tumor must be properly nourished with nutrients and oxygen in addition to being cleared of metabolic wastes and carbon dioxide [57]. Angiogenesis is the process of the creation of new blood vessels from existent capillaries to support the growth and metastasis of the tumor [59]. This dynamic process is carefully regulated by pro- and anti-angiogenic molecules, the major ones being vascular endothelial growth

factor (VEGF) and tyrosine kinase inhibitors (TKIs), respectively [89]. Amentoflavone induces anti-angiogenesis of breast cancer cells by inhibiting the expression and secretion of VEGF through NF-κB inactivation [90]. Angiogenesis is not only required to sustain tumor growth but is also a pivotal trait for potentiating invasiveness, metastasis and tumor recurrence [91].

3.5. Dimeric Flavonoids and Tissue Invasion and Metastasis

Eventually, the primary tumor spreads and invades adjacent tissues and ultimately metastasizes to distant sites from the initial cancer. The metastatic cascade includes three phases: dissemination and tissue invasion, dormancy and organ colonization [92]. The capability of migration and invasion of surrounding tissues is the primary property accounting for metastasis. Cancer cells must undergo alterations involving cell–cell adhesion molecules, cell–matrix adhesion molecules and extracellular matrix remodeling enzymes. During malignant transformation, cells lose adherens junctions that are mainly mediated by cadherins [93]. E-cadherin is the best-characterized tumor suppressor protein and therefore an antagonist of invasion and metastasis [94]. Integrins are connected to the actin cytoskeleton and provide an anchor to the matrix through related proteins. In this way, besides being responsible for cell adhesion, integrins are also a connector to the extracellular environment, regulating pathways downstream of the actin cytoskeleton involved in cell growth and proliferation. Matrix metalloproteinases (MMPs) are responsible for degrading the blood vessels and extracellular matrix to enable extravasation [95]. In turn, increased expression of MMP enhances epithelial-to-mesenchymal transition (EMT) [96]. During carcinogenesis, the cells undergo a coordinated program in which cells lose their epithelial characteristics and transition to a mesenchymal phenotype [97].

In lung cancer cells, sotetsuflavone suppresses invasion and metastasis by reversing EMT, upregulating E-cadherin expression and decreasing MMP-9 and MMP-13 expression via the TNF-α/NF-κB and PI3K/AKT signaling pathways [98]. Hinokiflavone significantly inhibited migration and invasion by impairing EMT in breast cancer cells, by upregulating the expression levels of E-cadherin and reducing the expression levels of N-cadherin [99]. Moreover, the same diflavonoid is able to interfere with migration and invasion by downregulation of MMP-2 and MMP-9, conjugated with inhibition of the phosphorylation of p38 and Akt signaling molecules [61]. This compound also demonstrated an anti-metastatic effect by decreasing MMP-9 in human nasopharyngeal carcinoma cells [100].

The adaptation of cancer cells in the metastatic site is also dependent on hypoxia, mainly sustained by HIF-1α, which also promotes angiogenesis by increasing VEGF [101]. Morelloflavone inhibits tumor angiogenesis by blocking VEGF in ex vivo and in vivo prostate cancer models. The phosphorylation and activation of the Raf/MEK/ERK pathway affect the activity of the VEGF receptor (VEGFR2) [102].

3.6. Dimeric Flavonoids and Reprogramming of Energy Metabolism

Cancer cells undergo metabolic reprogramming processes that fuel the increase in their growth and proliferation rate [103]. Regardless of the presence of oxygen, cancer cells shift their metabolism, relying on glycolysis for energy production. Despite the lower efficiency of ATP production, glycolysis is linked to oncogene activation and mutation of tumor suppressors [58]. Pyruvate kinase type M2 (PKM2) is an enzyme that rate-limits the final reaction of glycolysis and is activated by the oncogene MYC being upregulated in cancer cells [104–106]. In addition, Myc also increases the uptake of glutamine and glutaminolysis for the synthesis of Glutathione (GSH). GSH is an antioxidant that plays a primary role in eliminating excessively produced reactive oxygen species (ROS) responsible for oxidative stress damage. Is responsible for clearing hydrogen peroxide (H_2O_2), singlet

oxygen (O_2^-), hydroxyl radicals and lipid peroxides [39]. Both Procyanidin A and B have reportedly protected prostate cancer cells against H_2O_2-induced oxidative stress [105].

Studies relating the potential anticancer activity of dimeric flavonoids in the disruption of the hallmark features are indicated in Table 1.

Table 1. Summary of dimeric flavonoids' anticancer activity and mechanism of action related to the hallmarks of cancer.

Dimeric Flavonoid	Cancer Type	Cell Lines	Mechanism of Action	Hallmark of Cancer	Literature Reference
I-4, II-4-di-O-methylrobustaflavone	Blood Colon	P-388 HT-29	Promotes cell death.	Evading programmed cell death	[106]
Brachydin A	Prostate	PC-3	Induces apoptosis. Decreases expression of pAKT.	Evading programmed cell death	[107]
		DU145	Suppresses cell migration and tumor invasion. Increases levels of effector caspases (CASP3, CASP7, and CASP8) and inflammation markers (NF-kB and TNF-α).	Activating tissue invasion and metastasis Evading programmed cell death	[108]
			Induces necrosis and apoptosis. Decreases cell proliferation.	Evading programmed cell death	[109]
Brachydin B	Prostate	PC-3	Induces apoptosis and necrosis. Overexpression of the p21 protein and cell cycle arrest. Decreases expression of pAKT.	Evading programmed cell death Evasion of growth suppressors	[107]
		DU145	Suppresses cell migration and tumor invasion in 2D and 3D cultures.	Activating tissue invasion and metastasis	[110]
Brachydin C	Prostate	PC-3	Induces apoptosis. Overexpression of the p21 protein and cell cycle arrest.	Evading programmed cell death Evasion of growth suppressors	[107]
		DU145	Suppresses cell migration and tumor invasion in 2D cultures.	Activating tissue invasion and metastasis	[111]
Brachydin E and F	Prostate	PC-3	Targets nuclear receptors, mainly glucocorticoid receptors, having anti-proliferative effects.	Self-sufficiency in growth signals	[112]
Chamaejasmine	Breast	MDA-MB-231	Induces apoptosis (activates Bax and inhibits Bcl-2) and cell cycle arrest in the G2/M phase (decreases cyclins Cdk2 and cdc2).	Evading programmed cell death Evasion of growth suppressors	[113]
	Lung Bone	A549 KHOS	Anti-proliferative effect. Induces cell cycle in G0/G1 phase and apoptosis by PARP cleavage and caspase-3 activation. Leads to accumulation of p53 protein expression. Induces DNA damage by phosphorylation of H2AX. Downregulates CDK2, cyclin E, Rb and pRb proteins in A549 cell line.	Self-sufficiency in growth signals Evasion of growth suppressors	[114]
	Liver Bone Colon Cervical	HepG2 and SMMC-7721 MG63 and U-2 OS HCT-116 HeLa	Anti-proliferative effect.	Self-sufficiency in growth signals	[114]

Table 1. *Cont.*

Dimeric Flavonoid	Cancer Type	Cell Lines	Mechanism of Action	Hallmark of Cancer	Literature Reference
7,7″-di-O-methylchamaejasmivon	Breast	MDA-MB-231	Induces apoptosis through alteration of mitochondrial membrane potential and increases reactive oxygen species.	Evading programmed cell death Reprogramming of energy metabolism	[62]
Cupressoflavone	Prostate	PC-3	High cytotoxic selectivity.	Evading programmed cell death	[115]
	Lung	A549	Specific cytotoxicity.	Evading programmed cell death	[116]
Delicaflavone	Colorectal	HT29, HCT116	Inhibits PI3K/Akt/mTOR and Ras/MEK/Erk signaling cascades. Leads to cell cycle arrest.	Evasion of growth suppressors	[117]
	Cervical	HeLa, SiHa, H8	Induces apoptosis through mitochondrial pathway.	Evading programmed cell death	[118]
	Lung	A549, PC-9	Induces cell autophagy by increasing LC3-II/LC3-I.	Evading programmed cell death	[119]
Hinokiflavone	Nasopharynx	HONE-1	Inhibits cell migration and invasion (effects concentration-dependent).	Activating tissue invasion and metastasis	[100]
	Breast	MDA-MB-231	Inhibits cell migration and invasion by interfering with epithelial–mesenchymal transition.	Activating tissue invasion and metastasis	[99]
	Colon	HCT116	Inhibits oncoprotein MDM2, which consequently increases p53 protein expression and leads to cell cycle arrest in G2/M phase and induces apoptosis.	Evasion of growth suppressors Evading programmed cell death	[120]
	Nasopharynx	KB	Inhibition of cell growth (effect is time- and concentration-dependent).	Self-sufficiency in growth signals	[121]
	Colorectal	CT26	Induces apoptosis by upregulating protein Bax and downregulating Bcl-2. In vivo, reduced cell growth and induced apoptosis, without toxicity.	Evading programmed cell death	[122]
	Melanoma	A375, B16	Inhibits cell proliferation, induces caspase-dependent apoptosis and inhibits cell migration by inhibiting MMP-2 and MMP-9.	Evading programmed cell death Activating tissue invasion and metastasis	[123]
	Breast	MDA MB-231	Reduction in tumor volume in vivo studies with mice.	Self-sufficiency in growth signals	[99]
Isochamaejasmin	Cervix	HeLa	Induces the expression of an NF-kB-directed reporter gene. Induces time-dependent phosphorylation of the mitogen-activated protein kinases and p38.	Evading programmed cell death	[124]
	Leukemia	K562	Induces apoptosis mediated by increasing the cleavage of caspase-9, caspase-3 and PARP, involved in the Bcl-2-induced apoptosis pathway.	Evading programmed cell death	[125]

Table 1. *Cont.*

Dimeric Flavonoid	Cancer Type	Cell Lines	Mechanism of Action	Hallmark of Cancer	Literature Reference
Isoginkgetin	Breast	MCF7	Specific cytotoxicity.	Evading programmed cell death	[126]
		MDA-MB-231	Induces apoptosis. Inhibits invasion by decreasing the production of matrix metalloproteinases (MMP-9, Akt and PI3K). In vivo, inhibited tumor growth in mice, with dose-dependent effects. Treatment with this compound decreases the expression of Ki67 and MMP-2 in tumor cells.	Evading programmed cell death Self-sufficiency in growth signals Activating tissue invasion and metastasis	[127]
Japoflavone D	Liver	SMMC-7721	Induces ERK-mediated apoptosis and suppresses cell proliferation. Decreases ROS by activating the KEAP1/NRF2/ARE signal axis and inhibiting ERK phosphorylation.	Self-sufficiency in growth signals Reprogramming of energy metabolism	[128,129]
Lateriflavanone	Colorectal	HT-29	Inhibits proteasome and promotes cell death.	Evading programmed cell death	[129]
Neochamaejasmin A	Prostate	LNCaP	Inhibits cell cycle regulatory proteins (cyclin D and cyclin-dependent kinase inhibitor p21) and leads to cell arrest cycle in G1 phase. Alters mitochondrial membrane potential. Induces apoptosis by the Fas–caspase8–caspase3 pathway. Inhibits cell proliferation by cellular uptake of [3H]-thymidine.	Evasion of growth suppressors Reprogramming of energy metabolism Evading programmed cell death Self-sufficiency in growth signals	[130]
Neochamaejasmin C	Lung Bone	A549 KHOS	Anti-proliferative effect. Induces cell cycle in G0/G1 phase and apoptosis. Induces DNA damage by phosphorylation of H2AX.	Evasion of growth suppressors Reprogramming of energy metabolism	[114]
Rhusflavanone	Breast	MCF-7	Promotes cell death by inducing ferroptosis (downregulates the ACSL4, NOXO1, NOXA1, ACSL5, STEAP3, LPCAT3, ATG7 and TP53 genes). Promising anti-resistance chemotherapy agent in breast cancer.	Evading programmed cell death	[131]
Oxitrodiflavanone A	Prostate	PC-3	Promotes cell death.	Evading programmed cell death	[132]
Ochnaflavone	Breast	MCF-7	Strong cytotoxic effects.	Evading programmed cell death	[133,134]
Podocarpusflavone A	Breast	MCF7	Induces cell cycle arrest at the S phase, leading to alterations in Topoisomerase I enzyme.	Evasion of growth suppressors	[133]
	Melanoma	A375	Inhibition of JAK2/STAT3 pathway. Cell cycle arrests and induces apoptosis.	Evasion of growth suppressors Evading programmed cell death	[134]
	Ovarian	A2780CP	Inhibits human topoisomerase II alpha enzyme.	Self-sufficiency in growth signals	[135]

Table 1. *Cont.*

Dimeric Flavonoid	Cancer Type	Cell Lines	Mechanism of Action	Hallmark of Cancer	Literature Reference
Propolone A and B	Prostate	PC-3	Inhibits cell proliferation in 2D in vitro cultures.	Self-sufficiency in growth signals	[115]
Robustaflavone	Breast	MCF7	Induces cell death through ferroptosis (accumulation of reactive oxygen species).	Evading programmed cell death	[136]
Sotetsuflavone	Lung	A549	Induces cell autophagy through PI3K/Akt/mTOR pathway.	Evading programmed cell death	[98,137,138]
Volkensiflavone	Ovarian	OVCAR-3	High cytotoxicity.	Evading programmed cell death	[121]
Amentoflavone	Esophageal squamous	KYSE-150 and Eca-109 cell lines	Suppressed cell proliferation, adhesion and invasion; induced cell cycle arrest in G1 phase by targeting cyclin B and CDK1; promoted apoptosis.	Self-sufficiency in growth signals Evasion of growth suppressors Evading programmed cell death	[139]
Ginkgetin	Bladder	TSGH8301 cell line	Diminished proliferation; reduced angiogenesis.	Self-sufficiency in growth signals Promoting angiogenesis	[88]
	Ovarian cancer	A2780,SK-OV-3 and CP70 cell lines	Suppression of cell growth through inhibition of JAK2/STAT3 and MAPK signaling pathway.	Self-sufficiency in growth signals	[140]
	Liver	HepG2 and SK-HEP-1 cell lines	Induction of cell cycle arrest and promotion of apoptosis.	Evasion of growth suppressors Evading programmed cell death	[79]
Involucrasin A	Colon cancer	HCT-116 cell line	Inhibits cell proliferation by modulating Akt/MDM2/p53 pathway and induced apoptosis by upregulating caspases 6 and 9.	Self-sufficiency in growth signals Evading programmed cell death	[141]

4. Conclusions

Dimeric flavonoids have demonstrated various bioactivities, including anticancer, antimicrobial, anti-inflammatory, analgesic, antioxidant and vasorelaxant activities [50]. These compounds are abundant in nature and food, and their chemical structure rearrangement is possible [62]. Additionally, these compounds seem to show some selectivity for tumor cells, a fact that has sparked great interest in the scientific community for their use as anticarcinogens [20].

Those mechanisms are correlated with the hallmarks of cancer, so dimeric flavonoids can cause cell cycle arrest, induce apoptosis, inhibit angiogenesis and invasion, and lead to anti-inflammatory/immunoregulatory effects and the inhibition of proinflammatory enzyme effects [20]. In addition, dimeric compounds have antioxidant and analgesic activities that contribute to anticarcinogen behavior [20]. The findings summarized in this review highlight the great potential of applying dimeric compounds in cancer therapy, residing in their availability in nature and possible laboratory restructuring, in reducing toxicity levels of conventional drugs, in amplifying the action of chemotherapeutic drugs and combating the mechanisms of resistance [60]. The main limitations related to the use of dimeric flavonoids as future targets for anticancer therapy are still the lack of studies carried out to elucidate their mechanisms of action. Furthermore, studies carried out with these compounds use different methodologies, cancer models and concentrations, which complicates a comparison between various compounds.

This review reflects the present literature, showing that some dimeric flavonoids are more extensively studied than others due to the wide range of biological action.

Thus, future work on the long road to implementing the clinical use of these dimeric compounds is needed to clarify their mechanisms of action and toxicity. Further tests on animal models and clinical trials that provide information on their safety and efficacy must be developed [51].

Author Contributions: Conceptualization, R.M. and F.C.; writing—original draft preparation, I.L., I.M. and R.R.; writing—review and editing, R.M., F.C., I.L., I.M. and R.R. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded and sponsored by the national funds of FCT/MCTES—Foundation for Science and Technology I.P. from the Ministry of Science, Technology, and Higher Education (PIDDAC) and the European Regional Development Fund (ERDF) by the COMPETE—Programa Operacional Factores de Competitividade (POFC) under the Strategic Funding and the Research Center of the Portuguese Oncology Institute of Porto (project No. PI86-CI-IPOP-66-2019) and Foundation Fernando Pessoa. Isabel Meireles is a PhD scholarship holder (Grant reference: 2024.04184.BDANA) supported by Fundação para a Ciência e Tecnologia (FCT), co-financed by European Social Funds (FSE) and national funds of MCTES.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Brown, J.S.; Amend, S.R.; Austin, R.H.; Gatenby, R.A.; Hammarlund, E.U.; Pienta, K.J. Updating the Definition of Cancer. *Mol. Cancer Res.* **2023**, *21*, 1142–1147. [CrossRef]
2. Gutiérrez-Rodríguez, A.G.; Juárez-Portilla, C.; Olivares-Bañuelos, T.; Zepeda, R.C. Anticancer activity of seaweeds. *Drug Discov. Today* **2018**, *23*, 434–447. [CrossRef]
3. Debela, D.T.; Muzazu, S.G.; Heraro, K.D.; Ndalama, M.T.; Mesele, B.W.; Haile, D.C.; Kitui, S.K.; Manyazewal, T. New approaches and procedures for cancer treatment: Current perspectives. *SAGE Open Med.* **2021**, *9*, 1–10. [CrossRef]
4. Kaur, R.; Bhardwaj, A.; Gupta, S. Cancer treatment therapies: Traditional to modern approaches to combat cancers. *Mol. Biol. Rep.* **2023**, *50*, 9663–9676. [CrossRef] [PubMed]
5. Wang, X.; Zhang, H.; Chen, X. Drug resistance and combating drug resistance in cancer. *Cancer Drug Resist.* **2019**, *2*, 141–160. [CrossRef] [PubMed]
6. Zraik, I.M.; Heß-Busch, Y. Management von Nebenwirkungen der Chemotherapie und deren Langzeitfolgen. *Urologe* **2021**, *60*, 862–871. [CrossRef]
7. Khan, H.; Ullah, H.; Martorell, M.; Valdes, S.E.; Belwal, T.; Tejada, S.; Sureda, A.; Kamal, M.A. Flavonoids nanoparticles in cancer: Treatment, prevention and clinical prospects. *Semin. Cancer Biol.* **2021**, *69*, 200–211. [CrossRef] [PubMed]
8. Kim, C.; Kim, B. Anti-Cancer Natural Products and Their Bioactive Compounds Inducing ER Stress-Mediated Apoptosis: A Review. *Nutrients* **2018**, *10*, 1021. [CrossRef] [PubMed]
9. Siddiqui, A.J.; Jahan, S.; Singh, R.; Saxena, J.; Ashraf, S.A.; Khan, A.; Choudhary, R.K.; Balakrishnan, S.; Badraoui, R.; Bardakci, F.; et al. Plants in Anticancer Drug Discovery: From Molecular Mechanism to Chemoprevention. *BioMed Res. Int.* **2022**, *2022*, 5425485. [CrossRef] [PubMed]
10. Cragg, G.M.; Grothaus, P.G.; Newman, D.J. Impact of Natural Products on Developing New Anti-Cancer Agents. *Chem. Rev.* **2009**, *109*, 3012–3043. [CrossRef] [PubMed]
11. Atanasov, A.G.; Zotchev, S.B.; Dirsch, V.M.; Supuran, C.T. Natural products in drug discovery: Advances and opportunities. *Nat. Rev. Drug Discov.* **2021**, *20*, 200–216. [CrossRef] [PubMed]
12. Yu, J.; Wang, J.; Yang, J.; Ouyang, T.; Gao, H.; Kan, H.; Yang, Y. New insight into the mechanisms of *Ginkgo biloba* leaves in the treatment of cancer. *Phytomedicine* **2024**, *122*, 155088. [CrossRef]
13. Lee, H.K.; Bae, S.; Lee, J.; Cha, H.S.; Nam, M.J.; Lee, J.; Park, K.; Yang, Y.-H.; Jang, K.Y.; Liu, K.-H.; et al. Bilobetin induces apoptosis in human hepatocellular carcinoma cells via ROS level elevation and inhibition of CYP2J2. *Arab. J. Chem.* **2023**, *16*, 105094. [CrossRef]
14. Liu, D.; Li, Z.; Yang, Z.; Ma, J.; Mai, S. Ginkgoic acid impedes gastric cancer cell proliferation, migration and EMT through inhibiting the SUMOylation of IGF-1R. *Chem. Interact.* **2021**, *337*, 109394. [CrossRef]

15. Liang, J.-R.; Yang, H. Ginkgolic acid (GA) suppresses gastric cancer growth by inducing apoptosis and suppressing STAT3/JAK2 signaling regulated by ROS. *Biomed. Pharmacother.* **2020**, *125*, 109585. [CrossRef] [PubMed]
16. Kim, D.H.; Yang, E.J.; Lee, J.; Chang, J.H. *Ginkgo biloba* Leaf Extract Regulates Cell Proliferation and Gastric Cancer Cell Death. *Biomed. Sci. Lett.* **2022**, *28*, 92–100. [CrossRef]
17. Zoi, V.; Galani, V.; Lianos, G.D.; Voulgaris, S.; Kyritsis, A.P.; Alexiou, G.A. The Role of Curcumin in Cancer Treatment. *Biomedicines* **2021**, *9*, 1086. [CrossRef]
18. Foumani, E.A.; Irani, S.; Shokoohinia, Y.; Mostafaie, A. Colchicine of *Colchicum autumnale*, a Traditional Anti-Inflammatory Medicine, Induces Apoptosis by Activation of Apoptotic Genes and Proteins Expression in Human Breast (MCF-7) and Mouse Breast (4T1) Cell Lines. *Cell J.* **2022**, *24*, 647–656. [CrossRef]
19. Liskova, A.; Samec, M.; Koklesova, L.; Brockmueller, A.; Zhai, K.; Abdellatif, B.; Siddiqui, M.; Biringer, K.; Kudela, E.; Pec, M.; et al. Flavonoids as an effective sensitizer for anti-cancer therapy: Insights into multi-faceted mechanisms and applicability towards individualized patient profiles. *EPMA J.* **2021**, *12*, 155–176. [CrossRef]
20. Mercader, A.G.; Pomilio, A.B. Naturally-occurring Dimers of Flavonoids as Anticarcinogens. *Anti-Cancer Agents Med. Chem.* **2013**, *13*, 1217–1235. [CrossRef] [PubMed]
21. Medhat, A.M.; Azab, K.S.; Said, M.M.; El Fatih, N.M.; El Bakary, N.M. Antitumor and radiosensitizing synergistic effects of apigenin and cryptotanshinone against solid Ehrlich carcinoma in female mice. *Tumor Biol.* **2017**, *39*, 101042831772848. [CrossRef] [PubMed]
22. Li, Y.; Wang, Z.; Jin, J.; Zhu, S.-X.; He, G.-Q.; Li, S.-H.; Wang, J.; Cai, Y. Quercetin pretreatment enhances the radiosensitivity of colon cancer cells by targeting Notch-1 pathway. *Biochem. Biophys. Res. Commun.* **2020**, *523*, 947–953. [CrossRef] [PubMed]
23. Riahi-Chebbi, I.; Souid, S.; Othman, H.; Haoues, M.; Karoui, H.; Morel, A.; Srairi-Abid, N.; Essafi, M.; Essafi-Benkhadir, K. The Phenolic compound Kaempferol overcomes 5-fluorouracil resistance in human resistant LS174 colon cancer cells. *Sci. Rep.* **2019**, *9*, 195. [CrossRef]
24. Chen, C.-H.; Huang, Y.-C.; Lee, Y.-H.; Tan, Z.-L.; Tsai, C.-J.; Chuang, Y.-C.; Tu, H.-F.; Liu, T.-C.; Hsu, F.-T. Anticancer Efficacy and Mechanism of Amentoflavone for Sensitizing Oral Squamous Cell Carcinoma to Cisplatin. *Anticancer Res.* **2020**, *40*, 6723–6732. [CrossRef]
25. Hu, X.-L.; Feng, J.-H.; Pham, T.-A.; Ma, H.-Y.; Ma, M.-X.; Song, R.; Shen, W.; Xiong, F.; Zhang, X.-Q.; Ye, W.-C.; et al. Identification of amentoflavone as a potent highly selective PARP-1 inhibitor and its potentiation on carboplatin in human non-small cell lung cancer. *Phytomedicine* **2018**, *50*, 88–98. [CrossRef]
26. Wang, B.; Hu, X.; Wang, R.; Long, H.; Wang, H. Evaluation of amentoflavone metabolites on PARP-1 inhibition and the potentiation on anti-proliferative effects of carboplatin in A549 cells. *Bioorg. Med. Chem. Lett.* **2022**, *56*, 128480. [CrossRef]
27. Su, C.-M.; Li, C.-H.; Huang, M.-C.; Yueh, P.-F.; Hsu, F.-T.; Lin, R.-F.; Hsu, L.-C. Reinforcement of Sorafenib Anti-osteosarcoma Effect by Amentoflavone Is Associated with the Induction of Apoptosis and Inactivation of ERK/NF-κB. *In Vivo* **2022**, *36*, 1136–1143. [CrossRef]
28. Tsai, J.-J.; Hsu, F.-T.; Pan, P.-J.; Chen, C.-W.; Kuo, Y.-C. Amentoflavone Enhances the Therapeutic Efficacy of Sorafenib by Inhibiting Anti-apoptotic Potential and Potentiating Apoptosis in Hepatocellular Carcinoma In Vivo. *Anticancer Res.* **2018**, *38*, 2119–2125. [CrossRef] [PubMed]
29. Wu, Q.; Yang, Z.; Nie, Y.; Shi, Y.; Fan, D. Multi-drug resistance in cancer chemotherapeutics: Mechanisms and lab approaches. *Cancer Lett.* **2014**, *347*, 159–166. [CrossRef] [PubMed]
30. Li, B.; Feng, F.; Jia, H.; Jiang, Q.; Cao, S.; Wei, L.; Zhang, Y.; Lu, J. Rhamnetin decelerates the elimination and enhances the antitumor effect of the molecular-targeting agent sorafenib in hepatocellular carcinoma cells *via* the miR-148a/PXR axis. *Food Funct.* **2021**, *12*, 2404–2417. [CrossRef] [PubMed]
31. Şirin, N.; Elmas, L.; Seçme, M.; Dodurga, Y. Investigation of possible effects of apigenin, sorafenib and combined applications on apoptosis and cell cycle in hepatocellular cancer cells. *Gene* **2020**, *737*, 144428. [CrossRef] [PubMed]
32. Huang, S.; Yu, M.; Shi, N.; Zhou, Y.; Li, F.; Li, X.; Huang, X.; Jin, J. Apigenin and Abivertinib, a novel BTK inhibitor synergize to inhibit diffuse large B-cell lymphoma in vivo and vitro. *J. Cancer* **2020**, *11*, 2123–2132. [CrossRef] [PubMed]
33. Wang, F.; Bao, M.; Xu, J.; Shi, L.; Niu, R.; Wang, T.; Liu, J. Scutellarin inhibits the glioma cell proliferation by downregulating BIRC5 to promote cell apoptosis. *J. Cell. Mol. Med.* **2023**, *27*, 1975–1987. [CrossRef]
34. Lu, J.-J.; Wang, Y.-T. Identification of anti-cancer compounds from natural products. *Chin. J. Nat. Med.* **2020**, *18*, 481–482. [CrossRef] [PubMed]
35. Naeem, A.; Hu, P.; Yang, M.; Zhang, J.; Liu, Y.; Zhu, W.; Zheng, Q. Natural Products as Anticancer Agents: Current Status and Future Perspectives. *Molecules* **2022**, *27*, 8367. [CrossRef]
36. Hashem, S.; Ali, T.A.; Akhtar, S.; Nisar, S.; Sageena, G.; Ali, S.; Al-Mannai, S.; Therachiyil, L.; Mir, R.; Elfaki, I.; et al. Targeting cancer signaling pathways by natural products: Exploring promising anti-cancer agents. *Biomed. Pharmacother.* **2022**, *150*, 113054. [CrossRef]
37. Panche, A.N.; Diwan, A.D.; Chandra, S.R. Flavonoids: An overview. *J. Nutr. Sci.* **2016**, *5*, e47. [CrossRef] [PubMed]

38. Romagnolo, D.F.; Selmin, O.I. Flavonoids and Cancer Prevention: A Review of the Evidence. *J. Nutr. Gerontol. Geriatr.* **2012**, *31*, 206–238. [CrossRef] [PubMed]
39. Ponte, L.G.S.; Pavan, I.C.B.; Mancini, M.C.S.; Da Silva, L.G.S.; Morelli, A.P.; Severino, M.B.; Bezerra, R.M.N.; Simabuco, F.M. The Hallmarks of Flavonoids in Cancer. *Molecules* **2021**, *26*, 2029. [CrossRef]
40. Mir, S.A.; Dar, A.; Hamid, L.; Nisar, N.; Malik, J.A.; Ali, T.; Bader, G.N. Flavonoids as promising molecules in the cancer therapy: An insight. *Curr. Res. Pharmacol. Drug Discov.* **2024**, *6*, 100167. [CrossRef]
41. Dias, M.C.; Pinto, D.C.G.A.; Silva, A.M.S. Plant Flavonoids: Chemical Characteristics and Biological Activity. *Molecules* **2021**, *26*, 5377. [CrossRef] [PubMed]
42. Pandey, P.; Khan, F.; Qari, H.A.; Oves, M. Rutin (Bioflavonoid) as Cell Signaling Pathway Modulator: Prospects in Treatment and Chemoprevention. *Pharmaceuticals* **2021**, *14*, 1069. [CrossRef]
43. Deep, G.; Agarwal, R. Antimetastatic efficacy of silibinin: Molecular mechanisms and therapeutic potential against cancer. *Cancer Metastasis Rev.* **2010**, *29*, 447–463. [CrossRef]
44. Zou, H.; Ye, H.; Kamaraj, R.; Zhang, T.; Zhang, J.; Pavek, P. A review on pharmacological activities and synergistic effect of quercetin with small molecule agents. *Phytomedicine* **2021**, *92*, 153736. [CrossRef]
45. Ozbey, U.; Attar, R.; Romero, M.A.; Alhewairini, S.S.; Afshar, B.; Sabitaliyevich, U.Y.; Hanna-Wakim, L.; Ozcelik, B.; Farooqi, A.A. Apigenin as an effective anticancer natural product: Spotlight on TRAIL, WNT/β-catenin, JAK-STAT pathways, and microRNAs. *J. Cell. Biochem.* **2019**, *120*, 1060–1067. [CrossRef] [PubMed]
46. Wang, J.; Li, T.; Zang, L.; Pan, X.; Wang, S.; Wu, Y.; Wang, G. Apigenin Inhibits Human SW620 Cell Growth by Targeting Polyamine Catabolism. *Evid. Based Complement. Altern. Med.* **2017**, *2017*, 3684581. [CrossRef]
47. Hu, W.-J.; Liu, J.; Zhong, L.-K.; Wang, J. Apigenin enhances the antitumor effects of cetuximab in nasopharyngeal carcinoma by inhibiting EGFR signaling. *Biomed. Pharmacother.* **2018**, *102*, 681–688. [CrossRef] [PubMed]
48. Lopes, I.; Campos, C.; Medeiros, R.; Cerqueira, F. Antimicrobial Activity of Dimeric Flavonoids. *Compounds* **2024**, *4*, 214–229. [CrossRef]
49. Tomas, M.K.; Jurčević, I.; Šamec, D. Tissue-Specific Profiling of Biflavonoids in Ginkgo (*Ginkgo biloba* L.). *Plants* **2022**, *12*, 147. [CrossRef] [PubMed]
50. Zou, P.; Otero, P.; Mejuto, J.C.; Simal-Gandara, J.; Xiao, J.; Cameselle, C.; Chen, S.; Lin, S.; Cao, H. Exploring the mechanism of flavonoids modification by dimerization strategies and their potential to enhance biological activity. *Food Chem.* **2025**, *467*, 142266. [CrossRef] [PubMed]
51. de Lima, C.A.; Maquedano, L.K.; Jaalouk, L.S.; dos Santos, D.C.; Longato, G.B. Biflavonoids: Preliminary Reports on Their Role in Prostate and Breast Cancer Therapy. *Pharmaceuticals* **2024**, *17*, 874. [CrossRef]
52. Nishida, N.; Yano, H.; Nishida, T.; Kamura, T.; Kojiro, M. Angiogenesis in cancer. *Vasc. Health Risk Manag.* **2006**, *2*, 213–219. [CrossRef] [PubMed]
53. Banerjee, T.; Van der Vliet, A.; Ziboh, V. Downregulation of COX-2 and iNOS by amentoflavone and quercetin in A549 human lung adenocarcinoma cell line. *Prostaglandins Leukot. Essent. Fat. Acids* **2002**, *66*, 485–492. [CrossRef] [PubMed]
54. Lee, S.J.; Son, K.H.; Chang, H.W.; Kang, S.S.; Kim, H.P. Inhibition of arachidonate release from rat peritoneal macrophage by biflavonoids. *Arch. Pharmacal Res.* **1997**, *20*, 533–538. [CrossRef]
55. Ullah, A.; Munir, S.; Badshah, S.L.; Khan, N.; Ghani, L.; Poulson, B.G.; Emwas, A.-H.; Jaremko, M. Important Flavonoids and Their Role as a Therapeutic Agent. *Molecules* **2020**, *25*, 5243. [CrossRef]
56. Zhang, Z.; Shi, J.; Nice, E.C.; Huang, C.; Shi, Z. The Multifaceted Role of Flavonoids in Cancer Therapy: Leveraging Autophagy with a Double-Edged Sword. *Antioxidants* **2021**, *10*, 1138. [CrossRef]
57. Hanahan, D.; Weinberg, R.A. The Hallmarks of Cancer. *Cell* **2000**, *100*, 57–70. [CrossRef]
58. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. *Cell* **2011**, *144*, 646–674. [CrossRef]
59. Hanahan, D. Hallmarks of Cancer: New Dimensions. *Cancer Discov.* **2022**, *12*, 31–46. [CrossRef]
60. Menezes, J.C.; Diederich, M.F. Bioactivity of natural biflavonoids in metabolism-related disease and cancer therapies. *Pharmacol. Res.* **2021**, *167*, 105525. [CrossRef]
61. Goossens, J.-F.; Goossens, L.; Bailly, C. Hinokiflavone and Related C–O–C-Type Biflavonoids as Anti-cancer Compounds: Properties and Mechanism of Action. *Nat. Prod. Bioprospect.* **2021**, *11*, 365–377. [CrossRef] [PubMed]
62. Adem, F.A.; Mbaveng, A.T.; Kuete, V.; Heydenreich, M.; Ndakala, A.; Irungu, B.; Yenesew, A.; Efferth, T. Cytotoxicity of isoflavones and biflavonoids from *Ormocarpum kirkii* towards multi-factorial drug resistant cancer. *Phytomedicine* **2019**, *58*, 152853. [CrossRef] [PubMed]
63. Ungefroren, H. Autocrine TGF-β in Cancer: Review of the Literature and Caveats in Experimental Analysis. *Int. J. Mol. Sci.* **2021**, *22*, 977. [CrossRef] [PubMed]
64. Ungefroren, H.; Christl, J.; Eiden, C.; Wellner, U.F.; Lehnert, H.; Marquardt, J.-U. Autocrine TGFβ1 Opposes Exogenous TGFβ1-Induced Cell Migration and Growth Arrest through Sustainment of a Feed-Forward Loop Involving MEK-ERK Signaling. *Cancers* **2021**, *13*, 1357. [CrossRef]

65. Lane, R.; Cilibrasi, C.; Chen, J.; Shah, K.; Messuti, E.; Mazarakis, N.K.; Stebbing, J.; Critchley, G.; Song, E.; Simon, T.; et al. PDGF-R inhibition induces glioblastoma cell differentiation via DUSP1/p38MAPK signalling. *Oncogene* **2022**, *41*, 2749–2763. [CrossRef] [PubMed]
66. Brahmi, M.; Lesluyes, T.; Dufresne, A.; Toulmonde, M.; Italiano, A.; Mir, O.; Le Cesne, A.; Valentin, T.; Chevreau, C.; Bonvalot, S.; et al. Expression and prognostic significance of PDGF ligands and receptors across soft tissue sarcomas. *ESMO Open* **2021**, *6*, 100037. [CrossRef]
67. Zhao, X.; Yu, Z.; Zang, K. Platelet-Derived Growth Factors Affect Clinical Features and Prognosis of Gastric Cancer. *J. Oncol.* **2022**, *2022*, 2108368. [CrossRef] [PubMed]
68. Xiu-Ying, H.; Yue-Xiang, Z.; Hui-Si, Y.; Hong-Zhou, Y.; Qing-Jie, X.; Ting-Hua, W. PDGFBB facilitates tumorigenesis and malignancy of lung adenocarcinoma associated with PI3K-AKT/MAPK signaling. *Sci. Rep.* **2024**, *14*, 4191. [CrossRef]
69. Pandey, P.; Khan, F.; Upadhyay, T.K.; Seungjoon, M.; Park, M.N.; Kim, B. New insights about the PDGF/PDGFR signaling pathway as a promising target to develop cancer therapeutic strategies. *Biomed. Pharmacother.* **2023**, *161*, 114491. [CrossRef]
70. Farooqi, A.A.; Siddik, Z.H. Platelet-derived growth factor (PDGF) signalling in cancer: Rapidly emerging signalling landscape. *Cell Biochem. Funct.* **2015**, *33*, 257–265. [CrossRef]
71. Park, Y.; Woo, S.H.; Seo, S.-K.; Kim, H.; Noh, W.C.; Lee, J.K.; Kwon, B.-M.; Min, K.N.; Choe, T.-B.; Park, I.-C. Ginkgetin induces cell death in breast cancer cells via downregulation of the estrogen receptor. *Oncol. Lett.* **2017**, *14*, 5027–5033. [CrossRef]
72. Kjær, I.M.; Olsen, D.A.; Brandslund, I.; Bechmann, T.; Jakobsen, E.H.; Bogh, S.B.; Madsen, J.S. Prognostic impact of serum levels of EGFR and EGFR ligands in early-stage breast cancer. *Sci. Rep.* **2020**, *10*, 16558. [CrossRef]
73. Schrevel, M.; Osse, E.M.; Prins, F.A.; Trimbos, J.B.M.; Fleuren, G.J.; Gorter, A.; Jordanova, E.S. Autocrine expression of the epidermal growth factor receptor ligand heparin-binding EGF-like growth factor in cervical cancer. *Int. J. Oncol.* **2017**, *50*, 1947–1954. [CrossRef] [PubMed]
74. Asati, V.; Mahapatra, D.K.; Bharti, S.K. PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways inhibitors as anticancer agents: Structural and pharmacological perspectives. *Eur. J. Med. Chem.* **2016**, *109*, 314–341. [CrossRef] [PubMed]
75. Guo, Y.J.; Pan, W.W.; Liu, S.B.; Shen, Z.F.; Xu, Y.; Hu, L.L. ERK/MAPK signalling pathway and tumorigenesis (Review). *Exp. Ther. Med.* **2020**, *19*, 1997–2007. [CrossRef]
76. Engeland, K. Cell cycle regulation: p53-p21-RB signaling. *Cell Death Differ.* **2022**, *29*, 946–960. [CrossRef] [PubMed]
77. Jansen, R.W.; de Bloeme, C.M.; Cardoen, L.; Göricke, S.; van Elst, S.; Jessen, J.L.; Ramasubramanian, A.; Skalet, A.H.; Miller, A.K.; Maeder, P.; et al. MRI Features for Identifying *MYCN*-amplified *RB1* Wild-type Retinoblastoma. *Radiology* **2023**, *307*, 222264. [CrossRef]
78. Imbert-Bouteille, M.; Gauthier-Villars, M.; Leroux, D.; Meunier, I.; Aerts, I.; Lumbroso-Le Rouic, L.; Lejeune, S.; Delnatte, C.; Abadie, C.; Pujol, P.; et al. Osteosarcoma without prior retinoblastoma related to RB1 low-penetrance germline pathogenic variants: A novel type of RB1-related hereditary predisposition syndrome? *Mol. Genet. Genom. Med.* **2019**, *7*, e913. [CrossRef]
79. Liu, Q.; Chen, L.; Yin, W.; Nie, Y.; Zeng, P.; Yang, X. Anti-tumor effect of ginkgetin on human hepatocellular carcinoma cell lines by inducing cell cycle arrest and promoting cell apoptosis. *Cell Cycle* **2022**, *21*, 74–85. [CrossRef]
80. Zhao, M.; Mishra, L.; Deng, C.-X. The role of TGF-β/SMAD4 signaling in cancer. *Int. J. Biol. Sci.* **2018**, *14*, 111–123. [CrossRef]
81. Yang, N.; Gao, J.; Hou, R.; Xu, X.; Yang, N.; Huang, S. Grape Seed Proanthocyanidins Inhibit Migration and Invasion of Bladder Cancer Cells by Reversing EMT through Suppression of TGF-β Signaling Pathway. *Oxidative Med. Cell. Longev.* **2021**, *2021*, 5564312. [CrossRef]
82. Li, Q.; Wang, Y.; Xiao, H.; Li, Y.; Kan, X.; Wang, X.; Zhang, G.; Wang, Z.; Yang, Q.; Chen, X.; et al. Chamaejasmenin B, a novel candidate, inhibits breast tumor metastasis by rebalancing TGF-beta paradox. *Oncotarget* **2016**, *7*, 48180–48192. [CrossRef] [PubMed]
83. Baar, M.P.; Brandt, R.M.C.; Putavet, D.A.; Klein, J.D.D.; Derks, K.W.J.; Bourgeois, B.R.M.; Stryeck, S.; Rijksen, Y.; Van Willigenburg, H.; Feijtel, D.A.; et al. Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging. *Cell* **2017**, *169*, 132–147.e16. [CrossRef]
84. Jan, R.; Chaudhry, G.-E. Understanding Apoptosis and Apoptotic Pathways Targeted Cancer Therapeutics. *Adv. Pharm. Bull.* **2019**, *9*, 205–218. [CrossRef]
85. Neophytou, C.M.; Trougakos, I.P.; Erin, N.; Papageorgis, P. Apoptosis Deregulation and the Development of Cancer Multi-Drug Resistance. *Cancers* **2021**, *13*, 4363. [CrossRef] [PubMed]
86. Gu, G.; Jiang, M.; Hu, H.; Qiao, W.; Jin, H.; Hou, T.; Tao, K. Neochamaejasmin B extracted from *Stellera chamaejasme* L. induces apoptosis through caspase-10-dependent way in insect neuronal cells. *Arch. Insect Biochem. Physiol.* **2022**, *110*, e21892. [CrossRef]
87. Ngoi, N.Y.L.; Choong, C.; Lee, J.; Bellot, G.; LA Wong, A.; Goh, B.C.; Pervaiz, S. Targeting Mitochondrial Apoptosis to Overcome Treatment Resistance in Cancer. *Cancers* **2020**, *12*, 574. [CrossRef] [PubMed]
88. Chiang, C.-H.; Yeh, C.-Y.; Chung, J.G.; Chiang, I.-T.; Hsu, F.-T. Amentoflavone Induces Apoptosis and Reduces Expression of Anti-apoptotic and Metastasis-associated Proteins in Bladder Cancer. *Anticancer Res.* **2019**, *39*, 3641–3649. [CrossRef] [PubMed]

89. Liu, Z.-L.; Chen, H.-H.; Zheng, L.-L.; Sun, L.-P.; Shi, L. Angiogenic signaling pathways and anti-angiogenic therapy for cancer. *Signal Transduct. Target. Ther.* **2023**, *8*, 198. [CrossRef]
90. Lin, C.; Lin, K.; Ku, H.; Lee, K.; Lin, S.; Hsu, F. Amentoflavone induces caspase-dependent/−independent apoptosis and dysregulates cyclin-dependent kinase-mediated cell cycle in colorectal cancer in vitro and in vivo. *Environ. Toxicol.* **2023**, *38*, 1078–1089. [CrossRef]
91. Al-Ostoot, F.H.; Salah, S.; Khamees, H.A.; Khanum, S.A. Tumor angiogenesis: Current challenges and therapeutic opportunities. *Cancer Treat. Res. Commun.* **2021**, *28*, 100422. [CrossRef]
92. Massagué, J.; Ganesh, K. Metastasis-Initiating Cells and Ecosystems. *Cancer Discov.* **2021**, *11*, 971–994. [CrossRef] [PubMed]
93. Janiszewska, M.; Primi, M.C.; Izard, T. Cell adhesion in cancer: Beyond the migration of single cells. *J. Biol. Chem.* **2020**, *295*, 2495–2505. [CrossRef]
94. Na, T.-Y.; Schecterson, L.; Mendonsa, A.M.; Gumbiner, B.M. The functional activity of E-cadherin controls tumor cell metastasis at multiple steps. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 5931–5937. [CrossRef]
95. Mustafa, S.; Koran, S.; AlOmair, L. Insights into the Role of Matrix Metalloproteinases in Cancer and its Various Therapeutic Aspects: A Review. *Front. Mol. Biosci.* **2022**, *9*, 896099. [CrossRef]
96. Pang, L.; Li, Q.; Li, S.; He, J.; Cao, W.; Lan, J.; Sun, B.; Zou, H.; Wang, C.; Liu, R.; et al. Membrane type 1-matrix metalloproteinase induces epithelial-to-mesenchymal transition in esophageal squamous cell carcinoma: Observations from clinical and in vitro analyses. *Sci. Rep.* **2016**, *6*, 22179. [CrossRef]
97. Ribatti, D.; Tamma, R.; Annese, T. Epithelial-Mesenchymal Transition in Cancer: A Historical Overview. *Transl. Oncol.* **2020**, *13*, 100773. [CrossRef]
98. Wang, S.; Yan, Y.; Cheng, Z.; Hu, Y.; Liu, T. Sotetsuflavone suppresses invasion and metastasis in non-small-cell lung cancer A549 cells by reversing EMT via the TNF-α/NF-κB and PI3K/AKT signaling pathway. *Cell Death Discov.* **2018**, *4*, 26. [CrossRef]
99. Huang, W.; Liu, C.; Liu, F.; Liu, Z.; Lai, G.; Yi, J. Hinokiflavone induces apoptosis and inhibits migration of breast cancer cells via EMT signalling pathway. *Cell Biochem. Funct.* **2020**, *38*, 249–256. [CrossRef] [PubMed]
100. Hsin, C.-H.; Wu, B.-C.; Chuang, C.-Y.; Yang, S.-F.; Hsieh, Y.-H.; Ho, H.-Y.; Lin, H.-P.; Chen, M.-K.; Lin, C.-W. *Selaginella tamariscina* extract suppresses TPA-induced invasion and metastasis through inhibition of MMP-9 in human nasopharyngeal carcinoma HONE-1 cells. *BMC Complement. Altern. Med.* **2013**, *13*, 234. [CrossRef]
101. Moon, E.J.; Mello, S.S.; Li, C.G.; Chi, J.-T.; Thakkar, K.; Kirkland, J.G.; Lagory, E.L.; Lee, I.J.; Diep, A.N.; Miao, Y.; et al. The HIF target MAFF promotes tumor invasion and metastasis through IL11 and STAT3 signaling. *Nat. Commun.* **2021**, *12*, 4308. [CrossRef]
102. Pang, X.; Yi, T.; Yi, Z.; Cho, S.G.; Qu, W.; Pinkaew, D.; Fujise, K.; Liu, M. Morelloflavone, a Biflavonoid, Inhibits Tumor Angiogenesis by Targeting Rho GTPases and Extracellular Signal-Regulated Kinase Signaling Pathways. *Cancer Res.* **2009**, *69*, 518–525. [CrossRef]
103. Dong, Y.; Tu, R.; Liu, H.; Qing, G. Regulation of cancer cell metabolism: Oncogenic MYC in the driver's seat. *Signal Transduct. Target. Ther.* **2020**, *5*, 124. [CrossRef]
104. Zahra, K.; Dey, T.; Ashish; Mishra, S.P.; Pandey, U. Pyruvate Kinase M2 and Cancer: The Role of PKM2 in Promoting Tumorigenesis. *Front. Oncol.* **2020**, *10*, 159. [CrossRef] [PubMed]
105. Yan, F.; Chen, L.; Chen, W.; Zhao, L.; Lu, Q.; Liu, R. Protective effect of procyanidin A-type dimers against H_2O_2-induced oxidative stress in prostate DU145 cells through the MAPKs signaling pathway. *Life Sci.* **2021**, *266*, 118908. [CrossRef]
106. Chen, J.-J.; Duh, C.-Y.; Chen, J.-F. New Cytotoxic Biflavonoids from *Selaginella delicatula*. *Planta Medica* **2005**, *71*, 659–665. [CrossRef] [PubMed]
107. Nunes, H.L.; Tuttis, K.; Serpeloni, J.M.; Nascimento, J.R.D.; da Rocha, C.Q.; Silva, V.A.O.; Lengert, A.v.H.; Reis, R.M.; Cólus, I.M.d.S. Characterization of the in vitro cytotoxic effects of brachydins isolated from *Fridericia platyphylla* in a prostate cancer cell line. *J. Toxicol. Environ. Health Part A* **2020**, *83*, 547–558. [CrossRef]
108. Ribeiro, D.L.; Tuttis, K.; de Oliveira, L.C.B.; Serpeloni, J.M.; Gomes, I.N.F.; Lengert, A.v.H.; da Rocha, C.Q.; Reis, R.M.; Cólus, I.M.d.S.; Antunes, L.M.G. The Antitumoral/Antimetastatic Action of the Flavonoid Brachydin A in Metastatic Prostate Tumor Spheroids In Vitro Is Mediated by (Parthanatos) PARP-Related Cell Death. *Pharmaceutics* **2022**, *14*, 963. [CrossRef] [PubMed]
109. de Oliveira, L.C.B.; Nunes, H.L.; Ribeiro, D.L.; Nascimento, J.R.D.; da Rocha, C.Q.; Cólus, I.M.d.S.; Serpeloni, J.M. Aglycone flavonoid brachydin A shows selective cytotoxicity and antitumoral activity in human metastatic prostate (DU145) cancer cells. *Cytotechnology* **2021**, *73*, 761–774. [CrossRef] [PubMed]
110. Serpeloni, J.M.; Ribeiro, D.L.; Weiss, G.F.; de Oliveira, L.C.B.; Fujiike, A.Y.; Nunes, H.L.; da Rocha, C.Q.; Guembarovski, R.L.; Cólus, I.M.d.S. Flavonoid brachydin B decreases viability, proliferation, and migration in human metastatic prostate (DU145) cells grown in 2D and 3D culture models. *Toxicol. Res.* **2023**, *12*, 321–331. [CrossRef]
111. de Oliveira, L.C.B.; Ribeiro, D.L.; Nascimento, J.R.D.; da Rocha, C.Q.; Cólus, I.M.d.S.; Serpeloni, J.M. Anticancer activities of Brachydin C in human prostate tumor cells (DU145) grown in 2D and 3D models: Stimulation of cell death and downregulation of metalloproteinases in spheroids. *Chem. Biol. Drug Des.* **2022**, *100*, 747–762. [CrossRef] [PubMed]

112. de Lima, C.A.; Cubero, M.C.Z.; Franco, Y.E.M.; Rodrigues, C.D.P.; Nascimento, J.R.D.; Vendramini-Costa, D.B.; Sciani, J.M.; da Rocha, C.Q.; Longato, G.B. Antiproliferative Activity of Two Unusual Dimeric Flavonoids, Brachydin E and Brachydin F, Isolated from *Fridericia platyphylla* (Cham.) L.G.Lohmann: In Vitro and Molecular Docking Evaluation. *BioMed Res. Int.* **2022**, *2022*, 3319203. [CrossRef]
113. Zhang, T.; Yu, H.; Dong, G.; Cai, L.; Bai, Y. Chamaejasmine Arrests Cell Cycle, Induces Apoptosis and Inhibits Nuclear NF-κB Translocation in the Human Breast Cancer Cell Line MDA-MB-231. *Molecules* **2013**, *18*, 845–858. [CrossRef] [PubMed]
114. Zhang, C.; Zhou, S.-S.; Feng, L.-Y.; Zhang, D.-Y.; Lin, N.-M.; Zhang, L.-H.; Pan, J.-P.; Wang, J.-B.; Li, J. In vitro anti-cancer activity of chamaejasmenin B and neochamaejasmin C isolated from the root of *Stellera chamaejasme* L. *Acta Pharmacol. Sin.* **2013**, *34*, 262–270. [CrossRef] [PubMed]
115. Banzato, T.P.; Gubiani, J.R.; Bernardi, D.I.; Nogueira, C.R.; Monteiro, A.F.; Juliano, F.F.; de Alencar, S.M.; Pilli, R.A.; de Lima, C.A.; Longato, G.B.; et al. Antiproliferative Flavanoid Dimers Isolated from Brazilian Red Propolis. *J. Nat. Prod.* **2020**, *83*, 1784–1793. [CrossRef] [PubMed]
116. Al Groshi, A.; Jasim, H.A.; Evans, A.R.; Ismail, F.M.; Dempster, N.M.; Nahar, L.; Sarker, S.D. Growth inhibitory activity of biflavonoids and diterpenoids from the leaves of the Libyan *Juniperus phoenicea* against human cancer cells. *Phytother. Res.* **2019**, *33*, 2075–2082. [CrossRef]
117. Yao, W.; Lin, Z.; Shi, P.; Chen, B.; Wang, G.; Huang, J.; Sui, Y.; Liu, Q.; Li, S.; Lin, X.; et al. Delicaflavone induces ROS-mediated apoptosis and inhibits PI3K/AKT/mTOR and Ras/MEK/Erk signaling pathways in colorectal cancer cells. *Biochem. Pharmacol.* **2020**, *171*, 113680. [CrossRef] [PubMed]
118. Yao, W.; Lin, Z.; Wang, G.; Li, S.; Chen, B.; Sui, Y.; Huang, J.; Liu, Q.; Shi, P.; Lin, X.; et al. Delicaflavone induces apoptosis via mitochondrial pathway accompanying G2/M cycle arrest and inhibition of MAPK signaling cascades in cervical cancer HeLa cells. *Phytomedicine* **2019**, *62*, 152973. [CrossRef]
119. Sui, Y.; Yao, H.; Li, S.; Jin, L.; Shi, P.; Li, Z.; Wang, G.; Lin, S.; Wu, Y.; Li, Y.; et al. Delicaflavone induces autophagic cell death in lung cancer via Akt/mTOR/p70S6K signaling pathway. *J. Mol. Med.* **2017**, *95*, 311–322. [CrossRef]
120. Zhang, S.; Wang, Y.; Sun, Y.; Zhao, G.; Wang, J.; Liu, L.; Liu, F.; Wang, P.; Yang, J.; Xu, X. Hinokiflavone, as a MDM2 inhibitor, activates p53 signaling pathway to induce apoptosis in human colon cancer HCT116 cells. *Biochem. Biophys. Res. Commun.* **2022**, *594*, 93–100. [CrossRef]
121. Lin, Y.-M.; Chen, F.-C.; Lee, K.-H. Hinokiflavone, a Cytotoxic Principle from *Rhus succedanea* and the Cytotoxicity of the Related Biflavonoids. *Planta Medica* **1989**, *55*, 166–168. [CrossRef] [PubMed]
122. Zhou, J.; Zhao, R.; Ye, T.; Yang, S.; Li, Y.; Yang, F.; Wang, G.; Xie, Y.; Li, Q. Antitumor activity in colorectal cancer induced by hinokiflavone. *J. Gastroenterol. Hepatol.* **2019**, *34*, 1571–1580. [CrossRef] [PubMed]
123. Yang, S.; Zhang, Y.; Luo, Y.; Xu, B.; Yao, Y.; Deng, Y.; Yang, F.; Ye, T.; Wang, G.; Cheng, Z.; et al. Hinokiflavone induces apoptosis in melanoma cells through the ROS-mitochondrial apoptotic pathway and impairs cell migration and invasion. *Biomed. Pharmacother.* **2018**, *103*, 101–110. [CrossRef] [PubMed]
124. Tian, Q.; Li, J.; Xie, X.; Sun, M.; Sang, H.; Zhou, C.; An, T.; Hu, L.; Ye, R.D.; Wang, M.-W. Stereospecific Induction of Nuclear Factor-κB Activation by Isochamaejasmin. *Mol. Pharmacol.* **2005**, *68*, 1534–1542. [CrossRef]
125. Zhang, S.-D.; Shan, L.; Li, W.; Li, H.-L.; Zhang, W.-D. Isochamaejasmin induces apoptosis in leukemia cells through inhibiting Bcl-2 family proteins. *Chin. J. Nat. Med.* **2015**, *13*, 660–666. [CrossRef] [PubMed]
126. Zhang, G.-G.; Jing, Y.; Zhang, H.-M.; Ma, E.-L.; Guan, J.; Xue, F.-N.; Liu, H.-X.; Sun, X.-Y. Isolation and Cytotoxic Activity of Selaginellin Derivatives and Biflavonoids from *Selaginella tamariscina*. *Planta Medica* **2012**, *78*, 390–392. [CrossRef]
127. Yoon, S.-O.; Shin, S.; Lee, H.-J.; Chun, H.-K.; Chung, A.-S. Isoginkgetin inhibits tumor cell invasion by regulating phosphatidylinositol 3-kinase/Akt–dependent matrix metalloproteinase-9 expression. *Mol. Cancer Ther.* **2006**, *5*, 2666–2675. [CrossRef]
128. Wan, H.; Ge, L.; Li, J.; Zhang, K.; Wu, W.; Peng, S.; Zou, X.; Zhou, H.; Zhou, B.; Zeng, X. Effects of a novel biflavonoid of *Lonicera japonica* flower buds on modulating apoptosis under different oxidative conditions in hepatoma cells. *Phytomedicine* **2019**, *57*, 282–291. [CrossRef]
129. Ren, Y.; Lantvit, D.D.; de Blanco, E.J.C.; Kardono, L.B.; Riswan, S.; Chai, H.; Cottrell, C.E.; Farnsworth, N.R.; Swanson, S.M.; Ding, Y.; et al. Proteasome-inhibitory and cytotoxic constituents of *Garcinia lateriflora*: Absolute configuration of caged xanthones. *Tetrahedron* **2010**, *66*, 5311–5320. [CrossRef] [PubMed]
130. Liu, W.-K.; Cheung, F.W.K.; Liu, B.P.L.; Li, C.; Ye, W.; Che, C.-T. Involvement of p21 and FasL in Induction of Cell Cycle Arrest and Apoptosis by Neochamaejasmin A in Human Prostate LNCaP Cancer Cells. *J. Nat. Prod.* **2008**, *71*, 842–846. [CrossRef]
131. Xie, Y.; Zhou, X.; Li, J.; Yao, X.-C.; Liu, W.-L.; Xu, P.-S.; Tan, G.-S. Cytotoxic effects of the biflavonoids isolated from *Selaginella trichoclada* on MCF-7 cells and its potential mechanism. *Bioorg. Med. Chem. Lett.* **2022**, *56*, 128486. [CrossRef] [PubMed]
132. Liu, Y.; Kelsang, N.; Lu, J.; Zhang, Y.; Liang, H.; Tu, P.; Kong, D.; Zhang, Q. Oxytrodiflavanone A and Oxytrochalcoflavanones A,B: New Biflavonoids from *Oxytropis chiliophylla*. *Molecules* **2019**, *24*, 1468. [CrossRef] [PubMed]
133. Yeh, P.-H.; Shieh, Y.-D.; Hsu, L.-C.; Kuo, L.-M.Y.; Lin, J.-H.; Liaw, C.-C.; Kuo, Y.-H. Naturally Occurring Cytotoxic [3′→8″]-Biflavonoids from *Podocarpus nakaii*. *J. Tradit. Complement. Med.* **2012**, *2*, 220–226. [CrossRef]

134. Meng, H.; Pang, Y.; Liu, G.; Luo, Z.; Tan, H.; Liu, X. Podocarpusflavone A inhibits cell growth of skin cutaneous melanoma by suppressing STAT3 signaling. *J. Dermatol. Sci.* **2020**, *100*, 201–208. [CrossRef]
135. Al-Zahrani, A.A. The Potential Role of Phytochemicals of *Juniperus procera* in the Treatment of Ovarian Cancer and the Inhibition of Human Topoisomerase II Alpha Activity. *Bioinform. Biol. Insights* **2024**, *18*. [CrossRef]
136. Xie, Y.; Zhou, X.; Li, J.; Yao, X.-C.; Liu, W.-L.; Kang, F.-H.; Zou, Z.-X.; Xu, K.-P.; Xu, P.-S.; Tan, G.-S. Identification of a new natural biflavonoids against breast cancer cells induced ferroptosis via the mitochondrial pathway. *Bioorg. Chem.* **2021**, *109*, 104744. [CrossRef]
137. Wang, S.; Xu, X.; Hu, Y.; Lei, T.; Liu, T. Sotetsuflavone Induces Autophagy in Non-Small Cell Lung Cancer Through Blocking PI3K/Akt/mTOR Signaling Pathway In Vivo and In Vitro. *Front. Pharmacol.* **2019**, *10*, 1460. [CrossRef] [PubMed]
138. Wang, S.; Hu, Y.; Yan, Y.; Cheng, Z.; Liu, T. Sotetsuflavone inhibits proliferation and induces apoptosis of A549 cells through ROS-mediated mitochondrial-dependent pathway. *BMC Complement. Altern. Med.* **2018**, *18*, 235. [CrossRef] [PubMed]
139. Chen, L.; Fang, B.; Qiao, L.; Zheng, Y. Discovery of Anticancer Activity of Amentoflavone on Esophageal Squamous Cell Carcinoma: Bioinformatics, Structure-Based Virtual Screening, and Biological Evaluation. *J. Microbiol. Biotechnol.* **2022**, *32*, 718–729. [CrossRef] [PubMed]
140. Wu, L.; Qian, C.; Zhang, W.; Shi, M.; Chen, X.; Wang, Y.; Lin, F. Ginkgetin suppresses ovarian cancer growth through inhibition of JAK2/STAT3 and MAPKs signaling pathways. *Phytomedicine* **2023**, *116*, 154846. [CrossRef]
141. Wei, C.; Du, J.; Shen, Y.; Wang, Z.; Lin, Q.; Chen, J.; Zhang, F.; Lin, W.; Wang, Z.; Yang, Z.; et al. Anticancer effect of involucrasin A on colorectal cancer cells by modulating the Akt/MDM2/p53 pathway. *Oncol. Lett.* **2023**, *25*, 218. [CrossRef] [PubMed]