International Journal of
Molecular Sciences

MDPI

Review

Targeting PI3K/Akt/mTOR Pathway by Different Flavonoids: A Cancer Chemopreventive Approach

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Abstract: Cancer is, globally, one of the main causes of death. Even though various therapies are available, they are still painful because of their adverse side effects. Available treatments frequently fail due to unpromising responses, resistance to classical anticancer drugs, radiation therapy, chemotherapy, and low accessibility to tumor tissues. Developing novel strategies to minimize adverse side effects, improve chemotherapy sensitivity, and control cancer progression is needed. Many studies have suggested small dietary molecules as complementary treatments for cancer patients. Different components of herbal/edible plants, known as flavonoids, have recently garnered attention due to their broad biological properties (e.g., antioxidant, antiviral, antimicrobial, anti-inflammatory, anti-mutagenic, anticancer, hepatoprotective, and cardioprotective). These flavonoids have shown anticancer activity by affecting different signaling cascades. This article summarizes the key progress made in this area and discusses the role of flavonoids by specifically inhibiting the PI3K/Akt/mTOR pathway in various cancers.

Keywords: Akt; cancer; flavonoids; inhibitors; mTOR; PI3K

Citation: Zughaibi, T.A.; Suhail, M.; Tarique, M.; Tabrez, S. Targeting PI3K/Akt/mTOR Pathway by Different Flavonoids: A Cancer Chemopreventive Approach. *Int. J. Mol. Sci.* **2021**, *22*, 12455. https://doi.org/10.3390/ijms222212455

Academic Editors: Ylenia Zambito and Liangcan He

Received: 30 September 2021
Accepted: 13 November 2021
Published: 18 November 2021

1. Introduction

Cancer is a group of diseases where cells grow uncontrollably, and abnormal cells spread throughout the body via the bloodstream and the lymphatic system [1]. According to the World Health Organization (WHO), cancer was the second most lethal disease in 2019 [2]. Recently, a GLOBOCAN report estimated that there were approximately 10 million deaths due to cancer and 19.3 million new cases in 2020 [3]. Furthermore, a report published by WHO on 4 February 2020, warned that if the current upward trend in cancer incidences continues, the world will see a 60% rise in cancer cases in the next 20 years [2]. There are many reasons for the occurrence of cancer, but one possible cause is the aberrant regulation of different cell signaling pathways due to the acquisition of genetic and epigenetic changes [4]. One such pathway is the phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt)-mammalian target of rapamycin (mTOR). Several studies have reported the inappropriate PI3K/Akt/mTOR pathway regulation in different cancers, such as breast, liver, colorectal, prostate, and gastric cancer [5–7]. Hence, the PI3K/Akt/mTOR pathway has become a "hot spot" of molecular biomarker-based/targeted therapy of different tumors.

Natural compounds obtained from plant sources have recently garnered interest due to their easy availability, non-toxic/low adverse effects, cost-effectiveness, and ability to modulate multiple pathways [8]. Among the natural compounds, flavonoids have gained

attention as anticancer agents, and are documented as being effective against various types of cancer [9,10]. Flavonoids are of low-molecular-weight, comprising polyphenolic compounds, classified into six groups—isoflavonoids, flavanones, flavanols, flavonols, flavones, and anthocyanidins [11]. The primary source of these flavonoids is the regular human diet, including fruits, vegetables, grains, bark, roots, stems, flowers (Table 1 and Figure 1), plant-derived beverages, such as green tea, wine, and cocoa-based products [12–20]. Flavonoids have shown various activities, such as inhibiting cell proliferation and angiogenesis, cell cycle arrest, induction in apoptosis, and reversion in multidrug resistance [21,22]. Furthermore, it has also been reported to act as a pro-oxidant in some cases, and may interact with other therapeutic agents during biotransformation [23]. Rapid metabolism, low solubility, and poor absorption in the gastrointestinal tract hinder the real pharmacological potential of dietary flavonoids [24].

Table 1. Major dietary sources of different flavonoids inhibiting PI3K/Akt/mTOR pathway.

Class of Flavonoids	Inhibitors of PI3K/Akt/mTOR	Dietary Sources	References
Flavonols	Quercetin, myricetin, kaempferol, isorhamnetin, ampelopsin	Green tea, black tea, onion, apple with peel, oranges, blueberries, raw spinach, kale, broccoli, almonds, walnuts, dark chocolate, white wine, and red wine	[25–29]
Flavanol	EGCG	Green tea, black tea, cranberries, strawberries, red wine, almonds, hazelnuts, and dark chocolate	[30]
Flavanones	Hesperidin	citrus fruit, oranges, lemon, and grapefruit	[31]
Flavones	Baicalein, acacetin, genkwanin, oroxylin A, pectolinarigenin, galangin	Orange, yellow fruits, spices, and vegetables	[32–34]
Isoflavones	Genistein, lupiwighteone	Soy, tofu, legumes, *Glycyrrhiza glabra,* Lupinus, and *Lotus pedunculatus*	[35]
Flavonolignan	Silibinin	Milk thistle (*Silybum marianum*)	[36]
Anthocyanins	Delphinidin, cyanidin, pelargonidin	Red to purplish, blue-colored leafy vegetables, blueberries, other berries, currants, grapes, pomegranate, blue corn, grains, roots, tubers, and red wine	[37,38]

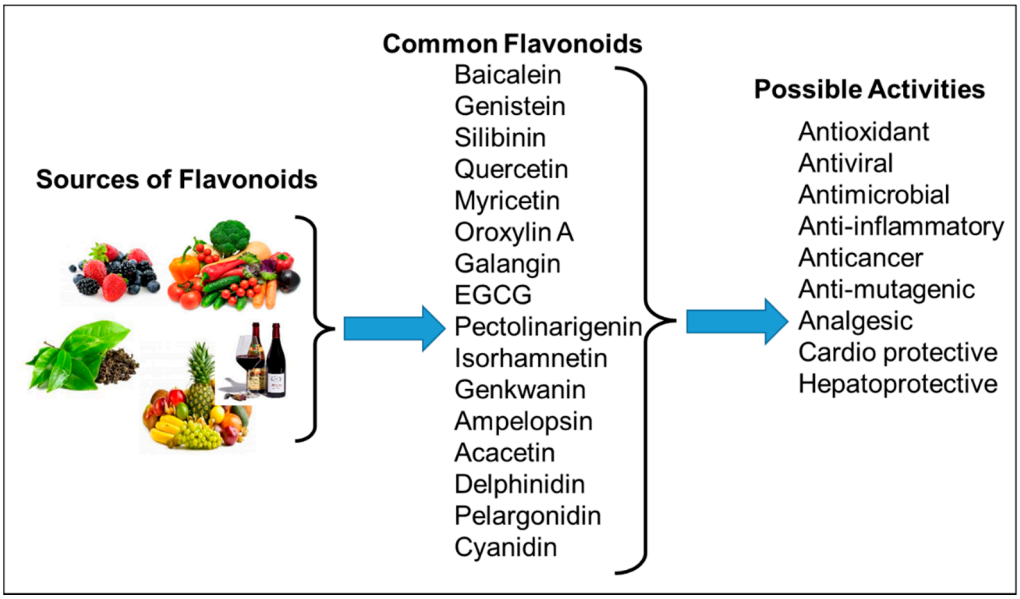


Figure 1. Common flavonoids from dietary sources, with their biological activities. EGCG; Epigallocatechin gallate. (Source: The effects of polyphenols and other bioactives on human health. https://pubs.rsc.org/image/article/2019/fo/c8fo01997e/c8fo01997e-f1_hi-res.gif accessed on 29 October 2021).

2. The Implication of PI3K/Akt/mTOR Pathway in Cancer

The PI3K/Akt/mTOR pathway is one of the most deregulated signaling cascades involved in the development of different human cancers. Each central node of this pathway is highly activated in most tumors [39,40]. The central nodes include phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), receptor tyrosine kinase (RTK) class I (Epidermal growth factor receptor; EGFR, human epidermal growth factor receptor 2; HER2, etc.), Akt, and phosphatase and tensin homolog deleted on chromosome 10 (PTEN). The *PIK3CA* gene encoding p110α catalytic subunit of PI3K is often mutated in most of cancer types [41,42]. Mutation in *PIK3CA* and independent activation of the PI3K pathway only (without Akt) can also induce cancer [43,44]. On the other hand, a mutation in the *EGFR* gene acts as an activator of PI3K and plays a role in the pathogenesis of non-small cell lung cancer [45]. Similarly, overexpression and amplification of the *EGFR* gene are frequently observed in glioblastoma [46]. Another member of the EGFR family, *HER2*, is overexpressed and amplified in invasive gastric and breast cancers. However, its overexpression is less frequently observed in other cancer types, such as ovarian, colon, salivary, biliary, and lung cancer [47]. The somatic mutations and amplification in pleckstrin homology (PH) domain (E17K) of Akt1 have been identified in various cancers, such as pancreatic, colorectal, and ovarian, and breast cancers [48]. The PI3K/Akt/mTOR pathway is a master regulator of cancer progression and is considered as one of the most important therapeutic targets. The PI3Ks phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3), leading to Akt phosphorylation that affects the cancer cell growth, cell survival, and cell cycle [49,50]. At the same time, phosphatase, and tensin homolog (PTEN) act as antagonists of PI3K and dephosphorylate PIP3 into PIP2 [51,52]. The complete blockage of PI3K signaling might effectively control the progression of different types of cancer [50,53].

Akt plays an important role in regulating tumor-associated cell processes, including cell survival, growth, migration, cell cycle progression, angiogenesis, and epithelial-mesenchymal transition [54]. Inhibition of the Akt pathway induces apoptosis and inhibits Akt-associated tumor cell growth [55,56]. The activation of the Akt pathway takes place through different receptors, such as integrin receptors, cytokine receptors, B and T cell receptors, tyrosine kinases receptor, and G-protein-coupled receptors (GPCRs) (Figure 2) through PIP3 generated by PI3Ks [57,58]. PIP3 does not activate Akt directly but modifies Akt configuration by binding to its PH domain and recruit Akt to the plasma membrane allowing phosphoinositide-dependent kinase-1 (PDK1) to phosphorylate the kinase domain at Thr308 residue [59,60]. The activated Akt leads to the phosphorylation of different downstream proteins present in the nucleus, cytosol, plasma membrane, supporting cell growth and survival, among other cellular effects [61]. On the other hand, dephosphorylation of Akt at Thr308 and Ser473 residues, by protein phosphatase 2A (PP2A), leads to its inhibition [62], and could increase fibroblast proliferation, vasodilatation, inhibition of the forkhead box O1 (FOXO1) protein, cell cycle arrest, and activation of B-cell lymphoma 2 (Bcl-2) associated agonist of cell death (BAD), leading to increased cell survival, stimulation of mTOR, resulting in reduced apoptosis and autophagy, and increased translocation of glucose transporter type 4 (GLUT4) [63]. Several scientific reports suggested an aberrant Akt signaling pathway in different types of cancer, resulting in tumor aggressiveness in some cases. Abnormalities in *Akt* genes have been reported in various human cancers, such as gastric carcinoma, glioblastoma, and gliosarcoma, whereas Akt2 amplification has been reported in head and neck squamous cell carcinoma, pancreatic, ovarian, and breast cancers [64].

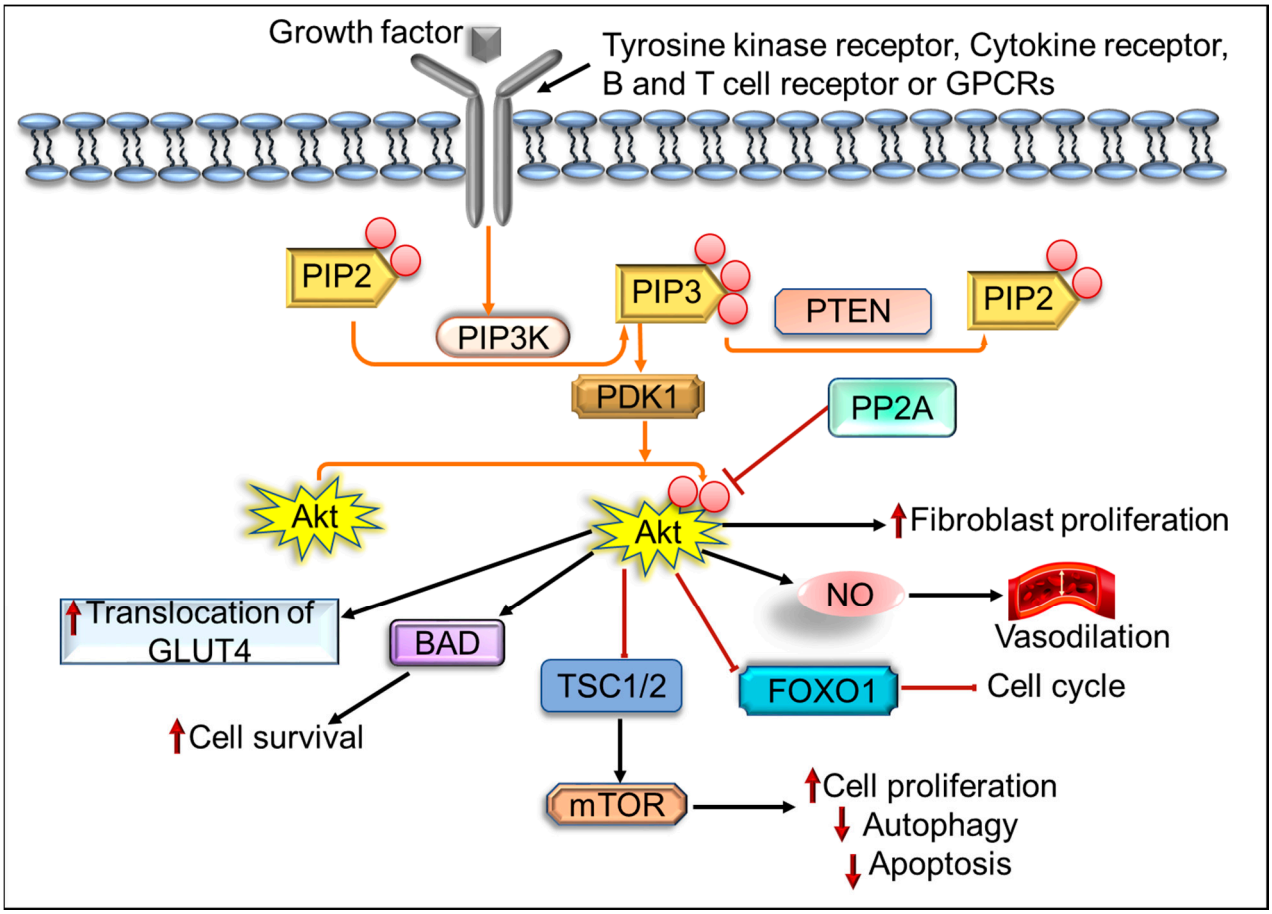


Figure 2. PI3K/Akt signaling pathway; PIP2, phosphatidylinositol 4, 5-bisphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PDK1, 3-phosphoinositide-dependent kinase 1; PP2A, protein phosphatase 2A; BAD, BCL2 associated agonist of cell death; GLUT4, glucose transporter type 4; GPCRs, G-protein-coupled receptors; TSC, tuberous sclerosis complex; FOXO1, forkhead box O1 protein; NO, nitric oxide.

The mTOR pathway also plays a vital role in regulating different activities, such as cell survival, cell growth, metabolism, and protein synthesis in response to upstream signals [65]. This is a downstream substrate of PI3K and Akt with two distinct complexes mTORC1 and mTORC2 [66]. Akt activates mTOR activity either by direct phosphorylation of mTOR at Ser2448 or by indirect phosphorylation and inhibition of tuberous sclerosis complex 2 (TSC2). Direct phosphorylation of TSC2 at S939 and T1462 [67,68] by Akt releases its inhibitory effect on mTOR and upregulates mTOR activity. TSC2 makes a heterodimeric complex with TSC1 and acts as a negative regulator of GTPase-activating protein (GAP) activity [69]. Because TSC2 suppresses the activity of the Ras-related GTPase Rheb, a selective activator of mTORC1, inhibition of TSC2 by Akt results in activation of mTORC1 [70]. The hyperactivation of this cascade can stimulate tumor development and progression through different mechanisms such as promoting growth factor receptor signaling, suppression of autophagy, lipid metabolism, glycolytic metabolism, angiogenesis, and cancer cell migration [71,72]. The different growth factors, such as vascular endothelial growth factor, hepatocyte growth factor, transforming growth factor, platelet-derived growth factor, insulin-like growth factor 1, and epidermal growth factor regulate the activity of mTOR signaling [73].

3. Inhibition of PI3K/Akt/mTOR Signaling Pathway by Different Flavonoids

PI3K/Akt/mTOR signaling pathways are crucial to multiple aspects of cell growth and survival in physiological and pathological conditions, such as cancer [74]. In response to extracellular stimuli, the recruitment of class IA PI3K to the plasma membrane occurs by interaction of p85 and insulin receptor substrate (IRS) through the activation of RTKs or GPCRs [75]. The heterodimeric class IA PI3Ks phosphorylate PIP2 at position 3 of the inositol ring to convert it into PIP3, which acts as a second cellular messenger that controls cell growth, cell survival, and proliferation [76–78]. PIP3 binds to the PH domain of Akt and translocates it to the plasma membrane (Figure 3), where PDK-1 phosphorylates Akt [60,79]. Once Akt is activated, it further phosphorylates a broad array of proteins involved in cell cycle regulation, growth, proliferation, apoptosis, and cell survival [63,80]. The phosphatase PTEN plays a negative modulator of mTOR cascade [81]. It inhibits the signaling through the PI3K-Akt pathway through the involvement of TSC1/2 [82]. Deregulation of various components of the mTOR pathway, such as PI3K amplification/mutation, loss of PTEN function, overexpression of Akt, ribosomal protein S6 kinase beta-1 (S6K1), eukaryotic translation initiation factor 4E binding protein 1 (4EBP1), and overexpression of eukaryotic translation initiation factor 4E (eIF4E), has been reported in numerous cancers, especially melanoma, where variation in key elements of the mTOR signaling have major effects on tumor growth [83]. One study suggested natural compounds and herbs, such as resveratrol, diosgenin, timosaponin III, 3,3′-diindolylmethane, epigallocatechin gallate (EGCC), pomegranate, curcumin, gallic acid, and genistein, could directly or indirectly inhibit the mTOR pathway [84]. In the below-mentioned section, we have listed some well-known flavonoids reported as anticancer agents in various cancer models (Table 2).

Table 2. Different flavonoids and their PI3K/Akt/mTOR inhibitory activity.

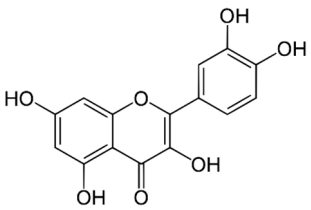
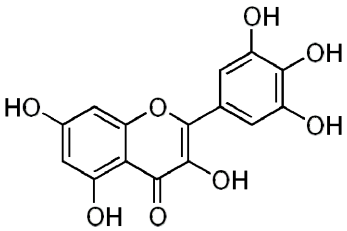
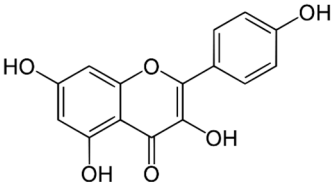
Name of Inhibitor	Structure of Inhibitor	Inhibitory Activity	Cancer/Cell Type	Reference
Quercetin		Triggers apoptosis by stimulating autophagy, inhibits the Akt/mTOR pathway	HCC	[26,27]
Myricetin		Suppresses angiogenesis by inducing apoptosis, inhibits the PI3K/Akt/mTOR pathway	Endothelial cells	[28]
Kaempferol		Induces apoptosis, cell cycle arrest at G2/M, inhibits cell migration, PI3k/Akt/mTOR downregulation	Melanoma and liver cancer	[29,85]

Table 2. *Cont.*

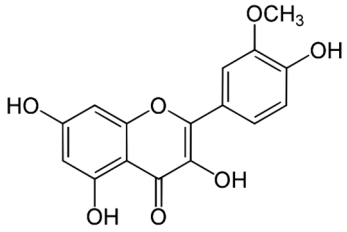
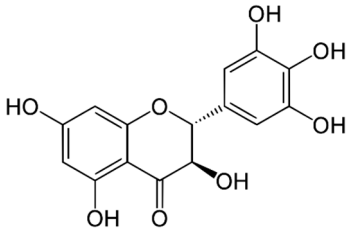
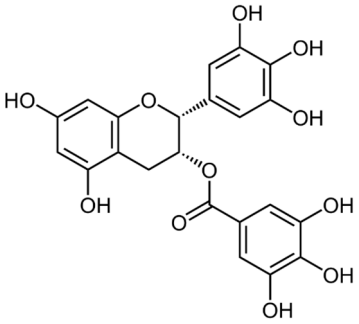
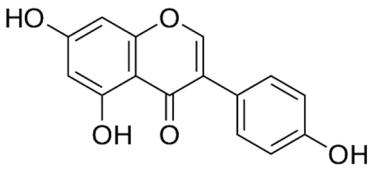
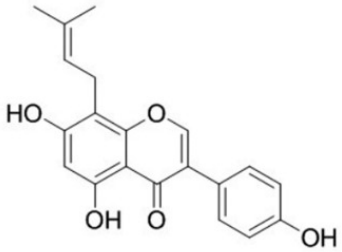
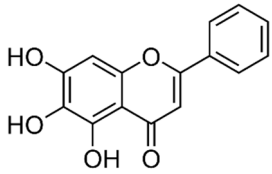
Name of Inhibitor	Structure of Inhibitor	Inhibitory Activity	Cancer/Cell Type	Reference
Isorhamnetin		Cell cycle arrest at G2/M phase, inhibits cell proliferation by suppressing PI3K/Akt/mTOR pathway	Colorectal and breast cancer	[33,86]
Ampelopsin		Induces apoptotic and autophagy through the Akt-mTOR pathway via ER stress	MDA-MB-231 and MCF-7 breast cancer	[87]
EGCG		Suppresses the proliferation and induces apoptosis, downregulates the expression of pAkt and p-mTOR, inhibits the PI3K/Akt/mTOR	Gastric carcinoma	[30,88]
Genistein		Suppresses Akt and the NF-κB pathway through different cascades	HCC	[89,90]
Lupiwighteone		Induces the antiangiogenic activities, triggers the caspase-dependent and independent apoptosis through PI3K/Akt/mTOR pathway inhibition	Prostate and breast cancer	[91,92]
Baicalein		Deactivate PI3K/Akt pathway	HCC	[32]

Table 2. *Cont.*

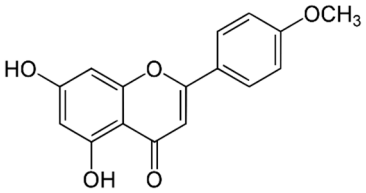
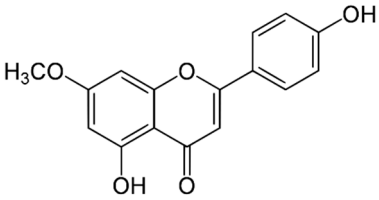
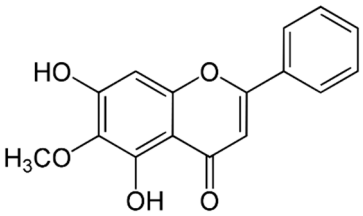
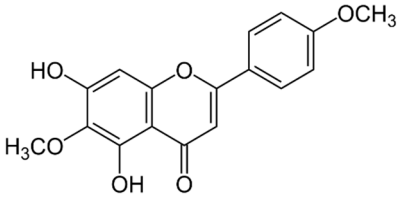
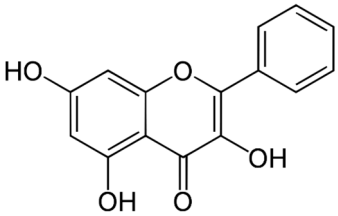
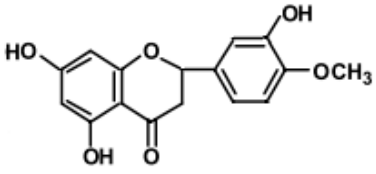
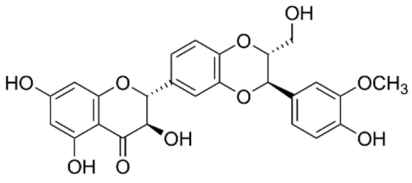
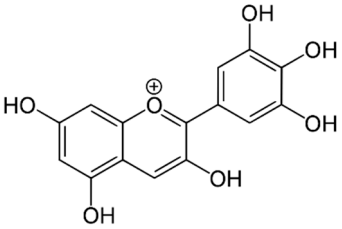
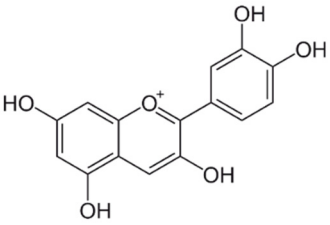
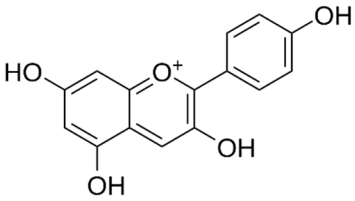
Name of Inhibitor	Structure of Inhibitor	Inhibitory Activity	Cancer/Cell Type	Reference
Acacetin		Induces cell cycle arrest at G2/M phase, induces apoptosis and autophagy by suppressing the PI3K/Akt/mTOR pathway	Breast cancer	[33]
Genkwanin		Significantly inhibits cell proliferation, induces cell cycle arrest at G2/M phase, induces apoptosis and autophagy by suppressing the PI3K/Akt/mTOR pathway	Colorectal and breast cancer	[33,34]
Oroxylin A		Inhibits the proliferation by inducing autophagy and suppresses the Akt and ERK activation and the phosphorylation of mTOR and STAT3	Glioma cells	[93,94]
Pectolinarigenin		Induces cell cycle arrest at G2/M phase, induces autophagic and apoptotic cell death through downregulation of PI3K/Akt/mTOR pathway	Gastric cancer	[95]
Galangin		Inhibits the cell proliferation, migration and invasion, induces apoptosis, suppresses PI3K/Akt/mTOR signaling	A498 cells	[96]
Hesperidin		Induces apoptosis and autophagy by inhibiting Aurora-A mediated PI3K/Akt/mTOR and GSK-3β pathways	Colon cancer	[31,97]
Silibinin		Anti-proliferative, inhibits HIF-1α and the mTOR/p70S6K/4E-BP1 signaling pathway	Hepatoma cells	[36,98]

Table 2. *Cont.*

Name of Inhibitor	Structure of Inhibitor	Inhibitory Activity	Cancer/Cell Type	Reference
Delphinidin		Inhibits cell proliferation by inactivating the PI3K/Akt, and ERK1/2 mitogen-activated protein pathway	Ovarian cancer	[99]
Cyanidin		Inhibits cell migration and reverses drug resistance by suppressing the PI3K/Akt pathway	HCC	[100]
Pelargonidin		Triggers autophagy and ROS-induced decline in MMP, cell cycle arrest at the G2/M phase through inhibiting PI3K and p-Akt signaling	Human osteosarcoma	[38]

HCC, hepatocellular carcinoma; MMP, mitochondrial membrane potential.

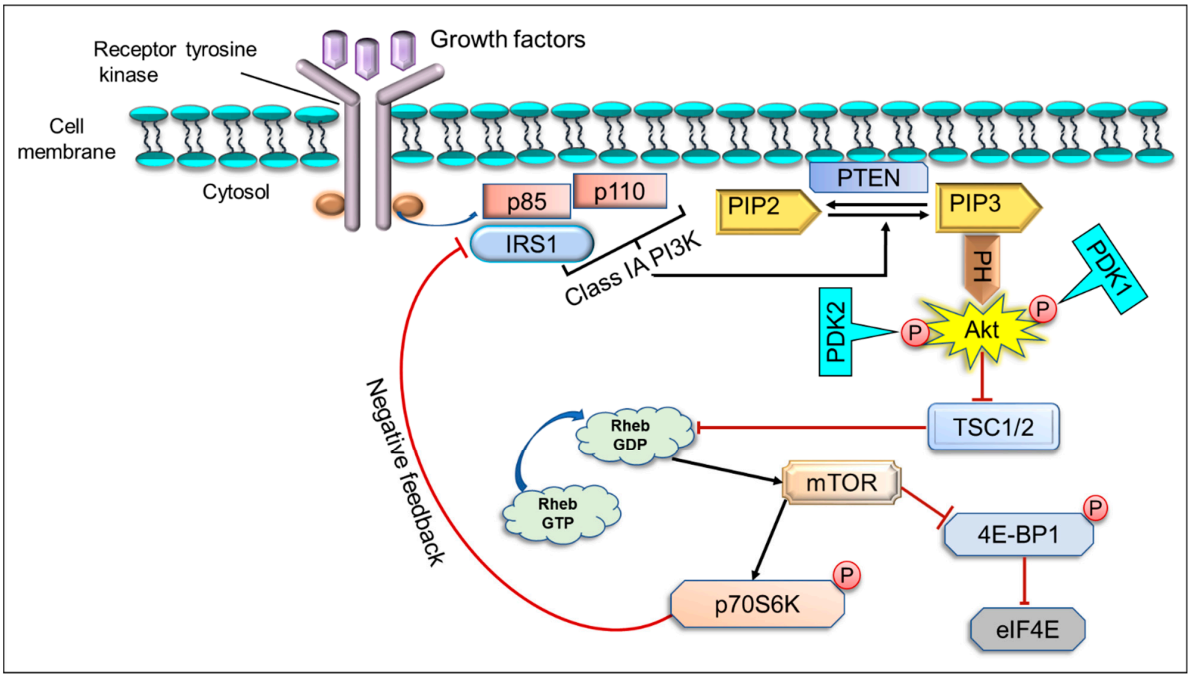


Figure 3. mTOR signaling cascade; IGF-1, insulin-like growth factor 1; EGF, epidermal growth factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; PIP2, phosphatidylinositol 4, 5-bisphosphate; PDK1, 3-phosphoinositide-dependent kinase 1; TSC1/2, tuberous sclerosis complex 1/2; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; eIF4E, eukaryotic translation initiation factor 4E; PTEN, phosphatase and tensin homolog deleted on chromosome 10; IRS1, insulin receptor substrate 1; 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; p70S6K1, p70 ribosomal S6 kinase 1; Rheb GDP, Ras homolog enriched in brain GDP; Rheb GTP, Ras homolog enriched in brain GTP.

3.1. Quercetin

Quercetin is a flavonol and is a subclass of flavonoids. Some vegetables and fruits, such as onions, scallions, kale, broccoli, apples, berries (and even teas), are the primary sources of quercetin [23]. Some studies reported that quercetin inhibits phosphorylation of the mTOR primary downstream targets, namely 4E-BP1 and ribosomal protein S6K [101–103]. It has shown a potential anticancer activity in various cancer cell lines and animal models in a dose-dependent manner. Quercetin has been reported to be more cytotoxic compared to ellagic acid and it inhibits cell cycle progression in the S phase in leukemia and breast cancer cells. It has also shown to have a ~5-fold increase in the life span of tumor-bearing mice than untreated mice [104].

3.2. Myricetin

Myricetin, a plant-derived flavonoid, commonly exists in fruits and other foods/beverages, such as oranges, berries, nuts, tea, red wine, and vegetables (tomatoes) [105], possessing anticancer effects [28,106]. It inhibits cell cycle progression and proliferation and induces apoptosis and autophagy in human colon cancer cells by inhibiting the PI3K/Akt/mTOR signaling [107]. Myricetin also suppresses breast cancer cell growth and inhibits UVB-induced skin cancer [108,109]. One study reported that myricetin induces apoptosis through ROS induction and inhibits cell migration, tube formation, and PI3K/Akt/mTOR signaling in human umbilical vascular endothelial cells [28].

3.3. Kaempferol

Kaempferol is a natural flavonol commonly found in plants and fruits, such as kale, beans, green tea, Brussels sprouts, spinach, apple, grapefruit, and broccoli [110]. It has been reported to have antioxidant and antitumor properties. Kaempferol exerts strong anticancer effects through inducing apoptosis, cell migration, cell cycle arrest at the G2/M phase, inhibiting and reducing the level of mTOR, pm-TOR, PI3K, p-PI3K, and Akt protein levels in the human malignant melanoma A375 cell line [29]. Further, it exerts anti-proliferative effects on lung cancer and human endothelial cells by activating mitogen-activated protein kinase (MAPK) signaling [111]. A recent study also suggested potent anticancer, anti-proliferation activity of kaempferol in liver cancer [112]. In addition, kaempferol has been reported to significantly inhibit HepG2 cell proliferation, invasion, and migration, and induce apoptosis by up/downregulating PTEN and microRNA-21 (miR-21), respectively, ultimately inhibiting the PI3K/Akt/mTOR pathway [85].

3.4. Isorhamnetin

Flavonoid isorhamnetin obtained from the medicinal plant *Hippophae rhamnoides* L. has shown anticancer effects in colorectal cancer. It has been reported to suppress cell proliferation and induce the G2/M phase cell cycle arrest by inhibiting the PI3K/Akt/mTOR pathway in colorectal and breast cancer [33,86].

3.5. Green Tea Catechins, Epicatechin, and Epigallocatechin-3-Gallate

Green tea catechin, such as epicatechin and epigallocatechin-3-gallate, is present in green tea, a typical refreshment drink enjoyed worldwide [113]. Epigallocatechin-3-gallate has shown significant anticancer activities in different cancer models [114]. Recent studies have suggested that epicatechin interacts and neutralizes reactive oxygen species (ROS) in the cell and modulates the MAP kinase pathway to inhibit cell proliferation [115]. In addition, it has shown inhibitory activities against Akt and NF-κB in combination with panaxadiol or cisplatin in HCT-116 and renal tubular carcinoma [116]. Some evidence shows that it downregulates doxorubicin-induced overexpression of P-glycoprotein through the inhibition of PI3K/Akt and mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (MEK/ERK) signaling pathways [117,118]. Additionally, it downregulates the PI3K/Akt and MEK/ERK signaling pathways and promote apoptosis in T47D cells of human breast cancer [119,120].

3.6. Fisetin

Fisetin is a flavonol commonly found in some fruits/plants, such as strawberries, grapes, apples, persimmons, onions, kiwi, kale, etc. It shares antioxidant properties with many other plant polyphenols [121]. A study reported that a dietary tetrahydroxyflavone, fisetin inhibited human non-small cell lung cancer cells by downregulating the PI3K/Akt/mTOR signaling pathway [122]. Fisetin has shown to downregulate the PTEN protein levels in multiple myeloma U266 cells and A549 lung carcinoma [122,123]. In addition, it reduces phosphorylation of Akt, mTOR, microphthalmia-associated transcription factor (MITF), and p70S6K proteins in human melanoma 451Lu cells in a dose-dependent manner [122,124].

3.7. Lupiwighteone

Isoflavone, lupiwighteone is majorly present in medicinal plants *Glycyrrhiza glabra*, *Lupinus* sp., and *Lotus pedunculatus*. Lupiwighteone has shown anticancer activity in various cancer cells of neuroblastoma, prostate, and breast cancer [91,92]. It could also induce caspase-dependent and independent apoptosis in breast cancer cells by inhibiting the PI3K/Akt/mTOR pathway [92].

3.8. Apigenin

Flavone, apigenin is an active plant-originated compound found in parsley, celery, and chamomile. It has shown to inhibit cancer progression and development by blocking inhibitory-κB kinase (IKK) alpha activation and the PI3K/Akt/FoxO pathway in a TRAMP mice model [125,126]. It also inhibits cell proliferation and induces autophagy by blocking the PI3K/Akt/mTOR pathway in liver cancer cells [127].

3.9. Nobiletin

Nobiletin (5,6,7,8,3′,4′-hexamethoxyflavone) is a polymethoxy flavonoid compound derived from citrus fruits [128]. It has shown several pharmacological activities, including antioxidative, anti-inflammatory, anticancer, cardio/neuro-protective, and anti-metabolic [128,129]. It has been reported to inhibit ovarian cancer cell growth by inhibiting the secretion of the primary angiogenesis mediators, Akt, hypoxia-inducible factor 1-alpha (HIF-1α), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and vascular endothelial growth factor (VEGF). Moreover, it does not affect the viability of normal ovarian epithelial cells at less than 40 μM [130].

3.10. Galangin

Galangin is a natural flavonoid obtained from honey and *Alpinia officinarum Hance* (*Zingiberaceae*), one of the Chinese herbal medicines. It has various beneficial properties, such as antidiabetic, anticancer, antiviral, and antimicrobial, and does not show any complications [131]. A study reported that galangin could inhibit the proliferation, migration, and invasion of the A498 cells of kidney cancer. Furthermore, it could also induce apoptosis and suppress the PI3K/Akt/mTOR signaling pathway [96].

3.11. Hesperidin

Hesperidin is a dietary flavanone widely distributed in citrus fruits, such as oranges, lemon, and lime. Data obtained from several in vitro and in vivo studies suggested a wide spectrum of biological properties associated with hesperidin, which include anticarcinogenic, antioxidant, and anti-inflammatory [97]. Scientific evidence has indicated that hesperidin induces apoptosis and cell cycle arrest and inhibits cancer cell proliferation by interacting with various cellular targets [31]. Further, it inhibits tumor metastasis, angiogenesis, and chemoresistance [31]. One study reported that hesperidin treatment could induce apoptosis and trigger autophagy by inhibiting the aurora-a mediated PI3K/Akt/mTOR and glycogen synthase kinase 3 beta (GSK-3β) pathway in colon cancer mouse model [132].

3.12. Anthocyanins

Anthocyanins are a subclass of flavonoids widely distributed in fruits, such as cherries, berries, grapes, and vegetables, as glycosides, attached to different sugars [133]. Cyanidin is one of the members of the anthocyanin family, which is reported to inhibit cell migration and reverse oxaliplatin-induced EMT biomarker changes through inactivation of PI3K/Akt signaling in hepatocellular carcinoma [100]. Pelargonidin is another member of anthocyanins, and exerts an anticancer effect in human osteosarcoma cells. This anthocyanin's family member induces autophagy, triggers the ROS induced reduction in mitochondrial membrane potential, and induces cell cycle arrest at the G2/M phase. It also inhibits the expression of p-PI3K and p-Akt in a dose-dependent manner [38].

3.13. Delphinidin

Delphinidin plays a vital role in preventing oxidative stress, inflammation, angiogenesis, metastasis, and carcinogenesis [134,135] in different cancers, such as breast [136], prostate [137], lungs [138], liver [139], colon [140], and fibrosarcoma [141] by regulating different cell signal transduction pathways. Delphinidin has shown anti-proliferative properties through inactivation of the PI3K/Akt and ERK1/2 MAPK signaling pathway in ovarian cancer cells [99]. The dose-dependent treatment of delphinidin reduce the SKOV3 cell proliferation by inhibiting the PI3K/Akt and ERK1/2 mitogen-activated protein kinase signaling pathway [99].

3.14. Sulforaphane

Sulforaphane is an isothiocyanate, commonly found in cruciferous vegetables. It also possesses anticancer properties and acts as an effective natural agent to modulate the PI3K/Akt signaling pathway. One study demonstrated that sulforaphane inhibits lung cancer cell growth by inhibiting Akt phosphorylation and reduces PTEN expression in lung cancer xenografts mice. Due to this property, sulforaphane could be considered as an important anticancer agent for lung cancer treatment [142].

4. Biodisponibility/Bioavailability of Flavonoids

It is well known that human beings have been consuming flavonoids since ancient times. In the modern world, these bioactive flavonoids are widely consumed as part of the diet or nutritional supplements [143,144]. However, low/limited biodisponibility has been an issue that significantly limits the clinical usage of these compounds as anticancer agents [145–147]. The poor bioavailability of these flavonoids is due to metabolism carried out by phase II enzymes, resulting in hydrophilic excretable conjugates. Failed or inefficient excretion of these metabolites could hurt overall cellular metabolism, leading to higher exposure to flavonoids [148,149]. To increase the biodisponibility of these flavonoids, the scientific community is focusing their research on limiting the metabolism or targeted delivery of these compounds. These approaches, if successfully implemented, could lead to potent utilization of flavonoids as anticancer agents.

5. Conclusions

The above-mentioned scientific literature indicates the role of different signaling pathways in the progression of various cancers. The PI3K/Akt/mTOR is a well-known "hot spot" target for anticancer compounds. Due to natural resources, cost-effectiveness, and ease of use, flavonoids are recommended as anticancer agents. However, even with significant pharmacological potential, they are not fully exploited clinically because of their inherent properties, such as limited bioavailability, rapid metabolism, untargeted delivery, cytotoxicity to normal cells, etc. To enhance their anticancer potential, the possible usage of a mixture of flavonoids has been suggested, considering the probability of affecting different signaling cascades simultaneously. The use of state-of-the-art techniques, including various nanotechnology-based approaches, is also recommended to reduce/nullify the above-listed

drawbacks. Their use, alongside currently available chemotherapeutic drugs, could help with reducing required doses, ultimately resulting in fewer side effects.

Author Contributions: T.A.Z.: original draft preparation and reviewing. M.S.: conceptualization, original draft preparation, and writing. M.T.: reviewing and editing. S.T.: reviewing, editing, and supervision. All authors have read and agreed to the published version of the manuscript.

Funding: The authors extend their appreciation to the Deputyship for Research & Innovation, Ministry of Education in Saudi Arabia for funding this research work through project number IFPRP: 30-141-1442, and King Abdulaziz University, DSR, Jeddah, Saudi Arabia.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare that they have no conflict of interest.

Abbreviations

Akt	Protein kinase
BAD	BCL2 associated agonist of cell death
BCL2	B-cell lymphoma 2
4EBP1	Eukaryotic translation initiation factor 4E binding protein 1
EGCG	Epigallocatechin gallate
EGFR	Epidermal growth factor receptor
eIF4E	Eukaryotic translation initiation factor 4E
ERK	Extracellular signal-regulated kinase
GPCRs	G-protein-coupled receptors
GSK-3β	Glycogen synthase kinase 3 beta
GLUT4	Glucose transporter type 4
HER2	Human epidermal growth factor receptor 2
HIF-1α	Hypoxia-inducible factor 1-alpha
IKK	Inhibitory-κB kinase
MAPK	Mitogen-activated protein kinase
MEK	Mitogen-activated protein kinase kinase
MITF	Microphthalmia-associated transcription factor
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
mTOR	mammalian target of rapamycin
PI3K	Phosphoinositide 3-kinase
PH	Pleckstrin homology
PDK1	Phosphoinositide-dependent kinase-1
p70S6K1	p70 ribosomal S6 kinase 1
PIK3CA	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha
PIP3	Phosphatidylinositol-3,4,5-triphosphate
PP2A	Protein phosphatase 2A
PTEN	Phosphatase and tensin homolog deleted on chromosome 10
RHEB GDP	Ras homolog enriched in brain GDP
RHEB GTP	Ras homolog enriched in brain GTP
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
S6k1	Ribosomal protein S6 kinase beta-1
TSC	Tuberous sclerosis complex
VEGF	Vascular endothelial growth factor

References

1. Paul, C.D.; Mistriotis, P.; Konstantopoulos, K. Cancer cell motility: Lessons from migration in confined spaces. *Nat. Rev. Cancer* **2017**, *17*, 131–140. [CrossRef]
2. WHO. WHO Outlines Steps to Save 7 Million Lives from Cancer. Available online: https://www.who.int/news/item/04-02-2020-who-outlines-steps-to-save-7-million-lives-from-cancer (accessed on 4 February 2020).
3. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [CrossRef]
4. Butti, R.; Das, S.; Gunasekaran, V.P.; Yadav, A.S.; Kumar, D.; Kundu, G.C. Receptor tyrosine kinases (RTKs) in breast cancer: Signaling, therapeutic implications and challenges. *Mol. Cancer* **2018**, *17*, 34. [CrossRef]
5. Wei, J.; Gou, Z.; Wen, Y.; Luo, Q.; Huang, Z. Marine compounds targeting the PI3K/Akt signaling pathway in cancer therapy. *Biomed. Pharmacother.* **2020**, *129*, 110484. [CrossRef]
6. Shorning, B.Y.; Dass, M.S.; Smalley, M.J.; Pearson, H.B. The PI3K-AKT-mTOR Pathway and Prostate Cancer: At the Crossroads of AR, MAPK, and WNT Signaling. *Int. J. Mol. Sci.* **2020**, *21*, 4507. [CrossRef]
7. Jiang, N.; Dai, Q.; Su, X.; Fu, J.; Feng, X.; Peng, J. Role of PI3K/AKT pathway in cancer: The framework of malignant behavior. *Mol. Biol. Rep.* **2020**, *47*, 4587–4629. [CrossRef]
8. Almatroodi, S.A.; Alsahli, M.A.; Almatroudi, A.; Verma, A.K.; Aloliqi, A.; Allemailem, K.S.; Khan, A.A.; Rahmani, A.H. Potential Therapeutic Targets of Quercetin, a Plant Flavonol, and Its Role in the Therapy of Various Types of Cancer through the Modulation of Various Cell Signaling Pathways. *Molecules* **2021**, *26*, 1315. [CrossRef]
9. Abotaleb, M.; Samuel, S.M.; Varghese, E.; Varghese, S.; Kubatka, P.; Liskova, A.; Büsselberg, D. Flavonoids in Cancer and Apoptosis. *Cancers* **2018**, *11*, 28. [CrossRef] [PubMed]
10. Badar Ul Islam, n.; Khan, M.S.; Husain, F.M.; Rehman, M.T.; Alzughaibi, T.A.; Abuzenadah, A.M.; Urooj, M.; Kamal, M.A.; Tabrez, S. mTor Targeting by Different Flavonoids for Cancer Prevention. *Curr. Med. Chem.* 2020. [CrossRef]
11. Patil, V.M.; Masand, N. Chapter 12—Anticancer Potential of Flavonoids: Chemistry, Biological Activities, and Future Perspectives. In *Studies in Natural Products Chemistry*; Attaur, R., Ed.; Elsevier: Amsterdam, The Netherlands, 2018; Volume 59, pp. 401–430.
12. Kopustinskiene, D.M.; Jakstas, V.; Savickas, A.; Bernatoniene, J. Flavonoids as Anticancer Agents. *Nutrients* **2020**, *12*, 457. [CrossRef]
13. Kozłowska, A.; Szostak-Węgierek, D. Flavonoids—Food Sources, Health Benefits, and Mechanisms Involved. In *Bioactive Molecules in Food*; Mérillon, J.-M., Ramawat, K.G., Eds.; Springer International Publishing: Cham, Switzerland, 2017; pp. 1–27.
14. Baby, J.; Devan, A.R.; Kumar, A.R.; Gorantla, J.N.; Nair, B.; Aishwarya, T.S.; Nath, L.R. Cogent role of flavonoids as key orchestrators of chemoprevention of hepatocellular carcinoma: A review. *J. Food Biochem.* **2021**, *45*, e13761. [CrossRef]
15. Qiao, D.; Li, Y.; Xing, J.; Sun, P.; Wang, Y.; Zhang, Y.; Chen, L.; Ren, X.; Lin, Z.; Jin, J.; et al. Baicalein inhibits PI3K/AKT signaling pathway and induces autophagy of MGC-803 cells. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* **2019**, *35*, 613–618. [PubMed]
16. Tao, Y.; Zhan, S.; Wang, Y.; Zhou, G.; Liang, H.; Chen, X.; Shen, H. Baicalin, the major component of traditional Chinese medicine Scutellaria baicalensis induces colon cancer cell apoptosis through inhibition of oncomiRNAs. *Sci. Rep.* **2018**, *8*, 14477. [CrossRef] [PubMed]
17. Cheriet, T.; Ben-Bachir, B.; Thamri, O.; Seghiri, R.; Mancini, I. Isolation and Biological Properties of the Natural Flavonoids Pectolinarin and Pectolinarigenin—A Review. *Antibiotics* **2020**, *9*, 417. [CrossRef] [PubMed]
18. Porras, G.; Bacsa, J.; Tang, H.; Quave, C.L. Characterization and Structural Analysis of Genkwanin, a Natural Product from Callicarpa americana. *Crystals* **2019**, *9*, 491. [CrossRef]
19. Zhou, Y.; Tu, Y.; Zhou, Q.; Hua, A.; Geng, P.; Chen, F.; Han, A.; Liu, J.; Dai, D.; Wang, S.; et al. Evaluation of acacetin inhibition potential against cytochrome P450 in vitro and in vivo. *Chem. Biol. Interact.* **2020**, *329*, 109147. [CrossRef]
20. Carneiro, R.C.V.; Ye, L.; Baek, N.; Teixeira, G.H.A.; O'Keefe, S.F. Vine tea (Ampelopsis grossedentata): A review of chemical composition, functional properties, and potential food applications. *J. Funct. Foods* **2021**, *76*, 104317. [CrossRef]
21. Chahar, M.K.; Sharma, N.; Dobhal, M.P.; Joshi, Y.C. Flavonoids: A versatile source of anticancer drugs. *Pharmacogn. Rev.* **2011**, *5*, 1–12. [CrossRef]
22. Jucá, M.M.; Cysne Filho, F.M.S.; de Almeida, J.C.; Mesquita, D.d.S.; Barriga, J.R.d.M.; Dias, K.C.F.; Barbosa, T.M.; Vasconcelos, L.C.; Leal, L.K.A.M.; Ribeiro, J.E.; et al. Flavonoids: Biological activities and therapeutic potential. *Nat. Prod. Res.* **2020**, *34*, 692–705. [CrossRef]
23. Islam, B.u.; Suhail, M.; Khan, M.K.; Zughaibi, T.A.; Alserihi, R.F.; Zaidi, S.K.; Tabrez, S. Polyphenols as anticancer agents: Toxicological concern to healthy cells. *Phytother. Res.* 2021. [CrossRef]
24. 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]
25. Fraga, C.G.; Croft, K.D.; Kennedy, D.O.; Tomás-Barberán, F.A. The effects of polyphenols and other bioactives on human health. *Food Funct.* **2019**, *10*, 514–528. [CrossRef]
26. Vásquez-Garzón, V.R.; Macias-Pérez, J.R.; Jiménez-García, M.N.; Villegas, V.; Fattel-Fazenta, S.; Villa-Treviño, S. The chemopreventive capacity of quercetin to induce programmed cell death in hepatocarcinogenesis. *Toxicol. Pathol.* **2013**, *41*, 857–865. [CrossRef]
27. Ji, Y.; Li, L.; Ma, Y.-X.; Li, W.-T.; Li, L.; Zhu, H.-Z.; Wu, M.-H.; Zhou, J.-R. Quercetin inhibits growth of hepatocellular carcinoma by apoptosis induction in part via autophagy stimulation in mice. *J. Nutr. Biochem.* **2019**, *69*, 108–119. [CrossRef]

28. Kim, G.D. Myricetin Inhibits Angiogenesis by Inducing Apoptosis and Suppressing PI3K/Akt/mTOR Signaling in Endothelial Cells. *J. Cancer Prev.* **2017**, *22*, 219–227. [CrossRef] [PubMed]
29. Yang, J.; Xiao, P.; Sun, J.; Guo, L. Anticancer effects of kaempferol in A375 human malignant melanoma cells are mediated via induction of apoptosis, cell cycle arrest, inhibition of cell migration and downregulation of m-TOR/PI3K/AKT pathway. *J. BUON* **2018**, *23*, 218–223.
30. Zhu, F.; Xu, Y.; Pan, J.; Li, M.; Chen, F.; Xie, G. Epigallocatechin Gallate Protects against MNNG-Induced Precancerous Lesions of Gastric Carcinoma in Rats via PI3K/Akt/mTOR Pathway. *Evid. Based Complement Alternat. Med.* **2021**, *2021*, 8846813. [CrossRef] [PubMed]
31. Aggarwal, V.; Tuli, H.S.; Thakral, F.; Singhal, P.; Aggarwal, D.; Srivastava, S.; Pandey, A.; Sak, K.; Varol, M.; Khan, M.A.; et al. Molecular mechanisms of action of hesperidin in cancer: Recent trends and advancements. *Exp. Biol. Med.* **2020**, *245*, 486–497. [CrossRef]
32. Zheng, Y.-H.; Yin, L.-H.; Grahn, T.H.M.; Ye, A.-F.; Zhao, Y.-R.; Zhang, Q.-Y. Anticancer effects of baicalein on hepatocellular carcinoma cells. *Phytother. Res.* **2014**, *28*, 1342–1348. [CrossRef] [PubMed]
33. Zhang, H.-W.; Hu, J.-J.; Fu, R.-Q.; Liu, X.; Zhang, Y.-H.; Li, J.; Liu, L.; Li, Y.-N.; Deng, Q.; Luo, Q.-S.; et al. Flavonoids inhibit cell proliferation and induce apoptosis and autophagy through downregulation of PI3Kγ mediated PI3K/AKT/mTOR/p70S6K/ULK signaling pathway in human breast cancer cells. *Sci. Rep.* **2018**, *8*, 11255. [CrossRef]
34. Wang, X.; Song, Z.-J.; He, X.; Zhang, R.-Q.; Zhang, C.-F.; Li, F.; Wang, C.-Z.; Yuan, C.-S. Antitumor and immunomodulatory activity of genkwanin on colorectal cancer in the APC(Min/+) mice. *Int. Immunopharmacol.* **2015**, *29*, 701–707. [CrossRef]
35. Tuli, H.S.; Tuorkey, M.J.; Thakral, F.; Sak, K.; Kumar, M.; Sharma, A.K.; Sharma, U.; Jain, A.; Aggarwal, V.; Bishayee, A. Molecular Mechanisms of Action of Genistein in Cancer: Recent Advances. *Front. Pharmacol.* **2019**, *10*, 1336. [CrossRef]
36. Bijak, M. Silybin, a Major Bioactive Component of Milk Thistle (Silybum marianum L. Gaernt.)-Chemistry, Bioavailability, and Metabolism. *Molecules* **2017**, *22*, 1942. [CrossRef] [PubMed]
37. Khoo, H.E.; Azlan, A.; Tang, S.T.; Lim, S.M. Anthocyanidins and anthocyanins: Colored pigments as food, pharmaceutical ingredients, and the potential health benefits. *Food Nutr. Res.* **2017**, *61*, 1361779. [CrossRef] [PubMed]
38. Chen, Y.; Wang, S.; Geng, B.; Yi, Z. Pelargonidin induces antitumor effects in human osteosarcoma cells via autophagy induction, loss of mitochondrial membrane potential, G2/M cell cycle arrest and downregulation of PI3K/AKT signalling pathway. *J. BUON* **2018**, *23*, 735–740.
39. Owusu-Brackett, N.; Shariati, M.; Meric-Bernstam, F. Role of PI3K/AKT/mTOR in Cancer Signaling. In *Predictive Biomarkers in Oncology: Applications in Precision Medicine*; Badve, S., Kumar, G.L., Eds.; Springer International Publishing: Cham, Switzerland, 2019; pp. 263–270.
40. Popova, N.V.; Jücker, M. The Role of mTOR Signaling as a Therapeutic Target in Cancer. *Int. J. Mol. Sci.* **2021**, *22*, 1743. [CrossRef] [PubMed]
41. Alqahtani, A.; Ayesh, H.S.K.; Halawani, H. PIK3CA Gene Mutations in Solid Malignancies: Association with Clinicopathological Parameters and Prognosis. *Cancers* **2020**, *12*, 93. [CrossRef]
42. German, S.; Aslam, H.M.; Saleem, S.; Raees, A.; Anum, T.; Alvi, A.A.; Haseeb, A. Carcinogenesis of PIK3CA. *Hered. Cancer Clin. Pract.* **2013**, *11*, 5. [CrossRef]
43. Zhang, W.; Haines, B.B.; Efferson, C.; Zhu, J.; Ware, C.; Kunii, K.; Tammam, J.; Angagaw, M.; Hinton, M.C.; Keilhack, H.; et al. Evidence of mTOR Activation by an AKT-Independent Mechanism Provides Support for the Combined Treatment of PTEN-Deficient Prostate Tumors with mTOR and AKT Inhibitors. *Transl. Oncol.* **2012**, *5*, 422–429. [CrossRef]
44. Bruhn, M.A.; Pearson, R.B.; Hannan, R.D.; Sheppard, K.E. AKT-independent PI3-K signaling in cancer—Emerging role for SGK3. *Cancer Manag. Res.* **2013**, *5*, 281–292. [CrossRef]
45. Fang, W.; Huang, Y.; Gu, W.; Gan, J.; Wang, W.; Zhang, S.; Wang, K.; Zhan, J.; Yang, Y.; Huang, Y.; et al. PI3K-AKT-mTOR pathway alterations in advanced NSCLC patients after progression on EGFR-TKI and clinical response to EGFR-TKI plus everolimus combination therapy. *Transl. Lung. Cancer Res.* **2020**, *9*, 1258–1267. [CrossRef]
46. Saadeh, F.S.; Mahfouz, R.; Assi, H.I. EGFR as a clinical marker in glioblastomas and other gliomas. *Int. J. Biol. Markers* **2018**, *33*, 22–32. [CrossRef] [PubMed]
47. Yuan, T.L.; Cantley, L.C. PI3K pathway alterations in cancer: Variations on a theme. *Oncogene* **2008**, *27*, 5497–5510. [CrossRef]
48. Chen, Y.; Huang, L.; Dong, Y.; Tao, C.; Zhang, R.; Shao, H.; Shen, H. Effect of AKT1 (p. E17K) Hotspot Mutation on Malignant Tumorigenesis and Prognosis. *Front. Cell Dev. Biol.* **2020**, *8*, 996. [CrossRef] [PubMed]
49. Zhao, L.; Vogt, P.K. Helical domain and kinase domain mutations in p110alpha of phosphatidylinositol 3-kinase induce gain of function by different mechanisms. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 2652–2657. [CrossRef] [PubMed]
50. Fruman, D.A.; Chiu, H.; Hopkins, B.D.; Bagrodia, S.; Cantley, L.C.; Abraham, R.T. The PI3K Pathway in Human Disease. *Cell* **2017**, *170*, 605–635. [CrossRef] [PubMed]
51. Maehama, T.; Dixon, J.E. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. *J. Biol. Chem.* **1998**, *273*, 13375–13378. [CrossRef]
52. Rascio, F.; Spadaccino, F.; Rocchetti, M.T.; Castellano, G.; Stallone, G.; Netti, G.S.; Ranieri, E. The Pathogenic Role of PI3K/AKT Pathway in Cancer Onset and Drug Resistance: An Updated Review. *Cancers* **2021**, *13*, 3949. [CrossRef] [PubMed]
53. Yang, J.; Nie, J.; Ma, X.; Wei, Y.; Peng, Y.; Wei, X. Targeting PI3K in cancer: Mechanisms and advances in clinical trials. *Mol. Cancer* **2019**, *18*, 26. [CrossRef]

54. Hinz, N.; Jücker, M. Distinct functions of AKT isoforms in breast cancer: A comprehensive review. *Cell Commun. Signal.* **2019**, *17*, 154. [CrossRef]
55. Cheng, J.Q.; Lindsley, C.W.; Cheng, G.Z.; Yang, H.; Nicosia, S.V. The Akt/PKB pathway: Molecular target for cancer drug discovery. *Oncogene* **2005**, *24*, 7482–7492. [CrossRef]
56. Xie, X.; Tang, B.; Zhou, J.; Gao, Q.; Zhang, P. Inhibition of the PI3K/Akt pathway increases the chemosensitivity of gastric cancer to vincristine. *Oncol. Rep.* **2013**, *30*, 773–782. [CrossRef]
57. Song, G.; Ouyang, G.; Bao, S. The activation of Akt/PKB signaling pathway and cell survival. *J. Cell Mol. Med.* **2005**, *9*, 59–71. [CrossRef] [PubMed]
58. Sugiyama, M.G.; Fairn, G.D.; Antonescu, C.N. Akt-ing Up Just About Everywhere: Compartment-Specific Akt Activation and Function in Receptor Tyrosine Kinase Signaling. *Front. Cell Dev. Biol.* **2019**, *7*, 70. [CrossRef] [PubMed]
59. Altomare, D.A.; Testa, J.R. Perturbations of the AKT signaling pathway in human cancer. *Oncogene* **2005**, *24*, 7455–7464. [CrossRef] [PubMed]
60. Truebestein, L.; Hornegger, H.; Anrather, D.; Hartl, M.; Fleming, K.D.; Stariha, J.T.B.; Pardon, E.; Steyaert, J.; Burke, J.E.; Leonard, T.A. Structure of autoinhibited Akt1 reveals mechanism of PIP3-mediated activation. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2101496118. [CrossRef] [PubMed]
61. Georgescu, M.-M. PTEN Tumor Suppressor Network in PI3K-Akt Pathway Control. *Genes Cancer* **2010**, *1*, 1170–1177. [CrossRef] [PubMed]
62. Liao, Y.; Hung, M.-C. Physiological regulation of Akt activity and stability. *Am. J. Transl. Res.* **2010**, *2*, 19–42. [PubMed]
63. Nitulescu, G.M.; Van De Venter, M.; Nitulescu, G.; Ungurianu, A.; Juzenas, P.; Peng, Q.; Olaru, O.T.; Grădinaru, D.; Tsatsakis, A.; Tsoukalas, D.; et al. The Akt pathway in oncology therapy and beyond (Review). *Int. J. Oncol.* **2018**, *53*, 2319–2331. [CrossRef] [PubMed]
64. Chalhoub, N.; Baker, S.J. PTEN and the PI3-kinase pathway in cancer. *Annu. Rev. Pathol.* **2009**, *4*, 127–150. [CrossRef]
65. Tian, T.; Li, X.; Zhang, J. mTOR Signaling in Cancer and mTOR Inhibitors in Solid Tumor Targeting Therapy. *Int. J. Mol. Sci.* **2019**, *20*, 755. [CrossRef]
66. Jhanwar-Uniyal, M.; Wainwright, J.V.; Mohan, A.L.; Tobias, M.E.; Murali, R.; Gandhi, C.D.; Schmidt, M.H. Diverse signaling mechanisms of mTOR complexes: MTORC1 and mTORC2 in forming a formidable relationship. *Adv. Biol. Regul.* **2019**, *72*, 51–62. [CrossRef]
67. Inoki, K.; Li, Y.; Zhu, T.; Wu, J.; Guan, K.-L. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. *Nat. Cell Biol.* **2002**, *4*, 648–657. [CrossRef] [PubMed]
68. Manning, B.D.; Tee, A.R.; Logsdon, M.N.; Blenis, J.; Cantley, L.C. Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberin as a target of the phosphoinositide 3-kinase/akt pathway. *Mol. Cell* **2002**, *10*, 151–162. [CrossRef]
69. Fruman, D.; Limon, J. Akt and mTOR in B Cell Activation and Differentiation. *Front. Immunol.* **2012**, *3*, 228. [CrossRef]
70. Carroll, B.; Maetzel, D.; Maddocks, O.D.K.; Otten, G.; Ratcliff, M.; Smith, G.R.; Dunlop, E.A.; Passos, J.F.; Davies, O.R.; Jaenisch, R.; et al. Control of TSC2-Rheb signaling axis by arginine regulates mTORC1 activity. *eLife* **2016**, *5*, e11058. [CrossRef]
71. Yin, Y.; Hua, H.; Li, M.; Liu, S.; Kong, Q.; Shao, T.; Wang, J.; Luo, Y.; Wang, Q.; Luo, T.; et al. mTORC2 promotes type I insulin-like growth factor receptor and insulin receptor activation through the tyrosine kinase activity of mTOR. *Cell Res.* **2016**, *26*, 46–65. [CrossRef]
72. Saxton, R.A.; Sabatini, D.M. mTOR Signaling in Growth, Metabolism, and Disease. *Cell* **2017**, *168*, 960–976. [CrossRef] [PubMed]
73. Gomez-Pinillos, A.; Ferrari, A.C. mTOR signaling pathway and mTOR inhibitors in cancer therapy. *Hematol. Oncol. Clin. N. Am.* **2012**, *26*, 483–505. [CrossRef] [PubMed]
74. Porta, C.; Paglino, C.; Mosca, A. Targeting PI3K/Akt/mTOR Signaling in Cancer. *Front. Oncol.* **2014**, *4*, 64. [CrossRef]
75. Hemmings, B.A.; Restuccia, D.F. PI3K-PKB/Akt pathway. *Cold Spring Harb. Perspect. Biol.* **2012**, *4*, a011189. [CrossRef]
76. Rodon, J.; Dienstmann, R.; Serra, V.; Tabernero, J. Development of PI3K inhibitors: Lessons learned from early clinical trials. *Nat. Rev. Clin. Oncol.* **2013**, *10*, 143–153. [CrossRef]
77. Mandal, K. Review of PIP2 in Cellular Signaling, Functions and Diseases. *Int. J. Mol. Sci.* **2020**, *21*, E8342. [CrossRef]
78. Vivanco, I.; Sawyers, C.L. The phosphatidylinositol 3-Kinase AKT pathway in human cancer. *Nat. Rev. Cancer* **2002**, *2*, 489–501. [CrossRef]
79. Alessi, D.R.; Deak, M.; Casamayor, A.; Caudwell, F.B.; Morrice, N.; Norman, D.G.; Gaffney, P.; Reese, C.B.; MacDougall, C.N.; Harbison, D.; et al. 3-Phosphoinositide-dependent protein kinase-1 (PDK1): Structural and functional homology with the Drosophila DSTPK61 kinase. *Curr. Biol.* **1997**, *7*, 776–789. [CrossRef]
80. Nicholson, K.M.; Anderson, N.G. The protein kinase B/Akt signalling pathway in human malignancy. *Cell Signal.* **2002**, *14*, 381–395. [CrossRef]
81. Chen, C.-Y.; Chen, J.; He, L.; Stiles, B.L. PTEN: Tumor Suppressor and Metabolic Regulator. *Front. Endocrinol.* **2018**, *9*, 338. [CrossRef]
82. Roudsari, N.M.; Lashgari, N.-A.; Momtaz, S.; Abaft, S.; Jamali, F.; Safaiepour, P.; Narimisa, K.; Jackson, G.; Bishayee, A.; Rezaei, N.; et al. Inhibitors of the PI3K/Akt/mTOR Pathway in Prostate Cancer Chemoprevention and Intervention. *Pharmaceutics* **2021**, *13*, 1195. [CrossRef]
83. Pópulo, H.; Lopes, J.M.; Soares, P. The mTOR signalling pathway in human cancer. *Int. J. Mol. Sci.* **2012**, *13*, 1886–1918. [CrossRef] [PubMed]

84. Tan, H.K.; Moad, A.I.H.; Tan, M.L. The mTOR signalling pathway in cancer and the potential mTOR inhibitory activities of natural phytochemicals. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 6463–6475. [CrossRef]
85. Zhu, G.; Liu, X.; Li, H.; Yan, Y.; Hong, X.; Lin, Z. Kaempferol inhibits proliferation, migration, and invasion of liver cancer HepG2 cells by down-regulation of microRNA-21. *Int. J. Immunopathol. Pharmacol.* **2018**, *32*, 2058738418814341. [CrossRef]
86. Li, C.; Yang, X.; Chen, C.; Cai, S.; Hu, J. Isorhamnetin suppresses colon cancer cell growth through the PI3K-Akt-mTOR pathway. *Mol. Med. Rep.* **2014**, *9*, 935–940. [CrossRef]
87. Zhou, Y.; Liang, X.; Chang, H.; Shu, F.; Wu, Y.; Zhang, T.; Fu, Y.; Zhang, Q.; Zhu, J.-D.; Mi, M. Ampelopsin-induced autophagy protects breast cancer cells from apoptosis through Akt-mTOR pathway via endoplasmic reticulum stress. *Cancer Sci.* **2014**, *105*, 1279–1287. [CrossRef]
88. Liu, S.; Wang, X.-J.; Liu, Y.; Cui, Y.-F. PI3K/AKT/mTOR signaling is involved in (-)-epigallocatechin-3-gallate-induced apoptosis of human pancreatic carcinoma cells. *Am. J. Chin. Med.* **2013**, *41*, 629–642. [CrossRef] [PubMed]
89. Wang, S.-D.; Chen, B.-C.; Kao, S.-T.; Liu, C.-J.; Yeh, C.-C. Genistein inhibits tumor invasion by suppressing multiple signal transduction pathways in human hepatocellular carcinoma cells. *BMC Complement Altern. Med.* **2014**, *14*, 26. [CrossRef] [PubMed]
90. Ma, Y.; Wang, J.; Liu, L.; Zhu, H.; Chen, X.; Pan, S.; Sun, X.; Jiang, H. Genistein potentiates the effect of arsenic trioxide against human hepatocellular carcinoma: Role of Akt and nuclear factor-κB. *Cancer Lett.* **2011**, *301*, 75–84. [CrossRef]
91. Ren, J.; Huang, Q.; Xu, Y.; Yang, M.; Yang, J.; Hu, K. Isoflavone lupiwighteone induces cytotoxic, apoptotic, and antiangiogenic activities in DU-145 prostate cancer cells. *Anticancer Drugs* **2015**, *26*, 599–611. [CrossRef]
92. Won, Y.-S.; Seo, K.-I. Lupiwighteone induces caspase-dependent and -independent apoptosis on human breast cancer cells via inhibiting PI3K/Akt/mTOR pathway. *Food Chem. Toxicol.* **2020**, *135*, 110863. [CrossRef] [PubMed]
93. Zou, M.; Hu, C.; You, Q.; Zhang, A.; Wang, X.; Guo, Q. Oroxylin A induces autophagy in human malignant glioma cells via the mTOR-STAT3-Notch signaling pathway. *Mol. Carcinog.* **2015**, *54*, 1363–1375. [CrossRef] [PubMed]
94. Zou, M.; Lu, N.; Hu, C.; Liu, W.; Sun, Y.; Wang, X.; You, Q.; Gu, C.; Xi, T.; Guo, Q. Beclin 1-mediated autophagy in hepatocellular carcinoma cells: Implication in anticancer efficiency of oroxylin A via inhibition of mTOR signaling. *Cell Signal.* **2012**, *24*, 1722–1732. [CrossRef]
95. Lee, H.J.; Venkatarame Gowda Saralamma, V.; Kim, S.M.; Ha, S.E.; Raha, S.; Lee, W.S.; Kim, E.H.; Lee, S.J.; Heo, J.D.; Kim, G.S. Pectolinarigenin Induced Cell Cycle Arrest, Autophagy, and Apoptosis in Gastric Cancer Cell via PI3K/AKT/mTOR Signaling Pathway. *Nutrients* **2018**, *10*, 1043. [CrossRef]
96. Zhu, Y.; Rao, Q.; Zhang, X.; Zhou, X. Galangin induced antitumor effects in human kidney tumor cells mediated via mitochondrial mediated apoptosis, inhibition of cell migration and invasion and targeting PI3K/AKT/mTOR signalling pathway. *J. BUON* **2018**, *23*, 795–799.
97. Roohbakhsh, A.; Parhiz, H.; Soltani, F.; Rezaee, R.; Iranshahi, M. Molecular mechanisms behind the biological effects of hesperidin and hesperetin for the prevention of cancer and cardiovascular diseases. *Life Sci.* **2015**, *124*, 64–74. [CrossRef]
98. García-Maceira, P.; Mateo, J. Silibinin inhibits hypoxia-inducible factor-1alpha and mTOR/p70S6K/4E-BP1 signalling pathway in human cervical and hepatoma cancer cells: Implications for anticancer therapy. *Oncogene* **2009**, *28*, 313–324. [CrossRef] [PubMed]
99. Lim, W.; Song, G. Inhibitory effects of delphinidin on the proliferation of ovarian cancer cells via PI3K/AKT and ERK 1/2 MAPK signal transduction. *Oncol. Lett.* **2017**, *14*, 810–818. [CrossRef]
100. Li, X.; Zhang, Z.-S.; Zhang, X.-H.; Yang, S.-N.; Liu, D.; Diao, C.-R.; Wang, H.; Zheng, F.-P. Cyanidin inhibits EMT induced by oxaliplatin via targeting the PDK1-PI3K/Akt signaling pathway. *Food Funct.* **2019**, *10*, 592–601. [CrossRef]
101. Bianchi, S.; Giovannini, L. Inhibition of mTOR/S6K1/4E-BP1 Signaling by Nutraceutical SIRT1 Modulators. *Nutr. Cancer* **2018**, *70*, 490–501. [CrossRef]
102. Wang, K.; Liu, R.; Li, J.; Mao, J.; Lei, Y.; Wu, J.; Zeng, J.; Zhang, T.; Wu, H.; Chen, L.; et al. Quercetin induces protective autophagy in gastric cancer cells: Involvement of Akt-mTOR- and hypoxia-induced factor 1α-mediated signaling. *Autophagy* **2011**, *7*, 966–978. [CrossRef]
103. Klappan, A.K.; Hones, S.; Mylonas, I.; Brüning, A. Proteasome inhibition by quercetin triggers macroautophagy and blocks mTOR activity. *Histochem. Cell Biol.* **2012**, *137*, 25–36. [CrossRef] [PubMed]
104. Srivastava, S.; Somasagara, R.R.; Hegde, M.; Nishana, M.; Tadi, S.K.; Srivastava, M.; Choudhary, B.; Raghavan, S.C. Quercetin, a Natural Flavonoid Interacts with DNA, Arrests Cell Cycle and Causes Tumor Regression by Activating Mitochondrial Pathway of Apoptosis. *Sci. Rep.* **2016**, *6*, 24049. [CrossRef]
105. Ross, J.A.; Kasum, C.M. Dietary flavonoids: Bioavailability, metabolic effects, and safety. *Annu. Rev. Nutr.* **2002**, *22*, 19–34. [CrossRef]
106. López-Lázaro, M.; Willmore, E.; Austin, C.A. The dietary flavonoids myricetin and fisetin act as dual inhibitors of DNA topoisomerases I and II in cells. *Mutat. Res.* **2010**, *696*, 41–47. [CrossRef]
107. Zhu, M.-L.; Zhang, P.-M.; Jiang, M.; Yu, S.-W.; Wang, L. Myricetin induces apoptosis and autophagy by inhibiting PI3K/Akt/mTOR signalling in human colon cancer cells. *BMC Complement Med. Ther.* **2020**, *20*, 209. [CrossRef]
108. Jung, S.K.; Lee, K.W.; Byun, S.; Kang, N.J.; Lim, S.H.; Heo, Y.-S.; Bode, A.M.; Bowden, G.T.; Lee, H.J.; Dong, Z. Myricetin suppresses UVB-induced skin cancer by targeting Fyn. *Cancer Res.* **2008**, *68*, 6021–6029. [CrossRef]
109. Sajedi, N.; Homayoun, M.; Mohammadi, F.; Soleimani, M. Myricetin Exerts its Apoptotic Effects on MCF-7 Breast Cancer Cells through Evoking the BRCA1-GADD45 Pathway. *Asian Pac. J. Cancer Prev.* **2020**, *21*, 3461–3468. [CrossRef]

110. Dabeek, W.M.; Marra, M.V. Dietary Quercetin and Kaempferol: Bioavailability and Potential Cardiovascular-Related Bioactivity in Humans. *Nutrients* **2019**, *11*, 2288. [CrossRef]
111. Kim, G.D. Kaempferol Inhibits Angiogenesis by Suppressing HIF-1α and VEGFR2 Activation via ERK/p38 MAPK and PI3K/Akt/mTOR Signaling Pathways in Endothelial Cells. *Prev. Nutr. Food Sci.* **2017**, *22*, 320–326. [CrossRef]
112. Sharma, N.; Biswas, S.; Al-Dayan, N.; Alhegaili, A.S.; Sarwat, M. Antioxidant Role of Kaempferol in Prevention of Hepatocellular Carcinoma. *Antioxidants* **2021**, *10*, 1419. [CrossRef]
113. Suhail, M.; Mohammad, T.; Naoshad, M.; Huma, N.; Abdul, H.; Torki, A.Z.; Mohammad, A.K.; Mohd, R. A Critical Transcription Factor NF-κB as a Cancer Therapeutic Target and its Inhibitors as Cancer Treatment Options. *Curr. Med. Chem.* **2021**, *28*, 4117–4132. [CrossRef]
114. Chen, B.-H.; Hsieh, C.-H.; Tsai, S.-Y.; Wang, C.-Y.; Wang, C.-C. Anticancer effects of epigallocatechin-3-gallate nanoemulsion on lung cancer cells through the activation of AMP-activated protein kinase signaling pathway. *Sci. Rep.* **2020**, *10*, 5163. [CrossRef]
115. Bernatoniene, J.; Kopustinskiene, D.M. The Role of Catechins in Cellular Responses to Oxidative Stress. *Molecules* **2018**, *23*, 965. [CrossRef] [PubMed]
116. Shay, J.; Elbaz, H.A.; Lee, I.; Zielske, S.P.; Malek, M.H.; Hüttemann, M. Molecular Mechanisms and Therapeutic Effects of (-)-Epicatechin and Other Polyphenols in Cancer, Inflammation, Diabetes, and Neurodegeneration. *Oxid. Med. Cell Longev.* **2015**, *2015*, 181260. [CrossRef]
117. Satonaka, H.; Ishida, K.; Takai, M.; Koide, R.; Shigemasa, R.; Ueyama, J.; Ishikawa, T.; Hayashi, K.; Goto, H.; Wakusawa, S. (-)-Epigallocatechin-3-gallate Down-regulates Doxorubicin-induced Overexpression of P-glycoprotein Through the Coordinate Inhibition of PI3K/Akt and MEK/ERK Signaling Pathways. *Anticancer Res.* **2017**, *37*, 6071–6077. [CrossRef]
118. Suhail, M.; Parveen, A.; Husain, A.; Rehan, M. Exploring Inhibitory Mechanisms of Green Tea Catechins as Inhibitors of a Cancer Therapeutic Target, Nuclear Factor-κB (NF-κB). *Biosci. Biotechnol. Res. Asia* **2019**, *16*, 715–723. [CrossRef]
119. Wang, J.; Man, G.C.W.; Chan, T.H.; Kwong, J.; Wang, C.C. A prodrug of green tea polyphenol (-)-epigallocatechin-3-gallate (Pro-EGCG) serves as a novel angiogenesis inhibitor in endometrial cancer. *Cancer Lett.* **2018**, *412*, 10–20. [CrossRef]
120. Moradzadeh, M.; Hosseini, A.; Erfanian, S.; Rezaei, H. Epigallocatechin-3-gallate promotes apoptosis in human breast cancer T47D cells through down-regulation of PI3K/AKT and Telomerase. *Pharmacol. Rep.* **2017**, *69*, 924–928. [CrossRef]
121. Grynkiewicz, G.; Demchuk, O.M. New Perspectives for Fisetin. *Front. Chem.* **2019**, *7*, 697. [CrossRef] [PubMed]
122. Khan, N.; Afaq, F.; Khusro, F.H.; Mustafa Adhami, V.; Suh, Y.; Mukhtar, H. Dual inhibition of phosphatidylinositol 3-kinase/Akt and mammalian target of rapamycin signaling in human nonsmall cell lung cancer cells by a dietary flavonoid fisetin. *Int. J. Cancer* **2012**, *130*, 1695–1705. [CrossRef]
123. Jang, K.Y.; Jeong, S.-J.; Kim, S.-H.; Jung, J.H.; Kim, J.-H.; Koh, W.; Chen, C.-Y.; Kim, S.-H. Activation of reactive oxygen species/AMP activated protein kinase signaling mediates fisetin-induced apoptosis in multiple myeloma U266 cells. *Cancer Lett.* **2012**, *319*, 197–202. [CrossRef]
124. Syed, D.N.; Afaq, F.; Maddodi, N.; Johnson, J.J.; Sarfaraz, S.; Ahmad, A.; Setaluri, V.; Mukhtar, H. Inhibition of human melanoma cell growth by the dietary flavonoid fisetin is associated with disruption of Wnt/β-catenin signaling and decreased Mitf levels. *J. Investig. Dermatol.* **2011**, *131*, 1291–1299. [CrossRef] [PubMed]
125. Shukla, S.; Bhaskaran, N.; Babcook, M.A.; Fu, P.; Maclennan, G.T.; Gupta, S. Apigenin inhibits prostate cancer progression in TRAMP mice via targeting PI3K/Akt/FoxO pathway. *Carcinogenesis* **2014**, *35*, 452–460. [CrossRef]
126. Shukla, S.; Kanwal, R.; Shankar, E.; Datt, M.; Chance, M.R.; Fu, P.; MacLennan, G.T.; Gupta, S. Apigenin blocks IKKα activation and suppresses prostate cancer progression. *Oncotarget* **2015**, *6*, 31216–31232. [CrossRef]
127. Yang, J.; Pi, C.; Wang, G. Inhibition of PI3K/Akt/mTOR pathway by apigenin induces apoptosis and autophagy in hepatocellular carcinoma cells. *Biomed. Pharmacother.* **2018**, *103*, 699–707. [CrossRef]
128. Goh, J.X.H.; Tan, L.T.-H.; Goh, J.K.; Chan, K.G.; Pusparajah, P.; Lee, L.-H.; Goh, B.-H. Nobiletin and Derivatives: Functional Compounds from Citrus Fruit Peel for Colon Cancer Chemoprevention. *Cancers* **2019**, *11*, E867. [CrossRef] [PubMed]
129. Huang, H.; Li, L.; Shi, W.; Liu, H.; Yang, J.; Yuan, X.; Wu, L. The Multifunctional Effects of Nobiletin and Its Metabolites In Vivo and In Vitro. *Evid Based Complement Alternat. Med.* **2016**, *2016*, 2918796. [CrossRef]
130. Chen, J.; Chen, A.Y.; Huang, H.; Ye, X.; Rollyson, W.D.; Perry, H.E.; Brown, K.C.; Rojanasakul, Y.; Rankin, G.O.; Dasgupta, P.; et al. The flavonoid nobiletin inhibits tumor growth and angiogenesis of ovarian cancers via the Akt pathway. *Int. J. Oncol.* **2015**, *46*, 2629–2638. [CrossRef] [PubMed]
131. Aloud, A.A.; Chinnadurai, V.; Govindasamy, C.; Alsaif, M.A.; Al-Numair, K.S. Galangin, a dietary flavonoid, ameliorates hyperglycaemia and lipid abnormalities in rats with streptozotocin-induced hyperglycaemia. *Pharm. Biol.* **2018**, *56*, 302–308. [CrossRef]
132. Saiprasad, G.; Chitra, P.; Manikandan, R.; Sudhandiran, G. Hesperidin induces apoptosis and triggers autophagic markers through inhibition of Aurora-A mediated phosphoinositide-3-kinase/Akt/mammalian target of rapamycin and glycogen synthase kinase-3 beta signalling cascades in experimental colon carcinogenesis. *Eur. J. Cancer* **2014**, *50*, 2489–2507. [CrossRef]
133. Diaconeasa, Z.; Știrbu, I.; Xiao, J.; Leopold, N.; Ayvaz, Z.; Danciu, C.; Ayvaz, H.; Stănilă, A.; Nistor, M.; Socaciu, C. Anthocyanins, Vibrant Color Pigments, and Their Role in Skin Cancer Prevention. *Biomedicines* **2020**, *8*, E336. [CrossRef]
134. Lamy, S.; Lafleur, R.; Bédard, V.; Moghrabi, A.; Barrette, S.; Gingras, D.; Béliveau, R. Anthocyanidins inhibit migration of glioblastoma cells: Structure-activity relationship and involvement of the plasminolytic system. *J. Cell Biochem.* **2007**, *100*, 100–111. [CrossRef]

135. Kim, M.-H.; Jeong, Y.-J.; Cho, H.-J.; Hoe, H.-S.; Park, K.-K.; Park, Y.-Y.; Choi, Y.H.; Kim, C.-H.; Chang, H.-W.; Park, Y.-J.; et al. Delphinidin inhibits angiogenesis through the suppression of HIF-1α and VEGF expression in A549 lung cancer cells. *Oncol. Rep.* **2017**, *37*, 777–784. [CrossRef]
136. Ozbay, T.; Nahta, R. Delphinidin Inhibits HER2 and Erk1/2 Signaling and Suppresses Growth of HER2-Overexpressing and Triple Negative Breast Cancer Cell Lines. *Breast Cancer* **2011**, *5*, 143–154. [CrossRef]
137. Ko, H.; Jeong, M.-H.; Jeon, H.; Sung, G.-J.; So, Y.; Kim, I.; Son, J.; Lee, S.-W.; Yoon, H.-G.; Choi, K.-C. Delphinidin sensitizes prostate cancer cells to TRAIL-induced apoptosis, by inducing DR5 and causing caspase-mediated HDAC3 cleavage. *Oncotarget* **2015**, *6*, 9970–9984. [CrossRef]
138. Pal, H.C.; Sharma, S.; Strickland, L.R.; Agarwal, J.; Athar, M.; Elmets, C.A.; Afaq, F. Delphinidin reduces cell proliferation and induces apoptosis of non-small-cell lung cancer cells by targeting EGFR/VEGFR2 signaling pathways. *PLoS ONE* **2013**, *8*, e77270. [CrossRef]
139. Feng, R.; Wang, S.Y.; Shi, Y.-H.; Fan, J.; Yin, X.-M. Delphinidin induces necrosis in hepatocellular carcinoma cells in the presence of 3-methyladenine, an autophagy inhibitor. *J. Agric. Food Chem.* **2010**, *58*, 3957–3964. [CrossRef]
140. Yun, J.-M.; Afaq, F.; Khan, N.; Mukhtar, H. Delphinidin, an anthocyanidin in pigmented fruits and vegetables, induces apoptosis and cell cycle arrest in human colon cancer HCT116 cells. *Mol. Carcinog.* **2009**, *48*, 260–270. [CrossRef]
141. Filipiak, K.; Hidalgo, M.; Silvan, J.M.; Fabre, B.; Carbajo, R.J.; Pineda-Lucena, A.; Ramos, A.; de Pascual-Teresa, B.; de Pascual-Teresa, S. Dietary gallic acid and anthocyanin cytotoxicity on human fibrosarcoma HT1080 cells. A study on the mode of action. *Food Funct.* **2014**, *5*, 381–389. [CrossRef] [PubMed]
142. Yang, M.; Wang, H.; Zhou, M.; Liu, W.; Kuang, P.; Liang, H.; Yuan, Q. The natural compound sulforaphene, as a novel anticancer reagent, targeting PI3K-AKT signaling pathway in lung cancer. *Oncotarget* **2016**, *7*, 76656–76666. [CrossRef]
143. Zduńczyk, Z.; Juśkiewicz, J.; Estrella, I. Cecal parameters of rats fed diets containing grapefruit polyphenols and inulin as single supplements or in a combination. *Nutrition* **2006**, *22*, 898–904. [CrossRef]
144. Rodrigo, R.; Libuy, M.; Feliu, F.; Hasson, D. Polyphenols in disease: From diet to supplements. *Curr. Pharm. Biotechnol.* **2014**, *15*, 304–317. [CrossRef]
145. Garcia-Oliveira, P.; Otero, P.; Pereira, A.G.; Chamorro, F.; Carpena, M.; Echave, J.; Fraga-Corral, M.; Simal-Gandara, J.; Prieto, M.A. Status and Challenges of Plant-Anticancer Compounds in Cancer Treatment. *Pharmaceuticals* **2021**, *14*, 157. [CrossRef]
146. Amawi, H.; Ashby, C.R.; Tiwari, A.K. Cancer chemoprevention through dietary flavonoids: What's limiting? *Chin. J. Cancer* **2017**, *36*, 50. [CrossRef]
147. Hu, M.; Wu, B.; Liu, Z. Bioavailability of Polyphenols and Flavonoids in the Era of Precision Medicine. *Mol. Pharm.* **2017**, *14*, 2861–2863. [CrossRef]
148. Wang, S.; Xing, H.; Zhao, M.; Lu, D.; Li, Z.; Dong, D.; Wu, B. Recent Advances in Understanding of Kinetic Interplay Between Phase II Metabolism and Efflux Transport. *Curr. Drug Metab.* **2016**, *17*, 922–929. [CrossRef]
149. Neri-Numa, I.A.; Cazarin, C.B.B.; Ruiz, A.L.T.G.; Paulino, B.N.; Molina, G.; Pastore, G.M. Targeting flavonoids on modulation of metabolic syndrome. *J. Funct. Foods* **2020**, *73*, 104132. [CrossRef]