







Review

Kaempferol: A Key Emphasis to Its Anticancer Potential

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Abstract: A marked decrease in human cancers, including breast cancer, bone cancer, and cervical cancer, has been linked to the consumption of vegetable and fruit, and the corresponding chemoprotective effect has been associated with the presence of several active molecules, such as kaempferol. Kaempferol is a major flavonoid aglycone found in many natural products, such as beans, bee pollen, broccoli, cabbage, capers, cauliflower, chia seeds, chives, cumin, moringa leaves, endive, fennel, and garlic. Kaempferol displays several pharmacological properties, among them antimicrobial, anti-inflammatory, antioxidant, antitumor, cardioprotective, neuroprotective, and antidiabetic activities, and is being applied in cancer chemotherapy. Specifically, kaempferol-rich food has been linked to a decrease in the risk of developing some types of cancers, including skin, liver, and colon. The mechanisms of action include apoptosis, cell cycle arrest at the G2/M phase, downregulation of epithelial-mesenchymal transition (EMT)-related markers, and phosphoinositide 3-kinase/protein kinase B signaling pathways. In this sense, this article reviews data from experimental studies that investigated the links between kaempferol and kaempferol-rich food intake and cancer prevention. Even though growing evidence supports the use of kaempferol for cancer prevention,

further preclinical and clinical investigations using kaempferol or kaempferol-rich foods are of pivotal importance before any public health recommendation or formulation using kaempferol.

Keywords: kaempferol; pharmacokinetics; pharmacodynamics; antioxidant; anticancer; chemoprevention; apoptosis; cell cycle arrest; metastasis; reactive oxygen species

1. Introduction

Kaempferol represents one of the most encountered aglycone flavonoids in the form of glycoside. It is a tetrahydroxyflavone in which the four hydroxy groups are located at positions 3, 5, 7, and 4', and it is a yellow compound [1]. Kaempferol is found in various plant parts, such as seeds, leaves, fruits, flowers, and even vegetables [2–4]. Kaempferol and its glycosylated derivatives have been shown to be cardioprotective, neuroprotective, anti-inflammatory, antidiabetic, antioxidant, antimicrobial, antitumor, and have anticancer activities [5].

Epidemiological studies showed that a high intake of kaempferol is associated with decreased incidence of different types of cancer, among which cancer in organs like skin, liver, colon, ovary, pancreas, stomach, and bladder [6,7]. In this context, kaempferol consumption and related application in cancer therapy are gaining huge attention among the research community [6–8]. The cancer prevention is mostly achieved by inhibiting the proliferation of cancer cells through increasing the apoptosis [9–11]. Indeed, kaempferol inhibits various cancer cells by triggering apoptosis, cell cycle arrest at G2/M phase, downregulation of signaling pathways and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), expression of epithelial-mesenchymal transition (EMT)-related markers (N-cadherin, E-cadherin, Snail, and Slug), and matrix metalloproteinase 2 (MMP-2), metastasis-related markers [12,13]. Kaempferol also induces the activation of cysteine proteases involved in apoptosis initiation and execution, caspases-3, -7, -9, and Poly (ADP-ribose) polymerase (PARP) [14], therefore preventing the accumulation of reactive oxygen species (ROS) involved in cancer development [15]. The inhibition of angiogenesis was also reported as well as the capacity of kaempferol to preserve normal cell viability [15]. In this context, this review summarizes data on pharmacodynamics, chemopreventive and anticancer effects, and mechanisms of action of kaempferol.

2. Metabolism and Pharmacokinetics of Kaempferol

Studies on the in vitro and in vivo pharmacokinetics of kaempferol commonly ingested as high polarity glycosides revealed that this polyphenol is poorly absorbed compared to the aglycones with intermediate polarity [16].

Kaempferol lipophilicity allowed its absorption in the small intestine through passive and facilitated diffusion or active transport [17]. Of note, intake of 14.97 mg kaempferol/day and 27 mg kaempferol from tea resulted in a plasma concentration of 16.69 ng/mL and 15 ng/mL, respectively [18]. The absorbed kaempferol undergoes metabolic transformation to yield the glucuronides and sulfoconjugates forms in the liver [19] and small intestine by intestinal conjugation enzymes [17]. As well, kaempferol and its glycosides are metabolized in the colon by the bacterial microflora that releases the aglycones and broke aglycone C3 ring to form compounds such as 4-methylphenol, phloroglucinol, and 4-hydroxyphenylacetic acid, that are either absorbed and can reach systemic circulation and tissues or be excreted in feces and urine [20–27]. To overcome the low bioavailability of kaempferol, its combination with quercetin increase its bioavailability, consequently improving its bio-efficacy. In fact, studies prove that nanoformulations (e.g., nanoparticles, nanoemulsions, nanoencapsulation) containing kaempferol will be extremely beneficial in improving their bioavailability and consequent efficacy and selectivity for mutated cells, while their effect on normal cells will be limited [28]. Indeed, kaempferol exerts protective effects in non-mutated cells, whereas it triggers apoptosis in those mutated ones. These aspects are mostly linked to the remarkable antioxidant effects of kaempferol, namely acting

directly in antioxidant enzymes, capable of efficiently inhibit ROS generation and lipid peroxidation, and, finally, preventing the occurrence of cell damages, in a broad-spectrum activity [29].

3. Antioxidant Potential of Kaempferol

Kaempferol and its glycosides, as well as kaempferol-containing plants, portray antioxidant potency both in culture and in animal models [26,27], and it has the capacity to decrease the production of free radicals and other products like reactive oxygen species (ROS). ROS are aerobic metabolism by-products that can induce malignant cell transformation. Thereafter, ROS production inhibition can reverse malignant cancer cell phenotype [28–31]. Usually, superoxide anion is either converted by superoxide dismutase into H_2O_2 that react with reduced metals (e.g., ferrous or cuprous ions), to yield the highly reactive hydroxyl radical or form peroxynitrite by reacting with nitric oxide. These two highly reactive species, hydroxyl radical and peroxynitrite, can cause lipids, proteins, or DNA damages [32]. At submicromolar concentrations, kaempferol is not only a potent scavenger of superoxide anion, hydroxyl radical, and peroxynitrite [32–34], but it also inhibits pro-oxidant enzymes, such as xanthine oxidase [35], and activates antioxidant enzymes such as superoxide dismutase, catalase, and heme oxygenase-1 (Figure 1) [36,37] and even prevents the generation of hydroxyl radical by chelating cuprous or ferrous [38,39]. Also, and not least important to highlight, is that kaempferol contains hydroxyl groups at C3, C5, and C4, an oxo group at C4, and a double bond at C2–C3 that might explain its antioxidant activity [32].

Conclusively, kaempferol can control the cancer through its antioxidative/antinitrosative and anti-inflammatory potential by restoring the cell redox hemostasis by inhibiting the NF- κ B pathway and to up-regulate the Nrf2 transcriptional pathway (Figure 1).

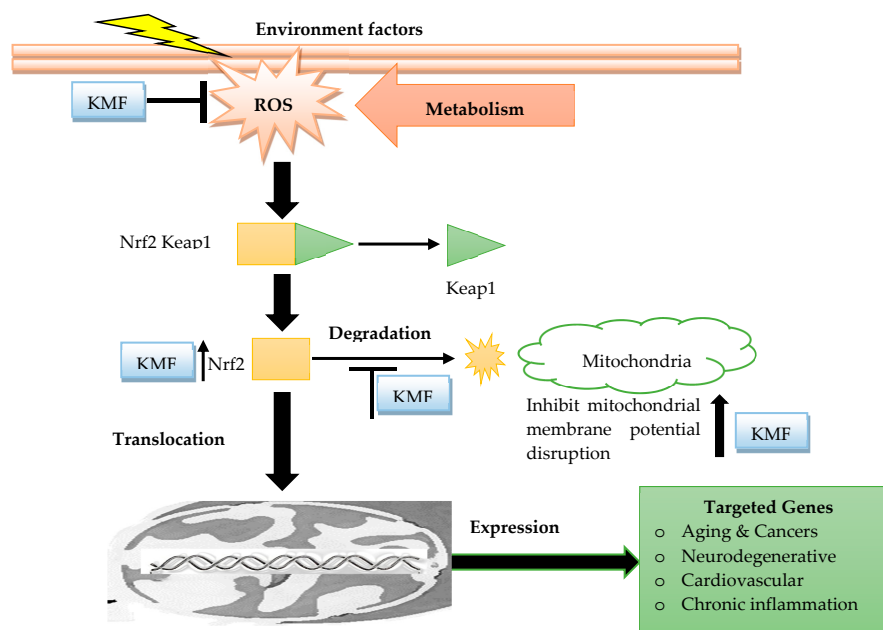


Figure 1. Antioxidant mechanisms of action of kaempferol: The kaempferol reduces the ROS metabolism, cleavage of anti-inflammatory membranes, and disrupts their molecular mechanism as a mechanistic concern to tackle cancer-related expressions (KMF: Kaempferol; Nrf2: Nuclear factor erythroid 2-related factor 2; Keap1: Kelch-like ECH-associated protein 1; RO: Reactive oxygen species).

4. Anticancer Properties of Kaempferol

4.1. Anti-Breast Cancer Activity

Breast cancer burden has been increasing over the years and it represents the most-encountered cancer in women [40]. At micromolar concentrations, kaempferol effectively inhibits the growth of breast

cancer cell lines (VM7Luc4E2, MDA-MB-231, MCF-7) [40–43]. Also, kaempferol markedly inhibits the bisphenol A (BPA) (endocrine-disrupting chemicals) and triclosan (TCS)-induced anti-apoptotic processes [44], causes cell arrest at the G2/M stage, and even induces apoptosis and DNA fragmentation at the sub-G0 phase (Table 1). Kaempferol increases the levels of pro-apoptotic enzymes and proteins, such as cleaved caspase-9, -7, -3, p21, p53, Bax, PARP, and p-ATM [45,46] and decreased the levels of anti-apoptotic proteins Bcl2, polo-like kinase 1 (PLK-1), pAKT, phosphorylated insulin receptor substrate 1 (pIRS-1), phosphorylated mitogen-activated protein kinase (pMEK)1/2, cyclin-dependent kinase 1 (CDK1), cyclins A, B, D1, and E, and cathepsin D [10,40,41,45–49]. In triple-negative breast cancer cells (TNBC), kaempferol decrease cell migration and invasion stages when compared to non-TNBC cells (control) [42]. This is explained by the downregulation of RhoA and activation of Rac1 in TNBC cells, as well as through activation of human epidermal growth factor receptor-2 (HER2)-silence SK-BR-3 and ER/PR-silence in non-TNBC cells [42], which suggests that the antiproliferative action of kaempferol is triggered via the ER-dependent pathway that mediates cellular processes including development, differentiation, and proliferation [50]. In addition, kaempferol significantly activates mitogen-activated protein kinase (MAPK) cascades, which are key signaling pathways involved in the regulation of normal cell proliferation, survival, and differentiation. Indeed, kaempferol activates extracellular signal-regulated kinase (ERK), concomitantly with MEK1 and ELK1; while it reduces EMT and metastasis. The MAPK signaling pathway, when activated, leads to the transcription factor activator protein-1 (AP-1), cathepsin B and D, MMP-2 and -9 activation, that consequently reduces cell adhesion, migration, and invasion [51–54]. Also, kaempferol also lowers the glucose transporter 1 (GLUT1) mRNA levels and prevents the uptake of (3)*H*-deoxy-D-glucose ((3)*H*-DG) and monocarboxylate transporter 1 (MCT1)-mediated lactate cellular leading to extracellular lactate accumulation (Figure 2) [40].

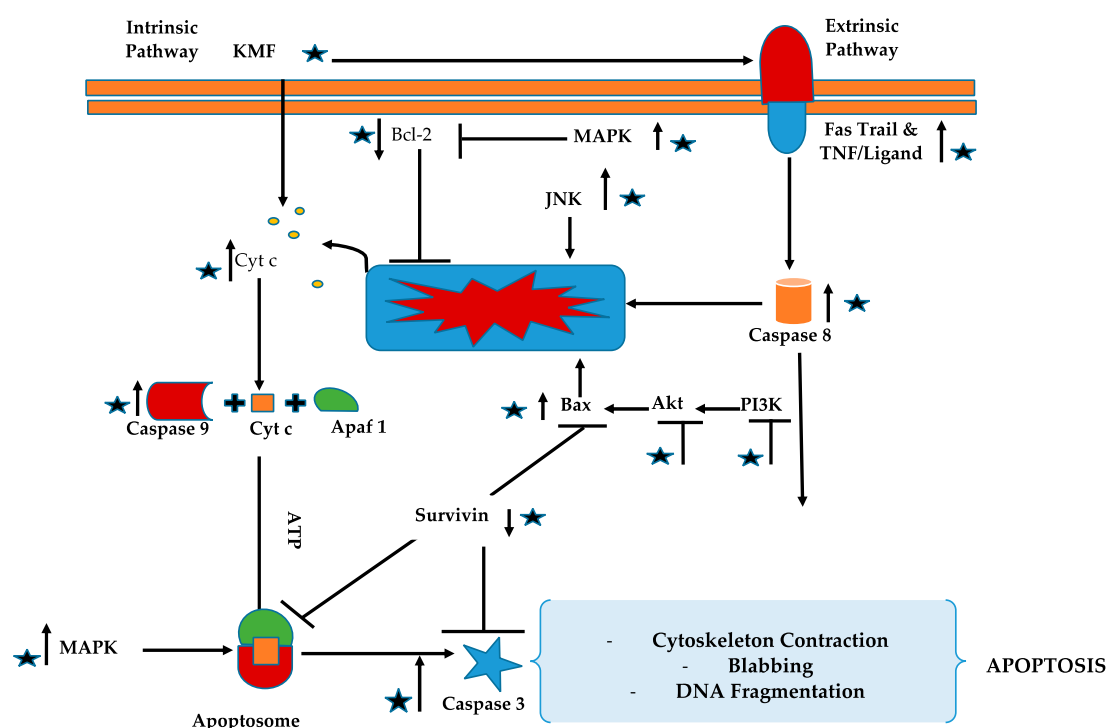


Figure 2. Anticancer role of kaempferol: Mechanistically, it can induce anticancer effects mainly through downregulation of the expressions of proteins involved in the cancer progression and formation alongside apoptosis induction, cell cycle arrest, and decreasing the expression for anti-inflammatory proteins.

4.2. Anti-Brain Cancer Activity

Glioblastoma is one of the most invasive and aggressive brain tumors, with a very poor prognosis, among other reasons, secondary to the development of resistance against current therapies [55]. It has been reported that Kaempferol inhibited both growth and migration of glioma cells, even when kaempferol was loaded to mucoadhesive nanoemulsion (KPF-MNE) or kaempferol-loaded nanoemulsion (KPF-NE) [55–57]. This flavonoid also triggers ROS generation and apoptosis, through reduction of the thioredoxin concentrations, superoxide dismutase activity, as well as to increase the levels of pro-inflammatory cytokines (interleukin-6, 8, chemokines, monocyte chemo-attractant protein-1), Bcl-2, cleaved caspase-3, -8, anti-apoptotic proteins survivin and XIAP, cleaved poly(ADP-ribose) polymerase expression, depolarization of mitochondrial membrane potential, and rapid reduction in phosphorylation of ERK and AKT [55,56,58].

4.3. Anti-Liver Cancer Activity

Hepatocellular carcinoma (HCC) is the most-encountered primary liver cancer among adults [59]. Kaempferol was revealed to significantly inhibit, in a dose-dependent manner, human hepatic cancer cells proliferation (HepG2, SK-HEP-1, Huh7). In addition, diethylnitrosamine and 2-acetylaminofluorene-induced HCC from rats treated with kaempferol combined to luteolin inhibited cell growth and induced cell death [60,61]. Indeed, kaempferol induces cell apoptosis and causes cell cycle arrest at the G2/M phase, therefore preventing cell migration and invasion. Kaempferol is also able to release cytochrome c via ROS generation triggering mitochondrial membrane potential loss and mitochondrial swelling and increasing the level of cleaved caspase-3 [59–61]. Kaempferol also decreases the expression level of miR-21, cytokine signaling 3 (SOCS3), signal transducer and activator of transcription 3 (STAT3), CDK1, cyclin B, PI3K/AKT/mTOR and p-mTOR signaling pathway, and hypoxia-inducible factor 1 (HIF-1) in human hepatic cancer cells and enhanced the expression of Janus kinase 1 (JAK1), tyrosine kinase 2 (Tyk2), STAT1/2, endogenous interferon (IFN)- α -regulated genes, phosphatase and tensin homologue (PTEN), microtubule-associated protein 1A/1B-light chain 3 (LC3-II), p44/42 MAPK, beclin 1, and autophagy-related gene (Atg) 5, 7, and 12 [60–63].

4.4. Anti-Colon Cancer Activity

Colorectal cancer is amongst the most frequently found cancers worldwide, with more than 1.8 million new cases per year [64]. Kaempferol was reported to possess cytotoxic effects on different human colorectal cancer cells lines, including HCT116, HT-29, HCT-15, LS174-R colon, and SW480 cells [64–66].

Even though 5-Fluorouracil is subjected to therapeutic failure due to resistance development, it is still the most recommended chemotherapeutic agent. Experimental studies combined kaempferol with 5-Fluorouracil in LS174-R cells and reported interesting antiproliferative effects [64]. In addition, kaempferol in combination with tumor necrosis factor ligand superfamily member (TRAIL) led to apoptosis in colon cancer cells, through up-regulation of TRAIL receptors and death receptor 5 (DR5) that improved the TRAIL activity [67]. Generally, kaempferol induces apoptosis and cell cycle arrest at G2/M, and reduces both cell migration and invasion [64,66]. Kaempferol also blocked ROS production and modulated the expression of MAPK, JAK/STAT3, PI3K/AKT, ATM, H2A histone family member X (H2AX), phospho-p38, p21, p53, PARP, caspase-3, -7, -8, -9, Bcl-2, p53 upregulated modulator of apoptosis (PUMA), the release of cytochrome c from mitochondria, connexin 43, ERK-1/2, and nuclear factor kappa B (NF- κ B). Also, kaempferol significantly reduced insulin-like growth factor (IGF)-II secretion, and heregulin (HRG)- β , CDK2, CDK4, Cdc25C, Cdc2, cyclins B1, D1, E, A, and connexin 43 expressions. Finally, it also suppressed the phosphorylation of retinoblastoma protein and enhanced the PARP cleavages [64–66,68–71].

4.5. Anti-Prostate Cancer Activity

Prostate cancer is one of the leading causes of death among man and the need for more effective treatments has driven further research [72]. Kaempferol-3-O-rhamnoside dose-dependently inhibits prostate cancer cells proliferation [72], by upregulating the expression of caspase-8, -9, -3, and poly (ADP-ribose) polymerase proteins [72,73]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is known to activate the host immune system and to facilitate host immunosurveillance by the dendritic cells (DC), thereby representing a promising strategy to thwart prostate cancer [73]. Kaempferol has been shown to induce GM-CSF release in PC-3 cells that, in turn, increase the chemotaxis of DC through activation of phospholipase C (PLC), MEK1/2, and protein kinase C (PKC) [73]. Obviously, the transcriptome of prostate cancers cells is also markedly affected by kaempferol treatment as evidenced by the down-regulation of androgen receptor genes expression [74]. In rats, orally administered kaempferol showed no significant toxicity and significantly increased survival, in addition to reducing the growth of PCa xenografts in athymic nude mice [74].

4.6. Anti-Pancreatic Cancer Activity

Pancreatic cancer is amongst the most common cancer-related causes of deaths worldwide with the nastiest prognosis [75]. Kaempferol dose-dependently inhibits the growth of pancreatic cancer cells, SNU-213, Panic-1, and Miapaca-2, through inducing apoptosis [75] and effectively inhibiting cell migration, ERK1/2, epidermal growth factor receptor (EGFR)-related Src, and AKT pathways [76]. Kaempferol also improves the suppressive activity of regulatory T cells (Tregs) by increasing the FOXP3 expression level [77,78].

4.7. Anti-Blood Cancer Activity

Acute promyelocytic leukemia is a life-threatening blood cancer, characterized by a defect in cell growth and apoptotic pathways [79]. Kaempferol (12.5–100 μ M) dose-dependently decreased cell viability in human leukemia cells, HL-60 and NB4 [79,80]. Kaempferol also promoted apoptosis, cell cycle arrest at the G2-M phase, and DNA damages [79–84], and down-regulated the expression of AKT, ABCB1, BCL2, and ABCC1 genes, protein expression associated with DNA repair system, as well as DNA-dependent serine/threonine protein kinase (DNA-PK), phosphate-ataxia-telangiectasia and Rad3-related (p-ATR), phosphate-ataxia-telangiectasia mutated (p-ATM), 14-3-3 proteins sigma (14-3-3 σ), p53, MDC1, O(6)-methylguanine-DNA methyltransferase (MGMT), while up-regulating caspase-3, -8, p-p53, p-H2AX, and cytochrome c expression [79–82,85,86]. In a rat model of leukemia, kaempferol reduced the release of beta-hexosaminidase as a marker of degranulation in basophilic leukemia (RBL-2H3) cells [87], and increased the accumulation of mediators and the secretory granule development in human leukemic mast cells (HMC-1) [88].

4.8. Anti-Lung Cancer Activity

Lung cancer, such as non-small-cell lung cancer, displays a poor prognosis and is currently contributing to increasing the number of cancer-related deaths worldwide [89]. Kaempferol concentration dependently prevented the growth of lung adenocarcinoma A549 cells [90–93], decreased colony formation, and triggered apoptosis [94]. Kaempferol also markedly prevented cell migration, recovered the loss of E-cadherin, and suppressed EMT [89]. Kaempferol still downregulated the expression of claudin-2, AKT/PI3K phosphorylation, ERK pathways, Bcl-2, Bcl-xL, MEK1/2, MMP2, tissue inhibitor of metalloproteinases 2 (TIMP2), MAPK and up-regulated the expression of Bax, Fas, cleaved-caspase-3,-7,-8,-9, AIF (caspase-independent), and miR-340 transcription, involved in the apoptosis pathway [90–95]. In a lung metastasis model, kaempferol was also able to reduce the volume of subcutaneous xenograft and the number of metastasis compared to the control group [94]. In addition, it showed a significant effect in killing cancer cells by radiation in a BALB/c nude mouse xenograft model of A-549 cells [96].

4.9. Anti-Kidney Cancer Activity

Renal cell carcinoma (RCC) represents the most prevalent primary kidney cancer [97]. Kaempferol significantly inhibits cell growth and triggers apoptosis in RCC (786-O and 769-P cells) [98,99]. Kaempferol exerts its anticancer activity through preventing cell migration and invasion, inhibiting MMP-2 protein, downregulating AKT phosphorylation, and increasing the focal adhesion kinase (FAK) activity [97]. It also up-regulates cyclin B1 expression, PARP cleavages, and p21 expression and promotes activation of the EGFR/p38 signaling pathway [98,99].

4.10. Anti-Bladder Cancer Activity

Bladder cancer is becoming the most common type of cancer of the urinary tract [100]. Kaempferol can strongly and selectively inhibit bladder cancer cells by promoting cell cycle arrest and apoptosis [100–103]. Also, kaempferol acts by downregulating the PTEN/PI3K/AKT pathway, DNA methyltransferases (DNMT3B), CDK4, CyclinD1, Mcl-1, Bid, and Bcl-xL, and upregulating p53, p38, p21, p-ATM, p-BRCA1, DNA methylation, and Bid and Bax expression [100,102,103]. These in vitro findings were further validated by experiments in subcutaneous xenografted mouse models. Kaempferol significantly suppressed tumor growth as well as cancer metastasis and invasion in xenografted mice with regards to the untreated control compared to the control group mice, and caused downregulation of growth-related markers and c-Met/p38 signaling pathway, yet upregulated apoptosis markers [101].

4.11. Anti-Oral Cancer Activity

Oral squamous cell carcinomas (OSCC) is the sixth most prevalent cancer worldwide [104]. In in vitro studies, kaempferol displayed antiproliferative effect on pharynx (FaDu) and oral cavity carcinoma (PCI-13) [105], human esophageal squamous carcinoma (Eca-109), and human tongue squamous carcinoma (SCC4, SCC-1483, SCC-25, SCC-QLL1) cells, prevented clone formation and cell migration and invasion, and induced substantial apoptosis [104,106–108]. Kaempferol also caused cell cycle arrest at G0/G1 phase and downregulated Bcl-2, MMP-2, c-Jun, and hexokinase-2 expression. Kaempferol also increased glucose uptake, EGFR activation, ERK1/2 phosphorylation, and upregulated Bax, cleaved caspase-3, -9, and PARP [104,106–108]. Finally, the anticancer potency of kaempferol was further confirmed in a mice xenograft model, revealing the ability to significantly prevent the growth of tumor size coupled with a marked decrease in hexokinase-2 expression and EGFR activity in tumor tissues [107].

4.12. Anti-Bone Cancer Activity

Kaempferol dose-dependently inhibits the growth of human osteosarcoma cells U-2 OS, 143B, and HOB cells and the migration of human U-2 osteosarcoma (OS) cells with poor toxicity on hFOB cells, a human fetal osteoblast progenitor [109,110]. Kaempferol acts by downregulating the AP-1 DNA binding activity, MMP-2, -9, and urokinase plasminogen activator (uPA) that, in turn, reduces phosphorylated p38, ERK, and JNK [110]. In BALB/c(nu/nu) mice inoculated with human osteosarcoma cells (U-2 OS), kaempferol significantly decreased the number of viable cells and reduced the tumor size [109]. The in vivo anti-bone cancer effects of kaempferol have also been demonstrated in BALB/c(nu/nu) mice inoculated with U-2 OS cells [109].

4.13. Anti-Cervical Cancer Activity

Kaempferol was found to selectively prevent the growth of human cervical cancers cells, such as HeLa, multidrug-resistant human cervical carcinoma, KB-V1, and SiHa cells with regards to the normal cells and HFF cells [111–114]. Kaempferol also caused cell cycle arrest at the G2/M phase and apoptosis, correlated with downregulation of PI3K/AKT and human telomerase reverse transcriptase (hTERT) pathways, Pgp, Rh123 efflux, cyclin B1, NF- κ B nuclear translocation, CDK1, Bcl-2, and upregulation of p53 with mitochondrial membrane potential disruption [111–115].

4.14. Anti-Stomach Cancer Activity

Experimental studies on stomach cancer revealed the antiproliferative activity of kaempferol on human gastric cancer cells (MKN28 and SGC7901) by promoting autophagy, cell cycle arrest at G2/M phase, and cell death [116,117]. The induced autophagic cell death was linked to the upregulation of Bax, cleaved caspase-3, -9, cleaved PARP, IRE1-JNK-CHOP signaling, and downregulation of p62, cyclin B1, Cdc25C, Bcl-2, CDK1, p-AKT, cyclooxygenase 2 (COX-2), and p-ERK expression [116,117].

4.15. Anti-Ovarian Cancer Activity

Experiments using human ovarian cancer cell lines (A2780/CP70, A2780/wt, SKOV-3, OVCAR-3) showed that kaempferol could inhibit tumor growth, proliferation, and angiogenesis by decreasing vascular endothelial growth factor (VEGF) expression [118]. Kaempferol also induces apoptosis and cell cycle arrest at G2/M phase via upregulation of Chk2/Cdc25C/Cdc2, DR5, DR4, JNK, CHOP, p38, p21, ERK1/2 proteins, caspase-3, -7, -8, Bad, Bax, and p53 proteins, with downregulation of hypoxia-inducible factor 1 α (HIF-1 α), a regulator of VEGF expression [118–123].

Table 1. Studies of anticancer activities of kaempferol in vitro.

Cancer Types	Mechanisms of Action	Cancer Cells Lines	Origin of Cells	References
Bladder	Downregulation: phosphorylated AKT (p-AKT), Cyclin D1, CDK4, Bid, Mcl-1 and Bcl-xL in human cells; DNMT3B expression in mouse cells Upregulation: p38, p53, p21, p-BRCA1, p-ATM, Bid, Bax expression in human cells; DNA methylation in mouse cells	SV-HUC-1 (human), T24 and 5637 (mouse)	Human, Mouse	[100,124]
Blood	Downregulation: p-ATM, phosphate-ataxia-telangiectasia, AKT, BCL2, ABCB1, and ABCC1 expression Upregulation: CASP3 and BAX/BCL-2 expression, subG1 population, Rad3-related (p-ATR), 14-3-3 proteins sigma (14-3-3 σ), DNA-dependent serine, MDC1 protein, p53 and p-H2AX expression	HL-60, NB4	Human	[79,80]
Bone	Downregulation: migration, MMP-2, MMP-9, and uPA expression, ERK, p38, and JNK phosphorylation and DNA binding activity of AP-1, endoplasmic reticulum stress and mitochondrial signaling pathways	U-2 OS, HOB, 143B	Human	[109,110]
Brain	Apoptosis Downregulation: phosphorylation of ERK, AKT, anti-apoptotic proteins XIAP and survivin expression, depolarization of mitochondrial membrane potential Upregulation: caspase-3 activity	C6, A172	Rats, Human	[55,57]
Breast	Downregulation: Bcl2, E2, EMT-markers (N-cadherin, E-cadherin, Slug, and Snail), cathepsin D, cyclin D1, cyclin E, pAkt, pMEK1/2, pIRS-1, RhoA and Rac1 activation of ER/PR-silence and HER2-silence SK-BR-3 Upregulation: p21, bax γ H2AX, cleaved caspase-3&-9, and p-ATM Suppression of migration and invasion Apoptosis, cell cycle arrest at G2/M and DNA damage, reduced cell migration and invasion ability	Triple-negative BC (TNBC) cell MDA-MB-231, MCF-7	Human	[10,41,42,47,51,60]
Cervical	Downregulation: PI3K/AKT and hTERT pathways Upregulation: mitochondrial membrane potential disruption, intracellular free calcium elevation Apoptosis	HeLa, SiHa	Human	[111,112,114]

Table 1. Cont.

Cancer Types	Mechanisms of Action	Cancer Cells Lines	Origin of Cells	References
Colon	Downregulation: CDK2, CDK4, cyclins D1, cyclin B1, cyclin E, cyclin A, Cdc25C, Cdc2, IGF-I&-II secretion, heregulin (HRG)- β expression and HRG- β -induced phosphorylation of the AKT, ERK-1/2, IGF-IR, and ErbB3 Upregulation: caspase-3,-8,-9, p21, p53, phospho-p38 MAPK and enhanced the PARP cleavages, JAK/STAT3, MAPK, PI3K/AKT, and NF- κ B expression Blocked ROS generation, cell cycle arrest at G1 and G2/M arrest, and cell migration	LS174, HCT15, HCT116, SW480, HT-29	Human	[64–66,125]
Kidney	Downregulation: MMP-2, AKT phosphorylation and FAK	786-O	Human	[97]
Liver	Downregulation: mitochondrial membrane potential, mitochondrial swelling, SOCS3, STAT3, miR-21, PI3K/AKT/mTOR signaling pathway Upregulation: PTEN, caspase-3, JAK1, Tyk2, STAT1/2, endogenous IFN- α -regulated genes expression	Hepatoma HepG2	Rat, Human	[59,60,63]
Lung	Downregulation: AKT/PI3K and ERK pathways, TIMP2, and MMP2 phosphorylation, Bcl-2, cyclin D1, claudin-2 expression Inhibited STAT3 factor binding Upregulation: PTEN, Bax, miR-340, Fas, cleaved-caspases 3, 8, and 9, and cleaved-PARP Apoptosis, cell cycle arrest at G2/M, prevent migration and invasion	A549, HCCC9810, QBC939	Human, mice	[90,92,94,96]
Oral	Suppress migration and invasion Downregulation: MMP-2, TIMP-2 mRNA, c-Jun activity, ERK1/2 phosphorylation	SCC4	Human	[104]
Ovarian	Upregulation: DR4, DR5, p53, p38, ERK1/2, CHOP, JNK, death receptors/FADD/Caspase-8 pathway Downregulation: anti-apoptotic proteins	A2780/CP70, OVCAR-3, SKOV-3	Human	[119–121]
Pancreatic	Downregulation: EGFR-related AKT, Src, and ERK1/2, pathways Upregulation: suppressive function of regulatory T cells (Tregs), FOXP3 expression Block cell migration	Miapaca-2, Panc-1, SNU-213, Treg cells	Human, Rats	[76,77]
Prostate	Downregulation: androgen receptor expression Upregulation: caspase-8, -9, -3 and poly (ADP-ribose) polymerase proteins cleavage	C4-2, LNCaP	Mice, Human	[72,74]
Stomach	Induce significant apoptosis and cell cycle arrest at G2/M Downregulation: COX-2, Bcl-2 p-ERK, p-AKT expression Upregulation: Bax, cleaved caspase-3 and -9	MKN28 and SGC7901	Human	[116]

5. Conclusions

Cancer accounts among the most overbearing human health problems, relying on chemoprevention approaches as a way to diminish both incidence and mortality. The scrutiny of kaempferol extraordinary list of cancer-fighting properties highlights its full potential. These studies are promising, especially because kaempferol selectively inhibits cancerous cells without affecting healthy ones. In vitro studies unveiled the broad spectrum of kaempferol anticancer targets, including apoptosis, metastasis, inflammation, and angiogenesis. Therefore, cancer cells that often adapt to VEGF inhibition, following treatment with kaempferol, may not escape other detrimental actions induced by this natural flavonoid. Even though kaempferol is questionable as a cancer treatment, it seems to constitute an interesting

option when it comes to safety. However, data on the long-term effect of kaempferol intake are scarce. Though kaempferol poor bioavailability represents a significant obstacle, the use of kaempferol-based nanoparticles has brought more hope on cancer chemoprevention strategies. Moreover, most of the research conducted on kaempferol anticancer potency was in vitro, making it difficult to draw a final conclusion on its usefulness. In vivo studies and clinical trials using an exact dose of kaempferol are scarce so far, thus stressing the need for more in-depth experiments varying the dose of kaempferol alone as well as using it with other flavonoids. These data will be of utmost interest to apprehend on kaempferol efficacy in the context of cancer.

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