# Anticancer Properties of Kaempferol on Cellular Signaling Pathways

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## Abstract

Polyhydroxy compounds are secondary metabolites that are ubiquitous in plants of higher genera. They possess therapeutic properties against a wide spectrum of diseases, including cancers, neurodegenerative disorders, atherosclerosis, as well as cardiovascular disease. The phyto-chemical flavonol (a type of flavonoid) kaempferol (KMP) (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4Hchromen-4-one) is abundant in cruciferous vegetables, including broccoli, kale, spinach, and watercress, as well as in herbs like dill, chives, and tarragon. KMP is predominantly hydrophobic in nature due to its diphenylpropane structure (a characteristic feature of flavonoids). Recent findings have indicated the promise of applying KMP in disease prevention due to its potential antioxidant, antimutagenic, antifungal, and antiviral activities. In the literature, there is evidence that KMP exerts its anticancer effects by modulating critical elements in cellular signal transduction pathways linked to apoptosis, inflammation, angiogenesis, and metastasis in cancer cells without affecting the viability of normal cells. It has been shown that KMP triggers cancer cell death by several mechanisms, including cell cycle arrest, caspase activation, metabolic alteration, and impacting human telomerase reverse-transcriptase gene expression. This review is aimed at providing critical insights into the influence of KMP on the intracellular cascades that regulate metabolism and signaling in breast, ovarian, and cervical cancer cells.

## Keywords

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CONFLICT OF INTEREST

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## 1. INTRODUCTION

Cell growth and survival are fueled by nutrients that are taken up from the environment and directed into the cellular metabolic pathways to generate energy-rich molecules such as ATP/GTP. In proliferating cells, including tumor/cancer cells, these metabolic processes require additional nutrients to produce ATP and generate all components necessary for continuous cell division. Cellular survival and functionality are heavily contingent on the energy provided through metabolic mechanisms. Minor changes in metabolic pathways have a detrimental impact on the regulation and proliferation of healthy and cancerous cells [1]. Given the increasing prevalence of cancer diagnoses [2] and deaths, a deeper understanding of the fundamental metabolic processes that act upon cellular regulation is required.

Cancer was reported to be responsible for 10 million deaths in 2020 worldwide, making it one of the leading causes of death [3]. Back in the 1920s, Warburg proposed that lactate fermentation from glucose (commonly referred to as aerobic glycolysis) [4] is increased in cancerous and normal proliferating cells. Since then, significant progress has been made in our understanding of the unique relationship between cancer cells and metabolism. Ying *et al.* and Son *et al.* [5, 6] found that pancreatic tumor cells function through a KRAS-regulated metabolic pathway. Yang *et al.* observed that lung cancer cells use the glutathione metabolic pathway [7]. In addition, Sanchez-Vega *et al.* [8] indicated the role of oncogenes, including Myc, Notch, and Nrf2, in promoting metabolic changes in different types of tumor cells. Studies by DeBerardinis & Chandel [9] and Pavlova & Thompson [10] also showed that changes in the levels of intracellular metabolites, enzymes, and transporters are associated with metabolic alterations leading to genetic modifications in cancer, which differ depending on the tissue type and stage of cancer [11].

Receptor-mediated signal transduction initiates metabolic pathways in mammalian cells to synthesize new nucleic acids, lipids, and proteins, as needed by the proliferating cells [12]. The regulation of cellular metabolism by signaling pathways is tightly coordinated through feedback control on signal transduction cascades, making the relationship bidirectional. Cellular processes, including proliferation, differentiation, apoptosis, and stress responses, are regulated by signaling pathways, most importantly by mitogen-activated protein kinase (MAPK) cascades. Some important genetically altered signaling pathways have been identified in cancer, including RTK/RAS-ERK (extracellular signal-regulated kinases)/ MAP-kinase (mitogen-activated protein kinase) and PI3K/Akt signaling [13], which occur heterogeneously depending on the tissue and cancer types [14, 15].

Since 1995, the National Cancer Institute (NCI) has supported researchers in screening novel chemicals as potential anticancer compounds. In 1993, the NCI initiated a campaign to discover therapeutically important natural products [16–18]. An important example is the naturally occurring chemical salicylic acid, which was extracted from the bark of the willow tree and eventually gave rise to the famous drug aspirin [19]. Phytochemicals are non-nutrient metabolites made by common fruits and vegetables to defend against pathogens, competitors, and other threats. There are different categories of phytochemicals based on their activities, such as antifungals [20], antivirals [21], antimutagens [22], antiinflammatories [23], antioxidants [24], and anticancer agents [25]. Some anticancer

phytochemicals act across categories [26], and some synergize with other chemotherapeutic agents [27], but perhaps their best attribute is the lack of toxicity to normal cells at therapeutic doses [28].

Flavonoids are a class of polyphenolic phytochemicals that are ubiquitous secondary metabolites in plants of higher genera [29]. This review focuses on the influence of the naturally occurring flavonol kaempferol (KMP, a tetrahydroxyflavone) on the signaling pathways of three common cancers that most often affect women: breast, ovarian, and cervical. The characteristic feature of flavonoids including KMP is the presence of a common skeleton of diphenyl propane (two phenyl rings connected by three carbon linkage). KMP is mostly found in leafy vegetables such as broccoli, kale, and watercress and exhibits antioxidant properties producing significant health benefits [30, 31]. The common sugar-conjugates of KMP include astragalin (kaempferol-3-O-glucoside), kaempferol-3-beta-D-galactoside, kaempferol-3-rutinoside [31]. Research has shown that an increase in the intake of food containing KMP reduces individuals' risk of developing cancer as well as the risk of cardiovascular disease. KMP can inhibit cancer progression by triggering cell cycle arrest at the $G_2/M$ phase, apoptosis, regulation of signaling pathways and protein kinase B, expression of metastasis-related markers, and epithelial–mesenchymal transition-related markers and inhibiting the accumulation of reactive oxygen species [29–31]. The anticancer effects of KMP can also be linked to nutrient delivery, processing, and storage, which create the pathway to starve cancer cells to initiate apoptosis [31]. However, as tumor cells are resilient and adapt well to poor nutrient and hypoxic conditions, under this condition AMP-activated protein kinase (AMPK) promotes the survival mechanism called autophagy, reducing apoptosis and allowing cancer proliferation. *In vitro* studies have been conducted on combining KMP and AMPK inhibitor to control the growth of cancer cells which showed promise for further exploration [31]. KMP contains four hydroxyl (-OH) groups at 3, 5, 7, and 4′ positions (structure is presented in Schemes 1–3), providing the opportunity of forming co-ordinate bonds between electron donor atom oxygen (of – OH groups) and metal atoms, which can further contribute to its therapeutic activity [31].

## 1.1. Kaempferol's Role in Breast Cancer

Breast cancer is one of the most prevalent forms of cancer found in women. According to the GLOBOCAN 2020 report, globally 7.8 million women have been diagnosed with breast cancer in the last 5 years [3]. Although advances in diagnostics and early prevention have increased survival rates since the 1980s, breast cancer is still the second largest cause of death in women [32]. Yi *et al.* [33] and others used estrogen receptor-positive mammary cancer cells (MCF-7) to investigate the mechanism by which KMP produces an apoptotic response. In addition, Azevedo *et al.* (2015) showed that KMP induced apoptosis in MCF-7 cells by disrupting the uptake of glucose, which is an essential sugar in the production of cellular energy [34]. They observed that the inability of MCF-7 to take up glucose was detrimental to cellular function and led to programmed cell death. They also found that KMP prevented the uptake of lactic acid, thereby inhibiting cell survival [34]. Moreover, research by Hung *et al.* [35] on MCF-7 cells demonstrated that KMP damages the endoplasmic reticulum (ER), thereby inhibiting MCF-7 cells from undergoing estradiol-mediated growth. Yi *et al.* [33] also found that KMP facilitated the inhibition of cancer

cell growth by activating the caspase pathway. Caspases are essential enzymes involved in apoptosis. The cleavage of poly(ADP-ribose) polymerase (PARP) leads to a caspase pathway cascade that eventually results in programmed cell death. Yi *et al.* also found that KMP effectively induced the cleavage of PARP in MCF-7 cells. Moreover, they showed that KMP has the ability to reduce the expression of antiapoptotic proteins (*e.g.*, Bcl12) and promote the expression of proapoptotic ones (*e.g.*, BAX). Furthermore, Liao *et al.* [36] showed that KMP elicits strong antiproliferative effects on different breast cancer cell types by disrupting mitochondrial function.

Research by Choi *et al.* (2008) showed that KMP induced apoptosis of breast cancer cells through $G_2/M$ cell cycle arrest [37]. They found that KMP-treated cancer cells had a decrease in numbers at the $G_1$ phase of the cell cycle and increased cell numbers at the $G_2/M$ phase. They showed that this cell cycle arrest occurred *via* the inhibition of cyclin-dependent kinase 1 (CDK1), which is an important protein involved in cell division. Their findings indicated the preventive role of KMP on the growth of human breast cancer cells by inhibiting the production of CDK1 at the $G_2/M$ phase of the cell cycle. Furthermore, Li *et al.* (2015) [38] observed that KMP has the ability to suppress the expression of matrix metalloproteinases (MMP), which are protein markers of malignancy in breast cancer cells. For example, increased expression of MMP-3 has been shown to correlate with more aggressive breast cancer. Among all polymorphs of MMP, MMP-1, MMP-3, and MMP-9 have been shown to play critical roles in the migration of breast cancer cells. Li *et al.* also found that KMP prevented the progression of breast cancer metastasis by decreasing the expression and overall activity of MMP-9.

Zhu *et al.* [39] treated MDA-MB-231 (triple-negative breast cancer) cells with KMP and monitored the cell cycle *via* flow cytometry. Their study showed that, at the $G_1$ phase of the cell cycle, the total number of cells decreased by 30%, whereas that at the $G_2$ phase increased by 28%. This led to the finding that KMP initiated cell cycle arrest at the $G_2/M$ phase, leading to apoptosis of MDA-MB-231, which also agrees with the findings of Choi *et al.* [37] Moreover, Zhu and colleagues found that KMP-treated cells exhibited increased expression of γH2AX, a molecular marker that is expressed due to DNA double-strand breaks.

In a more recent study, Nandi *et al.* (2022) [40] investigated the anticancer properties of KMP along with a calcium channel blocker drug, verapamil, on breast cancer stem cells (BCSCs). Verapamil is used in the treatment of Peyronie's disease and has a significant impact on fibroblast function (*e.g.*, cell proliferation). They treated the BCSCs MDA-MB-231 with KMP, verapamil, and KMP & verapamil simultaneously. They found that the treatment of MDA-MB-231 cells with KMP had an antiproliferative effect and deregulated specific chemo-evasion markers, such as CD44, NANOG, and multidrug resistance mutation 1 (MDR1). CD44 is a cell surface adhesion receptor that has been shown to be strongly associated with multiple cancer types and assists in the promotion of cancer cell metastasis. Meanwhile, NANOG is a homeobox protein that is responsible for maintaining the pluripotency of stem cells. The above study suggested that KMP mediates $G_2/M$ cell cycle arrest, thus disrupting the association of CD44, NANOG, and MDR1 with MDA-MD-231. KMP-treated cells also showed increased expression of γH2AX in response

to DNA damage, a finding similar to that of Zhu [39]. Moreover, Nandi's team discovered that the treatment of cells with both KMP and verapamil had higher efficacy at preventing the regulation of chemo-evasive proteins as well as the proliferation of BCSCs. Scheme 1 demonstrates the effect of KMP on pathways associated with breast cancer.

KMP was shown to prevent the proliferation of breast cancer cells by the upregulation of pro-apoptotic genes leading to G2/M cell cycle arrest [37, 39, 40]. KMP has been reported to trigger ER stress mediated ROS production in estrogen receptor positive cells due to KMP's ability to bind to estrogen receptor alpha [33, 41]. Likewise, KMP utilized the caspase pathway which is a mitochondrial-mediated apoptotic pathway in response to cellular stress [33, 41, 42]. Moreover, KMP prevented the uptake of glucose disrupting mitochondria from producing cellular ATP [34].

### 1.2. Kaempferol's Role in Cervical Cancer

Over the past 30 years, the number of young women affected by cervical cancer has increased by 30% [41]. Kashafi *et al.* used HeLa cells (a human epithelial cell line that plays an integral role in the investigation of various human pathologies) to study the mechanism by which KMP induces apoptosis in cervical cancer cells [43]. They compared HeLa cells and HFF cells (*i.e.*, healthy cells) that were treated with KMP. In the experiment, cellular viability and telomerase expression were measured using assays such as MTT and RT-PCR. They found that KMP induced apoptosis by a process of downregulating the PI3K/AKT pathway, an essential cellular signaling pathway responsible for regulating the cell cycle and promoting cellular proliferation. This pathway is initiated by the phosphorylation of PI3K activating AKT, in turn leading to various downstream effects. Kashafi *et al.* [43] discovered that the downregulation of this pathway resulted in a decrease in cellular growth and an increase in the expression of apoptotic genes such as p53, thereby triggering death in cervical cancer cells. They also found that KMP-induced apoptosis of cervical cancer cells occurs through suppression of the expression of the human telomerase reverse transcriptase gene (hTERT). The rate-limiting step in telomerase activity is hTERT, which has been shown to be involved in cellular proliferation. This study demonstrated that KMP has the ability to impede hTERT activity, thereby dysregulating the metastasis of cervical cancer cells.

Tu *et al.* (2016) investigated KMP-induced apoptosis based on changes in cellular topography at the subcellular and nanolevels [44]. Specifically, they used human cervical squamous cells (SiHa) treated with KMP for flow cytometry studies, which showed that KMP increased the intracellular $Ca^{2+}$ concentration as well as decreased mitochondrial potential. Tu *et al.* proposed that apoptosis is initiated by the release of cytochrome c from mitochondria, leading to the expression of various apoptotic caspases. This then leads to an increase in free $Ca^{2+}$ ions in the intracellular space, which has been identified as the cause of cell death. Moreover, Tu *et al.* confirmed cervical cell inhibition using laser confocal microscopy and atomic force microscopy, showing a decrease in cervical cell activity by observing the changes in cellular membrane topography. Therefore, they demonstrated that KMP prevents the metastasis of cervical cancer cells through the misregulation of essential

metabolic pathways, producing a cellular apoptotic response. Scheme 2 provides a summary of the effect of KMP on signaling pathways associated with cervical cancer.

KMP treatment in cervical cancer cells also initiates G2/M phase arrest followed by apoptotic cell death. KMP mediated apoptosis is assisted by p53 activation, intracellular calcium accumulation and disruption of mitochondrial membrane potential [43]. KMP downregulated the PI3K/AKT pathway which is essential for cellular proliferation [44].

### 1.3. Kaempferol's Role in Ovarian Cancer

Ovarian cancer (OVCAR) is the third leading cause of cancer-related death among females. In 2020–2021, 21,750 new ovarian cancer cases emerged. Many OVCAR cases are diagnosed at late disease stages, making treatment difficult and invasive [45]. The deletion or mutation of Checkpoint Kinase 2 (CHEK2) has been linked to the development of numerous cancers, including OVCAR [46]. CHEK2 is an essential regulatory gene that is associated with tumor suppression and cell cycle arrest in response to damage in the DNA sequence. Mutations can lead to the abnormal accumulation of cancer cells and the promotion of proto-oncogenes. Gao *et al.* used KMP-induced ovarian cancer cells A2780/CP70 to study the apoptotic mechanism [46]. They showed that KMP triggered apoptosis of A2780/CP70 cells through activating both intrinsic and extrinsic pathways. They proposed that the mechanism involved KMP-initiated cell cycle arrest at the $G_2/M$ phase through the upregulation of p21 by activating CHEK2. Interestingly, Gao *et al.* found in previous studies that KMP activated apoptosis through a p53-dependent pathway initiated by CHEK2. However, one study has shown that the upregulation of p53 was not affected by the deletion of the CHEK2 gene. Similarly, using flow cytometry, Gao and colleagues showed that KMP activated apoptosis of A2780/CP70 through the caspase 8 and caspase 9 pathways. To replicate their findings, Gao *et al.* used a high-grade ovarian cancer cell line (OVCAR-3). They found that KMP induced apoptosis in OVCAR-3 *via* cell cycle arrest at the $G_2/M$ phase. Furthermore, Yang *et al.* [47] observed that KMP induced apoptosis of OVCAR-3 cells through cell cycle arrest at the $G_0/G_1$ phase. This was shown to occur *via* the activation of caspases 3, 8, and 9 and BAX, and the downregulation of Cyclin B1 and Cdc2, as confirmed by immunoblot assay. Similarly, Zhao *et al.* showed that KMP sensitized OVCAR-3 and SKOV-3 cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [48]. They found that cells treated with KMP in conjunction with TRAIL showed increased expression of CHOP, which is involved in the regulation of death regulator 5 (DR5). DR5 plays an essential role in the TRAIL mechanism and caspase activation. Furthermore, cells stimulated with TRAIL and subsequently treated with KMP showed the upregulation of phosphorylated MAP-kinases ERK1/2, JNK, and p38 as well as DR4 and DR5. Some ovarian cancer cell lines are resistant to TRAIL. However, Zhao and colleagues showed that KMP increased TRAIL-mediated cell death in a dose-dependent manner by upregulating death receptors on the cell membrane [48]. Similarly, KMP-treated cells that were stimulated by TRAIL showed increased expression of phosphorylated MAP kinases (*i.e.*, ERK1/2, JNK, p38). These results clarify that KMP can assist TRAIL-mediated apoptosis through dysregulation of the JNK/ERK signaling pathway in OVCAR-3 and SKOV-3 ovarian cancer cells.

El-Kott *et al.* [49] found that KMP inhibited the proliferation of A2780 ovarian cancer cells through ER stress-mediated autophagy. Their study showed that KMP induced ER stress and autophagy by altering the concentration of intracellular $Ca^{2+}$. Increased expression of markers of ER stress and autophagy in KMP-treated A2780 cells was also observed. These cells also had increased sensitivity to cisplatin (DPP). This group also studied the effect of DPP in the presence of KMP and found that KMP/DPP-treated cells had a greater decrease in phosphorylated AKT and greater increases in p53 and caspase 3 than KMP- and DPP-treated cells. These studies confirmed that KMP facilitated DPP-mediated cell death through inhibition of the AKT signaling pathway. It is also evident that KMP enhances chemosensitization in drug-resistant OVCAR. Scheme 3 shows the role of KMP in regulating the pathways associated with OVCAR.

KMP induced apoptosis of ovarian cancer cells through a G2/M cell cycle arrest and the downregulation of essential signaling pathways such as MEK/ERK, JNK/ERK, and AKT pathway [46–49]. The downregulation of such pathways resulted in the apoptosis of ovarian cancer cells *via* caspases 8 and 9 released by the mitochondria [42, 48]. Secondly, the dysregulation of the JNK/ERK pathway also produced an upregulation of CHOP which is released in response to ER stress [49]. Moreover, KMP increased intracellular $Ca^{2+}$ concentrations leading to cell autophagy in response to ER stress. KMP inhibits ovarian tumor cell growth by G2/M phase arrest along with upregulation of p53, Chk2, Cdc25C/Cdc2 [48, 50]. KMP attenuates ER stress mediated cell death in non-cancerous cells whereas it can trigger ER mediated cell death *via* various mechanisms including autophagy in a selective manner in a range of cancer cells [49, 51].

### 1.4. Cytotoxic Role of Kaempferol

The dietary ingredient KMP has been found to be mutagenic in several studies on cell culture and animal models [52–58], with no reports on its tumerogenic activity. Carver *et. al.* (1982) [52] performed studies on hamster ovarian cells showing flavonols such as quercetin and KMP were involved with DNA damage and chromosomal aberrations without point mutation. Furthermore, Sahu *et al.,* (1994) [56] reported that polyphenolic flavonoid such as KMP induced nuclear DNA damage and lipid peroxidation in isolated rat liver nuclei, which are suggestive of pro-oxidative role of KMP. Takanashi *et al.* (1983) [57] conducted oral administration of KMP in rats over 540 days which triggered mutagenic activities without causing any tumor formation. In a more recent study by Yangzom *et al.* (2022) [58], oral administration of KMP over a 28-day period revealed no toxic effect on the physiological function of mice. Over this time period, no significant alterations in oxidative stress and lipid profiles were observed. Studies by Arif *et al.* [52] showed that flavonoids facilitate the copper-dependent oxidative DNA breakage, which can be exploited to treat cancer.

## CONCLUSION

Different cancer cells and subtypes clearly rely on a variety of strategies to promote cell survival and metastasis. Chemotherapeutic agents or targeted therapeutics do not always exhibit their full potential for inhibiting cancer. It is thus worthwhile to seek alternative strategies to resolve cellular abnormalities. Recent evidence has indicated that kaempferol

is a valuable anticancer therapeutic due to its low systemic toxicity and high potency for inhibiting multiple pro-cancerous pathways in a selective manner. Kaempferol has also been found to target cancer stem cells and could thus be a potent choice to treat recurrent tumors, which are a particular concern in cancer therapy. Kaempferol treatment has been proven to enhance the rate of apoptosis, making it a suitable candidate for treating cancer. Pharmaceutical applications of kaempferol either alone or in combination with conventional treatments, such as radio/chemotherapy, could be exploited to establish a new paradigm in cancer treatment.

## ACKNOWLEDGEMENTS

## LIST OF ABBREVIATIONS

| | |
|---|---|
| **AMPK** | AMP-activated Protein Kinase |
| **KMP** | Kaempferol |
| **MAPK** | Mitogen-activated Protein Kinase |
| **RTK/RAS-ERK** | Extracellular Signal-regulated Kinases |

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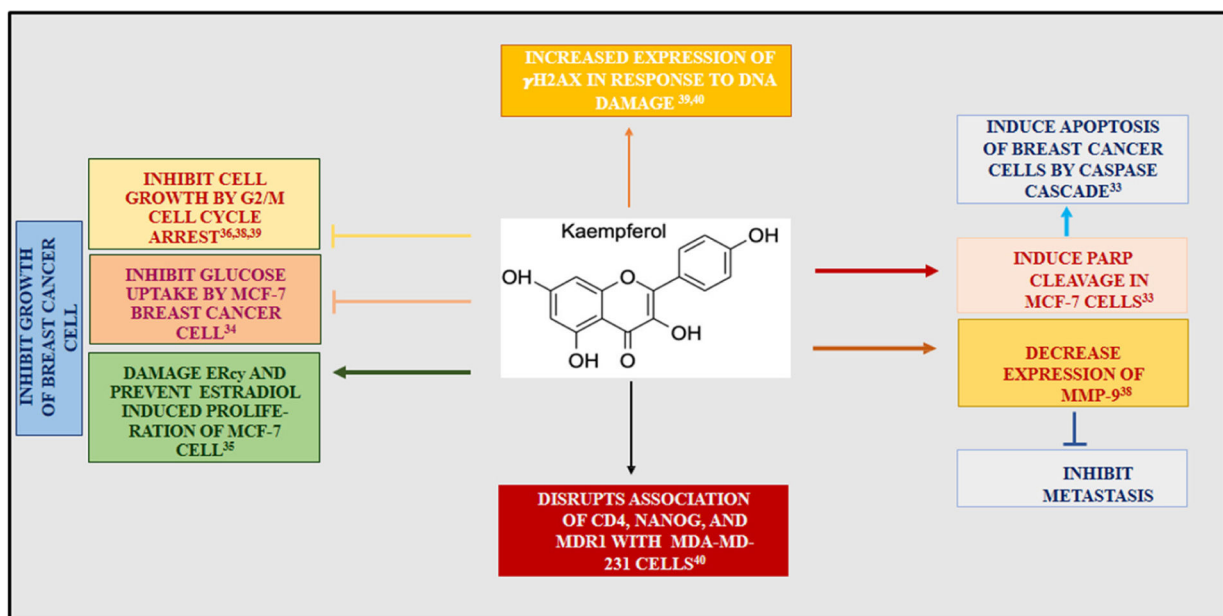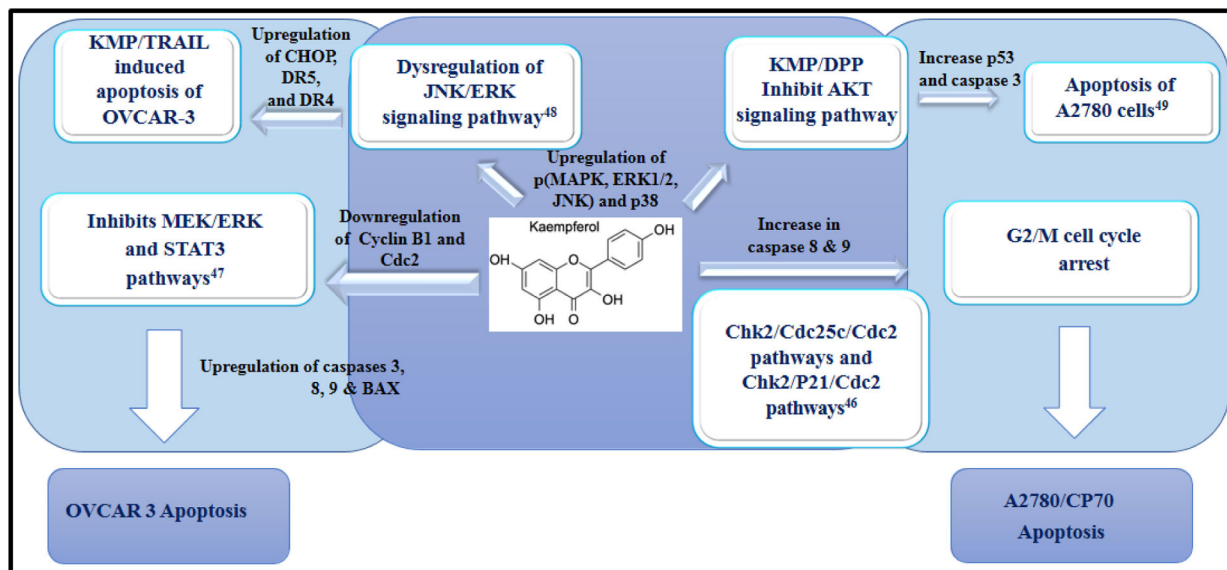
**Scheme 1.**

Illustration of the various pathways by which kaempferol (KMP) induces an apoptotic response in breast cancer cells. KMP decreased the uptake of glucose and lactic acid in MCF-7 cells [34]. In addition, KMP damaged the ER in MCF-7 cells inhibiting estradiol-mediated cell growth [35]. Moreover, KMP initiated the caspase cascade by the cleavage of PARP [33]. KMP was shown to induce apoptosis through G2/M cell cycle arrest [36–38]. Furthermore, KMP was shown to have facilitated dsDNA damage, leading to increased expression of $\gamma$H2AX [39, 40].
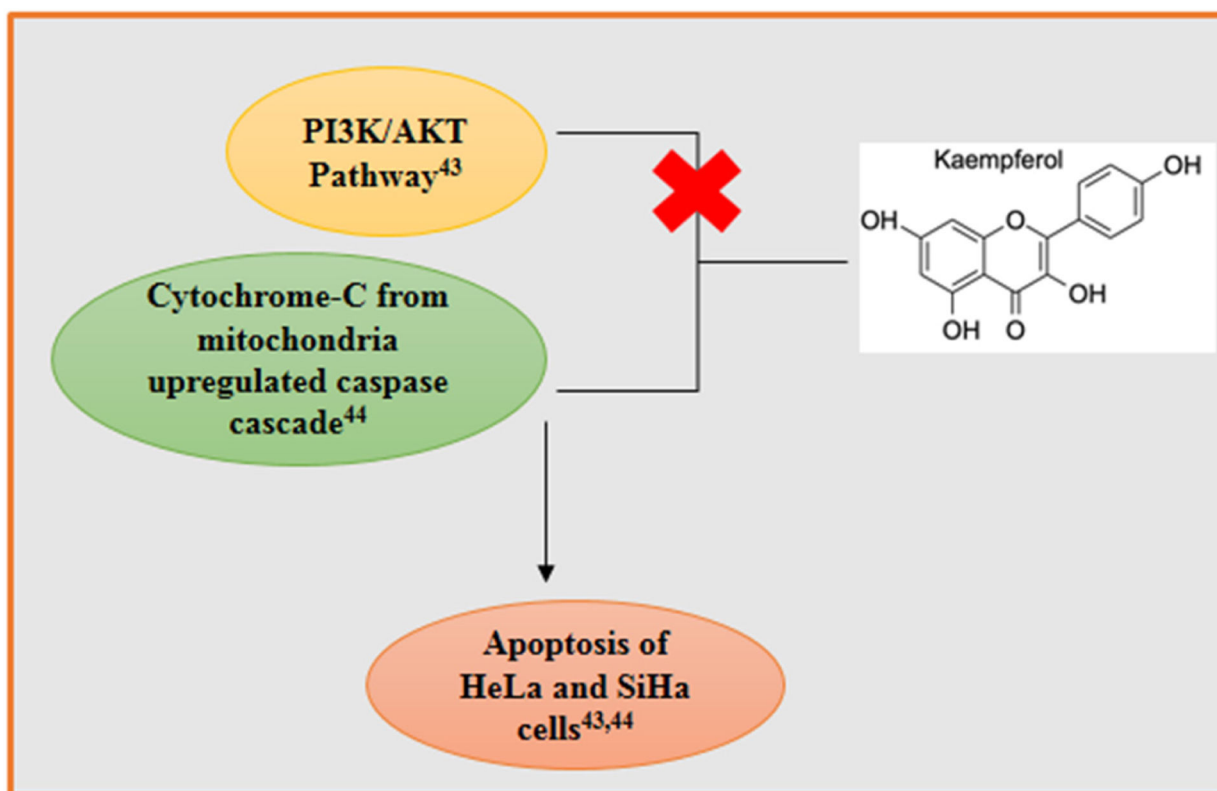
**Scheme 2.**
An illustration of kaempferol (KMP) inhibiting the PI3K/AKT signaling pathway, leading to downstream apoptotic effects [43]. KMP was shown to have an effect of decreasing mitochondrial potential, releasing cytochrome c, and thus upregulating the caspase cascade [44].

**Scheme 3.**
An illustration of the alterations in various cell signaling pathways that are responsible for inducing apoptosis of ovarian cancer cells. KMP causes cell cycle arrest at the $G_2/M$ phase through downregulation of the Chk2/p21/Cdc2 pathway [46]. In addition, KMP inhibits the MEK/ERK pathway [47]. Furthermore, KMP dysregulates the JNK/ERK pathway, facilitating KMP/TRAIL-induced apoptosis of OVCAR-3 [48]. Finally, KMP/DPP regulates cell death by inhibiting the AKT signaling pathway [49].