REVIEW ARTICLE

A Review on Apigenin [4', 5, 7-trihydroxy-flavone] – An Emerging Anti-Cancer Therapeutic Agent

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Abstract

Chemotherapy works by halting or decreasing the growth of cancer cells, which multiply rapidly. Apigenin can be used to treat cancer, reduce the likelihood of cancer recurrence, stop or delay tumor growth, or shrink tumors that are causing pain and other issues. Although chemical medications are effective, they have a variety of negative effects due to killing or delaying the growth of healthy cells that grow and divide quickly. Thus anticancer therapies based on natural ingredients are emerging. Among these natural ingredients, Apigenin (Api) is a flavonoid that has little toxicity with numerous bioactive qualities. Apigenin has several mechanisms to elicit its actions. Cell cycle arrest, anti-inflammatory, apoptosis, antioxidant activity, anti-carcinogenic, anti-mutagenic, anti-progression and anti-proliferative effects are all examples of Apigenin's actions. Apigenin is involved in the regulation of several proteins and factors such as Bcl-xL, Bcl-2, TNF-α, HIF-1alpha, VEGF, *etc.*, modulation of different cellular pathways such as TRAIL, PI3K/Akt/Mtor, JAK/STAT, Wnt/β Catenin & MAPK and regulation of signal transduction. Apigenin is effective in treating and preventing various prevailing cancers including, Breast, cervical, ovarian, colon, oral, prostate, lung, liver, leukemia, lymphoma, melanoma, *etc.* Apigenin can be used synergistically with cisplatin, 5-fluorouracil, Taxol (Paclitaxel), IFN-gamma, Bcl-2 inhibitors (ABT-263 & HA14-1), Doxorubicin, Chyrophanol and several nano-formulations. Apigenin is also involved in the inhibition of cyclin A, cyclin B & cyclin-dependent kinase-1 [CDK1] expression and Decrease in AKT, P70RSK, and S6 Phosphorylation whereas increasing ERK1/2 and P90RSK phosphorylation.

Keywords: *Apigenin, 4'-5-7-trihydroxy-flavone, flavonoids, anti-cancer therapy, mechanism of action, pharmacokinetics, combination therapies.*

INTRODUCTION

Cancer is the most prevalent cause of mortality around the world [1, 2]. It is contributing to around 7.6 million deaths globally, with a projected increase to 13.1 million by 2030. Despite innovations in cancer treatment, currently employed treatment modules remain useless due to detrimental effects, therefore efficient cancer therapy has to be made available [2]. Chemotherapy is still one of the most effective cancer treatments available today. With increased application and understanding, the adverse outcomes & developed drug resistance of synthesized small molecular drugs have become increasingly concerning [3]. Combination therapy holds possibilities for improving cancer treatment efficacy and dealing with numerous genetic changes in various cancer cells [4].

APIGENIN AND ITS STRUCTURE

Flavonoids are a type of polyphenolic substance that is abundant in vegetables, fruits, cereals, tea, seeds, and nuts. Many studies have found that flavonoids protect against cancers, cardiovascular diseases [CVDs], and age-related or senile disorders [1]. Among over 6000 different flavonoids, quercetin, kaempferol, myricetin, apigenin, and luteolin are the five most ubiquitous plant flavonoids [5, 6]. Based on the backbone's chemical structure, apigenin, also known as 4',5,7-trihydroxy-flavone, is a flavone (**Fig. 1**), one of the subclasses of flavonoids. Apigenin has attracted the interest of researchers due to its comparatively low levels of toxicity and numerous positive bioactivities [5]. Apigenin has long been used as a traditional medicine due to its natural antioxidant and anti-inflammatory properties, capacity to decrease blood pressure, and antiviral and antibacterial properties [1]. Apigenin's antioxidant effects are widely known due to which, it can also be used for therapeutic purposes in disorders such as inflammation, autoimmune disease, neurological disease, and even multiple types of cancer. Principally, glycosylated Apigenin is present in significant amount

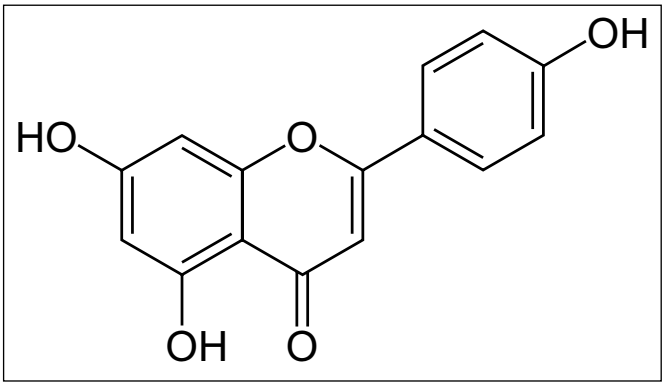

Fig. (1): Structure of apigenin [4',5,7-trihydroxy-flavone].

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in fruits (oranges), vegetables (onions, celery, parsley), herbs (thyme, chamomile, basil, oregano), and plant-based beverages (beer, tea and wine) [7]. Flavonoids like quercetin, apigenin and luteolin were discovered to be the most abundant phenolic ingredients in Rhus coriaria fruits [2]. Since they frequently feature 1 or >1 hydroxyl substituents in their structure, they can also be categorized as polyphenols in terms of their chemical makeup. They are diphenyl-propanoids with a 15 carbon atoms flavane nucleus [C6-C3-C6]. A genetic byproduct of the phenylpropanoid pathway, apigenin can be produced from either phenylalanine or tyrosine [7].

Mechanism of Action of Apigenin (Api)

Apigenin's potential therapeutic effects were investigated through a variety of pathways, including apoptosis, cell cycle arrest, antioxidant and anti-inflammatory activity [7]. Apigenin also has anti-mutagenic, anti-carcinogenic, anti-proliferative, and anti-progression actions [5]. According to Ghițu A *et al.*'s thorough evaluation of Api against the A375 human melanoma cancer cell line, the flavone exhibits an anticancer mechanism under the specified experimental conditions that includes inhibition of angiogenesis, induction of apoptosis, modification of the bioenergetic profile, and inhibition of proliferation [8]. Fig. **(2)** provides a concise synopsis of the process by which Apigenin causes cell cycle arrest, apoptosis, anti-inflammatory, and anti-oxidative actions.

a) Induction of Cell Cycle Arrest

By modifying the expression of certain CDKs and some other genes, apigenin causes cell cycle arrest at various proliferative stages, such as G1/S-phase or G2/M phase [7].

b) Induction of Apoptosis

It is understood that by changing the potential of mitochondrial membrane, apigenin is capable of regulating pathways of apoptosis. Apigenin induces cytochrome C release into the cytoplasm, forms APFA, and activates caspase-3, thus initiating apoptotic cell death. Apigenin affects the expression of the proteins STAT-3, Bax, Bcl-2, and Akt to stimulate apoptotic cell death, specifically in cancerous cells [7]. Another study suggests that, in cell lines of squamous cell carcinoma of the skin, Apigenin causes the activation of the Mitogen-activated Protein Kinase [MAPK] signaling pathway, along with down-regulation of Srx expression, both of which leads to induction of apoptosis. Moreover, a different study's findings indicated that apigenin was also involved in potentiating 5-fluorouracil-induced apoptosis of HCT116 cells besides increased disruption of cell cycle. Furthermore, Ca2+ concentrations inside the cell and mitochondria were also increased by apigenin along with the increased potential of mitochondrial membrane and release of hazardous reactive oxygen species [ROS], when co-treated with 5-fluorouracil [2].

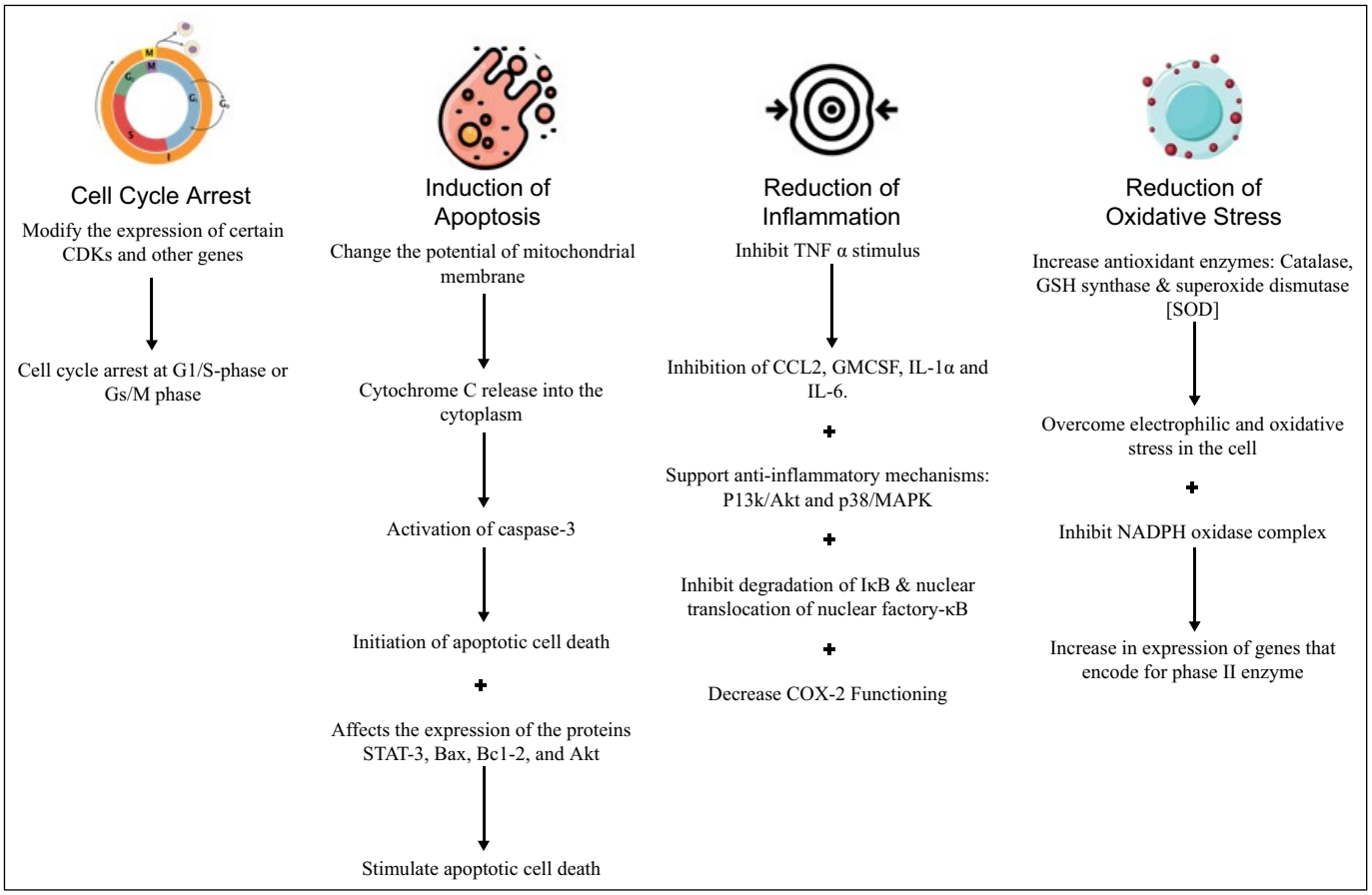

Fig. (2): Summarized mechanism of apigenin involved in induction of cell cycle arrest, apoptosis, anti-inflammatory and anti-oxidative effects.

c) Anti-Inflammatory Actions

Due to the TNFα stimulus, there is a massive increase of CCL2 [a chemotactic protein], growth factors such as granulocyte-macrophage colony-stimulating factor [GMCSF], and interleukins [IL-1α as well as IL-6], all prevented by the apigenin therapy [2]. Various anti-inflammatory mechanisms are supported by apigenin, including PI3K/Akt and p38/MAPK, in addition to inhibition of degradation of IκB and also nuclear translocation of nuclear factor-κβ, and decrease in COX-2 functioning. It is well known that in lipopolysaccharide [LPS]-activated mice macrophages, apigenin significantly reduced levels of IL-6, which generally acts as an anti-inflammatory myokine as well as a pro-inflammatory cytokine [7].

d) Anti-oxidative Actions

Apigenin increases antioxidant enzymes such as Catalase, GSH synthase & superoxide dismutase [SOD] to overcome electrophilic and oxidative stress in the cell. Apigenin also increases the expression of specific genes that encode for phase II enzyme by inhibiting the NADPH oxidase complex and their downstream target genes responsible for inflammation as well as by promoting the nuclear translocation of Nrf-2 [7].

According to research, the interaction of apigenin with signaling molecules occurs in three main mitogen-activated protein kinase [MAPK] pathways to cause the suppression of metastasis and angiogenesis: extracellular-signal-regulated kinase [ERK], c-Jun N-terminal kinases [JNK], and p38 in human cell culture models. Apigenin also suppresses TNF-α [tumor necrosis factor], CD40 [cluster of differentiation 40] and IL-6 production by inhibiting phosphorylation of signal transducers, induced by interferon-gamma [IFN-γ], and transcription-1 [STAT1] activators in murine microglia [7].

Effects on Tumor Suppressor Gene

In a study, the usefulness of apigenin in treating primary effusion lymphoma [PEL] has been studied. Physiologically, apigenin is known to inhibit STAT3 and activate the protein p53, which is associated with upregulating catalase. According to research, in samples that received apigenin treatment, there has been a reported increase in p53 protein accumulation. Additionally, apigenin has been proven to phosphorylate p53 in a dose-dependent manner [2].

Mechanisms that Leads to Anti-Cancer Effects of Apigenin

Apigenin controls various molecular pathways such as angiogenesis, NF- κβ and regulation of genes that cause tumor suppression. Apigenin initiates the cell cycle, autophagy and apoptosis. Mechanism of cancer treatment is mainly based on modulating gene activity [2], and is briefed in Table **1**.

Table 1: Targeted genes and effects of apigenin.

No.	Target of Apigenin	Effect of Apigenin
1	Chemokines mediated by TNFα	Downregulation of release of chemokines mediated by TNFα and suppression of IL-6 and IL-1α
2	Mucin Gene	Regulation of synthesis along with the mucin gene expression in airway epithelial cells through regulation of the NF-κβ signaling pathway
3	Pro-apoptotic gene	Boosting of the cisplatin's cytotoxic effect by initiating p53 accumulation and pro-apoptotic gene expression regulated by p53 (Greater p53 accumulation will lead to higher detection of Bax)
4	Bcl xL and Bcl 2	Decreasing levels of Bcl xL and Bcl 2, in addition to increasing the dynamic form of the Bax protein An enhanced Bax/Bcl-2 ratio that leads to apoptosis following the apigenin treatment (revealed by PARP cleavage DNA fragmentation)
5	Cyclin A, cyclin B, and CDK-1	Inhibition of cyclin A, cyclin B, and CDK-1 expression, which contributes to G2-to-M transition in the cell cycle
6	HIF 1α and VEGF	Inhibition of HIF 1α and VEGF manifestation in the tumor tissues leads to inhibition of angiogenesis & prevention of the expression of VEGF mRNA induced by hypoxia
7	Cell cycle and DNA	Arrest of the cell cycle in G2/M phase, rupture of DNA, apoptosis and accumulation of p53, which together suppress the proliferation of cancer cells
8	PI3K/Akt/mTOR pathway	Induction of apoptosis and autophagy by suppression of the PI3K/Akt/mTOR pathway
9	Inhibitory κβ kinase-α [IKKα]	Binding with Inhibitory κβ kinase-α [IKKα], decreasing activity of IKKα kinase, and subduing activation of NF- κβ/p65 in cancer cells a lot more efficiently as compared to an IKK inhibitor
10	AKT, Cyclin D1 and ERK	Suppression of AKT and ERK activation Decrease in AKT, P70RSK, and S6 Phosphorylation whereas increasing ERK1/2 and P90RSK phosphorylation Decrease in p-Akt, p-Signal transducer & activator of transcription 3, p-epidermal growth factor receptor and Cyclin D1 expressions
11	p53 and STAT-3	Activation of p53 that induces catalase, an enzyme that removes reactive oxygen species [ROS], whereas Signal Transducer and Activator of Transcription 3 [STAT-3] is inhibited
12	STAT-3 target genes: MMP-2, MMP-9 and VEGF	Down-regulation of STAT-3 target genes MMP-2, MMP-9 and VEGF, involved in migration and invasion of cell

The mechanism of action of apigenin also significantly involves interactions with different signaling pathways [9], as discussed in Table **2**.

Table 2: Apigenin-induced modulations of various signaling pathways.

No.	Pathway	Modulations
1	TRAIL Pathway	Several investigations have clarified apigenin's function as a modulator of the TRAIL pathway [10, 11]. Apigenin and TRAIL together reduce the expression of BCL2 and enhance the expression of ERK1 and ERK2 in anaplastic thyroid cancer cells [12]. Apigenin altered the expression of NF- κβ, which is in charge of activating multiple anti-apoptotic proteins, in TRAIL-resistant cancerous cells like the A549 cell line. Nevertheless, if combined, TRAIL and apigenin led to a long-lasting buildup of p65, which prevented NF- κβ from having the ability to proliferate in A549 cells [13].

No.	Pathway	Modulations
2	PI3K/Akt/mTOR pathway	The PI3K/Akt/mTOR signaling pathway is essential for tumor development, metastasis, and invasion [14]. A research reports that the effect of apigenin on the PI3K/AKT/mTOR pathway is by regulation of expression of important proteins like PTEN, ERK, AkT, and others [15]. Since AkT directly targets GSK-3, apigenin stops PI3K from phosphorylating it [9]. Calcium/calmodulin protein kinase is activated by apigenin, which then stimulates AMPK, which phosphorylates TSC2 and suppresses mTOR action [9, 16].
3	JAK/STAT signaling	A variety of cellular events, which include cellular responses to inflammation, cellular migration, apoptotic cell death, cell survival, and also the development of cells, are regulated by the evolutionarily conserved JAK/STAT signaling cascade. Different malignancies have abnormal JAK-STAT signaling as a defining feature [9, 17]. Apigenin controls this cellular pathway through the suppression of JAK/SRC phosphorylation as part of its method of action [9, 18]. Activation of STAT3 and nuclear translocation of the STAT dimmers, as well as the activation of important genes, are all prevented through the inhibition of phosphorylation of kinases. There is evidence that STAT3 controls the expression of membrane metalloproteases [MMPs], VEGF and TWIST1 which are responsible for angiogenesis, tumor invasion, and migration. Apigenin prevents activation of the MMPs, TWIST1, and VEGF through inhibition of the phosphorylation of STAT-3 [9, 19].
4	Wnt/βCatenin signaling	The development, differentiation, cellular migration, organogenesis, neural patterning, and homeostasis of tissues, all depend on Wnt/-catenin signaling [9, 20]. Wnt/-catenin expression is modulated by apigenin. According to data, apigenin concentration directly affects the expression of Wnt/-catenin. Additionally, apigenin has been shown to alter the expression of Wnt/-catenin signaling's downstream effectors, including cyclin D1, AXIN2, and c-MYC. Further research has shown that apigenin primarily targets the downstream molecules of Wnt/-catenin signaling and has no outcome on LRP5 and Dishevelled [Dvl] [9, 21].
5	MAPK signaling	The MAPK enzyme family is categorically classified into three major classes: ERK/MAPK, c-JUN/SAPK, and p38 kinase [9]. These enzymes are crucial for maintaining tissue homeostasis and cellular development. There are various members of the family of ERK protein that are only involved in the regulation of the MAPK-ERK pathway. Thus, the appropriate operation of both upstream and downstream targets of the MAPK/ERK pathway is disturbed by the overexpression of any protein of the ERK family [8, 22]. By the inhibition of the MAPK/ERK signaling pathway's expression, apigenin can cause apoptosis [9].

In vitro Trials of Apigenin

In a clinical trial, apigenin suppresses the PI3K/Akt/mTOR pathway in hepatocellular carcinoma cells, inhibiting cell proliferation and inducing death. This suggests that apigenin may be a viable chemotherapeutic approach for the treatment of liver cancer [23]. Apigenin exhibits promise as an anticancer drug by causing cell growth arrest and apoptosis in a variety of tumor types, modifying a number of signaling pathways, and inhibiting invasion, according to a different clinical trial conducted by Imran M, *et al.* The administration of apigenin results in a decrease in the expressions of Akt, PI3K, NF-κB p105/p50, and p-Akt phosphorylation [24]. Through suppression of the STAT1/COX-2/iNOS signaling cascade, apigenin suppresses inflammation and induces apoptosis, suggesting potential as a therapy for multiple myeloma in another in vitro trial [25]. When human dendritic cells (DCs) were stimulated with high concentrations of API, their metabolic activity was significantly reduced during LPS activation. TNF alpha secretion was decreased by almost 60% whereas IL-6 and IL-10 secretion was virtually entirely stopped [8]. Apigenin successfully stopped the growth of cervical cancer cells and tumors in xenograft mice in a study conducted by Chen Y, *et al.* Additionally, apigenin induced G2/M-phase cell cycle arrest, reduced EMT to inhibit HeLa and C33A cancer cell migration and down-regulated both FAK signaling (FAK, paxillin, and integrin β1) and PI3K/AKT signaling (PI3K, AKT, and mTOR). Apigenin also inactivated or activated several signaling targets, including Bcl-2, Bax, p21cip1, CDK1, CDC25c, cyclin B1, fibronectin, N-cadherin, vimentin, laminin, and E-cadherin. Thus, it was determined that apigenin might function as a chemotherapeutic agent in the management of cervical cancer [26]. Increased phosphorylation of ERK1/2 and JNK1/2 was brought on by apigenin administration; this prolonged activation reduced ELK-1 phosphorylation and c-FOS expression, which in turn inhibited cell survival. When compared to apigenin therapy, the use of kinase inhibitors caused ERK1/2 phosphorylation, albeit at differing levels, and did not lead to cell cycle arrest. Apigenin significantly reduced the expression of cyclin D1 despite the activation of the MAPK pathway. This reduction coincided with the loss of Rb phosphorylation and the prevention of cell cycle progression. The phosphorylation and expression of p38 and PI3K-Akt, two proteins that regulate cyclin D1 protein, also decreased in tandem with the decreased expression of cyclin D1 protein. Remarkably, apigenin significantly decreased the levels of cyclin D1, D2, and E as well as the regulatory partners CDK 2, 4, and 6, which are involved in the G0-G1 phase of the cell cycle [27].

Pharmacokinetics: Absorption, Distribution, Metabolism and Excretion

Due to considerable inter-individual variability as well as the various biological pathways of its effects on human health, it is generally exceedingly challenging to obtain general or unambiguous information regarding its bioavailability and bioactivity [7]. Because apigenin is poorly soluble with low bioavailability, the colon bacteria may come into contact and break Apigenin down into more readily absorbed forms [5]. It's recommended to administer Apigenin through the diet. A bioactive substance like apigenin goes through several metabolic processes after consumption to exercise its therapeutic effects, and its pharmacokinetic behavior determines

how it is distributed throughout the body and how active it is in the body's tissues. The metabolism of apigenin is affected in different ways due to the effect of O-glycosylation or C-glycosylation and thus its antioxidant potential and biological advantages are affected. The unaffected absorption of vitexin-2-O-xyloside [VOX], an apigenin-8-C-glucoside, has been documented in a rat model about the bioavailability of apigenin-C-glycosides. The monoglycoside obtained from hydrolysis, as well as apigenin-8-C-glycoside, the reduced and conjugated glucuronide, undergo enterohepatic recirculation. Apigenin is also capable of crossing the blood-brain barrier after being absorbed into the digestive tract and moving through the circulatory system to the brain, where it can use its affinity for the GABA receptor to affect the central nervous system. Due to the significant potential of food-drug interactions, the use of apigenin in patients receiving traditional pharmaceutical therapy should be cautiously considered [7]. An oral active medication cannot have a logP >5 (*i.e.* the medicine cannot be too lipophilic) by Lipinski's "Rule of Five" requirements. With a logP of 2.84, apigenin is classified as a lipophilic substance that can pass through the blood-brain barrier and be permeable to drug membranes while maintaining oral activity. There are currently no thorough in vivo investigations on people that examine the pharmacokinetic characteristics of pure apigenin administered orally [28], and a significant amount of trials have been conducted in rats.

a) Absorption

The small intestine may absorb between 5 and 10% of the total amount of polyphenols consumed, primarily as monomers and dimers [5, 29]. Before apigenin enters the systemic or hepatic circulation, it undergoes extensive metabolic and conjugative changes in the gastrointestinal tract [5]. In the duodenum and jejunum, apigenin gets transported through saturable passive and active transports mediated by carrier proteins, as well as by passive mechanisms of transport in the ileum and the colon [5, 30]. Because radioactivity first emerged in the blood after 24 hours of a single oral dosage of radioactive apigenin in rat research, it was determined that the compound has a relatively slow rate of absorption. On the other hand, the maximal plasma concentration of apigenin was attained in another study's rats 3.9 hours after the first oral administration of Chrysanthemum morifolium extract, which contains apigenin, leading to the contradictory conclusion that apigenin has a rapid absorption rate in rats [5].

b) Distribution

Apigenin disperses easily throughout the tissues. In a study, the mean value of the systemic clearance, after an IV dose of apigenin at 20 mg/kg, was 6.12 0.79 L/h/kg. In another study done on rats, after a single oral injection of radioactive apigenin, the elimination half-time was long, measuring 91.8 hours. The plasmatic clearance was 1.95 mL/h, and the distribution volume was 259 mL. The body excreted and urinated around half of the apigenin is ingested [5].

c) Metabolism

Apigenin may undergo substantial Phase I and Phase II metabolism after being ingested [5, 29]. Free apigenin can be absorbed systemically directly or can be metabolized downstream in phases I and II in the liver and small intestine to produce glucuronidated and sulfonated metabolites and hydroxylated metabolites like luteolin. These metabolites can go through four different routes: i) enteric recycling locally, ii) elimination (usually through the urine, less frequently through the feces), iii) direct systemic absorption, or iv) enterohepatic recycling through the bile [28]. In the liver of a rat, it was found that the apigenin metabolism involves enzymes of Phase I in the presence of factors such as Cyt-P450 [cytochrome P450 enzymes], nicotinamide adenine dinucleotide phosphate [NADPH], or Flavin-containing monooxygenase [FMO]. In Phase II, both enteric and enterohepatic cycling are involved. The conjugation reactions which are glucuronidation and sulfation, are vital Phase-II pathways of the metabolism of this flavonoid. According to reports, apigenin produces significant amounts of glucuronidated and sulfated conjugate metabolites in both rats and humans. Lutein is the primary hepatic metabolite of apigenin. In human Hep G2 [hepatic cell line], plus Caco-2 [intestinal cell line], apigenin-initiates UDP-glucuronosyltransferase [UGT1A1], a phase II detoxifying enzyme. Intestinal disposition possesses more significance than the hepatic disposition in apigenin's first-pass metabolism because glucuronidation processes also take place there [5]. Lutein and conjugates of sulfated and glucuronic acids are the main metabolic metabolites of apigenin during metabolism [31], Furthermore, there is proof that these metabolites are active since absorbed apigenin takes the form of luteolin, glucuronide, or sulfate conjugates in tissues and blood circulation [5].

d) Excretion

A good sign is the excretion of apigenin following oral consumption through feces since the ingested apigenin is accessible to be metabolized by the intestinal bacteria [5]. Apigenin has a sluggish metabolic and elimination phase, according to a study. Thus, this flavonoid may build up inside the body [32].

Doses, Sources and Routes of Administration of Apigenin

The apigenin dosages that were evaluated in rats were 13.5 and 60 mg/kg. Rat gastrointestinal physiology is difficult to compare to human physiology, but in an adult weighing 70 kg, this corresponds to 0.9 and 4.2 g of apigenin, respectively. When compared to the previously described dosage with dietary parsley, this would result in a roughly 50-240-fold decrease in bulk intake; yet, plasma concentrations should reach the bioactive range in humans (*i.e.* at least 5μmol/L) through simple extrapolation. Rats given the larger oral dosage during

measurements had a maximum plasma concentration of 1330 ng/ml. Apigenin has a molecular mass of 270g/mol, which is equivalent to 4.9µmol/L. The rat model and extrapolation from human data so imply that doses employed and approved in experimentation reach systemic levels into the range to generate biological effects, however, this is an approximation based upon limited evidence. In fact, it should be mentioned that mice have been exposed to far larger doses of apigenin—up to 300 mg/kg—without experiencing any overt toxicity or changes in body weight after 68 days. With a 4.2g dose that is greater and an apigenin density of around 1.5g/ml, the resulting product volume would be 2.8 ml. The biggest regularly used capsules have a capacity of 1.37 milliliters. Therefore, to administer this oral dosage in humans, 2.8ml of apigenin powder (representing the dose we predict should yield a 5µmol/L plasma concentration of apigenin) would require two big capsules of purified flavone. As shown above, rats have a T1/2 of 2.1-4.2 hours and humans have a persistence of 6-9 hours after oral administration of parsley. Effective levels could be sustained for long enough to have an impact on the cell behaviors covered in this review with moderate dosages multiple times daily [28].

Since whole plant products like parsley cannot be consumed orally to produce therapeutically relevant apigenin concentrations, the oral dosage form required in a therapeutic context must be of an adequately purified form of apigenin itself. As a health supplement, parsley leaf is available in capsule form; two capsules, or 900 mg, is the usual suggested daily intake. Given that dried parsley has an apigenin level of 45 mg/g, this would translate into a daily dosage of about 40 mg of apigenin—less than 1% of what is required for a significant clinical impact on the behavior of cancer cells—while also potentially having other positive health effects. Therefore, crude plant products are inadequate in this situation [28].

While the major source of Apigenin is nature including fruits [oranges], vegetables [onions, celery, parsley], herbs [thyme, chamomile, basil, oregano], and plant-based beverages [beer, tea and wine] [7], In the form of capsules, powders, apigenin-loaded water-in-oil-in-water emulsions, and apigenin nanoparticles, apigenin is widely utilized in studies and clinical trials. These preparations can be derived synthetically (by using liquid antisolvent precipitation (LAP) technique, bead milling, or high-pressure homogenization) or from natural sources (mainly extracts), but insufficient data was discovered to determine which source is most frequently utilized. According to a study, it is unlikely that eating plant materials high in apigenin—like parsley, which has extremely high levels of the compound—will have biologically significant effects on cells *via* the vascular route at doses below heroic levels [28], making the synthetic and naturally sourced preparations more important in clinical and research uses.

However, purified apigenin (CAS# 520–36–5) is easily accessible for study and might be scaled up for human consumption by following the right procedures. There are numerous vendors worldwide that offer purity levels between 95% and 98%, derived from both synthetic and natural materials (citrus, chamomile). Apigenin obtained from natural sources is purified using chromatographic techniques and produced as a powder or as a recrystallized form. Feasibility would not be compromised by incorporation into capsules at a normal 97% purity level, and no additional excipients (binding agents, lubricants, fillers, colors) would be needed outside of the cellulose or gelatin capsule casing [28].

Although intravenous apigenin administration is not recommended for people due to a lack of clear justification, it is expected to facilitate biologically active concentrations. Apigenin (20 mg/kg) administered intravenously (IV) in rats resulted in a Cmax of 11.0 ± 1.7µg/ml, indicating a plasma concentration over 40µmol/L, adequate to elicit an effect in every cell system examined [28].

Apigenin and Combination Therapies

The efficacy of apigenin is significantly enhanced when used in combination with other chemotherapeutic agents, resulting in synergistic effects that improve therapeutic outcomes (**Table 3**).

Table 3: Synergistic effects of apigenin in combination with various chemotherapeutic agents.

No.	Drugs	Effects
1	Cisplatin	As opposed to cisplatin alone, it has been demonstrated that apigenin in combination with cisplatin significantly raises the levels of p53 protein. Additionally, it was hypothesized that apigenin increased the cytotoxic effects of cisplatin by causing the accumulation of p53 and the production of p53-regulated pro-apoptotic genes [2]. Cisplatin alone induced 3% vitality at low dose whereas apigenin therapy alone leads to 10–30% low cellular viability. The inhibitory effects of cisplatin were amplified by the combination of both [2, 33]. In cisplatin-treated cancerous cells, apigenin may drastically lower the amounts of the GLUT-1 transporter, the GLUT-1 mRNA, and the p-Akt proteins [2, 34].
2	5-fluorouracil	When combined with 5-fluorouracil, apigenin raised intracellular and intra-mitochondrial Ca2+ concentrations, ROS generation and mitochondrial membrane potential [2]. Apigenin was added to the therapy regimen, which significantly reduced the resistance. 5-fluorouracil and apigenin exposure greatly reduced the ability of cells to proliferate [2, 35]. Apigenin with 5-fluorouracil therapy dramatically slowed the in vivo growth of hepatic cancer xenograft tumors. Additionally, combined therapy for liver cancer cells resulted in an increase in ROS [2, 36]. Low doses of Api or Lut can significantly increase the antiproliferative effects of chemotherapy by pretreating pancreatic cancer cells [2, 37].
3	Bcl-2 inhibitor HA14-1	According to dose-response studies, the Bcl-2 inhibitor HA14-1 [HA] and apigenin together decreased the survival of cells in human malignant neuroblastoma [2].

No.	Drugs	Effects
4	Taxol (Paclitaxel)	Apigenin lowers cellular proliferation and increases the activation of enzyme mitogen-activated protein kinase and subsequent phosphorylation of p53 when combined with cisplatin or Taxol [2, 33]. Apigenin and paclitaxel both induced dose-dependent cellular toxicity, with apigenin causing a 29% decrease in cellular viability while paclitaxel caused a 24% decrease, according to a study. The synergistic actions of apigenin and paclitaxel are demonstrated by the combination index, which was 0.3918 0.0436 at the dose of 15 M apigenin while 4 nM paclitaxel [2]. Both apigenin and paclitaxel persuaded cytotoxicity dose-dependently [2, 38].
5	IFN-gamma	Through targeting CDK-1, apigenin boosted the anticancer effects of IFN-gamma in cancer cell lines [2, 39].
6	Doxorubicin	Combining doxorubicin and etoposide with polyphenols leads to a synergistic reduction in ATP, an increase in arrest of cell cycle at S or/ and G2/M phase, and an induction of apoptotic cell death [2, 40].
7	ABT-263	A novel approach to increase apigenin-induced anticancer activity in cancer cells by inhibiting the pro-survival regulators Mcl-1, AKT, and ERK [2, 41].
8	Chyrophanol	A pharmacological formulation including chyrophanol and apigenin has anticancer effects on cells of choriocarcinoma. The mixture inhibited cellular migration and, in a dose-dependent way, raised apoptosis rates [9].
9	Nano-formulations	According to a study, apigenin-loaded nanoparticles stop the growth of hepatocellular carcinoma in mice [9, 22]. Epidermoid squamous carcinoma cells A431 have demonstrated anti-cancer activity when exposed to apigenin-linked gold [Au] nanoparticles [ap-AuNPs] [9]. Experimental results from a different investigation on albumin nanoparticles, loaded with apigenin, present in bovine serum [BSA-Api-NPs] demonstrated that BSA-Api-NPs may be a novel delivery strategy against pulmonary injury with strong anti-oxidant properties [9, 42]. Apigenin-loaded Poly Lactic Co-Glycolide [PLGA] nanoparticles were effective in decreasing Ultraviolet B and Benzopyrene-mediated cutaneous Cancer in mice Model [9, 43].
10	Gemcitabine	In vitro, the combination therapy of down-regulating NF-κB activity and suppressing Akt activation led to increased growth inhibition and apoptosis in pancreatic cancer cell lines (MiaPaca-2, AsPC-1). By suppressing Akt in tumor tissue and downregulating NF-κB activity, the combination treatment improved tumor growth inhibition in vivo. Gemcitabine and apigenin together improved anti-tumor efficacy *via* inducing apoptosis and suppressing Akt and NF-κB activation [44].
11	Gefitinib	When paired with gefitinib, apigenin inhibits several oncogenic drivers, including EGFR, HIF-1α, and c-Myc. The combination also decreases the expression of the proteins Gluts and MCT1, and deactivates the signaling pathway of 5′ adenosine monophosphate-activated protein kinase (AMPK), which controls glucose uptake and preserves energy metabolism. This results in decreased energy utilization in EGFR L858R-T790M-mutated H1975 lung cancer cells. Apigenin + Gefitinib therapy causes dysregulated metabolism and apoptotic cell death in H1975 cells. As a result, the combination of apigenin and gefitinib treatment offers a compelling alternative for treating NSCLC patients who have developed an EGFR-TKI resistance [45].

Preventive and Therapeutic Roles of Apigenin in Cancer

4’,5,7-trihydroxy-flavone (Apigenin) plays a significant role in the inhibition and thus prevention and treatment of various types of cancer, as mentioned in Table **4**.

Table 4: Effects of apigenin on various types of cancer.

No.	Type of Cancer	Effect of Apigenin
1	Breast Cancer	In breast cancer cells, apigenin displayed strong growth-inhibitory properties. Furthermore, breast cancer cells that overexpressed neu/HER2 exhibited apoptotic induction. Human breast cancer cell growth was considerably reduced after treatment with the apigenin in a time and dose-dependent manner [2].
2	Prostate Cancer	In a time and dose-dependent manner, apigenin decreases the proliferation and prevents cellular migration as well as invasion [2]. Apoptosis was induced and cell viability significantly decreased as a result of apigenin treatment [46].
3	Cervical Cancer	Apigenin inhibits tumor cell infiltration into healthy tissue, which is how Apigenin has an anti-tumorigenic effect in vivo [2].
4	Ovarian Cancer	Cancer cells treated with apigenin had much more caspase-9 activity, and apigenin also stopped the cell division cycle at the G2/M phase [47]. Apigenin reduced the ability of SKOV3-derived SFCs to self-renew and was engaged in downregulating the expression of Gli1 through inhibition of CK2α [48].
5	Brain Cancer	Apigenin’s ability to suppress glioblastoma stem cells may be a result of the c-Met signaling pathway being downregulated [49]. Through the mitochondrial route, miR-423-5p downregulation enhances the predisposition of glioma stem cells to apigenin [50].
6	Colon Cancer	Apigenin prevents cisplatin-resistant cancer cells from activating the mTOR/PI3K/AKT signaling pathway [51]. Based on the in vitro and in vivo studies, apigenin prevents cancer cells from undergoing the epithelial-mesenchymal transition, migrating, and encroaching [52]. By blocking the phosphorylation of STAT-3, apigenin causes death-inducing proteins, the Mcl-1 and Bcl-xL, to be downregulated [53].
7	Esophageal Cancer	Apigenin substantially and dose-dependently decreased VEGF [vascular endothelial growth factor] expression, tumor-initiated angiogenesis, and cell proliferation while promoting apoptosis [2]. Membrane toxicity, such as increased membrane permeability and damage to the membrane’s ultrastructure, played significant roles in the apigenin-induced death of cancer cells [54].
8	Lung Cancer	By increasing the levels of death receptors 4 and 5, apigenin made cancerous cells of the lung, more vulnerable to TRAIL-induced apoptotic cell death [10]. The combination of apigenin and gefitinib effectively suppresses growth and malignant behavior in EGFR-resistant mutant non-small cell lung cancer cells by inhibiting multiple oncogenic drivers and regulating glucose metabolism [45].

No.	Type of Cancer	Effect of Apigenin
9	Oral Cancer	Apigenin's anticancer potential in an oral squamous cell carcinoma was identified and its potential as a chemo-preventive drug was suggested [2].
10	Lymphoma	Apigenin significantly reduces the expression of proliferative promoting pathways in mTOR/PI3K, which inhibits the survival of cancer cells [55]. The antioxidant enzyme catalase was produced when apigenin activated p53, which also prevented the STAT-3 [2].
11	Leukemia	By arresting the cell division cycle in leukemia, apigenin has potential as a chemo-preventive drug. Apigenin administration slowed the growth of tumors in xenografts, and U937 signaled the inactivation of Akt and the activation of JNK [2].
12	Pancreatic Cancer	Against cancer cells, apigenin had a stronger cytotoxic effect. Additionally, apigenin's increased cytotoxicity was associated with decreased mutant p53 expression and increased ROS [reactive oxygen species] within the cell [56]. Combination therapy with gemcitabine and apigenin enhances anti-tumor efficacy in pancreatic cancer by suppressing Akt and NF-kappa B activity and inducing apoptosis [44].
13	Bile duct Cancer	In cancer cells, apigenin exhibits an activation of apoptosis and proliferation inhibition [57].
14	Urinary Bladder Cancer	Apigenin stimulates apoptotic cell death and arrest of the cell division cycle in the G2/M phase, which also prevents cellular migration, invasion, and lowered growth of bladder cancerous cells in a dose and time-dependent manner [2]. By reducing uPAR expression, apigenin has anti-invasion actions [58]. Polymerization of actin filaments, which accentuates muscular contraction and the cellular migration, was blocked by apigenin [2].
15	Liver Cancer	Apigenin inhibited the mTOR/PI3K/Akt pathway, which led to autophagy and death [23]. Apigenin dose-dependently caused G1 arrest in a cancer cell [59]. Apigenin significantly increased doxorubicin sensitivity, elevated the expressions of miR-520b, and prevented ATG7-dependent autophagy [60].
16	Renal Cancer	The treatment with apigenin slowed tumor development and volume in vivo. Apoptosis, p53 accumulation, DNA damage, and the G2/M phase arrest of the cell division cycle are all caused by apigenin exposure [61].
17	Skin Cancer	In addition to causing the arrest of the cell division cycle in G2/M phase and the apoptotic cell death, apigenin hindered cell migration and invasion [62].
18	Myeloma	In multiple myeloma cells, apigenin therapy reduced the expressions of proteins that are anti-apoptotic, and survivin, which ultimately led to apoptosis [2].
19	Osteosarcoma	Through the activation of caspase and BAX, apigenin effectively reduced cell viability and promoted apoptosis. By deactivating Wnt/-catenin signaling, apigenin prevents osteosarcoma cells from proliferating into tumors [2].
20	Thyroid Cancer	Apigenin and TRAIL interact favorably due to the control of Bcl2 family proteins. Following the generation of severe DNA damage, apigenin increased the formation of ROS [2]. Drug resistance and decreased apoptosis are caused by mutations in the TRAIL signaling pathway in a variety of malignancies [9].

Possible Clinical Application and Future Perspectives

Apigenin supplements, which contain pure apigenin in pill form, can be used to raise plasma concentrations that are physiologically significant and may have an impact on cellular activity. Therapeutically speaking, the flavonoid structure presents difficulties for the body's absorption and subsequent metabolism of the bioactive molecule, despite the fact that Apigenin is easily metabolized by the body as a natural product. Apigenin and similar flavones have weak solubility, moderate permeability, and chemical instability as a result of their molecular makeup. This creates a barrier to a successful treatment plan. However, methods to alter and enhance apigenin's transport and access to the target region are also made easier by the chemical simplicity of apigenin and the availability of modifiable groups. By using prodrugs, glycosylation, absorption enhancers like cyclopentadecalactone, and nanotechnologies, it is possible to overcome the hindrance caused by fundamental physicochemical properties. There is indeed a chance to profit from this little molecule's special qualities. The flavone structure can be easily modified by the application of medicinal chemistry [28].

It will take targeted research that combines precise measurements of plasma apigenin levels with clinical outcomes during chemotherapy to determine whether the injection of apigenin will have clinically favorable results. Even though apigenin's oral and parenteral administration in rat models has yielded some useful pharmacokinetic data, very little direct pharmacokinetic assessment has been conducted in humans, and what has been done is limited to dosing with dietary natural products like parsley [28]. In additional future research, the role of apigenin in the therapy of cancer must be examined based on clinical trials, and any potential modes of action must be clarified.

CONCLUSION

As a naturally occurring Flavonoid, Apigenin has attracted the interest of researchers due to its low toxicity and numerous positive bioactivities. In addition to its well-known antioxidant effects, Apigenin can be used as a treatment for illnesses like autoimmune diseases, inflammation, neurological diseases, and even various types of cancer including Breast, colon, lung, liver, prostate, brain, oral, skin, cervical, ovarian, pancreatic and esophageal cancers, leukemia, lymphoma and melanomas. Its mechanism of action is mainly based on arrest of the cell division cycle, apoptotic cell death and

anti-oxidant and anti-inflammatory function. Apigenin possesses features that are anti-mutagenic, anti-carcinogenic, anti-proliferative, and anti-progression. Additionally, interactions with other signaling pathways (TRAIL, Wnt/β Catenin, JAK/STAT, PI3K/Akt/mTOR, and MAPK) are crucial to understanding how apigenin works. Given the significant inter-individual variation and the numerous molecular mechanisms by which Apigenin affects human health, it is generally exceedingly challenging to obtain general or unambiguous information regarding its bioavailability and bioactivity. In summary, based on the literature to date, Apigenin has been demonstrated to be useful in combinatorial therapies [especially with cisplatin, 5-fluorouracil, Taxol, Gemcitabine, Gafitinib and Doxorubicin] but still lacks strong scientific evidence.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

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REFERENCES

1. Ghanbari-Movahed M, Shafiee S, Burcher JT, Lagoa R, Farzaei MH, Bishayee A. Anticancer Potential of apigenin and isovitexin with focus on oncogenic metabolism in cancer stem cells. Metabolites 2023; 13(3): 404. DOI: https://doi.org/10.3390/metabo13030404
2. Rahmani AH, Alsahli MA, Almatroudi A, Almogbel MA, Khan AA, Anwar S, *et al.* The potential role of apigenin in cancer prevention and treatment. Molecules 2022; 27(18): 6051. DOI: https://doi.org/10.3390/molecules27186051
3. Yan X, Qi M, Li P, Zhan Y, Shao H. Apigenin in cancer therapy: anti-cancer effects and mechanisms of action. Cell Biosci 2017; 7: 50. DOI: https://doi.org/10.1186/s13578-017-0179-x
4. Nozhat Z, Heydarzadeh S, Memariani Z, Ahmadi A. Chemoprotective and chemosensitizing effects of apigenin on cancer therapy. Cancer Cell Int 2021; 21(1): 574. DOI: https://doi.org/10.1186/s12935-021-02282-3
5. Wang M, Firrman J, Liu L, Yam K. A review on flavonoid apigenin: dietary intake, adme, antimicrobial effects, and interactions with human gut microbiota. Biomed Res Int 2019; 2019: 7010467. DOI: https://doi.org/10.1155/2019/7010467
6. Tang D, Chen K, Huang L, Li J. Pharmacokinetic properties and drug interactions of apigenin, a natural flavone. Expert Opin Drug Metab Toxicol 2017; 13(3): 323-30. DOI: https://doi.org/10.1080/17425255.2017.1251903
7. Salehi B, Venditti A, Sharifi-Rad M, Kręgiel D, Sharifi-Rad J, Durazzo A, *et al.* The therapeutic potential of apigenin. Int J Mol Sci 2019; 20(6): 1305. DOI: https://doi.org/10.3390/ijms20061305
8. Ghițu A, Schwiebs A, Radeke HH, Avram S, Zupko I, Bor A, *et al.* A comprehensive assessment of apigenin as an antiproliferative, proapoptotic, antiangiogenic and immunomodulatory phytocompound. Nutrients 2019; 11(4): 858. DOI: https://doi.org/10.3390/nu11040858
9. Javed Z, Sadia H, Iqbal MJ, Shamas S, Malik K, Ahmed R, *et al.* Apigenin role as cell-signaling pathways modulator: implications in cancer prevention and treatment. Cancer Cell Int. 2021; 21(1): 189. DOI: https://doi.org/10.1186/s12935-021-01888-x
10. Chen M, Wang X, Zha D, Cai F, Zhang W, He Y, *et al.* Apigenin potentiates TRAIL therapy of non-small cell lung cancer via upregulating DR4/DR5 expression in a p53-dependent manner. Sci Rep 2016; 6: 35468. DOI: https://doi.org/10.1038/srep35468
11. Kim EY, Yu JS, Yang M, Kim AK. Sub-toxic dose of apigenin sensitizes HepG2 cells to TRAIL through ERK-dependent up-regulation of TRAIL receptor DR5. Mol Cells 2013; 35(1): 32-40. DOI: https://doi.org/10.1007/s10059-013-2175-2
12. Kim SH, Kang JG, Kim CS, Ilm S-H, Choi MG, Y HJ, *et al.* Suppression of AKT potentiates synergistic cytotoxicity of apigenin with TRAIL in anaplastic thyroid carcinoma cells. Anticancer Res 2015; 35(12): 6529-6537.
13. Seo HS, Sikder MA, Lee HJ, Ryu J, Lee CJ. Apigenin inhibits tumor necrosis factor-α-induced production and gene expression of mucin through regulating nuclear factor-Kappa b signaling pathway in airway epithelial cells. Biomol Ther (Seoul) 2014; 22(6): 525-531. DOI: https://doi.org/10.4062/biomolther.2014.094
14. Tewari D, Patni P, Bishayee A, Sah AN, Bishayee A. Natural products targeting the PI3K-Akt-mTOR signaling pathway in cancer: A novel therapeutic strategy. Semin Cancer Biol 2022; 80: 1-17. DOI: https://doi.org/10.1016/j.semcancer.2019.12.008
15. Liu MM, Ma RH, Ni ZJ, Thakur K, Cespedes-Acuña CL, Jiang L, *et al.* Apigenin 7-O-glucoside promotes cell apoptosis through the PTEN/PI3K/AKT pathway and inhibits cell migration in cervical cancer HeLa cells. Food Chem Toxicol 2020; 146: 111843. DOI: https://doi.org/10.1016/j.fct.2020.111843
16. Kim I, He YY. Targeting the AMP-activated protein kinase for cancer prevention and therapy. Front Oncol 2013; 3: 175. DOI: https://doi.org/10.3389/fonc.2013.00175
17. Tabassum S, Abbasi R, Ahmad N, Farooqi AA. Targeting of JAK-STAT signaling in breast cancer: therapeutic strategies to overcome drug resistance. Adv Exp Med Biol 2019; 1152: 271-281. DOI: https://doi.org/10.1007/978-3-030-20301-6_14
18. Bose S, Banerjee S, Mondal A, Chakraborty U, Pumarol J, Croley CR, *et al.* Targeting the JAK/STAT signaling pathway using phytocompounds for cancer prevention and therapy. Cells 2020; 9(6): 1451. DOI: https://doi.org/10.3390/cells9061451
19. Cao HH, Chu JH, Kwan HY, Su T, Yu H, Cheng C-Y, *et al.* Inhibition of the STAT3 signaling pathway contributes to apigenin-mediated anti-metastatic effect in melanoma. Sci Rep 2016; 6: 21731. DOI: https://doi.org/10.1038/srep21731
20. Javed Z, Khan K, Sadia H, Raza S, Salehi B, Sharifi-Rad J, *et al.* LncRNA & Wnt signaling in colorectal cancer. Cancer Cell Int 2020; 20: 326. DOI: https://doi.org/10.1186/s12935-020-01412-7
21. Lin CM, Chen HH, Lin CA, Wu HC, Sheu JJ, Chen HJ. Apigenin-induced lysosomal degradation of β-catenin in Wnt/β-catenin signaling. Sci Rep 2017; 7(1): 372. DOI: https://doi.org/10.1038/s41598-017-00409-z
22. Mahmoudi S, Ghorbani M, Sabzichi M, Ramezani F, Hamishehkar H, Samadi N. Targeted hyaluronic acid-based lipid nanoparticle for apigenin delivery to induce Nrf2-dependent apoptosis in lung cancer cells. Int J Drug Deliv Technol 2019; 49: 268-76. DOI: https://doi.org/10.1016/j.jddst.2018.11.013
23. 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.
DOI: https://doi.org/10.1016/j.biopha.2018.04.072

24. Imran M, Gondal T, Atif M, Shahbaz M, Qaisarani T, Mughal M, *et al.* Apigenin as an anticancer agent. Phytother Res 2020; 34(8)-1812-28.
DOI: https://doi.org/10.1002/ptr.6647

25. Adham A, Abdelfatah S, Naqishbandi A, Mahmoud N, Efferth T. Cytotoxicity of apigenin toward multiple myeloma cell lines and suppression of iNOS and COX-2 expression in STAT1-transfected HEK293 cells. Phytomedicine 2020; 80: 153371.
DOI: https://doi.org/10.1016/j.phymed.2020.153371

26. Chen Y, Wu J, Yang S, Yang C, Chen T, Hsiao Y. Anticancer effects and molecular mechanisms of apigenin in cervical cancer cells. Cancers 2022; 14(7): 1824.
DOI: https://doi.org/10.3390/cancers14071824

27. Shukla S, Gupta S. Apigenin-induced cell cycle arrest is mediated by modulation of MAPK, PI3K-Akt, and loss of cyclin D1 associated retinoblastoma dephosphorylation in human prostate cancer cells. Cell Cycle 2007; 6: 1102-14.
DOI: https://doi.org/10.4161/cc.6.9.4146

28. DeRango-Adem EF, Blay J. Does oral apigenin have real potential for a therapeutic effect in the context of human gastrointestinal and other cancers? Front Pharmacol 2021; 12: 681477.
DOI: https://doi.org/10.3389/fphar.2021.681477

29. Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuño MI. Benefits of polyphenols on gut microbiota and implications in human health. J Nutr Biochem 2013; 24(8): 1415-22.
DOI: https://doi.org/10.1016/j.jnutbio.2013.05.001

30. Zhang J, Liu D, Huang Y, Gao Y, Qian S. Biopharmaceutics classification and intestinal absorption study of apigenin. Int J Pharm 2012; 436(1-2): 311-7.
DOI: https://doi.org/10.1016/j.ijpharm.2012.07.002

31. Chen P, Chen F, Guo Z, Lei J, Zhou B. Recent advancement in bioeffect, metabolism, stability, and delivery systems of apigenin, a natural flavonoid compound: Challenges and perspectives. Front Nutr 2023; 10: 1221227.
DOI: https://doi.org/10.3389/fnut.2023.1221227

32. Gradolatto A, Basly JP, Berges R, Teyssier C, Chagnon M-C, Siess M-H, *et al.* Pharmacokinetics and metabolism of apigenin in female and male rats after a single oral administration. Drug Metab Dispos 2005; 33(1): 49-54.
DOI: https://doi.org/10.1124/dmd.104.000893

33. Suh YA, Jo SY, Lee HY, Lee C. Inhibition of IL-6/STAT3 axis and targeting Axl and Tyro3 receptor tyrosine kinases by apigenin circumvent taxol resistance in ovarian cancer cells. Int J Oncol 2015; 46(3): 1405-11.
DOI: https://doi.org/10.3892/ijo.2014.2808

34. Xu YY, Wu TT, Zhou SH, Bao Y-Y, Wang Q-Y, Fan J, *et al.* Apigenin suppresses GLUT-1 and p-AKT expression to enhance the chemosensitivity to cisplatin of laryngeal carcinoma Hep-2 cells: An in vitro study. Int J Clin Exp Pathol 2014; 7(7): 3938-47.

35. Choi EJ, Kim GH. 5-Fluorouracil combined with apigenin enhances anticancer activity through induction of apoptosis in human breast cancer MDA-MB-453 cells. Oncol Rep 2009; 22(6): 1533-7.
DOI: https://doi.org/10.3892/or_00000598

36. Singh JP, Selvendiran K, Banu SM, Padmavathi R, Sakthisekaran D. Protective role of Apigenin on the status of lipid peroxidation and antioxidant defense against hepatocarcinogenesis in Wistar albino rats. Phytomedicine 2004; 11(4): 309-14.
DOI: https://doi.org/10.1078/0944711041495254

37. Johnson JL, Gonzalez de Mejia E. Interactions between dietary flavonoids apigenin or luteolin and chemotherapeutic drugs to potentiate anti-proliferative effect on human pancreatic cancer cells, in vitro. Food Chem Toxicol 2013; 60: 83-91.
DOI: https://doi.org/10.1016/j.fct.2013.07.036

38. Xu Y, Xin Y, Diao Y, Lu C, Fu J, Luo L, *et al.* Synergistic effects of apigenin and paclitaxel on apoptosis of cancer cells. PLoS One 2011; 6(12): e29169.
DOI: https://doi.org/10.1371/journal.pone.0029169

39. Liu R, Ji P, Liu B, Qiao H, Wang X, Likun Zhou *et al.* Apigenin enhances the cisplatin cytotoxic effect through p53-modulated apoptosis. Oncol Lett 2017; 13(2): 1024-30.
DOI: https://doi.org/10.3892/ol.2016.5495

40. Mahbub AA, Le Maitre CL, Haywood-Small SL, Cross NA, Jordan-Mahy N. Polyphenols act synergistically with doxorubicin and etoposide in leukaemia cell lines. Cell Death Discov 2015; 1: 15043.
DOI: https://doi.org/10.1038/cddiscovery.2015.43

41. Shao H, Jing K, Mahmoud E, Huang H, Fang X, Yu C. Apigenin sensitizes colon cancer cells to antitumor activity of ABT-263. Mol Cancer Ther 2013; 12(12): 2640-50.
DOI: https://doi.org/10.1158/1535-7163.MCT-13-0066

42. Pápay ZE, Kósa A, Böddi B, Merchant Z, Saleem IY, Zariwala MG, *et al.* Study on the pulmonary delivery system of apigenin-loaded albumin nanocarriers with antioxidant activity. J Aerosol Med Pulm Drug Deliv 2017; 30(4): 274-88.
DOI: https://doi.org/10.1089/jamp.2016.1316

43. Das S, Das J, Samadder A, Paul A, Khuda-Bukhsh AR. Strategic formulation of apigenin-loaded PLGA nanoparticles for intracellular trafficking, DNA targeting and improved therapeutic effects in skin melanoma in vitro. Toxicol Lett 2013; 223(2): 124-38.
DOI: https://doi.org/10.1016/j.toxlet.2013.09.012

44. Lee SH, Ryu JK, Lee KY, Woo SM,Park JK, Yoo JW, *et al.* Enhanced anti-tumor effect of combination therapy with gemcitabine and apigenin in pancreatic cancer. Cancer Lett 2008; 259(1): 39-49.
DOI: https://doi.org/10.1016/j.canlet.2007.09.015

45. Chen Z, Tian D, Liao X, Zhang Y, Xiao J, Chen W, *et al.* Apigenin combined with gefitinib blocks autophagy flux and induces apoptotic cell death through inhibition of HIF-1α, c-Myc, p-EGFR, and glucose metabolism in EGFR L858R+T790M-mutated H1975 cells. Front Pharmacol 2019; 10: 260.
DOI: https://doi.org/10.3389/fphar.2019.00260

46. Ayyildiz A, Koc H, Turkekul K, Erdogan S. Co-administration of apigenin with doxorubicin enhances anti-migration and antiproliferative effects via PI3K/PTEN/AKT pathway in prostate cancer cells. Exp Oncol 2021; 43(2): 125-34.
DOI: https://doi.org/10.32471/exp-oncology.2312-8852.vol-43-no-2.16096

47. Ittiudomrak T, Puthong S, Roytrakul S, Chanchao C. α-Mangostin and apigenin induced cell cycle arrest and programmed cell death in SKOV-3 ovarian cancer cells. Toxicol Res 2019; 35(2): 167-79.
DOI: https://doi.org/10.5487/TR.2019.35.2.167

48. Tang AQ, Cao XC, Tian L, He L, Liu F. Apigenin inhibits the self-renewal capacity of human ovarian cancer SKOV3 derived sphere-forming cells. Mol Med Rep 2015; 11(3): 2221-6.
DOI: https://doi.org/10.3892/mmr.2014.2974

49. Kim B, Jung N, Lee S, Sohng JK, Jung HJ. Apigenin inhibits cancer stem cell-like phenotypes in human glioblastoma cells via suppression of c-Met signaling. Phytother Res 2016; 30(11): 1833-40.
DOI: https://doi.org/10.1002/ptr.5689

50. Wan Y, Fei X, Wang Z, Jiang D, Chen H, Wang M, *et al.* miR-423-5p knockdown enhances the sensitivity of glioma stem cells to apigenin through the mitochondrial pathway. Tumour Biol 2017; 39(4): 1010428317695526.
DOI: https://doi.org/10.1177/1010428317695526

51. Chen X, Xu H, Yu X, Wang X, Zhu X, Xu X. Apigenin inhibits in vitro and in vivo tumorigenesis in cisplatin-resistant colon cancer cells by inducing autophagy, programmed cell death and targeting m-TOR/PI3K/Akt signalling pathway. J BUON 2019; 24(2): 488-93.

52. Tong J, Shen Y, Zhang Z, Hu Y, Zhang X, Han L. Apigenin inhibits epithelial-mesenchymal transition of human colon cancer cells through NF-κB/Snail signaling pathway. Biosci Rep 2019; 39(5): BSR20190452.
DOI: https://doi.org/10.1042/BSR20190452

53. Maeda Y, Takahashi H, Nakai N, Yanagita T, Ando N, Okubo T, *et al.* Apigenin induces apoptosis by suppressing Bcl-xl and Mcl-1 simultaneously via signal transducer and activator of transcription 3 signaling in colon cancer. Int J Oncol 2018; 52(5): 1661-73.
DOI: https://doi.org/10.3892/ijo.2018.4308

54. Zhu H, Jin H, Pi J, Bai H, Yang F, Wu C, *et al.* Apigenin induced apoptosis in esophageal carcinoma cells by destruction membrane structures. Scanning 2016; 38(4): 322-328.
DOI: https://doi.org/10.1002/sca.21273

55. Huang S, Yu M, Shi N, Zhou Y, Li F, Li X, *et al.* Apigenin and abivertinib, a novel BTK inhibitor synergize to inhibit diffuse large B-cell lymphoma in vivo and vitro. J Cancer 2020; 11(8): 2123-32.
DOI: https://doi.org/10.7150/jca.34981

56. Gilardini Montani MS, Cecere N, Granato M, Romeo MA, Falcinelli L, Ciciarelli U, *et al.* Mutant p53, Stabilized by its interplay with HSP90, activates a positive feed-back loop between NRF2 and p62 that induces chemo-resistance to apigenin in pancreatic cancer cells. Cancers (Basel) 2019; 11(5): 703.
DOI: https://doi.org/10.3390/cancers11050703

57. Subhasitanont P, Chokchaichamnankit D, Chiablaem K, Keeratichamroen S, Ngiwsara L, Paricharttanakul NM, *et al.* Apigenin inhibits growth and induces apoptosis in human cholangiocarcinoma cells. Oncol Lett. 2017; 14(4): 4361-71.
DOI: https://doi.org/10.3892/ol.2017.6705

58. Xia Y, Yuan M, Li S, Thuan UT, Nguyen TT, Kang TW, *et al.* Apigenin suppresses the IL-1β-induced expression of the urokinase-type plasminogen activator receptor by inhibiting mapk-mediated AP-1 and NF-κB signaling in human bladder cancer T24 cells. J Agric Food Chem 2018; 66(29): 7663-73.
DOI: https://doi.org/10.1021/acs.jafc.8b02351

59. Li Y, Cheng X, Chen C, Wu H, Zhao H, Liu W, *et al.* Apigenin, a flavonoid constituent derived from P. villosa, inhibits hepatocellular carcinoma cell growth by CyclinD1/CDK4 regulation via p38 MAPK-p21 signaling. Pathol Res Pract 2020; 216(1): 152701.
DOI: https://doi.org/10.1016/j.prp.2019.152701

60. Gao AM, Zhang XY, Hu JN, Ke ZP. Apigenin sensitizes hepatocellular carcinoma cells to doxorubic through regulating miR-520b/ATG7 axis. Chem Biol Interact 2018; 280: 45-50.
DOI: https://doi.org/10.1016/j.cbi.2017.11.020

61. Meng S, Zhu Y, Li JF, Wang X, Liang Z, Li S-Q, *et al.* Apigenin inhibits renal cell carcinoma cell proliferation. Oncotarget 2017; 8(12): 19834-42.
DOI: https://doi.org/10.18632/oncotarget.15771

62. Zhao G, Han X, Cheng W, Ni J, Zhang Y, Lin J *et al.* Apigenin inhibits proliferation and invasion, and induces apoptosis and cell cycle arrest in human melanoma cells. Oncol Rep 2017; 37(4): 2277-85.
DOI: https://doi.org/10.3892/or.2017.5450