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Biological properties and therapeutic effects of apigenin and its evaluation on several types of cancer

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Abstract

Apigenin is a member of the flavonoid family that has been used in medicine for a long time. Apigenin is one of the compounds that has been used for a long time to treat various disorders and diseases. Apigenin is chemically known as 4',5,7, trihydroxyflavone and belongs to the family of flavones. Apigenin has many pharmacological activities such as anti-inflammatory, anti-viral, anti-bacterial, etc. Various studies have shown that apigenin plays an important role in suppressing diseases such as Parkinson's, Alzheimer's, inflammatory diseases, and different types of cancers. In the present study, various therapeutic properties, biological effects, and the effect of apigenin on different cancers are discussed. Different studies have been conducted on the anti-cancer effect of apigenin. It has been proven that apigenin has inhibitory effects on various cancers including lung, stomach, neuroblastoma, thyroid, liver, skin, and prostate cancer through different signaling pathways. In general, it can be mentioned that the anti-cancer properties of apigenin are due to its effects in various signaling pathways such as angiogenesis, tumor suppressor genes, apoptosis, cell cycle and nuclear factor kappa B (NF-κB), Janus kinase/signal transducer and activator of transcription (JAK/STAT3), phosphoinositide 3-kinase /protein kinase B /mammalian target of rapamycin (PI3K/AKT/mTOR), mitogen-activated protein kinase/ estrogen receptor 2 (MAPK/ER2), Wnt/B-catenin pathways.

Keywords: Inflammation, Apigenin, Cancer, Cell cycle, Apoptosis

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Introduction

Polyphenol compounds are described by phenolic structures. These biological molecules are used in the treatment of various diseases. They are a large family of natural compounds that have many biological, pharmacological, and physiological advantages for human health. They are known as protectors against oxidative stress, ultraviolet and other pathogens. Polyphenols can play their role in cell protection against oxidative stress and inflammation by activation of the transcription factor nuclear factor erythroid-2 related factor (Nrf2) (1-5). In addition, these compounds can modulate some of the most important cellular processes such as proliferation, cell growth, differentiation, etc. (6). Various studies have shown that polyphenols are effective in radiation protection. The main mechanisms are neutralizing free radicals caused by radiation, reducing inflammatory responses, repairing hematopoietic cells, and repairing deoxyribonucleic acid (DNA) (7). So far, more than 8000 polyphenolic compounds have been known in different plants. Polyphenols have different chemical structures, the most prominent of which are flavonoids, stilbenes, and phenolic acids. One of the most important polyphenolic compounds is flavonoids (1, 3, 8, 9). The first studies on flavonoid compounds were done in 1936. Flavonoids are low molecular weight compounds. Although flavonoids are not made by humans and animals, they are considered essential compounds in the human diet. The compounds are abundant in our diet, including nuts, fruits, flowers, seeds, stem, wine, and tea (10, 11). Flavonoids are divided into different classes according to their molecular structures such as flavanones, flavones, flavanols, isoflavones, flavanonols, neoflavanes, flavanes, and flavonols (10, 12). Flavonoids are almost 5000 compounds that chemically have a prevalent phenylchromanone structure (C6-C3-C6). The general structure of flavonoid is based on two benzene rings (A and B ring) that are connected by a heterocyclic pyran (C ring) that contains oxygen. They have indicated various biological effects such as anti-inflammatory, antiviral, anti-mutagenic, and free radical scavenging (11, 13, 14). One of the flavonoids that have attracted a lot of attention is apigenin (15). Apigenin is one of the sub-classes of flavones, the unique properties of flavones are non-toxic and non-mutagenic (Figure1). Apigenin is mainly found in fruits (oranges), vegetables (onion, parsley, celery), herbs (basil, oregano, thyme, chamomile), and in some seasonings (13, 16, 17). Table 1 demonstrates common plants contain the highest amount of apigenin. Apigenin is chemically represented as 4',5,7, trihydroxyflavone. It's a low molecular weight flavonoid (270.24=KDa). In general, apigenin is insoluble in water, but the best solvents for this substance are dilute dimethyl sulfoxide (DMSO), potassium hydroxide (KOH), dimethylformamide (DMF), and ethanol (12, 13, 20, 21). Its melting point is reported as 347.5. The pure form of apigenin is unstable and is usually recommended to be kept at -20oC (13). For a long time, apigenin has been used to treat various diseases, including insomnia, Parkinson's, asthma, nervous system disorders, indigestion, gastritis, cancers, and cardiovascular diseases (12, 13, 22). Apigenin can also modulate different intercellular and extracellular signaling pathways to prevent abnormal tissue growth. For this reason, the administration of apigenin can be one of the effective factors in cancer treatment (22). Although previous studies have indicated that flavonoid compounds cannot have a good effect on blood lipid metabolism, apigenin plays a considerable role in regulating blood lipid and reduces triglyceride, cholesterol, and low-density lipoprotein cholesterol in the serum of mice (23). As a result, apigenin has attracted a lot of attention due to its low toxicity and significant impacts on natural versus cancer cells compared to other flavonoids (24). In this article, the biological effects of apigenin are discussed first, and then the effect of this flavonoid compound on several cancers is investigated. It has been reported that apigenin and other medicinal herbs can have remarkable effects in preventing various diseases and cancers. And also, it has been shown that different phytochemicals including flavonoids are responsible for the therapeutic impacts of these plants (25). Various studies have demonstrated that apigenin has different biological effects such as anti-inflammatory, anti-carcinogenic, anti-mutagenic, antioxidant, anti-viral, anti-allergic cardioprotective, neuroprotective, and antibacterial. In general, it can be said that apigenin has attracted more attention due to its considerable effects on cancers and low toxicity compared to other flavonoids (13, 15, 24, 26, 27). The biological properties mentioned above are caused by the

functional mechanisms of flavonoid compounds such as apoptosis induction, stimulation of the immune system, improvement of the enzymatic detoxification activity, reduction of oxidative stress, and cell cycle inhibition (15, 28). Some of these biological effects of apigenin are discussed below.

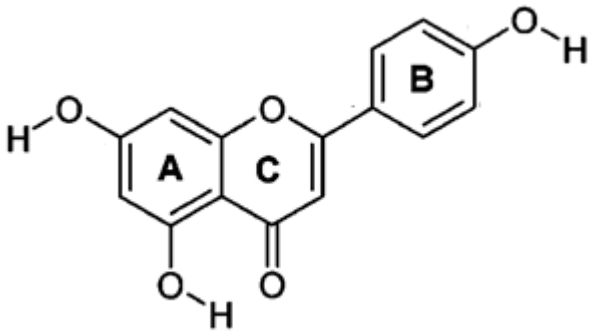

Figure 1. The basic structure of apigenin.

Table 1. Plants with the highest level of apigenin.

Scientific name	Commonly known
Achillea millefolium	Yarrow
Apium graveolens	Celery
Artemisia dracunculus	Tarragon
Chamaemelum nobile	Perennial chammomile
Coriandrum sativum	Cilantro
Digitalis purpurea	Purple foxglove
Echinacea spp	Coneflower
Gingko biloba	Biloba
Glycyrrhiza glabra	Licorice
Linum usitatissimum	Flax
Marrubium vulgare	Horehound
Matricaria retcutita	Annual chamomile
Mentha spicata	Spearmint
Ocimum basilicum	Basil
Origanum vulgare	Oregano

Anti-inflammatory effects of apigenin

Inflammation is a critical immune response to maintain tissue homeostasis. Two different types of inflammation are acute and chronic inflammation. Acute inflammation is a protective and essential response of therapeutic processes that initiates rapidly and its symptoms last for a short period up to a few days. In general, this response should be local and limited. Although acute inflammation tries to restore homeostasis, if it is not resolved, it leads to chronic inflammation (18). And also, Inflammation is one of the most important characteristics that confirm tumor progression and increase the risk of cancer. Flavonoids such as apigenin have been shown to suppress the activation of different cytokines and immune cells, so they may be considered natural inhibitors that can stop the activation of an adaptive and innate immune system. Apigenin can diminish inflammation by inhibiting tumor necrosis factor-alpha (TNF-α), C-C motif chemokine ligand 2 (CCL-2), granulocyte-macrophage colony-stimulating factor (GMCSF), interleukin 1-alpha (IL-1α) and IL-6 (19, 20). Many studies have indicated that apigenin can enhance various anti-inflammatory pathways, such as phosphatidylinositol 3-kinase/ protein kinase B (PI3k/Akt) and p38 mitogen-activated protein kinase (P38/MAPK). The inflammatory and antioxidant pathways of apigenin in cell lines are shown in figure 2. In addition, it reduces the activity of nitric oxide synthase-2 and ccyclooxygenase-2 (Cox-2). And also, apigenin prevents TNF-α-induced nuclear factor kappa B (NF-κB) activation and IkappaB kinase degradation (21). Apigenin can exert a wide range of molecular signaling effects (22). It has been reported that apigenin inhibits mitogen-activated protein kinase (MAPK) and the activity of protein kinase-C (23, 24). On the other hand, apigenin is a famous protein-tyrosine kinase inhibitor. In addition, it has been indicated that it can inhibit extracellular signal-regulated kinases (ERK) (25). Inactivation of NF-κB by apigenin in human cells culture medium is through suppression of the phosphorylation of the p65 subunit (26).

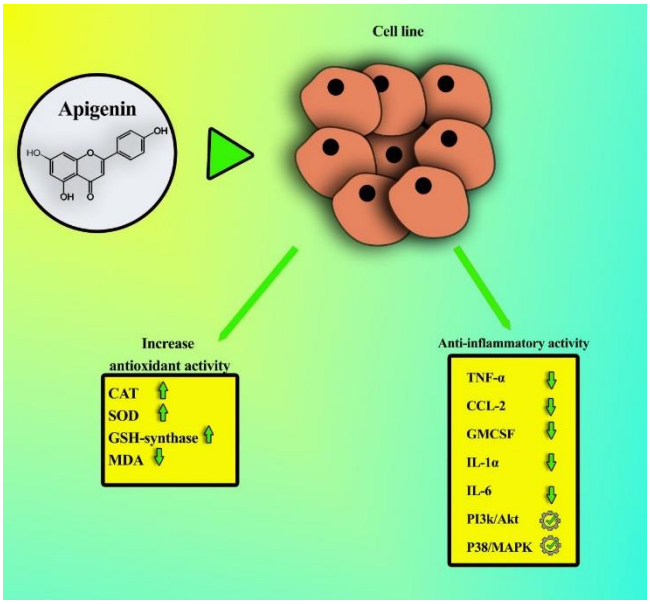

Figure 2. Anti-inflammatory and antioxidant effects of apigenin. Apigenin decreases malondialdehyde (MDA), increases antioxidants enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione synthetase (GSH-synthase), reduces the activity of anti-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), c-c motif chemokine ligand 2 (CCL-2), granulocyte-macrophage colony-stimulating factor (GMCSF), interleukin 1-alpha (IL-1α), interleukin 6 (IL-6), and also it can can promote different anti-inflammatory pathways, such as phosphatidylinositol 3-kinase/ protein kinase B (pI3k/Akt) and p38 mitogen-activated protein kinase (p38/MAPK).

The effect of apigenin on the cell cycle

Cell division activates cell proliferation and distributes the exact genetic copies to daughter cells which is essential for the reproduction of life (27). Studies have demonstrated that medicinal plants can have a considerable role in cell cycle arrest, which is done by inhibiting G0/G1 or G2/M checkpoints. Several biochemical events cause cells to progress through the cell cycle. Before cells enter the S phase, a cascade of events must occur, including in the level of D-type cyclins and cyclin E at the beginning and the end of G phase. In general, with the formation of D-type cyclins complex with cyclin-dependent kinase 2 and CDK 4, cell cycle progress occurs through phosphorylation tumor suppressor protein retinoblastoma (Rb), which is necessary to enter the S phase. Apigenin is known as an effective inhibitor of some protein tyrosine kinases such as steroid receptor coactivator (Src) tyrosine kinase and epidermal growth factor receptor. Apigenin also can suppress the activation of protein kinase B/AKt, phosphatidylinositol 3-kinase, and casein kinase-2, which can play an important role in the development of cancer. In fact, apigenin has been indicated to inhibit cyclin-dependent kinases (CDKS) and cyclins in vitro. In addition, apigenin can enhance CDK inhibitors such as KIP1/p17 and WAF1/p21, which reduces the activity of G1 CDK, p53 stabilization, and Rb dephosphorylation (39). In one of the studies, the inhibitory effect of apigenin on the growth of human prostate tumor cells was evaluated in nude mice. In this study, apigenin was administrated orally. The consumption of apigenin increased the expression of WAF1/p21, KIP1/p27, INK4c/p18 and INK4a/p16, decreased the expression of cyclins D1, D2, E; and cyclin-dependent kinase (CDK), including CDK2 and CDK4 (Figure 3). With the decrease of cyclin D1, the inhibitor of WAF1/p21 increases. On the other hand, CDK4 can be partially reduced while cyclin E remains unchanged. These findings show that the inhibitory effect of apigenin on the proliferation of cells in the G1 phase is due to its decrease of cyclins D1 and the increase of WAF1/p21.Another mechanism of cell growth inhibition by apigenin has also been investigated. When cells are exposed to apigenin, the amount of protein p53 and its downstream proteins, such as Protein p21(Cip1/Waf1), which is a potential CDK inhibitor in G1 and G2/M phases, increases and leads to the inhibition of the cell cycle (28, 29). As mentioned above, apigenin causes cell cycle arrest in different phases such as G1/S or G2/M, which is done by modulating the expression of CDKs and other related genes (30). It has been indicated that exposure to a broad range of malignant cells such as fibroblast and epidermal cells with apigenin causes a reversible G0/G1 and G2/M arrest through the inhibition of p53 (CDK2) kinase activity along with enhancement of the stability of the p53 protein (31, 32).

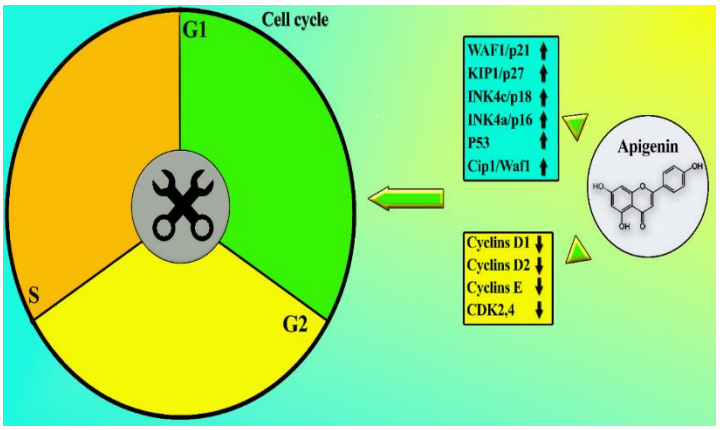

Figure 3. The above image shows the effects of apigenin on influencing factors in cell cycle. Apigenin can inhibit the cell cycle by increasing the expression of WAF1/p21, KIP1/p27, INK4c/p18 and INK4a/p16, (Cip1/Waf1), p53, and decreasing the expression of cyclins D1, D2, E; and cyclin-dependent kinase, including CDK2 and CDK4.

The effect of apigenin on apoptosis

Different types of cell death are necrosis, apoptosis, pyroptosis, and autophagy. Programmed cell death is an essential process in multicellular organisms that removes hazardous cells and keeps tissue homeostasis. Apoptosis is one of the types of regulated cell death, which is divided into two pathways, intrinsic and

extrinsic. Both pathways result in the activation of a group of caspases and proteases that are responsible for cell death. In addition, these pathways regulate apoptosis through proteins such as the B-cell lymphoma 2 (BCL-2) family (33). Apigenin plays an important role in apoptosis and its administration reduces cell survival. The function of apigenin is intensified by the reduction of BCL-2 and B-cell lymphoma-extra Large (BCL-XL) as well as the increase of Bcl-2-associated X (BAX) protein (34, 35). Studies have indicated apigenin causes apoptosis and cell growth inhibition in various tumors, including lung, skin, blood, liver, breast, stomach, colon, and prostate, by modulating different signaling pathways (36). Apigenin activates both intrinsic and extrinsic pathways of apoptosis. In general, in the process of internal pathway regulation, the mitochondrial membrane potential changes and leads to the secretion of cytochrome C in the cytoplasm, which activates caspase 3 with the formation of apoptotic protease activating factor (APAF), and as a result, apoptosis occurs (37). And also, apigenin regulates the extrinsic pathways of apoptosis by increasing the expression of mRNA of TNF-α, caspase-3, and caspase 8 (36-38). In cancer cells, apigenin induces apoptosis by regulating the expression of Bax, Bcl-2, Akt, and signal transducer and activator of transcription 3 (STAT-3) proteins (37, 38).

The effect of apigenin on oxidative stress

Oxidative stress is related to the imbalance between the antioxidant system and the production of free radicals. In general, reactive oxygen species (ROS) are essential in a limited amount for redox signaling and homeostasis of cells. Excessive production of reactive oxygen species/ reactive nitrogen species (ROS/RNS) neutralizes the body's defense system, which is called oxidative stress. Oxidative stress can be related to cancer, cardiovascular diseases, eye diseases, kidney disease, and diabetes. In addition, oxidative stress causes oxidative changes including protein carbonylation, nitration, sulfoxidation, lipid peroxidation, and DNA breaks such as single-strand breaks (SSB) and double-strand breaks (DSB) (39, 40). Various diseases, including cardiovascular diseases, diabetes, cancer, etc., are related to excessive production of free oxygen species and oxidative stress. Apigenin has significant antioxidant properties, such as enhancing enzymatic and non-enzymatic antioxidants, free radical scavenging, and modulating signaling pathways such as PI3/Akt, Nfr2, MAPK, and NF-KB. (41). Studies show that apigenin reduces adhesion molecules expression, which can be a useful strategy against oxidative stress, such as free-radical scavenging (42). Apigenin can also increase the activity of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione synthetase (GSH-synthase) and also decreased the level of malondialdehyde (MDA) to counteract oxidative stress (43). In one of the studies to investigate the antioxidant effect of apigenin, 25 mg/kg of apigenin was administrated for two weeks. It was demonstrated that apigenin was able to reduce the amount of lipid peroxidation product (malondialdehyde). On the other hand, it increased the activities of antioxidant enzymes, including CAT, GPX, and SOD as well as non-enzymatic antioxidants, such as vitamins C and E, which led to a reduction in oxidative stress (52).

The effect of apigenin on cancer cells

The anti-cancer property of apigenin is due to its ability to modulate various signaling pathways including angiogenesis, apoptosis, tumor suppressor genes, cell cycle, inflammation, and NF-κB, JAK/STAT3, PI3K/AKT/mTOR, MAPK/ER2, Wnt/B-catenin pathways. Evidence shows that reactive oxygen species are of great importance in the anti-tumor properties of apigenin (44). Apigenin can inhibit the invasion and metabolism of cancer cells by regulating the production of protease (45). Studies indicate that apigenin suppresses lung melanoma metastasis by eliminating the interaction of cancer cells with the endothelium (46). Moreover, the exposure of endothelial cells to apigenin can lead to the suppression of vascular endothelial growth factors (VEGF) expression, which is an essential factor in angiogenesis through the degradation of hypoxia-inducible factor 1-α (HIF-1a) protein (Figure 4) (47). Apigenin can also inhibit the expression of VEGF and HIF-1a through human double minute 2 (HDM2)/P53 and PI3K/AKT/P70s6K1 pathways in ovarian cancer cells (48).

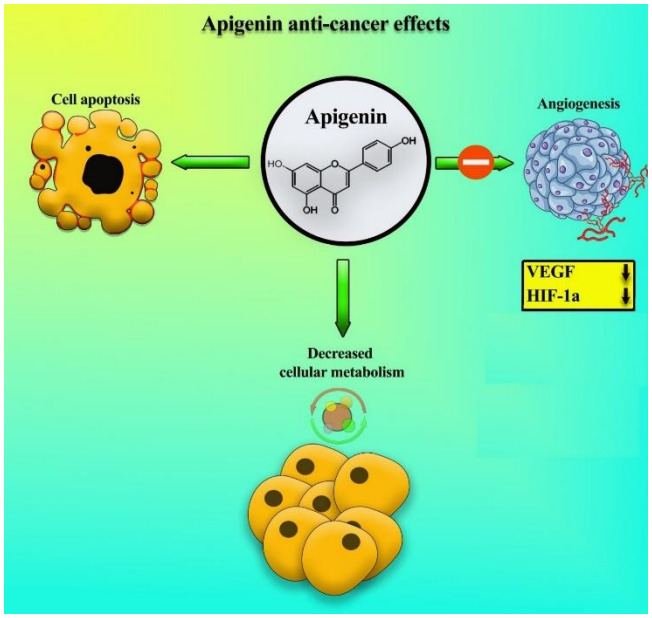

Figure 4. Anti-cancer effects of apigenin, including inhibition of angiogenesis through vascular endothelial growth factors (VEGF) suppression and protein hypoxia-inducible factor 1-α (HIF-1a) degradation, reduction of metabolism, and activation of apoptosis.

The effect of apigenin on different cancers

Despite, the significant progress made in cancer diagnosis and treatment in recent years, it is still considered the second main cause of death in the world. There are various modalities for cancer therapy, including hormone therapy, radiation therapy, chemotherapy, and target therapy. Some of the main challenges in cancer treatment, especially in the advanced stages, are the side effects of drugs, chemical resistance, the killing of normal cells, and treatment costs. Therefore, finding a treatment method with the least side effects is very important and is in the preliminary stages. Using natural products with strong therapeutic and preventive properties is of great value and importance. It should be noted that their importance is because of reducing the resistance of cancer cells to treatment and having fewer side effects (49, 50). Different studies have demonstrated that high consumption of polyphenolic compounds such as flavonoids can diminish the incidence of various cancers (51). In this study, we have tried to show the effect of apigenin on several types of cancers.

Lung cancer and apigenin

Lung cancer is one of the leading causes of death in the world (27). Biologically and histologically, lung cancer is considered a complex neoplasm. The four main histological kinds of lung cancer are small cell carcinoma, large cell carcinoma, adenocarcinoma, and squamous cell carcinoma (62). Knekt et al (63), investigated the relationship between the consumption of flavonoids such as apigenin, quercetin, luteolin, and myricetin and lung cancer. They have found that there is an inverse relationship between the occurrence of cancer and flavonoid consumption. They have concluded that onion and apple, as two sources rich in apigenin, can play a protective role against lung cancer. The relationship between the consumption of flavonoids and their protective role in the occurrence of various cancers, including breast cancer, ovarian cancer, and colorectal cancer, has also been investigated (13, 52). Lui et al (64), have suggested that apigenin could diminish the risk of lung cancer by inhibiting vascular endothelial growth factor (VEGF) transcription and proliferation of A549 lung cancer cells.

Gastric cancer and apigenin

Gastric cancer is one of the most common types of cancer around the world (53). There is compelling evidence that Helicobacter pylori infection can be associated with gastric cancer. Therefore, one of the preventive measures for gastric cancer is to eradicate the infection of Heliobacter pylori (H.pylori). In addition, another strategy to reduce the progress of gastric cancer is to use different flavonoid compounds such as apigenin, which have significant antioxidant properties. In one of the conducted studies, the effectiveness of apigenin on the progression of gastric cancer and atrophic gastric caused by helicobacter pylori was investigated. And the result showed that apigenin therapy significantly reduces the rates of histological changes of neutrophils and monocyte infiltration as well as H.pilori colonization in both gastric cancer and gastritis. In addition, apigenin could dramatically increase the expression of IKBa. Therefore, it could reduce the activation of NF-KB and inflammatory cytokines expression. Moreover, the level of ROS diminished due to the scavenging characteristic of apigenin (65, 66). Wu et al (67), evaluated the effect of apoptosis induction and cell cycle inhibition of apigenin on SGC-7910 gastric

carcinoma cells. They observed that apigenin inhibits clone formation and growth of these cells through apoptosis.

Neuroblastoma and apigenin

Neuroblastoma causes approximately 15% of childhood cancer-related deaths (53). Neuroblastoma is one of the most common extracranial solid tumors in children that originate from neural progenitor cells. These tumors can occur in the central nervous system, pelvic and thoracic regions. But they mainly appear in the abdominal region. Many factors play a role in the occurrence of this disease, such as inflammation, patient age, protein aggregation, tumor metastasis, etc. One of the important risk factors of neuroblastoma is MYCN Proto-Oncogene amplification, which can intensify neuroblastoma tumorigenesis. The age of the patient and elimination of a protein from chromosome 11 (11q aberration) are other risk factors (54, 55). It's notable for the wide range of clinical behavior. Some neuroblastoma tumors can differentiate into benign types (benign ganglioneuromas) and some undergo sudden regression (56, 57). Therapeutic modalities for neuroblastoma include surgery, chemotherapy, and radiotherapy (58). Stages 1 and 2 of the disease can only be treated by surgery (59). But in higher stages, favorable results are obtained with surgery and chemotherapy (60). Natural compounds have been proven to have valuable anti-cancer properties. Some of these compounds with few side effects can help prevent or even treat cancer. Flavonoids can suppress cancer by epithelial-mesenchymal transition (EMT) inhibition, extracellular matrix (ECM) protein modulation, and inhibiting the metabolism of cancer cells (61). Torkin et al (62), evaluated the effect of apigenin on human neuroblastoma cell lines. They found that apigenin inhibits the ability of colony formation and survival, and stimulates apoptosis in these cell lines. Apigenin elevated p53 protein level and products derived from p53, including Bax, p21WAF1/CIP1 gene. In addition, apigenin could increase the activity of caspase-3 and cause cell death.

Thyroid cancer and apigenin

Thyroid cancer, as an unusual cancer, can account for about 1% of all malignancies (53). Thyroid cancer is known as the fifth most prevalent cancer among women in the united states. The prevalence of this cancer is rising around the world. Treatment modalities for thyroid cancer in most patients are surgery combined with radioiodine therapy (63). Studies have shown that malignant thyroid cancer is divided into different types, including follicular thyroid cancer (FTC), papillary thyroid cancer (PTC), Hurthle cell cancer (HCC), and anaplastic thyroid cancer (ATC), all of which are derived from epithelial cancer cells. Other types include medullary thyroid cancer derived from parafollicular and non-epithelial types such as teratoma, sarcoma, and lymphoma. Among the different types of thyroid cancer, FTC, PTC, and HCC are called differentiated thyroid cancer. While ATC is considered a very malignant neoplasm. PTC is one of the most prevalent malignancies of thyroid cancer (64, 65). A study conducted on PCCL3 rat thyroid cells showed that apigenin was able to increase iodide influx by inhibiting AKT under thyrotropin stimulation (66). In addition, in the BCPAP cell line, apigenin caused a considerable cell accumulation in the G2/M phase through the reduction of cell division cycle 25 (Cdc25c) expression. Also, apigenin suppressed the viability of PTC cells through the stimulation of ROS production, which caused DNA damage and eventually resulted in autophagy cell death (67). Yin et al (68), assessed the impact of some flavonoid compounds such as apigenin on thyroid carcinoma cell lines, including UCLA Ro-w-1(WRO) (follicular carcinoma), UCLA RO-81A-1(ARO) (anaplastic carcinoma), and UClA NPA-87-1(NPA) (papillary carcinoma). Of all the flavonoids used, apigenin has been the most effective proliferation inhibitor of cell lines. Yin et al (69), in another study, showed that the inhibitory impact of apigenin on the proliferation of ARO cells was related to both phosphorylation of down-stream effector (MAPK) and epidermal growth factor receptor (EGFR) tyrosine autophosphorylation.

Elst et al (70), investigated the efficiency of flavonoid compounds on the growth of follicular cell lines and iodine transport. It was found that apigenin could suppress the expression of Sodium-iodide symporter (NIS) mRNA, and this finding can have useful therapeutic consequences for the treatment of thyroid cancer.

Liver cancer and apigenin

Liver cancer, more precisely hepatocellular carcinoma, can be considered as the second main reason for cancer deaths and its prevalence is rising worldwide (71). This disease occurs more in men than women, and it is also more common in West and Middle Africa, South and East Asia, and Melanesia (72). The consumption of flavonoids can be effective in preventing Hepatocellular carcinoma (73). Flavonoids such as apigenin reduced the survival of hepatocellular carcinoma HePG2 cells and induced apoptosis by diminishing the expression of low-density lipoprotein receptor-related protein (LRP6) and S-phase kinase-associated protein-2 (SKP2). Further studies on apigenin against liver cancer cells indicated that this anticancer agent suppressed cell proliferation and increased cell death. In addition, apigenin caused autophagy and apoptosis by inhibiting the phosphatidylinositol-3-kinase (PI3K/Akt) and mechanistic target of rapamycin (mTOR) pathways. It has been indicated that apigenin therapy caused G1 arrest in HepG2 cells. Also, the cells that were exposed to apigenin experienced an increase in the amount of cyclin D1 and a decrease in cyclin 4, which indicates that the cell cycle can be stopped by regulating the expression of CD1 and CDK4 (74, 75). Yee et al (76), studied the inhibitory efficiency of two flavonoid compounds named apigenin and luteolin on Hepatocellular carcinoma HepG2 cells. The results showed that both of these flavonoids had an effective role in inhibiting cell growth, which was caused by diminishing the expression of CDK4 and cell cycle arrest by inducing P21 and p53, respectively.

Skin cancer and apigenin

Skin cancer is one of the most prevalent types of cancer in the united kingdom (UK) and the united states (US) (77). The two most common types of skin cancer are melanoma and non-melanoma skin cancer. Most skin cancers are related to non-melanoma and result from keratinized epithelial cells. These types of cancers can be divided into squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). BCC is the most common form and progresses slowly. Melanoma accounts for approximately 2% of malignancies and causes the most mortality (77). It has been shown that ultraviolet B (UVB) radiation is the main cause of this disease. Various studies have indicated that apigenin can be remarkably effective in preventing skin carcinogenesis caused by ultraviolet A/B in SKH-1 mice (78). Caltagirone et al (79), investigated the combined impacts of apigenin and quercetin on suppressing the metastatic, invasiveness, and melanoma growth potential. They showed that the administration of quercetin and apigenin under in vivo conditions inhibited the metastatic potential of melanoma lung tumors in a BL6-BL6 murine model. This effect can be due to demolishing the interaction between malignant and endothelial cells.

Prostate cancer and apigenin

In addition to skin cancer, another common cancer in men is prostate cancer (53). This cancer is one of the multifactorial diseases. Prostate cancer is the second most common cancer and the fifth main cause of death in the world. The prevalence and mortality rate of prostate cancer is related to factors such as age, and the highest prevalence can be seen in older men. The most prevalent therapeutic modalities are surgery, radiotherapy, and/ or chemotherapy. It should be mentioned that these options are efficient in the early stages and become ineffective in the higher stages. This cancer can be reduced by increasing the consumption of fruits and vegetables as well as reducing the consumption of fatty foods. (80, 81). Flavonoids can be well tolerated by prostate cells, but it should be noted that these natural compounds act as mutagens, inhibitors of key regulatory enzymes, or pro-oxidant molecules in case of excessive consumption. Various types of polyphenols have been studied to kill prostate cancer cells(82, 83). In one of the studies, 22Rv1, PCa, and PC3 cells were exposed to different concentrations of apigenin (20 and 40μM) for 24 hours. The results indicated that the activity of histone deacetylation (HDAC) was reduced compared to that obtained from the famous HDAC inhibitor trichostatin A (TSA). Also, apigenin decreased the regulation of HDAC1 and HDAC3 at both protein and mRNA levels along with the simultaneous increase in H3 and H4 acetylation. As a result, this causes the DNA promoter to have more access to transcription factors and also, increases synthesis of cell cycle regulating protein p21/waf1 in prostate cancer cells. P21/waf1 can control cell cycle progression through cyclin-dependent kinase 2 (CDK2) inhibition (84). Prostate cancer cells showed induction of apoptotic pathways and cell cycle arrest 24 hours after apigenin administration. In one of the in-

vivo studies performed on PC3 xenografts in athymic nude mice, the antitumor effect of apigenin was investigated. Oral administration of apigenin (20 and 50 mg/mouse/d) during eight weeks caused a significant decrease in HDAC1 and HDAC3 protein expression, HDAC activity, and also a decrease in tumor growth. Mice were exposed to apigenin, the expression of P21/waf1 was higher than the control group, and the change in the amount of bax/bcl2 led to apoptosis induction (84). Knowles et al (85), evaluated the effectiveness of apigenin on prostate cancer PC3 cell proliferation, and it was demonstrated that when these cells are exposed to apigenin, their growth rate is delayed. Hessenauer et al (86), indicated the relationship between the growth of prostate cancer cells and casein kinase 2 (CK2) activity. They found that apigenin was able to suppress the activity of CK2 in both hormone-refractory PC3 and hormone-sensitive lymph node carcinoma of the prostate (LNCap), but only the latter underwent apoptosis. This result indicates that high activity of CK2 is not necessary for the proliferation and protection of PC3 cells against apoptosis. A summary of the effectiveness of apigenin on the mentioned cancers is indicated in Table 2.

Table 2. Summary of the several studies conducted on the effect of apigenin on the mentioned cancers.

Name	Year	Cancer	Result
Liu et al	2005	Lung	They have indicated that apigenin can diminish the risk of lung cancer by suppressing vascular endothelial growth factor transcription and the proliferation of A549 lung cancer
Wue et al	2005	Gastric	They found that apigenin inhibited the growth of SGC-7910 gastric carcinoma cells
Torkin et al	2005	Neuroblastoma	The result shows that apigenin can suppress growth, survival, and induce apoptosis in neuroblastoma cells
Elst et al	2004	Thyroid	They evaluated that apigenin plays an effective role in the treatment of thyroid cancer by inhibiting sodium- iodide symporter mRNA
Yee et al	2003	Liver	In this study, the results showed that apigenin and luteolin can inhibit the growth of Hepatocellular carcinoma HepG2cells by reducing the expression of CDK4 and stopping the cell cycle arrest by inducing P21 and p53, respectively
Caltagirone et al	2000	Skin	It has been observed that the combined effects of two flavonoid compounds, such as apigenin and quercetin inhibit the metastasis, invasiveness, and growth potential of melanoma
Knowles et al	2000	Prostate	They indicated that apigenin can have a beneficial effect on the proliferation of prostate cancer PC3 cells and also delay the growth of these cells

Conclusion

All the evidence obtained so far demonstrates that apigenin as a flavonoid compound has significant effectiveness against inflammation, oxidative stress, cancer, and various other diseases. Apigenin, due to its inherent low toxicity, non-mutagenicity, and its abundant presence in various vegetables, fruits, and herbal drinks, can be used as a preventive and reducing factor against various ailments, including inflammatory diseases and cancers. The useful functional mechanism of this compound, which play important roles in the prevention and treatment of different diseases, can be mentioned as induction of apoptosis, cell cycle arrest, stimulation of detoxification enzymes, neutralization of free radicals, and alterations in cellular signaling pathways. Based on the obtained results, apigenin has a significant effect in suppressing inflammation by reducing TNF-α, CCL-2, GMCSF, IL-1α, and IL-6 and increasing various anti-inflammatory pathways, including PI3K/Akt and P38/MAPK. It's worth mentioning that apigenin can reduce apoptosis by its effect on proteins such as BCL-2, BCL-XL, and BAX. Another beneficial effect of apigenin is on oxidative stress, which can inhibit oxidative stress by increasing enzymatic and non-enzymatic antioxidants and also by modulating different signaling pathways such as PI3/Akt, Nfr2, MAPK, and NF-κB. In recent years, a lot of progress has been made regarding the effect of apigenin in the treatment and prevention of various

types of disease such as cancer (in vivo- in vitro), but continuous efforts are still needed to confirm the impact of apigenin in human ailments by stimulating different diseases in animal models

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Conflict of Interests

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References

1. Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative stress and inflammation: what polyphenols can do for us? Oxidative medicine and cellular longevity. 2016;2016.
2. Khalil A, Tazeddinova D. The upshot of Polyphenolic compounds on immunity amid COVID-19 pandemic and other emerging communicable diseases: An appraisal. Natural Products and Bioprospecting. 2020;10(6):411-29.
3. Lee U-J, Sohng JK, Kim B-G, Choi K-Y. Recent trends in the modification of polyphenolic compounds using hydroxylation and glycosylation. Current Opinion in Biotechnology. 2023;80:102914.
4. Caponio GR, Noviello M, Calabrese FM, Gambacorta G, Giannelli G, De Angelis M. Effects of grape pomace polyphenols and in vitro gastrointestinal digestion on antimicrobial activity: Recovery of bioactive compounds. Antioxidants. 2022;11(3):567.
5. Lippolis T, Cofano M, Caponio GR, De Nunzio V, Notarnicola M. Bioaccessibility and Bioavailability of Diet Polyphenols and Their Modulation of Gut Microbiota. International Journal of Molecular Sciences. 2023;24(4):3813.
6. Rahman I, Biswas SK, Kirkham PA. Regulation of inflammation and redox signaling by dietary polyphenols. Biochemical pharmacology. 2006;72(11):1439-52.
7. Adnan M, Rasul A, Shah MA, Hussain G, Asrar M, Riaz A, et al. Radioprotective role of natural polyphenols: From sources to mechanisms. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2022;22(1):30-9.
8. Aravind SM, Wichienchot S, Tsao R, Ramakrishnan S, Chakkaravarthi S. Role of dietary polyphenols on gut microbiota, their metabolites and health benefits. Food Research International. 2021;142:110189.
9. Crozier A, Del Rio D, Clifford MN. Bioavailability of dietary flavonoids and phenolic compounds. Molecular aspects of medicine. 2010;31(6):446-67.
10. Banjarnahor SD, Artanti N. Antioxidant properties of flavonoids. Medical Journal of Indonesia. 2014;23(4):239-44.
11. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. Journal of nutritional science. 2016;5:e47.
12. Ginwala R, Bhavsar R, Chigbu DGI, Jain P, Khan ZK. Potential role of flavonoids in treating chronic inflammatory diseases with a special focus on the anti-inflammatory activity of apigenin. Antioxidants. 2019;8(2):35.
13. Patel D, Shukla S, Gupta S. Apigenin and cancer chemoprevention: progress, potential and promise. International journal of oncology. 2007;30(1):233-45.
14. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview. The scientific world journal. 2013;2013.
15. Rithidech KN, Tungjai M, Reungpatthanaphong P, Honikel L, Simon SR. Attenuation of oxidative damage and inflammatory responses by apigenin given to mice after irradiation. Mutation Research/Genetic Toxicology and Environmental Mutagenesis. 2012;749(1-2):29-38.
16. Salehi B, Venditti A, Sharifi-Rad M, Kręgiel D, Sharifi-Rad J, Durazzo A, et al. The therapeutic potential of apigenin. International journal of molecular sciences. 2019;20(6):1305.
17. Chen L, Zhao W. Apigenin protects against bleomycin-induced lung fibrosis in rats. Experimental and therapeutic medicine. 2016;11(1):230-4.
18. Pérez-Pérez A, Sánchez-Jiménez F, Vilariño-García T, Sánchez-Margalet V. Role of leptin in inflammation and vice versa. International journal of molecular sciences. 2020;21(16):5887.
19. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. nature. 2008;454(7203):436-44.
20. Bauer D, Redmon N, Mazzio E, Soliman KF. Apigenin inhibits TNFα/IL-1α-induced CCL2 release through IKBK-epsilon signaling in MDA-MB-231

human breast cancer cells. PloS one. 2017;12(4):e0175558.
21. Lee J-H, Zhou HY, Cho SY, Kim YS, Lee YS, Jeong CS. Anti-inflammatory mechanisms of apigenin: inhibition of cyclooxygenase-2 expression, adhesion of monocytes to human umbilical vein endothelial cells, and expression of cellular adhesion molecules. Archives of pharmacal research. 2007;30:1318-27.
22. Williams RJ, Spencer JP, Rice-Evans C. Flavonoids: antioxidants or signalling molecules? Free radical biology and medicine. 2004;36(7):838-49.
23. Lee SF, Lin JK. Inhibitory effects of phytopolyphenols on TPA-induced transformation, PKC activation, and c-jun expression in mouse fibroblast cells. 1997.
24. Lin JK, Chen YC, Huang YT, Lin-Shiau SY. Suppression of protein kinase C and nuclear oncogene expression as possible molecular mechanisms of cancer chemoprevention by apigenin and curcumin. Journal of cellular biochemistry. 1997;67(S28–29):39-48.
25. Mounho BJ, Thrall BD. The extracellular signal-regulated kinase pathway contributes to mitogenic and antiapoptotic effects of peroxisome proliferators in vitro. Toxicology and applied pharmacology. 1999;159(2):125-33.
26. Nicholas C, Batra S, Vargo MA, Voss OH, Gavrilin MA, Wewers MD, et al. Apigenin blocks lipopolysaccharide-induced lethality in vivo and proinflammatory cytokines expression by inactivating NF-κB through the suppression of p65 phosphorylation. The Journal of Immunology. 2007;179(10):7121-7.
27. Jones MC, Zha J, Humphries MJ. Connections between the cell cycle, cell adhesion and the cytoskeleton. Philosophical Transactions of the Royal Society B. 2019;374(1779):20180227.
28. Shukla S, Gupta S. Molecular targets for apigenin-induced cell cycle arrest and apoptosis in prostate cancer cell xenograft. Molecular cancer therapeutics. 2006;5(4):843-52.
29. Lee Y, Sung B, Kang YJ, Kim DH, Jang J-Y, Hwang SY, et al. Apigenin-induced apoptosis is enhanced by inhibition of autophagy formation in HCT116 human colon cancer cells. International journal of oncology. 2014;44(5):1599-606.
30. Takagaki N, Sowa Y, Oki T, Nakanishi R, Yogosawa S, Sakai T. Apigenin induces cell cycle arrest and p21/WAF1 expression in a p53-independent pathway. International journal of oncology. 2005;26(1):185-9.
31. Plaumann B, Fritsche M, Rimpler H, Brandner G, Hess RD. Flavonoids activate wild-type p53. Oncogene. 1996;13(8):1605-14.
32. Lepley DM, Pelling JC. Induction of p21/WAF1 and G1 cell-cycle arrest by the chemopreventive agent apigenin. Molecular Carcinogenesis: Published in cooperation with the University of Texas MD Anderson Cancer Center. 1997;19(2):74-82.
33. Singh P, Lim B. Targeting apoptosis in cancer. Current oncology reports. 2022;24(3):273-84.
34. Shukla S, Fu P, Gupta S. Apigenin induces apoptosis by targeting inhibitor of apoptosis proteins and Ku70–Bax interaction in prostate cancer. Apoptosis. 2014;19:883-94.
35. Wang W, Liu X, Zhang Z, Yin M, Chen X, Zhao S, et al. Apigenin Induced Apoptosis by Downregulating Sulfiredoxin Expression in Cutaneous Squamous Cell Carcinoma. Oxidative Medicine and Cellular Longevity. 2022;2022.
36. Imran M, Aslam Gondal T, Atif M, Shahbaz M, Batool Qaisarani T, Hanif Mughal M, et al. Apigenin as an anticancer agent. Phytotherapy Research. 2020;34(8):1812-28.
37. Shukla S, Gupta S. Molecular mechanisms for apigenin-induced cell-cycle arrest and apoptosis of hormone refractory human prostate carcinoma DU145 cells. Molecular Carcinogenesis: Published in cooperation with the University of Texas MD Anderson Cancer Center. 2004;39(2):114-26.
38. Seo H-S, Choi H-S, Kim S-R, Choi YK, Woo S-M, Shin I, et al. Apigenin induces apoptosis via extrinsic pathway, inducing p53 and inhibiting STAT3 and NFκB signaling in HER2-overexpressing breast cancer cells. Molecular and cellular biochemistry. 2012;366:319-34.
39. Pisoschi AM, Pop A, Iordache F, Stanca L, Predoi G, Serban AI. Oxidative stress mitigation by antioxidants-an overview on their chemistry and influences on health status. European Journal of Medicinal Chemistry. 2021;209:112891.
40. Yaribeygi H, Sathyapalan T, Atkin SL, Sahebkar A. Molecular mechanisms linking oxidative stress and diabetes mellitus. Oxidative medicine and cellular longevity. 2020;2020.
41. Kashyap P, Shikha D, Thakur M, Aneja A. Functionality of apigenin as a potent antioxidant with emphasis on bioavailability, metabolism, action mechanism and in vitro and in vivo studies: A review. Journal of food biochemistry. 2022;46(4):e13950.
42. Myhrstad MC, Carlsen H, Nordström O, Blomhoff R, Moskaug JØ. Flavonoids increase the intracellular glutathione level by transactivation of the γ-glutamylcysteine synthetase catalytical subunit promoter. Free Radical Biology and Medicine. 2002;32(5):386-93.
43. Rahimi A, Alimohammadi M, Faramarzi F, Alizadeh-Navaei R, Rafiei A. The effects of apigenin administration on the inhibition of inflammatory responses and oxidative stress in the lung injury

models: a systematic review and meta-analysis of preclinical evidence. Inflammopharmacology. 2022;30(4):1259-76.
44. Zhou Y, Yu Y, Lv H, Zhang H, Liang T, Zhou G, et al. Apigenin in cancer therapy: From mechanism of action to nano-therapeutic agent. Food and Chemical Toxicology. 2022:113385.
45. Lindenmeyer F, Li H, Menashi S, Soria C, Lu H. Apigenin acts on the tumor cell invasion process and regulates protease production. Nutrition and cancer. 2001;39(1):139-47.
46. Piantelli M, Rossi C, Iezzi M, La Sorda R, Iacobelli S, Alberti S, et al. Flavonoids inhibit melanoma lung metastasis by impairing tumor cells endothelium interactions. Journal of Cellular Physiology. 2006;207(1):23-9.
47. Osada M, Imaoka S, Funae Y. Apigenin suppresses the expression of VEGF, an important factor for angiogenesis, in endothelial cells via degradation of HIF-1α protein. FEBS letters. 2004;575(1-3):59-63.
48. Fang J, Xia C, Cao Z, Zheng JZ, Reed E, Jiang B-H. Apigenin inhibits VEGF and HIF-1 expression via PI3K/AKT/p70S6K1 and HDM2/p53 pathways. The FASEB Journal. 2005;19(3):342-53.
49. 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.
50. Ahmed SA, Parama D, Daimari E, Girisa S, Banik K, Harsha C, et al. Rationalizing the therapeutic potential of apigenin against cancer. Life Sciences. 2021;267:118814.
51. Abbaszadeh H, Keikhaei B, Mottaghi S. A review of molecular mechanisms involved in anticancer and antiangiogenic effects of natural polyphenolic compounds. Phytotherapy Research. 2019;33(8):2002-14.
52. Knekt P, Järvinen R, Seppänen R, Heliövaara M, Teppo L, Pukkala E, et al. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. American journal of epidemiology. 1997;146(3):223-30.
53. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. Cancer statistics, 2005. 2005.
54. Maris JM, Matthay KK. Molecular biology of neuroblastoma. Journal of clinical oncology. 1999;17(7):2264-.
55. Zhai K, Brockmüller A, Kubatka P, Shakibaei M, Büsselberg D. Curcumin's beneficial effects on neuroblastoma: Mechanisms, challenges, and potential solutions. Biomolecules. 2020;10(11):1469.
56. Draper G, Kroll M, Stiller C. Childhood cancer. Cancer surveys. 1994;19: 493-517.
57. Weinstein JL, Katzenstein HM, Cohn SL. Advances in the diagnosis and treatment of neuroblastoma. The oncologist. 2003;8(3):278-92.
58. Strother DR, London WB, Schmidt ML, Brodeur GM, Shimada H, Thorner P, et al. Outcome after surgery alone or with restricted use of chemotherapy for patients with low-risk neuroblastoma: results of Children's Oncology Group study P9641. Journal of clinical oncology. 2012;30(15):1842.
59. Alvarado CS, London WB, Look AT, Brodeur GM, Altmiller DH, Thorner PS, et al. Natural history and biology of stage A neuroblastoma: a Pediatric Oncology Group Study. Journal of pediatric hematology/oncology. 2000;22(3):197-205.
60. Schmidt ML, Lukens JN, Seeger RC, Brodeur GM, Shimada H, Gerbing RB, et al. Biologic factors determine prognosis in infants with stage IV neuroblastoma: a prospective Children's Cancer Group study. Journal of Clinical Oncology. 2000;18(6):1260-8.
61. Liskova A, Koklesova L, Samec M, Smejkal K, Samuel SM, Varghese E, et al. Flavonoids in cancer metastasis. Cancers. 2020;12(6):1498.
62. Torkin R, Lavoie J-F, Kaplan DR, Yeger H. Induction of caspase-dependent, p53-mediated apoptosis by apigenin in human neuroblastoma. Molecular cancer therapeutics. 2005;4(1):1-11.
63. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. The Lancet. 2016;388(10061):2783-95.
64. Brown RL, de Souza JA, Cohen EE. Thyroid cancer: burden of illness and management of disease. Journal of Cancer. 2011;2:193.
65. Gosain R, Alexander JS, Gill A, Perez C. Radioactive iodine-refractory differentiated thyroid cancer in the elderly. Current Oncology Reports. 2018;20:1-6.
66. Lakshmanan A, Doseff AI, Ringel MD, Saji M, Rousset B, Zhang X, et al. Apigenin in combination with Akt inhibition significantly enhances thyrotropin-stimulated radioiodide accumulation in thyroid cells. Thyroid. 2014;24(5):878-87.
67. Zhang L, Cheng X, Gao Y, Zheng J, Xu Q, Sun Y, et al. Apigenin induces autophagic cell death in human papillary thyroid carcinoma BCPAP cells. Food & function. 2015;6(11):3464-72.
68. Yin F, Giuliano A, Van Herle A. Signal pathways involved in apigenin inhibition of growth and induction of apoptosis of human anaplastic thyroid cancer cells (ARO). Anticancer Research. 1999;19(5B):4297-303.
69. Hirano T, Oka K, Akiba M. Antiproliferative effects of synthetic and naturally occurring flavonoids on tumor cells of the human breast carcinoma cell line,

ZR-75-1. Research communications in chemical pathology and pharmacology. 1989;64(1):69-78.
70. Schröder-van der Elst JP, van der Heide D, Romijn JA, Smit J. Differential effects of natural flavonoids on growth and iodide content in a human Na*/I-symporter-transfected follicular thyroid carcinoma cell line. European journal of endocrinology. 2004;150(4):557-64.
71. Llovet JM, Castet F, Heikenwalder M, Maini MK, Mazzaferro V, Pinato DJ, et al. Immunotherapies for hepatocellular carcinoma. Nature reviews Clinical oncology. 2022;19(3):151-72.
72. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer. 2010;127(12):2893-917.
73. Eaton EA, Walle UK, Lewis AJ, Hudson T, Wilson AA, Walle T. Flavonoids, potent inhibitors of the human P-form phenolsulfotransferase. Potential role in drug metabolism and chemoprevention. Drug Metabolism and Disposition. 1996;24(2):232-7.
74. Yang J, Pi C, Wang G. Inhibition of PI3K/Akt/mTOR pathway by apigenin induces apoptosis and autophagy in hepatocellular carcinoma cells. Biomedicine & Pharmacotherapy. 2018;103:699-707.
75. Li Y, Cheng X, Chen C, Huijuan W, 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. Pathology-Research and Practice. 2020;216(1):152701.
76. Yee S-B, Lee J-H, Chung H-Y, Im K-S, Bae S-J, Choi J-S, et al. Inhibitory effects of luteolin isolated from Ixeris sonchifolia Hance on the proliferation of HepG2 human hepatocellular carcinoma cells. Archives of pharmacal research. 2003;26(2):151-6.
77. Linares MA, Zakaria A, Nizran P. Skin cancer. Primary care: Clinics in office practice. 2015;42(4):645-59.
78. Birt DF, Mitchell D, Gold B, Pour P, Pinch HC. Inhibition of ultraviolet light induced skin carcinogenesis in SKH-1 mice by apigenin, a plant flavonoid. Anticancer research. 1997;17(1A):85-91.
79. Caltagirone S, Rossi C, Poggi A, Ranelletti FO, Natali PG, Brunetti M, et al. Flavonoids apigenin and quercetin inhibit melanoma growth and metastatic potential. International journal of Cancer. 2000;87(4):595-600.
80. Rawla P. Epidemiology of prostate cancer. World journal of oncology. 2019;10(2):63.
81. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxidative medicine and cellular longevity. 2009;2:270-8.
82. Caporali A, Davalli P, Astancolle S, D'Arca D, Brausi M, Bettuzzi S, et al. The chemopreventive action of catechins in the TRAMP mouse model of prostate carcinogenesis is accompanied by clusterin over-expression. Carcinogenesis. 2004;25(11):2217-24.
83. Skibola CF, Smith MT. Potential health impacts of excessive flavonoid intake. Free radical biology and medicine. 2000;29(3-4):375-83.
84. Pandey M, Kaur P, Shukla S, Abbas A, Fu P, Gupta S. Plant flavone apigenin inhibits HDAC and remodels chromatin to induce growth arrest and apoptosis in human prostate cancer cells: in vitro and in vivo study. Molecular carcinogenesis. 2012;51(12):952-62.
85. Knowles LM, Zigrossi DA, Tauber RA, Hightower C, Milner JA. Flavonoids suppress androgen-independent human prostate tumor proliferation. Nutrition and cancer. 2000;38(1):116-22.
86. Hessenauer A, Montenarh M, Götz C. Inhibition of CK2 activity provokes different responses in hormone-sensitive and hormone-refractory prostate cancer cells. International journal of oncology. 2003;22(6):1263-70.