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# Unlocking the Anticancer Potential of Apigenin: A Review of Its Chemistry, Health Benefits, and Future Prospects

**Ms. Pooja Bharti[1*] Prof.(Dr.) Dharmendra Ahuja[2]**

1. Faculty of Pharmaceutical Science Jayoti Vidyapeeth women's University, Vedant Gyan Velly, Jharna, Jaipur Rajasthan 303122
2. Dean & Professor, Faculty of Pharmaceutical Science, Jayoti Vidyapeeth Women's University, Vedant Gyan Velly, Jharna, Jaipur Rajasthan 303122

**Correspondence**

**Pooja Bharti**

Faculty of Pharmaceutical Science Jayoti Vidyapeeth women's University

Vedant Gyan Velly, Jharna, Jaipur Rajasthan 303122

**Abstract**

Apigenin, a naturally occurring flavonoid, has garnered significant attention for its potent anticancer properties and diverse health benefits. This review aims to provide a comprehensive overview of apigenin's chemistry, biological sources, health benefits, and future prospects as a cancer therapeutic agent. Chemically, apigenin is a flavone, specifically 4′,5,7-trihydroxyflavone, with a molecular formula of $C_{15}H_{10}O_5$ and a molecular weight of 270.24 g/mol. Its chemical structure consists of three hydroxyl groups, with the first and second in the C5 and C7 positions, and the third at C4′ of the B ring. Apigenin is abundant in various biological sources, including fruits (apples, grapes, and citrus fruits), vegetables (parsley, celery, and chamomile), and medicinal plants. Its widespread presence in the human diet and notable biological activities have made it a subject of extensive research. Apigenin's anticancer effects are attributed to its ability to modulate key signaling pathways involved in cancer cell proliferation, invasion, and metastasis. This review highlights apigenin's promising potential as a natural anticancer agent and underscores the need for further research to unlock its full therapeutic potential.

**Keywords**: Apigenin, flavonoids, chemical structure, pharmacological activities, therapeutic applications, Cancer Therapy, Natural Compounds, Phytochemicals

## Introduction

Cancer is a disease that originates and evolves through genetic and epigenetic modifications involving genes that control cell cycle, adhesion, motility, differentiation, and apoptosis. Human cancers develop as products of multistep processes in which cells acquire functional capabilities that are crucial for their ability to induce malignant tumors.[1] Such capabilities are called “Hallmarks of Cancer” and consist of sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing/accessing vasculature, activating invasion and metastasis, reprogramming cellular metabolism, and avoiding immune destruction.[2-5] These hallmarks are further enriched by two “enabling characteristics” involved in tumor growth and progression: tumor-promoting inflammation and genome instability and mutation. The tumor microenvironment plays an integral role in tumorigenesis and malignant progression, too.[6] Emerging hallmarks also include unlocking phenotypic plasticity, a capability that enables various disruptions of cellular differentiation and appears to be operative in multiple cancer types during primary tumor formation, malignant progression, and/or response to therapy. Another emerging hallmark is non-mutational epigenetic reprogramming, since growing evidence shows that gene-regulatory circuits and networks in tumors can be governed by numerous corrupted and added mechanisms, independent of genome instability and gene mutation. Moreover, the polymorphic microbiomes resident in the colon, other mucosa, and connected organs, or in tumors themselves, can diversely influence cancer development, progression, and response to therapy.[7-10] Finally, an increasing body of evidence reveals that, in certain contexts, senescent cells variously stimulate tumor development and malignant progression. Throughout centuries, natural compounds have been used to treat and prevent diseases, thereby creating new knowledge of the potential of natural agents. Almost 47% of the anticancer drugs available on the market today are derivatives of natural products. Considering natural compounds, polyphenols (flavonoids, stilbenoids, lignans, polyphenolic acids, and other polyphenols) display many anti-carcinogenic properties and, in addition, they can modulate immune system responses and protect normal cells against damage from free radicals. A plethora of studies have documented these anticancer effects: noteworthy examples include anthocyanins from blueberries, epigallocatechin gallate from green tea, resveratrol from red wine, isoflavones from soy, and curcumin from Curcuma longa. Among the over 6000 different flavonoids, quercetin, kaempferol, myricetin, luteolin, and apigenin are the five most ubiquitous plant flavonoids.[10-18]

Apigenin, above all, has gained attention among researchers, partly due to its low toxicity and multiple beneficial bioactivities. Apigenin is one of the most widespread flavonoids in the plant kingdom and one of the most studied phenolic compounds. For centuries, apigenin-containing plant preparations have been used as traditional medicines to treat diseases with an inflammatory and/or degenerative component, such as asthma, insomnia, neuralgia, Parkinson’s disease, and shingles. At the end of the 1950s, apigenin gained scientific interest, primarily due to its modulation of histamine release and bronchodilator properties. In the 1980s, apigenin was proposed to interfere with the process of carcinogenesis. Since then, more and more evidence has suggested its power as an adjuvant chemotherapeutic agent for cancer therapy, both in in vitro and in vivo models.[19-20]

Polyphenols have been proposed to be instrumental to the medicinal activities of many anticancer plant extracts and phytomedicines (Oyenihi & Smith, 2019). The sheer importance of the polyphenol sub-class, flavonoids in cancer chemo-prevention, is evidenced by the amounts of reports from many laboratories and study groups worldwide. In the early 20th century, plant pigments were identified as flavonoids, a group of plants secondary metabolites found in fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine (Nijveldt et al., 2001). Also, the research of Albert Szent-Györgyi mostly in the 1930s advanced the knowledge on the potential health benefits of flavonoids (Szent-Györgyi (1937). Subsequently, the global interest in healthy foods led to a research impulse from the 1960s to date on the health-promoting potential of flavonoids. Epidemiological studies, short-term randomized controlled clinical trials, and preclinical studies showed a relationship between intake of foods rich in fruits and vegetables and the incidence of some cancers, suggesting that certain dietary constituents may thus be effective cancer chemo- preventives (Bode & Dong, 2009; Bondonno et al., 2019; Carocho & CFR Ferreira, 2013; Den Hartog et al., 1965; Kromhout et al., 1982; Perez-Vizcaino & Fraga, 2018).[20-22]

Apigenin (4′,5,7-trihydroxy-flavone) structurally belongs to the flavone subclass of flavonoids with three hydroxyl substituents on the backbone of two benzene rings that are linked via a heterocyclic pyrane ring (**Figure 01**). Apigenin is commonly found in varying concentrations in many herbs, grains, fruits, and vegetables such as parsley, onions, grapefruit, oranges, and chamomile tea, rice, maize, letuce, cabbage, chicory leaves (Awika, 2017; Hostetler et al., 2017). It occurs naturally in the form of apigenin O-glycosides in dry chamomile flowers (Matricaria chamomilla) and parsley (Petroselinum crispum) at concentrations up to 5.3 and 1.3 mg/100 g; about 5% and 1% of the dried plant material, respectively. Apigenin is also present in many plants, vegetables, and spices such as celery, peppermint, thyme green peppers, Aspalathus linearis (Rooibos/redbush tea), and Citrus bergamia (Bergamot juice) (Hostetler et al., 2017).[22-25]

The pharmacological versatility of apigenin are antioxidant, neuroprotective, anti-inflammatory, antidiabetic, blood pressure-lowering, and antimicrobial properties have been well- reported (Ali et al., 2017; Nabavi et al., 2018). The phytocompound has also demonstrated tissue-protective actions against toxicities induced by many xenobiotic and chemotherapeutic drugs (He et al., 2016; Liu et al., 2018; Wu et al., 2021; Zhong et al., 2018). Its high selectivity in terms of toxicity against cancerous cells versus normal cells in comparison to other structurally related flavonoids is valuable in chemoprevention (Gupta et al., 2001; Madunić et al., 2018). The relatively tolerable safety profile coupled with the little scientific evidence of adverse metabolic reactions following apigenin supplementation has further increased its therapeutic utility. The cytotoxic and antitumor effects of apigenin have been reviewed in many recent articles. (Ahmed et al., 2020; Ashrafizadeh et al., 2020; Imran et al., 2020; Javed et al., 2021; Khan et al., 2021; Yan et al., 2017).[26-31]

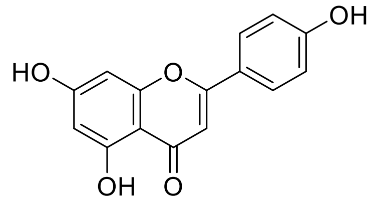

**Figure 01: Structure of Apigenin**

These studies suggest the potential of Apigenin to modulate different signaling pathways implicated in cancer progression by inhibiting cell growth and migration and mediating cell death. Some of the cytotoxic mechanisms of apigenin include blockage of the Wnt/β-catenin signaling pathway, inhibition of cell cycle proteins, activation of p21WAF1/CIP1, modulation of Akt pathway and inhibition of NF-κB/p65 pathway. Others include the downregulation of proteins involved in tumor invasion and metastasis, modulation of pro- and anti-apoptotic proteins expression, inhibition of the Hedgehog/Gli1 signaling pathway, modulation of ATM signaling, deactivation of Wnt/β-catenin pathway and blockage of cellular nutrient transport via inhibition of transporter activity (Bao et al., 2015; Cao et al., 2016; Erdogan et al., 2016; Lin et al., 2017; Meng et al., 2017; Tang et al., 2015).[32-34]

Cancer remains one of the leading causes of morbidity and mortality worldwide, necessitating the development of novel therapeutic strategies. Natural compounds, particularly flavonoids, have emerged as promising anticancer agents due to their minimal toxicity and broad-spectrum efficacy. Apigenin (4′,5,7-trihydroxyflavone) is a bioactive flavonoid found in parsley, chamomile, celery, and citrus fruits, among others.[35]

**Biosynthesis of Apigenin**

Apigenin, a flavonoid, is synthesized in plants via the phenylpropanoid pathway, starting from either L-phenylalanine or L-tyrosine, and involves several enzymatic steps, ultimately leading to the formation of naringenin,[36-38] which is then oxidized to apigenin (**Figure 02)**.

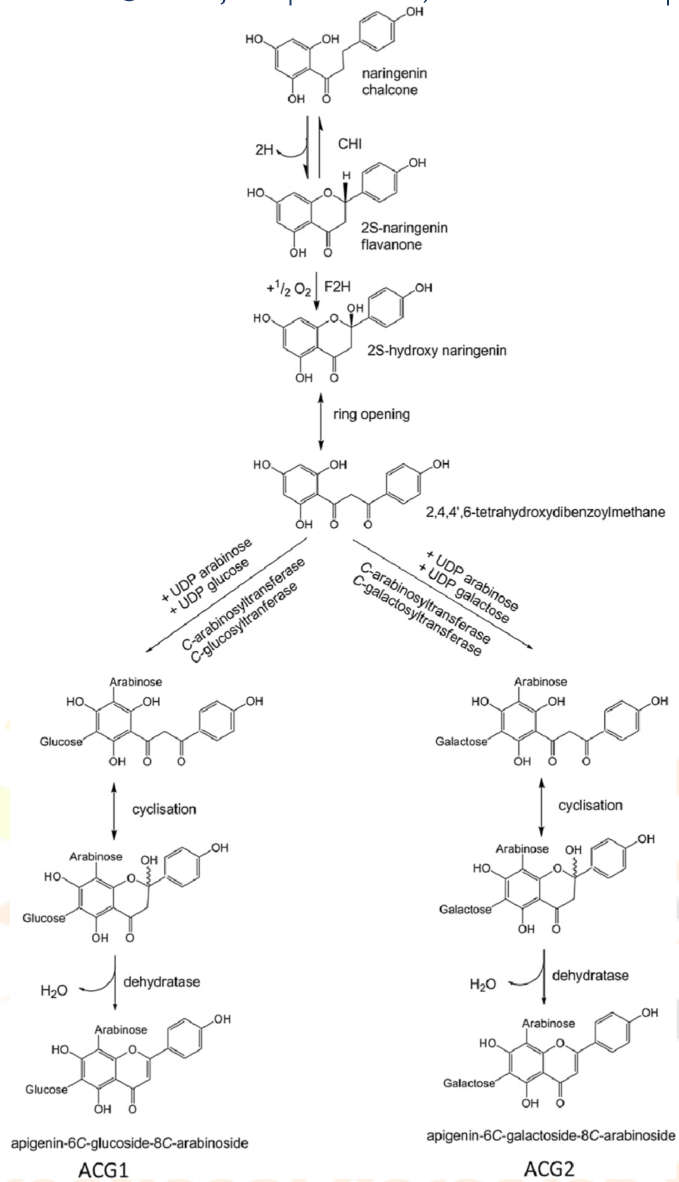


**Figure 02: Biosynthesis of Apigenin**

## General Aspects of Apigenin

Natural Sources of all the flavonoids, apigenin is the most widely distributed in the plant kingdom, found in numerous types of vegetables, fruits, herbs, and spices. Its name is derived from the Apium genus in Apiaceae or Umbelliferae, to which parsley and celery belong, species constituting its major sources in nature. In a 100 g edible portion, parsley (Petroselinum crispum) contains 215.46 mg if it is consumed fresh and 4503.50 mg if it is consumed dried, while fresh celery (Apium graveolens) contains 19.10 mg and its seeds contain 78.65 mg. Other sources of high apigenin content include Chinese celery, celeriac, white and red sorghum, onions, tea, maize, oranges, wheat sprouts, oregano, thyme, peppermint, rosemary, sage, artichoke, juniper berries, and kumquat.[39-45] Apigenin is the most prevalent flavonoid in the dried flowers of Matricaria chamomilla: infusions of chamomile contain maximum concentrations of apigenin ranging from 0.8 to 1.2%. In nature, apigenin also exists as a dimer, biapigenin, mainly isolated from the buds and flowers of Hypericum perforatum. Moreover, the cannabis plant produces a considerable number of flavonoids, and their distribution varies in the plant, focusing mainly on flowers, leaves, and stems. Their total content reaches about 2.5% of the dry weight of flowers and leaves, while it is almost non-existent in seeds and roots. Apigenin is one of the flavonoidal molecules that (together with kaempferol, quercetin, vitexin, and isovitexin, luteolin, and orientina) modifies the activity of Δ-9-tetrahydrocannabinol through a mechanism shared with cannabidiol and some terpenes.[46]

**Chemistry and Biological Activity**

Flavonoids are plant secondary metabolites that share a common carbon skeleton of diphenyl-propane, containing two benzene rings (A and B) connected by a three-carbon linking chain that forms a heterocyclic ring containing oxygen, the C ring, with a benzenic A ring. In most cases, the B ring is attached to position 2 of the C ring, but it can also bind in position 3 or 4. Flavonoids in which the B ring is linked in position 3 are called isoflavones and those in which the B ring is linked in position 4 are called neo-flavonoids. Those in which the B ring is linked in position 2 can be further subdivided into 6 subgroups, based on the structural features of the C ring: flavones, flavonols, flavanones, flavanonols, flavanols or catechins, anthocyanins, and chalcones. Flavones differ from other flavonoids in that they have a double bond between C2 and C3;[47-58] there is no substitution at the C3 position, and they are oxidized at the C4 position (The compound apigenin (4′,5,7-trihydroxyflavone) is a natural flavone with the molecular formula $C_{15}H_{10}O_5$ and a molecular weight of 270.24 g/mol. It has three hydroxyl groups, with the first and second in the C5 and C7 positions, and the third at C4′ of the B ring. It is a yellow crystalline powder that is insoluble in water and soluble in dimethyl sulfoxide and hot ethanol. According to the Biopharmaceutics Classification System, apigenin is categorized as a Class II drug, whose characteristics are low solubility and high permeability: its absorption is therefore limited by its slow dissolution in the gastrointestinal tract. In nature, apigenin mainly exists in O- and C- glycosidic forms and occasionally as aglycone.[59-60] The most common apigenin glycosides are apigenin-7-Oapiosylglucoside (apiin), apigenin-7-O-glucoside, apigenin-8-C-glucoside (vitexin), and apigenin-6-C-glucoside (isovitexin). Flavonoids are characterized by a wide range of biological activities, such as antioxidant, anti-inflammatory, anti-mutagenic, and antiviral activities, demonstrated by numerous in vitro and in vivo studies. Moreover, flavonoids can reduce plasma low-density lipoprotein levels, inhibit platelet aggregation, and reduce cell proliferation. In the context of systemic inflammation and the reactivations of the Zoster and Epstein–Barr virus (EBV), the results of the interference of apigenin in viral reactivations are highlighted. The EBV, a member of the γ-herpesviruses, infecting the majority of the world's human population, plays a causal role in infectious mononucleosis, hairy leukoplakia, and post-transplant lymphoproliferative disorders, and is highly associated with several human malignancies, including Burkitt's lymphoma and nasopharyngeal carcinoma (NPC).[62-65] The EBV primarily infects circulating human B cells and is kept in a latent state. The lytic reactivation of the EBV plays an important role in various human malignancies, being highly correlated with cancer progression, poor prognosis, and tumor recurrence of NPC, peculiarly. The ability of apigenin to inhibit the lytic induction of the EBV, reactivation in the lytic cycle, and virion production by EBV-positive NPC cells, appears to be beneficial for cancer prevention. Wu et al. have provided new insights into the biological application of apigenin for anti-EBV therapy. The detection of lytic proteins using a Western blot analysis showed that the EBV could normally express lytic proteins. However, the protein expression was gradually repressed after apigenin treatment, demonstrating that apigenin can inhibit EBV reactivation and repress EBV lytic protein expressions, acting as a potential dietary compound for preventing EBV reactivation.[66-70]

Apigenin promotes different anti-inflammatory pathways, including the p38/MAPK and PI3K/Akt pathway, prevents the IKB degradation and nuclear translocation of the NFκB, and reduces COX-2 activity. Apigenin enhances the expression of anti-oxidant enzymes such as GSH-synthase, catalase, and superoxide dismutase to counteract cellular oxidative stress. Furthermore, apigenin has been shown to inhibit, in vitro, rat brain monoamine oxidases and to have potential activity against depression and neurodegenerative diseases, such as Parkinson’s and Alzheimer’s disease. Apigenin has also demonstrated anti-diabetic properties thanks to its capacity to inhibit glucosidase activity, increase the secretion of insulin, and interact with and neutralize reactive oxygen species (ROS) in the cell, contributing to the prevention of diabetic complications. Studies carried out over the years have suggested that apigenin can be a therapeutic agent against different types of cancers. It has the ability, in vitro and in vivo, to modulate different hallmarks of cancer, such as cell proliferation, metastasis, apoptosis, invasion, and cell migration, and it can also stimulate an immune response.[71-89]

**Chemical Structure and Properties**

Apigenin is a low-molecular-weight flavonoid ($C_{15}H_{10}O_5$) with a structure characterized by three hydroxyl groups that contribute to its antioxidant and biological activities. Its flavone backbone comprises two benzene rings (A and B) linked by a heterocyclic pyrone ring (C), with a specific hydroxylation pattern at positions 4′, 5, and 7. This structure facilitates interactions with various biomolecules, underpinning its pharmacological effects. However, apigenin's poor water solubility and rapid metabolism limit its bioavailability. Strategies to enhance its absorption, such as nanoparticle-based formulations, liposomes, and conjugation with phospholipids, are being explored to improve its therapeutic efficacy.[90]

**Pharmacological Activities**

**Apigenin as antioxidant Activity**

Apigenin exhibits potent antioxidant properties by scavenging free radicals and upregulating endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT). These actions help mitigate oxidative stress, a contributor to aging and various chronic diseases.[91-96]

**Apigenin as anti-Inflammatory Effects**

The anti-inflammatory potential of apigenin is attributed to its ability to inhibit pro-inflammatory mediators and cytokines. It suppresses pathways like NF-κB, thereby reducing inflammation-related pathologies.[97-99]

**Apigenin as gastro-intestinal agent**

Colitis is an inflammation-causing illness of the intestine with an unidentified etiology with many immunological, genetic, and environmental components factors. They were interested in examining the effect of total extract from Dracocephalum kotschyi (D. kotschyi) Boiss. Apigenin is administered 2 h prior to the induction of colitis, which is induced by intrarectal administration of acetic acid 4% in rats. Prednisolone is additionally employed as a standard drug. Inflammation inside the colon is evaluated by measuring myeloperoxidase (MPO) activity.[100] Mucosal ulcerations is evaluated. Instillation of acetic acid caused inflammatory reactions. Pre-treating the animals with D. kotschyi extract, apigenin, or prednisolone before treatment brought about a rise in MPO activity in the vehicle-treated groups, whereas the animal levels returned to normal. The groups given apigenin treatment and D. kotschyi exhibited notably reduced macroscopic and microscopic characters. Apigenin's positive effects were similar to those of prednisolone. Their studies have demonstrated the anti-inflammatory properties among apigenin and D. kotschyi extract in colitis which was induced. Conversely, pretreatment with apigenin at doses of 10 and 20 mg/kg led to a dose-dependent improvement in both the macroscopic and microscopic features of the gastric mucosa, similar to the effects of omeprazole.[101-103] The gastro protective properties of apigenin may stem from its anti-inflammatory, antioxidant, and anti-apoptotic activities, along with its ability to enhance TGF-β1 expression. Apigenin effectively alleviated DSS-induced ulcerative colitis (UC) by balancing the gut microbiome, which helped to inhibit inflammation and protect the gut barrier. With its low toxicity and high efficacy, apigenin could be a promising therapeutic strategy for treating UC by regulating the interactions and mechanisms between the host and microorganisms. Gamma irradiation and apigenin significantly improved the biochemical and histopathological changes induced by acetic acid. Both treatments effectively restored the levels of the investigated biomarkers in the colon, as well as modulated body weight, colon weight-to-length ratio, and disease activity index (DAI).[104-107] This study suggests that low-dose gamma irradiation could serve as a new therapeutic option for managing ulcerative colitis (UC). Additionally, we found that apigenin also offers therapeutic benefits in UC management.[108]

**Apigenin as anti-asthmatic agent**

Apigenin has anti-inflammatory and antioxidant activities that have occurred widely documented in recent years. Chronic inflammation of the lungs and airway resistance are frequent in patients with asthma and COPD and cannot be disregarded. In order to eliminate such lung diseases, they examine how API functions in many ways across numerous routes. The ovalbumin (OVA) sensitization model in BALB/c mice was first exposed to oral gavage intervention with either API or dexamethasone. Asthma-related inflammatory mediators, including IGE, IL-4, IL-5, IL-13, and IL-17, showed a decrease in alveolar lavage fluid release in the API-administered group in contrast to the model group.[109-110] Various doses of API intervention effectively reduced airway resistance in the administered group, decreased inflammation, reduced mucus secretion, and inhibited airway resistance. By blocking the MAPK pathway, the given group of APIs exhibits anti-inflammatory and anti-apoptotic properties. Accordingly, in contrast with the model group, the administered group's phosphorylation levels of ERKs, JNKs, and p38 MAPKs are reduced. API was able to reduce apoptosis in airway epithelial cells via the MAPK pathway in the in vitro model stimulated by house dust mites (HDMs). The findings indicate that apigenin demonstrated both anti-allergic and anti-neutrophil-related inflammatory activities in a murine asthma model exposed to PM2.5.[111-115] This effect may be due to its modulation of IL-17 and down-regulation of NF-κB expression. Therefore, apigenin could be a promising candidate for preventing the exacerbation of pre-existing asthma caused by PM2.5 exposures.[116]

**Apigenin as antidiabetic agent**

These days, diabetes is among the primary causes; global research indicates that the majority of people have the disease. Diabetes results from an insulin shortage in the body. Apigenin has been shown in studies to have antidiabetic properties. Because of apigenin's biological action of reducing blood sugar levels, rats with diabetes were given streptozotocin. The lipid profile, malondialdehyde, and á-amylase activity in serum are all decreased in streptozotocin-induced diabetic rats. The findings of the immunohistochemistry and histopathology analyses verified that apigenin can lessen progressive changes in pancreatic cells. In diabetic rats, apigenin acts as a hypoglycemic drug and modifies some metabolic markers.[117-120] These results indicate that apigenin is a promising candidate with significant anti-diabetic effects on β-cells. It enhances glucose-stimulated insulin secretion and protects against ER stress-induced β-cell apoptosis, potentially by reducing the expression of CHOP and TXNIP. This action helps to promote β-cell survival and function.[121]

**Apigenin as neuroprotective Properties**

Apigenin has demonstrated neuroprotective effects, including muscle relaxation and sedation, depending on the dose. It also exhibits potential in treating neurodegenerative disorders such as Alzheimer's disease, owing to its antioxidant and anti-inflammatory activities.[122-123]

**Apigenin as hepatoprotective agent**

These days, alcohol consumption leads to liver damage such as hepatocarcinoma, cirrhosis, fibrosis, and steatohepatitis. There are currently no pharmaceutical treatments that may correct these disorders. One of the most prevalent flavonoids, apigenin, has several impacts on different activities, one of which is connected to its liver activity. So that calculate the results observed, 56% erguotou wine was given to experimental mice to induce liver injuries. Simultaneously, apigenin was given by gavage to the mice.[124-125] Hepatic cytochrome P450 2E1 (CYP2E1), nuclear factor kappa B proteins, hepatic malondialdehyde contents, and tumor necrosis factor-alpha were all reduced in apigenin-treated mice.[126-128] The amount of liver-reduced glutathione, glutathione reductase, glutathione peroxidase, and glutathione S-transferase are increased by large doses of apigenin. The preliminary treatment with apigenin may boost hepatic peroxisome synthesis. The magnitude of expression of fatty acid synthase, diacylglycerol acyltransferase, hepatic sterol regulatory element binding protein-1c, proliferator-activated receptor alpha (PPARα), and carnitine palmitoyltransferase-1 proteins is decreased. These studies showed that apigenin had a reduced protective effect against alcohol-induced liver damage. Overall, the results indicate that apigenin alleviated liver injury by reducing inflammation and oxidative stress via suppression of the non-canonical NF-κB pathway. This suggests that apigenin has potential as a treatment for liver injury. Apigenin administration also restored the hepatic architecture disrupted by lipopolysaccharide treatment. This study demonstrated the potential of extracts from E. ritro leaves (ERLE) and flowering heads (ERFE) as hepatoprotective agents against diclofenac-induced lipid peroxidation and oxidative stress in both in vitro and in vivo conditions.[129-135]

**Apigenin as haemopoietic agent**

Flavonoid apigenin, which is present in fruits and vegetables, inhibits the growth of cancer by inducing apoptosis. Erythrocytes can also experience eryptosis, or suicide cell death. Cell shrinkage and phosphatidylserine exposure at the cell surface are features of eryptosis. Eryptosis causes an increase in ceramide production, cytosolic calcium activity, and ATP depletion.[136-137] Ca was determined by measuring fluorescence, cell volume by forward scatter, hemolysis by hemoglobin release, phosphatidylserine exposure by annexin V binding, ceramide by using antibodies, and cytosolic ATP using luciferin-luciferase by providing apigenin. A prolonged 48-h exposure to Apigenin did not cause a notable change in hemolysis, despite increased calcium (Ca2 ($\geq$1 µM), increased in ceramide production (15 µM), decreased ATP concentration (15 µM), decreased forward scatter ($\geq$1 µM), and increased annexin V binding ($\geq$5 µM). This demonstrates the positive effects of apigenin on stimulation of calcium entry, ATP depletion in erythrocytes, and suicidal erythrocyte death. Research has shown that apigenin is highly effective in suppressing activated NF-κB and pro-inflammatory cytokines. This suggests that apigenin, when given as a dietary supplement, protects irradiated male C57BL/6 J mice from Si-ion-induced damage to hematopoietic tissues through its anti-inflammatory activity.[138-142]

**Apigenin as antiosteoporosis agent**

As is well known, apigenin has several positive impacts on a variety of processes, including osteoclast activity. Studies on the bone-protective properties of apigenin in estrogen-deficient ovariectomized rats show that it both inhibits and causes osteoclast apoptosis, 9-month-aged Sprague Dawley rats taken.[143-144] To cause bone loss, the AIN-93G diet was provided to three-month-old female Sprague–Dawley rats with ovariectomies and a sham operation for seven weeks. For fifteen weeks, apigenin was given three times a week by a non-invasive method using zoom-in micro-computed tomography. Following bone loss, apigenin lowers body weight and food intake, and it also raises mineral content and the density of the trabecular bone at the left femur's neck. According to biochemical studies, apigenin increases bone turnover.[145-148]

**Apigenin as nephroprotective properties**

In a study, the nephroprotective efficacy of apigenin as dietary supplements against cisplatin-induced renal injury, using human embryonic kidney (HEK-293) cells was evaluated through in vitro model. The findings from MTT assays, morphological studies, comet assays, and ROS analysis indicate that the combinations of CIS 11.36 µM +API 12.5 µg/mL provide protection against cisplatin-induced nephrotoxicity. Additionally, western blot analysis suggests that NGAL is involved in the nephroprotective effects of both API and KMP.[149-150] Overall, the results indicated that apigenin is promising candidates for further development as renoprotective agents against cisplatin-induced toxicity. Apigenin showed promising result as a novel renoprotective agent, mitigating kidney injury induced by hypercholesterolemia (HC). It does so by modulating the KIM-1, Fn1, and Nrf2 signaling pathways. This effect suggests that apigenin could be a valuable adjunct to antihypercholesterolemic medications, potentially addressing the severe renal complications associated with HC. Apigenin administration reduced renal inflammation and apoptosis by lowering levels of interleukin-1β, tumor necrosis factor-alpha, nuclear factor Kappa-B, Bax, and caspase-3, while increasing B-cell lymphoma-2 compared to the GM administered group.

These findings suggest that apigenin treatment could help alleviate renal impairments associated with gentamicin administration.[151-153]

**Apigenin as antimicrobial Effects**

Studies have reported that apigenin possesses antimicrobial properties, including antibacterial, antifungal, and antiparasitic activities. Its interactions with human gut microbiota suggest potential in modulating microbial balance and enhancing gut health.[154]

**Apigenin as cardio protective properties**

Celery, chamomile, lemon, papaya, guava, etc. are foods high in apigenin. Apigenin's cardio protective activity against the isoproterenol drug was investigated. Rats were given isoproterenol to cause myocardial damage and (ISO)-induced oxidative stress during β-adrenergic receptor stimulation by sustained hemodynamic stimulation. To assess and normalize myocardial damage and biochemical and histological alterations in both the vehicle and control groups, apigenin is given at varied dosages. Rats treated with ISO showed a substantial decrease in both the diastolic and systolic arterial pressures, although a maximum positive rate of developed left ventricular pressure. Taking everything into account, it was a notable decrease in the functioning of the creatine kinase-MB isoenzymes, as well as an increase in the content of malondialdehyde and a decrease in glutathione, superoxide dismutase, catalase, and glutathione levels. the impact of apigenin function on myocardial harm brought about by isoproterenol. By reducing all of the internal parameters and the membrane-bound enzymes, damage was shown. Histopathological investigations verified it. The impact of AP administered at 50 and 75 mg/kg and the actions of AP that shield the myocardium against experimentally induced myocardial infarction. The present new evidence revealed that apigenin promotes the unfolded protein response in mitochondria (UPRmt) by regulating the Sirt1/Atf5 pathway. The findings suggest that apigenin could serve as an effective therapeutic agent to reduce cardiotoxicity caused by Doxorubicin.[155-157]

**Apigenin as anticancer Activity**

Apigenin has been studied for its chemo preventive properties, inducing apoptosis and cell cycle arrest in various cancer cell lines. Its low toxicity and ability to target multiple signaling pathways make it a promising candidate for cancer therapy.[158]

**Mechanisms of Anticancer Action**

**Induction of Apoptosis**

Apigenin promotes programmed cell death in various cancer types by modulating intrinsic and extrinsic apoptotic pathways. It upregulates pro-apoptotic proteins such as Bax and caspases while downregulating anti-apoptotic proteins like Bcl-2. Additionally, apigenin triggers mitochondrial dysfunction, leading to cytochrome c release and subsequent activation of the apoptotic cascade.[159]

**Cell Cycle Arrest**

One of the key anticancer mechanisms of apigenin is its ability to induce cell cycle arrest at different phases, primarily G2/M and G1 phases. By inhibiting cyclin-dependent kinases (CDKs) and reducing the expression of cyclins, apigenin prevents uncontrolled cell proliferation.[155]

**Inhibition of Metastasis and Angiogenesis**

Metastasis and angiogenesis play crucial roles in cancer progression. Apigenin suppresses the epithelial-mesenchymal transition (EMT), reduces matrix metalloproteinase (MMPs) activity, and inhibits vascular endothelial growth factor (VEGF), thereby limiting cancer cell invasion, migration, and new blood vessel formation.[160]

**Modulation of Key Signaling Pathways**

Apigenin interacts with several oncogenic signaling pathways, including: PI3K/Akt/mTOR Pathway: Inhibits Akt phosphorylation, leading to decreased cancer cell survival. NF-κB Pathway: Suppresses NF-κB activation, reducing inflammation-driven tumor progression. MAPK/ERK Pathway: Modulates MAPKs to induce apoptosis and inhibit proliferation. Wnt/β-catenin Pathway: Downregulates β-catenin, thereby reducing cancer stem cell-like properties.[161]

**Synergistic Effects with Conventional Therapies**

Apigenin has been shown to enhance the efficacy of chemotherapeutic agents such as doxorubicin, cisplatin, and 5-fluorouracil while reducing their toxicity. Combination therapy with apigenin improves drug sensitivity, prevents resistance, and minimizes side effects, making it a promising candidate for adjunct cancer therapy.[162]

**Preclinical and Clinical Studies**

Several preclinical studies have demonstrated apigenin's efficacy in various cancers, including breast, prostate, lung, colorectal, and skin cancers. However, clinical trials are limited. Early-phase clinical studies suggest that apigenin is well tolerated with minimal side effects, highlighting its potential for further investigation in human trials.[163-168]

**Challenges and Future Directions**

Future research on apigenin should focus on enhancing its bioavailability, which is crucial for maximizing its therapeutic potential. This can be achieved by investigating innovative delivery systems, such as nanoparticles, liposomes, and emulsions, as well as exploring dietary strategies and co-administration with other compounds to improve absorption and efficacy. However, apigenin's poor solubility (log P = 2.34) and rapid metabolism, resulting in limited systemic exposure, pose significant challenges. Its major metabolites, apigenin-7-O-glucuronide and apigenin-4'-O-glucuronide, further limit its bioavailability, which is estimated to be < 1%.

To overcome these challenges, Nano formulations can be developed to improve apigenin's solubility and bioavailability. Nanoparticle composition can include lipids, polymers, or metal-organic frameworks. Additionally, prodrug design can improve apigenin's solubility and stability, and enhance its therapeutic efficacy. Prodrug strategies can involve phosphate, sulfate, or amino acid conjugation. Combination therapies can also be explored to enhance apigenin's therapeutic outcomes, including chemotherapy and targeted therapy.

In-depth mechanistic studies are necessary to elucidate the specific molecular pathways and targets influenced by apigenin. By gaining a clearer understanding of its mechanisms across various diseases, researchers can refine its therapeutic applications and identify optimal contexts for use. Clinical research should be prioritized through well-designed clinical trials that assess apigenin's efficacy and safety in diverse populations and medical conditions. Investigating apigenin's interactions with the gut microbiome is also a promising avenue, as it may reveal how apigenin modulates microbial populations and, consequently, metabolic and inflammatory responses.

Further emphasis on formulation development is warranted, including exploring new formulations such as solid dispersions and transdermal patches, which can enhance the delivery and clinical efficacy of apigenin. Thorough safety and toxicology assessments are essential for establishing the safety profile of apigenin, especially regarding potential side effects and interactions with other medications in long-term usage scenarios. The concept of personalized medicine can also be applied to apigenin research, where genetic factors that may influence individual responses to apigenin can be investigated to develop personalized therapeutic strategies. Lastly, examining the regulatory landscape for apigenin as a dietary supplement or therapeutic agent is crucial for developing clear guidelines for its use in clinical practice.

## Conclusion

In conclusion, apigenin, a naturally occurring flavonoid, has emerged as a promising anticancer agent, exhibiting potent inhibitory effects against various types of cancer through multiple mechanisms of action. Its ability to induce apoptosis, regulate cell cycle progression, inhibit metastasis, and modulate key signaling pathways, including the PI3K/Akt, MAPK/ERK, and NF-κB pathways, underscores its potential as a multifaceted anticancer agent.

However, despite its promising preclinical profile, several challenges need to be addressed to optimize its clinical application. These include its poor water solubility, rapid metabolism, and limited bioavailability, which can be overcome through innovative drug delivery systems, such as nanoparticles, liposomes, and Nano emulsions. Additionally, prodrug design and combination therapies with conventional anticancer agents may enhance its therapeutic efficacy.

Furthermore, apigenin's potential for personalized medicine, particularly in the context of genetic variations affecting its metabolism and efficacy, warrants further investigation. Elucidating the molecular mechanisms underlying its anticancer effects and exploring its synergistic interactions with other phytochemicals and conventional therapies may also provide valuable insights into its therapeutic applications.

In light of these considerations, continued research efforts are necessary to unlock apigenin's full therapeutic potential and translate its anticancer properties into clinical practice. Future studies should focus on optimizing its formulation, exploring its combination with other therapies, and investigating its efficacy in diverse cancer types and patient populations. Ultimately, the development of apigenin as a clinically effective anticancer agent holds promise for improving cancer treatment outcomes and enhancing patient quality of life.

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**Conflicts of Interest**

The authors declare no conflicts of interest.

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