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To cite this article: Fahad Ali, Rahul, Falaq Naz, Smita Jyoti & Yasir Hasan Siddique (2017) Health functionality of apigenin: A review, International Journal of Food Properties, 20:6, 1197-1238, DOI: [10.1080/10942912.2016.1207188](https://doi.org/10.1080/10942912.2016.1207188)

To link to this article: <https://doi.org/10.1080/10942912.2016.1207188>



Published online: 18 Dec 2016.



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Health functionality of apigenin: A review

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ABSTRACT

Apigenin is being used by humans in the form of plant extract for the treatment of a number of disorders and inflammatory conditions, until its discovery as a core compound. Apigenin, chemically known as 4', 5, 7,-trihydroxyflavone is a yellow crystalline powder belonging to the flavone class, that is the aglycone of several naturally occurring glycosides. It is insoluble in water but soluble in organic solvents. Numerous pharmacological activities, including anti-inflammatory, anti-toxicant, anti-cancer, etc., are attributed to apigenin. Research has shown that apigenin has numerous molecular targets involved in inflammation. Based on the *in vivo*, *in vitro*, and clinical trial studies suggested that apigenin is a potent therapeutic agent to overcome diseases such as rheumatoid arthritis, autoimmune disorders, Parkinson's disease, Alzheimer's disease, and various type of cancers. Delayed plasma clearance and slow decomposition in liver increases its systemic bioavailability, and makes it a strong therapeutic agent in pharmaceutical studies. In the present review, detailed accounts of the properties of apigenin have been discussed.

ARTICLE HISTORY

Received 11 March 2016
Accepted 25 June 2016

KEYWORDS

Apigenin; anti-inflammatory;
anti-toxicant; anti-cancer;
natural plant product

Introduction

Flavonoids have been known as an important plant product for over a century. Rusznyak and Szent-Gyorgyi for the first time in 1936 published literature regarding their biological activity.^[1] The term “vitamin P” was suggested for flavonoids, but it was later dismissed.^[2] Flavonoids belong to the large group of polyphenolic compounds that are widely distributed in all foods of plant origin and are divided into sub classes, including flavones, flavanones, flavanols, isoflavones, anthocyanidins, and flavanols.^[3] Polyphenols are produced as a result of the secondary metabolism of plants and are frequently found attached to sugars (glycosides), thus tending to be water-soluble. Occasionally, polyphenols also occur in plants as aglycones. Polyphenols arise biogenetically from two main synthetic pathways: the shikimate pathway and the acetate pathway.^[4] More than 8000 polyphenolic structures are currently known.^[5]

The basic carbon skeleton of a flavonoid is the flavan nucleus, containing 15 carbons arranged in two aromatic rings connected by a 3 carbon bridge, forming a diphenyl propane structure (C₆-C₃-C₆), which may or may not be the part of third ring.^[7] For convenience the rings are named as A, B, and C (Fig. 1). Biogenetically, ring A usually arises from a molecule of resorcinol or phloroglucinol synthesized from the acetate pathway and has a characteristic hydroxylation pattern at the 5th and 7th position.^[8] The B ring comes from the shikimate pathway and is usually 4', 3', 5'-hydroxylated. Flavonoids occur as aglycones, glycosides, and methylated derivatives.^[9] For the nomenclature of flavonoids A and C rings have simple numerals, while primed numerals are used for B-ring. Primed modified numbering system is not used for chalcones and the isoflavones derivatives: the pterocarpan and the rotenoids.^[10]

Literature exists regarding flavonoids content in food and beverages of plant origin, such as fruits, vegetables, tea, cocoa, and wine.^[11–16] Flavonoids have been reported to exert wide range of biological

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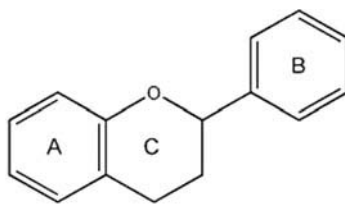


Figure 1. Basic structure of flavonoids.^[6]

activities. These includes: anti-inflammatory, antibacterial, antiviral, antiallergic^[17-19], cytotoxic antitumor, treatment of neurodegenerative diseases, vasodilatory action.^[18,20-22] In addition flavonoids are known to inhibit lipid-peroxidation, platelet aggregation, capillary permeability and fragility, cyclooxygenase, and lipoxygenase enzyme activities. They exert these effects as antioxidants, free radical scavengers, chelators of divalent cation.^[19,22,23] These are also reported to inhibit variety of enzymes like hydrolases, hyaluronidase, alkaline phosphatase (ALP), arylsulphatase, cAMP phosphodiesterase, lipase, α -glucosidase kinase.^[24] Apart from these studies, one group of researchers showed that there was no significant association between the total dietary intake of flavonoids in food and the incidence of site specific cancers.^[25] The dietary intake of flavonoids is estimated to be 1–2 g/day.^[26] The average intake of flavonoids as flavonols and flavones have ranged from 6 mg/day in Finland to 64 mg/day in Japan, with intermediate intake in the United States (13 mg/day), Italy (27 mg/day), and the Netherlands (33 mg/day). The estimates were based on the intake of five major flavonoids: quercetin, luteolin, apigenin, myricetin, and kaempferol in composite food.^[27]

Apigenin

Apigenin, chemically known as 4', 5, 7,-trihydroxyflavone, is a natural product belonging to the flavone class that is the aglycone of several naturally occurring glycosides with molecular formula $C_{15}H_{10}O_5$ and molecular weight 270.24 (Fig. 2). Flavones, as well as some of their synthetic derivatives, have been shown to exhibit several biological activities, including antioxidant, anti-inflammatory, antitumor, ant-genotoxic, anti-allergic, neuroprotective, cardioprotective, and antimicrobial.^[28] Apigenin is a yellow crystalline solid that has been used to dye wool.

Apigenin derivatives or natural analogues

Apigenin is a flavonoid derivative with three hydroxyl substituent, as suggested by its chemical name (4', 5, 7,-trihydroxyflavone). Removal of the hydroxyl groups yields basic structure of flavones (a). Apigenin can be mono-substituted separately at positions 4', 5 and 7, resulting in the formation of different compounds 4'-hydroxyflavone (b), 7-hydroxyflavone (c), and 5-hydroxyflavone (d). Further hydroxylation can generate three dihydroxy-flavones 4',7-dihydroxyflavone (e), 4',5-dihydroxyflavone (f), and 5,7-dihydroxy flavones (g; Fig. 3). Overall, the apigenin has at most seven possible derivatives/analogues generated from the selective hydroxyl substitutions at positions 4', 5, and 7 of the basic flavonoid skeleton.^[29]

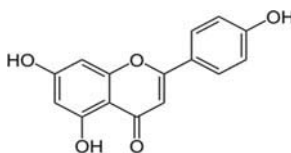


Figure 2. Structure of Apigenin.

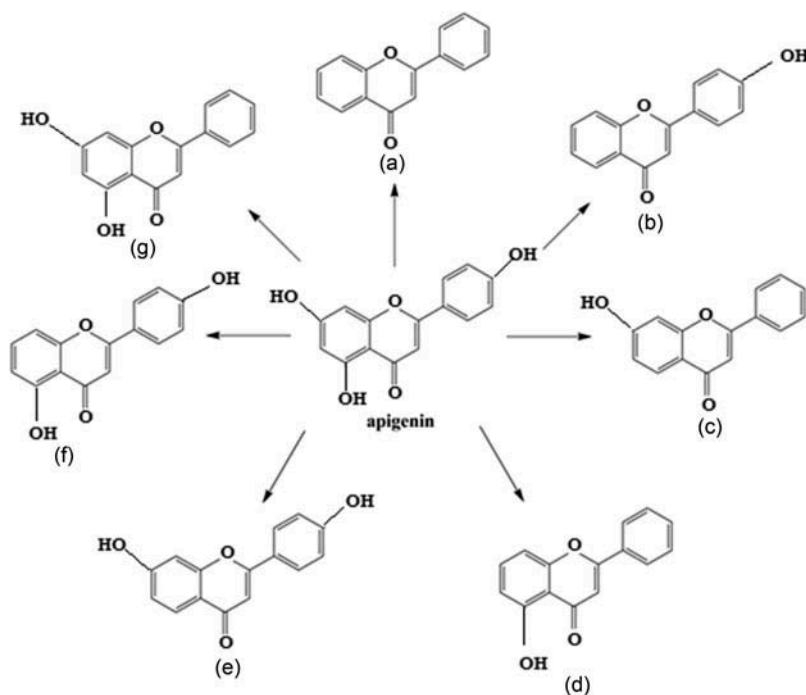


Figure 3. Apigenin derivatives and natural analogues.^[29]

Genkwanin which is an O-methyl derivative of apigenin has been indentified so far in plants like *Daphne genkwa*, seeds of *Alnus glutinosa*.^[30,31] Another methoxy derivative of apigenin is acacetin (Apigenin-7-O- β -D-galactopyranoside) synthesized by the action of an enzyme apigenin 4'-O methyl transferase. Acacetin is isolated from *Turnera diffusa* and *Chrysanthemum morifolium*.^[32,33] The enzyme apigenin 4'-O methyltransferase uses S-adenosyl methionine and 5,7,4'-trihydroxyflavone (apigenin) to produce S-adenosylhomocysteine and 4-methoxy 5,7-dihydroflavone (Acacetin). In nature, apigenin also exists as a dimer, bi-apigenin, mainly isolated from the buds and flowers of *Hypericum perforatum* (Fig. 4),^[34] which has neuroprotective effects.^[34,35]

Biosynthesis of apigenin and its derivatives

Apigenin is synthesized in a number of plants as secondary metabolite. A variety of plants, such as parsley, celery, onions, oranges, chamomile, maize, rice, tea, wheat sprouts, some grasses, etc., are known to synthesis apigenin and its derivatives.^[3,36–38] All flavonoids are basically synthesized in plants from a

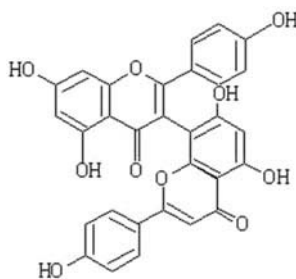


Figure 4. Structure of bi-apigenin.^[34]

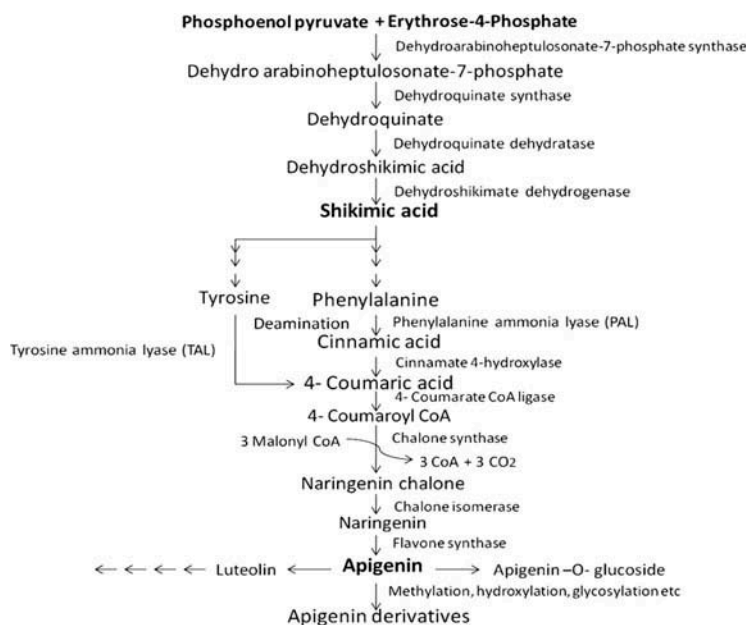


Figure 5. Biosynthesis of apigenin and its derivatives.

single basic pathway called shikimic acid pathway. This pathway converts simple carbohydrate precursor's erythrose-4-phosphate (E4P) and phosphoenol pyruvate (PEP) to aromatic aminoacids. E4P and PEP act as initiating molecules which fuse together under the influence of dihydroarabino heptulosonate-7-phosphate synthase (DAHP synthase) to form dihydroarabino heptulosonate-7-phosphate. The product is subsequently transformed into dehydroquininate, dehydro shikimate, shikimic acid, and aromatic ring containing aminoacids (phenylalanine and tyrosine) under the influence of respective enzymes shown in Fig. 5. Most abundant classes of flavonoids in plants are derived from deamination of phenylalanine and tyrosine to cinnamic acid. Cinnamic acid undergoes several downstream biosynthetic steps producing naringenin (Fig. 5). Naringenin is the key intermediate of the flavone/anthocyanin pathway, serving as the common precursors for a large number of downstream flavonoids as described previously.^[37–39] A complete, well-defined proposed pathway for apigenin and its derivatives biosynthesis is given in Fig. 5. Certain glycosyl transferases, hydroxyl transferases, and methyl transferases are thought to be involved in O- or C-glycosylation, methylation, and hydroxylation of apigenin to form its derivatives. Recent studies have shown that O-methyl derivatives of apigenin like genkwanin can be synthesized in *E.coli* cells on introducing six plant derived genes viz; tyrosine ammonia lyase (TAL), 4-coumaroyl coenzyme-A ligase (4-CL), chalcone synthase (CHS), chalcone isomerase (CHI), flavone synthase (FNS), and apigenin 7-O-methyl transferase (POMT7) in them. Recombinant *E. coli* strain was able to produce 41 µg/L genkwanin (7-O-methyl apigenin) in culture.^[40]

Apigenin conjugates in plants

Conjugation of apigenin with sugars forms a number of naturally occurring glycosides in plants (Fig. 6).

- (1) Apiin (apigenin 7-O-apioglucoside), isolated from parsley and celery.^[41]
- (2) Apigetarin (apigenin 7-glucoside), found in *Teucrium gnaphalodes*^[42] and in the roots of dandelion coffee.
- (3) Vitexin (apigenin 8-C-glucoside), present in mung bean^[43] and in the bamboo leaves,⁴⁴ *Ficus deltoidea*.⁴⁵

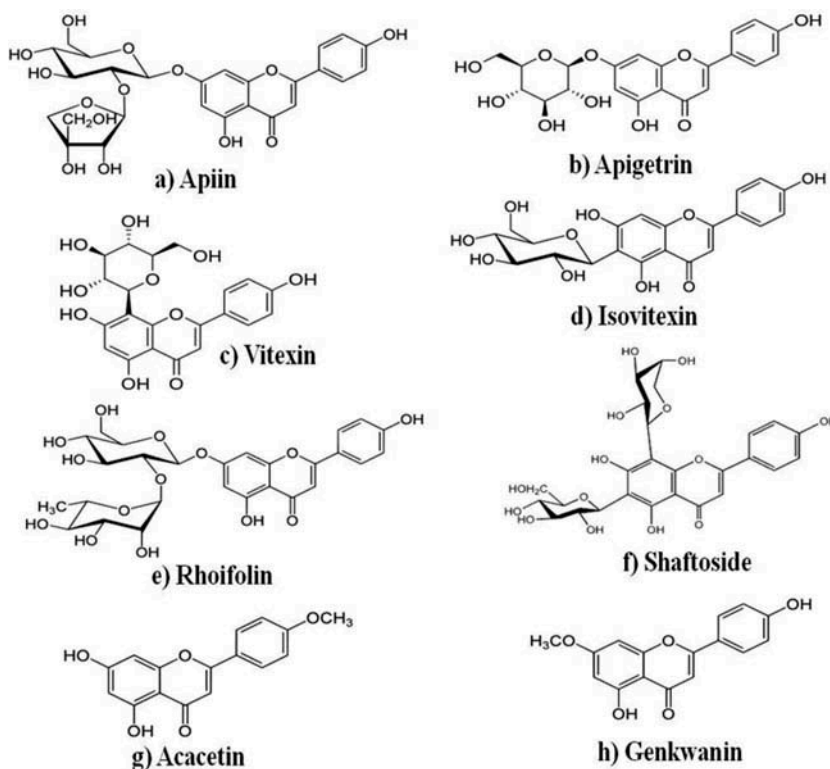


Figure 6. Apigenin conjugates in plants.^[30,33,41,42,45,47,48]

- (4) Isovitexin (apigenin 6-C-glucoside), found in mung bean,^[43] *Ficus deltoidea*.^[45]
- (5) Rhoifolin (apigenin 7-O-neohesperidoside), isolated from the leaves of *Rhus succedanea*,^[46] *Citrus grandis*.^[47]
- (6) Shaftoside (apigenin 6-C-glucoside 8-C-arabinoside), isolated from *Arisaema heterophyllum*.^[48]
- (7) Acacetin (4'- methoxy 5,7-dihydroxyflavone), found in *Turnera diffusa*,^[32] *Chrysanthemum morifolium*.^[33]
- (8) Genkwanin (4',5-Dihydroxy-7-methoxyflavone), it is synthesised in *Daphne genkwa*,^[30] seeds of *Alnus glutinosa*.^[31]

Apigenin-6-C- β -fucopyranoside and apigenin-6-C-(2''-O- α -rhamnopyranosyl)- β -fucopyranoside obtained from *Averrhoa carambola*,^[49] cosmosiin from *Citrus grandis*,^[47] apigenin 7-O (6-malonyl β -Dglucoside) are among many other apigenin derivatives.

Bioavailability and metabolism of apigenin

Apigenin is abundantly present in common fruits such as grapefruit, plant-derived beverages, and vegetables such as parsley, onions, oranges, tea, maize, rice, wheat sprouts chamomile, wheat sprouts, and in some seasonings.^[3,36,37] Parsley (*Petroselinum crispum*) and peppers (*Piper nigrum*) are two major sources of flavones containing 13.526 mg/100 g and 4.98 mg/100 g, respectively.^[36] Celery is also a good source of apigenin containing 108 mg apigenin per kg.^[50,38] One of the most common sources of apigenin consumed as single ingredient herbal tea is chamomile, prepared from the dried flowers from *Matricaria chamomilla*.^[51] Other sources for apigenin include beverages such as wine and beer brewed from natural ingredients^[12,14] in natural sources like *Chamomilla recutita*, apigenin is present as apigenin-7-O-glucoside and various other acylated derivatives.^[52] Some among the

numerous other plants from which apigenin and its derivatives are obtained include *Daphne genkwa*,^[30,53] *Acacia farnesiana*,^[54] *Apium graveolens*,^[55] *Mentha longifolia*,^[56] *Euterpe oleracea* Mart.,^[57] *Jatropha gossypifolia*,^[58,59] *Scutellaria barbata*,^[60] *Ginkgo biloba*,^[61] *Equisetum fluviatile*,^[62] *Wedella chinensis*,^[63] *Andrographis paniculata*,^[64] *Chrysanthemum morifolium*,^[65,66] *Teucrium gnaphalodes*,^[42] *Lycopodium clavatum*,^[67] *Perilla frutescens*,^[68] and *Thevetia peruviana*.^[69]

Factors that affect the circulating levels and subsequent bio-distribution of apigenin is its conversion to larger molecules in tissues. For example, glucuronides that are formed in the intestinal mucosa can be secreted back into the lumen of the gut, reducing net absorption.^[70,71] These conjugated flavonoids may also be transported through the efflux transporters multi-drug resistance protein-1 (also referred to P-gp, ABCB1, CD-243) and multi-drug resistance-associated protein-2 (also referred to ABCG2 and CMOAT),^[72] the distribution of which can be dramatically altered in cancer.^[73] Apigenin is also subject to methylation, sulfation, and glucuronidation, each of which affects its distribution and bioactivity.^[74] Apigenin metabolism within the intestinal epithelium has been studied in the Caco-2 cell monolayer system. Apigenin is a substrate for glucuronidation by the uridine 5'-diphospho-glucuronosyl transferase present in intestinal epithelial cells.^[75] Metabolism of scutellarin given intravenously and *Chrysanthemum morifolium* extract given orally to rats suggests that most first-pass metabolism of this flavonoid takes place in the intestinal mucosa, with very little contribution of presystemic hepatic elimination.^[76–78] However, other work has shown that apigenin can be efficiently glucuronidated and also sulfated in hepatocyte subcellular fractions, suggesting that precise kinetics depend upon the form of flavonoids.^[79] A generalized model of apigenin absorption and distribution in various tissues/organs and its excretion is presented in (Fig. 7). Microbes along with some plant enzymes also play an important role in bio-transformation of different flavonoid groups, exactly mimicking mammalian and plant metabolism at least in some cases. This study may be useful with reference to the microflora present in the human gut and their effect on flavonoids.^[80] Flavonoids has poor bioavailabilities largely because of the metabolism via UDP-glucuronosyltransferases (UGTs). The two flavonoids namely apigenin and genistein are metabolized more rapidly in intestine than in liver through the involvement in UGTs. This was demonstrated using yeast cells expressing UGT1A isoform isolated from rats. Intestinal excretion of flavonoids in Gunn rats (deficient in UGT1A) compared to Wistar rats were found to be higher for apigenin, suggesting up-regulation of UGT isoforms in Gunn rats. Flavonoids are efficiently metabolized by UGT1A deficient Gunn rats because of compensatory up-regulation of intestinal UGT2B and hepatic anion efflux transporters, which increases their disposition and limited their bioavailabilities.^[81]

From an *in vivo* and *ex vivo* study on rat liver it was found that apigenin undergoes phase I metabolism to produce monohydroxy derivatives viz; luteolin, scutellarein, iso-scutellarein, which in turn subjects through phase II metabolism producing conjugation products. Of them, three were monoglucurono conjugates and one monosulpho conjugate. However, luteolin a product of phase I

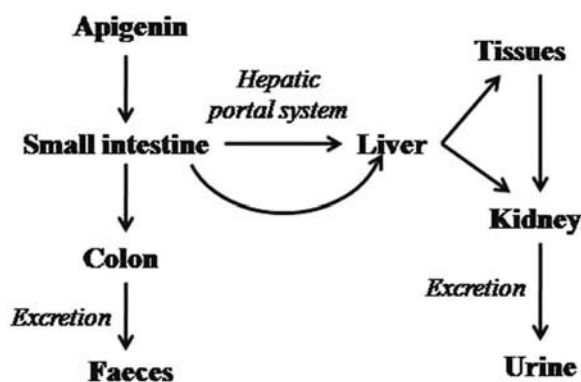


Figure 7. A generalized model of apigenin absorption and distribution in humans and other mammalian models.^[82]

metabolism produced four monoglucurono conjugates, two sulphoconjugates, and one methyl conjugate (identified as diosmetin) in *in vitro*. In contrast to this, none of the phase I metabolites were found in rat livers perfused with apigenin (*ex vivo*). But, two monoglucurono conjugates and one sulpho conjugate of apigenin were recovered as a part of phase II metabolism.^[83] In a similar study a single oral administration of radio labeled apigenin, 51.0% of radioactivity was recovered in urine, 12.0% in faeces, 1.2% in the blood, 0.4% in the kidneys, 9.4% in the intestine, 1.2% in the liver, and 24.8% in the rest of the body within 10 days. Adding to this, immature male and female rats, excreted a higher percentage of the mono-glucuronoconjugate of apigenin than the mono-sulfoconjugate of apigenin (10.0–31.6% versus 2.0–3.6%, respectively), which is similar to mature female rats. Mature male rats excreted the same compounds in an inverse ratio (4.9 and 13.9%, respectively). Results also showed the half life of apigenin in blood to be 91.8 h, a distribution volume of 259 mL, and a plasmatic clearance of 1.95 mL/h, suggesting apigenin's slow absorption and elimination in the body.^[84] Apigenin as a component in *Chrysanthemum morifolium* extract have shown to be absorbed in the intestinal mucosa more efficiently as compared to luteolin and also showed slow elimination rate in serum. Apigenin reached highest peak level at 1.1 and 3.9 h after dosing while total recovery in urine and faeces was found to be 16.6 and 28.6%, respectively.^[77] This is in supported from the study on human volunteers receiving diet low in flavones and other naturally occurring antioxidants during the 2 weeks of intervention. When this basic diet was supplemented with parsley providing 3.73–4.49 mg apigenin in one of the intervention weeks, the urinary excretion of apigenin was 1.59–409.09 mg/per 24 h as compared to 0–112.27 mg per 24 h on the basic diet. The fraction of apigenin intake excreted in the urine was found to be 0.58 (SE \pm 0.16%) during parsley intervention.^[85]

Pharmacological properties of apigenin

Apigenin has gained importance in recent years as a beneficial and health promoting agent because of its low intrinsic toxicity and its striking effects on normal versus cancer cells, compared with other structurally related flavonoids.^[86] There are numerous research evidences that have shown apigenin's strong therapeutic potential against a number of diseases (Fig. 8). There is very little evidence to date to suggest that apigenin promotes adverse metabolic reactions *in vivo* when consumed as part of a normal diet. However, some results have suggested the oxidative stress induced liver damage, which may be due to the activation of multiple genes by apigenin at higher doses in swiss mice.^[87] The possible cancer preventive effect of apigenin is due to its potent antioxidant and anti-inflammatory activities.^[87,88] It has also been demonstrated that apigenin promotes metal chelation, scavenges free radicals and stimulates phase II detoxification enzymes in cell culture and *in vivo* tumor models.^[22] Apigenin plays an important role in cancer prevention by inducing apoptosis in various cell lines and animal models.^[89–92] Indirect support to this assumption is correlated with a study where consumption of flavonoid free diets by healthy human volunteers has been reported to decrease in markers of oxidative stress in blood viz. plasma antioxidant vitamins, erythrocyte superoxide dismutase (SOD) activity and lymphocyte DNA damage commonly associated with enhanced disease risk, suggesting the beneficial effects of flavonoids.^[88]

A number of biological effects of apigenin in numerous mammalian systems *in vitro* as well as *in vivo* are related to its antioxidant and antigenotoxic effect and its role in scavenging free radicals.^[93,94] Apigenin executes its anti-atherogenic effect by inducing oxidized low density lipoprotein (OxLDL)-loaded murine peritoneal macrophages apoptosis. The pro-apoptotic effect of apigenin was partly attributed to down-regulation of plasminogen activator inhibitor -2(PAI-2) through suppressing phosphorylation of AKT at Ser473.^[95] It is also known to reduce LPS-induced inflammation in IPEC-J2 non-transformed intestinal epithelial cells by reducing expression of COX-2, IL-8, and TNF- α .^[96] Goto et al. suggested that apigenin inhibits osteoblastogenesis, osteoclastogenesis, and also prevents bone loss in ovariectomized mice.^[97]

Several beneficial properties have been attributed to apigenin and its derivatives, including anti-oxidant, anti-inflammatory, and anti-carcinogenic effects.^[98–100] Apigenin-7-glycoside a derivative of apigenin prevents LPS-induced acute lung injury via downregulation of oxidative enzyme expression

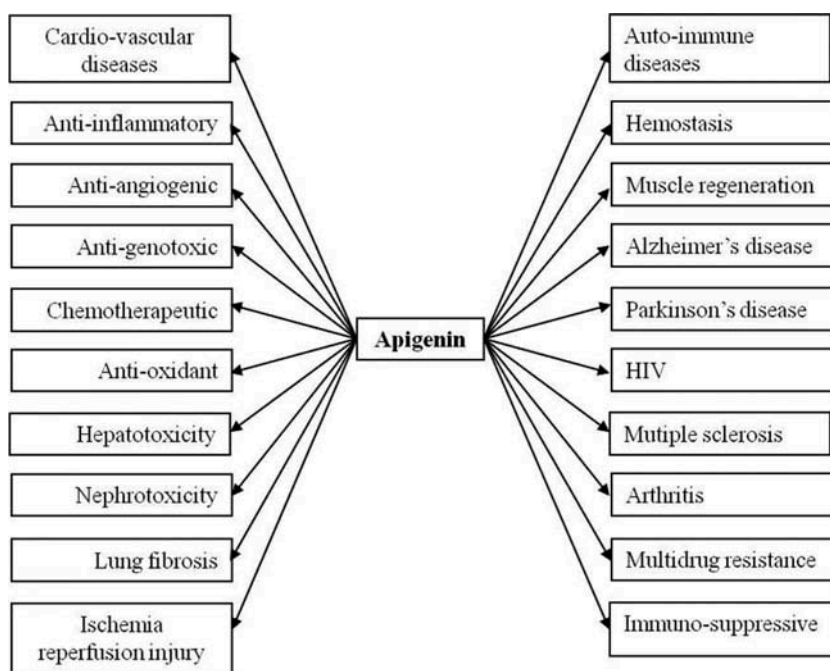


Figure 8. Pharmacological properties of apigenin.

and protein activation through inhibition of MAPK phosphorylation.^[101] It was earlier shown that apigenin induces a process called autophagia (a kind of cellular dormancy) that may well explain its chemopreventive properties, but at the same time it induces resistance against chemotherapy.^[102] Apigenin is a potent competitive inhibitor of CYP2C9 an enzyme responsible for metabolism of many pharmaceutical drugs in the body.^[103] Apigenin has been shown to reverse the adverse effects of cyclosporine. Research has been conducted to study the effects of apigenin on the reversal of cyclosporine induced damage and was assessed by immuno-histochemical estimation of bcl-2, and estimation of apoptosis in histological sections.^[104]

Rheumatoid arthritis

It is reported that inflammatory cytokines produced by fibroblast-like synoviocytes are involved in joint destruction and inflammation. Apigenin is known to induce ROS production and cause apoptosis through oxidative stress-activated ERK1/2 pathway in fibroblast-like synoviocytes.^[105] In addition to this, intake of apigenin has also showed immune-modulating effects triggered by TNF- α in a mouse model of rheumatoid arthritis.^[106]

Auto-immune disorders

In a study with SFN-1 mice model for lupus, it was shown that apigenin reduces response of Th1 (T-helper 1) and Th17 cells to major lupus autoantigen and consequently suppresses the lupus B cells ability to produce auto-antibodies. Moreover, apigenin also downregulated the expression of COX-2 and cellular FLICE-like inhibitory protein (c-FLIP) in immune cells and thereby, directing them toward apoptosis.^[107] Resistance of T cells to activation-induced cell death (AICD) is associated with autoimmunity and lymphocyte proliferation. Apigenin potentiated AICD by inhibiting NF- κ B activation and suppressing NF- κ B regulated anti-apoptotic molecules, cFLIP,

Bcl-xL, Mcl-1, XIAP, and IAP, but not Bcl-2. Apigenin suppressed NF- κ B translocation to nucleus and inhibited I- κ B α phosphorylation and degradation in response to T-cell receptor (TCR) stimulation in reactivated peripheral blood CD4 T-cells, as well as in leukemic Jurkat T-cell lines.^[108] In a similar study Verbeek et al.^[109] demonstrated that flavones luteolin and apigenin inhibit *in vitro* antigen-specific proliferation and interferon-gamma (INF- γ) production by murine and human autoimmune T-cells.

Hemostasis

In an *in vitro* study, it was found that 2500 μ mol/L of the flavonol quercetin and the flavone apigenin significantly inhibited collagen and ADP-induced aggregation in platelet-rich plasma and washed platelets by approximately 80–97%. However, to test the *in vivo* role of the two compounds, 18 healthy volunteers were fed with 220 g onions/day providing 114 mg quercetin/d, 5 g dried parsley/day providing 84 mg apigenin/day, or a placebo for 7 days each in a randomized crossover experiment with each treatment period lasting 2 weeks. The results indicate that due to the lower concentrations both the compounds had no significant effect.^[110] The mechanism of platelet anti-aggregating activity of apigenin and other flavonoids was studied *in vitro* by Landolfi et al.^[111] The study showed that, flavonoids inhibited platelet aggregation by depressing the cyclooxygenase pathway. In addition, the platelet cyclic AMP response to PGI₂ was also reduced via inhibition of adenylyl cyclase.

Anti-viral activity

Apigenin 7-O β D-glucopyranoside and apigenin 7-O β D- (4' caffeoyl) glucuronide extracted from medicinal herb *Kummerowia striata* and *Chrysanthemum morifolium*, respectively, have shown to induce anti-HIV activity in T-cell line (H9) transfected with HIV-I and HIV-1 (IIIB) infected MT-4 cells, respectively, by imparting strong integrase inhibitory activity.^[112,113] Most viral infections can be suppressed by preventing viral internal ribosomal entry site (IRES) mediated translational activity and by modulating cellular c-Jun N-terminal kinase (JNK) pathway. Lv et al.^[114] and Qian et al.,^[115] in separate studies, found that apigenin restricts enterovirus or Hand, Foot, and Mouth (HFM) virus induced HFM disease (HFMD) by inhibiting cellular JNK pathway and by preventing viral entry to IRES, which is otherwise essential for viral replication. Critchfield et al.^[116] examined the anti-HIV effect of apigenin and other related flavonoids on TNF- α induced OM-10.1 cells. The compounds have shown varied therapeutic indices in response to their inhibition to HIV expression. They also concluded that inhibition of NF- κ B pathway was not associated with the inhibition of viral replication, as the same was not downregulated by flavonoid treatment.

Behavior

Many neuropsychological disorders are due to abnormal synaptic activity which, in turn, is associated with altered monoamine transporters activity. A study with two flavonoids luteolin and apigenin isolated from *Perilla frutescent* on Chinese hamster ovary (CHO) cells and wild type dopaminergic cell lines have shown to act as monoamine transporter antagonists and help in improving several hyper-monoaminergic neuropsychological disorders by upregulating monoamine transporter activity.^[68] A behavioral study conducted on rats after intraperitoneal administration of apigenin and chrysin to them showed that chrysin had anxiolytic effect when injected at a dose of 1 mg/mL. While, at the same dose, apigenin had no effect. Chrysin might mediate its effect by binding to gamma amino butyric acid-benzodiazepine (GABA-benzodiazepine) receptors. This was cross-examined by treating mice with flumazenil (benzodiazepine antagonist), which prevented the anxiolytic effect by blocking the benzodiazepine receptors and, thus, confirming the interaction of chrysin with GABA receptor to mediate anxiolytic effect.^[117] Similar results were obtained in another study, in which apigenin as methanolic extract was derived from the dried flowers of

Matricaria chamomilla and which when injected intra peritoneally in rats was found to reduce locomotory activity but, did not demonstrate any anxiolytic, myorelaxant, or anticonvulsant activities in them. The inhibitory activity of apigenin on locomotory behavior seems to be ascribed to its interaction with GABA-benzodiazepine receptors, which was confirmed by the use of benzodiazepine receptor antagonist Ro 15-1788.^[52] However, as shown from the study by Viola et al.,^[11] the extract from the flowers of *Matricaria recutita* also having apigenin as a component, can induce anxiolytic effect mediated by binding to the same receptors. Thus, effect of apigenin on the behavioral activity of animal models is a bit controversial.

Ischemia reperfusion injury

Many studies were performed earlier to investigate the role of apigenin in preventing the Ischemia reperfusion injury in different tissues of model organisms like acute transient focal cerebral ischemia-reperfusion injury and spinal cord injury in rats and mice,^[119–121] lung ischemia-reperfusion injury in rats,^[122] myocardial ischaemia/reperfusion injury in Langendorff-perfused rat hearts,^[123,124] oxygen-glucose deprivation/reperfusion induced injury in rat hippocampal neurons,^[125] and liver ischemia reperfusion injury in rats,^[126] by inhibiting the production of nitric oxide (NO), prostaglandin E (PGE), Fas protein for apoptosis, glutathione peroxidase (GSH-Px), SOD, malondialdehyde (MDA), tumor necrotic factor alpha (TNF- α), etc. Although positive results were obtained with apigenin, no strong mechanism was elucidated until the very recent study by Hu et al.^[55] These researchers in their current study demonstrated the role of apigenin with possible mechanism in isolated rat heart model of ischemia-reperfusion. The result suggests that apigenin conferred a cardioprotective effect, showed an improved ischemic cardiac functional recovery, decreased myocardial infarct size, and reduced activities of creatine kinase isoenzyme and lactate dehydrogenase (LDH) in the coronary flow. These changes may rely on less number of cardiomyocytes undergoing apoptosis due to reduced activity of caspase-3, up-regulation of the anti-apoptotic protein Bcl-2, down-regulation of the pro-apoptotic protein Bax and inhibition of p38 MAPK (mitogen activated protein kinase) signaling during I/R. In another study, Li et al.^[101] demonstrated that apigenin-7-glycoside prevents lipopolysaccharide (LPS)-induced acute lung injury via downregulation of inducible nitric oxide synthase (iNOS) and COX 2 expression and protein activation through inhibition of MAPK phosphorylation and NF- κ B pathway. A number of deaths occur in the form of brain injury caused due to subarachnoid haemorrhage. In such cases there occurs increased expression of toll like receptor 4 (TLR-4), necrotic factor kappa B (NF- κ B), and their downstream pro-inflammatory cytokines in CNS. Apigenin could suppress the activation of TLR-4 induced by subarachnoid haemorrhage and inhibit apoptosis of cells in the cortex.^[127]

Anti-inflammatory and anti-oxidant activity

Many flavonoids are now known to be the selective, as well as non-selective, inhibitors of COX, LOX, PLA, and NOS. These molecules are the major contributors in inducing inflammation. Some flavonoids inhibit only a single inflammatory enzyme while others inhibit a series of enzymes. For example, flavones such as luteolin, apigenin are known to suppress iNOS and COX 2 expression in contrast flavanols like quercetin and myricetin are preferential LOX and PLA 2 inhibitors, with quercetin also showing the ability to inhibit NOS. Moreover, where on one hand, flavonoids (quercetin, myricetin, kaempferol, scutellarin) and biflavonoids (ochrethflavone, amentoflavone, ginkgetum, and isognetonum) are inhibitors of PLA, 2 amentoflavone, and apigenin, on other hand, showed no inhibition to PLA 2.^[128] Flavones better activity in inhibiting NO production and iNOS and COX inhibition is attributed to their C-2,3 double bond and substitution of hydroxyl groups on A and B rings, respectively.^[128] Apigenin, quercetin, and morin were also found to inhibit NO production in LPS induced and INF- γ activated C6 astrocytes and LPS induced RAW 264.7 cells, not by inhibiting the iNOS activity, but rather strongly suppressing the expression of iNOS.^[129,130] In addition to iNOS/COX 2, several cytokines IL-1 β , IL-6, INF- γ , IL-4, IL-5, TNF- α , MCP-1 α (Monocyte

chemotactic protein), MIP-1 α (Monocyte inflammatory protein), and ICAMS are also associated with the inflammatory responses. The possible role of apigenin to inhibit the expression of several cytokine genes has been shown to be associated with a number of protein kinases involved in signal transduction including PKC, ERK, and MAPK. Through the inhibition of these molecules, DNA binding capacity of transcription factors such as NF- κ B, Fos-Jun, or AP-1 is regulated.^[128] Although, some of the signaling molecules inhibited by apigenin are already been demonstrated many others are yet to be deciphered.^[131] A possible pathway for inflammatory modulation induced by apigenin is shown in Fig. 9. In one of the studies Reuter has shown that ROS induces the activation of a number of transcription factors like NF- κ B, AP-1, p53, HIF-1 α , PPAR- γ , β -catenin/Wnt, STAT-3, Sp-1, and Nrf2, most of which are also known to be involved in cancer and inflammatory diseases. Activation of these transcription factors can lead to the expression of more than 500 different genes, including those for growth factors, inflammatory cytokines, chemokines, cell cycle regulatory molecules, and anti-inflammatory molecules.^[131,132] Apigenin has shown its role in modulating the inflammatory pathways by interacting with these transcription factors. Inhibition of TNF- α induced NF- κ B, CCL2/MCP-1, and CXCL 1/KC expression by apigenin has been reported. NF- κ B is responsible for the activation of transcription factors involved in COX 2 and iNOS synthesis. The inhibition of NF- κ B is achieved through the inhibition of LPS induced I κ B kinase activity in mouse macrophages.^[133] However, apigenin had no effect on the degradation of I κ B proteins and nuclear translocation and DNA binding activity of NF- κ B p65.^[210] Possible role of apigenin in inducing anti-inflammatory affect is shown in Fig. 9.

In addition to anti-inflammatory properties apigenin also shows anti-oxidant properties mediated by anti oxidant enzymes like SOD, GSH-Px, catalase (CAT), NOS, glutathione reductase (GR) and also by reduced glutathione (GSH). Human subjects supplemented with parsley providing 3.73–4.49 mg

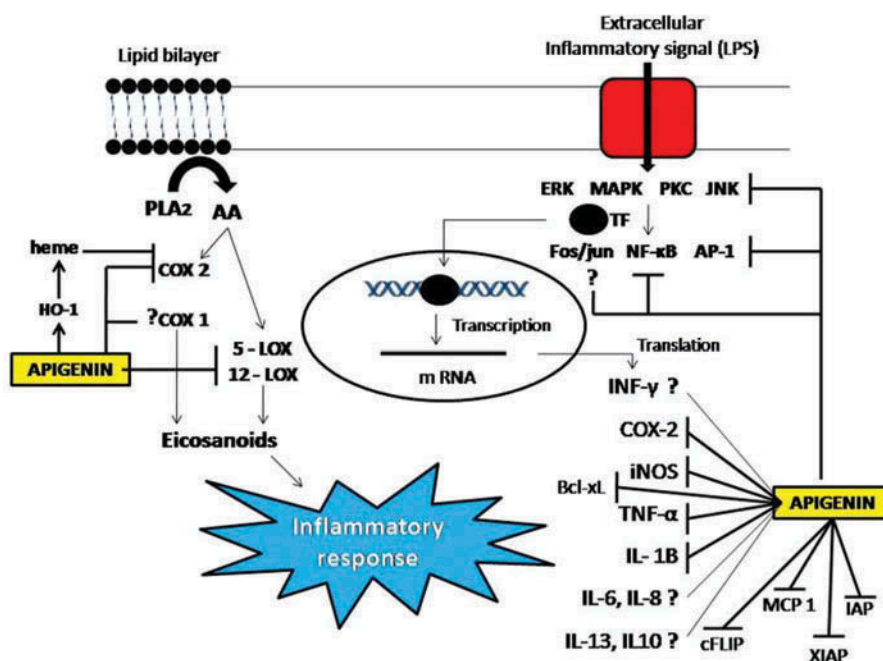


Figure 9. Possible role of apigenin in inducing anti-inflammatory affect by modulating the expression of cytokines and other inflammatory molecules at both transcriptional and post transcriptional level. COX 1/2 (Cyclooxygenase 1/2), LOX (Lipoxygenase), HO-1 (Haeme oxygenase 1), PLA (Prostaglandins), IL (Interleukins), TNF- α (Tumor necrotic factor alpha), iNOS (inhibitor of nitric oxide synthase), INF- γ (Interferon gamma), XIAP (X-linked inhibitor of apoptosis protein), c-FLIP (Cellular FLICE like inhibitory protein). Lines with arrow heads represent activation while lines without arrow heads represent inhibition.

apigenin for 2 weeks resulted in increased levels of GR and SOD in comparison to group supplemented with low flavones rich diet.^[85] One of the studies demonstrated that apigenin at low concentrations (10, 20, and 40 mg/kg b.w) provides protection to rat livers against reactive oxygen species (ROS) induced oxidative damage by reducing lipid peroxidation (LPO) and membrane protein damage and also by reducing the secretion of blood serum enzyme markers viz; LDH, ALP, alanine amino transferase (ALT), and aspartate transaminase (AST).^[93] Table 1 shows the effect of apigenin on the regulation of various inflammatory and antioxidant molecules.

However, apigenin administration (intragastric) at concentrations as high as 468 and 936 mg/kg b.w had inverse effect on rat livers, showing that apigenin can induce oxidative stress at very high doses. This might be conferred from reduction in the levels of SOD, CAT, GSH-Px, and total antioxidant capacity (T-AOC).^[134] Lotito and Frei,^[135] and Panes et al.^[136] demonstrated that flavones apigenin and its other counterparts inhibit expression of intracellular adhesion molecules (ICAM), thereby providing protection against inflammation in different organs including atherosclerosis in human aortic endothelial cells. Authors also suggested that 5,7-dihydroxyl substitution of a flavonoid A ring; 2,3 double bond and 4-keto group of the C ring were the main structural requirements for inhibition of adhesion molecule expression. Hydroxyl substitutions only on B and C rings but not on ring A were essential for antioxidant activity. Chemosensitivity assays with control transfected and multi-drug resistant protein (MRP1)-transfected HeLa cell lines showed that the IC₅₀ values for apigenin, naringenin, genistein, and quercetin were similar, demonstrating that overexpression of MRP1 does not confer resistance to these bio-flavonoids. The results from the study suggest that flavonoids stimulate MRP1-mediated GSH transport by increasing the apparent affinity of the transporter for GSH and thus conferring antioxidant property to them.^[137,138] Xanthineoxidase causes gout and is responsible for oxidative damage to living tissues. Lin et al.^[139] studied the effect of various flavonoids including apigenin on xanthine oxidase (XO) induced oxidative stress in human promyelocytic leukemic (HL-60) cells. Few studies have shown to have no anti-inflammatory effect on application of some selected flavonoids, which also include apigenin as a therapeutic agent. In one of the

Table 1. Effect of apigenin on the regulation of various inflammatory molecules.

Experimental models and cell lines	Modulatory effect on oxidative stress markers	References
Human volunteers fed on parsley	↑GR and ↑SOD	[85]
Albino rats (<i>in vivo</i>)	↓LDH, ↓AST, ↓ALP, ↓ALT and ↓LPO, ↓PCC	[93]
IPEC-J2 cells	↓IL-6, ↓IL-8, ↓COX-2, ↓H ₂ O ₂	[96]
Rats (contusive spinal cord injury) (<i>in vivo</i>)	↑SOD, ↑GSH-Px, ↓MDA, ↓IL-1β, ↓TNF-α, ↓ICAM	[121]
Rats (Lung ischemia Reperfusion Injury)	↓IL-6, ↓IL-10, ↓TNF-α, ↓iNOS	[122]
RAW 246.7 Mouse macrophages	↓COX-2, ↓iNOS	[133]
HL-60 cells (<i>in vitro</i>)	↓XO	[139]
HCEC cervical cancer cell line	↓COX-2	[145]
Mice <i>in vivo</i> and <i>in vitro</i> (keratinocyte cell lines)	↓COX-2	[146, 147, 148]
Mice (<i>in vitro</i>)	↑GSH, ↑GST, ↑SOD, ↓MPO, ↓MDA, ↓AST, ↓ALT, ↓LDH, ↓Creatine and ↓BUN	[149]
Male mice (<i>in vivo</i>)	↑GSH, ↑GSH-Px, ↑SOD, ↓ALT, ↓AST, ↓COX-2, ↓iNOS and ↓TNF-α	[150]
Mice (<i>in vivo</i>)	↑GSH, ↑GST, ↑QR	[151]
LPS and human THP-1-induced macrophages and mouse J774A cells	↓IL-6, ↓IL-1β, ↓TNF-α	[152]
<i>In vitro</i> and <i>in vivo</i> rat hepatocytes	↑GSH, ↑GST, ↑SOD, ↑GSH-Px, ↑GSH-R, ↑CAT	[153]
Hep G2 cells	↓NO, ↓iNOS, and ↓cPLA2	[154]
Copper induced AD cell model (<i>in vitro</i>)	↑GSH, ↑SOD, ↑GSH-Px	[155]
LPS induced RAW 264.7 cells	↓COX-2, ↓iNOS, ↓NO	[156]
Wistar rats (<i>in vivo</i>)	↓LPO	[157]
Human PBMC (<i>in vitro</i>)	↓IL-6, ↓IL-1β, ↓TNF-α	[158]
Murine macrophage cells and mice (<i>in vivo</i>)	↓IL-6, ↓IL-1β, ↓TNF-α	[159]

NO: nitric oxide, iNOS: nitric oxide synthase, MDA: malondialdehyde, COX: cyclooxygenase, TNF: tumor necrotic factor, ICAM: intracellular adhesion molecules, LOX: lipooxygenase, GST: glutathione-S-transferase, LPO: lipid peroxidation, cPLA2: cytosolic phospholipase A2, GPx: glutathione peroxidase, GR: glutathione reductase.

researches, mice treated with selected flavonoids showed no reduction in the serum uric acid levels. As far as XO activity is concerned, it was not significantly affected *in vitro* but significant changes were found in *in vivo* systems.^[140] Among all flavonoids studied, apigenin was found to be the most potent inhibitor of XO. Other studies indicate that apigenin, chrysin, and luteolin dose-dependently up-regulated the protein expression of heme oxygenase 1 (HO-1) and glutamate cysteine ligase (GCL) catalytic (GCLC) and modifier subunit (GCLM). They also increased the intracellular glutathione (GSH) content and the ratio of GSH to oxidized GSH (GSSG) by activating extracellular signal-regulated protein kinase 2 (ERK2), nuclear factor erythroid 2-related factor 2 (Nrf2), both of which are in turn responsible for activating the TRE and EpRE genes involved in GCL synthesis.^[141,154] The magnitude of HO-1 induction after apigenin uptake and the wide distribution of this enzyme in systemic tissues coupled with the intriguing biological activities of the catalytic byproducts of heme, i.e., carbon monoxide (CO), iron (Fe), and bilirubin (bil) makes it an important molecule for stress response, as on one hand CO is known to have anti-inflammatory and anti-apoptotic affect, on the other, ferritin and bilirubin act as antioxidants (bilirubin enhances SOD and CAT activity and inhibits adiponectin).^[142,143]

Thus, the literature searched suggests that apigenin reduces oxidative stress induced inflammation in tissues by modulating various oxidative stress markers, blood enzyme markers, interleukins, and expression of several other related enzymes. However, in contrast to the studies discussed above, some reports have showed oxidative damage and hepatic architecture loss in rats exposed to sub-chronic or higher doses of apigenin.^[144] The antioxidant activity of apigenin could be mediated through the increased production of antioxidant enzymes. Based on the observations shown in Table 1 of this section and antioxidant properties given in other sections of this review, a sketch of oxidative mechanism and possible apigenin targets are depicted in Fig. 10.

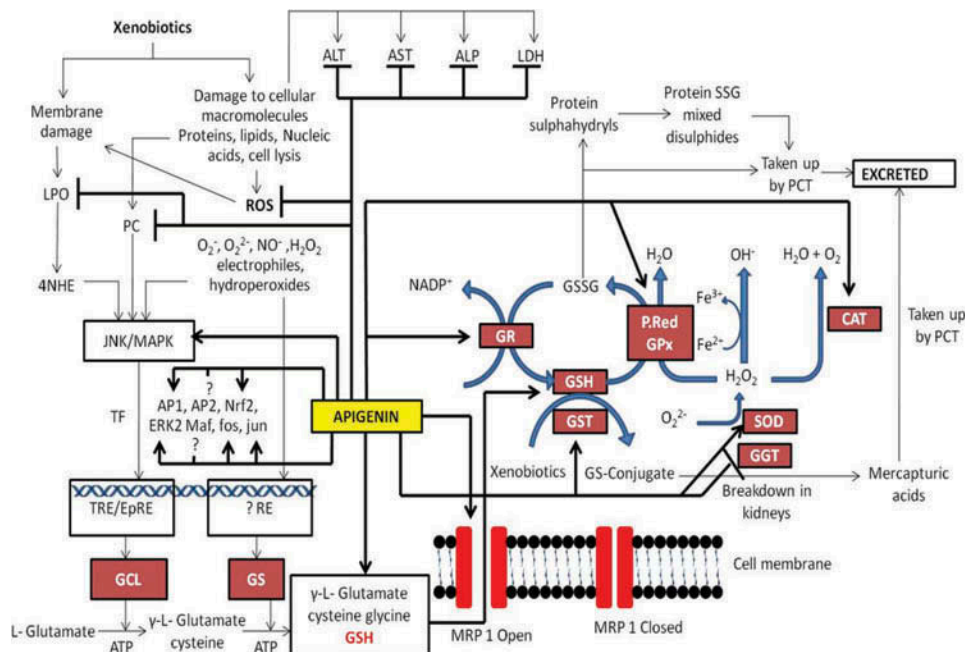


Figure 10. Antioxidant enzyme targets of apigenin at both transcriptional and post transcriptional level. AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), ALP (Alkaline phosphatase), LDH (Lactate dehydrogenase) GSH (Glutathione), GST (Glutathione S transferase), GPx (Glutathione peroxidase), GR (Glutathione reductase), P.Red (Peroxireductase), CAT (Catalase), SOD (Superoxide dismutase, 4-HNE (4 hydroxy 2 nonenal), LPO (Lipid peroxidation), GCL (Glutamylcysteine ligase), GS (Glutathione synthase), TF (Transcriptional factors). Lines with arrow heads represent activation while lines without arrow heads represent inhibition.

Anti-toxicant

Numerous studies have been performed using apigenin and its analogues to demonstrate its protective effect *in vivo* and *in vitro*. The results from one of the studies suggested that apigenin ameliorates cisplatin-induced apoptosis in human renal proximal tubular epithelial (HK-2) cells through reduction of p53 activation and promotion of PI3K/Akt pathway.^[160] LPS is known to disturb the anti-oxidative mechanism, impair mitochondrial redox activity and consequently induce inflammation in the brain. Farkas et al.^[96] demonstrated that LPS-induced inflammation in IPEC-J2 non-transformed intestinal epithelial cells can be reduced on application of apigenin and its methylated derivative (apigenin-trimethylether) by down-regulating the expression of IL-6, IL-8, COX-2, and extracellular H₂O₂. Endoplasmic reticulum (ER) stress induced by tunicamycin also brings about mitochondrial alterations in adipocytes. These mitochondrial alterations were significantly reduced on treatment of cells with apigenin and quercetin.^[161] From the study by Hussein et al.,^[162] it was concluded that apigenin reduces LPS induced COX-1 and COX-2 expression, LPO, NO, and monoamines synthesis along with an increase in serum paraoxonase activity (PON-1). Another study has shown that trinitrobenzene sulphonic acid and dextran sulphate sodium induced intestinal inflammation (Colitis) in rat models can be minimized on their pre-treatment with a soluble form of apigenin, namely apigenin K. There was a reduction of 30 and 21% in myeloperoxidase (MPO) and ALP activity, respectively, in apigenin K treated rats, in addition to its ameliorating effect on internal morphological damage and reduction in the expression of immunological inflammatory marker like TNF- α , TGF- β , IL-6, and ICAM-1.^[163] Protective effect of apigenin against some of the numerous toxic compounds has been listed in Table 2.

Antigenotoxic

Genotoxicity is the property of chemical agents that alters the genetic information within a cell causing mutations, which may lead to cancer. Every cell has the property to prevent chemical induced genotoxicity either by DNA repair mechanisms or diverting cell toward apoptosis. However, the damage may not always be fixed leading to mutations. To evaluate the genotoxic effects of chemical substances *in vitro* and *in vivo*, various methods are available differing in their sensitivity, their practicability, and their genetic end-points considered. The most commonly used genotoxic assays include micronucleus assay, sister chromatid exchange, and comet assay. All these assays hold well, when the DNA or chromosomes get fragmented in response to toxicity of a chemical compound but, for other nuclear abnormalities such as nucleoplasmic bridges and nuclear bud formation which are also the biomarkers of genotoxic events and chromosomal instability, recently developed method called cytokinesis block micronucleus cytome assay is used. Another widely applied and one of the oldest methods employed for *in vitro* testing is Ames test, which employs the estimation of number of mutant revertants in the concerned cell culture after the application of test compound. Drosophila wing spot test is also a simple method to determine genotoxicity without involving cellular processing. A method which provides results with better resolution is fluorescent *in situ* hybridization (FISH). By this method it can be determined whether the chemical employed for genotoxic test is aneugenic or clastogenic. The protective effect of apigenin against various genotoxic compounds has been widely studied. Variable parameters are used by different research groups to detect the protective effect of apigenin as a parent compound or as plant extracts against numerous genotoxic compounds *in vivo* and *in vitro*^[93,171,172] (Table 3). Apigenin may also act as a pro-oxidant, genotoxicant, or as an inhibitor of key enzymes to produce clastogenic effect in cancer cell lines, depending upon the levels consumed^[173,174] (Table 4).

Alzheimer's disease

Choi et al.^[156] treated LPS induced RAW 264.7 mice macrophage cells with apigenin and its two c-glycosylated derivatives, vitexin, and iso-vitexin. From the study, iso-vitexin was found to be more

Table 2. Protective effect of apigenin against some of the numerous toxic compounds. Carbon tetrachloride (CCl₄), N-nitrosodiethylamine (NDEA), trinitrobenzene-sulfonic acid (TNBS), dextran sulphate sodium (DSS).

Toxicant	Dose of toxicant (T)/Dose of Apigenin or its derivative (A)	Experimental models and cell lines	Target organ/cell line	References
Acetaminophen	T- 350 mg/Kg b.w A- 100 & 200 mg/Kg b.w for 7 days	Mice	Liver	[164]
Copper	NA	AD cell lines	neuronal cell	[155]
Cisplatin	A- 5, 10, 20 mg/Kg b.w For 1 hr T- 40 µmol/L for varying durations	HK-2 cell line	human renal proximal tubular epithelial cells	[160]
Furan	NA	Mice	Liver and kidney	[149]
Cyclosporine	T- NA A- 10, 15, 20 mg/Kg b.w	Rats	Kidney	[165]
CCl ₄	NA	Male mice	Liver	[150]
CCl ₄ (<i>in vivo/ in vitro</i>)	T- 86 µmol/L (<i>in vitro</i>) A- 60- 0.006 µg/ml T- 1.25 ml/Kg b. w A- 80 mg/Kg b.w	Rats	Liver	[153]
Benzo(a)pyrene	T- 125 mg/Kg b.w A- 2.5 – 5 mg/Kg b.w	Mice	Liver	[166]
NDEA	T- 0.1 mg/ml in drinking water A- 10, 20, 40 mg/ml For 21 days	Rats	Liver	[93]
TNBS and DSS	T- NA A- 1, 3, 10 mg/Kg b.w	Rats	Intestine (colitis)	[163]
Alloxan induced diabetic rats	A- 0.78 mg/Kg b.w For 10 days	Rats	Liver, Thyroid, Pancreas	[167]
Arsenic, nickel chromium and cadmium	A- 100mg/ml (<i>in vitro</i>) and 0- 40 mg/Kg b.w for 5 days/ 3weeks (<i>in vivo</i>)	Beas-2B cells	Transformed human bronchial epithelial cells (CXCR4)	[168]
Ethinylestradiol	T- 0.5, 1.0 ml/ml A- 0.1, 0.5, 1.0 ml/ml	Transgenic <i>Drosophila melanogaster</i> (hsp70-lacZ) Bg9	<i>Drosophila</i> larva	[169]
DMBA painting in buccal pouch	A- 2.5 mg/ml	Golden Syrian hamster	Plasma and Buccal epithelial cells	[170]
Trinitrobenzenesulfonic acid (TNBS) model and the Dextran sulphate sodium (DSS) induced colitis model, 7,12-dimethylbenz(a) anthracene (DMBA). NA: not available, T: toxicant/s, A: apigenin and its derivatives.				

Table 3. Antigenotoxic potential of apigenin on various cell lines and animal models against different genotoxic agents.

Test compound	Animal models and cell lines	Ames test	Parameters used	References
Ethyl methane sulphonate (EMS), acridine, sodium azide and 9- amino acridine	EMS and acridine was used in <i>Saccharomyces cerevisiae</i> and sodium azide and 9- amino acridine was used in <i>Salmonella typhimurium</i>			[56]
Doxorubicin	Mice bone marrow cells, polychromatic erythrocytes, blood lymphocytes, hepatocytes, kidney cells	Micronucleus test and comet assay		[57]
NDEA	Rat liver, lymphocyte and bone marrow cells	Micronucleus test (MNT) and comet assay		[93]
Benzo (a) pyrene	Mice	DNA strand breaks		[166]
Mitomycin c	Mouse bone marrow cells	Sister chromatid exchanges and chromosomal aberrations		[171]
Mitomycin c and cyclo-phosphamide	NA	Chromosomal aberrations, sister chromatid exchanges and cell cycle kinetics		[172]
Cyclophosphamide and doxorubicin	Bacterial culture <i>in vitro</i> and mice blood cells <i>in vivo</i>	Micronucleus test		[175]
UV-B and benzo (a) pyrene induced	Mice skin cancer	Cytogenetic determination of chromosomal aberrations (CA)		[176]
1-nitropyrene or 1,6-dinitropyrene	CHO cells	cytotoxicity and sister chromatid exchanges (SCEs)		[177]
Gamma Radiations	Human blood lymphocytes	Cytokinesis block micronucleus (CBMN) assay		[178]
Apigenin (in <i>Matricaria chamomilla</i> extract)	Drosophila wing	Drosophila wing spot test		[179]
Ethinylestradiol	Human blood lymphocytes	Chromosomal aberrations, sister chromatid exchanges and cell cycle kinetics		[180]
Hydrogen peroxide	Drosophila melanogaster	Somatic mutation and recombination test or wing spot test		[181]
Hydrogen peroxide	Human blood lymphocytes	Sister chromatid exchanges and cytokinesis blocked micronucleus assay		[182]
Radiation and mitomycin c	Human blood lymphocytes	Sister chromatid exchanges and cytochalacin blocked micronucleus assay		[183]
Gamma radiations	Human blood lymphocytes	Cytokinesis blocked micronucleus assay, nucleoplasmic bridges, nuclear buds and comet assay		[184]
UV-rays, Lomifloxacin, 4-nitroquinolineN-oxide	Episkin (a reconstructed skin model)	Comet assay		[185]
Crude latex obtained from <i>Jatropha gossypifolia</i>	Erythrocytes of a fresh water fish <i>Channa punctatus</i>	Micronucleus test and comet assay		[186]
<i>S. typhimurium</i> strain (TA1538 uvrB ⁻ and TA1978 uvrB ⁻) and <i>E. coli</i> K12 strain PQ37	-	Ames test		[187]

Table 4. Apigenin as pro-oxidant, genotoxicant, or as an inhibitor of key enzymes to produce clastogenic effect in cancer cell lines.

Test compound	Animal models and cell lines	Parameters used	References
Apigenin	Human blood lymphocytes	Cytochalasin B blocked micronucleus assay	[173]
Apigenin	HepG2 cells	Sister chromatid exchange and chromosomal aberrations	[174]

powerful inhibitor of rat eye lense aldolase reductase (RLAR), human recombinant aldolase reductase (HRAR), acetylcholine esterase (AChE), and butyrylcholine esterase (BChE) enzymes and advanced glycation end products (AGE). On the other hand, vitexin showed to inhibit only protein tyrosine phosphatase 1B (PTP 1B). In contrast, both these derivatives apigenin showed powerful anti-inflammatory activity by inhibiting NO production and iNOS and COX-2 expression. In this context, vitexin and iso-vitexin were found to be inactive. Using *invitro* screens, AChE, and BChE inhibitory activities of various phenolic compounds including apigenin were analyzed by Orhan et al.^[188] Upon evaluating various polyphenolic compounds at a concentration of 1 mg/mL, using microplate reader assay it was found that only quercetin had inhibitory effect against AChE while, genistein, luteolin-7-O rutinoside, and silibinin had moderate inhibitory effect on BChE and apigenin exerted no inhibitory effect on either of the enzymes. In an *in vivo* study, 3-month oral treatment with apigenin inrescued learning deficits and relieved memory retention in APP/PS1 double transgenic AD mice. Apigenin has shown its ameliorating effect not only by reducing the oxidative stress (by increasing SOD and GSH-Px activity), but also by preventing A β burden through down-regulating BACE1 and β -CTF levels.^[189] Apigenin treatment to copper-induced A β -toxicity in neuronal cells showed reduction in neuronal apoptosis, regulated redox imbalance, and preserved mitochondrial function by blocking ROS induced p38 mitogen activated protein kinase (p38 MAPK) and stress activated protein kinase (SAPK)/c-JNK pathways.^[190] ER is the main organelle for the synthesis and processing of almost all kinds of proteins including A β peptides responsible for developing AD. It is suggested that stress in ER may activate ER specific pathways causing the accumulation of misfolded proteins within the ER lumen. Many studies have proposed that neuronal death in AD arises from dysfunction of the ER. Thus, these findings lay insights for therapeutic strategies that can be made to target ER for treating AD.^[191] Apigenin (IC₅₀ = 38.5 μ mol L⁻¹) inhibits the activity of β -secretase (the principle enzyme responsible for break releasing the β -amyloid fragment) in a concentration dependent manner in both cell-free and cell-based assay systems.^[192,193]

Parkinson's disease (PD)

Expression of parkinsonism biomarkers, i.e., brain derived neutrotrophic factor (BDNF) and tyrosine hydroxylase (TH) were decreased and glial fibrillary acid protein (GFAP) was increased in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). On the other hand, treatment of MPTP induced mice group with different doses of apigenin, luteolin, and bromocriptine brought about significant reversal in the levels of the previously mentioned PD biomarkers by reducing oxidative damage, neuro inflammation, and microglial activation.^[194]

Immunomodulatory effect

It is well known that IgE antibody produced by mast cells mediate allergic reactions in living systems. Yano et al.^[195] demonstrated that the generation of IgE can be suppressed on pre-feeding C57BL/6N mice, with diet rich in apigenin. Moreover, the expression of regulated upon activation normal T cell expressed and secreted (RANTES) and soluble tumor necrosis factor receptor I (sTNFRI) in mice sera was also down regulated in apigenin supplemented diet. Studies on the murine models of asthma have also shown that apigenin can decrease the degree of the inflammatory cell infiltration, airway hyper-responsiveness, and total immunoglobulin E levels in the serum and also diverting the allergic response towards Th 1 profile.^[211]

Miscellaneous

TNF- α has recently been identified to be a mediator of retinal ganglion cell (RGC) death, while glial cells are relatively protected against this death stimulus. Exposure of RGCs to TNF- α is thought to contribute to RGC apoptosis. In one study, MTT assays showed that apigenin significantly inhibited the decrease of RGC viability induced by TNF- α in a dose-dependent manner. Pretreatment with apigenin prevented TNF- α induced apoptosis through inhibition of caspase-dependent apoptotic pathway and activation of nuclear factor-kappa B.^[196] Apigenin has shown to prevent alloxan induced hyperglycaemia, thyroid dysfunction, and LPO in rat models. Apigenin reduces inflammation and imparts its protective effect by reducing LPO and an increasing the activity of cellular antioxidants, such as CAT and SOD, and in glutathione (GSH) content.^[159] In a similar kind of study, Crazolli et al.^[49] found that apigenin-6-C- β -fucopyranoside and apigenin-6-C-(2''-O- α -rhamnopyranosyl)- β -fucopyranoside, derivatives of apigenin induced glucose uptake via alternate pathways in rats treated with insulin signal inhibitors like wortmannin, an inhibitor of phosphoinositide 3-kinase (PI3K), RO318220, an inhibitor of protein kinase C (PKC), PD98059, an inhibitor of mitogen-activated protein kinase (MAK), and HNMPA(AM)3, an inhibitor of insulin receptor tyrosine kinase.

One study demonstrated that apigenin inhibited ovalbumin induced asthma in mice models characterized by increase in airway resistance and eosinophil count. In addition, levels of interleukin (IL)-6, TNF- α , and IL-17A were also suppressed after treatment with apigenin.^[197] Apigenin and tangeretin enhance gap junctional intercellular communication in rat liver epithelial cells which could be one of the major mechanisms responsible for apigenin's anti-tumor promoting action *in vivo*.^[198] From their study with apigenin treatment on isolated rat atria, Lorenzo et al.^[199] concluded that apigenin possesses the property to increase the atrial rate, by minimizing noradrenaline uptake and by reducing monoamine oxidase activity. A number of amyloid related diseases exist in nature, which are due to the deposition of proteins either inside or outside the cell. Inhibiting or reversing amyloid aggregation via the use of small molecules is proposed as two useful approaches in hampering the development of these diseases. In one such approach, Amini et al.^[200] have shown that apigenin reduces human insulin fibrillation *in vitro* and protects SK-N-MC cells against insulin induced amyloids. A reduction in the expression of cellular adhesion molecules (CAMs) viz, ICAM, vascular cell adhesion molecules (VCAM) and E-selectins was observed in the culture of vascular endothelial cells when treated with apigenin, dissolved in the medium as such and after being processed through hepatocytes conditioned medium. The results of this study also suggested that the C ring double bond, the keto group and the A ring 5,7-dihydroxyl groups but not the B ring are essential requirements for the flavonoids to function as inhibitors of CAM expression.^[135] Choi et al.^[201] investigated the effect of apigenin against ovalbumin (OVA) induced asthma in female BALB/c mice. Results obtained reveal that administration of apigenin in mice leads to a reduction in the expression of MMP-9 and GATA-3 mRNA and also in Th2 cytokine (IL-4 and IL-5) levels in BAL fluid. Thus, suggesting its role in ameliorating pathogenesis of OVA induced asthma in mice. Hossein et al.^[202] have demonstrated that apigenin can impart anti-diabetic affect in animal models by modulating GLUT4 and CD38 trans-membrane proteins. The flavonols (fisetin, quercetin, and 3,3',4'-trihydroxyflavone) and flavones (apigenin, chrysin, and luteolin) are known to show concentration dependent vasorelaxant effect in isolated rat thoracic aorta. Moreover, all the flavonoids have shown a similar potency in inhibiting contraction caused by the influx of extracellular Ca²⁺, except for 3,3',4'-trihydroxyflavone.^[203,204] In one of the recent studies apigenin has shown to impart protection against Leishmaniasis caused by leishmanial parasite by generating ROS and inducing an extensive swelling in parasite mitochondria, leading to an alteration of the mitochondrial membrane potential, rupture of the trans-Golgi network, and cytoplasmic vacuolization.^[205] One of the studies has shown that apigenin at a concentration as high as 25 mg/kg b.w. resulted in impaired reproductive health of male mice. The adverse effect on the reproductive system was in terms of reduced sperm density and sperm motility, which in turn is due to slow proliferation of germ cells and blockage of spermatogonia in G0-G1 stage.^[206]

Apigenin extract from plant *Thevetia peruviana* at concentrations 3.65 mg/L for 24 h, 2.98 mg/L for 48 h, 1.63 mg/L for 72 h, and 0.73 mg/L for 96 h showed molluscicidal effect on snail (*Lymnaea acuminata*) without affecting the non-target species *Channa punctatus*. Exposure to sub-lethal doses of apigenin (3.65 mg/L, 24 h) caused significant ($p < 0.05$) alteration in carbohydrate and nitrogen metabolism in nervous, hepatic, pancreatic, testicular, and ovarian tissues in snail. However, at the same time the non-target fish species when exposed to the same doses for 96 h showed similar pathological hallmarks, which were withdrawn after 7 days of treatment. So, as far as this study is concerned direct conclusion cannot be reached, suggesting the use of apigenin as molluscicide.^[207]

Zhang et al.^[208] demonstrated that apigenin could promote the type-I and type-III collagen synthesis of dermal fibroblasts *in vitro* as well as *in vivo* by activating Smad2/3 pathways, without affecting cell viability and survival. This suggested the use of apigenin for esthetic and reconstructive skin rejuvenation and delaying ageing signs.^[208] One report has suggested that *Chrysanthemum morifolium* extract containing apigenin as an active compound prevented oxazolone and phorbol 12-myristate 13-acetate (TPA) induced acute allergic contact dermatitis and acute irritant contact dermatitis, respectively, in murine rat models. This was evidenced by significant reduction in trans-epidermal water loss, lowered skin surface pH, and increased stratum corneum hydration. Although, proper mechanism for the protective effect was not provided it may be thought that Smad2/3 signaling pathways may be involved in skin recovery as suggested in the previous study.^[209]

Anti-tumor and anti-cancer

There are number of studies suggesting the protective role of apigenin against various types of cancers. A brief description of the protective role of apigenin against various cancer cell lines and experimental animal models is shown in Table 5.

An overview of molecular targets of apigenin

In one of the recent studies about 160 high confidence candidate apigenin target molecules were identified which were divided into three functional categories: GTPase activation, membrane transport, and mRNA metabolism/alternative splicing.^[314] Other research papers have also revealed a number of apigenin targets, summarised in Table 6 given below.

Apigenin drug delivery systems

Numerous studies are performed to develop and evaluate a novel delivery system for apigenin. In one of the recent studies Shen et al.^[148] and Vanic^[315] demonstrated that the efficiency of apigenin encapsulation increases with an increase in the amount of phospholipids in ethosome formulations. Ethosomes are small hydrophobic molecules formed by the combination of phospholipids (lipoid S 75) and short chain alcohols (propylene glycol and ethanol). Apigenin loaded ethosomes showed effective targeting on mice skin tumorigenesis induced by UV-B radiations in both *in vivo* and *in vitro* models. Apigenin's solubility in water was increased by 148 times, thereby increasing its protective efficiency when used against HepG2 and MCF-7 cancer cell lines in the form of polymeric micelles. Moreover, the *in vitro* drug release study showed nearly 84% apigenin release from the micelles within 36 h, marking its sustainable release. The micelles were made up of either pluronic p123 + solutol HS15 having a diameter of 16.9 nm or 60% Cremophor EL + 30% Transcutol HP and 10% capryol 90 having a diameter of 17.1 nm.^[316,317] In another study pre-cutaneous absorption of apigenin was investigated in three vehicles viz; DMSO (D) alone, acetone+DMSO(A/D; 4:1), and polypropylene glycol+DMSO (PG/D; 4:1). Apigenin absorption in mouse skin *in vitro* followed the order of A/D > D > PG/D. However, sub-tissue distribution analysis showed that DMSO delivered more apigenin in epidermis than A/D while, A/D deposited more apigenin in stratum corneum. In an *in vivo* study both DMSO and A/D showed saturation kinetics while apigenin in PG/D showed very low absorption in initial

Table 5. Protective role of apigenin among various cancer cell lines and in experimental animal models.

S. No	Types	Experimental models and cell lines	Conclusions	References
1.	Prostate cancer	virally transformed human (PZ HPV-7) and human prostate adeno carcinoma (CA HPV-10) cells.	Apigenin treatment resulted in significant apoptosis of human prostate adeno carcinoma (CAHPV-10) cells, but not of virally transformed human prostate epithelial (PZ-HPV-7) cells. Apigenin at 1–10 mM concentration also resulted in a dose-dependent G2-M phase cell cycle arrest of CA-HPV-10 cells but not of PZ-HPV-7 cells.	[86]
		PC-3 cells	Apigenin inhibits Akt kinase activity by dephosphorylating it, which was confirmed by reduced phosphorylation of pro-apoptotic proteins BAD and glycogen synthase kinase-3.	[89,212]
		PC-3M cells	Apigenin markedly decreased HIF-1 α and VEGF expression under both normoxic and hypoxic conditions in PC-3M cells time dependently. In recent studies it was observed that apigenin inhibited the focal adhesion kinase (FAK)/Src, motility and invasion in the metastatic prostate carcinoma.	[213, 214]
		PWR-1E, LNCaP, PC-3 & DU-145 cells	Apigenin drives the production of reactive oxygen species and initiates a mitochondrial mediated cell death pathway in several lines of prostate cancer epithelial cells by inhibiting PI3K/Akt signalling.	[215]
		PC-3 cells	Apoptosis was achieved in PC-3 cell lines by suppressing the expression of NF- κ B-regulated genes, specifically, Bcl2, cyclin D1, cyclooxygenase-2, matrix metalloproteinase 9, nitric oxide synthase-2, and VEGF	[216]
		22RV1 tumor, xenograft in athymic nude mice	Induces cell cycle arrest and apoptosis by down-regulating the protein expression of cyclin D1, D2, and E, cdk2, cdk4, and cdk6, decrease in Rb phosphorylation and increased accumulation of WAF1/p21, KIP1/p27, INK4a/p16, and INK4c/p18 protein in prostate cancer cell xenograft in athymic nude mice. Later studies demonstrated that apigenin at different doses resulted in ROS generation, which was accompanied by rapid glutathione depletion, disruption of mitochondrial membrane potential, cytosolic release of cytochrome-c, p53 activation and apoptosis in human prostate cancer 22RV1 cells.	[217, 218, 219]
		PC-3 cells, DU-145 cells and PC-3 Xenograft in athymic nude mice	Apigenin resulted in a dose dependent suppression of apoptosis suppressor proteins XIAP, cIAP1, cIAP2 and survivin. This is accompanied by decrease in BclxL and Bcl2 and an increase in Bax. An increase in Bax is due to the inhibition of Class II histone deacetylase protein which results in its dissociation from Ku 70, followed by apoptotic progression in both the cell lines and athymic nude mouse xenograft model.	[220]
		LNCaP and PC-3 cells	Apigenin causes G0/G1 phase arrest, decrease in total Rb protein and its phosphorylation at Ser780 and Ser807/811 in dose- and time-dependent fashion. Apigenin treatment also results in increased phosphorylation of ERK1/2 and JNK1/2 which resulted in decreased ELK-1 phosphorylation and c-FOS expression thereby promoting apoptosis.	[221]
		TRAMP model	Using Transgenic Adenocarcinoma of the Mouse Prostate (TRAMP) model, it was demonstrated that oral administration of apigenin at doses of 20 and 50 μ g/mouse/day, 6 days per week for 20 weeks, significantly decreased tumor progression of the prostate as well as completely abolished distant-site metastases to lymph nodes, lungs, and liver. Administration of apigenin resulted in increased levels of E-cadherin and decreased levels of nuclear β -catenin, c-Myc, and cyclin D1.	[222]
		DU-145 cell lines	Apigenin was found to suppress insulin-like growth factor-I receptor signaling in human prostate cancer cells.	[223]

(Continued)

Table 5. (Continued).

S. No	Types	Experimental models and cell lines	Conclusions	References
2.	Liver cancer	DU-145 cell lines	Apigenin suppressed the proliferation and inhibited the migration and invasive potential of the DU145 prostate cancer cells in a dose- and time-dependent manner.	[224]
		Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) model	Apigenin inhibits prostate cancer progression in TRAMP mice via targeting PI3K/Akt/FoxO pathway and also by blocking β -catenin signaling.	[225]
		LNCaP cells	Exposure of apigenin to hormone sensitive LNCaP cells brought about apoptosis in them by inhibiting casein kinase 2 (CK2) activity in the same.	[226]
		PC-3 cells	Apigenin induce apoptosis in prostate cancer cells by modulating ubiquitin mediated proteasomal system to rescue estrogen receptor- β (ER- β) from degradation.	[227]
		H4IIE hepatoma cells	C8-prenylation of apigenin enhances the cytotoxicity and induces apoptotic cell death in H4IIE hepatoma cells without affecting anti-oxidative properties	[228]
		Hepatocellular carcinoma Hep G2 cells	Apigenin exhibited cell growth inhibitory effects which were due to cell cycle arrest and down regulation of the expression of CDK4 with induction of p53 and p21 protein respectively. The results also suggest that ROS generated through the activation of the NADPH oxidase may play an essential role in the apoptosis induced by apigenin in HepG2 cells.	[229]
		H411E hepatoma cells	Addition of prenyl group at 8C on apigenin increases its cytotoxicity and induces apoptosis in H411E hepatoma cells.	[230]
		Doxorubicin hepatocellular carcinoma BEL 7402/ADM cells	Apigenin sensitises doxorubicin resistant BEL 7402 cells to doxorubicin and increases intracellular concentration of doxorubicin. Apigenin imparts its effect by downregulating Nrf-2 expression at both the mRNA level and protein level through downregulating PI3K/Akt pathway.	[231]
		Hep G2 cells	Apigenin was found to induce apoptosis in Hep G2 cells by reducing expression of CDK4, enhancing the expression of p53 and activating p21/WAF1 pathway. This was in turn associated with cell cycle arrest in G2/M phase.	[232]
		Wistar albino rats with induced hepatocarcinogenesis	Results have also shown <i>in vivo</i> protective effects of apigenin against NDEA induced and phenobarbital promoted hepatocarcinogenesis in Wistar albino rats. Apigenin treatment at 25 mg/kg body weight for two weeks showed protection against the oxidative stress and DNA damage caused by the NDEA.	[233]
3.	Adrenal cancer	HeLa cell line	Findings from the study suggested that apigenin inhibited SOD activity without altering its concentration in the culture cells. But, apigenin as well as paclitaxel at the same time brought about apoptosis of the cancer cell line via over expression of caspase-2.	[234]
		H295R human adrenocortical cancer cells	Laboratory studies using various flavonoids against adrenocortical cancers have shown induction and inhibition of aromatase (CYP19) associated with increased intracellular cAMP concentrations. Further investigation of plant flavonoids on cortisol production in H295R cells indicate that cells exposed to apigenin results in a decrease in cortisol production, 3 β -HSD II and P450-c21 activity.	[235]
4.	Hematologic cancer	Leukaemia HL-60	Apigenin was shown to be markedly more effective than other tested flavonoids in inducing apoptosis in human leukaemia cells through cytochrome-c release and activation of caspase-9 and caspase-3.	[237]
		Human leukaemia cell lines	Apigenin in different leukemia cell lines resulted in selective antiproliferative and apoptotic effects in monocytic and lymphocytic leukemias; this selective apoptosis is mediated by induction of protein Kinase C delta.	[238]

(Continued)

Table 5. (Continued).

S. No	Types	Experimental models and cell lines	Conclusions	References
5.	Skin cancer	Human platelets	Apigenin inhibits platelet adhesion and thrombus formation and synergizes with aspirin in the suppression of the arachidonic acid pathway	[239]
		U937 cells	Apigenin and other flavones but not the isoflavones or flavanones tested were shown to induce apoptosis in U937 cells.	[240]
		Infant leukaemia	Another study evaluated the role of dietary bioflavonoids in inducing cleavage in the MLL gene, which may contribute to infant leukemia.	[241]
		A375 and A549 melanoma cell lines	<i>Lycopodium clavatum</i> extract having apigenin as a parent compound exerted apoptosis in melanoma cell lines by modulating caspase 3, 9, PARP, bax, bcl-2 and cyt-c activity and thus, showed to have anti-cancer property.	[67]
		Mice keratinocyte cell lines	Apigenin suppresses the UV B-induced COX-2 expression (a key enzyme which converts the arachidonic acid to prostaglandins and its over-expression results in carcinogenesis) and mRNA in mouse and even in human keratinocyte cell lines.	[146, 147]
		Benzo(a)pyrene and UV-B induced skin tumor in mouse	Apigenin loaded with poly (lactic-co-glycolide) (PLGA) nanoparticles (Nap) was found to produced far better effects than apigenin alone against Benzo(a)pyrene and UV-B induced skin tumor and mitochondrial dysfunction in rat model.	[176]
		Mouse epidermal JB6 P+ cells	Apigenin can restore the silenced status of Nr1f2 in skin epidermal JB6 P+ cells by CpG demethylation coupled with attenuated DNMT and HDAC activity, thus suggesting the therapeutic role of apigenin in preventing skin cancer.	[242]
		Murine B16 melanoma cells	Apigenin along with hyperosid and icariin were found to significantly increase cellular melanin content without affecting cell proliferation.	[243]
		Mice SHK-1 cells	Apigenin is effective in the prevention of UVA/B-induced skin carcinogenesis in SKH-1 mice.	[244]
		Mice Keratinocytes	In other studies with exposure of mice keratinocytes to apigenin it was seen that apigenin induced G1/S and G2/M cell cycle arrest and accumulation of the p53 tumor suppressor protein with increased expression of p21/WAF1. This arrest was accompanied by inhibition of p34 (cdk2) kinase protein level and activity, which was found to be independent of p21/WAF1.	[245, 246]
		Human diploid fibroblast cells	Apigenin produced G1 cell-cycle arrest by inhibiting cdk2 kinase activity and inducing p21/WAF1 in Human diploid fibroblast cells.	[247, 248]
		Tumorigenic epidermal keratinocytes xenograft in mice	Increased expression of Thrombospondin-1(TPS-1), RNA binding protein HuR and reduction in COX-2 and HIF-1 α production by apigenin controls UVB-induced tumorigenic epidermal keratinocytes xenograft in mice.	[249]
		Female SENCAR mice	Skin tumorigenesis initiated by 7,12-dimethylbenz(a)anthracene (DMBA) and promoted by 12-O-tetradecanoyl phorbol-13-acetate (TPA) in SENCAR mice, was found to be attenuated by topical application of apigenin dose dependently. Anti-tumorigenic effect might be attributed to the inhibition epidermal ornithine decarboxylase enzyme by apigenin treatment.	[250]
		Human HL-60 and mouse C-50 and 308	Exposure of human HL-60 and mouse C-50 and 308 cell lines to apigenin induced G2/M cell cycle arrest by preventing the accumulation of Cyclin B and also by inhibiting the p34 ^{cdc2} H kinase activity.	[251]
				(Continued)

Table 5. (Continued).

S. No	Types	Experimental models and cell lines	Conclusions	References
5.		Normal human Keratinocyte cell lines	In this study apigenin and curcumin were found to inhibit differentiation of keratinocytes via modulating MAPK pathway and reducing AP-1 expression. EGCG on the other hand showed inverse effect as evidenced by increased keratinocyte morphological differentiation. This is due to increased expression of involucrin, transglutaminase type-1 and caspase 14.	[252]
6.	Brain cancer	SH-SY5Y neuroblastoma cells	SH-SY5Y neuroblastoma cells when exposed to flavonoid apigenin were found to undergo apoptosis associated with an increase in Bax:Bcl-2 ratio, cyt c release and activation of calpain, caspase 3,9 and 12 .	[91]
		Human neuroblastoma cells.	Apigenin has shown to induce caspase-dependent, p53-mediated apoptosis in human neuroblastoma cells.	[253]
		PC 12 cell line (Neuron like cells)	Oxygen and glucose deprived reperfusion injury (OGD/R) significantly decreased cell viability, mitochondrial membrane potential, mRNA levels of antioxidant and detoxifying enzymes and Nrf2 protein expression, while elevated the release of LDH, cell apoptosis, intracellular ROS, p53 protein expression and also upregulated downstream genes in PC12 cells. However, treatment of cells with apigenin has reversed the effects.	[254]
		T98G and U87MG	Glioblastoma cell lines T98G and U87MG were found to undergo apoptosis when treated with apigenin thus reducing cancer progression. However, no apoptotic effect was observed in normal human astrocytes.	[255]
7.	Thyroid cancer	UCLA RO-81A-1 (ARO) anaplastic carcinoma cell line	Inhibitory effect of apigenin on ARO cell proliferation was associated with inhibition of both EGFR tyrosine autophosphorylation and phosphorylation of its downstream effector MAPK.	[256]
		FTC 133 transfected with hNIS	When human follicular thyroid cancer cell lines (FTC 133), stably transfected with human Na ⁺ /I ⁻ symporter (hNIS) were treated with apigenin a reduction in the expression of NIS mRNA was observed. This study opens up the gateway for the radioliodine treatment of thyroid cancers.	[257]
		FRO anaplastic thyroid carcinoma cells	Apigenin is found to induce apoptosis via increased c-myc expression and by simultaneous phosphorylation of p38 and p53 tumor suppressor genes.	[258]
8.	Ovarian cancer	HO-8910PM cells SKOV3 and SKOV3/TR cell lines	Apigenin inhibited the activity of MAPK and PI3K in human ovarian carcinoma HO-8910PM cells. Circumvention and antiproliferative effect of apigenin in taxol resistant SKOV3/TR and SKOV3 ovarian cancer cell lines is due to the inhibition of IL-6/STAT3 axis and targeting Axl and Tyro3 receptor tyrosine kinases.	[259]
		OVCA3 and A2780/CP70 cell lines	On treatment with apigenin inhibition of tumor angiogenesis was observed, which was associated with the decrease in the levels of hypoxia inducible factor -1 α (HIF-1 α) and vascular endothelial growth factor (VEGF) in tumor tissues via: PI3-K/Akt, HDM2/p70S6K1 and p53 pathways.	[261,262]
		A2780 cell lines	Apigenin reduced the tumor progression in ovarian cancer cell line A2780 by acting as an inhibitor of differentiation or DNA binding protein 1 (Id1).	[263]
9.	Colo- rectal cancer	Endometrial cancer cells	Analysis of DNA in endometrial cancer cells treated with phyto-estrogenic compounds including apigenin using comparative genomic hybridisation microarrays have suggested that apigenin may play a role in the treatment of endometrial cancer and in the treatment of postmenopausal women.	[264]

(Continued)

Table 5. (Continued).

S. No	Types	Experimental models and cell lines	Conclusions	References
10.	Lung cancer	HT-29 and HCT- 15	Treatment of colorectal cell lines HT-29 and HCT-15 with apigenin resulted in anti-proliferative and apoptotic effects characterized by biochemical and morphological changes. Inhibition of Rb phosphorylation and up-regulation of p21 regulation of p21 led to simultaneous suppression of cyclins D1 and E which indicated the onset of senescence.	[265]
		HCT-116 cell line	Apigenin resulted in G2/M phase arrest of HCT-166 cells by suppressing the expression of cyclin B1, cdc-2 and cdc-25. In addition expression of cell cycle inhibitors, such as p53 and p53-dependent p21CIP1/WAF1 was reduced after apigenin treatment.	[266]
		SW480 and Caco-2	Apigenin along with the combination of its 5 analogues (acacetin, chrysin, kampherol, luteolin and myricetin) at different concentrations inhibit SW480 and Caco2 cell line proliferation by arresting them at G2/M phase of cell cycle.	[267]
		HT-29 and SW620 cell lines	Apigenin induces G2/M arrest in colon cancer cell lines by downregulating expression of cyclin dependent kinase 1(CDK1) through binding and inhibition of ribosomal protein S9.	[268]
		B16-BL6 murine melanoma cells	<i>In vivo</i> administration of apigenin was effective in inhibiting melanoma lung tumor metastasis in B16-BL6 murine melanoma metastasis model.	[269]
		A549 and H460 cell lines	Apigenin downregulates Axl expression, which subsequently results in the inhibition of A-549 and H460 cell line proliferation, through an increase in p21 and decrease in (X linked inhibitor of apoptosis protein) XIAP expression.	[270]
		Human lung squamous carcinoma (SQ-5) cells	Radiosensitising sphere forming human lung squamous carcinoma (SQ-5) cells, when incubated with apigenin underwent apoptosis and necrosis in a dose and time dependent manner. This was due to the over expression of WAF/p21 and decreased expression of Bcl-2 genes.	[271]
		Lewis lung carcinoma (LLC), C-6 glioma and DHDK-12 cell lines	In contrast to the high <i>in vitro</i> sensitivity of LLC, C-6 glioma, DHDK-12 colonic cancer and endothelial cancer cell lines to 50 mg/kg/day (for 12 days) of apigenin, the <i>in vivo</i> response in rats was found to be negligible. The inhibition was achieved due to cytotoxicity and anti-angiogenic effect of apigenin.	[272]
		B57BL/6N mice model injected with B16-BL6 murine myeloma cells	Apigenin along with two other flavonoids at a concentration of 50mg/kg (for 6 to 14 days) were found to inhibit VCAM-, TNF- α and ICAM-1 expression in a dose-dependent manner in human umbilical vein endothelial cells (HUVEC) and murine pulmonary endothelial cells.	[273]
		T-24 cell line	Treatment of T-24 cells with apigenin was associated with an increase in the phospho-p53, p53, p21, and p27 levels, and a decrease in the Cyclin A, Cyclin B1, Cyclin E, CDK2, Cdc2, and Cdc25C levels thereby, blocking cell cycle progression during G1/S and G2/M. In addition, apigenin increases the Bax, Bad, and Bak levels, but reduces the Bcl-xl, Bcl-2, and Mcl-1 levels, which subsequently triggers the mitochondrial apoptotic pathway.	[274]
11.	Bladder cancer	T-24 cell line	Results demonstrated that apigenin suppressed proliferation and inhibited the migration and invasion T-24 bladder cancer cells in a dose- and time-dependent manner, which was associated with induced G2/M Phase cell cycle arrest and apoptosis. The mechanism involves PI3K/Akt pathway and Bcl-2 family proteins. Increase in caspase-3 activity and PARP cleavage guides the cell towards apoptosis.	[275]

(Continued)

Table 5. (Continued).

S. No	Types	Experimental models and cell lines	Conclusions	References
12.	Breast cancer	HER2/neu overexpressing breast cancer cells	HER2/neu overexpressing breast cancer cells are known to cause breast cancer by inhibiting apoptosis through activation of PI3K and Akt/PKB signalling pathways. Apigenin reduced HER2/neu gene expression without affecting the cells expressing basal levels of HER2/neu by inhibiting PI3K activity and consequently inhibiting Akt kinase activity.	[276, 277]
		MDA-MB 453 cell line	Apigenin has shown to induce apoptosis through cytochrome-c release and rapid production of DNA fragmentation factor 45 in MDA-MB-453 human breast cancer cells	[278]
		MCF-7 cell line	PKC-activating phorbol ester (PMA) prevents apoptosis by activating cellular signaling pathways such as MAPK and PI3K and suppression of TNF- α in MCF-7 breast cancer cells. Apigenin was found to induce apoptosis in these breast cancer cells by suppressing the PMS mediated AP1 activity which in turn is due to the suppression of MAPK and PI3K pathways.	[279]
		SK-BR 3 breast cancer cells	Apigenin induces G 2/M arrest associated with the modulation of p21 (Cip1) and Cdc2 and activates p53-dependent apoptosis pathway in human breast cancer SK-BR-3 cells.	[280]
		MDA-MB – 231cell line	The effect of apigenin on protease-mediated invasiveness was evaluated in estrogen-insensitive breast tumor cell line MDA-MB231 showing that apigenin strongly inhibit tumor cell invasion.	[281]
		MDA-MB – 453 cell line	Apigenin inhibited the proliferation of MDA-MB-453 cells by inhibiting JAK2-STAT3 pathway and inducing apoptosis via up-regulation of cleaved caspase 8 and caspase 3.	[282]
		MB-468	Decreased proliferation of MB-468 cell line was observed after treatment with apigenin. This was due to the inhibition of Akt (Protein kinase B), which is essential for tumor progression and arrest of cells in G2/M phase.	[283]
		SKBR3 breast cancer cells	Apigenin induces caspase-dependent apoptosis by inhibiting signal transducer and activator of transcription 3 (STAT 3) signaling in HER2-overexpressing SKBR3 breast cancer cells.	[284]
		MCF-7 cell line	Apigenin inhibits growth and induces G2/M arrest by regulating cyclin-cdk complexes and ERK-MAP Kinase pathway in given cell lines	[285]
		MCF 7 breast cancer cells	Apigenin targets both ERalpha-dependent and ERalpha-independent pathways on estrogen-responsive, anti-estrogen sensitive MCF7 breast cancer cells and growth inhibitory effect on two MCF7 sub-lines with acquired resistance to anti-estrogens viz. tamoxifen or fulvestrant.	[286]
		MCF-7, T47D and MDA-MB-435 breast cancer cells	Apigenin has been shown to stimulate the proliferation of MCF-7 and T47D cells estrogen receptor alpha (ER alpha-positive), but do not stimulate the proliferation of an ER alpha negative cell line MDA-MB-435 cells.	[287]
		MDA-MB 231 breast cancer cells	Apigenin induces apoptosis by the activation of caspase 3, 7 and poly (ADP-ribose) polymerase cleavage and also by inhibiting proteasomal chymotrypsin-like activity in cultured MDA-MB-231 cells and also in MDA-MB-231 xenografts.	[65]
			Apigenin inhibits hepatocyte growth factor-induced MDA-MB-231 cells invasiveness and metastasis by blocking Akt, ERK and JNK phosphorylation and also inhibits clustering of β -4-integrin function at actin rich adhesive site.	[288]
		Mammary Adeno-carcinoma (AMN3) bearing mice	After 24 days of oral administration of apigenin at a dose of 300 mg/kg body weight, a significant reduction in the volume of mammary adenocarcinoma was found in treated animals, along with the decrease in lipid peroxidation and a subsequent increase in reduced glutathione content.	[289]
		SK-BR and MCF-7/HER2 cells	Apigenin derived from extra virgin olive oil was able to suppress the expression of lipogenic enzyme fatty acid synthase in SKBR and MCF-7/HER2 cells	[290]

(Continued)

Table 5. (Continued).

S. No	Types	Experimental models and cell lines	Conclusions	References
13.	Cervical cancer	HeLa cell lines	Apigenin inhibited cell growth, G1 growth phase arrest and induced p53 dependent apoptosis and was associated with a marked increase in the expression of p21/WAF1 protein with the induction of Fas/APO-1 and caspase-3 expression. Apigenin also decreased the expression of Bcl-2 protein, an antiapoptotic factor.	[291]
		HeLa C-43 cell lines	The effect of apigenin on cell proliferation was less pronounced especially at low apigenin concentration, whereas its influence on cell motility correlated with the reduction of the invasive potential of HeLa C-43 cells.	[292]
		Sphere-forming cells (SF)/ HeLa cells	Results suggested that apigenin inhibits the self-renewal capacity of HeLa derived SFCs through down-regulation of protein kinase casein kinase 2 (CK2a) expression.	[293]
14.	Gastric cancer	SGC-7901 and gastric mucosa epithelial cells (GES-1)	Apigenin modulated growth inhibition in SGC-7901 cell lines by inducing apoptosis	[294, 295]
		HGC-27 and SGC-7901 cell lines	Apoptosis was induced in gastric carcinoma cells through mitochondrial signalling pathway after apigenin treatment.	[296]
		-	Apigenin is able to reduce cancer cell glucose uptake, inhibit remodeling of the extracellular matrix, inhibit cell adhesion molecules that participate in cancer progression, and oppose chemokine signaling pathways that direct the course of metastasis into other locations, thereby suggesting its anti carcinogenic potential against gastric carcinoma.	[297]
		BGC823 cells	Human gastric carcinoma cells BGC823 when exposed to flavonoid apigenin were found to undergo apoptosis associated with a reduction in Bcl-2 expression and an increase in the expression of Bax, cyt c release and activation of caspase 3 and 9.	[298]
		Mongolian Gerbils	The study reveals the protective effect of apigenin on the progression of Helicobacter pylori induced atrophic gastritis and gastric cancer in Mongolian gerbils.	[299]
		Human gastric cancer cell line SGC-7901	In this study apigenin was found to inhibit proliferation of gastric cancer cell lines by inhibiting PKB/Akt signalling and anti-apoptotic protein Bad. Authors also reported that apigenin promoted apoptosis in the cancer cells by specific phosphorylations on Akt and Bad without affecting their expression levels.	[300]
15.	Leukaemia cell lines	K562 human chronic leukaemia cells	Apigenin induced erythrocyte differentiation in K562 human chronic leukaemia cells via 2-3 double bond and hydroxyl group in its moiety.	[301]
		K562 and K562/IMA3 cell lines	The study concluded that apigenin inhibits cell proliferation and induces apoptosis by up-regulating the activity of caspase-3 and arresting the cells in G2/M phase of cell cycle respectively.	[302]
		Myeloma cell lines U266 and RPMI 8226	Apigenin was found to kill MM cells by targeting the trinity of CK2-Cdc37-Hsp90. By depleting these kinases, apigenin suppresses both constitutive and inducible activation of STAT3, ERK, AKT and NF- κ B.	[303]
		Mouse macrophage ANA-1 cells	Apigenin increased the level of intracellular ROS, downregulated the expression of Bcl-2 and upregulated the expression of caspase-3 and caspase-8 in ANA-1 cells. Furthermore, apigenin downregulated the expression of phospho-ERK and phospho-JNK and upregulated the expression of phospho-p38, which leads the cell towards apoptosis.	[304]
16.	Multidrug resistant (MDR) tumor cells	MDR tumor cells over expressing ABC transporters, BCRP/ ABCG2, P-glycoprotein /ABCB1 and ABCB5.	Apigenin overcomes multi drug resistance by increasing cellular uptake of doxorubicin and synergistic inhibition of cell viability in combination with doxorubicin or docetaxel in multidrug-resistant cells.	[305]

(Continued)

Table 5. (Continued).

S. No	Types	Experimental models and cell lines	Conclusions	References
17.	Pancreatic cancer	BxPC 3 and PANC 1	Flavonoid apigenin induced apoptosis in human pancreatic cancer cells by arresting them at G2/M stage through inhibition of GSK-3 β /NF- κ B signaling cascade. Apigenin highly upregulated the expression of cytokine genes IL-17F, LTA, IL-17C, IL-17A, and IFN- β 1 in BxPC-3 and PANC1 cells, thereby driving them towards apoptosis.	[306]
		CD18 and S2-013 cell lines	Apigenin inhibits Glucose transporter GLUT-1 and PI3-K/Akt pathway in human pancreatic cancer cell lines and thus, evoke apoptosis in them.	[307]
		Mia Paca-2 and As PC-1 cell lines	A combination of gemcitabine and apigenin was found to enhance apoptosis in pancreatic cancer cell lines via: NF- κ B and Akt pathway.	[308]
		PC cell xenograft in athymic nude mice	Inhibition of pancreatic cancer cell growth was observed in athymic nude mice xenograft on treatment with apigenin. Apigenin down-regulates basal as well as TNF- α -induced NF- κ B DNA binding activity, NF- κ B transcription activity, inhibitor of κ B (I κ B)- α phosphorylation, translocation of p65 and p50, accompanied with the blockade of I κ B kinase (IKK)- β activity.	[309]
		Pancreatic stellate cells (PSC)	Through <i>in vitro</i> and <i>in vivo</i> studies it was demonstrated that apigenin and its analogs (HJ05-61) and HJC05-100 inhibit PSC proliferation and induced apoptosis in the concerned cells at concentrations as low as 13 μ M, 4 μ M and 1 μ M respectively.	[310]
18.	Others	Retinal pigment epithelial cells (RPE)	Apigenin along with other flavonoids have shown to induce cellular necrosis in RPE cells by decreasing the expression of VEGF and were also able to induce apoptosis by reducing the phosphorylation of Src kinase/Akt modulators.	[311]
		Human embryonic kidney (HEK) 293 cells	Flavonoids namely quercetin, kaempferol and apigenin inhibited organic anion transported polypeptide 1A2 (OATP1A2) and 2B1 (OATP2B1) mediated transport of two anti-allergic drugs fexofenadine and atorva statin. This was determined by dixon plot analysis using BSP as substrate.	[312]
		Laryngeal carcinoma Hep2 cells	The study revealed that apigenin at a concentration 50 mM reduced the expression of GLUT-1 and down regulated PI3K/Akt pathway thereby promoting better action of cisplatin and preventing chemotherapeutic resistance to laryngeal carcinoma.	[313]

Table 6. Molecular targets of apigenin.

Gene expression	Protein kinases	Transcription factors	Enzymes	Membrane proteins	Others
Cyclin D	Ikk/IkB kinase	STAT-3	FTPase	VCAM	Bcl-2
Cyclin A	JAK	NF-κB	GST	ICAM	Bcl-xl
Cyclin B1	Src	AP-1	GSH-Px	VEGF	EGFR
Cyclin E	JNK	PI-3	GSH-R	EGFR	Bax
5-LOX	HER-2	Egr-1	CAT	MRPs	p53
COX-1	Akt/PKB	Erβ	SOD	MMPs	p21
COX-2	PKA	CBP	ALT	FAK	p27
P53	PKC	PPAR	ALP	IGF-1R	TRAIL
P21	PI3K	EpRE	GGT		APC
p27	MAPK	β-catenin	LDH		PTEN
iNOS		Nrf-2	AST	VEGF	IGF-1
IL-6		HIF-1α	XO		XIAP/IAP
IL-5		Elk-1	HO		β-CTF
IL-8		GATA-3	ODC		BDNF
IL-12			Cyt-P450		TGF-β
IL-17			Aromatase		HO-1
TNF-α			Caspase 3,9		
c-Fos			AChE		
			BChE		

periods of the experiment which was later increased but well below saturable limits. In further study, the same group of researchers demonstrated that 12-O-tetradecanoylphorbol-13 acetate (TPA) induced ornithine decarboxylase (ODC) activity in dorsal skin of mouse cannot be inhibited by apigenin (5 μmol) in A/D delivered from abdominal skin. Thus, they suggested that topical delivery of apigenin should target the local affected tissue for better activity.^[247,248] Sen et al.^[318] reported that simultaneous administration of apigenin along with 5-fluorouracil (clinically approve drug), loaded in a single liposome can successfully impart strong anti-neoplastic and anti-tumorigenic effect in nude mice xenograft model, by overcoming the problem of drug resistance and 5-fluorouracil associated toxicity. Carbon nanopowder (CNP) solid dispersion is another much improved drug delivery system developed by Ding et al.^[319] Here the mixture of CNP and apigenin in ratio 6:1 has shown to tremendously improve the pharmacokinetic properties and bioavailability of the drug (apigenin) in both *in vivo* and *in vitro* systems. The efficiency of the drug was increased by 275% as compared to treatment with apigenin alone. Looking at the future aspects of better drug delivery systems the organogels prepared from lecithin (phopholipid) could also be used to deliver the drugs (bioactive agents) to the target sites. Such kind of gels can thus be used for treating disorders like skin aging, skin cancers, etc.

Conclusion

All evidences gathered so far clearly indicate that apigenin protects against cancer, cardiovascular diseases, arthritis, and diabetes, the most common ailments across the world. This compound has also shown preventive as well as therapeutic effects against Alzheimer's disease, PD, AIDS, auto-immune disorders, and reperfusion injury. In addition behavioural changes, anti-genotoxic, and anti-inflammatory effects are also attributed to apigenin, against a number of toxic compounds. Some of the studies have established apigenin's potential in *in vitro* cultures, while some in animal models. Human trials are only performed in the form of dietary supplements. Further testing of apigenin in humans is underway to confirm these observations. Apigenin's quick absorption in intestine and slow elimination increases its bioavailability thus, making it a good therapeutic agent. The discovery of new drug delivery systems like micelles, liposomes, nanocomposites, and others may aid in further enhancing the potency of such drugs in future. Although, it is not clearly understood of how apigenin produces its therapeutic effects, but they may probably be mediated

through antioxidant and anti-inflammatory actions of apigenin. More than two dozen different cellular proteins and enzymes have been identified to be the molecular targets of apigenin. High throughput ligand-interacting technology and microarray technology have begun to reveal more molecular targets and genes affected by apigenin.

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