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Natural Flavonoid Apigenin, an Effective Agent Against Nervous System Cancers

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Abstract

Cancer is a serious public health concern worldwide, and nervous system (NS) cancers are among the most life-threatening malignancies. Efforts have been devoted to introduce natural anticancer agents with minimal side effects. Apigenin is an edible flavonoid that is abundantly found in many vegetables and fruits. Various pharmaceutical activities, including anti-inflammatory, antioxidative, antimicrobial, and anticancer effects have been reported for apigenin. This review provides insights into the therapeutic effects of apigenin and flavonoids with similar structure on glioblastoma and neuroblastoma. Current evidence indicates that apigenin has the unique ability to cross the blood-brain barrier, and its antioxidative, anti-inflammatory, neurogenic, and neuroprotective effects have made this flavonoid a great option for the treatment of neurodegenerative disorders. Meanwhile, apigenin has low toxicity on normal neuronal cells, while induces cytotoxicity on NS cancer cells via triggering several signal pathways and molecular targets. Anticancer effects of apigenin have been contributed to various mechanisms such as induction of cell cycle arrest and apoptosis, and inhibition of migration, invasion, and angiogenesis. Although apigenin is a promising pharmaceutical agent, its low bioavailability is an important issue that must be solved before introducing to clinic. Recently, nano-delivery of apigenin by liposomes and poly lactic-co-glycolide nanoparticles has greatly improved functionality of this agent. Hence, investigating pharmaceutical effects of apigenin-loaded nanocarriers on NS cancer cell lines and animal models is recommended for future studies.

Keywords Apigenin · Natural flavonoids · Glioblastoma · Neuroblastoma · Anti-cancer effects · Nano-delivery

Abbreviations

AKT	Ak strain transforming
AMPK	AMP-activated protein kinase
BDNF	Brain-derived neurotrophic factor
CDK-1	Cyclin-dependent kinase 1
c-FLIP	Cellular FADD-like IL-1β-converting enzyme-inhibitory protein
c-Met	Mesenchymal-epithelial transition factor
EGFR	Epidermal growth factor receptor
ERK	Extracellular signal-regulated kinase
GDNF	Glial-derived neurotrophic factor
GFAP	Glial fibrillary acidic protein
GLUT	Glucose transporters
GPx	Glutathione peroxidase
hTERT	Human telomerase reverse transcriptase
HIF-1α	Hypoxia-inducible factor-1 α
IL	Interleukin
JAK	Janus kinase
KLF4	Krüpple-like factor 4
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MCL1	Myeloid cell leukemia 1
MMPs	Matrix metalloproteinases
mTOR	Mammalian target of rapamycin
NK	Natural killer
NF-κB	Nuclear factor kappa B
Nrf2	Nuclear factor erythroid 2–related factor 2
NS	Nervous system
PARP	Poly ADP-ribose polymerase
PCNA	Proliferating cell nuclear antigen
PI3K	Phosphatidylinositol-3 kinase
PKM2	Pyruvate kinase isozyme type M2
PLGA	Poly lactic-co-glycolide
ROS	Reactive oxygen species
STAT	Signal transducers and activators of transcription
TGFβ	Transforming growth factor-beta

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TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor
Wnt	Wingless-related integration site
XIAP	X-linked inhibitor of apoptosis protein

Introduction

Cancer is a serious public health concern worldwide, which is known as the first or second cause of death before the age of 70 years in most countries. According to the latest statistics, approximately 19.3 million new cases and 10.0 million deaths have been reported for cancer in 2020 [1]. During recent years, remarkable progress has been made in diagnostic and therapeutic approaches for cancer; however, development of resistance phenotypes, modulation of the immune system, and metastasis of cancer cells are still barriers to achieve satisfactory clinical outcomes.

Among all types of malignancies, cancers of the nervous system (NS) account for 1.59% new cases and 2.51% of cancer related deaths [1]. NS cancers are a heterogeneous group of neoplasms with more than 100 histologically different subtypes, including glioblastoma, neuroblastoma, medulloblastoma, and ependymoma [2]. Surgical resection followed by concurrent or sequential application of ionizing radiation and drugs such as temozolomide are available therapeutic modalities for NS cancers. Nevertheless, rapid recurrence and poor prognosis are main reasons for low survival rate of patients. Infiltrating growth of NS cancer cells, which makes their complete removal impossible, along with intolerable side effects of current chemotherapeutics describe clinical failure [3]. Hence, it is of great interest to develop novel therapeutic agents with minimal side effects for eradication of NS cancer cells. This review focuses on apigenin and natural flavonoids with similar structure as potent agents with anticancer effects against NS cancers.

Natural Agents with Anticancer Potential

Use of natural occurring agents with cytotoxic potential is a promising route toward lowering cancer incidence and mortality. In recent years, secondary metabolites of plants including flavonoids and coumarins have drawn much attention, and clinical trials are ongoing to evaluate their safety and efficacy. Flavonoids and coumarins are benzopyrone compounds synthesized in medicinal plants and vegetables as bioactive secondary metabolites. Wide range of pharmaceutical effects, including anti-inflammatory, anticoagulant, antioxidative, immunomodulatory, antibacterial, antifungal, antiviral, and antihyperglycemic activities, have been reported for these agents [4, 5]. In the field of cancer research, it has been demonstrated that natural coumarins not only inhibit survival and proliferation of malignant cells, but also have the potential to enhance the efficacy of various anticancer modalities [6–11]. Likewise, flavonoids exert their anticancer effects through the modulation of reactive oxygen species (ROS)-scavenging enzymes, induction of cell cycle arrest, apoptosis, autophagy, and suppression of cell proliferation and invasion [12–14].

Apigenin

Among numerous types of flavonoids, apigenin (4′,5,7-trihydroxyflavone) is a consumable flavonoid with valuable biological functions. The molecular formula and weight of apigenin are $C_{15}H_{10}O_5$ and 270.05 g/mol, respectively. Apigenin is abundantly found in vegetables and fruits such as celery, spinach, parsley, marjoram, oregano, sage, chamomile, pistachio, grape, and apple [15]. In traditional medicine, apigenin has been used for its antioxidant, antimicrobial, antihypertensive and antidiabetic effects [16–21]. Much attention has also been attracted to anti-inflammatory and immunomodulatory effects of apigenin, since this natural flavonoid inhibits the secretion of interleukin (IL)-4 and IL-13 by activated basophils [22]. In addition, apigenin has the potential to improve the proliferation and activity of natural killer (NK) cells via raising perforin and granulysin secretion [23, 24]. Apigenin also inhibits the production of TNF-α, IL-1β, and IL-6 by lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells [25], and prevents the expression and secretion of IL-31 and IL-33 in LPS-treated astrocytes [26]. Regarding neuro-immunomodulatory effects, it has been reported that apigenin treatment of microglia/glioma co-cultures reduced viability of C6 cells while increased microglia-activated phenotype, and such change was attributed to the alteration of TNFα /IL-10 levels that restores the immune profile of microglia against glioma cells [27, 28].

Studies have also introduced apigenin is a multi-target agent that induces anticancer effects on various solid tumors and hematological malignancies through modulation of the cell cycle, induction of apoptosis and/or autophagy, inhibition of cell proliferation and survival, and reduction of migration and drug resistance [29–42]. Mechanisms involved in anticancer activity of apigenin include regulation of apoptosis mediators such as P53, P21, BCL-2, BCL-xL, and BAX; processing of procaspases; release of cytochrome c; induction of the cell cycle arrest; and targeting of signaling pathways such as AKT/mammalian target of rapamycin (mTOR), Wnt/β-catenin, nuclear factor kappa B (NF-κB), PI3K/AKT, JAK/STAT, and mitogen-activated protein kinase (MAPK)/ERK [30, 38–41, 43–50]. Worth to note, apigenin has poor intrinsic toxicity and induces distinct effects on normal versus cancer cells [51].

The basic structure of apigenin consists of a tricyclic core, which is the flavone nucleus containing 15 carbons and forming a diphenyl propane structure (C_6-C_3-C_6). Apigenin has three hydroxyl substituents and can be linked to different chemical groups such as prenyl, sugar, and hydrogen oxide [52]. In nature, apigenin is typically found in glycosylated forms, in which the flavone nucleus is bounded to a sugar moiety via hydroxyl groups or directly to carbon (O-glycosides and C-glycosides, respectively). As shown in Fig. 1, common apigenin glycoside derivatives are apigenin 7-O-beta-D-glucuronide, apigenin 7-O-(6″-O-acetyl-beta-D-glucopyranoside), apigenin 7-O-beta-D-glucopyranoside, apigenin-8-C-glucoside (vitexin), and apigenin-6-*C*-glucoside (isovitexin). In addition, apigenin derivatives could be in dimeric forms, in which apigenin residues are variously coupled, with C–C linkage (as in cupressuflavone and amentoflavone) or C–O linkage (in hinokiflavone) to name a few (Fig. 2).

Apigenin has several advantages over other natural flavonoids, such as delayed plasma clearance and slow decomposition in liver. Moreover, apigenin has higher lipophilicity in comparison with its large derivatives and efflux transporters, like P-glycoprotein and multi-drug resistance proteins, use glucuronidated, methylated and sulfated conjugates of apigenin as substrates, and dramatically reduce their distribution and bioactivity [53, 54]. In addition, apigenin has the unique ability to cross the blood-brain barrier [55], and its antioxidative, anti-inflammatory, neurogenic, and neuroprotective effects have made this flavonoid a great option for the treatment of neurological disorders [56–59].

Therapeutic Potential of Apigenin Against NS Cancers

In general, flavonoids are known for their antioxidative potential, which is due to the presence of OH group in their structure; the higher the number of hydroxyl group, the stronger the antioxidant effect [60, 61]. Studies carried out on various models of NS diseases such as Alzheimer, Parkinson, and depression indicated beneficial effects of apigenin, as it reduced IL-1β, 6 and -18, β-amyloid, oxidative stress, and microglial activation; improved memory and learning; and increased brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), and tyrosine hydroxylase [62].

Another eccentric activity of apigenin is that it modulates the interaction between glioma and glial cells, and thus, eliminate cancer cells without damaging healthy nervous cells [63]. In this regard, studies have demonstrated that

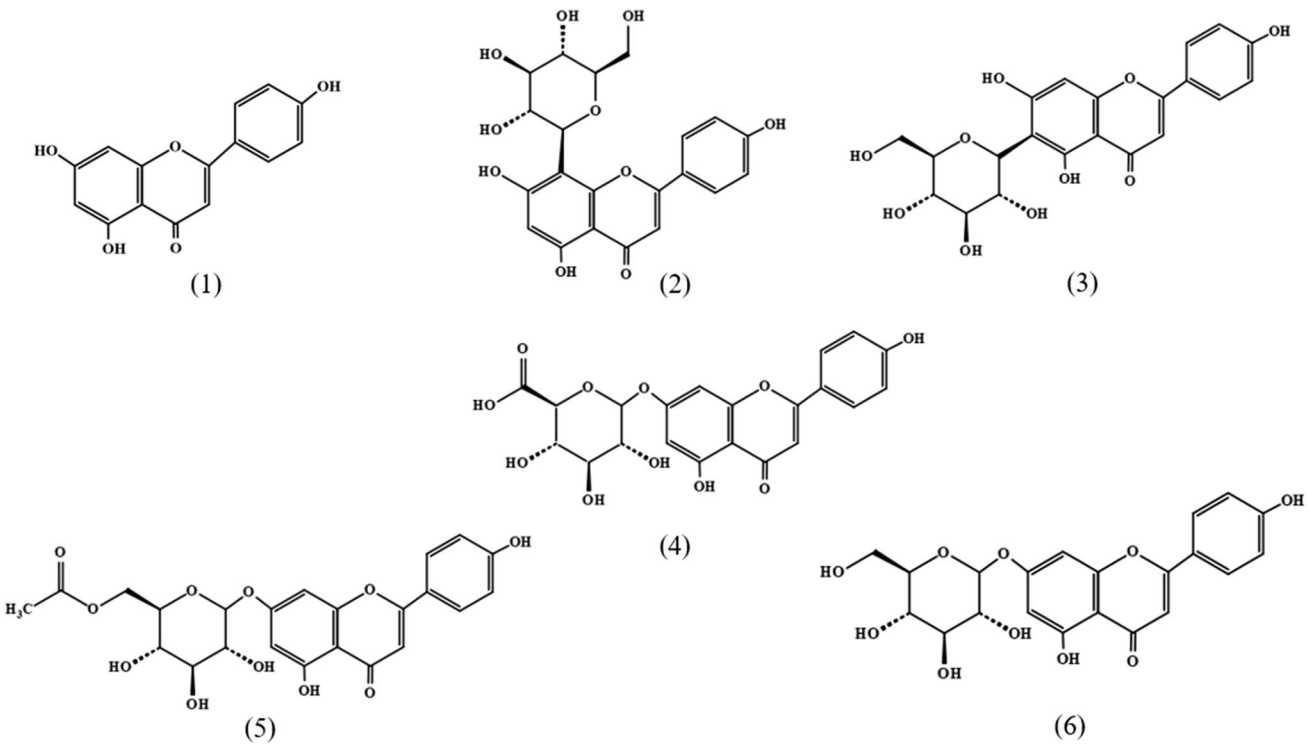

Fig. 1 Apigenin and its glycosylated derivatives; 1: apigenin (PubChem ID 5280443), 2: vitexin (PubChem ID 5080441), 3: isovitexin (PubChem ID 162350), 4: apigenin 7-O-beta-D-glucuronide (PubChem ID 5319484), 5: apigenin 7-O-(6"-O-acetyl-beta-D-glucopyranoside) (PubChem ID 21721966), 6: apigenin 7-O-beta-D-glucopyranoside (PubChem ID 5280704). This figure was drawn using Molsketch, a 2D molecular editor software

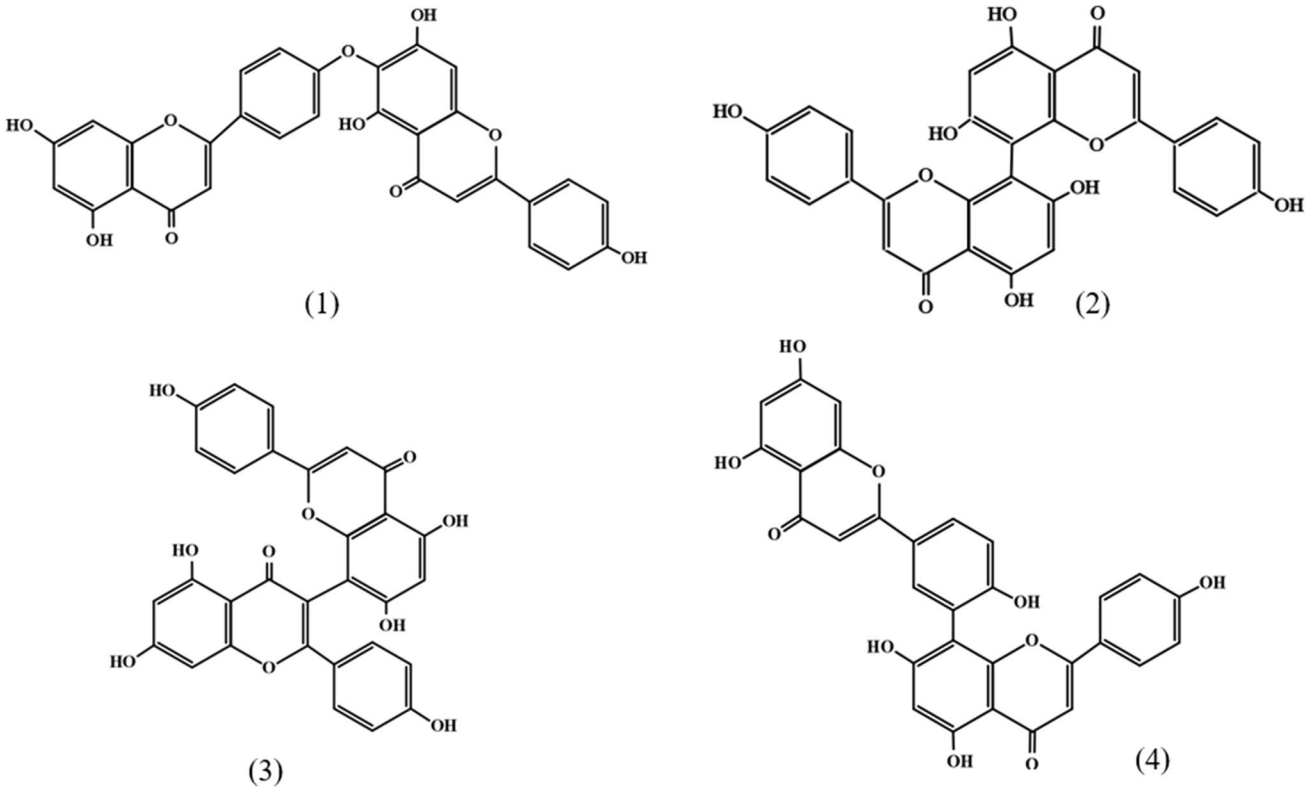

Fig. 2 Dimeric forms of apigenin; 1: hinokiflavone (PubChem ID 5281627), 2: cupressuflavone (PubChem ID 5281609), 3: 3,8-biapigenin (PubChem ID 10414856), 4: amentoflavone (PubChem ID 5281600). This figure was drawn using Molsketch, a 2D molecular editor software

apigenin decreased the viability and proliferation of glioblastoma and neuroblastoma cells, while induced no considerable effects on normal astrocytes or primary sympathetic neurons [64–67].

Figure 3 indicates the network of regulatory proteins that are affected by apigenin in glioma. These targets are related to the cell cycle, survival, proliferation, migration, metabolism, hypoxia, and apoptosis, and many of them are intrinsically linked.

Regarding antiproliferative effects of apigenin, accumulation of glioblastoma cells in the G_2/M phase of the cell cycle was observed upon apigenin treatment, which was mediated through downregulation of cyclin-A1, cyclin-B1, and CDK-1 [68]. It has also been shown that apigenin induced G_0/G_1 arrest in glioma cells [67]. In addition, apigenin reduced proliferation of glioblastoma cells via inhibition of EGFR-mediated phosphorylation of AKT, MAPK, and mTOR signaling pathways [66]. Apigenin also has the potential to suppress self-renewal capacity and clonogenicity of human glioblastoma and neuroblastoma cells via blocking the phosphorylation of c-MET and its downstream effectors [69].

As summarized in Table 1, apoptosis-inducing effects of apigenin on glioblastoma and neuroblastoma cells were attributed to the cleavage of poly ADP-ribose polymerase (PARP) that has a vital role in the continuation of apoptosis [68]. Moreover, downregulation of BCL-xL; upregulation of P53, P21, and BAX; truncation of BID; and activation of calpain and caspases-8, -9, and -3 were observed upon treatment of glioblastoma and neuroblastoma cells with apigenin [68]. In addition, it has been reported that apigenin triggered the production of ROS in glioblastoma cells and induced apoptosis with phosphorylation of MAPK and activation of the redox-sensitive c-Jun N-terminal kinase 1 pathway [70]. The blockade of TNFα-mediated NF-κB activation, along with caspase-3 activation and P53 stability has also been reported upon apigenin treatment of glioma cells [71]. In addition, apoptosis-inducing effects of apigenin in glioblastoma and neuroblastoma cells was accompanied by damages to the mitochondria and rough endoplasmic reticulum, increased level of intracellular free Ca^{2+} and cytochrome c release [72]. It has also been shown that apigenin and N-(4-hydroxyphenyl) retinamide synergistically inhibited autophagy and promoted apoptosis in serum-starved neuroblastoma cells through suppression of NF-κB, degradation of PARP, downregulation of BCL-2, induction of BAX, and activation of caspase-3 [73].

Apigenin also possesses the ability to reduce the migration and invasion of NS cancer cells. In this regard, reducing the expression and activity of metalloproteinase (MMPs), as well as upregulation of fibronectin and laminin, were

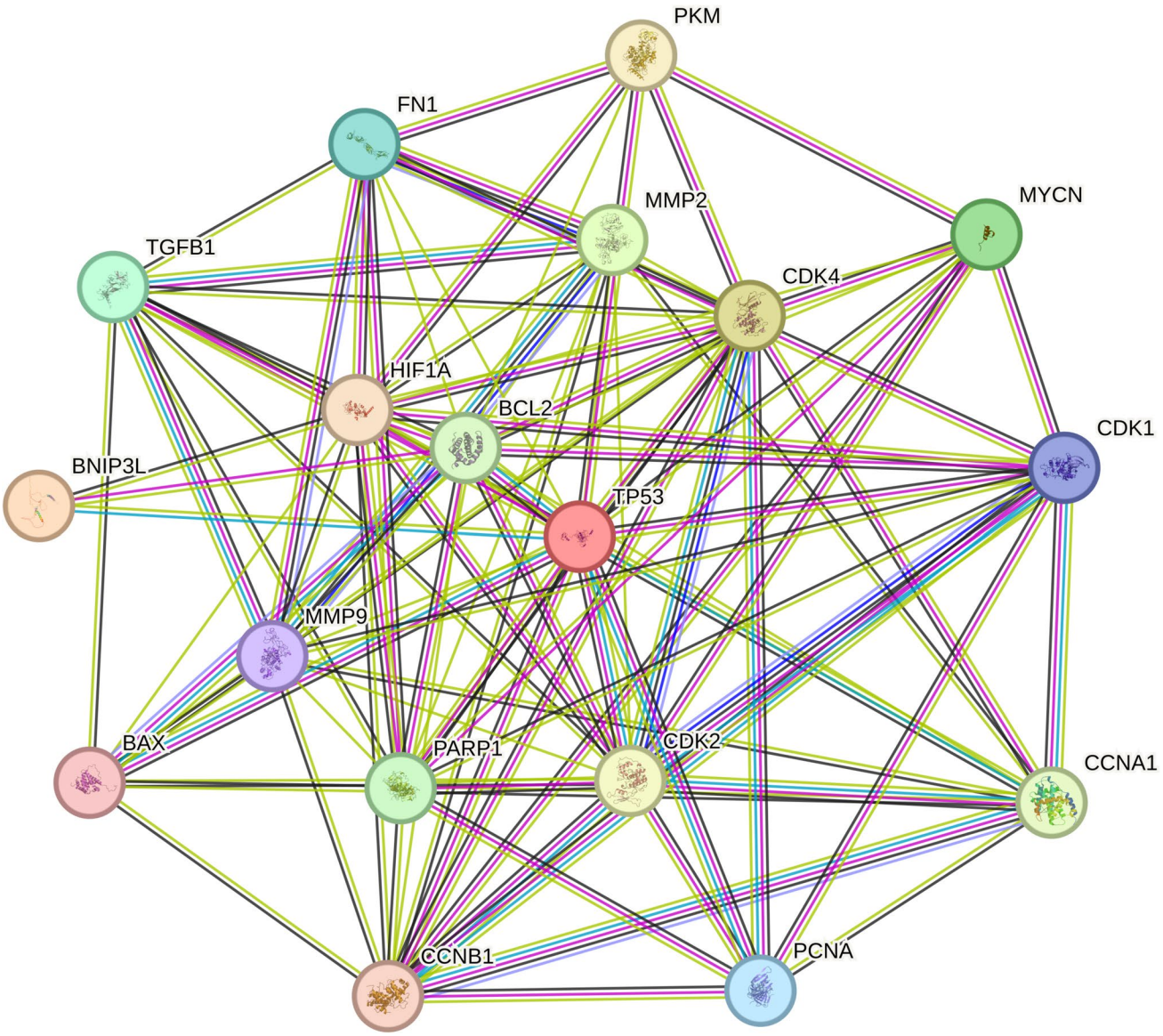

Fig. 3 The network of connections between apigenin targets in NS cancers. The functional protein association tool STRING was used to map the inter-connectedness of target proteins, which were identified through physical protein interactions in *Homo sapiens*. Connections between nodes are color coded depending on the interaction type: blue, curated databases; fuchsia, experimentally determined; green, textmining; light purple, protein homology. This figure was drawn using STRING online database, according to all data presented in this study

contributed to the inhibitory effects of apigenin on the migration of glioblastoma cells [72]. Remarkable reduction in the invasion of neuroblastoma cells has also been reported upon sequential knockdown of human telomerase reverse transcriptase (hTERT) and apigenin treatment. Moreover, downregulation of molecules involved in cell invasion and proliferation, such as MMP-2, MMP-9, N-MYC, PCNA, CDK-2, CDK-4, and cyclin D1 were contributed to apigenin effects [74]. Similarly, it was shown that N-MYC knockdown and apigenin treatment reduced the migration and invasion of neuroblastoma cells [75]. In addition, apigenin treatment along with ectopic expression of Krüpple-like factor 4 (KLF4) prevented the migration of neuroblastoma cells by impairing the transcription and translation of MMP-2 and MMP-9 [76].

Reports have also indicated anti-angiogenic effects of apigenin on NS cancer cells, as combinatorial treatment of neuroblastoma cells with apigenin and HA14-1 (a small molecule Bcl-2 inhibitor) synergistically suppressed the expression of angiogenic factors [77]. Likewise, apigenin reduced TGF-β1 production in glioblastoma cells and acted as an effective angiogenic inhibitor [78].

Table 1 Summary of *in vitro* and *in vivo* studies on the effects of apigenin, amentoflavone, and vitexin in glioblastoma and neuroblastoma

Type of flavonoid	Type of study	Effects	Mechanisms	Reference
Apigenin	*In vitro* (C6 glioblastoma cells)	induction of differentiation, apoptosis and autophagy reduction of survival, proliferation and migration	↓ IL-10, TNF, Nestin ↑ NO, GFAP	[67]
Apigenin	*In vitro* (U87 glioblastoma cells)	Induction of cell cycle arrest (G_2/M phase) and apoptosis	↑P21, BAX, t-BID, caspase 8, caspase 9, caspase 3, PARP ↓Cyclin-A1, Cyclin-B1, Cdk-1	[68]
Apigenin	*In vitro* (U1242 and U87 glioblastoma cells)	Inhibition of proliferation and survival	↓ BCL-xL and phosphorylation of MAPK, AKT, mTOR	[66]
Apigenin	*In vitro* (U87 and U373 glioblastoma cells)	Inhibition of stemness	↓ CD133, NANOG, SOX2 pAKT	[69]
Apigenin	*In vitro* (T98G and U87 glioblastoma cells)	Induction of apoptosis	↑ROS, ↓BCL-2, COX-2	[70]
Apigenin	*In vitro* (A172, U87 and T98G glioblastoma cells)	Induction of apoptosis	↓NF-κB, CK2 ↑ P53	[71]
Apigenin	*In vitro* (GL-15 and U251 glioblastomacells)	Induction of differentiation inhibition of migration and invasion	↓MMP2 ↑Fibronectin, Laminin	[72]
Apigenin	*In vitro* (SH-SY5Y, SK-N-BE2, and IMR-32 neuroblastoma cells)	Synergic activity with N-(4-Hydroxyphenyl) retinamide induction of autophagy	↓BCL-2, Beclin 1, LC3 II, TLR-4, AKT/mTOR, NF-κB, PARP ↑ BAX, caspase-3	[73]
Apigenin	*In vitro* (SH-SY5Y, SK-N-DZ, SK-N-BE2, and IMR-32neuroblastoma cells)	Inhibition of invasion and proliferation induction of apoptosis	↓ hTERT, MMP-2, MMP-9, N-MYC, PCNA, CDK-2, CDK-4, cyclin D1	[74]
Apigenin	*In vitro* (SK-N-DZ and SK-N-BE2neuroblastoma cells)	Induction of apoptosis	↓ NF-κB, VEGF, b-FGF, MMP-2, MMP-9, p-AKT	[75]
Apigenin	*In vitro* (SK-N-DZ and IMR-32neuroblastoma cells)	Induction of apoptosis Inhibition of migration	↓ MMP-2, MMP-9, BCL-2 ↑ P53, BAX	[76]
Apigenin	*In vitro* (SK-N-DZ, SH-SY5Y and IMR32 neuroblastoma cells)	Induction of apoptosis	↓BCL-2, EGFR ↑ BAX, tBID	[77]
Apigenin	*In vitro* (GL-15 glioblastoma cells)	Inhibition of angiogenesis	↓TGF-β1	[78]
Apigenin	*In vitro* (SU3 and SU3-5R glioblastoma cells) *In vivo*	Improvement of radiosensitivity	↓ HIF-1α, GLUT-1/3, NF-κB, PKM2	[79]
Apigenin	*In vitro* (PC12 and SH-SY5Y glioblastoma cells)	Induction of apoptosis	↑ P53, PARP	[80]
Apigenin	*In vivo* glioblastoma	Improvement of radiosensitivity	↓ NF-κB, HIF-1α, GLUT3, PKM2	[81]
Apigenin	*In vivo* glioblastoma	Synergic activity with temozolomide	↓p-AKT, MMP-2, MMP-9, cyclin D1, BCL-2	[82]
Amentoflavone	*In vitro* (U87 glioblastoma cells)	Induction of apoptosis	↓ MCL1, c-FLIP	[83]
Amentoflavone	*In vitro* (GBM8401 glioblastoma cells) *In vivo*	Inhibition of tumor growth	↓ ERK, MMP-2, MMP-9, XIAP, cyclinD1, VEGF	[84]
Amentoflavone	*In vitro* (U87, LV229, U251, LN18 and U373 glioblastoma cells)	Induction of apoptosis inhibition of glycolysis	↑ ROS, AMPK	[85]
Amentoflavone	*In vitro* (U251 and U373 glioblastoma cells) *In vivo*	induction of autophagy	↓ AMPK/mTOR ↑ BAX, FASL	[86]
Vitexin	*In vitro* (LN-18 glioblastoma cells)	induction of cell cycle arrest (G_2/M phase) and apoptosis	↓ Akt/mTOR	[87]
Vitexin	*In vitro* (U251 glioblastoma cells)	inhibition of proliferation and invasion induction of apoptosis	↓JAK/STAT3	[88]
Vitexin	*In vivo* glioblastoma	improvement of radiosensitivity	↓GPx, HIF-1α, VEGF, GLUT-1/3	[89]

Up- and downregulation in gene/protein expression are presented as ↑ and ↓, respectively

Another interesting effect of apigenin is the ability to improve sensitivity of NC cancer cells to ionizing radiation and chemotherapy. In this regard, it has been shown that apigenin and radiation synergically reduced survival, colony formation, and migration ability of glioma stem cells. Radiosensitization mechanisms of apigenin were attributed to the attenuation of hypoxia-inducible factor-1 α (HIF-1α)-mediated glycolysis, which resulted from subsequent reductions of glucose transporters (GLUT-1/3), NF-κB, and pyruvate kinase isozyme type M2 (PKM2) expressions [79]. Likewise, it has been reported that pretreatment of radioresistant SU3-5R stem cells-inoculated subcutaneous glioma model with apigenin followed by irradiation decreased tumor volume and weight via attenuating cell stemness and inhibiting NF-κB/HIF-1α-mediated glycolytic proteins GLUT-3 and PKM2 [81]. In another study, it was shown that combination of apigenin and temozolomide induced apoptosis and inhibited the invasion of glioblastoma cells via downregulation of p-AKT, cyclin D1, BCL-2, MMP-2, and MMP-9. Moreover, compared with single administration of each agent, combinatorial use of apigenin and temozolomide significantly inhibited the growth of subcutaneous tumors in mice models [82].

To note, two reports have indicated protective effects of apigenin on NS cancer cells; apigenin attenuated insulin fibril-induced ROS production and lipid peroxidation and apoptosis in neuroblastoma cells, due to its antioxidative and anti-inflammatory properties [90]. Likewise, apigenin reduced proteasome inhibitor-induced apoptosis in neuroblastoma cells by suppressing the production of ROS and depletion and oxidation of glutathione [80].

Flavonoids with Similar Structure to Apigenin

Amentoflavone (3′, 8″-biapigenin) is a dimeric form of apigenin and has molecular formula and weight of $C_{30}H_{18}O_{10}$ and 538.45 g/mol, respectively. This biflavonoid is found in many medicinal plants and exhibits multiple pharmaceutical activities, including anti-inflammatory, antioxidative, antimicrobial, and anti-diabetic effects [91–95]. Meanwhile, antidepressant and neuroprotective effects have been reported for amentoflavone, which were mediated by the suppression of NF-κB and activation of PI3K/AKT and ERK signaling pathways [96–100]. In addition, it has been shown that amentoflavone protected neuronal cells from β amyloid-induced deficits via inhibiting β-secretase, reducing oxidative damage, and modulating Nrf2 expression [101, 102].

Accumulating evidence have demonstrated that amentoflavone induced anticancer effects on various types of cancers, such as osteosarcoma and melanoma, and carcinomas of lung, cervix, ovary, bladder, liver, and breast via modulation of the cell proliferation, metastasis, angiogenesis, drug-resistance, autophagy, and apoptosis [103–113]. Regarding NS cancers, it has been revealed that amentoflavone induced intrinsic and extrinsic apoptosis in glioblastoma cells by inhibiting NF-κB, reducing the expression of cellular Fas-associated protein with death domain-like IL-1 beta-converting enzyme inhibitory protein (c-FLIP) and myeloid cell leukemia 1 (MCL1), and activating caspase-3 and caspase-8 [83]. As presented in Fig. 4, amentoflavone diminished NF-κB activation followed by down-regulation of its downstream targets such as MMP-2, MMP-9, XIAP, cyclin D1, and VEGF in glioblastoma cells [84]. Amentoflavone also decreased the viability of glioma cells via triggering apoptosis, inhibiting glycolysis, and activating ROS/AMPK signaling pathway [85]. Likewise, treatment of glioma cells with amentoflavone blocked the cell cycle progression and induced cell death by triggering autophagy-dependent ferroptosis, reducing mitochondrial membrane potential, and altering AMPK/mTOR signaling pathway [86].

Vitexin (5, 7, 4-trihydroxyflavone-8-glucoside) is an apigenin-8-C-D-glucopyranoside that is found in various medicinal plants. The molecular formula and weight of vitexin are $C_{21}H_{20}O_{10}$ and 432.38 g/mol, respectively. This natural flavone possesses several pharmaceutical activities, such as antioxidative, anti-inflammatory, anti-nociceptive, anti-hypertensive, anti-spasmodic, and antiviral effects [114]. In addition, neuroprotective effects have been reported for vitexin; it reduced hypoxia–ischemia neonatal brain injury via inhibiting HIF-1α and protecting neuronal cells from toxicity of β amyloid peptide. Furthermore, vitexin prevented *N*-methyl-D-aspartate-induced apoptosis in neuronal cells by regulating the balance of BCL-2/BAX and the cleavages of PARP and pro-caspase-3 [115–117].

There is also evidence regarding anticancer effects of vitexin against hepatocellular, lung, breast, uterine, esophageal, and oral carcinomas, which were mediated through the promotion of apoptosis and autophagy and/or inhibition of proliferation and survival [114, 115, 118–121]. Regarding NS cancers, vitexin induced G_2/M cell cycle arrest and apoptosis in glioblastoma cells via inhibition of AKT/mTOR signaling pathway [87]. Similarly, it has been shown that treatment of glioblastoma cells with vitexin not only inhibited proliferation, colony formation, and invasion, but also promoted apoptosis through the suppression of JAK/STAT3 signaling pathway [88]. In addition, cooperation of vitexin with hyperbaric oxygen improved radiotherapy sensitization in glioma mouse model through the inhibition of glutathione peroxidase (GPx), HIF-1α, vascular endothelial growth factor (VEGF), and GLUT-1/3 [89].

Isovitexin (apigenin-6-C-glucoside) is an isomer of vitexin that is generally purified together with vitexin. Due to their similar chemical structure, isovitexin exerts similar biological activities to vitexin, such as antioxidative, anti-inflammatory, and neuroprotective effects [117, 122]. Isovitexin has also demonstrated anticancer effects on cervical,

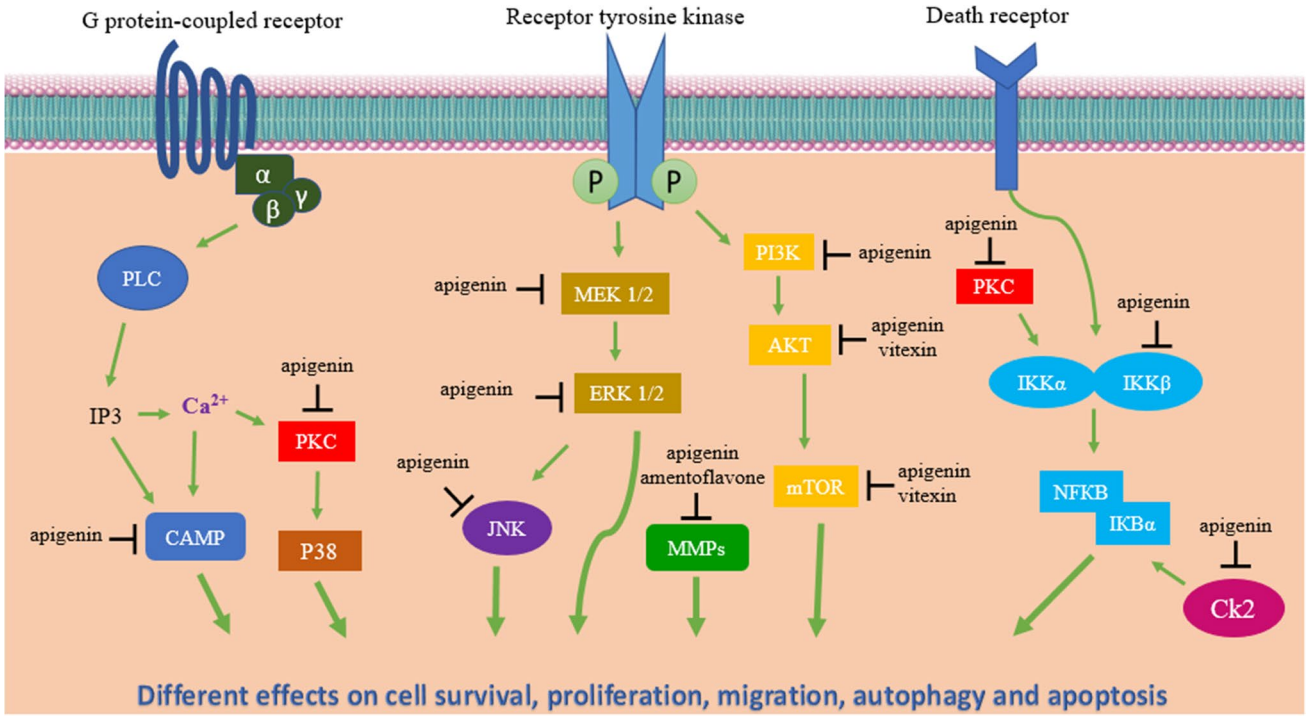

Fig. 4 Signaling pathways and molecular targets of apigenin, vitexin and amentoflavone. This figure was drawn using Adobe Illustrator, according to all data presented in this study

hepatocellular, and prostate carcinomas, which was mediated via apoptosis and autophagy induction [123–126]. Nevertheless, no study has yet reported effects of isovitexin on NS cancers.

Future Perspectives and Conclusion

As a naturally occurring flavonoid, apigenin has shown anticancer efficacy against a wide variety of human malignancies including NS cancers. Low toxicity of apigenin on neuronal cells, along with wide range of signaling pathways and targets that it simultaneously triggers in glioblastoma and neuroblastoma cells have justified the role of apigenin as a promising pharmaceutical agent. However, low bioavailability of apigenin is an important issue that must be solved before introducing this valuable flavonoid to clinic.

Until now, anticancer activity of apigenin has been mainly studied in vitro and on animal models, and clinical studies on other beneficial effects of apigenin, such as its neuroprotective effects, are very limited. According to the reported information in the clinical trials.gov, only one trial has been documented about effects of apigenin on a neurodegenerative disorder (NCT05696665). The main reasons that restrict clinical trials on apigenin are its very low solubility in water and non-polar solvents and high permeability and degradation [127–129].

To overcome the poor bioavailability of apigenin and improve its functionality, use of nanocarriers is an interesting strategy. Nano-delivery of hydrophobic drugs provides several advantages, such as protection from degradation, drug release in a controlled and site-specific manner, prolonged half-life, and thus, increased pharmacological effects [130]. During recent years, liposomes and poly lactic-co-glycolide (PLGA) nanoparticles have been developed for apigenin delivery. It has been reported that nano-encapsulation of apigenin using PLGA showed ameliorative potentials against melanoma [131] and hepatocellular carcinoma[132]. In another study, it has been shown that loading apigenin into chitosan-albumin-folic acid nanoparticles improved apoptosis-induction in hepatocellular carcinoma cells [133]. Likewise, increased cytotoxicity of apigenin, as well as improved efficacy of docetaxel in combinatorial use, were reported upon treatment of lung carcinoma cells with nanostructured lipid carriers encapsulating apigenin [134]. Similarly, increased efficiency of chemotherapy in colon cancer cells was reported upon administration of dual drug-loaded liposome bearing apigenin and 5-fluorouracil [135]. In addition, carbopol-based nanoemulsion gel formulation of apigenin showed high biocompatibility and enhanced cytotoxicity on melanoma cells without effects on normal cells were reported [136]. Importantly, it has been demonstrated that degradation of apigenin-beta amino ester nanoparticles provided longer term and localized release of

apigenin, and subsequently led to more targeted anticancer effects on breast carcinoma cells [137]. Among other nanoscale approaches, conjugation of apigenin with metal nanoparticles has also been considered; it has been shown that stable apigenin-gold nanoparticles were biocompatible toward normal cells, while induced apoptosis in cervix and bile duct carcinoma cells [138, 139].

According to the above-mentioned reports, nanocarriers such as liposomes, lipid nanocapsules, and polymer-based nanocapsules are great candidates to subdue the limitations of apigenin bioavailability. Since there is no evidence regarding the efficacy of nano-formulated apigenin on NS cancers, investigating pharmaceutical effects of apigenin-loaded nanocarriers on NS cancer cell lines and animal models is recommended for future studies.

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Author Contribution Mohammad-Saegh Lotfi was responsible for conceptualization and investigation, and Fatemeh B. Rassouli supervised and edited the manuscript.

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Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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