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Apigenin: A Natural Flavonoid with Therapeutic Potential in Cancer Mechanisms, Physiochemical and Biopharmaceutical Properties, and Future Perspectives

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Abstract: Apigenin (APG), a flavonoid found in various fruits, vegetables, and herbs, has gained attention for its anticancer properties. This review summarizes the various botanical origins, physiochemical & biopharmaceutical properties of APG and its anticancer activity across different cancer types by investigating its effects on various cancer cell lines, underlying mechanisms, and effective doses. Studies indicate that APG exerts its anticancer effects by inhibiting cell proliferation, inducing apoptosis, and promoting autophagy. Additionally, APG has been shown to trigger necroptosis in cancer cells, contributing to its anticancer potential. The data highlights the ability of APG to suppress cancer cell growth, migration, and invasion, with varying effective doses depending on the cancer type. This review exhibits the potential of APG as a promising anticancer agent, revealing its therapeutic applications. However, further research, particularly clinical trials, is needed to optimize dosing and assess its full therapeutic potential in cancer treatment.

Keywords: Apigenin; Anti-Cancer Activity; Flavonoids; Mechanism of action; Pharmacokinetic

1. Introduction

Cancer is a pathological condition characterized by genetic or epigenetic modifications in somatic cells, leading to uncontrolled cell proliferation. This abnormal growth, classified as a neoplasm, can spread to other parts of the body. Neoplasms, commonly referred to as tumors, arise from deregulated cell division and may present as localized masses or diffuse cellular distributions (Saini et al., 2020). Several factors contribute to cancer, including tobacco consumption (22% of deaths), poor diet, obesity, physical inactivity, and alcohol consumption (10% of deaths). Other risk factors include exposure to ionizing radiation, environmental pollutants, and infections. Approximately 15% of global cancer cases are linked to infections such as hepatitis B and C, HPV, H. pylori, HIV, and Epstein-Barr virus, which alter genetic material. Aging also plays a significant role, as cancer incidence rises with age (Yan et al., 2017).

Cancer emerges due to genetic predisposition and external carcinogens, classified into physical (ionizing radiation like radon, UV rays, and X-rays), chemical (asbestos, benzene, arsenic, aflatoxin, and tobacco toxins), and biological (viruses, bacteria, and parasites). Certain cancers, such as ovarian, breast, prostate, skin, and colorectal, are strongly linked to genetic factors. Dietary habits also influence cancer risk, with excessive consumption of red meat, dairy, and processed foods increasing the likelihood of colon and breast cancer, whereas vegetable intake is protective (Saini et al., 2020; Correa, 1981).

Cancer is the fastest-growing disease globally, with 12 million new diagnoses and 7 million deaths annually. The 2024 Cancer Statistics update from the American Cancer Society reports a record-high 2 million cancer diagnoses this year. Early detection has improved survival rates, with 4.1 million lives saved since 1991. While cancer incidence in men has remained stable, rates in women have risen due to breast, uterine corpus, and melanoma cancers, likely linked to lifestyle factors (Dizon & Kamal, 2024). Cancer remains the leading cause of death in developed nations and the second in developing countries, after heart disease (Popat et al., 2013). Traditional cancer treatments include surgery, chemotherapy, and radiotherapy (Jahan Oni et al., 2024). Recent advancements incorporate stem cell therapy, targeted therapy, ablation therapy,

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nanoparticles, natural antioxidants, and innovative approaches like chemodynamic therapy, sonodynamic therapy, and ferroptosis-based therapy. Nanoparticles and targeted therapy aim to minimize damage to healthy tissues, while natural antioxidants neutralize free radicals, potentially preventing cancer. Many of these therapies are undergoing clinical trials or have been approved (Debela et al., 2021). However, cancer treatments face challenges such as resistance, severe side effects, tumor heterogeneity, and high costs (Coussens & Werb, 2002; Hanahan & Weinberg, 2011; Topalian et al., 2015).

Natural products, particularly plant-derived compounds, play a crucial role in cancer therapy. Over 1,000 plant species exhibit significant anticancer properties, with key examples including Taxol, Etoposide, Camptothecin, Vincristine, Vinblastine, and Flavopiridol (Mukherjee et al., 2001). Flavonoids, found in fruits, vegetables, and seeds, offer strong antioxidant and anti-inflammatory benefits. APG, a flavonoid in fruits, vegetables, and Chinese medicinal herbs, has gained attention for its anticancer potential due to its ability to induce apoptosis, autophagy, cell cycle arrest, and immune modulation while suppressing cancer cell migration and invasion. It targets multiple signaling pathways, including PI3K/AKT, MAPK/ERK, JAK/STAT, NF-κB, and Wnt/β-catenin, and is also being analyzed for enhancing chemotherapy effects (Rahmani et al., 2022; Yan et al., 2017).

This study aims to review the anticancer effects of APG by analyzing data on different cancer types, cell lines used in research, underlying mechanisms, and reported IC_{50} values, highlighting its potential as a therapeutic agent.

2. Methodology

A comprehensive search was conducted using Google Scholar and PubMed to collect data on the anticancer effects of APG. Only primary research articles were included, while review papers were used solely for theoretical information. Keywords such as “anticancer activity of apigenin,” “cancer cell lines,” “pharmacokinetic,” and "mechanisms of action" were used. Studies focusing on apigenin’s effects on cancer, mechanisms like apoptosis, autophagy, and relevant signaling pathways were prioritized. Data from selected articles were analyzed and summarized to highlight apigenin's anticancer potential.

3. Results and discussion

3.1. Botanical sources

Plants possess potent biochemical compounds referred to as phytomedicines. These natural constituents can be obtained from different parts of the plant, such as the bark, leaves, flowers, roots, fruits, and seeds. Since ancient times, humans have relied on these plant-derived compounds for medicinal applications (Cragg & Newman, 2001). APG is a naturally occurring flavonoid found in various plant species, primarily in the leaves, flowers, and aerial parts. It is commonly obtained from *Matricaria recutita* (chamomile) flowers (Švehlíková et al., 2004), *Chrysanthemum morifolium* (Lii et al., 2010), and *Petroselinum crispum* (parsley) leaves (Chaves et al., 2011). Among herbs, chamomile (*Matricaria chamomilla)* is one of the richest sources; celery (*Apium graveolens*), oregano (*Origanum vulgare*), and thyme (*Thymus vulgaris*) also contain significant amounts. In fruits, oranges (*Citrus sinensis*), grapefruit (*Citrus paradisi*), and apples (*Malus domestica*) contribute to dietary APG intake. Additionally, vegetables like onions (*Allium cepa*), spinach (*Spinacia oleracea*), and bell peppers (*Capsicum annuum*) provide notable amounts. Other sources include tea (*Camellia sinensis*) and *Ginkgo biloba*. These plants are widely studied for their potential health benefits, including antioxidant, anti-inflammatory, and anticancer properties (Salehi et al., 2019). Additionally, several other botanical sources of APG are listed in **Table 1**, highlighting its diverse plant origins.

3.2. Physiochemical and biopharmaceutical properties

APG ($C_{15}H_{10}O_5$) has a molecular weight of 270.24 g/mol (Sung et al., 2016; Kashyap et al., 2022). It is a yellow crystalline powder

Table 1. Different botanical origins of apigenin

Botanical name (Family)	Plant parts	References
Ailanthus excelsa Roxb. (Simaroubaceae)	Leaves	Loizzo et al., 2007
Chrysanthemum morifolium Ramat. (Asteraceae)	Flowers	Lii et al., 2010
Cynara cardunculus L. (Asteraceae)	Leaves	Rossoni et al., 2005
Gentiana veitchiorum Hemsl. (Gentianaceae)	Flowers	Dou et al., 2020
Matricaria recutita L. (Asteraceae)	Leaves	Hwang et al., 2018
Merremia tridentata (L.) Hallier f. (Convolvulaceae)	Stem; roots	Vo van et al., 2022
Petroselinum crispum (Mill.) (Apiaceae)	Leaves	Chaves et al., 2011
Premna foetida (Lamiaceae)	Leaves	Dianita & jantan, 2019
Platycodon grandiflorum (Campanulaceae)	Flowers	Jang et al., 2010
Morus indica L. (Moraceae)	Leaves	Anandan & Urooj, 2021
Sophora alopecuroides L. (Leguminosae)	Aerial parts; root; seeds;	Zhang et al., 2021
Teucrium polium L. (Lamiaceae)	Aerial parts	Esmaeil et al., 2009
Ziziphora clinopodioides Lam. (Lamiaceae)	Whole plant	Senejoux et al., 2012
Portulaca oleracea L. (Portulacaceae)	Aerial parts	Nayaka et al., 2014
Chamomilla recutita [L.] Rauschert (Asteracea)	Flowers	Švehlíková et al., 2004

with limited solubility in water but dissolves well in organic solvents like methanol, ethanol, and dimethyl sulfoxide (DMSO) (Kashyap et al., 2022). It exhibits poor solubility in both highly hydrophilic and lipophilic solvents, with optimal solubility occurring in phosphate buffer at pH 7.5.

APG exhibits high intestinal membrane permeability and is classified as a Class II compound in the Biopharmaceutical Classification System (BCS) (Tang et al., 2017). Although it is absorbed throughout the gastrointestinal tract, its overall bioavailability remains low, limiting its clinical application (Kashyap et al., 2022). Once absorbed, APG undergoes metabolism, primarily forming glycosides, with a significant portion remaining unabsorbed (Tang et al., 2017). Transport across biological membranes occurs via active carriers in the duodenum and jejunum or through passive diffusion in the duodenum, jejunum, ileum, and colon (Alam et al., 2021).

APG has a half-life ranging from 1.8 to 4.2 hours, with an average of 2.52 ± 0.56 hours (DeRango-Adem & Blay, 2021). It is metabolized through the Phase I and II enzymatic processes, including methylation, sulfation, and glucuronidation (Alam et al., 2021). The primary metabolic pathways produce 3-monoglucuronides and apigenin-7-sulfate via conjugation reactions such as glucuronidation and sulfation (El Daibani et al., 2020). In nature, APG is commonly found in glycosylated forms, as these derivatives enhance its solubility and bioavailability, given that the aglycone form is relatively unstable (Bak et al., 2016). APG is primarily excreted through urine and feces, with approximately 73% of the orally administered dose detected in excretory pathways (Tang et al., 2017).

3.3. Cellular and molecular anticancer mechanisms of apigenin

3.3.1. Stomach cancer

APG exhibits potent anticancer activity against stomach cancer by inducing apoptosis and reducing inflammation. Studies using HGC-27 and SGC-7901 cell lines showed that APG enhances apoptosis through caspase-3 activation and Bcl-2-associated X protein (Bax) upregulation while decreasing the expression of B-cell leukemia-2 protein (Bcl-2), an anti-apoptotic protein (Chen et al., 2014). Additionally, in an *in vivo* study using Mongolian gerbils, APG at doses of 30–60 mg/kg/day significantly reduced Helicobacter pylori colonization, atrophic gastritis, and monocyte infiltration, which are key factors in stomach cancer development (Kuo et al., 2014).

3.3.2. Breast cancer

The anticancer effects of APG against breast cancer have been observed in various cell lines. In MDA-MB-231 cells, APG inhibited cell proliferation and increased histone H3 acetylation and p21WAF1/CIP1 expression, leading to cell cycle arrest (Tseng et al., 2017). Similarly, in HER2-overexpressing cells, APG promoted apoptosis by downregulating vascular endothelial growth factor (VEGF) and signal transducer and activator of transcription 3 (STAT3) expression (Seo et al., 2015). In MCF-7 cells, treatment with 80 μM APG induced apoptosis while reducing reactive oxygen species (ROS) production (Bai et al., 2014). These findings suggest that APG acts through multiple mechanisms, including cell cycle regulation, apoptosis induction, and oxidative stress modulation.

3.3.3. Cervical cancer

APG has been shown to effectively target cervical cancer cells through apoptosis and mitochondrial dysfunction. In HeLa sphere-forming cells (SFCs), APG (37–74 μM) increased p21WAF1, caspase -3, and Fas/Apo-1 expression while reducing Bcl-2 levels, leading to apoptosis (Zheng et al., 2005). Additionally, in other cervical cancer cell lines (SiHa, C33A, and CaSki), APG induced mitochondrial redox impairment, further contributing to cancer cell death (Souza et al., 2017).

3.3.4. Ovarian cancer

In ovarian cancer cells, APG exhibited antiproliferative effects. In A2780 cells, 40 μM of APG significantly inhibited cell proliferation (Li et al., 2009). Similarly, in Skov3 and Skov3/TR cells, APG suppressed Axl and TYRO3 receptor tyrosine kinases and reduced Akt phosphorylation and Bcl-xl expression, thereby inhibiting survival and resistance mechanisms in ovarian cancer cells (Suh et al., 2015).

3.3.5. Colon cancer

APG effectively induces apoptosis in colon cancer cells. In HCT-116 cells, APG at concentrations ranging from 40 to 160 μM triggered apoptosis by activating caspases, including caspase-3 (Wang & Zhao, 2017). The IC_{50} values for different time points were 98.2 μM (24 h), 83.3 μM (48 h), and 77.9 μM (72 h), indicating that prolonged exposure increases its efficacy. These findings suggest that APG plays a crucial role in colon cancer treatment by inducing programmed cell death.

3.3.6. Biliary tract cancer

APG exhibits anticancer effects against biliary tract cancer by inducing cell cycle arrest and apoptosis. In KKU-M055 cells, APG at concentrations ranging from 20 to 120 μM promoted apoptosis through caspase-8, -9, and -3/7 activation while reducing cell migration (Kaewmanee et al., 2025). The IC_{50} values were 78 μM and 61 μM for different experimental conditions, supporting its role as a potential therapeutic agent.

3.3.7. Prostate cancer

APG suppresses prostate cancer cell growth by inducing apoptosis. In DU-145 and PC-3 cell lines, 20 μM APG significantly increased caspase-3 activation, leading to apoptosis while inhibiting cancer cell proliferation (Mak et al., 2006). APG (15 μM) with cisplatin (7.5 μM) increased cytotoxicity and apoptosis by upregulating APAF-1, caspase-8, and p53 while downregulating Bcl-2, sharpin, and survivin, suggesting enhanced cisplatin efficacy and reduced chemoresistance (Erdogan et al., 2017). These results suggest that APG may be a promising candidate for prostate cancer treatment.

3.3.8. Brain cancer

APG exhibits anticancer activity against brain cancer by inducing oxidative stress and apoptosis. In glioblastoma stem-like cells (GSCs), APG increased ROS production and caspase-4 activation, promoting apoptosis (Das et al., 2010). Additionally, it reduced clonogenicity and the expression of cancer stem cell markers such as CD133, SOX-2, and Nanog in U87MG and U373MG cells (Kim et al., 2016). These findings highlight APG's potential in targeting glioblastoma stem cells.

3.3.9. Lung cancer

APG demonstrates strong pro-apoptotic effects in lung cancer cells. In A549 and H1299 cells, APG upregulated death receptors (DR4 and DR5), Bax, and Bad, while downregulating Bcl-xl, Bcl-2, NF-κB, Akt, and ERK, leading to apoptosis (Chen et al., 2016). These results indicate that APG disrupts survival signaling pathways, making it a potential therapeutic agent for lung cancer.

3.3.10. Pancreatic cancer

The combination of APG (1 or 20 μM) with metformin (5 mM) induced apoptosis, autophagy, and necroptosis, indicating its ability to trigger multiple cell death pathways. *In vivo*, APG (50/40 mg/kg) significantly reduced tumor growth in athymic nude mice. These findings suggest that APG not only enhances metformin's

anticancer activity but also acts independently to inhibit tumor progression, highlighting its potential as a promising therapeutic agent for pancreatic cancer (Warkad et al., 2021).

APG shows significant anticancer potential across various cancers by inducing apoptosis, regulating cell cycles, and modulating oxidative stress, several limitations persist. The primary challenge is its low bioavailability and rapid metabolism, which restrict its therapeutic efficacy. Nanoparticle-based delivery systems have the potential to enhance the bioavailability and targeted delivery of APG. Future studies should focus on developing innovative nanoparticle formulations that can overcome delivery challenges, thereby improving the therapeutic efficacy of APG in cancer treatment (Prakash et al., 2024). Additionally, most studies are limited to *in vitro* and animal models, with insufficient clinical trials to confirm safety and effectiveness in humans. Future strategies could include improving APG's bioavailability through advanced drug delivery systems, such as nanoparticles or liposomes, and conducting more extensive clinical trials. Combining APG with other chemotherapeutic agents may also enhance its therapeutic potential while addressing resistance mechanisms. **Table 2** summarizes the anticancer mechanisms of APG against several cancers while, **Fig. 1** illustrates how APG interacts with different cancer cell lines.

Table 2. Mechanism of anticancer activity of apigenin

Cancer type	Cell Lines/ experimental model	Tested dose/ concentration (R/A)	IC_{50}	Mechanisms/ results	References
Stomach cancer	Cell lines HGC-27 & SGC-7901, *in-vitro*	-	-	↑ Apoptosis, capspase-3, Bax ↓ Bcl-2	Chen et al., 2014
	Mongolian gerbils, *in-vivo*	30–60 mg/kg (bw/day)	-	↓H. pylori colonization, atrophic gastritis, monocyte infiltration	Kuo et al., 2014
Breast cancer	MDA-MB-231, *in-vitro*	-	-	↑H_3 acetylation, p21WAF1/CIP1 ↓Cell proliferation, HDAC, cyclin A&B,	Tseng et al., 2017
	T47-D, *in-vitro*	50 or 100 µM	-	↑VEGF, mRNA, Protein	Mafuvadze et al., 2010
	MCF-7, *in-vitro*	80µM	-	↑Apoptosis ↓ ROS, MDA-MB-468 cells	Bai et al., 2014
	HER2, *in-vitro*	-	-	↑Apoptosis ↓BT-474, VEGF, STAT3	Seo et al., 2015
Cervical cancer	(SFCs) of HeLa cell lines, *in-vitro*	37–74 µM	35.89 µM	↑Apoptosis, p21WAF1, caspase-3, Fas/Apo-1 ↓ Bcl-2	Zheng et al., 2005
	Silt a, c33a, caski, *in-vitro*	-	-	↑Apoptosis, mitochondrial redox impairment	Souza et al., 2017
Ovarian cancer	A2780 cells, *in-vitro*	40 µM	-	↓Proliferation	Li et al., 2009
	Skov3, Skov3/TR, *in-vitro*	-	-	↓Axl, TYRO3, Akt phosphorylation, Bcl-xl	Suh et al., 2015
Colon cancer	HCT-116 cells, *in-vitro*	40–160 µM	24, 48 & 72 h were 98.2, 83.3 & 77.9 µM	↑Apoptosis, casps, casps3 ↓T-24 cells	Wang & Zhao, 2017
Biliary tract cancer	KKU-M055 cell line, *in-vitro*	20 to 120 µM (KKu)	78 µM and 61 µM	↑Cell cycle arrest, apoptosis, caspase 8,9,3/7 ↓ Migration of cells	Kaewmanee et al., 2025
Prostate cancer	DU-145 and PC-3, *in-vitro*	20 µM	-	↑Apoptosis, caspase-3 ↓ Cell growth	Mak et al., 2006
Brain cancer	GSCs cell, *in-vitro*	-	-	↑ROS, Apoptosis, caspase-4 ↓Cell growth, clonogenicity, u87mg, u373mg, cd133, SOX-2, nanog	Das et al., 2010 Kim et al., 2016
Lung cancer	A 549 & H 1299, *in-vitro*	-	-	↑DR4, DR5, Bax, Bad ↓Bcl-xl, Bcl-2, NF-κB, Akt, ERK	Chen et al., 2016

Table 2. *Continued*

Cancer type	Cell Lines/ experimental model	Tested dose/ concentration (R/A)	IC_{50}	Mechanisms/ results	References
Combination therapy of apigenin					
Prostate cancer	CD44+ PCa stem cell, *in-vitro*	15 µM with cis-platin (7.5 µM)	-	↑Cytotoxicity, Apoptosis, APAF-1, caspase-8, p53 mRNA ↓Bcl2, sharpin, survivin	Erdogan et al., 2017
Pancreatic cancer	AsPC-1, *in-vitro*	Apigenin (1 or 20 µM) with metformin (5 mM)	-	↑Apoptosis, autophagy, necroptosis	Warkad et al., 2021
	Athymic nude mice, *in-vivo*	50/40 mg/kg	-	↓Tumor growth	

↑: Increase/Upregulate/Activation; ↓: Decrease/Downregulate/Inactivation; IC_{50}: Half maximal inhibitory concentration; Bcl-2: B-cell leukemia/ lymphoma 2 protein; Bax: Bcl-2-associated X protein; HDAC: Histone Deacetylase; IL-6: Interleukin-6; IFN: Interferons; PD-L1 : Programmed Death-Ligand 1; TNF: Tumor Necrosis Factor; LRP-6: Low-density lipoprotein receptor-related protein 6; Skp2: S-phase kinase-associated protein-2 ;HER2: (human epidermal growth factor receptor 2) overexpression; STAT3: Signal transducer and activator of transcription 3; VEGF: Vascular endothelial growth factor ;ROS: Reactive Oxygen Species; SFCs: Sphere forming cells ; APAF-1: Apoptotic Protease Activating Factor 1; Axl: Axl receptor tyrosine kinase; TYRO3: Protein tyrosine kinase; Akt: Protein Kinase B; CASP: Cysteinyl Aspartate Specific Proteinase (caspase/CASP); NF-κB: Nuclear Factor-kappa B; DR: Death Receptor; Bad: Proapoptotic protein; ERK: Extracellular Signal Regulated Kinase; SOX-2: SRY(Sex determining regionY)-box 2;

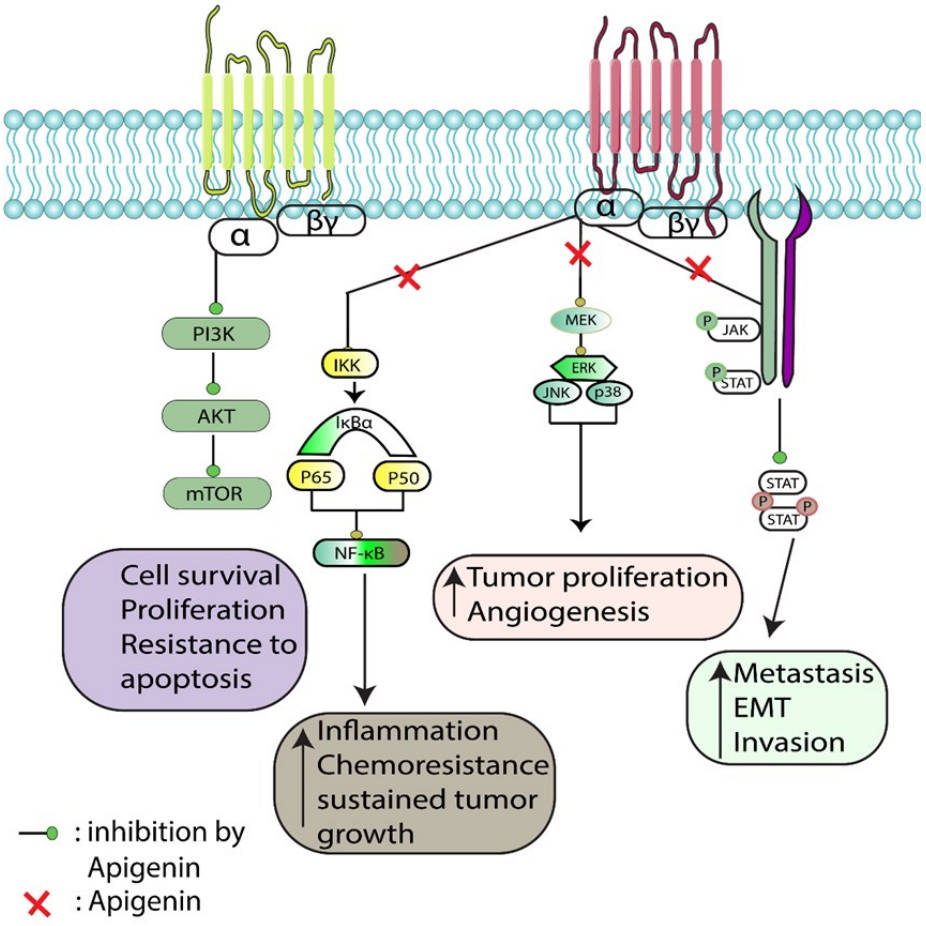

Fig. 1. Possible mechanism of the anti-cancer activity of apigenin. [This figure illustrated the anticancer mechanisms of APG. This picture illustrates the molecular pathways involved in cancer progression, focusing on inflammation, tumor proliferation, and metastasis. APG is depicted as an inhibitor, targeting key signaling components like PI3K/AKT/mTOR, NF-κB, MEK/ERK, and JAK/STAT pathways, which regulate processes such as cell survival, angiogenesis, and epithelial-to-mesenchymal transition (EMT). The red crosses signify pathways inhibited by APG, showcasing its potential as an anti-cancer agent.

3.4. Clinical evidence

Preclinical studies on various cancer cell lines and animal models have demonstrated APG's anticancer properties. These studies have identified its mechanisms of action, including inducing apoptosis, halting cell cycle progression, inhibiting angiogenesis, and modulating signaling pathways associated with cancer development and progression. While clinical research on APG's therapeutic potential in cancer treatment remains limited, it is gradually expanding, with current studies focusing on its safety, pharmacokinetics, and initial efficacy in cancer patients (Tamayose et al., 2017; Jakobušić Brala et al., 2023).

4. Conclusion

APG, a naturally occurring flavonoid found in various fruits, vegetables, and herbs, has drawn attention for its anticancer potential because of its capability to induce apoptosis, autophagy, cell cycle arrest and immune modulation while suppressing cancer cell migration and invasion. It also targets multiple signaling pathways, including PI3K/AKT, MAPK/ERK, JAK/STAT, NF-κB, and Wnt/β-catenin, and is also being analyzed for enhancing chemotherapy effects. This study highlighted the anticancer activity of APG by using different cell lines. Although preclinical studies are available for APG's, therapeutic potential in cancer treatment remains limited due to its low bioavailability. To overcome those barriers, future research should focus on well-structured clinical trials to evaluate APG's safety, efficacy, and optimal dosage in cancer patients.

Conflict of interest

The authors declared no conflict

Data availability

Data will be made available on request.

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Author's contributions

Conceptualization, J.S., and M.I.J.O.; methodology, J.S.; validation, J.S.; formal analysis, M.I.J.O., and M.S.; data curation, J.S., and M.I.J.O.; writing—original draft preparation, J.S.; writing—review and editing, J.S.; mechanisms drawing, M.S.; supervision, M.I.J.O.; project administration, M.I.J.O. All authors have read and agreed to the published version of the manuscript.

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