

Flavonoid Apigenin in Cancer Counteraction

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Apigenin is one of the most widespread flavonoids in the plant kingdom. For centuries, apigenin-containing plant preparations have been used in traditional medicines to treat diseases that have an inflammatory and/or degenerative component. In the 1980s, apigenin was proposed to interfere with the process of carcinogenesis. Since then, more and more evidence has demonstrated its anticancer efficacy, both in vitro and in vivo. Apigenin has been shown to target signaling pathways involved in the development and progression of cancer, such as PI3K/Akt/mTOR, MAPK/ERK, JAK/STAT, NF-κB, and Wnt/β-catenin pathways, and to modulate different hallmarks of cancer, such as cell proliferation, metastasis, apoptosis, invasion, and cell migration.

apigenin

flavonoids

neoplasms

bioavailability

1. Introduction

In countries with higher economic development levels, cancer is the second leading cause of death behind cardiovascular disease. According to recent data, in Italy, 415,269 new diagnoses of cancer occurred, with 174,759 cancer deaths (96,579 in men and 78,180 in women) ^[1].

Cancer is a disease that originates and evolves through genetic and epigenetic modifications involving genes that control cell cycle, adhesion, motility, differentiation, and apoptosis ^[2]. Human cancers develop as products of multistep processes in which cells acquire functional capabilities that are crucial for their ability to induce malignant tumors ^{[2][3]}. Such capabilities are called “Hallmarks of Cancer” and consist of sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing/accessing vasculature, activating invasion and metastasis, reprogramming cellular metabolism, and avoiding immune destruction ^{[4][5][6]}. These hallmarks are further enriched by two “enabling characteristics” involved in tumor growth and progression: tumor-promoting inflammation and genome instability and mutation. The tumor microenvironment plays an integral role in tumorigenesis and malignant progression, too ^{[7][8]}. Emerging hallmarks also include unlocking phenotypic plasticity, a capability that enables various disruptions of cellular differentiation and appears to be operative in multiple cancer types during primary tumor formation, malignant progression, and/or response to therapy. Another emerging hallmark is non-mutational epigenetic reprogramming, since growing evidence shows that gene-regulatory circuits and networks in tumors can be governed by numerous corrupted and added mechanisms, independent of genome instability and gene mutation. Moreover, the polymorphic microbiomes resident in the colon, other mucosa, and connected organs, or in tumors themselves, can diversely influence cancer development, progression, and response to therapy. Finally, an increasing body of evidence reveals that, in certain contexts, senescent cells variously stimulate tumor development and malignant progression ^[5].

Throughout centuries, natural compounds have been used to treat and prevent diseases [9][10], thereby creating new knowledge of the potential of natural agents. Almost 47% of the anticancer drugs available on the market today are derivatives of natural products [11]. Considering natural compounds, polyphenols (flavonoids, stilbenoids, lignans, polyphenolic acids, and other polyphenols) display many anticarcinogenic properties and, in addition, they can modulate immune system responses and protect normal cells against damage from free radicals [12]. A plethora of studies have documented these anticancer effects: noteworthy examples include anthocyanins from blueberries [13], epigallocatechin gallate from green tea [14], resveratrol from red wine [15], isoflavones from soy [16], and curcumin from *Curcuma longa* [14][17]. Among the over 6000 different flavonoids, quercetin, kaempferol, myricetin, luteolin, and apigenin are the five most ubiquitous plant flavonoids [18][19].

Apigenin, above all, has gained attention among researchers, partly due to its low toxicity and multiple beneficial bioactivities [18]. Apigenin is one of the most widespread flavonoids in the plant kingdom and one of the most studied phenolic compounds [20]. For centuries, apigenin-containing plant preparations have been used as traditional medicines to treat diseases with an inflammatory and/or degenerative component, such as asthma, insomnia, neuralgia, Parkinson's disease, and shingles [21][22][23][24]. At the end of the 1950s, apigenin gained scientific interest, primarily due to its modulation of histamine release and bronchodilator properties [21]. In the 1980s, apigenin was proposed to interfere with the process of carcinogenesis. Since then, more and more evidence has suggested its power as an adjuvant chemotherapeutic agent for cancer therapy, both in in vitro and in vivo models [20].

2. Combination Therapy for Apigenin

Chemotherapy drugs play a considerable and unavoidable role in the extension of the overall survival rates of cancer patients. However, their undesired toxicity remains a significant source of concern for both patients and clinicians. The integration of natural bioactive compounds, in specific cases, could potentiate anticancer efficacy and reduce the side effects of chemotherapy drugs [25].

Studies have shown that co-administration with apigenin significantly enhances the anticancer efficacy of chemotherapy drugs and helps to overcome their limitations in various types of cancers by targeting multiple signaling pathways [20][26]. The most common mechanisms apigenin uses to amplify the chemotherapy drugs' efficacy are autophagy and apoptosis. Various mechanisms, such as cell-cycle regulation, tumor cell migration inhibition, invasion, and the stimulation of the immune response, can be responsible for chemo-sensitizing properties of apigenin in co-therapies [27].

Recent studies have evaluated the combination of apigenin with the following chemotherapy drugs: 5-FU, Cetuximab, Cisplatin, Cyclophosphamide, Doxorubicin, Gemcitabine, Paclitaxel, Sorafenib, Tamoxifen, Abivertinib, Gefitinib, Methotrexate, and Vincristine [28][29][30][31][32][33]. In all cases, synergic and/or additive effects were shown compared to monotherapy and there was a reduction in the side effects of monotherapies.

Furthermore, apigenin has been displayed to have significant chemo- and radio-protective properties [34][35]. Apigenin was found to have protective effects against doxorubicin and adriamycin-induced cardiotoxicity in vivo [36][37], and to prevent Cisplatin-induced nephrotoxicity by reducing the serum levels of TNF- α , IL-6, COXI, COXII, creatinine, and blood urea nitrogen, and increasing serum GSH levels [38]. As a radioprotector, apigenin has shown protective effects on human lymphocytes exposed to 137 Cs and to Cobalt 60 radiation. Apigenin pretreatment significantly reduced DNA damage and radiation-induced anomalies such as micronuclei, nucleoplasmic bridges, and nuclear buds in human peripheral-blood lymphocytes [34].

Furthermore, apigenin has shown protective effects against the UVA-induced senescence of normal human dermal fibroblasts and significantly inhibited UVB-induced carcinogenesis by promoting the expression of the antiangiogenic protein thrombospondin-1 in skin keratinocytes in vitro and in vivo [34].

3. Critical Aspects of Apigenin for Therapeutic Purposes

3.1. Bioavailability of Apigenin

A crucial aspect of a potential therapeutic drug is its bioavailability, the fraction of a drug reaching the systemic circulation, and the site of action where it can exert its biological effects. It is influenced by numerous factors, such as the substance's chemical structure, the bond with other molecules (e.g., by acetylation or glycosylation), and intrinsic factors of the organism (e.g., the composition of the intestinal microbiota).

Apigenin has low bioavailability because of its low lipid (0.001–1.63 mg/mL) and water (2.16 μ g/mL) solubility [39][40]. The bioavailability of apigenin also depends on its bioaccessibility, which refers to the extraction of apigenin from the food matrix during gastrointestinal digestion and the transformation into compounds available for absorption [41]. The degree and site of glycosylation influence gastrointestinal digestion: glycosides of apigenin survive acid hydrolysis in the stomach, and it goes to the duodenum unbroken. Further digestion and absorption depend on the nature of the modification and distribution of enzymes required to produce bioactive apigenin. Various cells can metabolize apigenin intracellularly through the enzymes present in the brush border epithelium, while the indigestible glycosides require extracellular de-glycosylation through bacterial enzymes present in the colon [42].

Apigenin taken orally is absorbed systemically with an availability of approximately 30% higher in the colon (40%) and lower in the terminal ileum (21%) via passive transport and independently of concentration. In vivo, in the duodenum and in the jejunum, apigenin was also mediated by active transport, as well as by the concentration-dependent membrane permeability whose highest level (maximum plasma concentration—C_{max}) is, however, reached with a maximum plasma concentration time (T_{max}) of 0.5–2.5 h. It should be remembered that the glycosylated forms of apigenin (e.g., 7-O-glucoside, 6-C-glucoside, or 8-C-glucoside) are metabolized by β -glucosidases in the stomach and small intestine to generate free apigenin (i.e., a form of aglycone). *Eubacterium ramulus* and *Bacteroides distasonis* have been identified as the main bacterial species essential for the biotransformation of 7-glycosides into aglycone apigenin [43][44].

Various strategies and techniques have been investigated to improve the bioavailability of apigenin:

- Water-in-oil-in-water (W/O/W) double emulsions loaded with apigenin. In vitro studies have confirmed the double emulsion's capacity to transport bioactive compounds in an aqueous phase, minimizing degradation and potentially increasing in vivo bioavailability [45];
- Gold nanoparticles, widely used for their good biodistribution, stability, and low toxicity. Au³⁺ can be reduced by apigenin at a pH of 10 and at room temperature, forming highly stable and spherical apigenin-AuNPs. The apigenin-AuNPs are found to exhibit toxicity towards the A431 (epidermoid squamous cell carcinoma) cell line while being non-toxic towards normal epidermoid cells. This technique shows promise in the treatment of skin cancer [46];
- Phytosome, a phospholipid-based complex of apigenin, i.e., apigenin–phospholipid phytosome (APLC). Phytosome is highly compatible with human physiology and bioavailable thanks to its ability to cross the lipid bilayer membrane of enterocytes and reach systemic circulation. A study shows that APLC formulation demonstrated an over 36-fold higher aqueous solubility of apigenin, compared to that of pure apigenin [47];
- Self-microemulsifying drug-delivery systems (SMEDDSs). They are mixtures of oils, surfactants, solvents, and drug substances that form oil-in-water microemulsions with droplet sizes less than 100 nm when introduced into aqueous phases under gentle agitation or gastrointestinal motility [48]. A study shows that SMEDDSs could enhance the solubility and dissolution of apigenin and would be a potential carrier to improve the oral absorption of apigenin [49];
- Bioactive self-nanoemulsifying drug-delivery systems (BioSNEDDSs). They form a nanoemulsion with droplet sizes significantly smaller (by a factor of ten or similar) than droplets found in ordinary emulsions. The decreased droplet size increases the absorption rate and extent and prevents drug degradation in the gastrointestinal tract [50]. The BioSNEDDSs differ from conventional SNEDDSs for using bioactive lipid excipients such as black seed oil, *Moringa oleifera* seed oil, avocado oil, apricot oil, grape seed oil, safflower oil, and coconut oil fatty acid. A study shows that BioSNEDDSs formulated for apigenin provide collective advantages, such as a superior self-emulsification efficiency with an improved physical stability, high drug-loading capacity, antibacterial activity, and elevated apigenin bioavailability [51].

3.2. Absorption, Distribution, Metabolism, Excretion

Absorption, distribution, metabolism, and excretion are four processes that together describe a drug's passage through the body.

3.2.1. Absorption

Flavones are typically present in food as glycosides. The absorption of orally delivered apigenin has been the subject of animal studies, particularly in rats [52]. Most of these studies show that apigenin aglycones and O-

glycosides are absorbed quickly: the T_{max} is generally ≤ 1 h, with a C_{max} of 1–100 mmol/L, depending on the dose and the food matrix [53]. Studies in humans that used celery leaves or parsley show plasma concentrations of <0.2 mmol/L with a T_{max} > 7 h [54]. As for apigenin O-glycosides, rats are the most common animal model used for the absorption of apigenin C-glycoside. The T_{max} for C-glycosides studied was <1 h and the C_{max} was 1–29 mmol/L, varying with the dose. Depending on the sugar fraction, the absorption could occur in the small intestine or colon after deglycosylation. Glucosides are generally the only glycosides that can be absorbed from the small intestine and the absorption involves the glucose transport pathway. It is hypothesized that apigenin glucosides can be hydrolyzed by cytosolic β-glucosidase (CBG) and lactase-phlorizin hydrolase (LPH). The aglycone resulting after deglycosylation may then enter epithelial cells by passive diffusion. LPH is a membrane-bound enzyme found in the brush border of the small intestine and CBG is a broad-specificity cytosolic enzyme found in abundance in the liver, kidney, and small intestine of mammals. For CBG to cleave flavonoid glycosides, the molecules must first be actively or passively transported into the cytosol [54].

Although the sugar transporter SGLT1 may facilitate the absorption of certain glycosides, such as quercetin-3-glucoside and quercetin-4'-glucoside, into epithelial cells, it does not appear to transport flavones. In fact, apigenin and its glycosides (apigenin-6-C-glucoside, apigenin-7-O-glucoside, apigenin-8-O-glucoside) seem to be absorbed by epithelial cells of the small intestine only after hydrolyzation into aglycones. Flavonoids that cannot be absorbed from the small intestine, as well as the absorbed flavonoids secreted with bile, will be degraded in the colon by the microbiota [18].

3.2.2. Distribution

Multiple in vivo studies have shown that apigenin has a good distribution to tissues, mainly the liver and intestine, due to its capacity to bind to soluble proteins in the blood and tissues. Wan et al. [55] showed that following the IV administration of 20 mg/kg of apigenin in rats, the initial blood concentration of apigenin (10 µg/mL) dropped rapidly within 30 min (100 ng/mL). Still, this rapid decline was followed by a slow disappearance of apigenin from the circulation, with a T_½ close to 8 h. Furthermore, the V_d of apigenin was much larger than the total body water of rats. In another study [56], mice were fed a diet containing apigenin for 5, 6, or 7 days. It was found that with a dose of 1.1 mmol/kg apigenin, the plasma levels of apigenin reached a steady state after 5 days with concentrations of apigenin in plasma, liver, and the small intestinal mucosa of 0.09 ± 0.08 nmol/mL, 1.5 ± 1.0 nmol/g, and 86 ± 47 nmol/g, respectively. Following the oral administration of *Chrysanthemum morifolium* extracts in rats [57], apigenin and luteolin were observed to be distributed along all the tissues of the gastrointestinal tract with concentrations three to ten times higher in the jejunum, as compared to other segments of the intestines.

The post-absorption tissue distribution of apigenin is driven by its compatibility with the human serum transferrin glycoprotein at the Fe³⁺ binding site using the interaction between the electrostatic and hydrogen bonds of the C5 and C7 hydroxyl groups of the apigenin B ring, the component amino acids Lys-291 and Tyr-188 of transferrin, and between the carbonyl of the C ring of apigenin and Arg-124 of transferrin. It is useful to remember that the distribution to the tissues as a consequence of the intrinsic lipophilicity is, for apigenin, supported by the LogP of 2.84 (the LogP or Log Kow measure of the differential of the solubility of chemical compounds in two solvents).

Therefore, it is well below the LogP threshold > 5 (high lipophilicity) for a drug to be active orally and by passive diffusion to cross the membrane and bypass the blood–brain barrier, according to Lipinski's rule [58].

3.2.3. Metabolism

The absorbed apigenin may go through functionalization reactions (phase I metabolism) and conjugation reactions (phase II metabolism) in the intestine and liver [57][59]. Phase I reactions lead to the introduction of functional groups that give the molecule a particular chemical reactivity. In the presence of NADPH, these reactions are catalyzed by two families of liver enzymes: cytochromes and flavin-containing monooxygenase [60]. Phase II reactions lead to the formation of a covalent bond with endogenous molecules such as glucuronic acid, sulfate, glutathione, amino acids, or the acetate ion. 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 ABCC2 and CMOAT), whose distribution can be dramatically altered in cancers that regulate the intra-individual variability of the absorption in the intestinal tract [61].

Metabolites generated during phase I (luteolin) and phase II (sulfated and glucuronated conjugates) have four possible pathways [50]:

- Direct systemic absorption;
- Excretion;
- Passage with the bile from the liver to the intestine, where they are hydrolyzed by bacterial beta-glucuronidases, returning to an absorbable form again (entero-hepatic circulation);
- Passage into the intestinal lumen, where they are subject to hydrolysis and subsequently reabsorbed (entero-enteric circulation and local enteric circulation) [62].

3.2.4. Excretion

Apigenin's high volume of distribution and enterohepatic/enteric recycling processes indicate that the elimination patterns of this lipophilic molecule will be delayed [50]. A study [63] observed that, following a single oral administration of radio-labeled apigenin, approximately 50% of apigenin was recovered in urine and 12% in feces. Although most products were excreted within the first 24 h, about 25% of the original apigenin dose was retained 10 days after treatment, suggesting apigenin's slow absorption and elimination in the body [59].

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