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Review

Naringenin in Cancer Therapy: Molecular Mechanisms, Signaling Networks, and Translational Perspectives

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Abstract

Cancer remains a significant global health challenge, underscoring the need for active therapeutic strategies that target the key molecular determinants of tumor progression. Naringenin, a flavonoid prevalent in the diet and abundant in citrus fruits, has emerged as a promising anticancer agent due to its ability to regulate multiple oncogenic signaling pathways involved in cancer initiation, progression, and therapeutic resistance. This review highlights the molecular mechanisms through which naringenin modulates essential signaling networks, such as the PI3K/Akt/mTOR, NF-κB, MAPK, and TGF-β pathways, thereby suppressing cancer cell proliferation, inducing apoptosis, inhibiting angiogenesis, and preventing metastatic spread. Compared with previous reviews that mainly summarized the general pharmacological properties of naringenin, this review provides an integrated and critical analysis of cancer-related signaling networks, chemoresistance, therapeutic combinations, and emerging translational strategies. Importantly, it highlights the persistent gap between promising pre-clinical results and limited clinical evidence, and it emphasizes the pharmacokinetic, bioavailability, and safety challenges that need to be addressed for clinical translation. Finally, we highlight the existing challenges, knowledge gaps, and future perspectives for clinical translation to encourage the development of naringenin-based cancer therapeutics.

Keywords: apoptosis pathways; drug synergism; flavonoids; nano-delivery systems; oxidative stress; pharmacokinetics

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1. Introduction

Natural products have played a major role in cancer drug discovery, with more than 60% of currently approved anticancer agents being natural products or their derivatives [1]. Among plant-derived phytochemicals, flavonoids have attracted considerable attention because of their ability to modulate multiple molecular targets involved in tumor initiation, progression, metastasis, and therapeutic resistance [2,3]. This multitargeted activity is particularly relevant in cancer therapy, where tumor heterogeneity, pathway redundancy, metastatic progression, and therapeutic resistance frequently limit the efficacy of conventional treatments. Consequently, naturally occurring compounds capable of simultaneously

influencing several oncogenic processes have emerged as potential candidates for cancer prevention and adjunctive therapy.

Naringenin (4′,5,7-trihydroxyflavanone) is a naturally occurring flavanone found predominantly in citrus fruits, including grapefruit and oranges, and it is also present in tomatoes [4–7]. It is produced primarily through the enzymatic hydrolysis of naringin, a major citrus flavonoid responsible for the characteristic bitterness of citrus fruits. The three hydroxyl groups at the 4′, 5, and 7 positions contribute to its interactions with signaling proteins, kinases, transcription factors, and redox-sensitive molecular targets [2,6,8]. In addition, emerging structure–activity relationship studies suggest that the hydroxylation pattern, glycosylation status, and structural modifications of the flavanone scaffold can influence cellular uptake, metabolic stability, target binding, and anticancer activity [9].

The therapeutic relevance of naringenin is supported by accumulating evidence from diverse experimental cancer models. Rather than acting through a single molecular target, naringenin can modulate interconnected signaling networks that regulate cancer cell survival, proliferation, apoptosis, inflammation, angiogenesis, invasion, and metastasis [10,11]. In particular, modulation of the PI3K/Akt/mTOR, NF-κB, MAPK, and TGF-β pathways has been associated with the inhibition of cancer cell proliferation and survival, induction of apoptosis and cell-cycle arrest, suppression of inflammatory signaling, and inhibition of epithelial–mesenchymal transition (EMT) and metastatic behavior [10,12]. These interconnected effects provide a mechanistic rationale for examining naringenin as a multitargeted anticancer molecule rather than solely as a conventional antioxidant or dietary flavonoid.

Recent evidence further indicates that the anticancer activity of naringenin extends beyond its direct effects on tumor cells. Naringenin may influence the tumor microenvironment through the regulation of oxidative stress, inflammatory responses, immune-cell function, autophagy, and ferroptosis-related processes [13]. Moreover, its ability to modulate survival pathways, drug-efflux mechanisms, and redox homeostasis has generated interest in its potential to enhance the activity of conventional anticancer agents and mitigate therapeutic resistance [14]. These findings provide a rationale for investigating naringenin not only as a potential standalone anticancer compound but also as an adjuvant in combination-based therapeutic strategies.

Despite these promising findings, a substantial translational gap remains between experimental evidence and clinical application. The therapeutic development of naringenin is constrained by poor aqueous solubility, limited oral bioavailability, rapid metabolism, and extensive first-pass elimination, resulting in low systemic exposure following oral administration [15]. Consequently, considerable research has focused on nanotechnology-enabled delivery approaches, including polymeric nanoparticles, lipid-based nanocarriers, nanoemulsions, liposomes, solid lipid nanoparticles, and targeted nanoplatforms, to improve stability, bioavailability, tissue distribution, and tumor-specific delivery [15,16].

Earlier reviews have summarized the wide spectrum of pharmacological and anticancer properties of naringenin (Table 1), but a comprehensive review of cancer-related signaling pathways, interactions with the tumor microenvironment, chemoresistance, combination strategies, and translational potential is still desirable. In this context, the present review critically analyzes the existing evidence regarding the molecular mechanisms underlying the anticancer effects of naringenin, with a special focus on the PI3K/Akt/mTOR, NF-κB, MAPK, and TGF-β signaling pathways and their reported associations with apoptosis, oxidative stress, inflammation, autophagy, ferroptosis, angiogenesis, and metastasis. Crucially, the review distinguishes mechanistic findings from in vitro cancer cell models and animal studies from the limited evidence from human studies and clinical investigations. We also review preclinical data on the ability of naringenin to overcome therapeutic resistance and potentiate conventional anticancer agents, and we discuss emerging nanoformulation

strategies to overcome its pharmacokinetic limitations. Finally, the review critically evaluates the translation of preclinical findings into human evidence, highlights the major knowledge gaps and translational challenges, and discusses the future directions for the development and clinical evaluation of naringenin-based cancer therapeutics.

At the same time, the structural optimization of naringenin has resulted in the development of several semi-synthetic derivatives and analogs with improved pharmacokinetic properties and better anticancer activity [17]. These next-generation molecules demonstrate increased cellular uptake, better metabolic stability, and improved interaction with oncogenic molecular targets, which could lead to new opportunities for flavanone-based anticancer drug development [15].

The pharmacological properties, anticancer mechanisms, signaling pathways, combination therapies, pharmacokinetics, and nanoformulations of naringenin have been reviewed in the past [2,18,19], but they have been mainly reported separately with limited integration of their relevance to cancer therapy. Missing is a comprehensive cancer-focused synthesis linking the naringenin-mediated regulation of interlinked oncogenic signaling networks and tumor microenvironment with chemoresistance, therapeutic sensitization, structure–activity relationships, pharmacokinetic barriers, and emerging nanoformulation strategies. Therefore, this review offers a critical assessment of the molecular and cellular mechanisms of naringenin's anticancer effects and relates these findings to approaches to enhance its therapeutic efficacy and avoid its pharmacokinetic limitations. The relationship between mechanistic and pre-clinical evidence and the limited clinical evidence available to date is particularly emphasized to identify key knowledge gaps and challenges that must be addressed for successful clinical translation. The novelty of the current review is thus to bring together all of these interconnected mechanistic, therapeutic, pharmacokinetic, and translational aspects into a single cancer-centric framework.

Table 1. Representative preclinical studies of naringenin in cancer: mechanisms, molecular targets, combination strategies, nano-delivery approaches, and level of evidence.

Cancer	Principal Anticancer Mechanism and Molecular Target(s)	Combination Strategy or Delivery Approach	Pharmacokinetic/Formulation Finding	Level of Evidence	Human Clinical Evidence	References
Breast cancer	Reduced proliferation, migration, and invasion; induction of apoptosis; epigenetic modulation involving HDAC4 and HDAC8	Free naringenin	Not assessed	In vitro	No human interventional oncology evidence reported	[20]
Breast cancer, MCF-7	Targeted cytotoxicity and apoptosis through nucleolin-associated uptake	AS1411 aptamer-modified liposomes containing naringenin-loaded silk fibroin nanoparticles	Controlled-release, targeted nanoparticle system; systemic PK not assessed	In vitro and in vivo	No human interventional oncology evidence reported	[21]
Breast cancer, MCF-7	Inhibition of proliferation and migration; increased ROS and apoptosis; PI3K–AKT and MAPK-associated targets	Free naringenin	Not assessed	In vitro, supported by network pharmacology and molecular-dynamics analyses	No human interventional oncology evidence reported	[22]
Breast cancer combination model	Enhanced cytotoxicity with HER2- and FOXM1-associated molecular modulation	Ibrutinib + naringenin in a self-nanoemulsifying drug-delivery system (IBR–NRG-SNEDDS)	Approximately 1.76-fold higher C_{max} and 1.41-fold higher oral bioavailability than drug suspension	In vitro and pharmacokinetic/formulation evidence	No human interventional oncology evidence reported	[23]

Table 1. *Cont*.

Cancer	Principal Anticancer Mechanism and Molecular Target(s)	Combination Strategy or Delivery Approach	Pharmacokinetic/Formulation Finding	Level of Evidence	Human Clinical Evidence	References
Colorectal cancer	Suppressed proliferation, migration, invasion, and tumor growth via the gankyrin/PI3K/AKT/GSK-3β/β-catenin axis	Free naringenin	Systemic PK not assessed	In vitro and in vivo xenograft evidence	No human interventional oncology evidence reported	[24]
Colorectal cancer combination model	Enhanced antiproliferative and pro-apoptotic effects; AMPK activation and altered mitochondrial dynamics; attenuation of 5-FU-associated cardiotoxicity and liver injury in animals	Naringenin + 5-fluorouracil	Systemic PK not assessed	In vitro and in vivo animal evidence	No human interventional oncology evidence reported	[25]
Gastric cancer, AGS cells	ROS accumulation, oxidative stress, and apoptosis	Glutaraldehyde-crosslinked naringenin-loaded albumin nanoparticles	Nanoparticle size approximately 128 nm; human PK not assessed	In vitro and formulation evidence	No human interventional oncology evidence reported	[26]
Glioma /glioblastoma	Increased cancer-cell death and pro-apoptotic modulation of Bax/Bcl-xL balance	Cationic DOTAP/POPC liposomes co-delivering naringenin with acteoside or other natural compounds	Liposomal formulation intended to improve delivery; systemic PK not assessed	In vitro and formulation evidence	No human interventional oncology evidence reported	[27]
Breast cancer /angiogenesis	Inhibition of cancer-cell viability and migration; suppression of angiogenic and inflammatory mediators, including VEGF, NRP-1, NRP-2, CD93, NF-κB, IL-1β, and TNF-α	Naringenin nanoparticles	Improved physicochemical properties reported; systemic PK not assessed	In vitro and in vivo -like chick chorioallantoic membrane evidence	No human interventional oncology evidence reported	[28]
Triple-negative breast cancer, MDA-MB-231	ROS generation, apoptosis, and G0/G1 arrest; predicted involvement of SRC, ESR1, BCL2, and MMP9	PEGylated CuO nanoparticles loaded with naringenin	Formulation developed to address poor solubility and bioavailability; systemic PK not assessed	In vitro and in silico evidence	No human interventional oncology evidence reported	[29]
Bladder cancer, J82 and UM-UC-3	Inhibition of proliferation, clonogenicity, migration, and cell-cycle progression; altered lncRNA expression	Naringenin nanoemulsions, including chitosan-containing mucoadhesive nanoemulsion	Stable sustained-release system; mucoadhesion and ex vivo tolerability reported	In vitro, ex vivo, and formulation evidence	No human interventional oncology evidence reported	[30]

Note: No convincing human interventional oncology evidence of the anticancer activity of naringenin was found in the reviewed literature. Abbreviations: 5-FU, 5-fluorouracil; AMPK, AMP-activated protein kinase; HDAC, histone deacetylase; NF-κB, nuclear factor kappa B; PK, pharmacokinetics; ROS, reactive oxygen species; SNEDDS, self-nanoemulsifying drug-delivery system.

2. Literature Search Methodology

This is a narrative review. A structured search and selection procedure was followed as described below to ensure that the identification of literature was transparent and reproducible. We did not register a review protocol or perform a formal risk-of-bias assessment or meta-analysis. Electronic databases such as PubMed/MEDLINE, Scopus, Web of Science Core Collection, and Google Scholar were searched. Searches covered records from database inception to {3 May 2025} the date of the most recent search. The first search was performed on {3 May 2025} and updated on {4 July 2026} to include recent publications. Keywords like

naringenin, 4′,5,7-trihydroxyflavanone, cancer, phytochemicals, PI3K, MAPK, synergistic, and nanoformulation were utilized for search to each database. The inclusion criteria are: (i) peer-reviewed original research articles and reviews; (ii) studies on naringenin (free, derivative, complexed, or nanoformulated), alone or in combination with other agents; (iii) in vitro, in vivo, in silico, or clinical studies in a cancer context; (iv) studies reporting molecular mechanisms, signaling pathways, tumor microenvironment effects, chemosensitization, pharmacokinetics, delivery systems, or clinical translation; (v) articles published in English only. The exclusion criteria include: (i) conference abstracts, preprints, thesis, editorials, and other non-peer reviewed material; (ii) studies not related to cancer, except when necessary for explanation of chemistry, metabolism, or pharmacokinetics; (iii) studies of naringin or other flavonoids without naringenin data (naringin studies were only used as supporting context and are identified as such in the text); (iv) articles without accessible full text or not in English; (v) duplicate records. All records in the database were combined and duplicates were removed. Titles and abstracts were screened for relevance and potentially eligible articles were read in full and checked against the above criteria.

3. Naringenin: Chemistry, Metabolism, and Absorption

The chemical name of naringenin is 4′,5, 7-trihydroxyflavanone [31]. It is a member of subclass 4 hydroxy flavanones [32]. It is the aglycone of flavonoid naringin. Naringin is abundantly present in citrus fruits and known to contribute to the bitter taste of citrus juices. Naringin is hydrolyzed by the enzyme naringinase and converted into naringenin. The urinary recovery rate of naringenin has been reportedly found to be almost 5.81% [31,33]. Further, naringenin is absorbed through both passive diffusion and active transport in the gastrointestinal tract [31,33]. It has been reported that the absorption rates of naringenin are 47, 42, and 39% in the deudenum, terminal illeum, and jejunum, respectively [34]. After absorption, naringenin binds to albumin, followed by distribution in highly perfused organs such as the liver, cerebrum, kidney, spleen, and heart [35]. Finally, metabolites of naringenin can be excreted through biliary and urinary pathways [31,36]. Hydrolysis of naringin into naringenin by the naringinase enzyme occurs in two steps (Figure 1): (a) the hydrolysis of naringin leading to the production of rhamnose and prunin (glucoside) due to the α-L-rhamnosidase activity of naringinase, and (b) the hydrolysis of prunin into glucose and naringenin due to the β-D-glucosidase activity of naringinase [2,6,7,37].

As a valuable citrus flavonoid, naringenin has garnered a lot of interest because of its various biological actions and possible health advantages. It has a variety of pharmacological characteristics, such as anti-inflammatory, antioxidant, and glucolipid metabolism-regulating activities. Through interactions along the host–microbial metabolic axis, it also helps maintain the balance of the gut microbiota. Research on enhanced manufacturing and synthesis methods, such as microbial metabolic engineering techniques and green extraction technologies, has increased due to the growing interest in its therapeutic potential [38]. In spite of its promising biological activities, the in vivo relevance of naringenin concentrations used in vitro must be critically considered for clinical application. The poor oral bioavailability of the drug leads to the use of doses that are difficult to achieve in vivo in many experimental models. Once ingested, naringenin is extensively metabolized during the first pass and is rapidly conjugated by glucuronidation in the intestine and liver. The resulting glucuronides are more soluble and are more easily excreted, but they also decrease the level of free naringenin in circulation. However, these conjugates may be biologically active or be reconverted to the aglycone in target tissues, so that metabolites may contribute to the overall therapeutic effect. To overcome these bioavailability limitations and improve absorption and systemic availability, advanced delivery strategies such as nano-delivery systems are being developed [15]. The oral bioavailability of narin-

genin is low, although its absolute bioavailability has not been established in humans. In a study of six healthy volunteers who received a single oral dose of 135 mg naringenin aglycone as solid-dispersion capsules under fasting conditions, the mean plasma elimination half-life was 2.31 ± 0.40 h, the peak plasma concentration (Cmax) was approximately ~2009.5 ng/mL, and the cumulative urinary excretion was 5.81 ± 0.81% of the administered dose, indicating extensive conjugation and low recovery of the parent compound [33,39]. In a single-ascending-dose trial in healthy adults given 150–900 mg naringenin from an orange extract, the half-life was approximately 2.7–3.0 h with a stated LD50 of 5000 mg/kg, indicating that it is rather safe [40,41]. Naringenin has been reported to inhibit CYP1A2 and CYP3A4, mainly in in vitro and animal studies [2]. Naringenin has been shown to inhibit the drug metabolizing enzymes CYP1A2 and CYP3A4, and in some systems the efflux transporter P-glycoprotein, but the evidence is largely limited to in vitro enzyme assays and animal studies [2,42]. For example, the administration of naringenin altered the pharmacokinetics of ranolazine in rats, which was partly attributed to the inhibition of CYP3A4 and P-glycoprotein [42]. Such findings suggest a potential for interaction, but in vitro inhibition does not necessarily translate into a clinically relevant effect, which is dependent on the achievable plasma and intestinal concentrations, the extent of first-pass metabolism, and the pharmacokinetics of the co-administered drug. Grapefruit juice has been shown to have clinically significant interactions with CYP3A4 substrates and, to a lesser extent, CYP1A2 substrates. However, these effects are not attributable to naringenin alone, as the juice contains other active constituents (in particular furanocoumarins). To the best of our knowledge, there are no reports on clinically confirmed drug–drug interactions between purified naringenin and anticancer agents. Hence, a theoretical risk remains for drugs with a narrow therapeutic index, such as certain chemotherapeutics, anticoagulants, and immune suppressants, especially when high-dose supplements or enhanced-bioavailability nanoformulations increase systemic exposure. Before combining naringenin with such drugs in patients, dedicated pharmacokinetic interaction studies and careful monitoring are required.

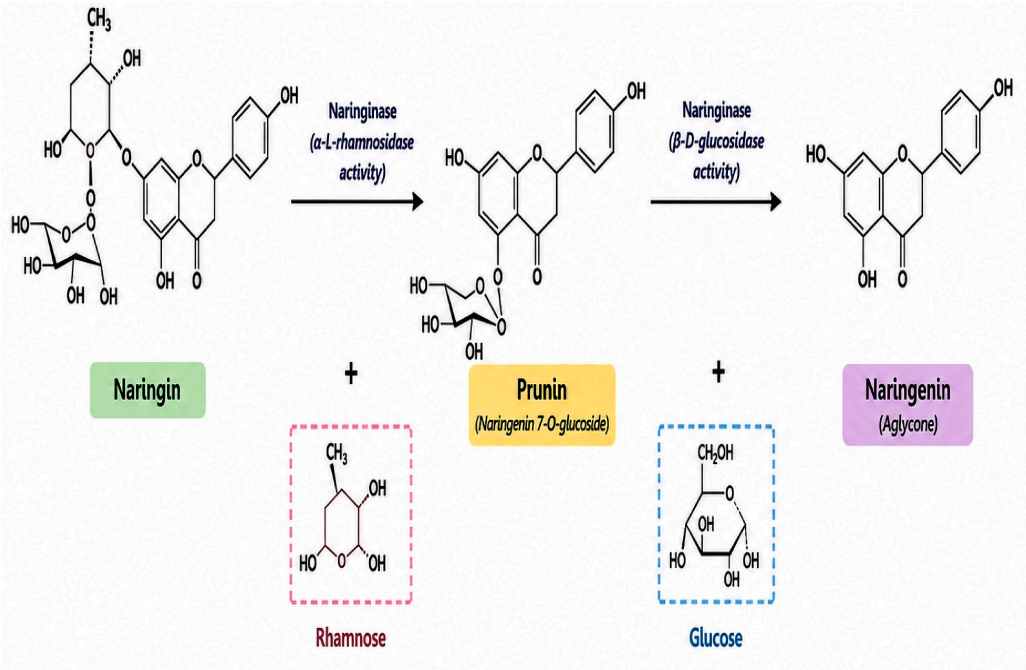


Figure 1. Hydrolysis of naringin by the naringinase enzyme. Naringin is sequentially hydrolyzed by the naringinase enzyme. Initially rhamnose is cleaved to form prunin, followed by the hydrolysis of glucose to release naringenin [6,7].

4. Anticancer Mechanisms and Cellular Interactions

Natural products have been an important source for drug discovery in oncology, but effective treatments are still hampered by tumor heterogeneity, metastasis, and drug resistance. Therefore, it is important to characterize the interaction of natural compounds with specific molecular targets and signaling pathways for their rational development as anticancer agents. In preclinical studies, naringenin has been reported to induce apoptosis in cancer cells via the intrinsic (mitochondrial) pathway involving ROS generation, loss of ΔΨm potential, Bax/Bcl-2 modulation, cytochrome c release, and caspase activation [43–45], and via death receptor-mediated signaling, including the upregulation of DR5 and DR4/DR5 sensitization to TRAIL/APO2L [46,47]. Furthermore, a synthetic derivative of naringenin upregulated Fas/FasL in lung cancer cells [48]. Naringenin has been shown to induce cell-cycle arrest at G2/M by downregulating CDK1 and cyclin B1 and upregulating p21 [44,45,49] and at G0/G1 in hepatocellular and epidermoid carcinoma cells [43,50]. Decreased migration and invasion in cervical and breast cancer cells has been reported with the downregulation of MMP-9 and other invasion-related proteins by naringenin [49,51,52]. The anti-angiogenic activity of naringenin is relevant because angiogenesis supports metastasis: it inhibited endothelial migration, tube formation, and microvessel sprouting in melanoma models and through the ERRα/VEGF/KDR axis and TPC2 inhibition in endothelial cells [53–55]. Naringenin has also been reported to reduce inflammatory mediators, including NF-κB signaling, IL-1β, IL-6, COX-2, iNOS, and TNF-α, in macrophage, glioma, breast, and cancer-pain models [56–60], which may contribute to its antitumor effects [11].

These molecular effects are often reported together, but evidence for them varies in strength, and direct molecular targets should be distinguished from downstream associations inferred from pathway changes. Few molecules are known to directly interact with a protein target. The inhibition of estrogen-related receptor α (ERRα) in endothelial cells by naringenin [53] and blocking of the activity of the endolysosomal two-pore channel 2 (TPC2) to suppress VEGF-induced angiogenic responses [54] were reported. Other proposed targets, such as sphingosine kinase-1 [61], AKT1 [24], SRC, PIK3CA, BCL2, and ESR1 [22,29], are mostly based on molecular docking, network pharmacology, or limited cellular validation, and direct binding in cells or in vivo is not demonstrated.

By contrast, most of the signaling effects described in this review are downstream associations, based on changes in the expression of proteins or their phosphorylation after treatment with naringenin. These include decreased phosphorylation of Akt and mTOR, altered MAPK/ERK, JNK, and p38 activity, decreased NF-κB signaling, changes in Bax/Bcl-2 ratio and caspase activation, downregulation of CDKs and cyclins, and decreased MMP expression [45,62]. The mechanistic basis for these changes—whether direct kinase or transcription-factor binding or upstream events such as ROS accumulation, mitochondrial dysfunction, or ER stress [44,45]—is generally unresolved. Similarly, the causal relationships between pathways, e.g., whether PI3K/Akt inhibition precedes NF-κB suppression and apoptosis, have rarely been tested with pathway specific inhibitors, genetic knockdown, or rescue experiments.

Therefore, naringenin seems to exert its effects via a multi-targeted, network-based mechanism by simultaneously modulating survival signaling, apoptosis, cell-cycle control, inflammation, invasion, and angiogenesis in preclinical models. The integrated scheme in Figures 2 and 3 summarizes the reported associations and unconfirmed direct targets, and it should be considered as a working hypothesis that needs to be validated by target-engagement and mechanistic studies.

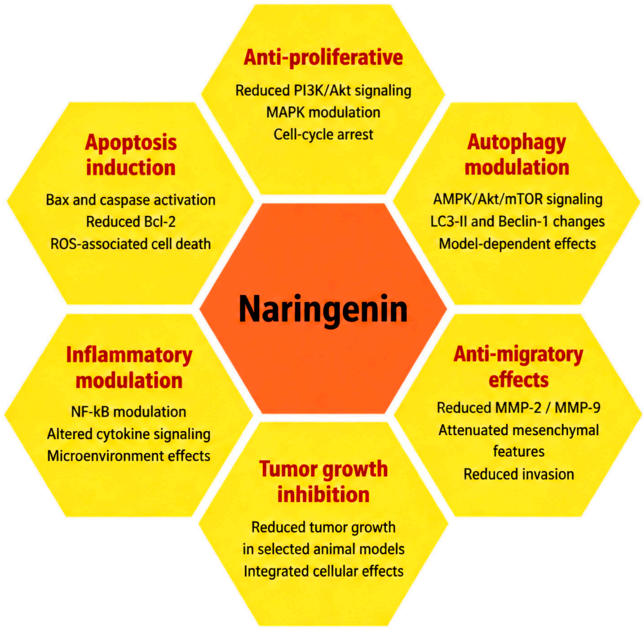


Figure 2. Representation of molecular targets of naringenin in cellular processes of cancer.

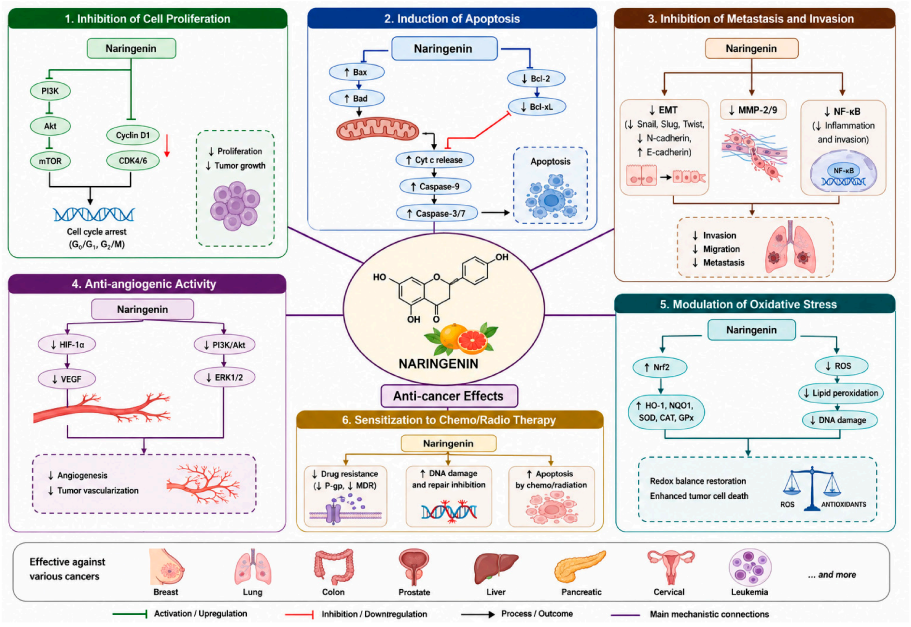


Figure 3. Diagrammatic representation of anticancer mechanisms of naringenin against various cancer types.

Further mechanistic work is needed to identify the direct molecular targets of naringenin and to determine whether the effects observed in preclinical models are achievable at clinically relevant concentrations.

4.1. Apoptosis and Cell-Cycle Arrest

Natural products have contributed significantly to anticancer drug discovery [1,63] and naringenin has been reported to exert antioxidant, antimicrobial, and cytotoxic effects in a range of cancer cell lines [64–67]. Here, in vitro findings are grouped by common mechanisms. Where available, concentrations are given and mitochondrial membrane potential is abbreviated as ΔΨm to distinguish it from matrix metalloproteinase (MMP).

ROS-related effects and mitochondrial (intrinsic) apoptosis. Naringenin reduced the viability of non-small cell lung cancer cells (H1299 and A549) in a dose-dependent manner (tested up to 500 μM), without affecting normal lung fibroblasts (MRC-5). It increased intracellular reactive oxygen species (ROS), decreased ΔΨm, decreased Bcl-2 and Bcl-xL, increased Bax and Bak, and increased the cleavage of caspase-9, caspase-3, and PARP. Apoptosis was confirmed by flow cytometry using annexin V/propidium iodide and TUNEL staining [45]. Similar ROS- and mitochondrial-mediated apoptosis was observed in HepG2 hepatocellular carcinoma cells (50–300 μM), with increased expression of p53, Bax, cytochrome c, and caspase-3 and decreased expression of Bcl-2 [43]. Also reported in A431 epidermoid carcinoma cells with mitochondrial depolarization (0–750 μM, [50]). Mitochondrial dysfunction, increased cytochrome c release, and caspase-3/-9 activation were observed in osteosarcoma cells (HOS and U2OS; 100–500 μM) [44].

In the same osteosarcoma cell lines, naringenin induced intracellular Ca^{2+} and the ER stress markers GRP78 and GRP94 with the activation of calpain. The apoptosis was attributed to ROS-mediated ER stress and mitochondrial signaling [44].

Naringenin upregulates death receptor 5 (DR5) and enhances TRAIL-induced apoptosis in A549 cells [46]. It restored APO2L/TRAIL sensitivity in glioma cells by upregulating DR4/DR5 and p53 and downregulating antiapoptotic Bcl-2 family proteins, and these effects were verified in vivo [47]. Naringenin reduced viability (MTT assay) and induced apoptosis via p38-dependent expression of activating transcription factor 3 (ATF3) (0–200 μM, [68]) in HCT116 and SW480 colon cancer cells. A synthetic naringenin derivative (N101-43; 10–40 μM) has been shown to induce activation of Fas/FasL, whereas naringenin itself does not [48].

G2/M arrest was the most commonly reported effect. It was associated with downregulation of CDK1 and cyclin B1 in NSCLC and osteosarcoma cells and upregulation of p21 in the latter [44,45], and also in MDA-MB-231 breast cancer cells (0–200 μM, [49]). G0/G1 arrest alone or with G2/M arrest in HepG2 and A431 cells [43,50]. The phase of arrest is thus dependent on cell type and concentration.

Changes in morphology, such as nuclear condensation, membrane blebbing, and DNA damage, were reported in MDA-MB-231 cells. These are compatible with apoptosis but not conclusive, as necrosis and other types of cell death can produce similar appearances. We therefore consider apoptosis to be supported when complementary assays have also been used, i.e., annexin V/PI flow cytometry and caspase or PARP cleavage [45,49]. We note that results based on morphology or viability assays alone (e.g., MTT) indicate reduced viability rather than a defined mode of death.

Most of the above studies used naringenin at approximately 50–500 μM, while plasma concentrations in humans are much lower. After a single oral dose of 135 mg of naringenin aglycone, the maximum plasma concentration was about 2 μg/mL (about 7 μM), present mainly as glucuronide and sulfate conjugates [33]. After the ingestion of blood orange juice, peak concentrations were only about 16–34 ng/mL (about 0.06–0.12 μM), with more than 95% present in the conjugated form [69]. In a dose-escalation trial with 300 mg naringenin, serum concentrations were ~10 μM at 4 h but dropped off sharply by 24 h [70]. Thus, the in vitro concentrations inducing apoptosis and cell-cycle arrest are one to three orders of magnitude higher than those achievable by oral intake of the free aglycone. The described mechanisms should be considered hypothesis-generating until validated at achievable exposures or by enhanced-delivery formulations.

4.2. Anti-Angiogenic and Anti-Metastatic Action

Angiogenesis promotes tumor development and spread, and many flavonoids have been shown to block VEGF, MMP, EGFR, NF-κB, PI3K/Akt, and ERK1/2 signaling [71].

The evidence specific to naringenin is summarized below by experimental model, as these systems vary in the extent to which the findings can be extrapolated.

Naringenin inhibited migration, tube formation, and microvessel sprouting ex vivo in human umbilical vein endothelial cells (HUVECs) (0–400 μM, [55]). In the same study, it showed a dose-dependent inhibition of proliferation and migration of B16F10 murine and SK-MEL-28 human melanoma cells and induced apoptosis [55]. In a different study with endothelial cells, naringenin decreased angiogenic responses via the ERRα/VEGF/KDR axis and decreased pro-angiogenic inflammatory cytokines (0–400 μM). Naringenin was reported to be an inhibitor of ERRα, but direct binding of naringenin to ERRα has not been independently confirmed [53]. Naringenin also decreased the activity of the endolysosomal two-pore channel 2 (TPC2) and thus inhibited VEGF-induced angiogenic responses (0–300 μM, [54]).

In the in ovo CAM assay, a nanoformulated naringenin inhibited the formation of blood vessels and suppressed the mRNA expression of VEGF-A to a greater extent than the unformulated compound [72]. CAM assays are fast non-mammalian screens. Results provide supportive evidence of anti-angiogenic activity but do not reflect tumor vasculature, pharmacokinetics, or immune context.

Naringenin (100–200 μM) inhibited the migration and invasion of HeLa cervical cancer cells by downregulating MMP-9, EGFR/PI3K/Akt signaling, and mTOR [52]. Naringenin inhibited the migration and invasion of MDA-MB-231 cells in breast cancer [49,51]. In a mouse model with E0771 breast tumors, 10–20 mg/kg/day suppressed tumor growth and metastatic lesions and decreased vimentin and N-cadherin, mainly due to changes in estrogen metabolism rather than a direct anti-metastatic effect [73].

Most of the anti-angiogenic data are derived from endothelial cultures, ex vivo assays, and the CAM model. Studies in mammalian tumors are few and the concentrations used are generally higher than plasma levels obtainable by oral intake. These data suggest anti-angiogenic potential in preclinical systems. They do not demonstrate anti-angiogenic efficacy in patients. No clinical studies have reported naringenin as an anti-angiogenic agent.

4.3. Induction of Autophagy

Autophagy is a lysosomal degradation pathway with a context-dependent role in cancer. It is capable of limiting tumor initiation through the removal of damaged organelles and proteins, but in established tumors it is capable of promoting survival under hypoxia, nutrient deprivation, and drug exposure, including resistance to chemotherapy [74,75]. In some situations, excessive autophagy leads to cell death, either with apoptosis or when apoptosis is impaired [76,77]. The level of autophagic activity is normally assessed through the conversion of LC3-I to LC3-II, Beclin-1, and ATG proteins (initiation and autophagosome formation) and p62 (the degradation of p62 suggests completed autophagic flux), and it is regulated by the AMPK and mTOR pathways [78,79]. This dual role makes the benefit or harm of autophagy modulation dependent on the tumor type, stage, and treatment. This also influences the interpretation of naringenin-induced autophagy and only studies with naringenin itself are discussed below.

Naringenin inhibited the proliferation of human osteosarcoma cells (U2OS and HOS; 100–500 μM) with minimal toxicity to normal human bone cells. It also induced increases in LC3-II, ATG5, and Beclin-1, G2/M arrest (decreased CDK1 and cyclin B1, increased p21), ROS production, ER stress, and apoptosis [44]. Naringenin (up to 500 μM) increased the ratio of LC3-II/LC3-I, decreased p62 and phosphorylated Akt/mTOR, and increased AMPKα phosphorylation in NSCLC cells (H1299 and A549), along with ROS-mediated apoptosis and G2/M arrest [45]. Naringenin induced “pro-apoptotic” autophagy along

with S-phase arrest and apoptosis in MCF-7 breast cancer cells [22]. A breast cancer study reported that naringenin regulated autophagy via the FKBP4/NR3C1/NRF2 axis [80]. To summarize, these studies show that naringenin is linked to changes in autophagy markers, ROS generation, AMPK/mTOR, and apoptosis.

Most studies reported changes in marker levels (LC3, Beclin-1, and p62) at one or some time points. Few used autophagic flux assays (e.g., lysosomal inhibitors such as bafilomycin A1, chloroquine) or autophagy-gene knockdown. It is generally not established whether autophagy contributes to naringenin-induced cell death, accompanies it, or is a protective response. Some reports describe autophagy as pro-death or as 'pro-apoptotic' in some cell lines [22,44] and attenuated in others [80], which may reflect differences in cell type, concentration, and time. As autophagy can also mediate chemoresistance, the effect of naringenin on autophagy should be tested in combination regimens before considering it therapeutically beneficial. Studies of naringin (the glycoside) have also documented autophagy-related growth inhibition [81]; we do not utilize those findings to support conclusions about naringenin because of differences in the absorption and metabolism of naringin.

4.4. Antioxidant and Anti-Inflammatory

Chronic inflammation and redox imbalance play roles in tumor initiation, progression, and therapy resistance. Pro-inflammatory cytokines and NF-κB signaling stimulate tumor-cell survival, angiogenesis, and invasion, and persistent oxidative stress may induce DNA damage and activate oncogenic signaling [11]. Therefore, the antioxidant and anti-inflammatory properties of naringenin are relevant to cancer mainly through its effects on the tumor microenvironment and on these survival pathways.

The hydroxyl groups of naringenin contribute to its capacity to scavenge reactive oxygen and nitrogen species and to limit lipid peroxidation and oxidative DNA damage in a dose-dependent manner [31,82–84]. These data come mostly from non-cancer or cell-free systems. In cancer cells, the effect of naringenin on redox status is concentration-dependent: lower concentrations are associated with antioxidant and cytoprotective effects, whereas higher concentrations increase ROS and induce apoptosis. Naringenin should therefore not be described uniformly as an antioxidant in tumor cells.

Naringenin has been shown to inhibit NF-κB signaling and the expression of pro-inflammatory mediators in a variety of cancer-relevant models, such as LPS-stimulated RAW264.7 macrophages, where it reduced IL-1β and COX-2 expression and inhibited NF-κB and p38 MAPK signaling [58]. It reduced TNF-α, phosphorylated IKKβ and p65, and NF-κB activity in a mouse model of cancer-induced bone pain at 50 mg/kg/day [59], and it inhibited microglia-mediated neuroinflammation in a rat model of cancer-induced bone pain [57]. In breast cancer cells, it reduced IL-6 and apoptosis [56], and in an angiogenesis-focused study, it correlated with decreased NF-κB, IL-1β, and TNF-α [28]. It lowered IL-6 and CCL2 through aryl hydrocarbon receptor (AhR) signaling in glioma cells but increased TNF-α expression [60], indicating that the effect is not always anti-inflammatory.

Naringenin might also influence antitumor immunity. It increased CD169-positive macrophage activation, IL-12, and CXCL10, and it increased the infiltration of $CD8^+$ T cells in mouse models of oral squamous cell carcinoma [82]. In breast cancer, naringenin was associated with dendritic cell differentiation and maturation [80]. The data presented here suggest that naringenin has the potential to modulate inflammatory signaling in either direction depending on the context, and the net effect on tumor immunity has not been defined clinically.

Most mechanistic literature on naringenin's anti-inflammatory activity is based on non-cancer disease models (e.g., liver injury and adipocytes; [83–85]) and is not used here to support anticancer conclusions. Evidence in tumor models is limited, mostly based on changes in cytokine and pathway markers without direct demonstration that the anti-inflammatory

effect leads to tumor suppression. The anticancer effects of naringenin discussed in previous sections are summarized in Table 2.

Table 2. Anticancer effects of naringenin based on both in vitro and in vivo studies.

Type of Cancer	Cell Lines	Effects	Mechanisms	Concentration	References
Acute Myeloid Leukemia	THP-1	Induces cell cycle arrest and apoptosis	↓ cancer cell viability; ↑ G2/M phase; ↓ G0/G1; ↑ % apoptotic cells; ↑ cleaved caspase-3; ↑ p53; ↓ p-Akt; ↓ Akt; ↑ p-JNK; ↑p-ERK1/2	25, 50, 100, 200, or 400 µm for naringenin, 20 or 40 µm for curcumin)	[86]
	HL60 and KG-1	Triggered apoptosis	↓ cancer cell viability; ↓ XIST; ↓ Bcl-2; ↓ HDAC1; ↑ miR-34a and caspase-3; ↑ cleaved caspase-3; ↑ ROS	5, 10, 20, 40, and 80 µM	[87]
Oral Squamous Cell Carcinoma (OSCC)	NR-S1 and SCC VII	Potentiates antitumor immunity	↑ cytotoxicity toward OSCC cells	50, 100, 150, and 200 µM	[82]
	C3H/HeNCrl mice xenografted with NR-S1 cells (2.0 × 107) and SCC VII cells (1.0 × 107)	Potentiates antitumor immunity	↑ CD169; ↑ IL-12 and p40; ↑ CD169 protein; ↑ CD^{3+} T and CD^{8+} T cell counts; ↑ CD169; ↑ IL-12; ↑ CXCL10; ↑ CTL infiltration	40 mg/kg/day	[82]
	CAL-27 cells	Triggered apoptosis	↑ Bid; ↓ Bcl-xl	–	[88]
Osteosarcoma	HOS and U2OS	Induced cell-cycle arrest and apoptosis	↓ cyclin B1; ↓ CDK1; ↑ p21; ↑ ROS; ↑ acidic vesicular organelle formation; ↑ autophagolysosomes; ↑LC-3-II; ↑ G2/M phase; ↑ Ca2+ level; ↑ GRP78 and GRP94; ↑ calpain I and II; ↑ Bak and Bax; ↑ cytochrome c; ↑ caspase-3 and caspase-9; ↑ ATG5; ↑ Beclin 1; ↑ p62	100, 250, and 500 µM	[44]
	C57BL/6 mice xenografted with LL2 cells	Attenuates bone damage	↓ bone damage; ↓ bone destruction score; ↑ bone structure; ↓TNF-α; ↓ p-IKKβ and p-p65; ↓ NF-κB; ↓ PAR2, PKC-γ, PKA, and TRPV1	50 mg/kg/day	[59]
Breast	MCF-7 ER+ breast cancer cells (HTB-22)	Triggered apoptosis	↓ cell proliferation and viability; ↓ ERK1/2; ↓ caspase 7; ↓ PARP; ↑ ER α localization to peri-nuclear region	100–200 µM	[89]
	MDA-MB-231	Triggered apoptosis	↓ cell viability; ↑ BAX; ↓ Bcl-2; ↑ caspases (3 and 9); ↓ IL-6	0–500 µM	[56]
	MCF10A, MCF7, T47D, BT549, MDA231, and SKBR3	Attenuates autophagy	↓ FKBP4; ↑ NRF2; ↑ NR3C1; ↑ P62	0–100 µM	[80]
	C57BL/6 mice xenografted with E0771 breast cancer cells	Inhibits metastasis	↓ tumor growth; ↓ metastatic lesions; ↓ vimentin; ↓ N-cadherin; ↑ estradiol conversion to estradiol-3- O-sulfate; ↓ estradiol; ↓ cholic acid; ↑ nucleic HNF4a; ↓ cytosolic HNF4a	10 and 20 mg/kg/Day	[73]
	C57BL/6 female mice	Inhibited cancer growth	↓ cancer growth; ↑ hepatic EST expression	10 mg/kg/day	[90]
	WRL-68, MCF-7, Caco-2, HUVEC, E0771, and HBL- 100	Triggered estrogen metabolism	↑ intestinal barrier crossing; ↑ penetration and absorption; ↓ toxicity toward normal cells; ↑ EST gene expression; ↑ transformation from E2 to E2-3-O-sulfate	Different naringenin nanoparticles (50–200 nmol/L)	[90]

Table 2. *Cont*.

Type of Cancer	Cell Lines	Effects	Mechanisms	Concentration	References
Colon	HCT116 and SW480	Triggered apoptosis	↓ cancer cells; ↑ nuclear fragmentation; ↑ chromatin condensation; ↑ apoptotic bodies; ↑ G0/G1 phase of the cell cycle; ↑ Bax; ↑ caspase-3; ↑ caspase-8; ↑ caspase-9; ↑ p53; ↓ Bcl-2; ↓ NF-κB; ↓ IKK-α; ↓ IKK-β	10 to 320 µM of NR and DS Diosmin	[91]
Non-Small Cell Lung	NCI-H460, A549, and NCI-H1299	Triggered apoptosis	↓ proliferation; ↑ sub-G1 cell-cycle arrest; ↓ cyclins A and D1; ↑ p21; ↑ p27; ↑ p53; ↑ Fas; ↑ FasL; ↓ PI3K; ↓ p-Akt; ↑ cleavage caspase-3, caspase-8, and PARP.	Naringenin derivative (N101-43) 0,10,25 and 40 µM	[48]
	H1299 and A459	Triggered apoptosis and cell-cycle arrest	↓ cancer cell viability; ↑ intracellular ROS; ↓ MMP; ↓ Bcl-xL and Bcl-2; ↑ Bax and Bak; ↑ cleavage of caspase 9, caspase 3, and PARP; ↓ CDK1 and cyclin B1; ↓ p62; ↑ LC3II/LC3I; ↓ p-Akt and p-mTOR; ↑ AMPKα phosphorylation	0–500 µM	[45]
	Nu/Nu mice xenografted with H1299 cells	Suppressed lung cancer growth	↓ tumor growth; ↑ cleaved caspase 3 and cleaved PARP; ↑ cancer cell apoptosis	00 to 200 mg/kg/day	[45]
Hepatocellular	HepG2	Cell-cycle arrest and triggered apoptosis	↓ proliferation of HepG2; ↑ apoptotic bodies; ↑ cell-cycle arrest at G0/G1 and G2/M; ↓ S phase decreased; ↑ p53; ↓ Bcl-2; ↑ Bax; ↑ caspase-3; ↑ cytochrome C	50, 100, 150, 200, 250, 300 µM	[43]
	HepG2	Triggered apoptosis	↑ mitochondrial depolarization; ↑ apoptotic cells; ↑ caspase-3; ↑ caspase-9; ↑ ROS; ↑ cleaved PARP; ↑ JAK-2/STAT-3,	0, 80, 160, 240, and 320 µM	[73]
	BALB/c nude mice xenografted with HepG2 cells	Inhibited tumor growth	↓ CDK2; ↓ CDK6; ↓ cyclin D1; ↓ harmful effects on normal tissues, heart, liver, spleen, lung, and kidney tissues	50 mg/kg/day	[59]
	HepG2, Hep3B, SNU182, Huh-7, MIHA	Inhibits liver cancer aerobic glycolysis	↑ toxicity toward cancer cells; ↓ cell proliferation; ↑ ROS; ↑ lipid peroxidation; ↓ GSH production; ↑ glucose uptake; ↑ ATP production; ↓ lactate production; ↑ PGC1α	less than 0.2 mM naringenin, 5 µM erastin, and 0.1 µM RSL3	[59]
Cervical	HeLa	Anti-metastasis	↓ migration and invasion of cancer cells; ↓ EGFR/PI3K/AKT; ↓ cancer cell viability and proliferation; ↓ number of invading cells; ↓ MMP9; ↓ EGFR, PI3K, p-PI3K, p-AKT, and mTOR; ↑ caspase-3	0 µM, 100 µM, and 200 µM.	[52]
Cancer-Induced Bone Pain	Sprague–Dawley female rats	Anti-inflammatory	↑ GPx4; ↓ microglia-mediated neuroinflammation; ↓ p-NF-κB; ↓ p65; ↓ cancer-induced mechanical allodynia; ↑ CD86 and iNOS; ↓ p-AMPK; ↓ PGC-1α	10, 50, and 100 mg/kg mg/kg/day	[57]

Table 2. *Cont*.

Type of Cancer	Cell Lines	Effects	Mechanisms	Concentration	References
Human Placental Choriocarcinoma	JAR and JEG3	Triggered apoptosis	↓ viability and migratory functions; ↑mitochondria related apoptosis; ↑ ROS; ↑ lipid peroxidation; ↓ glutathione; ↓ ΔΨm; ↑ p-ERK1/2; ↑ p-P90RSK and p-JNK; ↑ p-P38 and p-P70S6K	0, 5, 10, 20, 50, 100, and 200 µM	[92]
Multi-disciplinary Cancers	RAW264.7 cells	Attenuated inflammation	↓ IL-1β; ↓ COX-2; ↓ NF-κB; ↓ MAPK; ↓ p-p38	–	[58]

5. Comparison of Naringenin with Structurally Related Flavonoids

Naringenin is a flavanone (4′,5,7-trihydroxyflavanone) with a saturated C2–C3 bond, C4 carbonyl, hydroxyl groups at C5, C7, and C4′, and no substituent at C3. Related compounds differ in only a few defined features, and these differences are expected to impact its pharmacological behavior in predictable ways [9,93]. Table 3 is organized according to these features and the main structure–property relationships are summarized below.

A further 3′-hydroxyl group, e.g., in eriodictyol, results in a catechol pattern that generally increases radical scavenging and metal chelation. Methylation of the B-ring hydroxyl, as in isosakuranetin (4′-OCH_3) and hesperetin (3′-OH, 4′-OCH_3), increases lipophilicity and may decrease conjugation at that position, which can promote membrane permeability, but it usually reduces direct antioxidant capacity. Pinocembrin lacks the 4′-OH, resulting in a different hydrogen-bonding profile and polarity.

Removal of 5-OH (liquiritigenin) eliminates the hydrogen bond to the C4 carbonyl, thereby changing the electronic properties and target interactions. Methylation at 7-OH (sakuranetin) blocks a major site of glucuronidation and is anticipated to increase metabolic stability and lipophilicity.

The sugar moiety increases the polarity and molecular size and decreases passive absorption. Therefore, glycosides must be hydrolyzed by intestinal enzymes or microbiota to naringenin before absorption. In cell-based assays, glycosides tend to have lower activity than the corresponding aglycone. Thus, their in vivo activity depends on the conversion to naringenin and the gut microbiome [11].

Flavones and flavonols have a C2–C3 double bond, which gives a planar structure and extended conjugation, whereas the flavanone ring of naringenin is non-planar. This planarity is often associated with stronger kinase inhibition and greater potency in cell-based assays, but also with lower solubility and, for some compounds, broader off-target activity. Taxifolin has a 3-hydroxyl group, and quercetin has both a 3-OH and a catechol B-ring. These compounds are therefore stronger antioxidants than naringenin but also more prone to metabolism.

Some of these relationships are well-supported (e.g., the effect of glycosylation on absorption), while others are inferred from structural principles and comparisons across studies performed under different models and conditions. Direct side-by-side comparisons of potency, bioavailability, and selectivity under identical conditions are rare, and therefore the structure–activity relationships above should be considered as hypotheses.

Preclinical studies have shown that naringenin modulates several pathways relevant to cancer (e.g., PI3K/Akt/mTOR, MAPK, and NF-κB), has activity in combination with chemotherapeutic agents and other flavonoids, and can be formulated in nanocarriers (see Sections 6 and 7). However, it has low oral bioavailability, evidence of selectivity for tumor cells over normal cells is dose- and context-dependent (see Section 8), and there is no clinical evidence of anticancer efficacy. Thus, naringenin may be considered as a lead

compound of interest for further preclinical and translational study, rather than a candidate with proven benefits over related flavonoids.

Table 3. Summary of the structural similarities between naringenin and its closely related flavonoids.

Compound Name	Class	Structural Similarity with Naringenin	Structural Difference with Naringenin	Key Anticancer Properties	References
Eriodictyol	Flavanone	Identical flavanone (C6–C3–C6) backbone with hydroxyl groups at C-5 and C-7	Additional 3′-OH on the B-ring ↑↓	Promotes apoptosis, downregulates cell proliferation; decreases PI3K/Akt and NF-κB; downregulates oxidative stress; exhibits activity against breast, lung, colon, and liver cancers.	[94]
Naringin	Flavanone glycoside	Contains naringenin as the aglycone with identical flavanone core	Neohesperidose sugar attached at C-7	Induces apoptosis and autophagy; inhibits angiogenesis, metastasis, and EMT; modulates PI3K/Akt, NF-κB, and MAPK pathways; enhances chemosensitivity in several cancers.	[11]
Narirutin	Flavanone glycoside	Contains naringenin aglycone	Rutinoside sugar attached at C-7	Exhibits antioxidant and anti-inflammatory effects with moderate antiproliferative activity; suppresses oxidative stress-mediated carcinogenesis; may enhance the efficacy of conventional anticancer therapies.	[95]
Hesperetin	Flavanone	Same flavanone scaffold with C-5 and C-7 hydroxyl groups	4′-OH replaced by 4′-OCH_3	Promotes apoptosis and cell-cycle arrest; inhibits metastasis and angiogenesis; suppresses PI3K/Akt, MAPK, and STAT3 pathways; enhances sensitivity to chemotherapeutic agents.	[96]
Isosakuranetin	Flavanone	Same flavanone framework	4′-OH replaced by 4′-OCH_3	Demonstrates cytotoxicity toward multiple cancer cell lines; induces apoptosis; inhibits oxidative stress and inflammatory signaling; mechanistic studies remain relatively limited.	[97]
Homoeriodictyol	Flavanone	Same flavanone skeleton with C-5 and C-7 hydroxyl groups	Additional 3′-OH and 4′-OCH_3 substitutions	Inhibits cancer cell proliferation; induces apoptosis through ROS-mediated mitochondrial dysfunction; suppresses inflammatory signaling associated with tumor progression.	[98]
Pinocembrin	Flavanone	Same flavanone core with hydroxyl groups at C-5 and C-7	Lacks the 4′-OH group	Inhibits proliferation and migration; induces mitochondrial apoptosis; suppresses epithelial–mesenchymal transition (EMT); demonstrates efficacy in colorectal, melanoma, and glioma models.	[99]
Liquiritigenin	Flavanone	Same flavanone scaffold with 7-OH and 4′-OH	Lacks the 5-OH group	Suppresses proliferation; induces apoptosis; inhibits PI3K/Akt and Wnt/β-catenin signaling; reduces angiogenesis; exhibits activity against breast, colon, and cervical cancers.	[100]
Sakuranetin	Flavanone	Same flavanone backbone with 4′-OH	7-OH replaced by 7-OCH_3	Exhibits antiproliferative and pro-apoptotic effects; inhibits inflammatory mediators (NF-κB and COX-2); reduces tumor cell migration and invasion.	[101]

Key observations: All compounds share the flavanone scaffold of naringenin and differ structurally by hydroxylation, methoxylation, or glycosylation. Such minor structural modifications affect lipophilicity, membrane permeability, metabolic stability, target selectivity, and bioavailability, resulting in variations in anticancer potency. The anticancer effects of many analogs are mediated by common mechanisms, including induction of apoptosis, cell-cycle arrest, inhibition of PI3K/Akt, MAPK, NF-κB, STAT3, and Wnt/β-catenin signaling, suppression of angiogenesis and metastasis, and reversal of chemoresistance, suggesting the conserved pharmacological potential of the flavanone scaffold.

6. Synergistic Effects of Naringenin

Synergy is defined as a phenomenon where the effect of a combination is greater than expected from the agents acting alone. It must be validated against a reference model, not inferred from the combination being better than either agent alone. The most commonly used methods are the Chou–Talalay combination index (CI), the Loewe additivity model with isobologram analysis, and the Bliss independence model. In the CI method, synergism is defined by CI < 1, an additive effect by CI $= 1$, and antagonism by CI > 1. The CI value depends on the effect level (fraction affected, Fa) and on the dose ratio, so it should be reported with these values. Many authors consider 0.9–1.1 as indicating an additive effect [102]. Without such analysis, a greater cytotoxic or apoptotic response after co-treatment shows an enhanced effect, which may be additive or even sub-additive. In this review, we use the term "synergistic" only when a formal analysis was reported and refer to other studies as showing "enhanced" or "greater" activity.

In A549 and H1299 NSCLC cells, apigenin and naringenin produced CI values below 1, with greater G2/M arrest and apoptosis than either compound alone. This was accompanied by increased Bax and caspase-3, decreased Bcl-2, and increased ROS and lipid peroxidation [103]. In U87MG and LN229 glioblastoma cells, naringenin with temozolomide gave CI values below 1, together with increased cytotoxicity and apoptosis and reduced migration [104–107].

Naringenin potentiated the cytotoxicity of curcumin in THP-1 acute myeloid leukemia cells with increased apoptosis and cell-cycle arrest, decreased p-Akt and ERK, and increased JNK and p53 signaling [86]. Naringenin induced cytotoxicity, reduced Bcl-2 and mitochondrial membrane potential ($\Delta\Psi m$), and increased lipid peroxidation and caspase-3/7 activity in MCF-7 cells in the presence of quercetin [105]. The combination of quercetin or fisetin with naringenin resulted in increased cytotoxicity and apoptosis in MCF-7 and MDA-MB-231 cells [107], while the combination of resveratrol with naringenin enhanced antiproliferative and apoptotic effects in Y79 retinoblastoma cells [106]. Naringenin restored sensitivity to APO2L/TRAIL in glioma cells in vitro by increasing DR4/DR5, p53, and caspase activity and decreasing Bcl-2 family proteins, and the combination decreased tumor growth in xenografts [47].

The studies described above are preclinical, mostly in vitro, and use different cell lines, concentrations, and dose ratios. Many of the concentrations of naringenin are higher than plasma levels achievable by oral intake. Where formal analysis was performed, the mechanisms accompanying the interaction include the modulation of Bax/Bcl-2, caspase activation, oxidative stress, Akt/ERK inhibition, and death-receptor signaling, but whether these pathway changes cause the interaction has not been tested. The evidence therefore supports naringenin as a candidate adjuvant for further preclinical study but does not establish it as a clinically useful chemosensitizer. In vivo studies with validated interaction analysis, pharmacokinetic evaluation of combinations, and clinical trials are needed. Table 4 below presents the synergistic effects of naringenin with different compounds.

Table 4. Synergistic effects of naringenin on different types of cancer.

Drug Combination	Cancer/Cell Lines	Model	Mechanistic Effect	Ref.
Apigenin + naringenin	NSCLC: A549, H1299	in vitro	↑ Bax, ↓B cl-2, ↑ caspase-3, G2/M arrest	[103]
Naringenin + temozolomide	GBM: U87MG, LN229	in vitro	↑ apoptosis, ↓ migration	[104]
Naringenin + curcumin	AML: THP-1	in vitro	↓ Akt/ERK, ↑ p53/JNK	[86]
Naringenin + quercetin	Breast: MCF-7	in vitro	↓ Bcl-2, ↓ $\Delta\Psi m$, ↑ lipid peroxidation, ↑ caspase-3/7	[105]
Naringenin + APO2L/TRAIL	Glioma: LNZ308, U251-MG	in vitro + xenograft	↑ DR4/5, ↑ p53, ↑ caspases	[47]
Naringenin + resveratrol	Retinoblastoma: Y79	in vitro	↑ Bax, ↓ Bcl-2	[106]

7. Role of Nanotechnology in Naringenin Delivery

Nanotechnology-based delivery systems provide a promising way to improve the pharmaceutical performance of naringenin by improving its solubility, stability, absorption, biodistribution, and controlled release. However, it is critical to separate improved formulation characteristics from proven anticancer efficacy, as high drug loading or solubility does not automatically translate into better therapeutic activity [103,108].

Various nanocarriers, including liposomes, nanoemulsions, solid lipid nanoparticles (SLNs), polymeric nanoparticles, magnetic nanoparticles, and surface-functionalized systems, have been investigated for naringenin delivery [109] (Table 5). Lipid-based systems can lead to better incorporation and protection of hydrophobic naringenin, and PLGA- and PEG-PCL-based nanoparticles can provide controlled release and possibly prolonged systemic exposure. Further improvement of receptor-mediated cellular uptake can be achieved via surface modification with ligands, peptides, antibodies, or carbohydrates. However, passive tumor accumulation via the enhanced permeability and retention (EPR) effect differs significantly among tumor models and may not be reliably extrapolated to humans.

Data from individual studies support the promise of these approaches. [90] prepared naringenin–cell-penetrating peptide–galactose nanoparticles in an effort to improve intestinal permeability and hepatic accumulation. Importantly, oral administration showed greater inhibition in breast cancer xenografts compared to free naringenin and tamoxifen with increased hepatic estrogen sulfotransferase expression and decreased estradiol levels. In the same way, chitosan nanoparticles loaded with naringenin showed enhanced cytotoxicity and apoptosis in A549 lung cancer cells compared to free naringenin; however, they showed low toxicity toward normal fibroblasts [110]. However, these findings should be interpreted cautiously because the latter evidence was mainly based on an in vitro model. Furthermore, ref. [111] showed that the co-encapsulation of curcumin and naringenin in dextran-coated magnetic nanoparticles enhanced ROS-mediated apoptosis and improved tumor inhibition in combination with radiotherapy, suggesting its potential for combination treatment.

Comparative evaluation of these systems should include particle size, polydispersity, encapsulation efficiency, drug loading, release kinetics, pharmacokinetic parameters such as AUC and half-life, tumor accumulation, and ultimately tumor growth inhibition and survival. Importantly, improvements in these physicochemical or pharmacokinetic parameters should be deemed clinically relevant only if they are accompanied by a demonstrable pharmacodynamic or anticancer benefit.

The potential of naringenin nanoformulations should be considered against the concerns of large-scale production, batch-to-batch reproducibility, long-term stability, drug leakage, toxicity, biodegradation, and characterization for regulatory purposes. Moreover, much of the evidence is preclinical and the behavior of nanoparticles in cell culture and xenograft models may not predict tumor delivery or therapeutic responses in humans. Therefore, increased bioavailability or tumor accumulation should not be taken as evidence of clinical benefit. Future studies should explore standardized quantitative comparisons, clinically relevant models, long-term safety assessment, scalable manufacturing, and well-designed translational studies to determine whether naringenin nanoformulations can provide meaningful clinical advantages.

Table 5. Comparison of naringenin nanoformulations in cancer models.

Formulation	PK/Bioavailability vs. Free Drug	Model Used	Ref.
Naringenin-CPP-galactose NPs	Improved intestinal permeability; liver targeting (cell, zebrafish)	E0771 breast tumor, mouse, oral; greater inhibition than free naringenin and tamoxifen	[90]
Chitosan NPs	Not reported	A549 cells only; no in vivo data	[110]

Table 5. *Cont*.

Formulation	PK/Bioavailability vs. Free Drug	Model Used	Ref.
Curcumin-naringenin dextran-coated magnetic NPs	Not reported	Breast cancer in vitro and in vivo; with radiotherapy	[112]
Naringenin-PCL NPs (hyaluronic acid decorated)	Not reported	Urethane-induced lung cancer, rat	[113]
Albumin NPs (GNANPs)	Human PK unavailable	AGS gastric cells only	[26]
Zn/Mn nitrate NPs	No PK assessment	A-498 kidney cells only	[114]
Ibrutinib + naringenin SNEDDS	1.76-fold Cmax and 1.41-fold oral bioavailability; 4.89-fold cytotoxic potency vs. solution	In vitro and rat PK; no tumor model	[23]

8. Dose-Dependent Effects, Safety Considerations, and Conflicting Evidence

The biological effects of naringenin have been shown to be dose-dependent, cell-type-dependent, and context-dependent in numerous in vitro and in vivo models (Table 1); therefore, the available data should be interpreted with caution, considering that naringenin has consistently shown promising anticancer activity [115]. At low-to-moderate concentrations, naringenin generally exhibits antioxidant, anti-inflammatory, and cytoprotective activities by scavenging reactive oxygen species (ROS), inhibiting NF-κB-mediated inflammatory signaling, and restoring cellular redox homeostasis [11]. By contrast, higher concentrations frequently trigger overproduction of intracellular ROS, mitochondrial membrane depolarization, endoplasmic reticulum stress, DNA damage, and activation of intrinsic apoptotic pathways, exerting potent cytotoxic effects in cancer cells [73]. This pro-oxidant activity may be an important mechanism underlying the antitumor effect of naringenin, but there are concerns regarding possible nonspecific cytotoxicity at supraphysiological concentrations, particularly in experimental settings where doses are used that are unlikely to be achieved in vivo due to the low oral bioavailability and extensive first-pass metabolism of naringenin [116]. Furthermore, the published studies have very different effective concentrations, durations of treatment, cancer models, and formulation strategies, making direct comparisons challenging. In a number of studies, naringenin has been shown to selectively inhibit the proliferation of malignant cells with little toxicity toward normal cells. However, other studies have reported less selectivity at higher doses or with prolonged exposure, highlighting the need for careful dose optimization. These differences are probably due to the cancer type, genetic background, metabolic status, experimental design, and free-versus-nanoformulated naringenin. Collectively, these findings point to a narrow and context-dependent therapeutic window of naringenin's therapeutic efficacy, highlighting the importance of standardized pharmacokinetic studies, extensive toxicological assessment, and well-designed preclinical and clinical investigations to identify the optimal dosing regimens that ensure maximal anticancer efficacy with minimal potential adverse effects.

9. Limitations and Challenges

Although there is a strong evidence for the anticancer efficacy of naringenin in several in vitro and preclinical models, there are still a number of hurdles hindering its clinical application. The main limitation is its poor oral bioavailability because of low aqueous solubility, limited absorption from the intestine, and extensive first-pass metabolic process. Following ingestion, naringenin is quickly conjugated with glucuronide and sulfate in the intestine and liver, which leads to a significant reduction in the concentration of the physiologically active aglycone available to exert anticancer effects [117,118]. Moreover,

degradation in the gastrointestinal tract, interaction with gut flora, and possible efflux through P-glycoprotein transporters limit its systemic exposure and therapeutic efficacy.

One of the major challenges is the discordance between preclinical outcomes and clinical validation. Naringenin has been reported to modulate a number of oncogenic signaling pathways, such as PI3K/Akt/mTOR, NF-κB, MAPK, Wnt/β-catenin, and JAK/STAT. Nevertheless, the majority of the evidence comes from cell culture and animal studies. Few clinical trials are investigating naringenin as an anticancer agent, and no properly conducted clinical trials have demonstrated the efficacy of naringenin for the prevention or treatment of cancer. Questions about the correct dose, the drug's journey through the body, safety in the long-term, targeting of tumors, and potential interaction with standard chemotherapy drugs have not been answered satisfactorily. To overcome these limitations, future research should be directed toward advanced drug-delivery approaches, such as nanoformulations and customized delivery platforms, together with carefully designed clinical studies. Overcoming these hurdles will be essential to translate the promising pre-clinical and molecular results with naringenin into effective cancer therapies.

10. Conclusions and Future Perspectives

Naringenin has emerged as a promising anticancer phytochemical that can modulate many signaling networks involved in tumor development, metastasis, and therapy resistance. Preclinical studies have demonstrated that naringenin possesses anticancer properties through the modulation of apoptosis, cell-cycle progression, oxidative stress, inflammation, and crucial oncogenic pathways, such as PI3K/Akt/mTOR, MAPK, NF-κB, Wnt/β-catenin, and JAK/STAT signaling. Such multitargeted activities highlight its potential as a chemopreventive and therapeutic agent.

Nevertheless, the clinical use of naringenin is restricted due to its poor bioavailability, rapid metabolism, and lack of significant clinical validation. Further investigations should be directed at enhancing its pharmacokinetic properties through advanced delivery systems and structural modifications and assessing its efficacy in conjunction with existing anticancer therapies. Moreover, extensive in vivo studies and clinical trials are required to assess its safety, efficacy, appropriate dose, and therapeutic importance in cancer patients. Overcoming such hurdles is essential to translate naringenin from a promising experimental chemical to a clinically effective anticancer drug.

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Abbreviations

The following abbreviations are used in this manuscript:

AKT	Protein Kinase B
Bax	Bcl-2: B Cell Lymphoma 2
CDKs	Cyclin-Dependent Kinases
COX-2	Cyclooxygenase-2
ERK	Extracellular Signal-Regulated Kinase
IL-6	(Interleukin 6)TNF-α: Tumor Necrosis Factor Alpha
iNOS	Inducible Nitric Oxide Synthase
JNK	c-Jun N-terminal Kinase
MAPK	Mitogen-Activated Protein Kinase
MMPs	Matrix Metalloproteinases
mTOR	Mechanistic Target of Rapamycin
NF-κB	Nuclear Factor kappa B
PI3K	Phosphatidylinositol 3-Kinase
ROS	Reactive Oxygen Species

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