Nobiletin in cancer therapy: Emerging insights into multi-target mechanisms, overcoming drug resistance and therapeutic translation (Review)

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Abstract. Nobiletin, a polymethoxyflavone derived from *Citrus* peels, has emerged as a promising multi-target anticancer agent. The present review consolidates recent advances elucidating the efficacy of nobiletin in suppressing tumor growth across diverse cancer types, including breast, colon, lung and gastric cancer. Mechanisms for inducing cell cycle arrest and apoptosis, inhibiting metastasis and angiogenesis, and modulating key oncogenic pathways, such as phosphatidylinositol 3-kinase/protein kinase B/mechanistic target of rapamycin, mitogen-activated protein kinase and nuclear factor-κB are discussed. Crucially, the present review highlights the role of nobiletin in reversing chemoresistance and its synergistic potential with conventional therapeutics. Despite challenges in bioavailability, novel delivery strategies are paving the way for its clinical application. By reviewing current evidence, the present review underscores the notable potential of nobiletin as an integrative agent in oncology, offering a comprehensive perspective on its therapeutic prospects.

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Abbreviations: ACLY, ATP citrate lyase; AKT, protein kinase B; AML, acute myeloid leukemia; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; CDK, cyclin-dependent kinase; CHOP, C/EBP homology protein; CREB, cAMP response element-binding protein; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; GRP78, glucose-regulated protein 78 kDa; GSK-3β, glycogen synthase kinase-3β; HSC70, heat shock cognate 70; iNOS, inducible nitric oxide synthase; IRF3, interferon regulatory factor 3; JAK2, Janus tyrosine kinase 2; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinases; miRNA/miR, microRNA; MMP, matrix metalloproteinase; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2-related factor 2; PARP, poly(ADP-ribose) polymerase; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; SP-1, specificity protein 1; SREBP1, sterol regulatory element-binding protein 1; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-β; TLR, Toll-like receptor; VEGF, vascular endothelial growth factor

Key words: anticancer, natural product, nobiletin, polymethoxyflavone, chemoresistance reversal, drug delivery

Contents

1. Introduction

Cancer, a group of diseases characterized by the uncontrolled growth and spread of cells, poses a notable threat to global health and is a leading cause of mortality worldwide. In 2023, excluding non-melanoma skin cancers, there were an estimated 18.5 million new cancer cases and 10.4 million cancer-related deaths globally, with cancer ranking as the second leading cause of death after cardiovascular diseases (1). Despite the development of various treatment modalities, such as surgery, chemotherapy, radiation therapy and immunotherapy, there is an ongoing need for novel approaches that can effectively prevent or halt the progression of cancer at its early stages (2). Chemoprevention, which involves the use of natural or synthetic agents to reverse, suppress or prevent carcinogenesis, has

emerged as a promising strategy in the fight against cancer (3). Natural products, derived from a variety of sources, including plants (4), have been a rich source of chemopreventative agents due to their diverse chemical structures and potential for low toxicity and high efficacy (5). Plant-derived phytochemicals represent a crucial reservoir in the development of new pharmaceuticals and cancer treatments (6). Notable examples include nobiletin, a flavonoid from *Citrus* fruits, along with curcumin from turmeric and resveratrol found in grapes (7). Their mechanisms of action involve boosting antioxidant levels (8), deactivating carcinogens, curbing cell proliferation, triggering cell cycle halts and apoptosis, and fine-tuning the response of the immune system (9). Among these, nobiletin, a polymethoxyflavone primarily isolated from the peels of *Citrus* fruits, such as shekwasha (*Citrus depressa* Hayata) and ponkan (*Citrus reticulata* Blanco), has shown notable potential as an anticancer agent (10).

Citrus fruits, valued for their medicinal and aromatic qualities, possess a range of health benefits, including antitumor, heart-protective, antioxidant, antibacterial and antiviral effects (11). *Citrus* fruits contain higher levels of beneficial secondary metabolites in their peels, offering the opportunity to transform *Citrus* waste into valuable products (12). Nobiletin, a polymethoxyflavone primarily isolated from *Citrus* peels, is characterized by its multiple methoxy groups. This distinct chemical structure is associated with enhanced metabolic stability and membrane permeability compared with non-methylated flavonoids (13), which underlies its diverse pharmacological activities. Nobiletin has been extensively studied for its antitumor effects in various preclinical models. *In vitro* studies have demonstrated its ability to inhibit the growth of various cancer cell lines, including those derived from breast (14), colon (15) and prostate (16) cancer. These effects are mediated through multiple mechanisms, such as the induction of apoptosis, cell cycle arrest, targeting tumor suppressor genes and inhibition of invasion and migration (17). By influencing the behavior of cancer-associated fibroblasts and immune cells within the tumor stroma (18), nobiletin may disrupt the supportive network that facilitates tumor growth and spread (19). Additionally, the antioxidant properties of nobiletin contribute to neutralizing reactive oxygen species (ROS), thereby reducing oxidative stress that can lead to DNA damage and mutations (20), which are key events in carcinogenesis (21). Furthermore, the anti-inflammatory effects of the compound are notable (22), as chronic inflammation is increasingly recognized as a driver of cancer development (23). By inhibiting inflammatory signaling pathways, such as nuclear factor-κB (NF-κB), nobiletin may reduce the production of pro-inflammatory cytokines and chemokines that promote tumorigenesis and angiogenesis (24).

The multifaceted action of nobiletin on various aspects of cancer biology underscores its potential as a versatile chemopreventive agent. Notably, nobiletin exhibits a favorable safety profile with low toxicity compared to synthetic chemotherapeutic agents such as doxorubicin, cisplatin and paclitaxel, which are often associated with severe dose-limiting toxicities including cardiotoxicity, nephrotoxicity and neurotoxicity (25). This positions nobiletin as a promising adjunctive agent that could be integrated with conventional therapies to enhance efficacy while mitigating adverse effects. Collectively, the diverse antitumor mechanisms of this natural polymethoxyflavone, targeting multiple cellular and molecular pathways involved in carcinogenesis, highlight its potential for further development in cancer prevention and treatment (26).

The present review aims to offer a comprehensive analysis of the current body of research on the antitumor properties of nobiletin, highlighting its diverse mechanisms of action and the molecular pathways it modulates to exert its effects. By consolidating findings from various *in vitro* and *in vivo* studies, the review aims to elucidate how nobiletin inhibits tumor cell proliferation, induces apoptosis and impedes metastasis. Furthermore, it critically evaluates the latest preclinical evidence (up to 2025) and discusses innovative strategies to enhance its bioavailability, aiming to bridge the gap between mechanistic understanding and clinical translation. This comprehensive update aims to delineate the unique position of nobiletin in the future landscape of natural product-derived cancer therapeutics.

2. Effects of nobiletin on cancer cells

Nobiletin has demonstrated antitumor activity both *in vitro* and *in vivo* (27,28).

In vitro studies on the anticancer effects of nobiletin. Nobiletin has been extensively studied for its ability to modulate several signaling pathways that are often dysregulated in cancer cells. For instance, nobiletin has been shown to modulate the Toll-like receptor (TLR) signaling pathway, which is implicated in prostate cancer progression, by potentially inducing the TLR3/interferon regulatory factor (IRF)3 signaling pathway and enhancing its activation when combined with polyinosinic:polycytidylic acid (Poly I:C). This suggests that nobiletin may mediate the TLR3 signaling pathway, with the combined treatment of nobiletin and Poly I:C showing a more marked effect in LNCaP cells than in prostate cancer-3 cells. This cell type-dependent response is noteworthy, as it indicates that the immunomodulatory effects of nobiletin may vary according to the genetic background or androgen receptor status of prostate cancer cells, offering potential for patient stratification in future therapeutic applications. Furthermore, the study indicates that while nobiletin can improve the activation of the TLR3/IRF3 signaling pathway (which promotes apoptosis), it also leads to a reduction in the activation of the TIR-domain-containing adapter-inducing interferon-β/receptor-interacting protein kinase 1/Fas-associated protein with death domain signaling pathway, highlighting the complex regulatory role of nobiletin in influencing apoptotic cell death *in vitro* (16).

Moreover, through affinity chromatography, proteomics, computer modeling and various biochemical analyses, Gao *et al* (29) identified heat shock cognate 70 (HSC70) as a novel direct protein target of nobiletin in colon cancer cells. In these laboratory experiments, nobiletin was found to bind to HSC70 at its ATP-binding site, thereby inhibiting its ATPase activity and disrupting cancer cell proliferation. Furthermore, the study revealed that the major colonic metabolites of nobiletin, which are generated in the colon of nobiletin-fed mice, produced similar inhibitory effects on HSC70-mediated pro-carcinogenic events as nobiletin itself.

In vivo studies on the anticancer effects of nobiletin. *In vivo* studies have further confirmed the chemopreventative potential of nobiletin, showing reduced tumor incidence and progression in animal models of cancer (30). For example, nobiletin effectively inhibited the formation of metastatic lung nodules in nude mice (31). Chu *et al* (32) found that sweet orange peel extract and its bioactive compound nobiletin exhibit notable anti-proliferative effects against human hepatoma cells both *in vitro* and *in vivo*, potentially through inducing cell cycle arrest, apoptosis and the generation of ROS, which contribute to its antitumor activity. Additionally, Luo *et al* (33) observed a marked inhibitory effect of nobiletin on tumor growth in a nude mouse model of lung cancer (A549 xenograft). These findings suggest that nobiletin induces p53-mediated cell cycle arrest and apoptosis by modulating the B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax)/Bcl-2 protein ratio. Ma *et al* (34) performed a series of *in vitro* and *in vivo* experiments and discovered that nobiletin caused G_2 cell cycle arrest and altered protein expression levels by reducing Bcl-2 and cyclooxygenase-2 (COX-2) while increasing Bax and caspase-3 levels in SMMC-7721 cells. *In vivo*, nobiletin was shown to inhibit H22 tumor growth, significantly downregulating the expression of COX-2, Bax and caspase-3, and lower Bcl-2/Bax ratios, demonstrating its substantial inhibitory impact on hepatocellular carcinoma in both settings.

3. Mechanisms underlying the anticancer effects of nobiletin

The mechanisms of action of nobiletin are multifaceted, encompassing a range of biological processes that contribute to its antitumor effects (35,36). Nobiletin has been shown to induce apoptosis (37), regulate cell cycle progression and affect angiogenesis (38). The compound can interact with multiple targets within cancer cells, including proteins involved in cell survival (39), proliferation (40) and metastasis (41). Additionally, nobiletin has been found to influence the expression of microRNAs (miRNA/miR) (42), which can further regulate gene expression and impact cancer cell behavior (43). The ability of nobiletin to modulate the tumor microenvironment and enhance the body's immune response against cancer also adds to its therapeutic potential. For example, epithelial-mesenchymal transition (EMT) marks the initial phase of tumor metastasis, a process notably influenced by the tumor microenvironment, particularly hypoxia, which can trigger this transition (44). Nobiletin has been demonstrated to counteract hypoxia-induced EMT in lung cancer cells by deactivating Notch-1 signaling and activating miR-200b (45). Overall, the diverse mechanisms of action of nobiletin highlight its promise as a therapeutic agent in the prevention and treatment of cancer (Fig. 1).

Nobiletin regulates the cancer cell cycle through modulation of key protein expression. Nobiletin regulates protein expression which in turn affects the cell cycle, and it also has direct effects on cell cycle progression. The two processes are interconnected rather than separate. For example, Zhang *et al* (46) demonstrated that nobiletin markedly inhibits the proliferation of human pancreatic cancer cells (PANC-1) *in vitro* by inducing apoptosis and cell cycle arrest.

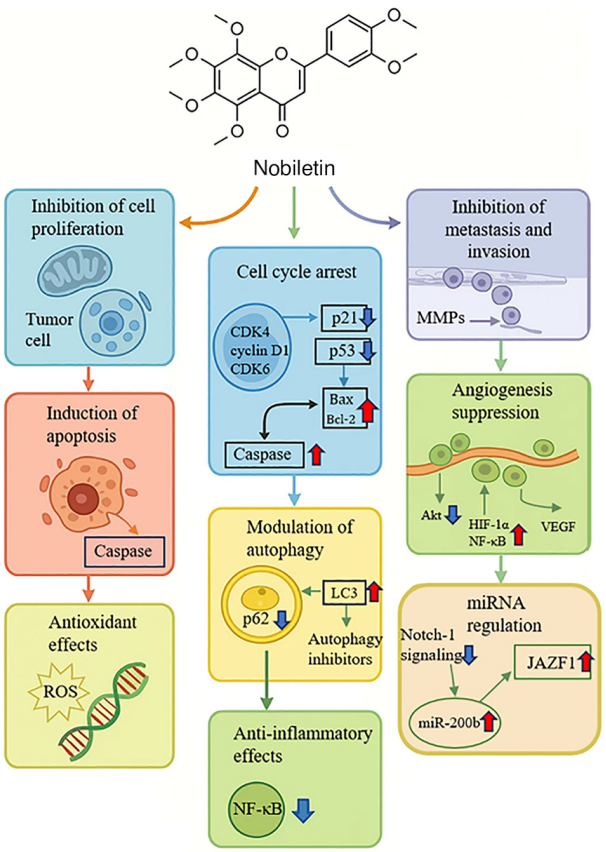

Figure 1. Antitumor mechanisms of nobiletin. The multifaceted antitumor effects of nobiletin, highlighting its ability to inhibit cancer cell proliferation, induce apoptosis, modulate autophagy, and suppress inflammation and angiogenesis. Nobiletin targets key cell cycle proteins (CDK4, cyclin D1 and CDK6) to arrest the cell cycle and induces apoptosis via caspase activation. It also reduces oxidative stress by decreasing ROS and modulates autophagy through proteins such as p62 and LC3. Additionally, nobiletin inhibits metastasis and invasion by suppressing MMP-9 and MMP-2, and upregulates miRNAs such as miR-200b. ROS, reactive oxygen species; CDK, cyclin-dependent kinase; MMP, matrix metalloproteinase; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; Akt, protein kinase B; VEGF, vascular endothelial growth factor; miR/miRNA, microRNA; JAZF1, JAZF zinc finger 1; NF-κB, nuclear factor-κB; HIF-1α, hypoxia-inducible factor 1α.

The study revealed that nobiletin upregulated the expression of the proapoptotic protein Bax and downregulated the anti-apoptotic proteins Bcl-2 and p53, leading to an accumulation of cells in the G_0/G_1 phase and a decrease in the S phase. Moreover, Jiang *et al* (47) reported that nobiletin inhibits the growth of multidrug-resistant SKOV3/TAX ovarian cancer cells by inducing G_0/G_1 cell cycle arrest and reducing G_2/M phase transition, accompanied by upregulation of p53 and p21 proteins (47). Nobiletin also promoted apoptosis in multidrug-resistant SKOV3/TAX ovarian cancer cells via the intrinsic apoptotic pathway, as evidenced by increased levels of cleaved caspase-9/-3 and poly(ADP-ribose) polymerase (PARP). Furthermore, nobiletin disrupted autophagic degradation in these cells, leading to autophagic flux blockade, which in turn amplified its apoptotic effect. A key mechanistic finding from this study was that nobiletin stimulated the AKT signaling pathway, and this activation was implicated in both the suppression of autophagic degradation and the enhancement of apoptosis (47).

Nobiletin exerts its antitumor effects through a complex interplay with multiple signaling pathways that regulate the cell cycle (48). For example, Cheng *et al* (41) revealed that nobiletin exerted its anti-metastatic effects on human osteosarcoma U2OS and HOS cells by downregulating the expression of matrix metalloproteinases (MMP)-2 and MMP-9. This was achieved through the inhibition of the extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) signaling pathways, leading to the inactivation of downstream transcription factors, including NF-κB, cAMP response element-binding protein (CREB) and specificity protein 1 (SP-1), thereby suppressing cellular motility, migration and invasion. Lien *et al* (49) found that nobiletin treatment led to a reduction in cell viability and cell cycle arrest at the G_0/G_1 phase in human U87 and Hs683 glioma cell lines. Western blotting data revealed that nobiletin attenuated the expression of cyclin D1, cyclin-dependent kinase (CDK)2, CDK4 and E2F1, as well as the phosphorylation of AKT and MAPKs, including p38, ERK and JNK. Furthermore, nobiletin was shown to inhibit glioma cell migration, as demonstrated by functional wound healing and Transwell migration assays. Wei *et al* (50) demonstrated that nobiletin exerts its antitumor effects on renal carcinoma cells through the inhibition of the proto-oncogene tyrosine-protein kinase Src (SRC)/AKT/signal transducer and activator of transcription (STAT)3/YY1-associated protein 1 (YY1AP1) signaling pathway, leading to cell cycle arrest in the G_0/G_1 phase and the promotion of apoptosis. The study showed that nobiletin decreased the nuclear localization of STAT3 and YY1AP1, and reduced the levels of phosphorylated (p-) SRC, AKT and STAT3, while increasing the phosphorylation of YY1AP1, suggesting a potential novel therapeutic strategy for kidney cancer treatment by targeting these signaling components.

Nobiletin also modulates protein expression to exert its anticancer effects. For example, Chen *et al* (51) demonstrated that nobiletin inhibits the growth and proliferation of human acute myeloid leukemia (AML) cells by downregulating the expression of the KIT proto-oncogene, receptor tyrosine kinase (c-KIT) gene, which is crucial for leukemia progression. Nobiletin treatment resulted in a marked reduction of c-KIT mRNA and protein levels in AML cells, confirmed by the inhibition of KIT promoter activity. The anti-leukemic effects of nobiletin were abolished by the overexpression of c-KIT, indicating that nobiletin exerts its anticancer effects through the downregulation of c-KIT gene expression. In a previous study, it was found that nobiletin and its colonic metabolites, nobiletin-Met, notably suppressed colitis-associated colon carcinogenesis by downregulating inducible nitric oxide synthase (iNOS) and upregulating the nuclear factor erythroid 2-related factor (Nrf2) signaling pathway, which is associated with the induction of antioxidative enzymes and cell cycle arrest (52). Jiang *et al* (53) demonstrated that nobiletin suppressed the growth and metastasis of MIAPaCa-2 pancreatic cancer cells by triggering autophagy (increased LC3-II/I and decreased p62), arresting the cell cycle at G_0/G_1 (downregulating cyclin D1 and CDK4) and blocking NF-κB signaling in a concentration-dependent manner, thereby inhibiting proliferation, migration and metastasis. Turdo *et al* (54) demonstrated that nobiletin selectively targets colorectal cancer stem cells (CSCs) and synergizes with 5-fluorouracil plus oxaliplatin (FOX). Nobiletin reduces stem cell viability by arresting the cell cycle at S and G_2/M phases and upregulating pro-apoptotic genes; it disrupts CSC maintenance by downregulating Wnt signaling, cluster of differentiation (CD)44v6 expression and clonogenic capacity, thereby reversing chemoresistance and inhibiting metastatic expansion.

Moreover, nobiletin has been found to influence the expression of miRNAs. miRNAs serve a crucial role in lung cancer by regulating key cellular processes and signaling pathways involved in tumorigenesis, including cell proliferation, differentiation, angiogenesis, apoptosis, invasion and metastasis, making them potential therapeutic targets and biomarkers in non-small cell lung cancer (NSCLC) (55). For example, Han *et al* (42) demonstrated that nobiletin repressed miR-15-5p, thereby relieving inhibition of the negative WNT regulators naked cuticle 1, axin 2 and Wnt inhibitory factor 1. This cascade reduced nuclear β-catenin and its transcriptional targets (c-Myc, c-Jun and cyclin D1), abrogating stem-like properties, colony formation and inducing apoptosis. These findings establish nobiletin as a miRNA-mediated WNT pathway modulator in NSCLC. Jahan *et al* (56) explored the neuroprotective potential of nobiletin in human neural progenitor cells, revealing that nobiletin treatment notably restores deregulated miRNAs and proteins induced by sodium arsenate exposure, which are associated with neurodegeneration, oxidative stress response and apoptotic processes. This restoration suggests that the neuroprotective effects of nobiletin may be mediated through the modulation of key signaling pathways, including p53 and Wnt, which are implicated in cell death and cell cycle regulation.

Nobiletin inhibits cancer cell growth and proliferation. Multiple independent studies across various cancer models consistently confirm that nobiletin targets key oncogenic pathways, including PI3K/AKT and MAPK, to block cancer cell expansion. However, emerging mechanisms such as epigenetic regulation and cancer stem cell targeting are supported by a more limited number of studies and require further validation (57). The broad-spectrum growth-inhibitory effects of nobiletin highlight its promise as a multi-mechanistic anticancer agent (58). For example, in a pulmonary carcinogenesis mouse model, oral administration of nobiletin markedly suppressed lung tumorigenesis, as evidenced by reduced tumor volume and attenuated cell proliferation. Furthermore, the effects were associated with notable cell cycle arrest, cellular apoptosis and the modulation of key proteins involved in cell proliferation and death, such as p21, cyclin B1, CDK1, cyclin D1, CDK6, CDK4, Bax, cleaved caspase-1 and cleaved PARP (59). Wang *et al* (14) elucidated the role of nobiletin in breast cancer cells, demonstrating its ability to inhibit cell proliferation in a dose-dependent manner and induce both apoptosis and pyroptosis. The research identified miR-200b as a key mediator of these effects, showing that nobiletin enhances miR-200b-induced pyroptosis and that JAZF zinc finger 1 (JAZF1) is a direct target of miR-200b. Furthermore, it revealed that nobiletin exerts its antitumor effects through the miR-200b/JAZF1/NF-κB signaling axis. The study by Gutiérrez-Venegas and Rosas-Martínez (60) showed that nobiletin and its derivative 5-demethylnobiletin can ameliorate hypopharyngeal squamous cell carcinoma by suppressing

transforming growth factor β (TGF-β)-mediated EMT. The study indicated that these flavonoids inhibit EMT by reversing TGF-β-induced morphological changes, migration and the expression of EMT markers, suggesting their potential as therapeutic agents for the treatment of oral squamous cell carcinoma.

Autophagy is a double-edged sword in the context of cancer. While it can be a protective mechanism under stress conditions, it can also be hijacked by cancer cells to promote their survival and progression (61). The balance of autophagy is therefore a critical factor in cancer development and treatment response (62). Inhibiting autophagy has been shown to induce cell death in certain cancer types, including pancreatic (46) and ovarian (47) cancer, and to improve the outcomes of standard cancer therapies (63). Conversely, promoting autophagy in cancer cells could be a potential therapeutic strategy to weaken tumor resistance and enhance treatment efficacy (64). Understanding the complex interplay between autophagy and cancer is essential for developing novel cancer treatments that target this cellular process effectively. Moon and Cho (65) demonstrated that nobiletin activates a complex cellular response in SNU-16 human gastric cancer cells, involving the induction of glucose-regulated protein 78 kDa (GRP78) and other endoplasmic reticulum stress-related proteins, such as inositol requiring enzyme 1-α, activating transcription factor 4 and C/EBP homology protein (CHOP), leading to endoplasmic reticulum stress-mediated apoptosis. Additionally, the study found that nobiletin triggers protective autophagy, which when inhibited by chloroquine markedly enhances apoptosis, suggesting that nobiletin-induced apoptosis in gastric cancer cells is mediated through endoplasmic reticulum stress and autophagy pathways. Moreover, PI3K acts as a molecular switch that converts tumor-associated macrophages from an immune-suppressive to an immune-stimulatory state, thereby unleashing $CD8^+$ T-cell cytotoxicity and enhancing antitumor immunity (66).

Chen *et al* (27) recently elucidated a lipid-metabolism-dependent mechanism by which nobiletin kills gastric cancer cells. The study showed that nobiletin directly binds sterol regulatory element-binding protein 1 (SREBP1), prevents its nuclear translocation and blocks SREBP1 occupancy on the ATP citrate lyase (ACLY) promoter. This leads to downregulation of ACLY-dependent fatty-acid synthesis and simultaneously inactivates the PI3K/AKT/mechanistic target of rapamycin (mTOR) axis. The resulting metabolic stress converts cytoprotective autophagy into autophagy-dependent cell death, an effect validated in a patient-derived xenograft model where nobiletin reduced tumor volume while suppressing SREBP1 nuclear accumulation and PI3K/AKT/mTOR signaling.

Nobiletin inhibits cancer cell invasion and migration. Nobiletin has emerged as a potent inhibitor of cancer cell invasion and migration (67). For example, research has found that nobiletin can affect the migration and invasion of hypopharyngeal squamous cell carcinoma (68). Nobiletin has been demonstrated to inhibit cancer cell invasion and migration by suppressing the activation of kinases that promote cell proliferation and survival, thereby reducing the downstream signaling involved in these processes (69). For example, Wu *et al* (58) revealed that nobiletin restrains breast cancer metastasis by blocking IL-6-driven ERK-STAT and JNK cascades. In MCF-7 and T47D cells, nobiletin dose-dependently suppressed phosphorylation of ERK1/2 and JNK, interrupting the downstream STAT and c-JUN transcriptional activity that underpins cell migration and invasion. Molecular docking analysis confirmed high-affinity binding of nobiletin to PI3K (-8.0 kcal/mol). Consistent with these *in vitro* findings, nobiletin reduced liver metastasis in xenograft models, underscoring its potential as a multi-pathway inhibitor against breast cancer dissemination. Liu *et al* (70) demonstrated that nobiletin inhibits EMT in renal carcinoma cells by inactivating the NF-κB and Wnt/β-catenin signaling pathways, thereby preventing hypoxia-induced migration and invasion, suggesting its potential as an anticancer agent in renal cell carcinoma.

The anti-invasive and anti-migratory effects of nobiletin are mediated through the modulation of several key signaling pathways and the regulation of MMPs (71). MMPs serve a crucial role in cancer progression by degrading the extracellular matrix, promoting the invasion and metastasis of cancer cells (72). For example, nobiletin inhibits MMP-9 enzymatic activity in retinal Müller cells by suppressing MMP-9 gene transcription and enhancing TIMP metallopeptidase inhibitor 1 (TIMP-1) production, which is mediated by the PI3K/AKT signaling pathway (73). This signaling pathway involves the participation of NF-κB, STAT3, ERK (74), JNK/SAPK, p38 MAPK and AKT/Nrf2 (75), which are modulated by nobiletin to inhibit cancer cell invasion (76). For example, Xu *et al* (77) revealed that nobiletin suppresses renal carcinoma by simultaneously blocking the Janus tyrosine kinase 2 (JAK2)/STAT3 and PI3K/AKT cascades. Exposure to nobiletin dose-dependently reduced phosphorylation of JAK2, STAT3, PI3K and AKT, thereby silencing downstream pro-survival signals and upregulating apoptotic proteins. This dual-pathway inhibition arrested cell cycle progression, curtailed migration and invasion, and triggered apoptosis in 786-O and ACHN cell lines. The PI3K/AKT pathway, which primarily affects distant metastasis by reducing tumor cell adhesion, is also modulated by nobiletin; it downregulates the expression of MMP-1 and MMP-9, and upregulates TIMP-1, thus inhibiting the invasion of cancer cells. In liver cancer, nobiletin reduces the levels of p-ERK2 and p-AKT, inhibiting cell metastasis involving ERK and PI3K/AKT pathways induced by hepatocyte growth factor (78) (Table I) (14,16,21,27,29,33,34,41,46,47,49-53,58,65,70,74).

Nobiletin also inhibits tumor angiogenesis in breast cancer cells by targeting the p38 mitogen-activated protein kinase, NF-κB and Nrf2 pathways. A previous study showed that nobiletin treatment led to decreased cell viability and induced apoptosis in MCF-7 cells, while also inhibiting cell migration by downregulating MMP-2 and MMP-9 expression (79). Additionally, in the TGF-β1/Smad3 signaling pathway, nobiletin inhibits EMT, a cellular process essential during cancer metastasis. It does so by inhibiting the expression of MMP-2, MMP-9, p-SRC, p-focal adhesion kinase (FAK), p-paxillin, Snail, Slug, Twist and zinc finger E-box-binding homeobox 1, thereby inhibiting the EMT of human NSCLC cells (31). The ERK/JNK pathway is another target of nobiletin, which inhibits the activities of ERK and JNK, decreasing the mRNA expression and protein levels of MMP-2 and MMP-9, and

Table I. Summary of anticancer effects and mechanisms of nobiletin across various cancer types.

Cancer type	*In vitro*/*in vivo* model	Key mechanisms and effects	(Refs.)
Breast cancer	MCF-7, T47D cells; xenograft models	Induces apoptosis and pyroptosis via miR-200b/JAZF1/NF-κB axis; inhibits migration and invasion by suppressing IL-6-induced ERK-STAT and JNK pathways; inhibits angiogenesis.	(14,58)
Colon cancer	Colon cancer cell lines; mouse models	Binds to HSC70 inhibiting ATPase activity; downregulates iNOS, upregulates Nrf2; induces cell cycle arrest and apoptosis; suppresses AKT signaling and angiogenic factors (VEGF and MMP-7).	(29,52)
Pancreatic cancer	PANC-1, MIAPaCa-2 cells	Induces G_0/G_1 cell cycle arrest and apoptosis (↑ Bax, ↓ Bcl-2 and p53); triggers autophagy and blocks NF-κB signaling.	(46,53)
Liver cancer (HCC)	SMMC-7721, H22 cells; mouse models	Causes G_2 cell cycle arrest; alters protein expression (↓ Bcl-2 and COX-2; ↑ Bax and caspase-3); inhibits tumor growth.	(34)
Lung cancer (NSCLC)	A549 cells; nude mouse models	Induces G_2/M cell cycle arrest and apoptosis (↓ Bcl-2, ↑ Bax and p53); inhibits TGF-β1/Smad3-mediated EMT; enhances chemosensitivity to Adriamycin via the AKT/GSK-3β/β-catenin pathway.	(31,33)
Prostate cancer	LNCaP, PC-3 cells	Modulates the TLR3/IRF3 signaling pathway; enhances apoptosis when combined with Poly I:C; downregulates NF-κB, STAT3, ERK activation.	(16,74)
Osteosarcoma	U2OS, HOS cells	Inhibits metastasis by downregulating MMP-2/9 via suppression of ERK and JNK pathways.	(41)
Glioma	U87, Hs683 cells	Induces G_0/G_1 cell cycle arrest (↓ cyclin D1 and CDK2/4); inhibits migration; suppresses AKT and MAPK phosphorylation.	(49)
Renal cell carcinoma	786-O, ACHN cells	Induces G_0/G_1 arrest and apoptosis via SRC/AKT/STAT3/YY1AP1 pathway; inhibits migration and invasion by inactivating NF-κB and Wnt/β-catenin.	(50,70)
Gastric cancer	SNU-16 cells; patient-derived xenograft models	Induces ER stress-mediated apoptosis and protective autophagy; inhibits *de novo* fatty acid synthesis by targeting SREBP1/ACLY and PI3K/AKT/mTOR axis.	(27,65)
AML	AML cell lines	Exerts antileukemic effects by downregulating c-KIT gene expression.	(51)
Ovarian cancer	SKOV3/TAX cells (multidrug-resistant)	Suppresses autophagic degradation and enhances apoptosis via AKT pathway; induces ROS-mediated pyroptosis.	(47)

miR, microRNA; JAZF1, JAZF zinc finger 1; NF-κB, nuclear factor-κB; ERK, extracellular signal-regulated kinase; STAT, signal transducer and activator of transcription; JNK, c-Jun N-terminal kinase; HSC70, heat shock cognate 70; iNOS, inducible nitric oxide synthase; Nrf2, nuclear factor erythroid 2-related factor 2; AKT, protein kinase B; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; COX-2, cyclooxygenase-2; TGF-β1, transforming growth factor-β; EMT, epithelial-mesenchymal transition; GSK-3β, glycogen synthase kinase-3β; TLR3, Toll-like receptor 3; IRF3, interferon regulatory factor 3; CDK, cyclin-dependent kinase; MAPK, mitogen activated protein kinase; SRC, proto-oncogene tyrosine-protein kinase Src; YY1AP1, YY1-associated protein 1; ER, endoplasmic reticulum; SREBP1, sterol regulatory element-binding protein 1; ACLY, ATP citrate lyase; PI3K, phosphatidylinositol 3-kinase; mTOR, mechanistic target of rapamycin; c-KIT, KIT proto-oncogene, receptor tyrosine kinase; ROS, reactive oxygen species; AML, acute myeloid leukemia; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; Poly I:C, polyinosinic:polycytidylic acid.

inhibiting the DNA binding activity of transcription factors NF-κB, CREB and SP-1 in tumor cells (41). Moreover, in the AKT/glycogen synthase kinase-3β (GSK-3β)/β-catenin signal pathway, nobiletin has been shown to enhance chemosensitivity to Adriamycin in A549 NSCLC cells by modulating key components of this pathway (Fig. 2). Moon *et al* (80) demonstrated that nobiletin treatment decreased the expression of multidrug resistance-associated protein 1 (MRP1) and neuroblastoma-derived MYCN proto-oncogene bHLH transcription factor (MYCN), as well as downregulating AKT, GSK-3β and β-catenin. This regulation led to the accumulation of intracellular Adriamycin and enhanced apoptosis in A549/ADR cells.

Beyond its anti-metastatic effects, nobiletin has demonstrated the ability to overcome multiple modes of drug resistance through distinct mechanisms. In efflux-mediated resistance, nobiletin downregulates MRP1 expression via the AKT/GSK-3β/β-catenin/MYCN pathway, increasing

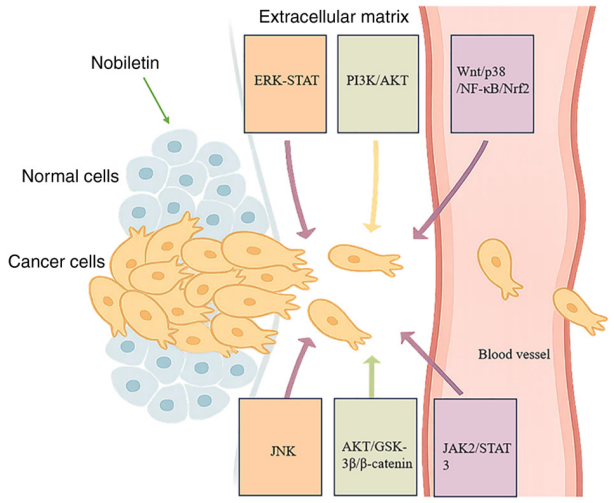

Figure 2. Nobiletin inhibits invasion and migration of cancer cells through multiple pathways. Nobiletin, a flavonoid compound, targets key pathways, including ERK-STAT, PI3K/AKT, Wnt/p38/NF-κB/Nrf2, JNK, AKT/GSK-3β/β-catenin and JAK2/STAT3. These pathways are crucial in regulating cancer cell behaviors, such as proliferation, survival and migration. By inhibiting the activation of these pathways, nobiletin reduces the downstream signaling involved in cancer cell invasion and metastasis. The diagram shows how nobiletin interferes with the interaction between cancer cells and the extracellular matrix, thereby preventing the detachment and migration of cancer cells towards blood vessels, a critical step in metastasis. ERK, extracellular signal-regulated kinase; STAT, signal transducer and activator of transcription; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2-related factor 2; JNK, c-Jun N-terminal kinase; GSK-3β, glycogen synthase kinase-3β; JAK2, Janus tyrosine kinase 2.

intracellular accumulation of chemotherapeutic agents, such as Adriamycin, in lung cancer cells (80). Regarding EMT-associated resistance, nobiletin reverses hypoxia-induced EMT by inactivating Notch-1 signaling and activating miR-200b, thereby restoring sensitivity to EGFR inhibitors in lung cancer models (45). For CSC-related resistance, nobiletin selectively targets colorectal CSCs by downregulating Wnt signaling and CD44v6 expression, reversing chemoresistance to FOX (54). Additionally, emerging evidence suggests nobiletin may counteract immune escape by modulating PI3Kγ signaling, which converts tumor-associated macrophages from an immunosuppressive to an immunostimulatory phenotype, thereby enhancing $CD8^+$ T-cell cytotoxicity (66).

Nobiletin inhibits tumor angiogenesis. Tumor angiogenesis, a critical process in the advancement of cancer, involves the development of new blood vessels to support the growing tumor (81). This process is initiated as a response to inadequate blood circulation, ensuring that the tumor receives the necessary oxygen and nutrients required for its expansion (82). Additionally, tumors release multiple angiogenic factors that stimulate the formation of these new blood vessels (83). Among these factors, vascular endothelial growth factor (VEGF) stands out as a notable contributor to the angiogenic activity associated with tumor growth (84). Kisacam (85) has shown that nobiletin exerts its anticancer effects in colon cancer cells through multiple pathways. Specifically, it inhibits AKT activity, which is crucial for cancer cell survival and angiogenesis, by targeting Bax, Bcl-2 and p70S6K at concentrations higher than 100, 500 and 1,000 μM, respectively. Nobiletin also modulates the levels of angiogenic factors VEGF and MMP-7, as well as cell cycle regulators 4EB1 and tubulin. Its ability to suppress AKT signaling and subsequently reduce angiogenic factors and regulators suggests that nobiletin could be an effective preventive agent against colon cancer progression by targeting these key pathways.

Additionally, STAT3 is involved in the regulation of various cellular processes, including cell survival, proliferation and differentiation (86). FAK is another key player in pancreatic cancer progression, as it contributes to cell adhesion, migration and invasion, which are critical steps in cancer metastasis. Inhibition of FAK can lead to compensatory activation of STAT3 signaling, which may promote cancer cell survival and resistance to treatment (87). Sp *et al* (88) identified a novel mechanism by which nobiletin inhibits tumor angiogenesis in estrogen receptor-positive (ER^+) breast cancer cells. The study revealed that nobiletin suppresses angiogenesis by targeting the Src/FAK/STAT3 signaling pathway through paxillin (PXN), leading to the inhibition of angiogenic markers and reduced cell migration and invasion. In another study by Sp *et al* (88), nobiletin was found to inhibit angiogenesis in ER^+ breast cancer cells by regulating the Src/FAK/STAT3 signaling pathway through PXN, which is a critical mediator of angiogenic activity. The research demonstrated that nobiletin treatment led to a marked reduction in angiogenesis markers, as evidenced by western blotting and quantitative PCR analysis, and further confirmed its anti-angiogenic activity in human umbilical vein endothelial cells. Additionally, electrophoretic mobility shift assay and chromatin immunoprecipitation (ChIP) assay results indicated that nobiletin inhibits STAT3/DNA binding activity and STAT3 binding to a novel binding site of the PXN gene promoter. Moreover, CD36, a protein with notable implications in tumor angiogenesis, is involved in the metabolism of fatty acids and thus influences the metastatic spread of cancer. A study demonstrated that nobiletin inhibits CD36-dependent tumor angiogenesis, migration, invasion and sphere formation through the CD36/STAT3/NF-κB signaling axis, providing a detailed mechanism of action (89). The study identified a g-interferon activation site element in the CD36 gene promoter that acts as a STAT3 binding site, confirmed by a ChIP assay, and showed that nobiletin also acts through the CD36/STAT3/NF-κB signaling axis. These findings suggest that nobiletin exerts its inhibitory effects on tumor angiogenesis by modulating CD36 signaling, which is crucial for tumor progression (90).

Yang *et al* (24) demonstrated that nobiletin exerted notable effects on the MAPK/NF-κB signaling pathway in the synovial membrane of rats with arthritis induced by collagen. The study showed that nobiletin treatment led to a marked reduction in angiogenesis and inflammatory infiltration within the synovial tissue, as well as decreased levels of key pro-inflammatory cytokines, such as IL-1β, monocyte chemotactic protein-1, IL-6 and tumor necrosis factor-α, in rats with collagen-induced arthritis. Additionally, the protein expression levels of p-p38, p-p65 and NF-κBα were downregulated by nobiletin, indicating its inhibitory role in the p38/NF-κB signaling pathway. Deng *et al* (91) reported a novel mechanism by which nobiletin exerts its anti-atherosclerotic effects,

involving activation of PINK1/Parkin-mediated mitophagy and suppression of the NLRP3 inflammasome signaling pathway. The study demonstrated that nobiletin modulates blood lipid metabolism and inflammation in mice, inhibiting arterial plaque formation. Notably, nobiletin was found to activate Parkin-ubiquitin kinase 1/Parkin-mediated mitophagy and suppress nucleotide-binding oligomerization domain 3 inflammasome production.

Nobiletin promotes tumor cell apoptosis. Apoptosis, a programmed cell death process, serves a pivotal role in maintaining tissue homeostasis and is frequently disrupted in cancer development. The induction of apoptosis in tumor cells by chemopreventative agents represents a promising strategy for cancer treatment (92). Previous studies have consistently shown that nobiletin treatment leads to a notable increase in apoptotic cell death, which is characterized by caspase activation (93), DNA fragmentation and cell membrane blebbing (94). For example, Zhang *et al* (95) revealed that nobiletin treatment led to a decrease in cell viability and cell membrane integrity, increased expression of hypoxia inducible factor 1α, cell cycle arrest in the G_1 phase and notable cell apoptosis in human choriocarcinoma JEG-3 cells. The protective effects of nobiletin were associated with its ability to modulate the p53 signaling pathway, as evidenced by the downregulation of the mRNA and protein levels of p53 and p21, and an upregulation of the Bcl-2/Bax mRNA and protein ratio in JEG-3 cells.

Nobiletin has been shown to cause the release of cytochrome *c* from the mitochondria, leading to the activation of caspase-9 and subsequent cleavage of caspase-3, which are critical executioner caspases in the apoptotic process (96). This effect is often accompanied by a decrease in the anti-apoptotic protein Bcl-2 and an increase in the pro-apoptotic protein Bax (97). For example, Li *et al* (98) demonstrated that nobiletin overcomes oxaliplatin resistance in colorectal cancer by simultaneously promoting apoptosis and suppressing the PI3K/AKT/mTOR axis. Co-treatment with nobiletin upregulated pro-apoptotic Bax and cleaved-caspase-3 while downregulating anti-apoptotic Bcl-2 in colorectal cancer cells (HCT116 and SW480), thereby amplifying oxaliplatin-induced cell death. Concurrently, nobiletin attenuated PI3K/AKT/mTOR signaling, a pathway frequently hyper-activated in drug-resistant tumors, leading to reduced cell survival and enhanced chemosensitivity. Additionally, nobiletin has been reported to trigger cancer cell apoptosis through caspase-3 activation and PARP cleavage in lung cancer cells (A549), and may serve as a key regulator in mitigating drug resistance by modulating various signaling pathways (Fig. 3), positioning it as a promising therapeutic agent for lung cancer treatment (25).

The molecular mechanisms underlying nobiletin-induced apoptosis appear to be multifaceted and involve the modulation of several key signaling pathways. One of the primary pathways affected by nobiletin is the mitochondrial apoptotic pathway (99). Zhang *et al* (100) demonstrated that nobiletin markedly inhibits cell proliferation and induces DNA damage in ovarian cancer cells in a dose-dependent manner, leading to apoptosis through the elevation of PARP levels. Additionally, the study revealed that nobiletin decreases mitochondrial membrane potential, triggers ROS generation and induces

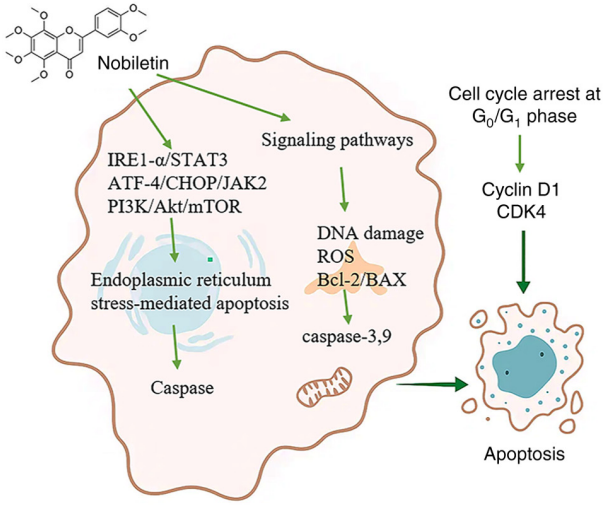

Figure 3. Mechanism of nobiletin-induced apoptosis in cancer cells. Nobiletin activates multiple signaling pathways, including IRE1-α/STAT3, ATF-4/CHOP/JAK2 and PI3K/AKT/mTOR, leading to endoplasmic reticulum stress-mediated apoptosis. It also causes DNA damage and increases ROS, activating Bcl-2/Bax and caspase-3, ultimately leading to cell death. Additionally, nobiletin arrests the cell cycle at the G_0/G_1 phase by downregulating cyclin D1 and CDK4, contributing to the inhibition of cell proliferation and promotion of apoptosis. ROS, reactive oxygen species; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; ATF-4, activating transcription factor 4; CHOP, C/EBP homology protein; JAK2, Janus tyrosine kinase 2; IRE1-α, inositol requiring enzyme 1-α; STAT3, signal transducer and activator of transcription 3; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; CDK, cyclin-dependent kinase.

autophagy, which collectively contribute to gasdermin D-mediated pyroptosis in human ovarian cancer cells. These findings suggest that nobiletin has a dual role in promoting apoptosis and triggering ROS-mediated pyroptosis through the regulation of autophagy. Luo *et al* (33) showed that nobiletin dose-dependently suppresses the proliferation of A549 cells and induces apoptosis, as evidenced by DNA fragment and comet assays. Additionally, flow cytometric analysis revealed that nobiletin causes cell cycle arrest at the G_2/M phase. Western blot analysis indicated that nobiletin pretreatment led to decreased Bcl-2 and increased Bax protein expression in A549 cells, which was associated with elevated p53 expression compared with that in the controls. The study also observed an overt inhibitory effect of nobiletin on tumor growth in a nude mouse xenograft model of lung cancer (A549 cells) *in vivo*. Chen *et al* (101) demonstrated that nobiletin suppresses gastric cancer by directly inhibiting ACLY, a key enzyme in fatty acid synthesis. This inhibition reduces neutral lipid accumulation and activates the IRE-1α/GRP78/CHOP-mediated endoplasmic reticulum stress pathway, leading to apoptosis. ACLY overexpression abolished these effects, confirming strict ACLY dependence. *In vivo*, nobiletin similarly suppressed tumor growth in a patient-derived xenograft (PDX) model of gastric cancer by disrupting *de novo* fatty acid synthesis, positioning it as a novel ACLY inhibitor for gastric cancer therapy.

Pathway crosstalk and context-dependent effects. While the preceding sections have delineated nobiletin's modulation of individual signaling cascades, its true therapeutic potential as

a multi-target agent lies in its ability to simultaneously influence the complex web of interconnected pathways that govern cancer cell behavior. One of the most clinically relevant interactions involves the PI3K/AKT and NF-κB pathways. AKT, a downstream effector of PI3K, can directly activate IκB kinase, leading to IκBα phosphorylation and degradation, thereby releasing NF-κB for nuclear translocation and transcriptional activation of pro-survival genes (98). Nobiletin's concurrent suppression of both PI3K/AKT phosphorylation and NF-κB nuclear translocation, observed in colorectal cancer and pancreatic cancer models, suggests that it may disrupt this positive feedback loop, thereby amplifying its apoptotic effects (53). The Wnt/β-catenin pathway, critical for stemness and proliferation, exhibits bidirectional crosstalk with the MAPK/ERK cascade. ERK can phosphorylate LDL receptor-related protein 6, a Wnt co-receptor, enhancing Wnt signaling, while β-catenin can transcriptionally regulate components of the MAPK pathway (102). In NSCLC, nobiletin was shown to simultaneously downregulate nuclear β-catenin (via miR-15-5p-mediated derepression of Wnt inhibitors) and suppress ERK phosphorylation, potentially disrupting this synergistic interaction to abrogate stem-like properties and colony formation (42).

Hierarchical regulation and upstream nodes. Emerging evidence suggests that nobiletin may target master upstream regulators that orchestrate multiple downstream pathways. For instance, the inhibition of PI3K by nobiletin, confirmed by molecular docking showing high-affinity binding to the PI3K active site, can simultaneously attenuate both AKT/mTOR and downstream NF-κB signaling, positioning PI3K as a hierarchical node in the multi-target action of nobiletin (58). Similarly, the direct binding of nobiletin to HSC70, a chaperone protein involved in stabilizing multiple oncogenic kinases, may represent an even more proximal mechanism that explains its broad-spectrum pathway inhibition (29).

The relative contribution of each pathway to the effects of nobiletin varies considerably by tumor type and genetic background. In KRAS-mutant pancreatic cancer, nobiletin appears to primarily exert its effects through MAPK pathway suppression and autophagy modulation, with NF-κB inhibition playing a secondary role (54). By contrast, in triple-negative breast cancer, the miR-200b/JAZF1/NF-κB axis emerges as the dominant mechanism, with PI3K/AKT modulation contributing to a lesser extent (14). In colorectal cancer, the HSC70 interaction and subsequent destabilization of multiple client proteins may represent the primary initiating event, with downstream pathway inhibition (including PI3K/AKT and Wnt/β-catenin) occurring as secondary consequences (54). These context-dependent differences likely reflect variations in pathway addiction, mutational landscape and tumor microenvironment composition across cancer types.

4. Structure-activity relationship of nobiletin

The multifaceted anticancer activities of nobiletin are intrinsically linked to its distinct chemical architecture. As a polymethoxyflavone, nobiletin features a hexamethoxy substitution pattern (5, 6, 7, 8, 3', 4') on its flavone backbone (103). This high degree of methoxylation is considered a critical determinant of its biological profile, contributing to enhanced metabolic stability and membrane permeability compared with the hydroxylated flavonoid counterparts. More importantly, specific structural features dictate its interaction with diverse molecular targets. The unique hydrophobic domain formed by the methoxy groups, particularly at the 5, 6, 7 and 8 positions, is likely a key factor enabling nobiletin to interact with and modulate a diverse array of molecular targets. This is reflected in its broad-spectrum inhibition of multiple pivotal oncogenic signaling pathways, including PI3K/AKT, MAPK/ERK and STAT3 (74).

Furthermore, the metabolism of nobiletin *in vivo* gives rise to several demethylated derivatives, which often exhibit altered and sometimes even potentiated biological activities (104). For instance, the metabolite 4'-demethylnobiletin exhibits enhanced inhibition against MMP-9 enzymatic activity compared with the parent compound, potentially through dual suppression of ERK1/2 and AKT phosphorylation (73). Similarly, 3',4'-didemethylnobiletin (3',4'-DDMN), a major colonic metabolite (105), demonstrates superior chemopreventative efficacy in colon carcinogenesis models and more potent anti-inflammatory effects by suppressing iNOS and COX-2 expression more effectively than nobiletin itself (106). Furthermore, 3',4'-DDMN has been shown to modulate the PI3K/Akt signaling pathway, which is crucial for cell survival and proliferation (107). The positioning of hydroxyl groups through specific demethylation, such as at the 4' position on the B-ring or the 5 position on the A-ring, appears critical for enhancing hydrogen-bonding interactions with target proteins or altering the compound's electronic distribution, thereby modulating biological activities, including anti-inflammatory responses, gelatinase inhibition and even neurite outgrowth (108). This nuanced structure-activity relationship not only deepens the understanding of the polypharmacology of nobiletin but also provides a rational basis for the design of novel flavonoid-based anticancer agents with optimized efficacy and selectivity.

5. Challenges and future prospects for using nobiletin in cancer treatment

Despite the promising findings on the antitumor effects of nobiletin, there are several challenges that must be addressed before it can be effectively utilized in clinical cancer treatment (Fig. 4). One of the primary challenges is the low bioavailability and solubility of nobiletin, which can limit its absorption and distribution in the body (109). Ongoing research is focused on optimizing the delivery and bioavailability of nobiletin to maximize its antitumor potential while minimizing any adverse effects (110). Hattori *et al* (111) demonstrated that the nobiletin/geranic acid (CAGE) sample exhibited 20-times higher bioavailability compared with oral administration of nobiletin crystal. This suggests that CAGE markedly enhanced the solubility of nobiletin and its transdermal absorption *in vitro* and *in vivo*. The translation of these findings into clinical practice could notably advance the management of cancer and improve patient outcomes. Previous research indicates that nobiletin and atorvastatin together have a synergistic impact on preventing colon cancer (112). The study found that this combination markedly hindered colon cancer

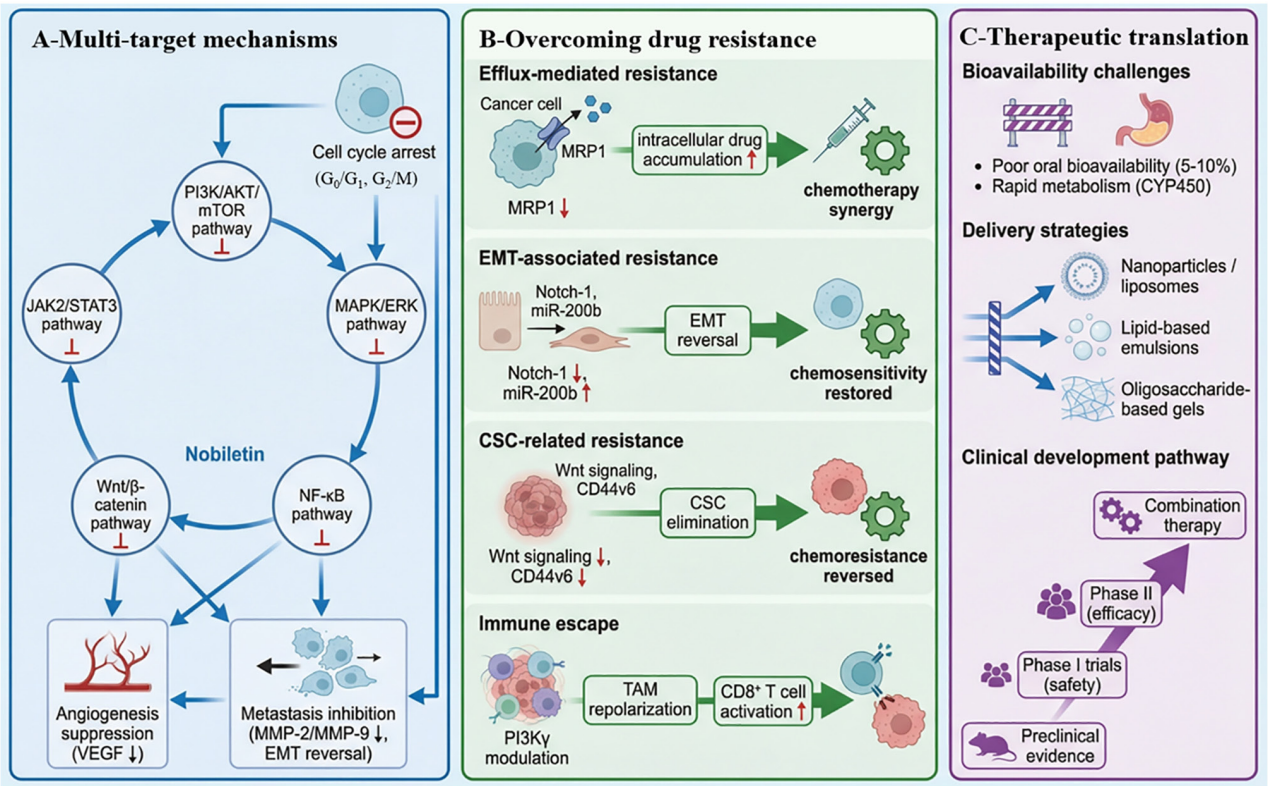

Figure 4. Overview of nobiletin's multi-target mechanisms, drug resistance reversal and translational strategies in cancer therapy. (A) Multi-target mechanisms: Nobiletin simultaneously inhibits multiple oncogenic signaling pathways (PI3K/AKT/mTOR, MAPK/ERK, NF-κB, Wnt/β-catenin and JAK2/STAT3), leading to downstream effects, including cell cycle arrest, apoptosis induction, metastasis inhibition and angiogenesis suppression. (B) Overcoming drug resistance: Nobiletin targets four distinct resistance mechanisms-efflux-mediated resistance (via MRP1 downregulation), EMT-associated resistance (via Notch-1/miR-200b axis), cancer stem cell-related resistance (via Wnt/CD44v6 suppression) and immune escape (via PI3Kγ-mediated TAM repolarization). (C) Therapeutic translation: Despite bioavailability challenges (5-10% oral bioavailability and rapid CYP450 metabolism), advanced delivery systems (nanoparticles, lipid emulsions and oligosaccharide-based gels) are being developed to facilitate clinical translation toward phase I/II trials and combination therapy. PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; ERK, extracellular signal-regulated kinase; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor-κB; JAK2, Janus tyrosine kinase 2; STAT3, signal transducer and activator of transcription 3; miR, microRNA; TAM, tumor-associated macrophage; EMT, epithelial-mesenchymal transition; CYP450, cytochrome p450; MRP1, multidrug resistance-associated protein 1; MMP, matrix metalloproteinase; CSC, cancer stem cell.

cell proliferation and triggered anti-inflammatory reactions in macrophages. The joint treatment also caused considerable cell cycle arrest and apoptosis in colon cancer cells. In a rat model of azoxymethane-induced colon carcinogenesis, oral administration of nobiletin and atorvastatin decreased tumor occurrence and number (113). Notably, the co-treatment at reduced doses was more effective than higher doses of either compound alone, highlighting a promising approach for colon cancer prevention. Additionally, the complexity of cancer biology also means that the effects of nobiletin may vary notably between different cancer types and stages, necessitating tailored approaches for specific cancers.

While the anticancer potential of nobiletin is supported by a substantial body of preclinical research, a critical appraisal of the existing evidence reveals several limitations that warrant consideration. First, there is a marked overreliance on *in vitro* studies. For example, the widely cited mechanisms of SREBP1/ACLY modulation in gastric cancer and miR-200b regulation in breast cancer were established primarily in 2D cell culture systems, with limited validation in physiologically relevant 3D models or patient-derived xenografts (14,27). Second, the field lacks standardized dosing regimens, and there is a notable disconnect between *in vitro* and *in vivo* concentrations. Concentrations of nobiletin shown to be effective *in vitro* (typically 20-100 μM) far exceed the peak plasma concentrations achievable *in vivo* ($\leq$5 μM in rodent models after oral administration), raising questions about whether the proposed mechanisms are operative at physiologically relevant doses (29,109). Third, key mechanistic findings await independent validation. The HSC70 targeting mechanism in colon cancer and the CD36/STAT3/NF-κB anti-angiogenic axis have each been reported by single research groups and have not been corroborated by independent laboratories (90). Beyond these preclinical limitations, notable gaps remain in the clinical translation of nobiletin. To date, no completed or ongoing clinical trials have specifically evaluated nobiletin as an anticancer monotherapy or in combination with conventional agents. However, several clinical studies assessing *Citrus* flavonoid mixtures containing nobiletin have provided preliminary insights into its safety and pharmacokinetic profile in humans (114). These data indicate that nobiletin has an oral bioavailability of 5-10%, with predominant distribution in the liver, kidneys and gastrointestinal tract. It is metabolized primarily by hepatic cytochrome p450 (CYP450) enzymes, notably CYP1A1 and CYP3A4 (115), and is excreted in feces and urine as demethylated metabolites and glucuronide conjugates. To overcome these translational barriers, ongoing

research is exploring advanced formulation strategies. For example, Sun *et al* (116) demonstrated that incorporating nobiletin into oligosaccharide-based pectin gels, using stachyose and α-dextran as sucrose replacers, enhanced its delivery and bioavailability, suggesting that prebiotic gelling agents may improve antitumor efficacy. Similarly, Wei *et al* (117) developed triacylglycerol-bergamot oil emulsions to improve nobiletin solubilization and absorption; the 3:1 corn oil-to-bergamot oil formulation showed the highest bioavailability, highlighting the potential of lipid-based delivery systems.

6. Conclusions

In conclusion, the present review consolidates evidence establishing nobiletin as a multifaceted anticancer agent with potent activity across various cancer types. The ability of nobiletin to concurrently modulate proliferation, apoptosis, metastasis and angiogenesis through key signaling pathways underpins its therapeutic value. Notably, the capacity of nobiletin to sensitize cancer cells to conventional chemotherapy and overcome drug resistance emerges as a particularly promising attribute. Future research should prioritize the development of advanced delivery systems to overcome bioavailability limitations and the design of well-controlled clinical trials to validate these promising preclinical findings. The integration of nobiletin into combination regimens represents a compelling strategy for next-generation cancer therapy.

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Availability of data and materials

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Authors' contributions

YZ designed the review article, researched references and wrote the majority of the manuscript. QL researched references and wrote the manuscript. WY and BH revised and edited the manuscript. JP and BY revised the manuscript and acquired funding. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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