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Targeting oncogenic signaling pathways in lung Cancer: The emerging role of nobiletin, a flavonoid from citrus peel

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ABSTRACT

Lung cancer continues to have a high incidence rate, exhibiting a five-year overall survival percentage of merely 18.6 %. Despite advancements in conventional therapeutic approaches, drug resistance and treatment-associated toxicities remain major challenges. Recent research has focused on plant-derived molecules as promising therapeutic alternatives due to their low toxicity and significant anticancer effects. Nobiletin, a flavonoid enriched with polymethoxylated groups present in citrus peel, has exhibited diverse therapeutic properties, including antioxidants, immunomodulatory, neuroprotective, and antitumor activities. This review highlights anti-lung cancer activity of nobiletin by modulating critical tumor-promoting signaling pathways thereby suppressing cancer cell proliferation, infiltration, and metastasis. Most importantly, nobiletin triggers cancer cell apoptosis by caspase-3 activation and poly-(ADP-ribose) polymerase cleavage and functions as a key regulator in mitigating drug resistance by regulating various signaling pathways. However, its medical use is constrained by poor aqueous solubility and limited bioavailability. To mitigate these challenges, advanced drug delivery systems have been explored, including polymeric nanoparticles, nano-dispersed solids, micelles, and nano emulsions. Nanotechnology-based formulations such as self-micro emulsifying drug delivery systems, chitosan-based microemulsions, and liposomal encapsulation have significantly improved the nobiletin's stability, solubility, and targeted delivery. These approaches enhance its therapeutic efficacy, positioning nobiletin as a potential therapeutic strategy for lung cancer treatment.

1. Overview of lung cancer

Lung cancer remains a significant global concern, exhibiting the second-highest occurrence rate in man following prostate cancer and in female individuals, following breast cancer (de Groot et al., 2018; Thandra et al., 2021). According to the American Cancer Society (2025) (American Cancer Society, 2025) and the Centers for Disease Control and Prevention (2024), lung cancer is the second most diagnosed cancer in U.S. men (following prostate cancer) and in women (following breast cancer) (Siegel et al., 2024). On a global scale, however, data from GLOBOCAN 2020 show that lung cancer is the second most frequently diagnosed cancer overall, after breast cancer. Among men worldwide, lung cancer is often the most diagnosed, while in women, it typically ranks lower—often third or fourth—behind breast cancer, which

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remains the most prevalent (Sung et al., 2021). Unfortunately, lung cancer progression leads to a poor prognosis, reflected in a five-year survival rate of just 18.6 %, a stark contrast to colorectal (64.5 %), breast (89.6 %), and prostate cancers (98.2 %) (Nojiri et al., 2017). This low survival rate is largely due to most lung cancer patients identified at advanced or metastatic phases. According to the World Health Organization (WHO), lung cancer represented 12.4 % of newly diagnosed cancer cases in 2022 and caused 18.7 % of all cancer deaths worldwide (WHO, 2024). Lung cancer is primarily categorized into two types: small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). SCLC, which makes up about 20 % of cases, exhibits the highest degree of aggressiveness and rapid growth, strongly linked to cigarette smoking. SCLC is characterized by rapid metastasis and is often diagnosed at advanced stages. Histologically, SCLC cells are smaller than those in NSCLC. SCLC typically originates centrally in the lungs, often near the hilum or major airways, and tends to grow along the bronchi (Chu et al., 2011). In contrast, NSCLC frequently arises in the peripheral regions of the lungs and is more likely to present as a peripheral mass (Zappa & Mousa, 2016). Non-small-cell lung cancer (NSCLC) is further categorized into several subtypes based on pathological characteristics, including squamous cell carcinoma, adenocarcinoma, and less common forms like large cell carcinoma (Li et al., 2013). Despite advances in treatment options in recent years, the prognosis for NSCLC patients remains poor. Presently, treatment strategies are primarily guided by histopathological classification. However, this approach has limitations—it cannot reliably predict tumor progression, likelihood of metastasis, or treatment response. Moreover, patients with NSCLC who share similar clinical profiles and tumor stages often experience divergent clinical outcomes (Herbst et al., 2008). Emerging research has shown that different histological types of lung cancer exhibit distinct molecular features, such as variations in mutational patterns, DNA copy number changes, and gene expression profiles (Charkiewicz et al., 2017; Faruki et al., 2017; Gentles et al., 2015). These findings have led to growing interest in classifying cancers based on their molecular genetics, which may offer more precise insights for diagnosis and therapy. SCLC generally arises centrally within the lungs and invades the walls of the major bronchi. Its rapid proliferation and early metastasis pose significant treatment challenges, emphasizing the importance of early detection and smoking cessation for prevention (Cersosimo, 2002). SCLC's rapid proliferation and early metastasis contribute to poor prognosis, making early detection extremely challenging. Although diagnosis often occurs at advanced stages due to subtle initial symptoms, emerging research into circulating tumor cells (CTCs) and liquid biopsy technologies offers potential for earlier identification (Hamilton et al., 2016). Specific genetic alterations, notably the inactivation of *TP53* and *RB1*, as well as amplification of *MYC* family genes, are nearly universal in SCLC and could serve as early molecular biomarkers (George et al., 2015; Peifer et al., 2012). Environmental exposures, particularly heavy tobacco use and occupational contact with carcinogens like radon and asbestos, have been strongly implicated in disease development (Couraud et al., 2012), reinforcing the critical role of smoking cessation and public health interventions in prevention. In lung adenocarcinoma (LUAD), key driver mutations include those in KRAS (Kirsten rat sarcoma viral oncogene homolog), EGFR (epidermal growth factor receptor), TP53 (tumor protein p53), KEAP1 (Kelch-like ECH-associated protein 1), STK11 (serine/threonine kinase 11, also known as LKB1), and NF1 (neurofibromin 1) (Pao & Hutchinson, 2012). For lung squamous cell carcinoma (LUSC), common mutations are found in TP53 and CDKN2A. In SCLC, frequent mutations involve RB1 and TP53, with some tumors exhibiting overexpression of MYC family oncogenes such as MYC, MYCL, and MYCN (Saab et al., 2020; Skoulidis & Heymach, 2019). As research on targeted therapies advances, efforts to classify lung cancers based on these mutations have gained momentum (Hung & Chirieac, 2020). MET amplification and MET exon 14 skipping mutations were identified in a notable proportion of both our patient cohort and the TCGA lung adenocarcinoma dataset ("Comprehensive molecular profiling of lung adenocarcinoma," 2014). When considering all potentially targetable genomic alterations responsive to the MET/ALK/ROS1 tyrosine kinase inhibitor crizotinib, approximately 10 % of lung adenocarcinomas exhibit actionable alterations in ALK, ROS1, or MET. The rarity of concurrent driver mutations involving multiple genes—such as ALK, RET, ROS1, and MET—is likely due to two main factors: (1) the inherently low incidence of these genetic alterations in lung cancer (Pan et al., 2014); and (2) changes in clinical practice that have promoted more comprehensive and systematic testing for such mutations (Hirsch et al., 2016).

The treatment modalities (Fig. 1) for lung cancer involve surgical procedures, cytotoxic chemotherapy, immune-based therapies, radiotherapeutic techniques, and precision-targeted agents. Classification is critically important in lung cancer because it directly guides treatment decisions (Hirsch et al., 2017; Travis et al., 2015). By identifying the specific type of lung cancer—whether it's small-cell or non-small-cell, and further subtypes like adenocarcinoma or squamous cell carcinoma—as well as molecular features (such as EGFR mutations or ALK rearrangements) (Lindeman et al., 2013; Mok et al., 2009), clinicians can select the most effective therapies for each patient. For example, certain genetic mutations may make tumors responsive to targeted therapies or immune checkpoint inhibitors, while others may require chemotherapy or radiotherapy (Garon et al., 2015; Hanna et al., 2017). Without proper classification, patients might receive treatments that are less effective or more toxic (Reck et al., 2013). In short, accurate classification enables personalized treatment plans, improves outcomes, and reduces unnecessary side effects (Reck et al., 2013). Immunotherapy, particularly immune checkpoint inhibitors (ICIs) such as nivolumab, atezolizumab, and pembrolizumab has emerged in the last two decades as a promising treatment approach (Jain et al., 2018). In spite of medical advancements, lung cancer persists as the foremost cause of cancer-related deaths, with around 1.8 million deaths reported globally in 2020 (Cao et al., 2021). Several factors contribute to the limited effectiveness and severe side effects of current therapies, including the toxicity of drugs like carboplatin, cisplatin, oxaliplatin, and docetaxel. Beyond immunotherapies, radiotherapies, and chemotherapies, therapeutic resistance is a critical issue in lung cancer treatment, often resulting in tumor relapse, metastasis, and reduced patient survival. This resistance can be either intrinsic or acquired and involves several well-characterized mechanisms. One major factor is the emergence of secondary genetic mutations, such as the EGFR T790M mutation, which can restore signaling through pathways that were initially blocked by targeted drugs (Yu et al., 2013). Tumors may also activate bypass signaling pathways, for example, through MET or HER2 amplification—that allow them to maintain growth and survival despite treatment (Gainor et al., 2013). Additionally, phenotypic transformation, such as the shift from non-small-cell lung cancer (NSCLC) to small-cell lung cancer (SCLC), can occur under therapeutic pressure, making the disease more aggressive and less responsive to previously effective treatments (Yu et al., 2013). Other mechanisms include the overexpression of drug efflux pumps like P-glycoprotein, which actively remove chemotherapeutic agents from cancer cells, and alterations in the tumor microenvironment that reduce immune cell infiltration or increase immunosuppressive signaling, diminishing the effectiveness of immunotherapy. Furthermore, defects in apoptotic pathways—such as the overexpression of anti-apoptotic proteins—enable tumor cells to evade cell death (Holohan et al., 2013). Understanding these resistance mechanisms is essential for developing more durable and effective treatment strategies in lung cancer. Beyond immunotherapies, radiotherapies, and chemotherapies, therapeutic resistance is a critical issue, leading to the re-emergence of cancer, metastasis, and shorter patient lifespans (Vasan et al., 2019). This has fueled interest in exploring alternative treatments, particularly plant-derived metabolites, which have shown promise in inhibiting tumor cell metabolism and proliferation (Luo et al., 2019). Recent advancements in pharmaceutical technology have addressed safety concerns by improving the bioavailability

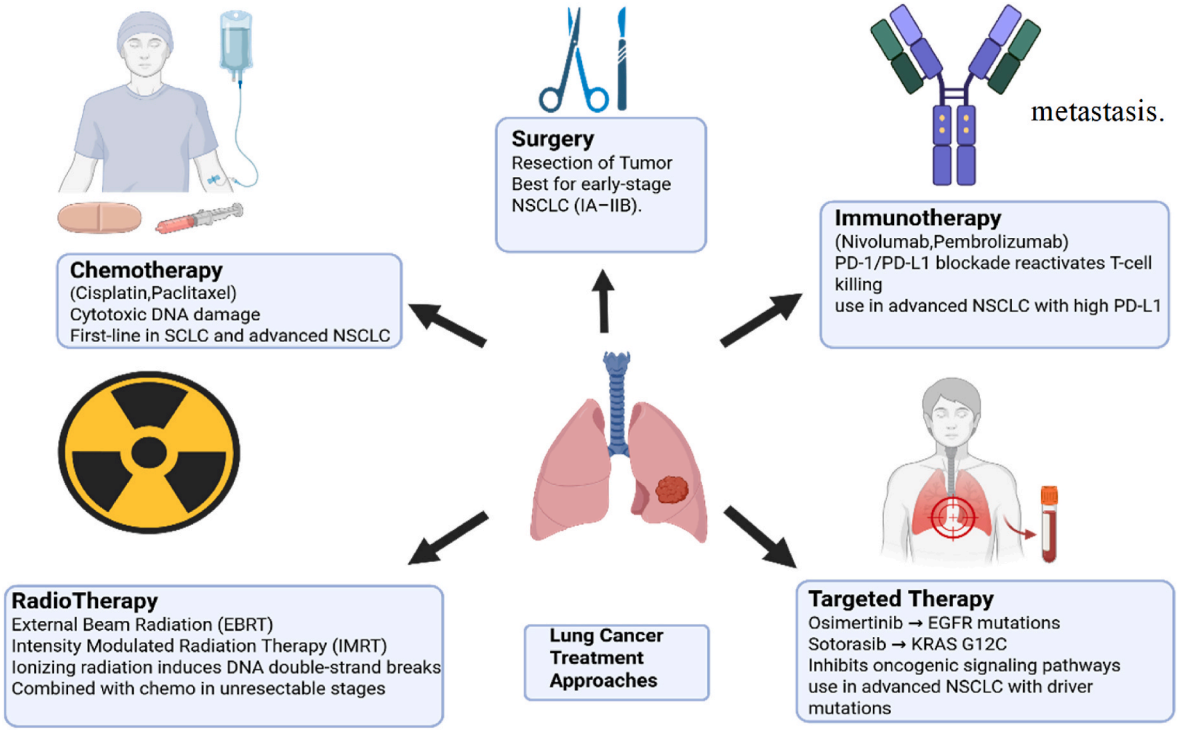

Fig. 1. Therapeutic Approaches of Lung cancer treatment.

and delivery of these compounds, making plant metabolites a viable option for lung cancer treatment. With low cytotoxicity and high effectiveness, these agents offer a hopeful alternative in the ongoing fight against lung cancer (Salehi et al., 2020). Compounds such as curcumin (from *Curcuma longa*), resveratrol (from grapes), berberine (from *Berberis* species), and quercetin (found in many fruits and vegetables) have demonstrated anti-cancer properties by targeting pathways such as PI3K/Akt/mTOR, AMPK, and NF-κB (Choudhari et al., 2019; Memarzia et al., 2023). Recent advancements in pharmaceutical technology, including nanoparticle-based drug delivery and structural modification to improve bioavailability, have helped address previous safety and efficacy concerns, making plant metabolites increasingly viable candidates for lung cancer therapy. With low cytotoxicity and high effectiveness, these agents offer a hopeful alternative in the ongoing fight against lung cancer (Salehi et al., 2020).

Lung cancer treatment involves multiple modalities, each customized based on the type and stage of disease progression. Standard treatment modalities include surgical resection, chemotherapy, immunotherapy, radiotherapy, and targeted therapeutic strategies, often used in combination to improve patient outcomes. Surgical excision is the preferred treatment for early-stage non-small cell lung cancer (NSCLC) when the tumor is localized and there is no distant metastasis. Chemotherapy is a key therapeutic approach in the management of lung cancer, particularly for SCLC and advanced NSCLC. It involves cytotoxic agents that target and eliminate rapidly dividing cancer cells. Lung cancer treatment has been revolutionized by immunotherapy, which enhances the immune system's ability to target and eliminate malignant cells. It shows significant efficacy in NSCLC with elevated PD-L1 expression and certain (Society, 2024). In treating localized lung cancer, brain metastases, and for palliative purposes, radiation therapy remains a critical therapeutic approach. It employs high-energy radiation to target and destroy cancer cells. Targeted therapies aim at molecular changes within lung cancer cells, making them more precise than chemotherapy. They are particularly effective in genetically driven NSCLC (Dempke et al., 2010; Mohiuddin & Choi, 2005).

2. Overview of nobiletin

Nobiletin (NOB), classified as a polymethoxylated flavonoid, is a major phytochemical constituent of citrus peels, particularly from tangerines, oranges, and lemons (Keshtkar et al., 2019; Nakajima & Ohizumi, 2019). Nobiletin has a molecular weight of 402.399 g/mol, with the chemical formula $C_{21}H_{22}O_8$ (Yarım et al., 2017). Due to its broad spectrum of potential therapeutic effects, nobiletin has gained significant attention. Studies have highlighted its diverse biological and therapeutic effects mostly on preclinical animal model and *in vitro* assay (Fig. 2), such as anti-diabetic (Keshtkar et al., 2019), anti-oxidant (Zhang et al., 2019), osteoprotective (Lin et al., 2019), anti-inflammatory (Tsuboi et al., 2020), hepatoprotective (Yuk et al., 2018), cardioprotective (Youn et al., 2019), and neuroprotective activities (Nohara et al., 2019), anti-microbial (Yao et al., 2012), anti-allergic (Onishi et al., 2014), anti-obesity (Lee et al., 2013) Alzheimer's disease (Kimura et al., 2018), in addition to its anticancer properties (Kisacam, 2023). Studies on the biotransformation of nobiletin have identified three main mono-demethylated metabolites: 6-desmethylnobiletin, 7-desmethylnobiletin, and 4′-desmethylnobiletin, with a ratio of 1:8.2:2.8. Among these, 7-desmethylnobiletin showed the highest enzymatic activity, primarily mediated by the cytochrome P450 enzyme CYP3A4 (Koga et al., 2011). In comparison, 6-desmethylnobiletin displayed reduced activity, whereas the development of 4′-desmethylnobiletin involved enzymes CYP1A1, CYP1A2, and CYP1B1, which showed high activity (R. W. Li, Theriault, et al., 2006). Due to nobiletin's rapid metabolism and due to low bioavailability, Various approaches have been investigated to enhance its bioavailability and therapeutic effectiveness. One such approach involves the use of ionic liquid CAGE (a combination of choline and geranic acid). Studies have demonstrated that CAGE significantly improves nobiletin's bioavailability, potentially through enhanced absorption *via* hydrogen bonding interactions. Research performed both *in vitro* and *in vivo* demonstrate that CAGE enhances bioavailability by up to 20-fold and significantly improves transdermal delivery efficiency. The reported enhancement of bioavailability by up to 20-fold using choline and geranic acid (CAGE)

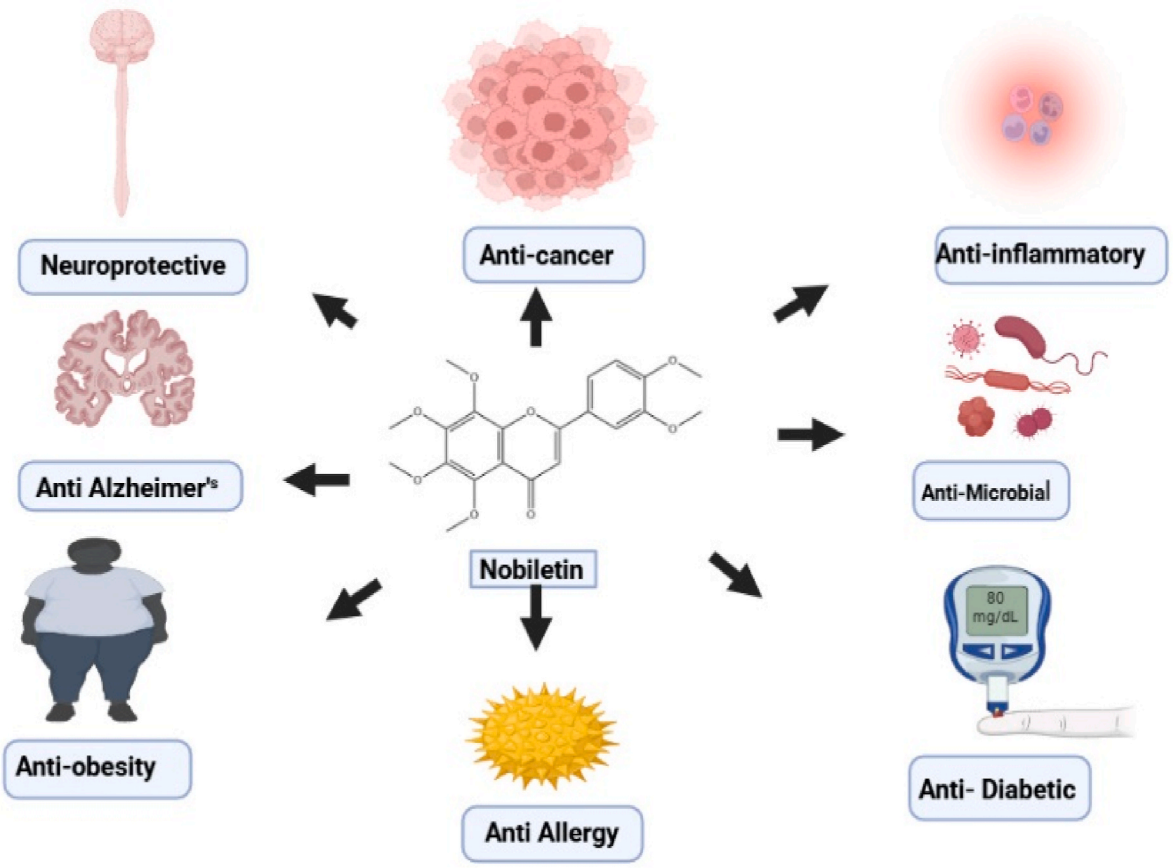

Fig. 2. Overview of the therapeutic actions of nobiletin.

for transdermal delivery was observed in rat as an animal model. In a study investigating the transdermal administration of nobiletin—a flavonoid with poor water solubility—CAGE significantly improved its solubility and facilitated its absorption through the skin. The *in vivo* experiments demonstrated that the area under the concentration-time curve (AUC) for nobiletin was substantially increased when delivered transdermal with CAGE compared to oral administration of nobiletin crystals. This enhancement in bioavailability was accompanied by a notable hypoglycemic effect, indicating the therapeutic potential of this delivery method in rats (Hattori et al., 2019). Another strategy for improving nobiletin's delivery is through the use of plant exine capsules, which have a high loading capacity for nobiletin (around 770 mg/g) and provide sustained release, making them a promising delivery method (Wu et al., 2020). Additionally, nanotechnology-based solutions, such as nobiletin-loaded nano emulsions, have emerged as an effective means to increase the therapeutic effects of nobiletin. For example, micelle formulations with small particle sizes (124 nm), high loading efficiency (7.6 %), and Substantial encapsulation (76.34 %) have been applied to treat bone loss (Wu et al., 2020).

3. Synergistic effect of nobiletin with chemotherapy agents

Tumor progression in lung cancer is caused by diverse cellular interactions, which renders single-agent therapies largely ineffective. Combination drug therapy, therefore, has gained the status of a gold-standard strategy of chemotherapy, carrying certain inherent advantages: simultaneous targeting of principal molecular pathways; lower doses of less toxic drugs that could be better tolerated by patients (van den Bent et al., 2020). Synergistic effects of drug combinations have been a focus of investigation in biomedical research, especially toward the treatment of cancer (Martínez-García et al., 2022). Uesato et al. discussed Nobiletin in combination with chemotherapeutic agents paclitaxel and carboplatin exerted a synergistic inhibition against human non-small-cell lung carcinoma (NSCLC) cell lines A549 and H460 proliferation whereas, in antitumor activity assays, it was shown that this combination inhibited subcutaneous growth in nude mice of the A549 tumor xenograft (Leirdal & Sioud, 2000). According to Kok-Tong Tan et al. paclitaxel (PTX) in combination with 5-demethylnobiletin (5-DMN) synergistically inhibited CL1–5 lung cancer cell proliferation, as evidenced by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) and propidium iodide assays. These low-dose combination treatments reduced cell viability in CL1–5 cells, leading to a concurrent increase in apoptosis. Moreover, this combination therapy remarkably inhibits tumor progression in a nude mouse xenograft model (Goodwin et al., 2018). Yu-Qian et al. reported that nobiletin and vorinostat synergistically inhibited SCLC H82 cell proliferation by inducing apoptosis and autophagic cell death. This combination suppressed tumor growth in xenograft models by inhibiting the PI3K-AKT-mTOR pathway and promoting Beclin 1-mediated autophagy (Wen et al., 2020). Wenzhe Ma et al. found that nobiletin enhanced chemosensitivity in ABCB1(ATP-Binding Cassette Subfamily B Member 1)-overexpressing A2780/T and A549/T cells (Paclitaxel-resistant A549 lung cancer cells), significantly reversing MDR (Multidrug Resistance) to paclitaxel and other drugs. This impact was connected to the inhibition of the AKT/ERK/Nrf2 pathway, reducing Nrf2 expression and AKT/ERK phosphorylation (Wen et al., 2018). Edy Meiyanto et al. reported that nobiletin enhanced the cytotoxic effect of doxorubicin in MCF-7 cells but not in T47D cells. The combination of 15 μmol/L nobiletin and 200 nM doxorubicin exhibited strong synergism in inducing apoptosis in MCF-7 cells (Mason et al., 2012). According to Sen-Ling et al., nobiletin inhibits the Nrf2/AKT/ERK pathways, leading to increased paclitaxel accumulation in tumors and effectively reversing paclitaxel resistance in a

multidrug-resistant xenograft cancer model (Chinnaiyan et al., 2013). In our previous studies, Feng Sen et al. found that nobiletin enhanced the accumulation of chemotherapeutic agents in ABCB1-overexpressing cancer cells by inhibiting P-gp. Additionally, it suppressed the Nrf2/AKT/ERK pathways, thereby enhancing the anticancer effects of paclitaxel in drug-resistant cancer cells (D. J. Ma, Galanis, et al., 2015). Novel approaches are urgently required to enhance the effectiveness and minimize the side effects of cancer treatment medications. In this direction, chemotherapy drugs combined with natural compounds are being investigated for their potential benefits. Treatment of HT-29 human colon cancer cells with 4′-DMN (36 μmol/L) or atorvastatin (18 μmol/L) alone inhibited growth by 25.89 % and 20.89 %, respectively. The inhibition rates were, however, significantly upregulated to 53.84 % when atorvastatin (7.2 μmol/L) and 4′-DMN (14.4 μmol/L) were used in combination, mediated by initiation of cellular apoptosis through upregulation of p53 and cleaved caspase-3 with subsequent greater suppression of cancer cells (Wick et al., 2016). In a similar manner, the combined effects of paclitaxel, carboplatin, and nobiletin synergistically inhibited the proliferation of A549 and H460 lung cancer cell lines. At increased concentrations, however, of nobiletin, paclitaxel, and carboplatin, a decrease in the proportion of apoptotic cells was seen (Galanis et al., 2005). In an alternative combination therapy wherein the concurrent administration of sorafenib and nobiletin markedly enhanced apoptotic cell death and G0/G1 cell cycle arrest for PC-3 prostate cancer cells, this ability was equal to elevated expression of Bax, Rb1, and CDKN1A (p21) relative to monotherapy with either agent. In a mouse xenograft model using adriamycin-resistant A549 NSCLC cells, a combination of adriamycin (10 mg/kg) and nobiletin (40 mg/kg) reduced tumor volume by over 84 % compared to controls. Tumor size was measured with calipers over a 2–4-week period. This suggests nobiletin can significantly enhance the effectiveness of adriamycin in resistant lung cancer (Lassen et al., 2013). Nobiletin was shown to inhibit the Akt/GSK3/β-catenin/MYCN signaling pathway and knock down MDR1 expression, enhancing adriamycin influx. Moreover, it triggered apoptosis with enhanced activation of caspase-3, PARP cleavage, and sub-G1-phase cell death compared to adriamycin alone (Dasgupta & Gutmann, 2003). A study by Zhang et al. demonstrated that MYCN is overexpressed in NSCLC tumor tissues and cell lines, and this overexpression correlates with a more invasive tumor phenotype and poor prognosis. *In vitro* experiments showed that MYCN promotes NSCLC cell proliferation, while its knockdown leads to cell cycle arrest at the G0/G1 phase (Grunblatt et al., 2020). The synergistic effect of Nobiletin (NOB) with various chemotherapy agents has shown promising potential in enhancing the effectiveness of cancer treatments as shown in Table 1. These findings highlight the potential of Nobiletin as an adjunct to chemotherapy, offering a dual advantage of enhanced therapeutic efficacy and reduced toxicity. The use of Nobiletin in combination with chemotherapy agents could provide a novel approach to overcome the limitations of single-agent therapies, paving the way for more effective cancer treatments with fewer side effects.

4. Safety evaluation, cytotoxicity, and potential adverse reactions

In toxicity studies, nobiletin has shown promising safety profiles. A 90-day chronic exposure study evaluating oral toxicity revealed that nobiletin was non-mutagenic, non-genotoxic, and caused no toxicity or Side effects observed at doses up to 540 mg/kg/day (Nakajima et al., 2020). Additionally, studies involving nobiletin combined with other polymethoxylated flavones confirmed their non-genotoxicity *in vitro* (Delaney et al., 2001). A study demonstrated that nobiletin could trigger apoptosis in cancer cells but had a low toxicity towards normal cells (M. Ashrafizadeh, Farhood, et al., 2020). Other studies, such as those by Wu et al. showed no substantial change in body weight was observed between the nobiletin-treated and control groups, suggesting the absence of overt toxicity (Wu et al., 2006). Similarly, Abe et al. reported no cytotoxicity in adipocytes treated with 50 μmol/L of nobiletin for 24 and 48 h (Abe et al., 2023). A 28-day study on immunogenicity found that long-term exposure to a nobiletin-polymethoxylated flavones mixture at high doses slightly inhibited natural killer (NK) cell activity, without affecting humoral immunity (Delaney et al., 2002). These results imply that nobiletin is a potent therapeutic agent with minimal toxicity at the recommended dosage levels as shown in Table 2.

5. Signaling mechanisms in lung cancer

Lung cancer develops due to disruptions in normal cellular functions, with factors such as oxidative stress, genetic mutations, and alterations in signaling pathways playing key roles (Yuan et al., 2022). Among these, receptor tyrosine kinases (RTKs) such as EGFR, MET, ALK, and ROS1 have been extensively studied for their role in driving carcinogenesis (Abolfathi et al., 2023). These transmembrane receptors activate intracellular signaling cascades that upregulate the pro-survival oncogenes, including XIAP, Mcl-1, survivin, and Bcl-2 (Iksen et al., 2021). Additionally, RTK signaling inhibits pro-apoptotic gene expression, such as FOXO, thereby facilitating cell proliferation, survival, and tumor progression (Alam et al., 2023). RTK signaling pathways, such as PI3K/AKT and MAPK/ERK, promote tumor cell survival by inhibiting

Table 1
Synergistic effects of nobiletin with chemotherapeutic agents in cancer models.

Study	Combination	Cancer Model	Main Outcome	Mechanism Involved
Uesato et al. (Uesato et al., 2014)	Nobiletin + Paclitaxel + Carboplatin	NSCLC (A549, H460 cells, mouse xenografts)	Synergistic inhibition of tumor proliferation and growth	Not specified
Kok-Tong Tan et al. (Tan et al., 2019)	5-DMN + Paclitaxel	CL1–5 lung cancer cells, mouse xenografts	Increased apoptosis and reduced tumor progression	Activation of apoptosis pathways
Yu-Qian et al. (Li et al., 2023)	Nobiletin + Vorinostat	SCLC (H82 cells, xenograft models)	Induced apoptosis and autophagic death, inhibited tumor growth	PI3K-AKT-mTOR inhibition, Beclin 1-mediated autophagy
Wenzhe Ma et al. (W. Ma, Galanis, et al., 2015)	Nobiletin	A2780/T, A549/T cells (MDR models)	Reversed MDR to paclitaxel and other drugs	Inhibition of AKT/ERK/Nrf2 pathways
Edy Meiyanto et al. (Meiyanto et al., 2012)	Nobiletin + Doxorubicin	MCF-7 breast cancer cells	Strong synergism in apoptosis induction	Not specified
Sen-Ling et al. (S.-L. Feng, Tian, et al., 2020)	Nobiletin + Paclitaxel	MDR lung cancer models	Increased paclitaxel accumulation and reversed resistance	Inhibition of Nrf2/AKT/ERK pathways
Feng Sen et al. (W. Ma, Galanis, et al., 2015)	Nobiletin + Chemotherapeutic agents	ABCB1-overexpressing cancer cells	Enhanced chemosensitivity	P-gp inhibition, Nrf2/AKT/ERK suppression
Xian Wu et al. (Wu et al., 2018)	4′-DMN + Atorvastatin	HT-29 colon cancer cells	Enhanced apoptosis and growth suppression	p53 and cleaved caspase-3 upregulation
Yu-Qian et al. (Guney Eskiler et al., 2019)	Nobiletin + Sorafenib	PC-3 prostate cancer cells	Enhanced apoptosis, G0/G1 arrest	Bax, Rb1, p21 elevation
Sen-Ling et al. (Moon et al., 2018)	Nobiletin + Adriamycin	NSCLC (parental and drug-resistant A549 cells)	Strong tumor volume reduction, reversal of MDR	Akt/GSK3/β-catenin/MYCN pathway inhibition, MDR1 downregulation

Table 2
Toxicity profile, formulation types, and conclusions on nobiletin (NOB).

Toxicity profile (ref)	Designates/specifies	Dosage	Formulation type	Outcomes	Conclusions
Cytotoxicity (Miyamoto et al., 2008)	HT-29 human colon cancer cells	100 μmol/L	Nobiletin (NOB) solution	No effect on cell proliferation was noted.	Nobiletin shows low cytotoxicity in normal colon cells, indicating potential safety for long-term use.
Long - term animaltoxicity (Miyamoto et al., 2008)	ICR mice (long-term feeding)	100 ppm	Nobiletin solution	After 17 weeks on a NOB-supplemented diet, mice showed no significant changes in body or liver weight were detected, and NOB intake was not associated with toxicity.	Researchers suggest NOB has a favorable toxicity profile in chronic exposure models.
Prevention of apoptosis (S. Li, Wang, et al., 2006)	Male Sprague Dawley rats (cadmium injury model)	200 mg/kg body mass	Nobiletin solution	NOB decreased Neurocellular death induced by cadmium exposure. It inhibited the Akt/mTOR signaling pathway, highlighting its protective role against metal-induced neurotoxicity.	Researchers highlight NOB's neuroprotective and anti-apoptotic potential under oxidative stress conditions.
Cytotoxicity (Abe et al., 2018)	HaCaT human keratinocyte cells	100 μmol/L	NOB solution	At a concentration of 100 μmol/L, NOB displayed significant growth inhibition; however, it triggered autophagy instead of apoptosis in HaCaT cells.	Authors noted potential anti-proliferative effects *via* autophagy, suggesting selective cytotoxicity.
Cytotoxicity (Huang et al., 2019)	H1299 human lung cancer cells	5–80 μg/ml	Zein nanoparticles (NPs) encapsulating NOB	Cytotoxicity was observed in a concentration-dependent manner	Encapsulation enhanced cellular uptake and anticancer activity according to researchers.
Cytotoxicity (Gan et al., 2024)	RAW264.7 murine macrophage cells	Up to 37.2 μmol/L	Solution of NOB and NOB nanoemulsion	Cell viability was greater than 95 % at the highest concentration.	Researchers concluded NOB nanoemulsions are biocompatible and suitable for drug delivery.

FOXO transcription factors, which normally induce pro-apoptotic genes. When activated, AKT phosphorylates FOXO proteins, leading to their nuclear exclusion and degradation, thereby blocking apoptosis and aiding tumor progression (Tzivion et al., 2011). Oncogenic signaling pathways, such as RAF/MEK/ERK, PI3K/Akt/mTOR, and JAK/STAT, play a pivotal role in lung cancer, significantly contributing to tumor growth and progression. The RAF/MEK/ERK pathway, often activated by mutations in KRAS or other oncogenes, regulates cell proliferation and survival, promoting lung cancer growth (Montagut & Settleman, 2009). The PI3K/Akt/mTOR pathway is another critical driver, involved in cellular processes like metabolism, growth, and survival. Dysregulation of this pathway is frequently observed in non-small cell lung cancer (NSCLC) and correlates with resistance to therapies and poor prognosis (Sanaei et al., 2022). Additionally, the JAK/STAT pathway, which mediates immune responses and inflammation, is commonly activated in lung cancer, driving tumor progression and metastasis (Zhao et al., 2024). Together, these signaling pathways contribute to the malignant phenotype of lung cancer by enhancing tumor cell survival, growth, and invasion. Oncogenic signaling pathways such as RAF/MEK/ERK, PI3K/Akt/mTOR, and JAK/STAT, are pivotal in lung cancer, playing a key contribution to tumor growth and advancement as shown in Fig. 3, Table 3.

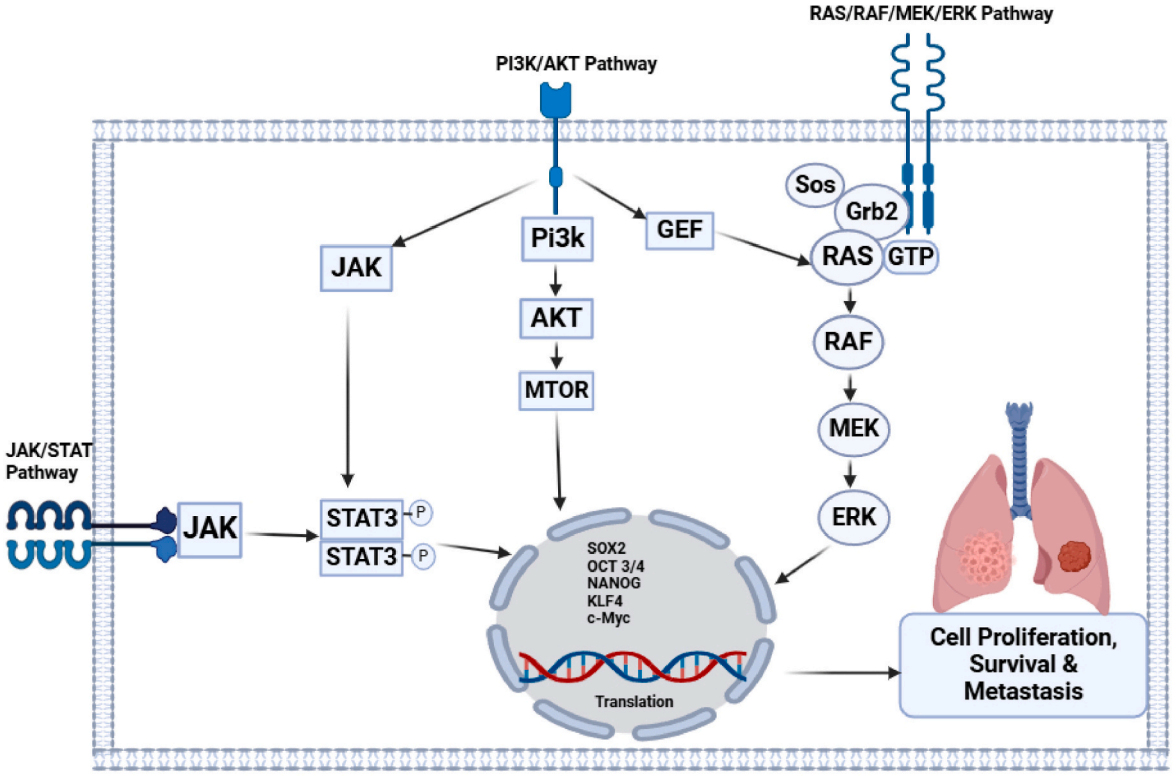

Fig. 3. Various cell signaling pathways involved in lung cancer progression.

Table: 3
Signaling pathways targeted by nobiletin and the cellular processes they regulate.

S. N	Signaling pathways	Cellular processes in which Signaling pathways regulate
1.	PI3K/Akt/ mTOR	Cell proliferation, apoptosis, angiogenesis (Sanaei et al., 2022)
2.	ARP-2/SIRT1/ AMPK	Growth inhibition and apoptosis (X. Wang, Lu, et al., 2021)
3.	Src/FAK/STAT3	Angiogenesis (Sp et al., 2017)
4.	STAT	Cell survival (Hu et al., 2021)
5.	p53	Cell survival, proliferation, senescence and apoptosis (Niazi et al., 2018)
6.	ERK (MAP kinase)	Control of gene transcription, cellular division, cell survival, apoptotic pathways, metabolic function, differentiation, and cellular motility (Lee et al., 2020)
7.	PI3K	Cell division, cellular expansion, survival, metabolic alterations, cell movement, and polarization (Lee et al., 2020)

5.1. RAS-RAF-MEK-ERK signaling cascade

The RAF/MEK/ERK signaling cascade is a central modulator of cell growth, apoptosis, and senescence (Henriques et al., 2015; Ritt et al., 2016). This pathway is implicated in both NSCLC and SCLC (Cristea & Sage, 2016). Upon activation by cell membrane receptors like EGFR and FGFR, RAS, a guanosine triphosphatase (GTPase), activates downstream networks, including the RAS/RAF/MEK/ERK, PI3K/Akt/mTOR, and Ral-GEF pathways (Iksen et al., 2021). Experimental elucidation of this cascade often utilizes Western blotting for phosphorylation status of RAF, MEK, and ERK, immunoprecipitation assays for studying RAF dimerization, and mass spectrometry to identify post-translational modifications. The Grb2/SOS complex becomes activated by growth factor binding to RTKs and subsequently activates RAS (Alam et al., 2023). The activation of RAS triggers a conformational shift which permits GTP binding and recruitment of RAF isoforms (A-RAF, RAF-1 or B-RAF) to the cell membrane. At this site, RAF is dimerized and overcomes its self-inhibitory regulation, forming a complex with additional Molecular chaperones like heat shock protein 90 (HSP90) (Iksen et al., 2021). An activated RAF then goes on to phosphorylate and activate MEK1 and MEK2, leading to the phosphorylation of ERK1 and ERK2. Once activated, ERK migrates to the nucleus and orchestrates the activation of gene expression, including genes such as c-Fos, c-Jun, c-Myc, CREB, MSK, and ELK-1 which regulate cell cycle progression and proliferation.

5.2. PI3K-akt-mTOR signaling cascade

The PI3K/Akt/mTOR pathway plays a significant contribution to lung cancer initiation and advancement of lung cancer. This signaling cascade is typically triggered upon the interaction of growth factors with RTKs, such as VEGFR, HER2, IGFR, EGFR, and PDGFR. Upon ligand binding, the p85 regulatory subunit of PI3K associates with the RTK, catalyzing the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3) by the catalytic subunit p110 (Iksen et al., 2021). PIP3 acts as a second messenger, recruiting and activating Akt through phosphorylation by PDK1 and mTOR complex-2. Experimental studies often employ phospho-specific antibodies in Western blotting to detect activated Akt and mTOR, CRISPR-Cas9 gene editing to knock out PTEN, and flow cytometry to assess downstream cell survival and proliferation changes (Tan, 2020). Once triggered, Akt dissociates from the membrane into the cytoplasm, where it influences mTOR complex-1, 4EBP1, and p70S6K, promoting cellular growth, survival, and proliferation. Akt also facilitates tumor progression through the upregulation of anti-apoptotic protein expression like XIAP and Bcl-2 while downregulating the expression of pro-apoptotic factors (Papadimitrakopoulou, 2012). In normal cells, the tumor suppressor PTEN negatively modulates this pathway through the dephosphorylation of PIP3, thereby preventing Akt activation. PTEN serves as a negative regulator; its loss—detected *via* Sanger sequencing or PCR-based genotyping—results in unrestrained Akt activation (Okudela et al., 2007; Yamamoto et al., 2008). However, in NSCLC, this pathway frequently becomes dysregulated due to PTEN inactivation or mutations and PIK3CA overexpression (Kawano et al., 2007). Variations in the helical and kinase segments of PIK3CA enhance the activity of the p110 catalytic subunit, further contributing to lung cancer progression (Samuels et al., 2004).

5.3. JAK-STAT signaling cascade

The signaling system which consists of Janus kinases (tyrosine kinase-2 and JAK1-3) and signal transducers and activators of transcription (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) is called JAK-STAT signaling. JAK behaves constitutively, acting upon transmembrane receptors, the interleukin-6 receptor, and erythropoietin receptor, granulocyte colony-stimulating factor receptor (Thomas et al., 2015). Each of the JAK family of proteins has Four distinct functional regions: the FERM domain for receptor attachment, the SH2 domain for recognition of phosphorylated tyrosines, the JH1 domain for the phosphorylation activity, and the JH2 domain for negative regulation (Hu et al., 2021). These STAT proteins possess specialized protein interaction Domains, with an N-terminal region responsible for dimerization, a coiled-coil domain for regulation, a DNA-recognizing domain, an SH2 domain able to recognize phosphorylated tyrosines, a structural adaptability domain, and a transcription-activation domain. Typical methodologies include electrophoretic mobility shift assays (EMSA) to study DNA binding of STAT dimers, Western blotting for phospho-STAT detection, and chromatin immunoprecipitation (ChIP)-qPCR to confirm STAT target gene binding (Hu et al., 2021). The pathway triggered upon ligand binding to the receptor, causing dimerization of receptors and conformational changes in the receptor that activate JAK proteins. Phosphorylation of tyrosine residues on the receptor by activated JAKs form docking sites for STAT binding. Upon recruitment, phosphorylated STAT dissociate from receptor, dimerize through their SH2 domains, allowing them to migrate to the nucleus, where they initiate gene activation programs involved in cell growth, differentiation, inflammation, and apoptosis (Khanna et al., 2015). Negative regulators exist for control of this signaling pathway. For instance, PIAS214 inhibits the activity of phosphorylated STATs in a DNA-independent manner, preventing the nuclear entry of STATs and thereby blocking gene activation. Protein tyrosine phosphatases (PTPs) dephosphorylate the receptor, JAK, and STAT, thus switching off the signaling pathway altogether (Lu et al., 2018). Additionally, Suppressor of Cytokine Signaling (SOCS) proteins Prevent STAT from interacting with the receptor and enhance its breakdown *via* ubiquitin-mediated pathways, ensuring proper regulation of the signaling process (Espert et al., 2005). Negative regulators like PIAS and SOCS proteins are studied through overexpression models in cell culture and ubiquitination assays.

5.4. PD-1/PD-L1 signaling cascade

The programmed-cell-death protein-1/programmed-cell-death-ligand-1 (PD-1/PD-L1) Signaling cascade contributes significantly to the immune evasion of lung cancer cells, actively hindering immune detection (Qin et al., 2019). PD-1 and PD-L1 are found on various immune compartments, including activated T lymphocytes, B lymphocytes, and antigen-presenting cells. Functional characterization typically involves flow cytometry (for surface PD-1/PD-L1 expression), co-culture assays with T cells and tumor cells to assess immune suppression, and ELISA to measure cytokine release (e.g., IFN-γ, IL-2) (Ghosh et al., 2021; Han et al., 2020). PD-L1 is also upregulated in many cancers, allowing these tumor cells to take benefits of the PD-1/PD-L1-mediated immunosuppression. When PD-L1 interacts to

PD-1 on activated T lymphocytes, these interactions lead to intracellular signaling to phosphorylate PD-1 and inhibit the PI3K/Akt pathway within T cells (Ohaegbulam et al., 2015). Ligand-receptor binding leads to SHP2-mediated deactivation of the PI3K/Akt pathway, verified experimentally *via* co-immunoprecipitation assays and reporter assays (luciferase under PI3K-responsive promoters). This inhibits the expression of pro-survival molecules like Bcl-xL, which in turn results in T cell programmed cell death, enabling cancer cells to evade immune detection (Jiang et al., 2019). With the understanding of these complex signaling mechanisms, researchers can begin to develop rational therapies that will interrupt these oncogenic pathways and allow for better treatment modalities for lung cancer.

6. Nobiletin's therapeutic impact on lung cancer

Nobiletin's potential impacts treatments for lung cancer as shown in Table 4. The epidermal growth factor receptor, a classic receptor tyrosine kinase, features an extracellular portion that binds ligands, including Epidermal growth factor (EGF), transforming growth factor-alpha (TGF-α), and an intracellular domain with a high concentration of tyrosine residues (Nurwidya et al., 2016). A transmembrane spacer links the two domains. Ligand binding leads to dimerization and a subsequent conformational change, which leads to intracellular autophosphorylation of tyrosine (Antonicelli et al., 2013). This event initiates signal transduction through RAS/RAF/MEK/ERK, PI3K/Akt/mTOR, or STAT pathways, regulating cell proliferation and preventing apoptosis (Bethune et al., 2010). After characterization of EGFR mutations in NSCLC tumor, Small-molecule tyrosine kinase inhibitors have been designed for use in tumors with mutations of EGFR. The most common mutation in NSCLC is the replacement of leucine with arginine at codon 858 in exon 21 (L858R) and deletions in exon 19 mutations (Scagliotti et al., 2020). These pathways harbor innumerable receptors, signaling, and effector proteins that could act as potential therapeutic targets to treat lung cancer (Boolell et al., 2015). However, despite these developments, the current treatments still have limited efficacy in controlling lung cancer. Recent studies have highlighted the anticancer activities of nobiletin, which inhibits proliferation of cancer cells, spread and migration (Huang et al., 2022). In the perspective of precision oncology, cuproptosis-related lncRNAs may present favorable therapeutic avenues for nobiletin concerning lung adenocarcinomas (Ma et al., 2022). Furthermore, research has revealed that nobiletin dose-dependently inhibited NSCLC cell proliferation (Luo et al., 2008). The consequences also involve the suppression of the Notch-1 pathway and an increase in miR-200 b expression; thus, suppressing hypoxia-driven epithelial-mesenchymal transition in H1299 cells (Gao et al., 2015). Suppression of the Notch-1 signaling pathway has been shown to inhibit hypoxia-induced epithelial-mesenchymal transition (EMT) in cancer cells by modulating microRNA expression. Specifically, downregulation of Notch-1 leads to the upregulation of miR-200 b, a microRNA that suppresses EMT by targeting transcription factors such as ZEB1 and ZEB2, which are responsible for repressing *E*-cadherin expression. In H1299 non-small cell lung cancer cells, this mechanism contributes to the inhibition of hypoxia-driven EMT, highlighting the interplay between signaling pathways and non-coding RNAs in regulating tumor cell plasticity (Patraşcu et al., 2025; Xiao et al., 2021) Nobiletin also induces apoptosis in tumor cells *via* caspase-3 activation and poly (ADP-ribose) polymerase (PARP) cleavage, leading to the suppression of tumor cell growth (Xiao et al., 2009). Nobiletin may inhibit Ras activity and the MEK/ERK pathway, probably through a Ca^{2+} sensitive PKC-dependent mechanism, hence suppressing the proliferation of C6 cells within the parameters of Ras-action and MEK/ERK signaling pathway (Aoki et al., 2013). Nobiletin facilitated the antiproliferative and triggering of apoptosis by oxaliplatin in colorectal carcinoma (CRC) cells *via* modulation of the PI3K/Akt/mTOR pathway. Considering that PI3K/Akt/mTOR signaling have been documented in essential roles in the development of different cancers, this modulation may hold employed therapeutic value in many other cancers (N. Li, Zhang, et al., 2019). Nobiletin elicits antitumor effects by acting as an EGFR antagonist, inhibiting phosphorylation of EGFR, and thus inhibiting downstream signaling cascades (Bole-Feysot et al., 1998). JAK2 is another very potent molecule that contributes to a plethora of signaling pathways that contribute to tumorigenesis, phosphorylated by nobiletin (Wang et al., 2017). Thereby, nobiletin interferes in the EGFR/JAK2 signaling axis and its interaction with proteins like STAT3 that influence PD-L1 regulation. All these will contribute significantly to tumor metastasis and immune evasion (Wu et al., 2017). The EGFR phosphorylation is in turn causing activation of many downstream targets, an event effectively suppressed by nobiletin in exerting its cancer-progression role through into the blockage of the EGFR/JAK2/STAT3-axis and inhibition of PD-L1 expression in NSCLC cells (Sp et al., 2021). By inhibiting PD-L1, nobiletin would prevent PD-1 binding, counteracting immune suppression, and aiding in blocking tumor immune resistance against CD8 cytotoxic T cells (Pardoll, 2012). Suppression of PD-L1 levels was also demonstrated in A549, H292, and H460 NSCLC cells by nobiletin treatment. By targeting STAT3-mediated regulation of PD-L1 expression, nobiletin inhibited tumor progression and counteracted immunosuppressive effects through p53-independent downregulation of PD-L1 (Sp et al., 2021). Drug resistance can be seen as a hindrance in effective cancer treatment. Moon and colleagues asserted that nobiletin enhances adriamycin chemoresistance by the regulation of the AKT/GSK3β/β-catenin/MYCN/MRP1 pathway in non-small cell lung cancer cells (Moon et al., 2018). Nobiletin may likely also serve as a regulator of the tumor microenvironment, making it a good candidate for NSCLC immunotherapy (Sp et al., 2021). More recently, the nobiletin derivative compound 29 d, which was designed to increase solubility and thus antitumor activity of Nobiletin has demonstrated to enhance paclitaxel (PTX) enrichment in lung cancer cells (A549) through inhibition of P-glycoprotein (P-gp) activity (S. Feng, Zhou, et al., 2020). Meanwhile, some studies suggest that Nrf2/PI3K/Akt, and ERK signaling may be responsible for the observed chemoresistance

Table 4
Impact of nobiletin on lung cancer therapy.

Nobiletin dose	Cell line	Results	Ref.
20, 40, and 80 μmol/L 600 μg	A549 and H460	G1 phase cell cycle arrest enhances cancer cell sensitivity to paclitaxel and carboplatin.	Uesato et al. (2014)
40 μg/ml	A549	Nobiletin can trigger p53-induced cell cycle arrest followed by apoptotic cell death are mediated by the regulation of the Bax: Bcl-2 protein ratio.	Luo et al. (2008)
20 μmol/L	A549 and H1299	Inhibited hypoxia-induced epithelial-mesenchymal transition, and migration in H1299. This outcome was linked to a decreased expression of Notch-1 and Jagged1/2, and downregulation of their downstream target genes, Hey-1 and Hes-1.	Da et al. (2016)
50 μmol/L (NOB) (0.5 μmol/L) (ADR)	A549	The co-administration of nobiletin (NOB) and adriamycin (ADR) significantly potentiated apoptosis in A549 cells, as indicated by increased caspase-3 activation, enhanced PARP cleavage, and an elevated sub-G1 cell population compared to ADR monotherapy.	Moon et al. (2018)
100 & 200 μmol/L	A549, H292 and H460	Nobiletin reduced PD-L1 expression through targeting the EGFR/JAK2/STAT3 signaling pathway, independent of p53 status. Furthermore, miR-197 is key in modulating STAT3 and PD-L1 expression, thus strengthening immune defenses against tumor cells.	Sp et al. (2021)

(Wesołowska et al., 2012). The findings concerning Nrf2 suppression by compound 29 d through downregulation of ERK and inhibition of the PI3K/Akt pathway support the proposal that NOB and its derivatives could enhance chemotherapy sensitivity in cancer cells *via* distinct molecular pathways. In parallel, the ability of NOB to boost PTX's antitumor activity was investigated. NOB was shown to enhances PTX-stimulated apoptosis in multidrug-resistant lung cancer cells by downregulating Nrf2 and suppressing Akt and ERK phosphorylation (S. Feng, Zhou, et al., 2020). In terms of its superior advantages in anti-cancer activities, Compound 29 d exhibited any notable influence on P-gp in contrast to NOB. Although this is the case, the mechanisms illustrated by these differences are duly noted as being more distant from one another that further studies are warranted in this regard. The *in vitro* experiments, nonetheless, obviously displayed that NOB induces apoptosis in cancer cells *via* a reduction of cell viability and survival in a dose-dependent effect that does not interfere with the cell cycle. Besides, the combination of NOB and cisplatin inhibited thyroid cancer cell viability better than either drug administered alone. NOB preferentially kills cancer cells and spares normal cells; hence, it has a good chance of being developed as a candidate for chemo-oncology purposes (Sousa et al., 2020). Lung cancer cell lines resistant to P-gp also exhibit expression of multidrug resistance-associated protein 1 (MRP1), also known as ABCC1. MRP1 stands as one among the very crucial molecules constituting the different chemoresistance mechanisms that have imputations of MYCN. Fibrous sheath-interacting protein 1 (FSIP1) through the upregulation of MRP1, promotes further chemoresistance while oncosuppressor miR-7 works against MRP1 whilst simultaneously sensitizing breast cancer cells to chemotherapy (Sousa et al., 2020). NOB also compromises MRP1 activity along with preventing adriamycin accumulation within cancer cells, resulting in apoptosis (Moon et al., 2018). The relationship between MYCN and MRP1 (ABCC1) has been well-documented in neuroblastoma studies. Research shows that MYCN directly regulates MRP1 expression by binding to E-box elements in the MRP1 promoter, leading to increased transcription and protein production. This upregulation enhances the drug efflux function of MRP1, contributing to chemoresistance in neuroblastoma cells (Norris et al., 1997). Additionally, broader analyses of ATP-binding cassette (ABC) transporter genes across various cancer cell lines have demonstrated that MYCN expression correlates with several ABC transporters, including ABCC1. In neuroblastoma, the induction of MYCN resulted in elevating ABCC1 protein levels, while its suppression led to a reduction in ABCC1 expression, indicating that MYCN significantly influences multidrug resistance mechanisms (Porro et al., 2010; Weiss et al., 1997). However, while these findings are established in neuroblastoma, the regulatory relationship between MYCN and MRP1 in other cancers, such as non-small cell lung cancer (NSCLC), remain unclear and warrants further investigation. The studies highlighted in Table 4 collectively suggest that nobiletin has a broad range of effects in lung cancer, including cell cycle regulation, apoptosis induction, inhibition of cancer cell migration, and immune evasion modulation. The doses of nobiletin used in these studies vary, with higher doses (e.g., 100 μmol/L) targeting immune modulation and lower doses (e.g., 20 μmol/L) focusing on cell cycle arrest and migration inhibition. Given nobiletin's ability to enhance chemotherapeutic efficacy and reduce immune evasion, it holds potential as an adjunct therapy in lung cancer, especially when used in combination with standard chemotherapies like paclitaxel, carboplatin, and adriamycin. These findings highlight the importance of further investigating nobiletin's mechanisms of action to optimize its use in clinical settings. The variability in the outcomes of the studies also underscores the need for dose optimization and a more detailed understanding of how nobiletin interacts with various molecular pathways in different lung cancer cell types.

7. Overcoming drug resistance mechanisms with nobiletin

Tumor cells develop resistance to anticancer therapies and radiation through dynamic processes, including genetic mutations and other adaptive mechanisms. Certain oncogenic mediators within these cells enhance their survival while reducing their responsiveness to therapy, ultimately leading to decreased treatment effectiveness (Seluanov et al., 2018). This section explores how nobiletin regulates the expression and activity of key factors involved in drug resistance, highlighting its potential role in improving therapeutic outcomes.

7.1. Nobiletin's role in overcoming drug resistance via the NF-κB pathway

NF-κB is a vital element for cell life and death and is one of the decisive factors in drug resistance. NF-κB promotes increased expression of Cell survival-promoting genes, initiates DNA damage repair mechanisms, and upregulates the expression of multiple genes associated with multidrug resistance, including the multidrug resistance 1 (MDR1) gene) (J. Chen, Creed, et al., 2014). The downregulation of NF-κB is facilitated by the inhibitory protein IκB, and the inhibition of this mechanism can thus be regarded as a valuable approach for sensitizing cancer cells toward being killed by anti-cancer drugs and radiotherapy. Other plant-derived compounds recognized for suppressing NF-κB activity in neoplastic cells include Nobiletin, which might reverse drug resistance through modulation of the NF-κB signaling pathway. Kim and co-workers studied the impact of NOB on the IκB/NF-κB signaling axis and drug resistance triggered by docetaxel in TNBC cells. Nobiletin increased IκB levels by inducing RORs. The increase in IκB levels in cancer cells resulted in degradation of NF-κB and reduced its activity. Nobiletin decreased tumor growth as well as cell viability *in vitro* and *in vivo*; moreover, it demonstrated a synergistic inhibitory effect when combined with docetaxel. The inhibition of NF-κB signaling is crucial for halting the proliferation of MIAPaCa-2 pancreatic cancer, prostate cancer cell lines PC-3 and DU-145, as well as ovarian cancer cell lines OVCAR-3 and CP70, alongside the effects of nobiletin (Chen et al., 2015; Jiang et al., 2020). In prostate cancer, this inhibition in turn facilitates androgen antagonism (Kim et al., 2022). Another possible mechanism of action for nobiletin involves suppression of NF-κB by inducing tumor-suppressive microRNA miR-200 b. By inhibiting TGF-β-activated kinase 1 (TAK1), a key regulator of NF-κB signaling, the microRNA miR-200 b serves to suppress this pathway. Accordingly, Wang et al. showed that NOB induces breast cancer cells through the Increase in expression of miR-200 b and inhibition of the TAK1/NF-κB axis (J. G. Wang, Jian, et al., 2021).

7.2. The PI3K/Akt pathway

Activation of apoptosis favors angiogenesis, metastasis, and protective autophagy (Collins et al., 2018). This activity can, nevertheless, be inhibited by the tumor suppressor protein PTEN. Mutations PTEN in tumor cells often come together with downregulation of the protein, hence compounding PI3K/Akt signaling (Narayanankutty et al., 2023). This pathway, in turn, triggered by the emission of the growth factors transforming growth factor (TGF)-β, epidermal growth factor (EGF), and insulin-like growth factor-1 (IGF-1) (Stefani et al., 2021; Yazdan et al., 2024). PI3K/Akt signaling induces phosphorylation that serves to activate mTOR, STAT3, and many other drug resistance mediators (Park et al., 2020). A pool of phosphorylated PI3K and Akt can increase the expression of survival-promoting proteins such as Bcl-2 and NF-κB and matrix metalloproteinases, thereby enabling Cancer cells' ability to evade programmed cell death, invasion and metastasis, and treatment (Muscella et al., 2021). Therefore, one therapeutic avenue would be inhibiting or disrupting this pathway to extinguish the viability of cancer cells, inhibit angiogenesis and metastasis, and restore sensitivity to chemotherapy and radiotherapy (Xu et al., 2020). Nobiletin, a natural compound, has shown the potential to target PI3K-Akt pathways to restore drug resistance in malignancy. The PI3K-Akt pathway was suppressed by nobiletin, thereby reducing cell survival, while increasing apoptosis in human ovarian cancer cells (Chen et al., 2015). NOB

inhibited the proliferation of MDA-MB-468 breast cancer cells and triggered apoptosis by inhibiting Akt, where, for the HER2+ SK-BR-3 and hormone receptor-positive MCF-7 breast cancer cell types, nobiletin acted independent of Akt (C. Chen, Creed, et al., 2014). It was shown that nobiletin has the potential to increase the susceptibility of colon cancer cells to oxaliplatin by inhibiting the PI3K/Akt signaling pathway. Stimulation of PI3K/Akt/mTOR signaling by IGF-1 countered the inhibitory apoptotic effects exerted by nobiletin, confirming that this pathway is indeed a mediator of drug resistance. This also suggests a role for this pathway in mediating apoptosis and chemo sensitization of colorectal cancer cells (N. Li, Zhang, et al., 2019). In addition, nobiletin decreased bladder cancer cell viability and triggered apoptosis by inhibiting the PI3K/Akt pathway (Goan et al., 2019). Taken together, through its suppression of the PI3K/Akt pathway, there is a suggestion that nobiletin could be connected to potential drug resistance in many cancers (Bentires-Alj et al., 2003; Seluanov et al., 2018). PD-L1 plays a significant role in promoting tumor progression by not only inhibiting immune responses but also fostering angiogenesis and facilitating metastasis. It achieves this by interacting with various signaling pathways, including the PI3K/Akt pathway and NF-κB, which are known to contribute to drug resistance (Tang et al., 2022). In the context of nobiletin, research suggests that it may modulate these processes, potentially reducing PD-L1 expression and disrupting its ability to enhance angiogenesis and metastasis, thus inhibiting tumor progression (Chen et al., 2020; Naugler & Karin, 2008)."Through PD-L1 and the promotion of angiogenesis and metastasis, it supports tumor progression (Milad Ashrafizadeh, Farhood, et al., 2020; Yu et al., 2021). Besides, it positively crosstalk with other drug resistance pathways like the PI3K/Akt pathway and NF-κB.

7.3. STAT3

Upon stimulation by certain ligands and receptors including EGFR and cytokines like IL-1 and IL-6, cancer cells activate STAT3 toward further epigenetic modulation (Li et al., 2020; Wang et al., 2016). Inhibition of STAT3, either upstream or downstream, has triggered cell death in cancer cells and reduced drug resistance and evasion (Mohan et al., 2022; Zou et al., 2020). Nobiletin is known to inhibit malignant cell STAT3 activation, thereby implicating inhibition of the EGFR/-JAK2/STAT3 signaling pathway in the NSCLC cells (Sp et al., 2021). Inhibition of Akt by nobiletin is thought to decrease phosphorylation of STAT3 (Wei et al., 2019). STAT3 downmodulation also reduces chemotherapy resistance for prostate cancer cells (Ma et al., 2020). Thus, the inhibition of STAT3 seems to be another important mechanism to induce drug sensitivity, and nobiletin could represent a natural inhibitor in targeting this pathway.

7.4. P-glycoprotein

A multidrug-resistance pump that is encoded by the ABCB1 gene and is essential for multidrug resistance is called P-glycoprotein 1. Resistance due to overexpression of ABCB1(Engle & Kumar, 2022). P-glycoprotein pumps drugs out of the cell. Essentially, overexpression and function of P-glycoprotein in cancer cells lower the anti-cancer drug intracellular concentration, thus reducing the effectiveness (Kimura et al., 2007). P-glycoprotein antagonists have been proposed as one approach to reverse drug resistance in cancer (W. Feng, Zhang, et al., 2020). Some of the compounds Isolated from plant sources have also been investigated, and proposed, for their ability to reverse multidrug resistance due to inhibition of P-glycoprotein (Efferth et al., 2021). The anti-cancer activities of nobiletin were shown in studies conducted by Ma et al. to modulate the transport activity of P-glycoprotein and thereby reverse multidrug resistance. The feasibility of nobiletin in reversing drug resistance was studied using chemotherapy agents' paclitaxel, docetaxel, and doxorubicin in ABCB1-overexpressing ovarian A2780/T and colorectal carcinoma Caco-2 cell lines. The result indicates that the accumulation of chemotherapy drugs was lower in ABCB1-overexpressing A2780/T cells compared to A2780 cells and other types of cancer. In contrast, in the presence of nobiletin, A2780/T was seen to accumulate more drugs during chemotherapy. Strangely enough, nobiletin did not alter ABCB1 expression in cancer cells but was shown to enhance the ATPase activity of P-glycoprotein to hamper its ability to transport drugs. Moreover, such findings were proved in colorectal cancer cells, where nobiletin was effective against P-glycoprotein-mediated drug resistance (Wenzhe Ma, Galanis, et al., 2015). Such experiments suggest that nobiletin can be utilized to counteract the malignant multidrug resistance associated with P-glycoprotein transport activity and may represent a great potential to enhance chemotherapy efficacy.

7.5. WNT/β-catenin signaling cascade

The WNT/β-catenin signaling cascade is crucial in the maintenance of stem cells, acting as a promoter of malignancy in the initiation and development of numerous cancers (Zhan et al., 2017). Modulating this pathway has been suggested as a treatment strategy to disrupt uncontrolled growth and spread of cancerous cells (Chatterjee et al., 2022). The WNT/β-catenin signaling pathway is modulated by many proteins and epigenetic modulators. GSK3 is an example of an inhibitor of WNT/β-catenin signaling, while SOX5 and SOX9 promote it (Liu et al., 2021). Nobiletin was found to potentially inhibit the development of therapeutic resistance through the WNT/β-catenin signaling pathway. Investigating the downregulation of WNT/β-catenin signaling activity in nobiletin-treated non-small cell lung cancer (NSCLC) cells, it was found to promote miR-15–5p expression while decreasing cancer stemness, invasion, and migration. Apoptosis in NSCLC cells was significantly enhanced by this downregulation of the WNT/β-catenin signaling pathway (Han et al., 2021). Nobiletin may also affect some of the upstream modulators of WNT/β-catenin signaling. Evident studies suggesting nobiletin negatively regulating SOX5 (Yazdan et al., 2024) and positively regulating expression of GSK3, a well-known WNT/β-catenin suppressor (You et al., 2022). Much still remains to be explained, however, concerning interaction of these mediators with WNT/β-catenin signaling in various cancer cell types after treatment with NOB. These observations place nobiletin on the list of probable therapeutic agents inhibiting the WNT/β-catenin pathway, which may enhance treatment outcome by limiting cancer progression and therapy resistance development.

8. Approaches to formulation development and drug delivery systems for nobiletin

With these health benefits and positive safety data, flavonoids are receiving noteworthy interest in therapeutic application. Most flavonoids, however, are BCS Class IV compounds: poorly water-soluble and low-permeable (Lipinski et al., 2001). In the search that targets overcoming challenges regarding dissolution, absorption, and systemic availability, various formulation strategies such as solubilization, emulsification, and the creation of amorphous solid dispersions, micelles, and nanoparticles are studied extensively (Amidon et al., 1995; Lin et al., 2017). Nobiletin: This polymethoxy flavone derived from citrus has been shown to exhibit broad-spectrum action in a number of diseases, specifically targeting the key pathophysiological processes in cancer progression and metastasis impacting ovarian, breast, and cervical cancers (Lin et al., 2003; Nagase et al., 2005; Seki et al., 2013). Nevertheless, poor solubility and stability of nobiletin keep it out of reach in clinical applications despite its far-reaching prowess; therefore, some biopharmaceutical attributes of NOB must be probed toward evolving a commercially viable therapeutic product (J. Li, Zhang, et al., 2019). Solving that would imply solving issues regarding poor water solubility, primarily in neutral or acidic medium; a low tendency to remain in stability in the crystallized form across the temperature of the

body and room, and exceedingly low bioavailability. Therefore, formulations should be designed to encapsulate and sustain NOB along its delivery pathway while augmenting solubility and bioavailability (Li et al., 2009). In dealing with the limitations just stated, nanoparticulate systems have been actively proposed for solution. Nanotechnology has enhanced chemical stability, bioavailability, and clinical efficacy of NOB. Through nanoparticles, localized delivery or increased metabolic degradation rate in the body of the drug can be ensured for controlling the fate of encapsulated NOB (Majumdar & Sahay, 2009). Multiple approaches have been designed to enhance the performance of NOB encapsulated with various polymeric matrices, including natural polymer-based nanoparticles, proteins, nano-dispersed solids, polymeric micelles, and nano emulsions (Baghel et al., 2016; He & Ho, 2015). Amorphous solid dispersions of NOB (ASDs) constitute an alternative approach to enhancing solubility and gastrointestinal absorption of NOB with low aqueous solubility. ASDs homogeneously blend NOB in the amorphous state with selected excipients that increase drug concentration through enhanced solubility and preventing recrystallization (Saito et al., 2003). The most commonly used excipients include synthetic polymers such as polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG), along with some cellulose chemical derivatives, including hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC) (Hu & Jiang, 2012). The advancement in pharmaceutical technology has further opened up the sophisticated drug delivery systems that include among others SMEDDS (Yao, Lu, & Zhou, 2008); chitosan-based microemulsions (Yao, Zhou, et al., 2008); SNEDDS and inclusion complexes (Onoue et al., 2011) in sec, while liposomes, dendrimers, and HPMC-stabilized emulsions grant significance in enhancing aqueous solubility and targeted delivery for NOB and NOB-like hydrophobic compounds. In research conducted by Ning et al. NOB/SD effectively preserved NOB in a stable amorphous form within matrix carriers and formed self-assembled NOB-loaded nano micelles in aqueous solutions. These Nano micelles exhibited increased solubility, enhanced release characteristics, and improved cellular uptake, while also showing anti-apoptotic effects *in vitro*. The findings suggest that NOB/SD holds potential as an effective hepatoprotective nano-drug delivery system, offering superior bioavailability and protection against APAP-induced acute liver injury (Ning et al., 2023). In research conducted by Bayoumi et al. nobiletin was encapsulated in vesicles using the thin film hydration method, resulting in the lowest IC50 value. As a result, it was chosen for an *in vivo* study, where it improved skin condition in mice with DMBA-induced skin carcinogenesis. This improvement was confirmed through histological and immunohistochemical analysis, biochemical assessment of skin oxidative stress biomarkers, and evaluations of miRNA21 and miRNA29A expression levels, both of which are known to play significant roles in regulating inflammation, oxidative stress, and cellular response to carcinogenesis. These evaluations supported the therapeutic effects observed by highlighting the modulation of key miRNAs involved in skin cancer progression (Bayoumi et al., 2021; Kumarswamy et al., 2011). In research conducted by Ana G. et al. Reported that nobiletin-loaded chitosan nanoparticles achieved an association efficiency of 69.1 % and a loading efficiency of 7.0 %. These nanoparticles demonstrated notable anticancer effects, with an IC_{50} value of 8 μg/ml, suggesting their promising potential for use in cancer chemotherapy (Luque Alcaraz et al., 2012). In the investigation carried out by Wang et al., NOB-loaded poly-(ethylene glycol)-block-poly (ε-caprolactone) (NOB-PEG-PCL) nanoparticles were synthesized using the dialysis method, exhibiting an encapsulation efficiency of 76.34 ± 3.25 % and a drug loading capacity of 7.60 ± 0.48 %. These nanoparticles effectively suppressed osteoclast differentiation in bone marrow-derived macrophages (BMMs) by regulating the RANKL-induced MAPK signaling pathway. Furthermore, they significantly attenuated bone loss and improved bone mineral density in an ovariectomized (OVX) mouse model (Wang et al., 2019).

9. Future perspectives

The therapeutic potential of NOB in lung cancer therapy is promising, particularly in targeting key oncogenic cascade such as RAF/MEK/ERK, PI3K/Akt/mTOR, and JAK/STAT. However, its clinical translation requires further investigation into its precise molecular mechanisms and pharmacokinetic properties. A major limitation of NOB is its poor aqueous solubility and bioavailability, necessitating advanced drug delivery approaches. Emerging nanotechnology-based strategies, including polymeric nanoparticles, liposomes, dendrimers, and self-nanoemulsifying drug delivery systems (SNEDDS), have exhibited Significant advancements in the stability and therapeutic effectiveness of NOB. Additionally, exploring hybrid drug delivery systems, such as ligand-targeted nanoparticles and stimuli-responsive carriers, could enhance tumor-specific accumulation while minimizing systemic toxicity. Another critical avenue for future research involves understanding NOB's role in modulating the tumor microenvironment (TME). Given its ability to regulate immune responses and inflammatory pathways, further studies should assess its potential synergy with immune checkpoint inhibitors and its effects on immune cell infiltration in lung tumors. Moreover, nobiletin's role in reversing drug resistance through the modulation of NF-κB, PI3K/Akt, STAT3, P-glycoprotein, and WNT/β-catenin signaling highlights its potential as a supportive therapy in non-small cell lung cancer (NSCLC). Future preclinical and clinical studies should focus on optimizing the dosage regimen, evaluating combinatorial therapeutic strategies, and conducting comprehensive pharmacokinetic and toxicological assessments to facilitate its transition from bench to bedside.

10. Conclusion

Lung cancer remains among the most aggressive cancers, with restricted therapeutic approaches and high drug resistance rates. Nobiletin, a polymethoxylated flavonoid isolated from citrus rinds, has demonstrated significant anticancer efficacy through different mechanisms, such as triggering apoptosis and suppressing cell proliferation and suppression of metastasis *via* modulation of key signaling pathways. Moreover, its ability to overcome chemoresistance through the regulation of oncogenic and tumor suppressor pathways further establishes its significance in lung cancer therapy. Despite its immense therapeutic promise, the therapeutic use of NOB is hindered by its poor solubility, poor systemic availability, and rapid metabolism. Advances in nanotechnology-driven Therapeutic delivery mechanisms, like polymer-based micelles, nano-dispersed solids, and inclusion complexes, have shown potential in addressing these limitations. Furthermore, the integration of NOB into combination therapy regimens with existing chemotherapeutics or targeted therapies may provide enhanced treatment efficacy while mitigating resistance mechanisms.

In summary, while nobiletin represents a promising candidate for lung cancer treatment, further extensive research is needed to improve its formulation, enhance its pharmacological properties, and confirm its clinical effectiveness through well-designed pre-clinical and clinical studies. The future of nobiletin-based therapy lies in the development of novel and refined delivery mechanisms and its incorporation into multimodal treatment approaches, potentially transforming the landscape of lung cancer therapeutics.

CRediT authorship contribution statement

Newton Suwal: Writing – review & editing, Writing – original draft, Validation, Software, Resources, Methodology, Investigation, Conceptualization. **Rajan Thapa:** Writing – review & editing. **Saroj Bashyal:** Writing – review & editing. **Vrashabh V. Sugandhi:** Writing – review & editing. **Sapana Subedi:** Writing – review & editing. **Nisha Panth:** Writing – review & editing. **Nadia Amorim:** Writing – review & editing. **Jaesung P. Choi:** Writing – review & editing. **Madhu Gupta:** Writing –

review & editing. **Sobia Idrees:** Writing – review & editing. **Kamal Dua:** Writing – review & editing. **Keshav Raj Paudel:** Writing – review & editing, Validation, Supervision, Conceptualization.

Availability of data and materials

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Ethics approval and consent to participate

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Consent for publication

All authors have approved to publish this manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

References

Abe, S., Hirose, S., Nishitani, M., Yoshida, I., Tsukayama, M., Tsuji, A., & Yuasa, K. (2018). Citrus peel polymethoxyflavones, sudachitin and nobiletin, induce distinct cellular responses in human keratinocyte HaCaT cells. *Biosci Biotechnol Biochem, 82*(12), 2064–2071. https://doi.org/10.1080/09168451.2018.1514246

Abe, T., Sato, T., & Murotomi, K. (2023). Sudachitin and nobiletin stimulate lipolysis via activation of the cAMP/PKA/HSL pathway in 3T3-L1 adipocytes. *Foods, 12*(10).

Abolfathi, H., Arabi, M., & Sheikhpour, M. (2023). A literature review of microRNA and gene signaling pathways involved in the apoptosis pathway of lung cancer. *Respiratory Research, 24*(1), 55. https://doi.org/10.1186/s12931-023-02366-w

Alam, M., Hasan, G. M., Eldin, S. M., Adnan, M., Riaz, M. B., Islam, A., Khan, I., & Hassan, M. I. (2023). Investigating regulated signaling pathways in therapeutic targeting of non-small cell lung carcinoma. *Biomedicine & Pharmacotherapy, 161*, Article 114452. https://doi.org/10.1016/j.biopha.2023.114452

American Cancer Society. (2025). *Cancer facts & figures 2025*. American Cancer Society. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2025/2025-cancer-facts-and-figures-acs.pdf.

Amidon, G. L., Lennernäs, H., Shah, V. P., & Crison, J. R. (1995). A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutical Research, 12*(3), 413–420. https://doi.org/10.1023/a:1016212804288

Antonicelli, A., Cafarotti, S., Indini, A., Galli, A., Russo, A., Cesario, A., Lococo, F. M., Russo, P., Mainini, A. F., Bonifati, L. G., Nosotti, M., Santambrogio, L., Margaritora, S., Granone, P. M., & Dutly, A. E. (2013). EGFR-Targeted therapy for non-small cell lung cancer: Focus on EGFR oncogenic mutation. *International Journal of Medical Sciences, 10*(3), 320–330. https://doi.org/10.7150/ijms.4609

Aoki, K., Yokosuka, A., Mimaki, Y., Fukunaga, K., & Yamakuni, T. (2013). Nobiletin induces inhibitions of Ras activity and mitogen-activated protein kinase kinase/extracellular signal-regulated kinase signaling to suppress cell proliferation in C6 rat glioma cells. *Biological and Pharmaceutical Bulletin, 36*(4), 540–547. https://doi.org/10.1248/bpb.b12-00824

Ashrafizadeh, M., Farhood, B., Eleojo Musa, A., Taeb, S., & Najafi, M. (2020). Damage-associated molecular patterns in tumor radiotherapy. *International Immunopharmacology, 86*, Article 106761. https://doi.org/10.1016/j.intimp.2020.106761

Baghel, S., Fox, H., & O'Reilly, N. (2016). Polymeric amorphous solid dispersions: A review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system Class II drugs. *Journal of Pharmaceutical Sciences, 105*. https://doi.org/10.1016/j.xphs.2015.10.008

Bayoumi, M., Arafa, M. G., Nasr, M., & Sammour, O. A. (2021). Nobiletin-loaded composite penetration enhancer vesicles restore the normal miRNA expression and the chief defence antioxidant levels in skin cancer. *Scientific Reports, 11*(1), Article 20197. https://doi.org/10.1038/s41598-021-99756-1

Bentires-Alj, M., Barbu, V., Fillet, M., Chariot, A., Relic, B., Jacobs, N., Gielen, J., Merville, M. P., & Bours, V. (2003). NF-kappaB transcription factor induces drug resistance through MDR1 expression in cancer cells. *Oncogene, 22*(1), 90–97. https://doi.org/10.1038/sj.onc.1206056

Bethune, G., Bethune, D., Ridgway, N., & Xu, Z. (2010). Epidermal growth factor receptor (EGFR) in lung cancer: An overview and update. *Journal of Thoracic Disease, 2*(1), 48–51.

Bole-Feysot, C., Goffin, V., Edery, M., Binart, N., & Kelly, P. A. (1998). Prolactin (PRL) and its receptor: Actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. *Endocrine Reviews, 19*(3), 225–268. https://doi.org/10.1210/edrv.19.3.0334

Boolell, V., Alamgeer, M., Watkins, D. N., & Ganju, V. (2015). The evolution of therapies in non-small cell lung cancer. *Cancers (Basel), 7*(3), 1815–1846. https://doi.org/10.3390/cancers7030864

Cao, W., Chen, H. D., Yu, Y. W., Li, N., & Chen, W. Q. (2021). Changing profiles of cancer burden worldwide and in China: A secondary analysis of the global cancer statistics 2020. *Chinese Medical Journal, 134*(7), 783–791. https://doi.org/10.1097/cm9.0000000000001474

Cersosimo, R. J. (2002). Lung cancer: A review. *American Journal of Health-System Pharmacy, 59*(7), 611–642. https://doi.org/10.1093/ajhp/59.7.611

Charkiewicz, R., Niklinski, J., Claesen, J., Sulewska, A., Kozlowski, M., Michalska-Falkowska, A., Reszec, J., Moniuszko, M., Naumnik, W., & Niklinska, W. (2017). Gene expression signature differentiates histology but not progression status of early-stage NSCLC. *Translational Oncology, 10*(3), 450–458. https://doi.org/10.1016/j.tranon.2017.01.015

Chatterjee, A., Paul, S., Bisht, B., Bhattacharya, S., Sivasubramaniam, S., & Paul, M. K. (2022). Advances in targeting the WNT/β-catenin signaling pathway in cancer. *Drug Discovery Today, 27*(1), 82–101. https://doi.org/10.1016/j.drudis.2021.07.007

Chen, J., Chen, A. Y., Huang, H., Ye, X., Rollyson, W. D., Perry, H. E., Brown, K. C., Rojanasakul, Y., Rankin, G. O., Dasgupta, P., & Chen, Y. C. (2015). The flavonoid nobiletin inhibits tumor growth and angiogenesis of ovarian cancers via the Akt pathway. *International Journal of Oncology, 46*(6), 2629–2638. https://doi.org/10.3892/ijo.2015.2946

Chen, K., Cheng, G., Zhang, F., Zhu, G., Xu, Y., Yu, X., Huang, Z., & Fan, Y. (2020). PD-L1 expression and T cells infiltration in patients with uncommon EGFR-mutant non-small cell lung cancer and the response to immunotherapy. *Lung Cancer, 142*, 98–105. https://doi.org/10.1016/j.lungcan.2020.02.010

Chen, J., Creed, A., Chen, A. Y., Huang, H., Li, Z., Rankin, G. O., Ye, X., Xu, G., & Chen, Y. C. (2014). Nobiletin suppresses cell viability through AKT pathways in PC-3 and DU-145 prostate cancer cells. *BMC Pharmacol Toxicol, 15*, 59. https://doi.org/10.1186/2050-6511-15-59

Chinnaiyan, P., Won, M., Wen, P. Y., Rojiani, A. M., Wendland, M., Dipetrillo, T. A., Corn, B. W., & Mehta, M. P. (2013). Rtog 0913: A phase 1 study of daily everolimus (RAD001) in combination with radiation therapy and temozolomide in patients with newly diagnosed glioblastoma. *International Journal of Radiation Oncology, Biology, Physics, 86*(5), 880–884. https://doi.org/10.1016/j.ijrobp.2013.04.036

Choudhari, A. S., Mandave, P. C., Deshpande, M., Ranjekar, P., & Prakash, O. (2019). Phytochemicals in cancer treatment: From preclinical studies to clinical practice. *Frontiers in Pharmacology, 10*, 1614. https://doi.org/10.3389/fphar.2019.01614

Chu, Z. G., Yang, Z. G., Shao, H., Zhu, Z. Y., Deng, W., Tang, S. S., Chen, J., & Li, Y. (2011). Small peripheral lung adenocarcinoma: CT and histopathologic characteristics and prognostic implications. *Cancer Imaging, 11*(1), 237–246. https://doi.org/10.1102/1470-7330.2011.0033

Collins, D. C., Chenard-Poirier, M., & Lopez, J. S. (2018). The PI3K pathway at the crossroads of cancer and the immune system: Strategies for next generation immunotherapy combinations. *Current Cancer Drug Targets, 18*(4), 355–364. https://doi.org/10.2174/1568009617666170927114440

Comprehensive molecular profiling of lung adenocarcinoma. *Nature, 511*(7511), (2014), 543–550. https://doi.org/10.1038/nature13385

Couraud, S., Zalcman, G., Milleron, B., Morin, F., & Souquet, P. J. (2012). Lung cancer in never smokers–a review. *European Journal of Cancer, 48*(9), 1299–1311. https://doi.org/10.1016/j.ejca.2012.03.007

Cristea, S., & Sage, J. (2016). Is the canonical RAF/MEK/ERK signaling pathway a therapeutic target in SCLC? *Journal of Thoracic Oncology, 11*(8), 1233–1241. https://doi.org/10.1016/j.jtho.2016.04.018

Da, C., Liu, Y., Zhan, Y., Liu, K., & Wang, R. (2016). Nobiletin inhibits epithelial-mesenchymal transition of human non-small cell lung cancer cells by antagonizing the TGF-β1/Smad3 signaling pathway. *Oncology Reports, 35*(5), 2767–2774. https://doi.org/10.3892/or.2016.4661

Dasgupta, B., & Gutmann, D. H. (2003). Neurofibromatosis 1: Closing the GAP between mice and men. *Curr Opin Genet Dev, 13*(1), 20–27. https://doi.org/10.1016/s0959-437x(02)00015-1

de Groot, P. M., Wu, C. C., Carter, B. W., & Munden, R. F. (2018). The epidemiology of lung cancer. *Translational Lung Cancer Research, 7*(3), 220–233. https://doi.org/10.21037/tlcr.2018.05.06

Delaney, B., Phillips, K., Buswell, D., Mowry, B., Nickels, D., Cox, D., Wang, H. B., & Manthey, J. (2001). Immunotoxicity of a standardized citrus polymethoxylated flavone extract. *Food and Chemical Toxicology, 39*(11), 1087–1094. https://doi.org/10.1016/s0278-6915(01)00058-8

Delaney, B., Phillips, K., Vasquez, C., Wilson, A., Cox, D., Wang, H. B., & Manthey, J. (2002). Genetic toxicity of a standardized mixture of citrus polymethoxylated flavones. *Food and Chemical Toxicology, 40*(5), 617–624. https://doi.org/10.1016/s0278-6915(02)00007-8

Dempke, W. C., Suto, T., & Reck, M. (2010). Targeted therapies for non-small cell lung cancer. *Lung Cancer, 67*(3), 257–274. https://doi.org/10.1016/j.lungcan.2009.10.012

Efferth, T., Kadioglu, O., Saeed, M., Seo, E.-J., Mbaveng, A., & Kuete, V. (2021). Medicinal plants and phytochemicals against multidrug-resistant tumor cells expressing ABCB1, ABCG2, or ABCB5: A synopsis of 2 decades. *Phytochemistry Reviews, 20*. https://doi.org/10.1007/s11101-020-09703-7

Engle, K., & Kumar, G. (2022). Cancer multidrug-resistance reversal by ABCB1 inhibition: A recent update. *European Journal of Medicinal Chemistry, 239*, Article 114542. https://doi.org/10.1016/j.ejmech.2022.114542

Espert, L., Dusanter-Fourt, I., & Chelbi-Alix, M. K. (2005). [Negative regulation of the JAK/STAT: Pathway implication in tumorigenesis]. *Bull Cancer, 92*(10), 845–857 (Les régulations négatives de la voie JAK/STAT: implication dans la tumorigenèse.).

Faruki, H., Mayhew, G. M., Serody, J. S., Hayes, D. N., Perou, C. M., & Lai-Goldman, M. (2017). Lung adenocarcinoma and squamous cell carcinoma gene expression subtypes demonstrate significant differences in tumor immune landscape. *Journal of Thoracic Oncology, 12*(6), 943–953. https://doi.org/10.1016/j.jtho.2017.03.010

Feng, S.-L., Tian, Y., Huo, S., Qu, B., Liu, R.-M., Xu, P., Li, Y.-Z., & Xie, Y. (2020). Nobiletin potentiates paclitaxel anticancer efficacy in A549/T xenograft model: Pharmacokinetic and pharmacological study. *Phytomedicine, 67*, Article 153141. https://doi.org/10.1016/j.phymed.2019.153141

Feng, W., Zhang, M., Wu, Z. X., Wang, J. Q., Dong, X. D., Yang, Y., Teng, Q. X., Chen, X. Y., Cui, Q., & Yang, D. H. (2020). Erdafitinib antagonizes ABCB1-mediated multidrug resistance in cancer cells. *Front Oncol, 10*, 955. https://doi.org/10.3389/fonc.2020.00955

Feng, S., Zhou, H., Wu, D., Zheng, D., Qu, B., Liu, R., Zhang, C., Li, Z., Xie, Y., & Luo, H.-B. (2020). Nobiletin and its derivatives overcome multidrug resistance (MDR) in cancer: Total synthesis and discovery of potent MDR reversal agents. *Acta Pharmaceutica Sinica B, 10*(2), 327–343. https://doi.org/10.1016/j.apsb.2019.07.007

Gainor, J. F., Varghese, A. M., Ou, S. H., Kabraji, S., Awad, M. M., Katayama, R., Pawlak, A., Mino-Kenudson, M., Yeap, B. Y., Riely, G. J., Iafrate, A. J., Arcila, M. E., Ladanyi, M., Engelman, J. A., Dias-Santagata, D., & Shaw, A. T. (2013). ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: An analysis of 1,683 patients with non-small cell lung cancer. *Clinical Cancer Research, 19*(15), 4273–4281. https://doi.org/10.1158/1078-0432.Ccr-13-0318

Galanis, E., Buckner, J. C., Maurer, M. J., Kreisberg, J. I., Ballman, K., Boni, J., Peralba, J. M., Jenkins, R. B., Dakhil, S. R., Morton, R. F., Jaeckle, K. A., Scheithauer, B. W., Dancey, J., Hidalgo, M., & Walsh, D. J. (2005). Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: A north central cancer treatment group study. *Journal of Clinical Oncology, 23*(23), 5294–5304. https://doi.org/10.1200/jco.2005.23.622

Gan, R., Liu, Y., Li, H., Xia, Y., Guo, H., Geng, F., Zhuang, Q., Li, H., & Wu, D. (2024). Natural sources, refined extraction, biosynthesis, metabolism, and bioactivities of dietary polymethoxyflavones (PMFs). *Food Science and Human Wellness, 13*(1), 27–49. https://doi.org/10.26599/FSHW.2022.9250003

Gao, X. J., Liu, J. W., Zhang, Q. G., Zhang, J. J., Xu, H. T., & Liu, H. J. (2015). Nobiletin inhibited hypoxia-induced epithelial-mesenchymal transition of lung cancer cells by inactivating of Notch-1 signaling and switching on miR-200b. *Pharmazie, 70*(4), 256–262.

Garon, E. B., Rizvi, N. A., Hui, R., Leighl, N., Balmanoukian, A. S., Eder, J. P., Patnaik, A., Aggarwal, C., Gubens, M., Horn, L., Carcereny, E., Ahn, M. J., Felip, E., Lee, J. S., Hellmann, M. D., Hamid, O., Goldman, J. W., Soria, J. C., Dolled-Filhart, M., … Gandhi, L. (2015). Pembrolizumab for the treatment of non-small-cell lung cancer. *New England Journal of Medicine, 372*(21), 2018–2028. https://doi.org/10.1056/NEJMoa1501824

Gentles, A. J., Bratman, S. V., Lee, L. J., Harris, J. P., Feng, W., Nair, R. V., Shultz, D. B., Nair, V. S., Hoang, C. D., West, R. B., Plevritis, S. K., Alizadeh, A. A., & Diehn, M. (2015). Integrating tumor and stromal gene expression signatures with clinical indices for survival stratification of early-stage non-small cell lung cancer. *J Natl Cancer Inst, 107*(10). https://doi.org/10.1093/jnci/djv211

George, J., Lim, J. S., Jang, S. J., Cun, Y., Ozretić, L., Kong, G., Leenders, F., Lu, X., Fernández-Cuesta, L., Bosco, G., Müller, C., Dahmen, I., Jahchan, N. S., Park, K. S., Yang, D., Karnezis, A. N., Vaka, D., Torres, A., Wang, M. S., … Thomas, R. K. (2015). Comprehensive genomic profiles of small cell lung cancer. *Nature, 524*(7563), 47–53. https://doi.org/10.1038/nature14664

Ghosh, C., Luong, G., & Sun, Y. (2021). A snapshot of the PD-1/PD-L1 pathway. *Journal of Cancer, 12*(9), 2735–2746. https://doi.org/10.7150/jca.57334

Goan, Y. G., Wu, W. T., Liu, C. I., Neoh, C. A., & Wu, Y. J. (2019). Involvement of mitochondrial dysfunction, endoplasmic reticulum stress, and the PI3K/AKT/mTOR pathway in nobiletin-induced apoptosis of human bladder cancer cells. *Molecules, 24*(16). https://doi.org/10.3390/molecules24162881

Goodwin, C. R., Rath, P., Oyinlade, O., Lopez, H., Mughal, S., Xia, S., Li, Y., Kaur, H., Zhou, X., Ahmed, A. K., Ho, S., Olivi, A., & Lal, B. (2018). Crizotinib and erlotinib inhibits growth of c-Met(+)/EGFRvIII(+) primary human glioblastoma xenografts. *Clinical Neurology and Neurosurgery, 171*, 26–33. https://doi.org/10.1016/j.clineuro.2018.02.041

Grunblatt, E., Wu, N., Zhang, H., Liu, X., Norton, J., Ohol, Y., Leger, P., Hiatt, J., Eastwood, E., Thomas, R., Ibrahim, A., Jia, D., Basom, R., Eaton, K., Martins, R., Houghton, A., & MacPherson, D. (2020). MYCN drives chemoresistance in small cell lung cancer while USP7 inhibition can restore chemosensitivity. *Genes & Development, 34*. https://doi.org/10.1101/gad.340133.120

Guney Eskiler, G., Deveci, A. O., Bilir, C., & Kaleli, S. (2019). Synergistic effects of nobiletin and sorafenib combination on metastatic prostate cancer cells. *Nutrition and Cancer, 71*(8), 1299–1312. https://doi.org/10.1080/01635581.2019.1601237

Hamilton, G., Moser, D., & Hochmair, M. (2016). Metastasis: Circulating tumor cells in small cell lung cancer. *Trends in Cancer, 2*(4), 159–160. https://doi.org/10.1016/j.trecan.2016.02.006

Han, S. H., Han, J. H., Chun, W. J., Lee, S. S., Kim, H. S., & Lee, J. W. (2021). Nobiletin inhibits non-small-cell lung cancer by inactivating WNT/β-Catenin signaling through downregulating miR-15-5p. *Evid Based Complement Alternat Med, 2021*, Article 7782963. https://doi.org/10.1155/2021/7782963

Han, Y., Liu, D., & Li, L. (2020). PD-1/PD-L1 pathway: Current researches in cancer. *American Journal of Cancer Research, 10*(3), 727–742.

Hanna, N., Johnson, D., Temin, S., Baker, S., Jr., Brahmer, J., Ellis, P. M., Giaccone, G., Hesketh, P. J., Jaiyesimi, I., Leighl, N. B., Riely, G. J., Schiller, J. H., Schneider, B. J., Smith, T. J., Tashbar, J., Biermann, W. A., & Masters, G. (2017). Systemic therapy for stage IV non-small-cell lung cancer: American society of clinical oncology clinical practice guideline update. *Journal of Clinical Oncology, 35*(30), 3484–3515. https://doi.org/10.1200/jco.2017.74.6065

Hattori, T., Tagawa, H., Inai, M., Kan, T., Kimura, S.-i., Itai, S., Mitragotri, S., & Iwao, Y. (2019). Transdermal delivery of nobiletin using ionic liquids. *Scientific Reports, 9*(1), Article 20191. https://doi.org/10.1038/s41598-019-56731-1

He, Y., & Ho, C. (2015). Amorphous solid dispersions: Utilization and challenges in drug discovery and development. *J Pharm Sci, 104*(10), 3237–3258. https://doi.org/10.1002/jps.24541

Henriques, A. F., Barros, P., Moyer, M. P., Matos, P., & Jordan, P. (2015). Expression of tumor-related Rac1b antagonizes B-Raf-induced senescence in colorectal cells. *Cancer Letters, 369*(2), 368–375. https://doi.org/10.1016/j.canlet.2015.08.027

Herbst, R. S., Heymach, J. V., & Lippman, S. M. (2008). Lung cancer. *New England Journal of Medicine, 359*(13), 1367–1380. https://doi.org/10.1056/NEJMra0802714

Hirsch, F. R., Scagliotti, G. V., Mulshine, J. L., Kwon, R., Curran, W. J., Jr., Wu, Y. L., & Paz-Ares, L. (2017). Lung cancer: Current therapies and new targeted treatments. *Lancet, 389*(10066), 299–311. https://doi.org/10.1016/s0140-6736(16)30958-8

Hirsch, F. R., Suda, K., Wiens, J., & Bunn, P. A., Jr. (2016). New and emerging targeted treatments in advanced non-small-cell lung cancer. *Lancet, 388*(10048), 1012–1024. https://doi.org/10.1016/s0140-6736(16)31473-8

Holohan, C., Van Schaeybroeck, S., Longley, D. B., & Johnston, P. G. (2013). Cancer drug resistance: An evolving paradigm. *Nature Reviews Cancer, 13*(10), 714–726. https://doi.org/10.1038/nrc3599

Hu, T., & Jiang, J.-G. (2012). Application of nanotechnology in traditional Chinese medicine. *Current Nanoscience, 8*, 474–484. https://doi.org/10.2174/157341312800620287

Hu, X., li, J., Fu, M., Zhao, X., & Wang, W. (2021). The JAK/STAT signaling pathway: From bench to clinic. *Signal Transduction and Targeted Therapy, 6*(1), 402. https://doi.org/10.1038/s41392-021-00791-1

Huang, J., Chang, Z., Lu, Q., Chen, X., & Najafi, M. (2022). Nobiletin as an inducer of programmed cell death in cancer: A review. *Apoptosis, 27*(5–6), 297–310. https://doi.org/10.1007/s10495-022-01721-4

Huang, Y., Wu, D., Bao, M., Li, B., & Liang, H. (2019). Coordination driven self-assembly for enhancing the biological stability of nobiletin. *Journal of Molecular Liquids, 292*, Article 111420. https://doi.org/10.1016/j.molliq.2019.111420

Hung, Y. P., & Chirieac, L. R. (2020). How should molecular findings be integrated in the classification for lung cancer? *Translational Lung Cancer Research, 9*(5), 2245–2254. https://doi.org/10.21037/tlcr-20-153

Iksen, Pothongsrisit, S., & Pongrakhananon, V. (2021). Targeting the PI3K/AKT/mTOR signaling pathway in lung cancer: An update regarding potential drugs and natural products. *Molecules, 26*(13).

Jain, P., Jain, C., & Velcheti, V. (2018). Role of immune-checkpoint inhibitors in lung cancer. *Therapeutic Advances in Respiratory Disease, 12*, Article 1753465817750075. https://doi.org/10.1177/1753465817750075

Jiang, H., Chen, H., Jin, C., Mo, J., & Wang, H. (2020). Nobiletin flavone inhibits the growth and metastasis of human pancreatic cancer cells via induction of autophagy, G0/G1 cell cycle arrest and inhibition of NF-kB signalling pathway. *J buon, 25*(2), 1070–1075.

Jiang, X., Wang, J., Deng, X., Xiong, F., Ge, J., Xiang, B., Wu, X., Ma, J., Zhou, M., Li, X., Li, Y., Li, G., Xiong, W., Guo, C., & Zeng, Z. (2019). Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. *Molecular Cancer, 18*(1), 10. https://doi.org/10.1186/s12943-018-0928-4

Kawano, O., Sasaki, H., Okuda, K., Yukiue, H., Yokoyama, T., Yano, M., & Fujii, Y. (2007). PIK3CA gene amplification in Japanese non-small cell lung cancer. *Lung Cancer, 58*(1), 159–160. https://doi.org/10.1016/j.lungcan.2007.06.020

Keshtkar, S., Kaviani, M., Jabbarpour, Z., Geramizadeh, B., Motevaseli, E., Nikeghbalian, S., Shamsaeefar, A., Motazedian, N., Al-Abdullah, I. H., Ghahremani, M. H., & Azarpira, N. (2019). Protective effect of nobiletin on isolated human islets survival and function against hypoxia and oxidative stress-induced apoptosis. *Scientific Reports, 9*(1), Article 11701. https://doi.org/10.1038/s41598-019-48262-6

Khanna, P., Chua, P. J., Bay, B. H., & Baeg, G. H. (2015). The JAK/STAT signaling cascade in gastric carcinoma. *International Journal of Oncology, 47*(5), 1617–1626. https://doi.org/10.3892/ijo.2015.3160 (Review).

Kim, E., Kim, Y. J., Ji, Z., Kang, J. M., Wirianto, M., Paudel, K. R., Smith, J. A., Ono, K., Kim, J. A., Eckel-Mahan, K., Zhou, X., Lee, H. K., Yoo, J. Y., Yoo, S. H., & Chen, Z. (2022). ROR activation by Nobiletin enhances antitumor efficacy via suppression of IκB/NF-κB signaling in triple-negative breast cancer. *Cell Death & Disease, 13*(4), 374. https://doi.org/10.1038/s41419-022-04826-5

Kimura, Y., Morita, S. Y., Matsuo, M., & Ueda, K. (2007). Mechanism of multidrug recognition by MDR1/ABCB1. *Cancer Science, 98*(9), 1303–1310. https://doi.org/10.1111/j.1349-7006.2007.00538.x

Kimura, J., Shimizu, K., Kajima, K., Yokosuka, A., Mimaki, Y., Oku, N., & Ohizumi, Y. (2018). Nobiletin reduces intracellular and extracellular β-amyloid in iPS cell-derived alzheimer's disease model neurons. *Biol Pharm Bull, 41*(4), 451–457. https://doi.org/10.1248/bpb.b17-00364

Kisacam, M. A. (2023). Nobiletin is capable of regulating certain anti-cancer pathways in a colon cancer cell line. *Naunyn-Schmiedeberg's Archives of Pharmacology, 396*(3), 547–555. https://doi.org/10.1007/s00210-022-02354-9

Koga, N., Ohta, C., Kato, Y., Haraguchi, K., Endo, T., Ogawa, K., Ohta, H., & Yano, M. (2011). In vitro metabolism of nobiletin, a polymethoxy-flavonoid, by human liver microsomes and cytochrome P450. *Xenobiotica, 41*(11), 927–933. https://doi.org/10.3109/00498254.2011.593208

Kumarswamy, R., Volkmann, I., & Thum, T. (2011). Regulation and function of miRNA-21 in health and disease. *RNA Biology, 8*(5), 706–713. https://doi.org/10.4161/rna.8.5.16154

Lassen, U., Sorensen, M., Gaziel, T. B., Hasselbalch, B., & Poulsen, H. S. (2013). Phase II study of bevacizumab and temsirolimus combination therapy for recurrent glioblastoma multiforme. *Anticancer Research, 33*(4), 1657–1660.

Lee, Y. S., Cha, B. Y., Choi, S. S., Choi, B. K., Yonezawa, T., Teruya, T., Nagai, K., & Woo, J. T. (2013). Nobiletin improves obesity and insulin resistance in high-fat diet-induced obese mice. *The Journal of Nutritional Biochemistry, 24*(1), 156–162. https://doi.org/10.1016/j.jnutbio.2012.03.014

Lee, S., Rauch, J., & Kolch, W. (2020). Targeting MAPK signaling in cancer: Mechanisms of drug resistance and sensitivity. *International Journal of Molecular Sciences, 21*(3). https://doi.org/10.3390/ijms21031102

Leirdal, M., & Sioud, M. (2000). Protein kinase calpha isoform regulates the activation of the MAP kinase ERK1/2 in human glioma cells: Involvement in cell survival and gene expression. *Molecular Cell Biology Research Communications, 4*(2), 106–110. https://doi.org/10.1006/mcbr.2000.0259

Li, Y., Chen, G., Han, Z., Cheng, H., Qiao, L., & Li, Y. (2020). IL-6/STAT3 signaling contributes to sorafenib resistance in hepatocellular carcinoma through targeting cancer stem cells. *OncoTargets and Therapy, 13*, 9721–9730. https://doi.org/10.2147/ott.S262089

Li, Y. Q., Fan, F., Wang, Y. R., Li, L. Y., Cao, Y. J., Gu, S. M., Liu, S. S., Zhang, Y., Wang, J., Tie, L., Pan, Y., Li, H. F., & Li, X. J. (2023). The novel small molecule BH3 mimetic nobiletin synergizes with vorinostat to induce apoptosis and autophagy in small cell lung cancer. *Biochemical Pharmacology, 216*, Article 115807. https://doi.org/10.1016/j.bcp.2023.115807

Li, T., Kung, H. J., Mack, P. C., & Gandara, D. R. (2013). Genotyping and genomic profiling of non-small-cell lung cancer: Implications for current and future therapies. *Journal of Clinical Oncology, 31*(8), 1039–1049. https://doi.org/10.1200/jco.2012.45.3753

Li, S., Pan, M.-H., Lo, C.-Y., Tan, D., Wang, Y., Shahidi, F., & Ho, C.-T. (2009). Chemistry and health effects of polymethoxyflavones and hydroxylated polymethoxyflavones. *Journal of Functional Foods, 1*(1), 2–12. https://doi.org/10.1016/j.jff.2008.09.003

Li, R. W., Theriault, A. G., Au, K., Douglas, T. D., Casaschi, A., Kurowska, E. M., & Mukherjee, R. (2006). Citrus polymethoxylated flavones improve lipid and glucose homeostasis and modulate adipocytokines in fructose-induced insulin resistant hamsters. *Life Sciences, 79*(4), 365–373. https://doi.org/10.1016/j.lfs.2006.01.023

Li, S., Wang, Z., Sang, S., Huang, M. T., & Ho, C. T. (2006). Identification of nobiletin metabolites in mouse urine. *Mol Nutr Food Res, 50*(3), 291–299. https://doi.org/10.1002/mnfr.200500214

Li, J., Yang, Y., Ning, E., Peng, Y., & Zhang, J. (2019). Mechanisms of poor oral bioavailability of flavonoid Morin in rats: From physicochemical to biopharmaceutical evaluations. *Eur J Pharm Sci, 128*, 290–298. https://doi.org/10.1016/j.ejps.2018.12.011

Li, N., Zhang, Z., Jiang, G., Sun, H., & Yu, D. (2019). Nobiletin sensitizes colorectal cancer cells to oxaliplatin by PI3K/Akt/MTOR pathway. *Frontiers in Bioscience (Landmark Edition), 24*(2), 303–312. https://doi.org/10.2741/4719

Lin, S. C., Chen, M. C., Li, S., Lin, C. C., & Wang, T. T. (2017). Antiviral activity of nobiletin against chikungunya virus in vitro. *Antiviral Therapy, 22*(8), 689–697. https://doi.org/10.3851/imp3167

Lin, N., Sato, T., Takayama, Y., Mimaki, Y., Sashida, Y., Yano, M., & Ito, A. (2003). Novel anti-inflammatory actions of nobiletin, a citrus polymethoxy flavonoid, on human synovial fibroblasts and mouse macrophages. *Biochemical Pharmacology, 65*(12), 2065–2071. https://doi.org/10.1016/s0006-2952(03)00203-x

Lin, Z., Wu, D., Huang, L., Jiang, C., Pan, T., Kang, X., & Pan, J. (2019). Nobiletin inhibits IL-1β-induced inflammation in chondrocytes via suppression of NF-κB signaling and attenuates osteoarthritis in mice. *Frontiers in Pharmacology, 10*, 570. https://doi.org/10.3389/fphar.2019.00570

Lindeman, N. I., Cagle, P. T., Beasley, M. B., Chitale, D. A., Dacic, S., Giaccone, G., Jenkins, R. B., Kwiatkowski, D. J., Saldivar, J. S., Squire, J., Thunnissen, E., & Ladanyi, M. (2013). Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: Guideline from the college of American pathologists, international association for the study of lung cancer, and association for molecular pathology. *Journal of Thoracic Oncology, 8*(7), 823–859. https://doi.org/10.1097/JTO.0b013e318290868f

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews, 46*(1–3), 3–26. https://doi.org/10.1016/s0169-409x(00)00129-0

Liu, X., Ma, R., Yi, B., Riker, A. I., & Xi, Y. (2021). MicroRNAs are involved in the development and progression of gastric cancer. *Acta Pharmacologica Sinica, 42*(7), 1018–1026. https://doi.org/10.1038/s41401-020-00540-0

Lu, H., Wu, S., Chen, H., Huang, Y., Qiu, G., Liu, L., & Li, Y. (2018). Crizotinib induces apoptosis of lung cancer cells through JAK-STAT pathway. *Oncology Letters, 16*(5), 5992–5996. https://doi.org/10.3892/ol.2018.9387

Luo, G., Guan, X., & Zhou, L. (2008). Apoptotic effect of citrus fruit extract nobiletin on lung cancer cell line A549 in vitro and in vivo. *Cancer Biology & Therapy, 7*(6), 966–973. https://doi.org/10.4161/cbt.7.6.5967

Luo, H., Vong, C. T., Chen, H., Gao, Y., Lyu, P., Qiu, L., Zhao, M., Liu, Q., Cheng, Z., Zou, J., Yao, P., Gao, C., Wei, J., Ung, C. O. L., Wang, S., Zhong, Z., & Wang, Y. (2019). Naturally occurring anti-cancer compounds: Shining from Chinese herbal medicine. *Chin Med, 14*, 48. https://doi.org/10.1186/s13020-019-0270-9

Luque Alcaraz, A., Lizardi-Mendoza, J., Goycoolea, F., Valdez, M., Acosta, A., Iloki Assanga, S. B., Higuera-Ciapara, I., & Argüelles-Monal, W. (2012). Characterization and antiproliferative activity of nobiletin-loaded chitosan nanoparticles. *Journal of Nanomaterials, 2012*, Article 265161. https://doi.org/10.1155/2012/265161

Ma, D. J., Galanis, E., Anderson, S. K., Schiff, D., Kaufmann, T. J., Peller, P. J., Giannini, C., Brown, P. D., Uhm, J. H., McGraw, S., Jaeckle, K. A., Flynn, P. J., Ligon, K. L., Buckner, J. C., & Sarkaria, J. N. (2015). A phase II trial of everolimus, temozolomide, and radiotherapy in patients with newly diagnosed glioblastoma: Nctg N057K. *Neuro-Oncology, 17*(9), 1261–1269. https://doi.org/10.1093/neuonc/nou328

Ma, J., Liu, X., Wei, Y., Lu, R., Xu, K., Tian, Y., & Li, J. (2022). Effective component compatibility of bufei yishen formula III which regulates the mucus hypersecretion of COPD rats via the miR-146a-5p/EGFR/MEK/ERK pathway. *Evid Based Complement Alternat Med, 2022*, Article 9423435. https://doi.org/10.1155/2022/9423435

Ma, Y., Ren, X., Patel, N., Xu, X., Wu, P., Liu, W., Zhang, K., Goodin, S., Li, D., & Zheng, X. (2020). Nobiletin, a citrus polymethoxyflavone, enhances the effects of bicalutamide on prostate cancer cells via down regulation of NF-κB, STAT3, and ERK activation [10.1039/C9RA10020B]. *RSC Advances, 10*(17), 10254–10262. https://doi.org/10.1039/C9RA10020B

Majumdar, S., & Sahay, S. (2009). A review of: "Biological and pharmaceutical nanomaterials. In C. Kumar (Ed.), *Materials and manufacturing processes - mater manuf process* (Vol. 24, pp. 517–518). https://doi.org/10.1080/10426910802714704

Martínez-García, M., Velasco, G., Pineda, E., Gil-Gil, M., Alameda, F., Capellades, J., Martín-Soberón, M. C., López-Valero, I., Tovar Ambel, E., Foro, P., Taus, Á., Arumi, M., Hernández-Laín, A., & Sepúlveda-Sánchez, J. M. (2022). Safety and efficacy of crizotinib in combination with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma: Phase ib GEINO 1402 trial. *Cancers (Basel), 14*(10). https://doi.org/10.3390/cancers14102393

Mason, W. P., Macneil, M., Kavan, P., Easaw, J., Macdonald, D., Thiessen, B., Urva, S., Lwin, Z., McIntosh, L., & Eisenhauer, E. (2012). A phase I study of temozolomide and everolimus (RAD001) in patients with newly diagnosed and progressive glioblastoma either receiving or not receiving enzyme-inducing anticonvulsants: An NCIC CTG study. *Investigational New Drugs, 30*(6), 2344–2351. https://doi.org/10.1007/s10637-011-9775-5

Meiyanto, E., Hermawan, A., & Anindyajati, A. (2012). Natural products for cancer-targeted therapy: Citrus flavonoids as potent chemopreventive agents. *Asian Pacific Journal of Cancer Prevention: Asian Pacific Journal of Cancer Prevention, 13*, 427–436. https://doi.org/10.7314/APJCP.2012.13.2.427

Memarzia, A., Saadat, S., Asgharzadeh, F., Behrouz, S., Folkerts, G., & Boskabady, M. H. (2023). Therapeutic effects of medicinal plants and their constituents on lung cancer, in vitro, in vivo and clinical evidence. *Journal of Cellular and Molecular Medicine, 27*(19), 2841–2863. https://doi.org/10.1111/jcmm.17936

Miyamoto, S., Yasui, Y., Tanaka, T., Ohigashi, H., & Murakami, A. (2008). Suppressive effects of nobiletin on hyperleptinemia and colitis-related colon carcinogenesis in male ICR mice. *Carcinogenesis, 29*(5), 1057–1063. https://doi.org/10.1093/carcin/bgn080

Mohan, C. D., Rangappa, S., Preetham, H. D., Chandra Nayaka, S., Gupta, V. K., Basappa, S., Sethi, G., & Rangappa, K. S. (2022). Targeting STAT3 signaling pathway in cancer by agents derived from Mother Nature. *Seminars in Cancer Biology, 80*, 157–182. https://doi.org/10.1016/j.semcancer.2020.03.016

Mohiuddin, M. M., & Choi, N. C. (2005). The role of radiation therapy in non-small cell lung cancer. *Seminars in Respiratory and Critical Care Medicine, 26*(3), 278–288. https://doi.org/10.1055/s-2005-871986

Mok, T. S., Wu, Y. L., Thongprasert, S., Yang, C. H., Chu, D. T., Saijo, N., Sunpaweravong, P., Han, B., Margono, B., Ichinose, Y., Nishiwaki, Y., Ohe, Y., Yang, J. J., Chewaskulyong, B., Jiang, H., Duffield, E. L., Watkins, C. L., Armour, A. A., & Fukuoka, M. (2009). Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *New England Journal of Medicine, 361*(10), 947–957. https://doi.org/10.1056/NEJMoa0810699

Montagut, C., & Settleman, J. (2009). Targeting the RAF-MEK-ERK pathway in cancer therapy. *Cancer Letters, 283*(2), 125–134. https://doi.org/10.1016/j.canlet.2009.01.022

Moon, J. Y., Manh Hung, L. V., Unno, T., & Cho, S. K. (2018). Nobiletin enhances chemosensitivity to adriamycin through modulation of the akt/gsk3β/β-catenin/MYCN/MRP1 signaling pathway in A549 human non-small-cell lung cancer cells. *Nutrients, 10*(12). https://doi.org/10.3390/nu10121829

Muscella, A., Stefano, E., Calabriso, N., De Pascali, S. A., Fanizzi, F. P., & Marsigliante, S. (2021). Role of epidermal growth factor receptor signaling in a Pt(II)-resistant human breast cancer cell line. *Biochemical Pharmacology, 192*, Article 114702. https://doi.org/10.1016/j.bcp.2021.114702

Nagase, H., Omae, N., Omori, A., Nakagawasai, O., Tadano, T., Yokosuka, A., Sashida, Y., Mimaki, Y., Yamakuni, T., & Ohizumi, Y. (2005). Nobiletin and its related flavonoids with CRE-dependent transcription-stimulating and neuritegenic activities. *Biochemical and Biophysical Research Communications, 337*(4), 1330–1336. https://doi.org/10.1016/j.bbrc.2005.10.001

Nakajima, A., Nemoto, K., & Ohizumi, Y. (2020). An evaluation of the genotoxicity and subchronic toxicity of the peel extract of Ponkan cultivar 'Ohta ponkan' (Citrus reticulata Blanco) that is rich in nobiletin and tangeretin with anti-dementia activity. *Regulatory Toxicology and Pharmacology, 114*, Article 104670. https://doi.org/10.1016/j.yrtph.2020.104670

Nakajima, A., & Ohizumi, Y. (2019). Potential benefits of nobiletin, A citrus flavonoid, against alzheimer's disease and Parkinson's disease. *International Journal of Molecular Sciences, 20*(14). https://doi.org/10.3390/ijms20143380

Narayanankutty, A., Nambiattil, S., & Mannarakkal, S. (2023). Phytochemicals and nanoparticles in the modulation of PI3K/Akt/mTOR kinases and its implications in the development and progression of gastrointestinal cancers: A review of preclinical and clinical evidence. *Recent Patents on Anti-Cancer Drug Discovery, 18*(3), 307–324. https://doi.org/10.2174/1574892817666220606104712

Naugler, W. E., & Karin, M. (2008). NF-kappaB and cancer-identifying targets and mechanisms. *Curr Opin Genet Dev, 18*(1), 19–26. https://doi.org/10.1016/j.gde.2008.01.020

Niazi, S., Purohit, M., & Niazi, J. H. (2018). Role of p53 circuitry in tumorigenesis: A brief review. *European Journal of Medicinal Chemistry, 158*, 7–24. https://doi.org/10.1016/j.ejmech.2018.08.099

Ning, J., Zheng, G., Cai, Y., Hu, Y., Liu, Y., Lai, E., Chen, B., Liu, Y., Liang, Z., Fu, J., & Wei, M. (2023). The self-assembly soluplus nanomicelles of nobiletin in aqueous medium based on solid dispersion and their increased hepatoprotective effect on APAP-induced acute liver injury. *Int J Nanomedicine, 18*, 5119–5140. https://doi.org/10.2147/ijn.S426703

Nohara, K., Mallampalli, V., Nemkov, T., Wirianto, M., Yang, J., Ye, Y., Sun, Y., Han, L., Esser, K. A., Mileykovskaya, E., D'Alessandro, A., Green, C. B., Takahashi, J. S., Dowhan, W., Yoo, S.-H., & Chen, Z. (2019). Nobiletin fortifies mitochondrial respiration in skeletal muscle to promote healthy aging against metabolic challenge. *Nature Communications, 10*(1), 3923. https://doi.org/10.1038/s41467-019-11926-y

Nojiri, T., Hamasaki, T., Inoue, M., Shintani, Y., Takeuchi, Y., Maeda, H., & Okumura, M. (2017). Long-term impact of postoperative complications on cancer recurrence following lung cancer surgery. *Annals of Surgical Oncology, 24*(4), 1135–1142. https://doi.org/10.1245/s10434-016-5655-8

Norris, M. D., Bordow, S. B., Haber, P. S., Marshall, G. M., Kavallaris, M., Madafiglio, J., Cohn, S. L., Salwen, H., Schmidt, M. L., Hipfner, D. R., Cole, S. P., Deeley, R. G., & Haber, M. (1997). Evidence that the MYCN oncogene regulates MRP gene expression in neuroblastoma. *European Journal of Cancer, 33*(12), 1911–1916. https://doi.org/10.1016/s0959-8049(97)00284-0

Nurwidya, F., Takahashi, F., & Takahashi, K. (2016). Gefitinib in the treatment of nonsmall cell lung cancer with activating epidermal growth factor receptor mutation. *Journal of Natural Science, Biology and Medicine, 7*(2), 119–123. https://doi.org/10.4103/0976-9668.184695

Ohaegbulam, K. C., Assal, A., Lazar-Molnar, E., Yao, Y., & Zang, X. (2015). Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway. *Trends in Molecular Medicine, 21*(1), 24–33. https://doi.org/10.1016/j.molmed.2014.10.009

Okudela, K., Suzuki, M., Kageyama, S., Bunai, T., Nagura, K., Igarashi, H., Takamochi, K., Suzuki, K., Yamada, T., Niwa, H., Ohashi, R., Ogawa, H., Mori, H., Kitamura, H., Kaneko, T., Tsuneyoshi, T., & Sugimura, H. (2007). PIK3CA mutation and amplification in human lung cancer. *Pathology International, 57*(10), 664–671. https://doi.org/10.1111/j.1440-1827.2007.02155.x

Onishi, S., Nishi, K., Yasunaga, S., Muranaka, A., Maeyama, K., Kadota, A., & Sugahara, T. (2014). Nobiletin, a polymethoxy flavonoid, exerts anti-allergic effect by suppressing activation of phosphoinositide 3-kinase. *Journal of Functional Foods, 6*, 606–614. https://doi.org/10.1016/j.jff.2013.12.005

Onoue, S., Uchida, A., Takahashi, H., Seto, Y., Kawabata, Y., Ogawa, K., Yuminoki, K., Hashimoto, N., & Yamada, S. (2011). Development of high-energy amorphous solid dispersion of nanosized nobiletin, a citrus polymethoxylated flavone, with improved oral bioavailability. *Journal of Pharmaceutical Sciences, 100*(9), 3793–3801. https://doi.org/10.1002/jps.22585

Pan, Y., Zhang, Y., Li, Y., Hu, H., Wang, L., Li, H., Wang, R., Ye, T., Luo, X., Zhang, Y., Li, B., Cai, D., Shen, L., Sun, Y., & Chen, H. (2014). ALK, ROS1 and RET fusions in 1139 lung adenocarcinomas: A comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features. *Lung Cancer, 84*(2), 121–126. https://doi.org/10.1016/j.lungcan.2014.02.007

Pao, W., & Hutchinson, K. E. (2012). Chipping away at the lung cancer genome. *Nat Med, 18*(3), 349–351. https://doi.org/10.1038/nm.2697

Papadimitrakopoulou, V. (2012). Development of PI3K/AKT/mTOR pathway inhibitors and their application in personalized therapy for non-small-cell lung cancer. *Journal of Thoracic Oncology, 7*(8), 1315–1326. https://doi.org/10.1097/JTO.0b013e31825493eb

Pardoll, D. M. (2012). The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer, 12*(4), 252–264. https://doi.org/10.1038/nrc3239

Park, J. Y., Kang, S. E., Ahn, K. S., Um, J. Y., Yang, W. M., Yun, M., & Lee, S. G. (2020). Inhibition of the PI3K-AKT-mTOR pathway suppresses the adipocyte-mediated proliferation and migration of breast cancer cells. *Journal of Cancer, 11*(9), 2552–2559. https://doi.org/10.7150/jca.37975

Patraşcu, A. V., Ţarcă, E., Lozneanu, L., Ungureanu, C., Moroşan, E., Parteni, D. E., Jehac, A., Bernic, J., & Cojocaru, E. (2025). The role of epithelial-mesenchymal transition in osteosarcoma progression: From biology to therapy. *Diagnostics, 15*(5). https://doi.org/10.3390/diagnostics15050644

Peifer, M., Fernández-Cuesta, L., Sos, M. L., George, J., Seidel, D., Kasper, L. H., Plenker, D., Leenders, F., Sun, R., Zander, T., Menon, R., Koker, M., Dahmen, I., Müller, C., Di Cerbo, V., Schildhaus, H. U., Altmüller, J., Baessmann, I., Becker, C., … Thomas, R. K. (2012). Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nature Genetics, 44*(10), 1104–1110. https://doi.org/10.1038/ng.2396

Porro, A., Haber, M., Diolaiti, D., Iraci, N., Henderson, M., Gherardi, S., Valli, E., Munoz, M. A., Xue, C., Flemming, C., Schwab, M., Wong, J. H., Marshall, G. M., Della Valle, G., Norris, M. D., & Perini, G. (2010). Direct and coordinate regulation of ATP-binding cassette transporter genes by Myc factors generates specific transcription signatures that significantly affect the chemoresistance phenotype of cancer cells. *Journal of Biological Chemistry, 285*(25), 19532–19543. https://doi.org/10.1074/jbc.M109.078584

Qin, W., Hu, L., Zhang, X., Jiang, S., Li, J., Zhang, Z., & Wang, X. (2019). The diverse function of PD-1/PD-L pathway beyond cancer. *Frontiers in Immunology, 10*, 2298. https://doi.org/10.3389/fimmu.2019.02298

Reck, M., Heigener, D. F., Mok, T., Soria, J. C., & Rabe, K. F. (2013). Management of non-small-cell lung cancer: Recent developments. *Lancet, 382*(9893), 709–719. https://doi.org/10.1016/s0140-6736(13)61502-0

Ritt, D. A., Abreu-Blanco, M. T., Bindu, L., Durrant, D. E., Zhou, M., Specht, S. I., Stephen, A. G., Holderfield, M., & Morrison, D. K. (2016). Inhibition of ras/raf/MEK/ERK pathway signaling by a stress-induced phospho-regulatory circuit. *Mol Cell, 64*(5), 875–887. https://doi.org/10.1016/j.molcel.2016.10.029

Saab, S., Zalzale, H., Rahal, Z., Khalifeh, Y., Sinjab, A., & Kadara, H. (2020). Insights into lung cancer immune-based biology, prevention, and treatment. *Frontiers in Immunology, 11*, 159. https://doi.org/10.3389/fimmu.2020.00159

Saito, M., Ugajin, T., Nozawa, Y., Sadzuka, Y., Miyagishima, A., & Sonobe, T. (2003). Preparation and dissolution characteristics of griseofulvin solid dispersions with saccharides. *International journal of pharmaceutics, 249*, 71–79. https://doi.org/10.1016/S0378-5173(02)00455-6

Salehi, M., Movahedpour, A., Tayarani, A., Shabaninejad, Z., Pourhanifeh, M. H., Mortezapour, E., Nickdasti, A., Mottaghi, R., Davoodabadi, A., Khan, H., Savardashtaki, A., & Mirzaei, H. (2020). Therapeutic potentials of curcumin in the treatment of non-small-cell lung carcinoma. *Phytotherapy Research, 34*(10), 2557–2576. https://doi.org/10.1002/ptr.6704

Samuels, Y., Wang, Z., Bardelli, A., Silliman, N., Ptak, J., Szabo, S., Yan, H., Gazdar, A., Powell, S. M., Riggins, G. J., Willson, J. K., Markowitz, S., Kinzler, K. W., Vogelstein, B., & Velculescu, V. E. (2004). High frequency of mutations of the PIK3CA gene in human cancers. *Science, 304*(5670), 554. https://doi.org/10.1126/science.1096502

Sanaei, M. J., Razi, S., Pourbagheri-Sigaroodi, A., & Bashash, D. (2022). The PI3K/Akt/mTOR pathway in lung cancer; oncogenic alterations, therapeutic opportunities, challenges, and a glance at the application of nanoparticles. *Translational Oncology, 18*, Article 101364. https://doi.org/10.1016/j.tranon.2022.101364

Scagliotti, G., Moro-Sibilot, D., Kollmeier, J., Favaretto, A., Cho, E. K., Grosch, H., Kimmich, M., Girard, N., Tsai, C. M., Hsia, T. C., Brighenti, M., Schumann, C., Wang, X. A., Wijayawardana, S. R., Gruver, A. M., Wallin, J., Mansouri, K., Wacheck, V., & Chang, G. C. (2020). A randomized-controlled phase 2 study of the MET antibody emibetuzumab in combination with erlotinib as first-line treatment for EGFR mutation-positive NSCLC patients. *Journal of Thoracic Oncology, 15*(1), 80–90. https://doi.org/10.1016/j.jtho.2019.10.003

Seki, T., Kamiya, T., Furukawa, K., Azumi, M., Ishizuka, S., Takayama, S., Nagase, S., Arai, H., Yamakuni, T., & Yaegashi, N. (2013). Nobiletin-rich citrus reticulata peels, a kampo medicine for alzheimer's disease: A case series. *Geriatrics and Gerontology International, 13*(1), 236–238. https://doi.org/10.1111/j.1447-0594.2012.00892.x

Seluanov, A., Gladyshev, V. N., Vijg, J., & Gorbunova, V. (2018). Mechanisms of cancer resistance in long-lived mammals. *Nature Reviews Cancer, 18*(7), 433–441. https://doi.org/10.1038/s41568-018-0004-9

Siegel, R. L., Giaquinto, A. N., & Jemal, A. (2024). Cancer statistics, 2024. *CA: A Cancer Journal for Clinicians, 74*(1), 12–49. https://doi.org/10.3322/caac.21820

Skoulidis, F., & Heymach, J. V. (2019). Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. *Nature Reviews Cancer, 19*(9), 495–509. https://doi.org/10.1038/s41568-019-0179-8

Society, A. C. (2024). Cancer facts & figures 2024. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2024/2024-cancer-facts-and-figures-acs.pdf.

Sousa, D. P., Pojo, M., Pinto, A. T., Leite, V., Serra, A. T., & Cavaco, B. M. (2020). Nobiletin alone or in combination with cisplatin decreases the viability of anaplastic thyroid cancer cell lines. *Nutrition and Cancer, 72*(2), 352–363. https://doi.org/10.1080/01635581.2019.1634745

Sp, N., Kang, D. Y., Joung, Y. H., Park, J. H., Kim, W. S., Lee, H. K., Song, K. D., Park, Y. M., & Yang, Y. M. (2017). Nobiletin inhibits angiogenesis by regulating src/FAK/STAT3-Mediated signaling through PXN in ER^{+} breast cancer cells. *International Journal of Molecular Sciences, 18*(5). https://doi.org/10.3390/ijms18050935

Sp, N., Kang, D. Y., Lee, J. M., & Jang, K. J. (2021). Mechanistic insights of anti-immune evasion by nobiletin through regulating miR-197/STAT3/PD-L1 signaling in non-small cell lung cancer (NSCLC) cells. *International Journal of Molecular Sciences, 22*(18). https://doi.org/10.3390/ijms22189843

Stefani, C., Miricescu, D., Stanescu, S., II, Nica, R. I., Greabu, M., Totan, A. R., & Jinga, M. (2021). Growth factors, PI3K/AKT/mTOR and MAPK signaling pathways in colorectal cancer pathogenesis: Where are we now? *International Journal of Molecular Sciences, 22*(19). https://doi.org/10.3390/ijms221910260

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 71*(3), 209–249. https://doi.org/10.3322/caac.21660

Tan, A. C. (2020). Targeting the PI3K/Akt/mTOR pathway in non-small cell lung cancer (NSCLC). *Thoracic Cancer, 11*(3), 511–518. https://doi.org/10.1111/1759-7714.13328

Tan, K. T., Li, S., Li, Y. R., Cheng, S. L., Lin, S. H., & Tung, Y. T. (2019). Synergistic anticancer effect of a combination of paclitaxel and 5-demethylnobiletin against lung

cancer cell line in vitro and in vivo. *Applied Biochemistry and Biotechnology, 187*(4), 1328–1343. https://doi.org/10.1007/s12010-018-2869-1

Tang, Q., Chen, Y., Li, X., Long, S., Shi, Y., Yu, Y., Wu, W., Han, L., & Wang, S. (2022). The role of PD-1/PD-L1 and application of immune-checkpoint inhibitors in human cancers. *Frontiers in Immunology, 13*, Article 964442. https://doi.org/10.3389/fimmu.2022.964442

Thandra, K. C., Barsouk, A., Saginala, K., Aluru, J. S., & Barsouk, A. (2021). Epidemiology of lung cancer. *Contemporary Oncology, 25*(1), 45–52. https://doi.org/10.5114/wo.2021.103829

Thomas, S. J., Snowden, J. A., Zeidler, M. P., & Danson, S. J. (2015). The role of JAK/STAT signalling in the pathogenesis, prognosis and treatment of solid tumours. *British Journal of Cancer, 113*(3), 365–371. https://doi.org/10.1038/bjc.2015.233

Travis, W. D., Brambilla, E., Nicholson, A. G., Yatabe, Y., Austin, J. H. M., Beasley, M. B., Chirieac, L. R., Dacic, S., Duhig, E., Flieder, D. B., Geisinger, K., Hirsch, F. R., Ishikawa, Y., Kerr, K. M., Noguchi, M., Pelosi, G., Powell, C. A., Tsao, M. S., & Wistuba, I. (2015). The 2015 World health organization classification of lung tumors: Impact of genetic, clinical and radiologic advances since the 2004 classification. *Journal of Thoracic Oncology, 10*(9), 1243–1260. https://doi.org/10.1097/jto.0000000000000630

Tsuboi, T., Lu, R., Yonezawa, T., Watanabe, A., Woo, J. T., Abe-Dohmae, S., & Yokoyama, S. (2020). Molecular mechanism for nobiletin to enhance ABCA1/G1 expression in mouse macrophages. *Atherosclerosis, 297*, 32–39. https://doi.org/10.1016/j.atherosclerosis.2020.01.024

Tzivion, G., Dobson, M., & Ramakrishnan, G. (2011). FoxO transcription factors; Regulation by AKT and 14-3-3 proteins. *Biochimica et Biophysica Acta, 1813*(11), 1938–1945. https://doi.org/10.1016/j.bbamcr.2011.06.002

Uesato, S., Yamashita, H., Maeda, R., Hirata, Y., Yamamoto, M., Matsue, S., Nagaoka, Y., Shibano, M., Taniguchi, M., Baba, K., & Ju-ichi, M. (2014). Synergistic antitumor effect of a combination of paclitaxel and carboplatin with nobiletin from Citrus depressa on non-small-cell lung cancer cell lines. *Planta Medica, 80*(6), 452–457. https://doi.org/10.1055/s-0034-1368321

van den Bent, M., Azaro, A., De Vos, F., Sepulveda, J., Yung, W. K. A., Wen, P. Y., Lassman, A. B., Joerger, M., Tabatabai, G., Rodon, J., Tiedt, R., Zhao, S., Kirsilae, T., Cheng, Y., Vicente, S., Balbin, O. A., Zhang, H., & Wick, W. (2020). A Phase Ib/II, open-label, multicenter study of INC280 (capmatinib) alone and in combination with buparlisib (BKM120) in adult patients with recurrent glioblastoma. *Journal of Neuro-Oncology, 146*(1), 79–89. https://doi.org/10.1007/s11060-019-03337-2

Vasan, N., Baselga, J., & Hyman, D. M. (2019). A view on drug resistance in cancer. *Nature, 575*(7782), 299–309. https://doi.org/10.1038/s41586-019-1730-1

Wang, J. G., Jian, W. J., Li, Y., & Zhang, J. (2021). Nobiletin promotes the pyroptosis of breast cancer via regulation of miR-200b/JAZF1 axis. *The Kaohsiung Journal of Medical Sciences, 37*(7), 572–582. https://doi.org/10.1002/kjm2.12371

Wang, X., Li, Y., Dai, Y., Liu, Q., Ning, S., Liu, J., Shen, Z., Zhu, D., Jiang, F., Zhang, J., & Li, Z. (2016). Sulforaphane improves chemotherapy efficacy by targeting cancer stem cell-like properties via the miR-124/IL-6R/STAT3 axis. *Scientific Reports, 6*(1), Article 36796. https://doi.org/10.1038/srep36796

Wang, X., Lu, Y., Tuo, Z., Zhou, H., Zhang, Y., Cao, Z., Peng, L., Yu, D., & Bi, L. (2021). Role of SIRT1/AMPK signaling in the proliferation, migration and invasion of renal cell carcinoma cells. *Oncology Reports, 45*(6). https://doi.org/10.3892/or.2021.8060

Wang, Y., Xie, J., Ai, Z., & Su, J. (2019). Nobiletin-loaded micelles reduce ovariectomy-induced bone loss by suppressing osteoclastogenesis. *International Journal of Nanomedicine, 14*(null), 7839–7849. https://doi.org/10.2147/IJN.S213724

Wang, H. B., Yao, H., Li, C. S., Liang, L. X., Zhang, Y., Chen, Y. X., Fang, J. Y., & Xu, J. (2017). Rise of PD-L1 expression during metastasis of colorectal cancer: Implications for immunotherapy. *J Dig Dis, 18*(10), 574–581. https://doi.org/10.1111/1751-2980.12538

Wei, D., Zhang, G., Zhu, Z., Zheng, Y., Yan, F., Pan, C., Wang, Z., Li, X., Wang, F., Meng, P., Zheng, W., Yan, Z., Zhai, D., Lu, Z., & Yuan, J. (2019). Nobiletin inhibits cell viability via the SRC/AKT/STAT3/YY1AP1 pathway in human renal carcinoma cells. *Frontiers in Pharmacology, 10*, 690. https://doi.org/10.3389/fphar.2019.00690

Weiss, W. A., Aldape, K., Mohapatra, G., Feuerstein, B. G., & Bishop, J. M. (1997). Targeted expression of *MYCN* causes neuroblastoma in transgenic mice. *The EMBO Journal, 16*(11), 2985–2995. https://doi.org/10.1093/emboj/16.11.2985, 2995.

Wen, P. Y., Drappatz, J., de Groot, J., Prados, M. D., Reardon, D. A., Schiff, D., Chamberlain, M., Mikkelsen, T., Desjardins, A., Holland, J., Ping, J., Weitzman, R., & Cloughesy, T. F. (2018). Phase II study of cabozantinib in patients with progressive glioblastoma: Subset analysis of patients naive to antiangiogenic therapy. *Neuro-Oncology, 20*(2), 249–258. https://doi.org/10.1093/neuonc/nox154

Wen, P. Y., Rodon, J. A., Mason, W., Beck, J. T., DeGroot, J., Donnet, V., Mills, D., El-Hashimy, M., & Rosenthal, M. (2020). Phase I, open-label, multicentre study of buparlisib in combination with temozolomide or with concomitant radiation therapy and temozolomide in patients with newly diagnosed glioblastoma. *ESMO Open, 5*(4). https://doi.org/10.1136/esmoopen-2020-000673

Wesołowska, O., Wiśniewski, J., Sroda-Pomianek, K., Bielawska-Pohl, A., Paprocka, M., Duś, D., Duarte, N., Ferreira, M. J., & Michalak, K. (2012). Multidrug resistance reversal and apoptosis induction in human colon cancer cells by some flavonoids present in citrus plants. *Journal of Natural Products, 75*(11), 1896–1902. https://doi.org/10.1021/np3003468

WHO. (2024). Global cancer burden growing, amidst mounting need for services. https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing–amidst-mounting-need-for-services.

Wick, W., Gorlia, T., Bady, P., Platten, M., van den Bent, M. J., Taphoorn, M. J., Steuve, J., Brandes, A. A., Hamou, M. F., Wick, A., Kosch, M., Weller, M., Stupp, R., Roth, P., Golfinopoulos, V., Frenel, J. S., Campone, M., Ricard, D., Marosi, C., … Hegi, M. E. (2016). Phase II study of radiotherapy and temsirolimus versus radiochemotherapy with temozolomide in patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation (EORTC 26082). *Clinical Cancer Research, 22*(19), 4797–4806. https://doi.org/10.1158/1078-0432.Ccr-15-3153

Wu, D., Liang, Y., Pei, Y., Li, B., & Liang, H. (2020). Plant exine capsules based encapsulation strategy: A high loading and long-term effective delivery system for nobiletin. *Food Research International, 127*, Article 108691. https://doi.org/10.1016/j.foodres.2019.108691

Wu, X., Song, M., Qiu, P., Li, F., Wang, M., Zheng, J., Wang, Q., Xu, F., & Xiao, H. (2018). A metabolite of nobiletin, 4'-demethylnobiletin and atorvastatin synergistically inhibits human colon cancer cell growth by inducing G0/G1 cell cycle arrest and apoptosis. *Food Funct, 9*(1), 87–95. https://doi.org/10.1039/c7fo01155e

Wu, X., Song, M., Qiu, P., Rakariyatham, K., Li, F., Gao, Z., Cai, X., Wang, M., Xu, F., Zheng, J., & Xiao, H. (2017). Synergistic chemopreventive effects of nobiletin and atorvastatin on colon carcinogenesis. *Carcinogenesis, 38*(4), 455–464. https://doi.org/10.1093/carcin/bgx018

Wu, Y. Q., Zhou, C. H., Tao, J., & Li, S. N. (2006). Antagonistic effects of nobiletin, a polymethoxyflavonoid, on eosinophilic airway inflammation of asthmatic rats and relevant mechanisms. *Life Sciences, 78*(23), 2689–2696. https://doi.org/10.1016/j.lfs.2005.10.029

Xiao, P., Liu, W., & Zhou, H. (2021). [Retracted] miR-200b inhibits migration and invasion in non-small cell lung cancer cells via targeting FSCN1. *Molecular Medicine Reports, 24*(2). https://doi.org/10.3892/mmr.2021.12218

Xiao, H., Yang, C. S., Li, S., Jin, H., Ho, C. T., & Patel, T. (2009). Monodemethylated polymethoxyflavones from sweet orange (Citrus sinensis) peel inhibit growth of human lung cancer cells by apoptosis. *Mol Nutr Food Res, 53*(3), 398–406. https://doi.org/10.1002/mnfr.200800057

Xu, Z., Han, X., Ou, D., Liu, T., Li, Z., Jiang, G., Liu, J., & Zhang, J. (2020). Targeting PI3K/AKT/mTOR-mediated autophagy for tumor therapy. *Applied Microbiology and Biotechnology, 104*(2), 575–587. https://doi.org/10.1007/s00253-019-10257-8

Yamamoto, H., Shigematsu, H., Nomura, M., Lockwood, W. W., Sato, M., Okumura, N., Soh, J., Suzuki, M., Wistuba, I. I., Fong, K. M., Lee, H., Toyooka, S., Date, H., Lam, W. L., Minna, J. D., & Gazdar, A. F. (2008). PIK3CA mutations and copy number gains in human lung cancers. *Cancer Research, 68*(17), 6913–6921. https://doi.org/10.1158/0008-5472.Can-07-5084

Yao, J., Lu, Y., & Zhou, J. P. (2008). Preparation of nobiletin in self-microemulsifying systems and its intestinal permeability in rats. *J Pharm Pharm Sci, 11*(3), 22–29. https://doi.org/10.18433/j3ms3m

Yao, J., Zhou, J. P., Ping, Q. N., Lu, Y., & Chen, L. (2008). Distribution of nobiletin chitosan-based microemulsions in brain following i.v. injection in mice. *Int J Pharm, 352*(1–2), 256–262. https://doi.org/10.1016/j.ijpharm.2007.10.010

Yao, X., Zhu, X., Pan, S., Fang, Y., Jiang, F., Phillips, G. O., & Xu, X. (2012). Antimicrobial activity of nobiletin and tangeretin against Pseudomonas. *Food Chemistry, 132*(4), 1883–1890. https://doi.org/10.1016/j.foodchem.2011.12.021

Yarım, G. F., Çenesiz, M., Yarım, M., & Kazak, F. (2017). [Nöroprotektif etkili bir flavonoid: Nobiletin]. *Harran University Journal of the Faculty of Veterinary Medicine, 6*(1), 102–107. https://doi.org/10.31196/huvfd.325789

Yazdan, M., Naghib, S. M., & Mozafari, M. R. (2024). Polymeric micelle-based nanogels as emerging drug delivery systems in breast cancer treatment: Promises and challenges. *Current Drug Targets, 25*(10), 649–669. https://doi.org/10.2174/0113894501294136240610061328

You, L., Lin, J., Yu, Z., Qian, Y., Bi, Y., Wang, F., Zhang, L., Zheng, C., Zhang, J., Li, W., Cai, Y., Gao, Y., Kong, X., & Sun, X. (2022). Nobiletin suppresses cholangiocarcinoma proliferation via inhibiting GSK3β. *International Journal of Biological Sciences, 18*(15), 5698–5712. https://doi.org/10.7150/ijbs.78345

Youn, K., Lee, S., & Jun, M. (2019). Discovery of nobiletin from citrus peel as a potent inhibitor of β-amyloid peptide toxicity. *Nutrients, 11*(11). https://doi.org/10.3390/nu11112648

Yu, H. A., Arcila, M. E., Rekhtman, N., Sima, C. S., Zakowski, M. F., Pao, W., Kris, M. G., Miller, V. A., Ladanyi, M., & Riely, G. J. (2013). Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clinical Cancer Research, 19*(8), 2240–2247. https://doi.org/10.1158/1078-0432.Ccr-12-2246

Yu, C., Yang, B., & Najafi, M. (2021). Targeting of cancer cell death mechanisms by curcumin: Implications to cancer therapy. *Basic Clin Pharmacol Toxicol, 129*(6), 397–415. https://doi.org/10.1111/bcpt.13648

Yuan, M., Zhao, Y., Arkenau, H. T., Lao, T., Chu, L., & Xu, Q. (2022). Signal pathways and precision therapy of small-cell lung cancer. *Signal Transduct Target Ther, 7*(1), 187. https://doi.org/10.1038/s41392-022-01013-y

Yuk, T., Kim, Y., Yang, J., Sung, J., Jeong, H. S., & Lee, J. (2018). Nobiletin inhibits hepatic lipogenesis via activation of AMP-activated protein kinase. *Evid Based Complement Alternat Med, 2018*, Article 7420265. https://doi.org/10.1155/2018/7420265

Zappa, C., & Mousa, S. A. (2016). Non-small cell lung cancer: Current treatment and future advances. *Translational Lung Cancer Research, 5*(3), 288–300. https://doi.org/10.21037/tlcr.2016.06.07

Zhan, T., Rindtorff, N., & Boutros, M. (2017). Wnt signaling in cancer. *Oncogene, 36*(11), 1461–1473. https://doi.org/10.1038/onc.2016.304

Zhang, B. F., Jiang, H., Chen, J., Guo, X., Li, Y., Hu, Q., & Yang, S. (2019). Nobiletin ameliorates myocardial ischemia and reperfusion injury by attenuating endoplasmic reticulum stress-associated apoptosis through regulation of the PI3K/AKT signal

pathway. *International Immunopharmacology, 73*, 98–107. https://doi.org/10.1016/j.intimp.2019.04.060

Zhao, R., Hu, Z., Zhang, X., Huang, S., Yu, G., Wu, Z., Yu, W., Lu, J., & Ruan, B. (2024). The oncogenic mechanisms of the Janus kinase-signal transducer and activator of transcription pathway in digestive tract tumors. *Cell Communication and Signaling, 22*(1), 68. https://doi.org/10.1186/s12964-023-01421-9

Zou, S., Tong, Q., Liu, B., Huang, W., Tian, Y., & Fu, X. (2020). Targeting STAT3 in cancer immunotherapy. *Molecular Cancer, 19*(1), 145. https://doi.org/10.1186/s12943-020-01258-7