Clinical and Experimental Health Sciences

Comprehensive Review of Nobiletin, a Citrus Flavonoid: Metabolism and Anti-tumor Properties

Meryem Saban Güler, Hilal Yıldıran

[1] Gazi University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Ankara, Türkiye.

Correspondence Author: Meryem Saban Güler
E-mail: meryemsaban@gmail.com
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ABSTRACT

Nobiletin is a polymethoxylated flavone found in citrus peels. Thanks to its chemical structure and biological activities, nobiletin has been shown to have a positive effect on many diseases. In recent years, there has been a growing interest in research focusing on the impact of nobiletin and its metabolites on different cancer types. Nobiletin exhibits anticancer properties by impeding the proliferation of cancer cells, disrupting the cancer cell cycle, facilitating apoptosis, and regulating signaling pathways implicated in cancer development. In addition, studies have shown that its use with chemotherapeutic agents inhibits multi-drug resistance. This review aims to evaluate the metabolic properties of nobiletin and its possible effects on cancer.

Keywords: Nobiletin, bioavailability, cancer, signaling pathways, antiproliferation

1. INTRODUCTION

Nobiletin, which is also known as 3',4',5,6,7,8-hexamethoxyflavone, is a significant compound belonging to the group of polymethoxylated flavones. It is typically found in the peel of citrus fruits such as Citrus reticulata (tangerine), Citrus depressa, Citrus sinensis (orange), and Citrus limon (lemon). Nobiletin has a molecular weight of 402.399 g and a chemical formula of C21H22O8 (1,2). The concentration of nobiletin within the peel oils of diverse citrus fruits can exhibit variability. For example, nobiletin contains 0.50 g/L in orange, 0.60 g/L in king tangerine, 0.40 g/L in clementine tangerine, and 1.50 g/L in tangerine peel oil. In citrus fruits, nobiletin content is estimated to range from 7 to 173 mg/kg of dry weight, and higher concentrations are found in unripe citrus fruits (3). In addition, the amount of nobiletin in the peels of the same citrus species grown in different geographical regions may vary. Nobiletin was detected at a concentration of 0.43 mg/g in dried orange peels collected from California, whereas orange peels collected from China exhibited higher levels of nobiletin at 7.79 mg/g (4).

Nobiletin possesses a notably lipophilic structure due to the presence of six methoxyl groups located at positions 5, 6, 7, and 8 on the A ring, as well as positions 3’ and 4’ on the B ring in its chemical structure (Figure 1). Many biological effects of nobiletin are associated with its lipophilicity (3). The ability of nobiletin to easily pass through the cell membrane, particularly the blood-brain barrier, and gain access to the central nervous system has been a focal point of investigation to prevent and treat various diseases, including neurodegenerative disorders, cardiovascular conditions, and cancer. These findings suggest that nobiletin holds promise as a potential novel pharmaceutical agent owing to its favorable impact on these medical conditions (1,5,6).

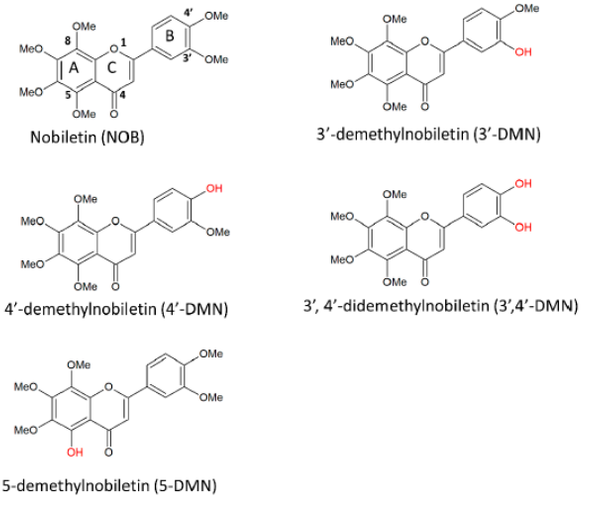

Figure 1. *Chemical structure of nobiletin and its compounds (adapted from source Goh JXH, et al., 2019.)*

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2. NOBILETIN METABOLISM

The bioactivities of a compound vary depending on its structure and metabolism (5). The molecular structure of the compound is one of the important factors affecting its absorption. Due to its lipophilic properties, nobiletin exhibits extensive distribution throughout the body. Nobiletin can be readily detected in organs such as the intestine, liver, stomach, brain, and kidney within four hours after administration, indicating its rapid distribution throughout the body (7). When nobiletin is administered by gastric intubation, it has been found to localize to the mucosa and muscularis of the digestive organs and is completely excreted within 24 hours of administration. The localization of nobiletin is attributed to its high hydrophobicity (6).

Polymethoxy flavones basically have two metabolic pathways: demethylation and conjugation (8). Bioinformatics analysis of nobiletin has unveiled a demethylation pathway leading to the generation of significant metabolites like mono-demethyl nobiletin (DMN). These include various forms such as 3',4',6-, or 7-DMN. Furthermore, di-demethylation processes can convert nobiletin into 3',4'-di-DMN, or 6,7-di-DMN (9). Following the ingestion of nobiletin, several metabolites are generated, with variations depending on the citrus plant source. Three prevalent nobiletin metabolites include 3'-DMN, 4'-DMN, and 3',4'-DMN (10). It has also been suggested that nobiletin may be converted to 5-DMN by gastric acid after oral consumption (7).

Nobiletin metabolites were found to be approximately 20 times more abundant than nobiletin, the main compound in the colonic mucosa. This result shows that nobiletin is immediately metabolized to its metabolites in the body (11). Nobiletin metabolism involves two phases: phase I and phase II metabolism. Cytochrome P450 is involved in phase I demethylation. The conversion of nobiletin to 3'-DMN involves the participation of Cytochrome P450 Family 1 Subfamily A Member 1 (CYP1A1), Cytochrome P450 Family 1 Subfamily A Member 2 (CYP1A2), Cytochrome P450 Family 1 Subfamily B Member 1 (CYP1B1), and Cytochrome P450 Family 3 Subfamily A Member 5 (CYP3A5) enzymes. However, the conversion of 3'-DMN to 3',4'-DMN is primarily catalyzed by CYP1A1 and CYP1A2 enzymes. Phase II metabolism of nobiletin takes place in the small intestine, where it undergoes sulfation and glucuronidation processes (7,10).

3. BIOAVAILABILITY OF NOBILETIN

The bioavailability of therapeutic compounds is a critical factor in their development for disease treatment (3). Comprehending the interactions between the substance and the human body offers opportunities for innovative approaches to addressing the issue, which necessitates the development of new formulations for the effective delivery of nobiletin for chemopreventive purposes (7). When it comes to oral administration, a key factor to take into account is the availability of the active substance. Hence, investigations into nobiletin's pharmacokinetic profile underscore the necessity for gaining a more profound comprehension of the absorption, metabolism, and elimination processes that influence bioavailability. A comprehensive understanding of these mechanisms plays a pivotal role in enhancing the precision of bioactivity prediction (12).

As mentioned in the metabolism section of nobiletin, the most important factor affecting the absorption of a compound is its molecular structure. Proper absorption of the compound is indicated by its solubility and permeability across physiological barriers. The lipophilic property of nobiletin helps it pass through the cell membrane easily. Nobiletin has been shown to have low water solubility (1-5 µg/mL) and minimal oral bioavailability (<1%), resulting in decreased therapeutic and biological activities (13,14).

Despite the proven ability of orally administered nobiletin to cross the blood-brain barrier and exhibit activity in the brain, it's important to note that orally ingested polymethoxyflavones typically exhibit low absorption rates (9). When nobiletin was given orally to rats at 50 mg/kg, the amount of nobiletin in the brain was found to be 3.6 mg/kg (15). In another study conducted with the same dose of nobiletin (>97% purity), it was found that the maximum concentrations in plasma and brain were recorded as 1.78 µg/ml and 4.20 µg/ml, respectively, one hour after administration (16).

Although the water solubility of nobiletin is low, the water solubility of its metabolites was found to be 2-3 times higher than the main compound. This observation may, in part, elucidate the enhanced activity of nobiletin derivatives when compared to the parent compound, as these derivatives possess an increased number of methoxy groups (7). Although the bioavailability of nobiletin is low, it is thought that a large part of its anticancer effect may be mediated by metabolites, so the biological activities of nobiletin metabolites should be further investigated.

As a result of the rapid metabolism and poor bioavailability of nobiletin, new strategies have been the subject of research to increase the bioavailability of nobiletin (10). Many applications such as using ionic liquids, encapsulation strategy, and nanoemulsion methods have been investigated to increase the bioavailability of nobiletin. In a study conducted to increase the bioavailability of nobiletin, it was found that transdermal application by dissolving nobiletin in an ionic liquid containing choline and geranic acid increased its bioavailability 20-fold compared to oral intake (14). As a result of the application of the encapsulation strategy in nobiletin, which is used to change the absorption and solubility of drugs, the release of nobiletin slowed down and the duration of its stay in the stomach and intestine was increased, increasing the absorption (17). Finally, one of the other methods used to increase the bioavailability of nobiletin is the use of nanotechnologies (18,19).

Nobiletin is derived from natural sources and is generally considered safe. Although most phytochemicals are considered nontoxic due to low bioavailability, toxicity

concerns may arise if systemic bioavailability is increased (20). In conclusion, although polymethoxyflavones exhibit promising bioactivities on cancer, research is based on in vitro and animal-based studies; Therefore, it is recommended that health benefits in humans be confirmed based on well-designed clinical studies (12).

4. RELATIONSHIP OF NOBILETIN WITH DISEASES

Nobiletin has demonstrated potential effectiveness in the treatment of certain diseases. The relationship of nobiletin with diseases and metabolic disorders is summarized in Figure 2 (1,5,7,10). Among the neuroprotective effects of nobiletin; are improvement in learning and memory impairment, improvement of ischemia-reperfusion injury, and reduction of dopaminergic neuron production. In the cardiovascular system, nobiletin improves metabolic syndrome, increases locomotor activity, and inhibits platelet aggregation. In addition, nobiletin can reduce insulin resistance, correct lipid metabolic disorders, down-regulate inflammatory and oxidative stress in the digestive system, inhibit osteoclastogenesis in the skeletal system, and reduce bone resorption by maintaining skeletal homeostasis. Among the anticancer properties of nobiletin, anti-angiogenesis, and anti-metastasis activities have been shown (5).

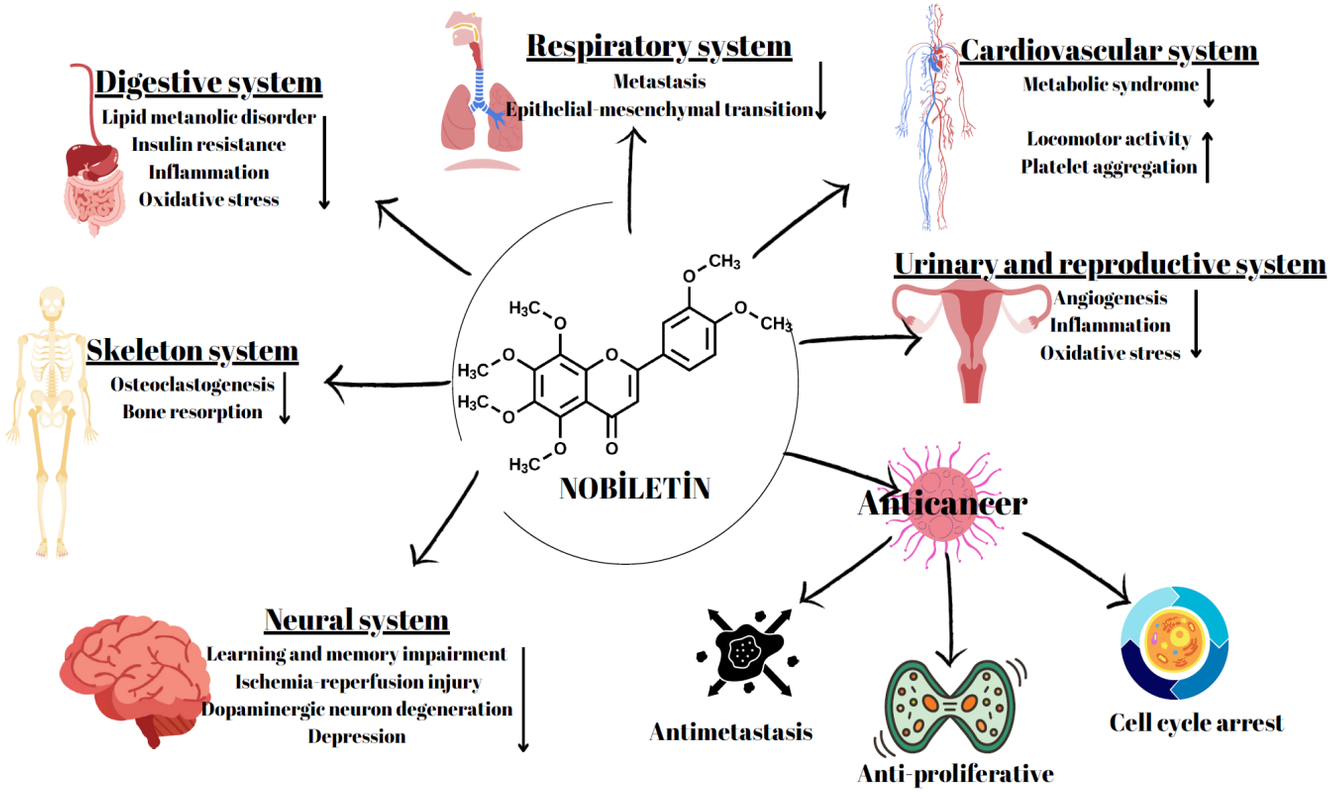

Figure 2. *Association of nobiletin with diseases and metabolic disorders (adapted from Huang H, et al., 2016)*

5. NOBILETIN AND CANCER

Citrus flavonoids have chemopreventive effects on various types of cancer. The anti-proliferative effectiveness of flavonoids depends on various factors, including the configuration and number of hydroxyl groups on the A and B rings of the flavonoid, the presence of methoxy groups, and their inherently low-polarity and planar molecular structure. Citrus flavonoids have attracted significant research attention due to their strong anti-inflammatory and chemopreventive properties, as well as their low toxicity in cellular and animal models (3).

Studies have examined the impact of nobiletin on various cancer types, including breast cancer (21-25), colorectal cancer (26,27), ovarian cancer (28-30), stomach cancer (31-33), lung cancer (34-37), liver cancer (38,39), prostate cancer (40-42), bladder cancer (43), thyroid cancer (44), nasopharyngeal cancer (45,46), kidney cancer (47,48), and bone cancer (49).

Nobiletin demonstrates inherent anti-cancer properties, and its derivatives have emerged as promising chemopreventive agents. Noteworthy derivatives renowned for their anti-cancer activity encompass 3'-DMN, 4'-DMN, 3',4'-DMN, and 5-DMN (7). Colonic metabolites of nobiletin are more potent than nobiletin in inhibiting cancer cell growth, arresting the

cell cycle, inducing apoptosis, and modulating key signaling proteins (11). While nobiletin metabolites, particularly 4'-DMN, and 3',4'-DMN, exhibit more potent anti-cancer and anti-inflammatory properties, it's worth noting that the conversion rate of nobiletin to these metabolites can be subject to variation (11,50).

Nobiletin and its derivatives can affect multiple pathways involved in cancer prognosis. Nobiletin demonstrates significant effects, encompassing cell cycle arrest in cancer cells, suppression of cell proliferation, promotion of apoptosis, inhibition of tumor development, attenuation of inflammatory responses, and limitation of angiogenesis (21,24,26,28,30,33,37,38,43).

5.1. Effects of Nobiletin in Signaling Pathways Playing a Role in Carcinogenesis

Signaling pathways are systems that control apoptosis, cell cycle, and cell growth (51). Alterations in signal transmission disrupt the regulation of cell proliferation and/or survival mechanisms. Consequently, oncogenic signal transduction actively contributes to processes such as tumor development, invasion, and metastasis (52). Signaling pathways altered in cancer affect many important cellular events such as apoptosis/cell cycle, chromatin modification, transcriptional modification, and DNA damage control. Basically, these pathways are; it is effective in processes parallel to the basic features of cancer such as cell proliferation, survival, metabolism, polarity, migration, differentiation, genomic instability, and tumor microenvironment (53).

Studies on nobiletin have shown its anti-carcinogenic effect by acting on different signaling pathways (Table 1), (53, 71). Nobiletin impacts various signaling pathways, including the nuclear factor erythroid 2-related factor 2 (Nrf2), Phosphoinositide-3 kinase (PI3K)/Akt, extracellular signal-regulated kinase (ERK), Myelocytomatosis (Myc), Wnt/β-catenin, transforming growth factor-beta (TGF-β), signal transducer and activator of transcription (STAT), and p53 pathways (10,39,49,54).

Table 1. *Signaling pathways in which nobiletin acts and cellular events in which the signaling pathway is involved*

Signal pathway	Cellular events in which the signaling pathway is involved
Nrf2	Oxidative stress response, cancer chemoresistance
PI3K	Cell proliferation, cell growth, cell survival, cellular metabolic changes, cell migration and polarity
Myc	Cell growth, proliferation, and apoptosis
Wnt	Cell proliferation, tissue homeostasis
ERK (MAP kinase)	Gene expression, cell division, cell viability, apoptosis, metabolism, differentiation, and motility
TGF-β	Cell proliferation and acquisition of stem/progenitor cell phenotype
p53	Cell survival, proliferation, senescence and apoptosis
STAT	Cell survival
JNK	Cell proliferation, apoptosis
Wnt/β-catenin (48)	Cell survival and proliferation, invasion
Src/FAK/STAT3 (24)	Angiogenesis
Cd36/Stat3/Nf-Kb (69)	Angiogenesis, migration, invasion
PARP-2/SIRT1/AMPK (45)	Growth inhibition and apoptosis
PI3K/Akt /mTOR (70)	Cell proliferation, apoptosis, angiogenesis

Akt: Protein kinase B, AMPK: AMP-activated protein kinase, Cd36: Differentiation cluster 36, ERK: Extracellular signal-regulated kinase, FAK: Focal adhesion kinase, JNK: Jun N-terminal kinase, MAP: Mitogen-activated protein, mTOR: Mechanistic target of rapamycin, Myc: Myelocytomatosis, Nf-Kb: Nuclear Factor kappa B, Nrf2: Nuclear factor erythroid 2 associated factor 2, p53: Tumor protein 53, PARP: Poly ADP ribose polymerase, PI3K: Phosphoinositide-3 kinase, SIRT1: Sirtuin 1, STAT: Signal converter and activator of transcription, TGF-β: Transforming Growth Factor Beta

5.2. Anti Proliferative Effect

Uncontrolled and unregulated cell proliferation is one of the most common features of cancer (26). Flavonoids have been reported to possess pharmacological properties that impede tumor progression by inhibiting both tumor cell proliferation and invasion (54).

In studies performed on hepatic, bladder, ovarian, thyroid, gastric, breast, nasopharyngeal, and renal cancer cells, it was found that nobiletin increases inhibition at varying rates depending on dose and time (25,28,31,38,43,44,47). When human ovarian cancer cells A2780 and OVCAR3 were incubated with nobiletin at doses ranging from 0-50 µM for 24 hours, the half-maximum inhibitory concentration (IC_{50}) was 35.31 and 34.85 µM, respectively, and had a strong effect on cell proliferation depending on the dose of nobiletin (30). Based on the results of treatments performed with 100 µl of nobiletin on MDA-MB-468, MCF-7, and SK-BR-3 breast cancer cells for 72 hours, the IC_{50} values were determined as 51.3 µM, 59.8 µM and 86.9 µM, respectively. After 168 hours, these values were determined as 20.3 µM, 39.6 µM, and 59.3 µM, respectively. IC_{50} values decreased as the incubation time with nobiletin increased (21).

Nobiletin exhibited an IC_{50} value of 23.82 ± 5.15 µg/ml in A549 lung cancer cells after 48 hours of exposure, demonstrating a dose-dependent and time-dependent inhibition of cell growth. In contrast, its anti-proliferative effect on the human umbilical vein endothelial cell line (ECV304) was less pronounced, with a 48-hour IC_{50} value of 157.78 ± 95.08 µg/ml (37). These results and other studies show that Nobiletin can show selectivity between cancer cells and healthy cells, and while reducing the viability of cancer cells, it causes less toxicity in healthy cells (37,44,55).

5.3. Effect on Cell Cycle and Apoptosis

Programmed cell death encompasses three distinct types, namely apoptosis, pyroptosis, and autophagy, which are executed by caspases, lysosomal proteases, and endonucleases (56). Apoptosis represents a natural form of cell death, triggered when multicellular organisms respond to internal or external stimuli. In contrast, autophagy represents a cellular process primarily dedicated to the degradation and recycling of intracellular components. Differing in both morphology and mechanisms from other modes of cell demise, pyroptosis is characterized as a pro-inflammatory form of cell death regulated by inflammation and caspase-1 activation (57). Apoptosis is regulated by the balance between antiapoptotic (such as B-cell lymphoma (Bcl)-2, Bcl-XL, Mcl-1) and proapoptotic proteins (such as Bcl-2-like protein 4 (Bax), Bcl2 cell death antagonist (Bad), caspase-3/-9) (47,58). Induction of apoptosis in cancer cells is an important approach to preventing and treating cancer (26). In apoptosis, three key proteins typically play pivotal roles: Bcl-2, Bax, and p53. The balance between Bcl-2 and Bax in the cell dictates the fate of the cell, determining whether it will survive or undergo apoptosis (37). Additionally, the activation of the p38 mitogen-activated protein kinase (MAPK) signal transduction pathway, triggered by the phosphorylation of p53, plays a crucial role in inducing apoptosis in cancer cells (25).

When 20 mg/L nobiletin was administered to liver cancer cells (SMMC-7721) for 48 hours, the cells were found to show signs of apoptosis. The observed morphological changes encompass cell shrinkage, the development of cytoplasmic vacuoles, disruption of the nuclear membrane, pycnosis, anisochromatin, and chromatin margination. Notably, cells treated with 80 mg/L of nobiletin exhibited heightened expression of caspase-3 (38).

Similarly, exposure of human bladder cancer cells to 60 µM of nobiletin led to increased DNA fragmentation, providing evidence of late apoptotic cell death induced by the treatment. This effect was associated with mitochondrial dysfunction, leading to the release of cytochrome C into the cytosol, activation of pro-apoptotic proteins, and suppression of anti-apoptotic proteins. Nobiletin-induced apoptosis was mediated through the modulation of endoplasmic reticulum stress via the PERK/eIF2/ATF4/CHOP pathway and downregulation of the PI3K/AKT/mTOR pathway (43). Furthermore, in SKOV3/TAX cells, nobiletin induced apoptosis by upregulating cleaved Caspase-9/-3 and poly ADP ribose polymerase (PARP). Additionally, it promoted apoptosis by inhibiting autophagic flow. Nobiletin activated the AKT signaling pathway, which played a role in autophagic degradation and apoptotic cell death (28).

Nobiletin also enhances increased reactive oxygen species (ROS) derived from damaged mitochondria, increased caspase 3 activity and PARP cleavage, and/or Beclin-1 triggers apoptosis by releasing mitochondrial cytochrome C into the cytosol to enhance autophagy by activating microtubule-associated protein 1A/1B-light chain 3B-II (LC3-II) and autophagy-related (ATG)5-ATG12 protein expression (30,33,45,56). In addition, nobiletin and its metabolites have effects such as induction of apoptosis and cell cycle arrest through the expression of p21, cyclin-dependent kinase (CDK), cyclin D1, CDK6, CDK4, Bax, and caspase (21,28,30,32,36,38).

Many cytotoxic agents have a cell cycle-arresting effect by acting on the G1, S, or G2/M phase (32). Treatment with 100 µM nobiletin provided inhibition of breast cancer cells through downregulation of ERK1/2, AKT, and the mechanical target of rapamycin (mTOR). Furthermore, there was an increase in the p21 protein in all cell lines, leading to the inhibition of Cyclin-D1, a critical regulator of the G0/G1 cell cycle checkpoint. This suggests that nobiletin arrests the cell cycle at the G0/G1 phase, resulting in reduced Cyclin-D1 levels (21). Furthermore, in the case of SMMC-7721 liver cancer cells, exposure to nobiletin at concentrations of 10, 20, and 40 mg/L for 48 hours led to an accumulation of cells in the G2/M phase. Following treatment with 40 mg/L nobiletin, the percentage of cells entering the G2/M phase increased to 15.13% and apoptosis rates increased to 31.73% (38). In addition, nobiletin induced G0/G1 phase arrest by suppressing growth and proliferation in SKOV3/TAX human ovarian cancer cells; it decreased the G2/M phase with the increase of p53 and p21 (28).

5.4. Effect on Metastasis

Tumor metastasis is a multifaceted process characterized by a sequence of alterations occurring at both intracellular and extracellular levels within cancer cells. As a result of the coordination of several signaling pathways, separation of tumor cells, motility, disruption of the extracellular matrix, invasion, migration, adhesion to endothelial cells, and regrowth at a distant site occur. The process of epithelial-mesenchymal transition is indeed considered a crucial factor in tumor metastasis (39,49). In the course of primary tumorigenesis, genetic and epigenetic modifications within tumor cells, coupled with alterations in the tumor microenvironment, promote the epithelial-mesenchymal transition. This transition enhances the propensity of cells to disseminate from the primary organ site, enter the bloodstream and lymphatic system, invade neighboring tissues, and ultimately establish secondary tumors in distant organs (59).

This can be attributed to the dysregulated control of various pathological processes related to tumor invasiveness and the activation of intracellular signaling molecules like mitogen-activated protein kinases and tyrosine kinases. (54).

Matrix metalloproteinase (MMP)-2 and MMP-9 are proteolytic enzymes responsible for the degradation and modification of the extracellular matrix. They also interact directly with cell surface molecules and facilitate the activation of the epithelial-mesenchymal transition process. Focal adhesion kinase, a non-receptor tyrosine kinase, is predominantly situated at sites of cell-matrix adhesions, where it functions as a central regulator of focal adhesions, thereby influencing cell adhesion and metastasis. Focal adhesion kinase is closely linked to the imbalance of E-cadherin during the epithelial-mesenchymal transition (35,49).

Studies have shown that nobiletin can regulate MMP expression in different cancer cells (35,39,46,48,49,54) (Figure 3).

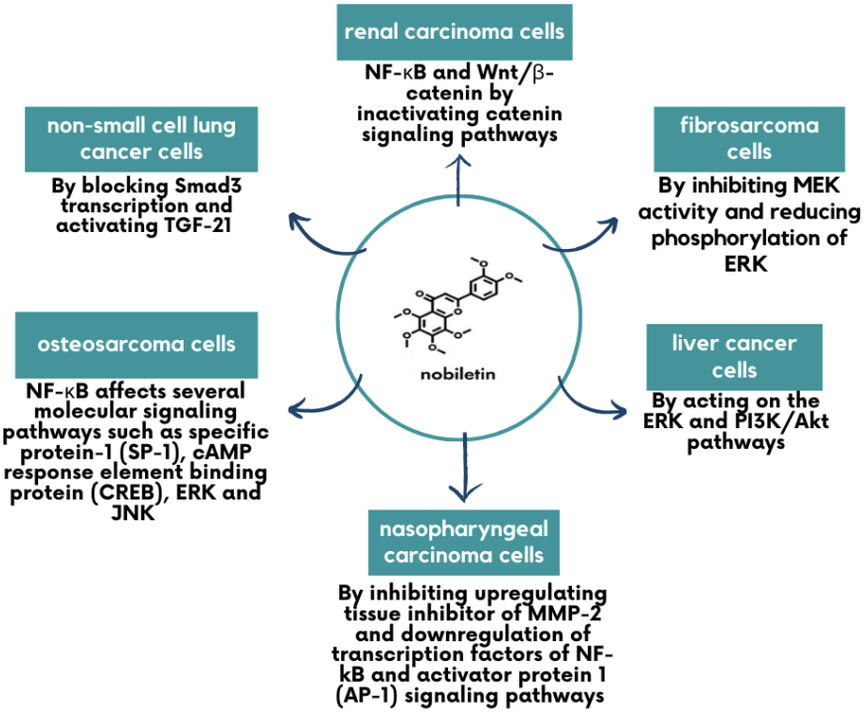

Figure 3. *Effects of nobiletin on MMP expression in different cancer cells. AKT: Protein kinase B, AP: Activator protein, cAMP: Cyclic adenosine monophosphate, CREB: cAMP response element binding protein, ERK: Extracellular regulated kinases, JNK: c-Jun N-terminal kinase, MEK: Mitogen-activated protein/extracellular signal-regulated kinase, MMP: Matrix metalloproteinase, NF-κB: Nuclear Factor kappa B, PI3K: Phosphoinositide-3 kinase, SP-1: Specificity protein 1, TGF: Transforming growth factor*

5.5. Drug Interactions and Use with Chemotherapy Agents

5.5.1. Drug Interactions with Nobiletin

Natural components found in foods can change the pharmacokinetics of drugs by affecting the activities of enzymes (cytochrome P450 (CYP)) that metabolize drugs or transporters (such as P-glycoprotein) that play a role in the absorption, distribution, metabolism, and excretion of drugs (60). Fruit juices are known to cause many food-drug interactions. It is reported that citrus juices, especially grapefruit juice, have more than 85 drug interactions because they inhibit CYP3A4, CYP1A2, and P-glycoprotein. Other juices may interact with medications; however, it is generally emphasized that there is not enough consumption to create interaction (61).

There is no clinical study yet on food-drug interaction for nobiletin. However, an in vitro study conducted to determine the drug interaction of nobiletin, sinensetin, and tangeretin compounds in clementine juice showed a possible inhibitory effect of nobiletin on CYP1A2 and CYP3A4. However, it has been reported that CYP3A4 inhibition is likely to be the result of additive or synergistic effects caused by various compounds. This research for nobiletin is the first report assessing interaction with CYP1A2 (62).

Predicting potential drug interactions caused by fruit juices is difficult due to the unknown number of phytochemicals found in fruit juice, unknown doses, and individual differences among individuals who consume them along with their medications (60). As stated in the literature, although there is evidence that some fruit juices may affect

drug distribution and therefore interact with drugs, there are not enough clinical studies to evaluate their role in drug interactions. Consequently, further research is needed to better understand the mechanisms behind nobiletin drug interactions.

5.5.2. Nobiletin Use with Chemotherapy Agents

New treatment strategies are needed to increase the therapeutic effects and reduce the side effects of drugs used in cancer treatment. For this reason, the potential effects of the combination of chemotherapy drugs and natural compounds have been frequently investigated recently (55,63). With the application of 4'-DMN (36 µM) or atorvastatin (18 µM) separately to HT-29 human colon cancer cells, growth inhibition was observed in these cells at rates of 25.89% and 20.89%, respectively. However, when these compounds were given in combination (7.2 µM atorvastatin with 14.4 µM 4'-DMN), a significant increase in the inhibition rate (53.84%) was found. This combined treatment triggered cellular apoptosis by synergistically elevating the expression levels of p53 and cleaved caspase-3, leading to stronger inhibition of cancer cells (26). Similarly, the combination therapy of paclitaxel and carboplatin with nobiletin demonstrated a synergistic preventive effect against the proliferation of A549 and H460 cell lines. Additionally, it was observed that as the ratios of nobiletin, paclitaxel, and carboplatin increased, the percentage of apoptotic cells decreased (36). In another combination therapy, the co-administration of sorafenib and nobiletin induced heightened apoptotic cell death and cell cycle arrest at the G0/G1 phase in PC-3 prostate cancer cells. This effect was characterized by the upregulation of Bax, Rb1, and CDKN1A (p21) levels compared to the treatment with nobiletin or sorafenib as individual agents (55).

Chemotherapy is often used to treat many types of cancer, but multi-drug resistance (MDR) often causes chemotherapy failure and kills the majority of patients (64). MDR phenotypes, both classical and non-classical, are accountable for the cellular mechanisms that lead to drug resistance. P-glycoprotein (P-gp) functions as an active component of the blood-brain barrier, serving as an ATP-dependent efflux pump. It is encoded by the MDR1 gene and plays a pivotal role in regulating the passage of diverse molecules across the blood-brain barrier (9,10). Overexpression of P-gp is associated with poor prognosis in many types of cancer and is frequently seen in clinically recurrent tumors (65). Increased expression of P-gp enhances the aggressive behavior and progression of cancer cells through its role in promoting the epithelial-mesenchymal transition. Anti-cancer drugs exert their inhibitory effects on the proliferation and survival of MDR cancer cells by targeting and suppressing the activity of P-gp (10). Nobiletin has been shown to work as an inhibitor of MDR-flux proteins by competing with chemotherapy drugs for the same P-gp binding site, thereby enabling in vitro enhancement of the efficacy of cancer chemotherapy (63). In the paclitaxel-resistant ovarian tumor cell line (A2780/T) and its parental line (A2780), nobiletin at a dose of 9 µM reversed the multidrug resistance of ovarian tumor cells of resistant A2780/T and rendered resistant cells 433 times more susceptible compared to A2780 cells (63).

A compound formed by the synthesis of nobiletin, 29d, exhibited 280 times greater water solubility than nobiletin and in a drug-resistant A549/T xenograft model, it has been shown to inhibit tumor growth more effectively than nobiletin and significantly increase the concentration of paclitaxine in tumors when administered together with paclitaxel (15 mg/kg) at a dose of 50 mg/kg (64). It has been shown that 0.5 µM adriamycin used in combination with 50 µM nobiletin in non-small cell lung cancer cells (parental and adriamycin-resistant A549 cells) has a good synergistic effect, and the combined treatment reduces tumor volume by 84%. It has been found that nobiletin suppresses the Akt/GSK3/β-catenin/MYCN signaling pathway and inhibits the expression of MDR1, resulting in increased accumulation of adriamycin. It has also been reported to potentiate apoptosis with increased caspase-3 activation, PARP cleavage, and sub-G1 accumulation compared to treatment with adriamycin alone (34).

6. RECOMMENDED DOSE-TOXICITY STUDIES

Many compounds from natural sources have become promising candidates for the development of a new drug because of their pharmacological benefits (1). Assessments of oral acute and chronic toxicity play a crucial role in evaluating the safety of pharmaceuticals and botanical substances for human consumption. It's worth noting that there is a scarcity of comprehensive toxicological data available regarding polymethoxy flavones (9).

Alterations in body weight are frequently employed as an indicator of potential toxicity. If any toxicity occurs, body weight is expected to be significantly reduced (7). In a research study examining the chemopreventive properties of nobiletin and its metabolites in colon cancer, it was found that after treatment of cells with 40 µM or oral ingestion of 0.05% concentration of nobiletin for 20 weeks, there was no significant change in body weight, liver weight, spleen appearance and behavior in rats and did not cause any adverse side effects (11). According to an in vitro study on prostate cancer cells, no toxic effect of nobiletin was observed in human umbilical vein endothelial cells at a concentration of 80 µM (66). In the study on lung cancer cells, mice were administered 100 mg, 200 mg, or 300 mg of nobiletin per body weight, and no signs of toxicity were observed by monitoring body weight in mice (37). Likewise, to assess the potential toxicity of nobiletin, doses of 200 and 400 mg/kg/day were administered to C57 mice via gastric lavage. The results of the study indicated that there were no substantial reductions in the mice's body weight following the nobiletin treatments. Furthermore, no noteworthy pathological alterations were detected in the heart, liver, kidney, spleen, or intestines of the mice (47).

In a research study, a liquid extract containing a high concentration of polymethoxy flavones obtained from orange peels, which included nobiletin (19.8 mg/g), sinensetin (17.4 mg/g), scutellarein tetramethyl ether (10.8 mg/g), and tangeretin (3.88 mg/g), showed similar IC_{50} values in both normal thyroid cells and anaplastic thyroid cancer cells. This extract demonstrated significant effectiveness in inhibiting the metabolic activity of cancer cells, but it also displayed some level of cytotoxicity towards normal cells (44). This study increases the importance of the application of nobiletin alone to selectively target cancer cells without toxic effects on healthy tissues. Taking into account both a mixture of polymethoxylated flavones containing 32.5% nobiletin and the in vivo mutagenic tests conducted with C. reticulata peel extract containing 50.3 mg/g nobiletin and 18.7 mg/g tangeretin, EFSA (European Food Safety Authority) has expressed the opinion that there are no concerns regarding genotoxicity related to polymethoxylated flavones (67). In a 90-day experimental study involving rats, a test substance characterized by its richness in nobiletin and tangeretin, containing 69.7 mg/g of nobiletin and 29.5 mg/g of tangeretin, was administered at varying doses of 54, 180, or 540 mg/kg body weight (bw) per day. Among male rats receiving the highest dose of 540 mg/kg bw per day, an occurrence of hyaline droplet nephropathy, a condition typically observed in adult male rats, was noted. However, this condition was not considered a relevant endpoint. No other adverse effects were observed throughout the study (68). The EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances Used in Animal Feed) identified NOAEL (No Observed Adverse Effect Level) values of 38 mg/kg bw per day for nobiletin (67). Due to differences between biological systems, certain doses may be beneficial for some people and harmful for others. Therefore, although the effects and mechanisms of nobiletin on various types of cancer have been demonstrated, further research is needed to develop individualized recommendations. In nobiletin studies, factors such as dose-effect relationship, dose interval, and time-effect relationship should be taken into consideration and appropriate models should be used to evaluate possible effects (20).

7. CONCLUSION AND RECOMMENDATIONS

In recent times, there has been a growing interest in utilizing plants and fruits for the treatment of various diseases. This inclination is rooted in the existence of advantageous natural compounds within plants and fruits, along with their metabolites. These compounds, upon absorption into the body, engender health-promoting benefits. The discernment, extraction, and refinement of these natural chemicals hold significant importance, particularly in the context of addressing diseases, notably human malignancies. A multitude of research endeavors have been dedicated to exploring the potential of natural plant-derived compounds in the treatment of cancer.

As nobiletin is derived from citrus peels, it is naturally abundant and demonstrates that its utilization in disease treatment represents a cost-effective approach. Both itself and its metabolites have important anti-cancer properties. It prevents cancer cell growth, proliferation, and metastasis by affecting important signaling pathways. It has been shown that nobiletin targets only cancerous cells and has little effect on healthy cells. However, although there are some suggestions that lower doses may affect cancer, it is necessary to increase the bioavailability of nobiletin. It is thought that it is not only limited to cancer but may have the potential to be a new drug due to its positive effects on other diseases. Despite its natural origin and the prevailing perception of safety, nobiletin's toxicity remains insufficiently investigated across various cell types and tissues. Acute and chronic toxicity studies are needed for oral consumption.

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