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Multifunctional role of Nobiletin in cancer chemoprevention

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ABSTRACT

The diversity of highly bioactive and pharmacologically active natural products which recognize essential biological targets having exquisite specificity, constitutes a massive pharmacological database for discovery of valuable drugs. The rapid accumulation of information has revealed chemopreventive role of nobiletin against wide variety of cancers. Recent efforts are now being expanded and new integrative omics technologies have illuminated continuously upgrading list of molecular mechanisms which underlie carcinogenesis and metastasis. In this mini-review, we explore the progress that has been made in the identification of promising molecular targets of nobiletin.

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Introduction

Natural product research remains one of the most vibrant areas of chemistry despite the fact that justifications for its pursual have been debated widely by proponents and opponents over decades (1-6). Intriguingly, significant interest of medicinal chemists and natural product researchers in the characterization of natural products arises not only because of transition from preclinical to clinical phases, but also because of their expectations that botanical drugs will fill unmet market needs for safer and clinically effective drugs. Molecular biologists have started to gain an increasingly sophisticated understanding of the complex nature of cancer. Pharmacologically active molecules from natural sources have attracted worldwide appreciation and because of encouraging results obtained from cell culture studies and animal models-based empirical evidence, there is tremendous advancement in identification of regulatory role of natural products in cancer chemoprevention (7-11).

Demystification of cell signaling networks have enabled us to pave the way for precise medicine and strengthen our arsenal in the fight against cancer (12-19). Target identification studies have revealed that a large majority of molecules have significant ability to modulate myriad of cell signaling pathways to inhibit/prevent cancer (20-22).

One of the most effective flavonoids that exhibits potent chemopreventive effects at molecular and cellular level is Nobiletin. Chemically, nobiletin is 5,6,7,8,3′,4′-hexamethoxyflavone that has been predominantly derived from the peel of citrus fruits. Literature has shown that nobiletin can be extracted from a wide range of plants as mandarin oranges, tangerines, valencia oranges, bitter oranges, koji oranges, satsuma mandarins and many more varieties. Studies have shown that nobiletin exhibits various pharmacological and biological activities as anti-inflammatory, antioxidant, antidiabetic effects, cardioprotective, hepatoprotective, antirheumatic and neuroprotective. Nobiletin has been shown to ameliorate diabetes (23-27) and inflammation (28-30).

One of the major side effects of chemotherapeutic agents is their low therapeutic index that renders cytotoxic effects on the normal cells. One of the biggest challenges in cancer research is the discovery of chemotherapeutic agents with maximum toxicity for the cancer cells with minimum effects on the normal cells. The inherent low toxicity of plant-based food-derived flavonoids is of particular importance for their chemotherapeutic and preventive effects. Ability of natural compounds to targets multiple sites, diverse mechanisms of action, lower cost, easy access and higher therapeutic index make them an attractive candidate for their application in cancer preven-

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tion. Epidemiological and laboratory studies have shown lower incidence of certain subtypes cancer with increased consumption of dietary flavonoids. Chemopreventive effects of flavonoids have been established in a number of studies in various cancers. Accumulating data suggests the high potential of nobiletin in cancer prevention in cell culture studies and animal models by modulating key molecular signaling pathways involved in inflammation, cell proliferation, cell cycle arrest, cell death, migration/invasion and metastasis (31-33). Apart from that, nobiletin has been shown to increase the chemopreventive effects of various drugs by its synergetic effects.

Nobiletin mediated cancer chemopreventive effects have been reviewed previously in different cancers (34-36). However, in this review we have portrayed and sketched the signaling landscapes regulated by nobiletin in wide variety of cancers.

Regulation of NF-κB pathway

Importantly, nuclear transcription factor-κB (NF-κB) remains in nucleus in an activated form in cancer cells compared to normal cells where it stays in the cytoplasm (37). This explains the extensive involvement of NF-κB in the development and progression of cancer. Moreover, inhibition of NF-κB in cancer cells can lead to anti-inflammatory response, antimetastatic effects, cell cycle arrest and apoptotic death therefore plays vital role in the prevention and spread of cancer (38). Available literature directs towards the pharmaceutical targeting of NF-κB by natural products in cancer chemoprevention (39).

Further, NF-κB has shown the ability to bind with the promoter regions of Matrix metallopeptidases and activated NF-κB has been linked with uncontrolled MMPs. Both MMP-2 and MMP-9 are the downstream targets of Nuclear Factor kappa B (NF-κB) (shown in figure 1) (40). MMPs are well known to degrade extracellular matrix and are considered the hallmark of metastasis (41). Specifically, MMP-2 and MMP-9 are known to initiate the epithelial-mesenchymal transition (EMT) and is characterized by the loss of e-cadherin (gene that maintains cell-to-cell adhesion) that further leads to migration and invasion. Importantly, MMP-2 and MMP-9 are frequently associated with the poor prognosis of cancer treatment (41).

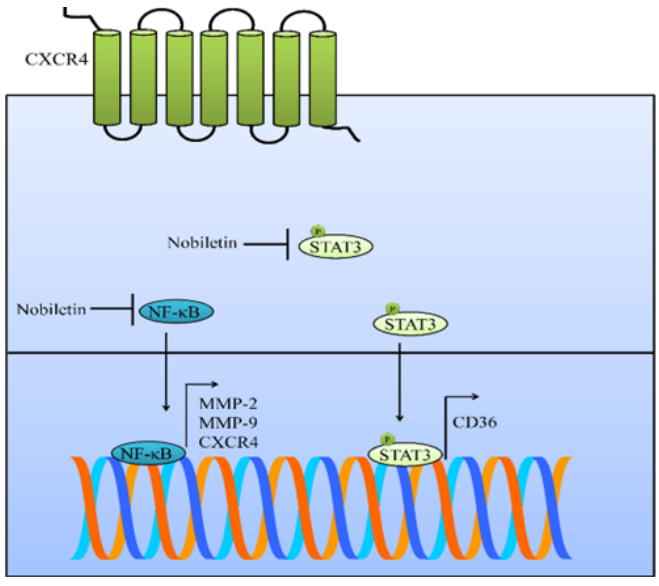

Figure 1. Nobiletin mediated inhibition of nuclear accumulation of NF-κB and STAT3. NF-κB stimulated the expression of MMP-2/9 and CXCR4. Whereas, STAT3 transcriptionally upregulated CD36. Nobiletin downregulated transcriptional networks of NF-κB and STAT3.

Nobiletin significantly inhibited MMP-2 enzyme activity and protein levels in HONE-1 and NPC-BM cells. Nobiletin also increased the expression of TIMP2 (Tissue inhibitor of metalloproteinase 2). Nobiletin significantly reduced the binding of NF-κB and AP-1 to the promoter regions of MMP-2. Nobiletin effectively reduced the numbers of pulmonary metastatic nodules in mice injected with HONE-1 cells (42).

Nobiletin downregulated the expression of CXCR4 in MDA-MB-231 cancer cells. CXCR4 promoter has several NF-κB binding sites. Nobiletin mediated inhibition of constitutive NF-κB activation resulted in the downregulation of CXCR4 in MDA-MB-231 cancer cells (43).

As already established, MMP-2/9 are the downstream targets of NF-κB and the previous literature emanates the role of focal adhesion kinase (FAK) in the regulation NF-κB phosphorylation and transcriptional activity (44). In human gastric adenocarcinoma AGS cells, nobiletin has been shown to inactivate FAK and phosphoinositide-3 kinase/Akt (PI3K/Akt) to curtail angiogenesis. Nobiletin reduced the levels of p-Akt and MMP-2/9 in Akt-transfected AGS cancer cells. Relevantly, nobiletin markedly decreased the nuclear level of NF-κB and its binding to NF-κB response elements (45). This suggests that nobiletin can inhibit/prevent carcinogenesis via FAK/Akt- NF-κB- MMP-2/9 pathway.

In osteocarcinoma cell lines (U2OS and HOS cells), nobiletin at the concentrations of 100 μM can downregulate MMP-2/9 by inhibiting extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and NF-κB. Further, nobiletin inhibited the migration, invasion and the mobility of osteocarcinoma cells. This suggests the possible role of NF- κB in regulating metastasis in cancer cells (46).

Previous literature has already established that AKT pathways can regulate the activation (47, 48) and translocation of NF-κB and NF-κB can directly regulate hypoxia-inducible factor-1α (HIF-1α) (49). Another study in prostate cancer cells (PC-3 and DU-145) has identified that the nobiletin inhibited nuclear translocation of NF-κB. Nobiletin inhibited phosphorylation of AKT and downregulated the expression of HIF-1α and VEGFA (50). A similar study validated the inhibition of VEGFA via AKT-NF-κB-HIF-1α pathway in ovarian epithelial cells. Nobiletin markedly inhibited the growth of the tumors derived from A2780/CP70 cancer cells subcutaneously injected in rodent models (51).

In human pancreatic cancer cells, nobiletin halted the proliferation of cells with IC50 at the concentrations of 6.12 μM by inducing G0/G1 arrest, depleting cyclin D1 and CDK4 expression. Further, nobiletin exhibited a dose-dependent inhibition of NF-κB, postulating its possible role in the anti-metastatic potential of nobiletin (52).

Nobiletin induced an increase in the nuclear levels of NF-κB and triggered apoptosis and pyroptosis. There was an evident increase in the expression of NLRP3 or GSDMD in cancer cells transfected with miR-200b mimics. Nobiletin remarkably potentiated the pyroptotic effects of miR-200b mimics. Nobiletin or miR-200b mimics independently exerted significant pyroptotic effects on breast cancer cells but intriguingly, these effects were

found to be more pronounced by combinatorial treatments with nobiletin and miR-200b mimics. JAZF1 (Juxtaposed with another zinc finger protein 1) is directly targeted by miR-200b. JAZF1 was notably inhibited in miR-200b-mimics-transfected cancer cells but the levels of JAZF1 were found to be enhanced significantly in the presence of miR-200b inhibitors. miR-200b inhibitors caused inactivation of NF-κB pathway in nobiletin-treated BT549 cancer cells but these effects were reported to be more pronounced in JAZF1-overexpressing cancer cells (53).

Growing data from genetic and epidemiological has shown that disruption in circadian clock is linked with the incidence of cancer (54). The nuclear receptors as retinoid-related orphan receptors (RORs) are well known to regulate circadian pathways, metabolic pathways, oncogenesis and much more (54). Nobiletin induced anti- tumor effects in Triple negative breast cancer (TNBC) cells primarily by attenuating NF-κB activation and NF-κB-mediated regulation of RORs. Interestingly, nobiletin has been shown to upregulate the binding of ROR to response elements at IκBα promoter and initiated powerful inhibited the translocation of p65 to nucleus. Conversely, induction of p65 expression abolished the anti-TNBC effects of nobiletin. Enhancement of nobiletin initiated circadian rhythm by suppressing NF-κB expression can be novel way of chemoprevention and treatment against this deadly and aggressive form of breast cancer. Docetaxel and nobiletin synergistically induced regression of the tumor xenografts in mice orthotopically transplanted with MDA-MB-231 cancer cells. Antitumor effects of nobiletin were also investigated in syngeneic xenograft models using DB7 cells in immune-competent mice. Importantly, the average tumor volume of the nobiletin-treated rodent models was significantly reduced. Moreover, TNFα levels of plasma and tumor were significantly decreased by nobiletin (55).

Role of JAK/STAT and AKT pathways

In contrast to the normal cells, cancer cells have higher proliferative potential. It has been observed that the transcription factor STAT3 (Signal transducer and activator of transcription 3) is constitutively over-expressed in numerous carcinoma cells (56). Upregulated STAT3 could abrogate apoptosis and regulate various pro-metastatic genes as MMPs, survivin and other genes that determine the survival of cancer cells. Nobiletin was shown to repress the metastatic potential of human renal carcinoma cells by down-regulating migration, invasion and proliferation of cells via inhibiting JAK2/STAT3 pathways (57). In human renal carcinoma cells, nobiletin can significantly inhibit STAT3, SRC and AKT activation in a dose-dependent manner. The in-vitro results were validated in *in vivo* experiments that showed that nobiletin can significantly reduce the tumor volume and weight compared to control, suggesting the promising anti-cancer potential of this phytochemical (57).

Cluster of differentiation 36 (CD36) is considered as an oncogenic marker that promotes tumor metastasis. It is a scavenger receptor that imports long chain fatty acids to the cells. Nobiletin has been shown to inhibit STAT3/CD36 signaling axis (shown in figure 1). Mechanistically, at molecular level, nobiletin inhibits angiogenesis when CD36 gene element i.e a Gamma interferon activation site (GAS) provides binding site for STAT3. Further, STAT3 activates NF-κB leading to the pro-metastatic signaling. Overall, this study illustrates that nobiletin can suppress migration, invasion, sphere formation in breast carcinomas and stem cells formation in cancer (58).

Majority of prostate cancers shows good initial response to the anti-androgen therapies. Nobiletin improved the therapeutic efficacy of an anti-androgen drug bicalutamide both in androgen independent prostate cancer cells. The combination of nobiletin and bicalutamide synergistically inhibited migration, colony formation and promoted apoptosis. Further, the anti-metastatic effects of the combined treatments of nobiletin and bicalutamide were modulated by the downregulation of Erk, STAT3 and NF-κB molecular pathways. Interestingly, nobiletin has shown more sensitivity to induce apoptosis in androgen-independent prostate cancer cell line. This makes nobiletin an attractive combination therapy option for the treatment of androgen-independent prostate carcinomas (59).

Another investigation in multidrug resistant cancer cell lines (ABCB1 overexpressing cells A2780/T and A549/T) has shown that nobiletin can increase the sensitivity of various chemotherapeutic agents by the suppression of AKT/ERK/NRF2 axis. The dose-response relationship of nobiletin and inhibition of ABCB1 transporter activity was seen that indicated the role of nobiletin in maximizing the combat against multidrug resistance (60).

Another signaling pathway that is highly upregulated in cancer cells and is strongly linked with the fate of cancer cells is SRC/AKT signal transduction pathway (61). SRC proteins are proto-oncogenes that belong to non-receptor tyrosine kinase family. They can induce mitosis and increase the migration/invasion of carcinoma cells (62).

Another finding in ACHN and Caki-2 renal carcinoma cells has demonstrated that nobiletin can inhibit proliferation, induce apoptosis and cell cycle arrest in a dose-time dependent manner. Nobiletin can suppress the levels of phosphorylated SRC, phosphorylated AKT and phosphorylated STAT3, highlighting the possible underlying mechanism. Nobiletin inhibited the nuclear accumulation of YY1AP1 and STAT3 in renal carcinoma cells. Levels of p-STAT3 were found to be reduced in nobiletin treated ACHN and Caki-2 cells. Whereas, levels of p-YY1AP1 were reported to be increased in nobiletin treated cancer cells. Nobiletin reduced the weights and volumes of the tumors in mice subcutaneously inoculated with ACHN cells (63).

In colorectal cells, nobiletin can improve the sensitivity of oxaliplatin chemotherapy by suppressing PI3K/Akt/mTOR pathway. Nobiletin improved the apoptotic potential of oxaliplatin by the activation of Bax and cleaved-caspase-3 and suppression of anti-apoptotic protein Bcl-2 (64).

In another study in hepatocarcinoma cells, potent inducers of invasiveness i.e hepatocyte growth factor (HGF) and c-Met upregulation were employed to promote metastasis prior to the treatments with various flavones to compare their anti-metastatic effects. Among all flavones (apigenin, tricetin, tangeretin, and nobiletin), nobiletin significantly inhibited the aggressiveness of cancer cells by inhibiting migration, adhesion and invasion. Nobiletin markedly decreased the phosphorylation of ERK2 and Akt in ERK2 or Akt siRNA-transfected HepG2 cell. This suggests nobiletin can exhibit its anti-metastatic possibly by regulating both ERK and PI3K/Akt pathways. Promisingly, all anti-metastatic effects of nobiletin were seen at

non-cytotoxic concentrations that makes nobiletin a potent anti-cancer agent against liver cancer (65).

mTOR signaling

Substantial evidence demonstrates that mammalian or mechanistic target of rapamycin (mTOR) plays vital role in the initiation of cancer by regulating proliferation and metabolism of cells (66). Nobiletin can inhibit the mTOR expression and STAT3 in pancreatic cancer cell line (PANC-1). Around 15-20% of the pancreatic cancers have elevated mTOR expression that is linked with poor survival and prognosis. Gemcitabine is a commonly used chemotherapeutic agent for the treatment of pancreatic cancer and nobiletin can improve the anticancer effects of gemcitabine by inhibiting the phosphorylation of mTOR and STAT3. Another study in bladder cancer has provided the role of mTOR pathway in the nobiletin mediated inhibition of cancer growth. Nobiletin has been shown to induce endoplasmic reticulum (ER) stress mediated apoptosis via suppression of PI3K/AKT/mTOR pathway (67). A comprehensive insight of the molecular pathway initiated by nobiletin to induce anticancer effects has been elaborated by Zheng and colleagues in human nasopharyngeal carcinoma C666-1 cells. PARP2 overexpression abrogated nobiletin-induced apoptotic cell death. Nobiletin downregulated the protein level and mRNA expression of poly (ADP-ribose) polymerase (PARP2) that upregulated a downstream target SIRT1, a NAD^+-dependent histone deacetylase. Binding of PARP2 to the promoter region of SIRT1 caused transcriptional downregulation of SIRT1. However, activation of SIRT1 by nobiletin induced an increase in the phosphorylation of AMPK that inactivated mTOR signaling leading to the induction of apoptosis (68).

Detoxification of environmental carcinogens

One of the most carcinogenic tobacco derived nitrosamine is 4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone (NNK) that is linked with the incidence of lung cancer. Nobiletin has been shown to reduce the genotoxicity of NNK by inhibiting CYP2A enzyme in the lung of gpt delta transgenic mice. It is important to note that NKK is metabolically activated by CYP2A enzyme to the genotoxic metabolites (69). Another study has shown that nobiletin can downregulate the mutagenic potential of food derived environmental pro-carcinogen PhIP by inhibiting CYP1A2 that is involved in the bioactivation of PhIP (70).

Regulation of miRNAs by Nobiletin

Non-coding RNAs are categorized into different RNAs, such as microRNAs (miRNAs) (71-79), long non-coding RNAs (lncRNAs) (80-83) and circular RNAs (84-86). Research to date makes it clear that non-coding RNAs are central components of a complex interactome that underlies cancer onset and progression. Volume of high-throughput profiling studies and mechanistic analysis of miRNAs, lncRNAs and circular RNAs in carcinogenesis and metastasis has increased exponentially. Evidence highlighted intricate interactions between non-coding RNAs and target gene networks. Nonetheless, this knowledge represents major fraction of the landscape of their gene regulatory potential. The emergence of high-throughput sequencing technologies has allowed researchers to comprehensively characterize various non-coding RNAs in multiple cancers.

miR-15-5p has been shown to directly target negative regulators of WNT/β-catenin pathway, including AXIN2, WIF1 and NKD1. Nobiletin significantly repressed the expression of miRNA-15-5p in NSCLC cell lines. Furthermore, overexpression of miRNA-15-5p led to inhibition of AXIN2, WIF1 and NKD1. miRNA-15-5p inhibition led to reduction in the levels of β-catenin, while miRNA-15-5p overexpression triggered an increase in the levels of β-catenin. Remarkably, overexpression of miRNA-15-5p abrogated nobiletin-mediated repression of β-catenin. These findings indicated that nobiletin inhibited WNT/β-catenin pathway mainly by downregulation of miRNA-15-5p in NSCLC (87).

Nobiletin induced upregulation of miR-200b upto threefold in H1299 cells. Importantly, transfections of miR-200b mimics reduced Notch-1 levels in hypoxic H1299 cells. Overall, re-expression of miR-200b significantly reduced invasive and metastasizing potential of H1299 cells under hypoxia (88).

Nobiletin-loaded vesicular systems displayed significantly enhanced penetrability. Nobiletin-loaded composite penetration enhancer vesicles restored skin conditions in 7,12-Dimethylbenz[a]anthracene (DMBA) induced skin carcinogenesis. Nobiletin efficiently regulated miR-21 (oncogenic miRNA) and miR-29a (tumor suppressor miRNA). Nobiletin-loaded formulations reduced miR-21 and simultaneously enhanced miR-29a (89).

Discovery of non-coding RNAs has opened new horizons for pharmacological research and natural products mediated regulation of non-coding RNAs is gradually gaining widespread appreciation. Nobiletin mediated regulation of miRNAs is intriguing and further research related to modulation of lncRNAs and circRNAs will enable molecular oncologists to reap maximum benefits of cancer chemopreventive effects of nobiletin.

Cancer chemopreventive roles of Nobiletin in animal models

TGFβ considerably reduced degradation of β-catenin by proteasomes. Therefore, nuclear accumulation of β-catenin was also upregulated due to stimulation with TGF. Nobiletin considerably diminished the tethering of β-catenin to Slug promoter. Oral administration of nobiletin induced regression of the tumors in mice subcutaneously injected with U87 cells. There was a marked reduction in the levels of N-cadherin and Slug in the surgically excised tumor tissues from nobiletin-treated mice (90).

TGFβ increased the expression of Snail, Slug, Twist and ZEB1. However, TGFβ-mediated upregulation of target gene network was reversed by nobiletin. Moreover, nobiletin potently inhibited transcriptional activities of SMADs induced by TGFβ in A549 cells. SMAD3 overexpression severely impaired nobiletin-mediated inhibitory effects on TGFβ-driven increment in N-cadherin. SMAD3 transcriptionally regulated the expression of N-cadherin as well as E-cadherin but nobiletin interfered with SMAD3-mediated transcriptional activities. Nobiletin remarkably reduced metastatic tumor nodules on the surface of lungs in rodent models injected with A549 cancer cells through the tail veins. Likewise, nobiletin effectively inhibited metastases in C57BL/6 mice injected with Lewis cells through tail veins. Furthermore, nobiletin proficiently restricted tumor xenografts in animal models subcutaneously

transplanted with A549 cancer cells (91).

Paclitaxel concentrations were found to be substantially increased in the tumor tissues in mice combinatorially treated with paclitaxel and nobiletin. In addition, paclitaxel and nobiletin remarkably induced shrinkage of the tumor xenografts (92).

FOXO3A, a transcriptional repressor effectively downregulated the expression of SKP2 gene by directly binding to the promoter regions of SKP2 (93). Nobiletin and palbociclib synergistically suppressed growth of the tumors in mice inoculated with 786-O cells (94).

Concluding remarks

Multidisciplinary team structures comprising of natural product researchers, molecular biologists and clinicians have collaboratively sketched a wholistic path for clinical translation of wide-ranging natural products. Tumors with a high degree of genomic diversity are therapeutically challenging. In accordance with this concept, better knowledge of the regulatory roles of nobiletin in cancer chemoprevention will be helpful in meticulous transition of nobiletin from animal model studies to various phases of clinical trials.

Contribution of authors

RA conceived the idea and technically edited the entire manuscript. DSM, UO, MAR, IMY and JP browsed the literature and prepared the draft. RA designed the diagram. All the authors read and approved the manuscript

References

1. Clardy J, Walsh C. Lessons from natural molecules. Nature. 2004 Dec 16;432(7019):829-37. doi: 10.1038/nature03194.
2. Marcus DM, Grollman AP. Botanical medicines--the need for new regulations. N Engl J Med. 2002 Dec 19;347(25):2073-6. doi: 10.1056/NEJMsb022858.
3. Mann, J. Natural products in cancer chemotherapy: Past, present and future. Nat. Rev. Cancer 2002, 2, 143–148. https://doi.org/10.1038/nrc723.
4. Rodrigues T, Reker D, Schneider P, Schneider G. Counting on natural products for drug design. Nat Chem. 2016 Jun;8(6):531-41. doi: 10.1038/nchem.2479.
5. Koehn FE, Carter GT. The evolving role of natural products in drug discovery. Nat Rev Drug Discov. 2005 Mar;4(3):206-20. doi: 10.1038/nrd1657.
6. Farooqi AA, Kapanova G, Kalmakhanov S, Tanbayeva G, Zhakipbekov KS, Rakhmetova VS, Syzdykbayev MK. Regulation of Cell Signaling Pathways and Non-Coding RNAs by Baicalein in Different Cancers. Int J Mol Sci. 2022 Jul 29;23(15):8377. doi: 10.3390/ijms23158377.
7. Farooqi AA, Attar R, Xu B. Anticancer and Anti-Metastatic Role of Thymoquinone: Regulation of Oncogenic Signaling Cascades by Thymoquinone. Int J Mol Sci. 2022 Jun 5;23(11):6311. doi: 10.3390/ijms23116311.
8. Wang SC, Chang HS, Tang JY, Farooqi AA, Kuo YT, Hsuuw YD, Lee JW, Chang HW. Combined Treatment with Cryptocaryone and Ultraviolet C Promotes Antiproliferation and Apoptosis of Oral Cancer Cells. Int J Mol Sci. 2022 Mar 10;23(6):2981. doi: 10.3390/ijms23062981.
9. Chen YC, Yang CW, Chan TF, Farooqi AA, Chang HS, Yen CH, Huang MY, Chang HW. Cryptocaryone Promotes ROS-Dependent Antiproliferation and Apoptosis in Ovarian Cancer Cells. Cells. 2022 Feb 12;11(4):641. doi: 10.3390/cells11040641.
10. Xu B, Guo M, Ma L, Farooqi AA, Wang L, Qiao G, Liu M, Zuo L, Ye H, Lin X, Cao S. Mere15, a novel polypeptide from Meretrix meretrix, inhibits proliferation and metastasis of human non-small cell lung cancer cells through regulating the PI3K/Akt/mTOR signaling pathway. Neoplasma. 2021 Nov;68(6):1181-1189. doi: 10.4149/neo_2021_210509N628.
11. Wang L, Cheng L, Ma L, Ahmad Farooqi A, Qiao G, Zhang Y, Ye H, Liu M, Huang J, Yang X, Lin X, Cao S. Alnustone inhibits the growth of hepatocellular carcinoma via ROS- mediated PI3K/Akt/mTOR/p70S6K axis. Phytother Res. 2022 Jan;36(1):525-542. doi: 10.1002/ptr.7337.
12. Dilmac S, Kuscu N, Caner A, Yildirim S, Yoldas B, Farooqi AA, Tanriover G. SIRT1/FOXO Signaling Pathway in Breast Cancer Progression and Metastasis. Int. J. Mol. Sci. 2022; 23(18):10227. doi.org/10.3390/ijms231810227.
13. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144(5):646-74. doi: 10.1016/j.cell.2011.02.013.
14. Puisieux A, Brabletz T, Caramel J. Oncogenic roles of EMT-inducing transcription factors. Nat Cell Biol. 2014 Jun;16(6):488-94. doi: 10.1038/ncb2976.
15. Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol. 2019 Feb;20(2):69-84. doi: 10.1038/s41580-018-0080-4.
16. Rosell R. Mediating resistance in oncogene-driven cancers. N Engl J Med. 2013 Apr 18;368(16):1551-2. doi: 10.1056/NEJMcibr1214549.
17. Hidalgo M, Maitra A. The hedgehog pathway and pancreatic cancer. N Engl J Med. 2009 Nov 19;361(21):2094-6. doi: 10.1056/NEJMcibr0905857.
18. Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell. 2011 Oct 14;147(2):275-92. doi: 10.1016/j.cell.2011.09.024.
19. Farooqi AA, Li Y, Sarkar FH. The biological complexity of RKIP signaling in human cancers. Exp Mol Med. 2015 Sep 25;47(9):e185. doi: 10.1038/emm.2015.70.
20. Gasparri ML, Attar R, Palaia I, Perniola G, Marchetti C, Di Donato V, Farooqi AA, Papadia A, Panici PB. Tumor infiltrating lymphocytes in ovarian cancer. Asian Pac J Cancer Prev. 2015;16(9):3635-8. doi: 10.7314/apjcp.2015.16.9.3635.
21. Naoum GE, Buchsbaum DJ, Tawadros F, Farooqi A, Arafat WO. Journey of TRAIL from Bench to Bedside and its Potential Role in Immuno-Oncology. Oncol Rev. 2017 Apr 28;11(1):332. doi: 10.4081/oncol.2017.332.
22. Saleem M, Abbas K, Manan M, Ijaz H, Ahmed B, Ali M, Hanif M, Farooqi AA, Qadir MI. Review-Epigenetic therapy for cancer. Pak J Pharm Sci. 2015 May;28(3):1023-32.
23. Yuan S, Ye Z, Li Y, Zou J, Wu M, Wang K, Liao W, Shen J. Hypoglycemic Effect of Nobiletin via Regulation of Islet β-Cell Mitophagy and Gut Microbiota Homeostasis in Streptozocin-Challenged Mice. J Agric Food Chem. 2022 May 18;70(19):5805-5818. doi: 10.1021/acs.jafc.2c00148.
24. Xu M, Wang R, Fan H, Ni Z. Nobiletin ameliorates streptozotocin-cadmium-induced diabetic nephropathy via NF-κB signalling pathway in rats. Arch Physiol Biochem. 2021 Aug 4:1-9. doi: 10.1080/13813455.2021.1959617.
25. Nguyen-Ngo C, Salomon C, Quak S, Lai A, Willcox JC, Lappas M. Nobiletin exerts anti-diabetic and anti-inflammatory effects in an in vitro human model and in vivo murine model of gestational diabetes. Clin Sci (Lond). 2020 Mar 27;134(6):571-592. doi: 10.1042/CS20191099.
26. Liu Z, Han Y, Zhao F, Zhao Z, Tian J, Jia K. Nobiletin suppresses high-glucose-induced inflammation and ECM accumulation in

human mesangial cells through STAT3/NF-κB pathway. J Cell Biochem. 2019 Mar;120(3):3467-3473. doi: 10.1002/jcb.27621.

27. Zhang N, Yang Z, Xiang SZ, Jin YG, Wei WY, Bian ZY, Deng W, Tang QZ. Nobiletin attenuates cardiac dysfunction, oxidative stress, and inflammatory in streptozotocin: induced diabetic cardiomyopathy. Mol Cell Biochem. 2016 Jun;417(1-2):87-96. doi: 10.1007/s11010-016-2716-z.
28. Chai W, Zhang J, Xiang Z, Zhang H, Mei Z, Nie H, Xu R, Zhang P. Potential of nobiletin against Alzheimer's disease through inhibiting neuroinflammation. Metab Brain Dis. 2022 Apr;37(4):1145-1154. doi: 10.1007/s11011-022-00932-7.
29. Yarim GF, Yarim M, Sozmen M, Gokceoglu A, Ertekin A, Kabak YB, Karaca E. Nobiletin attenuates inflammation via modulating proinflammatory and antiinflammatory cytokine expressions in an autoimmune encephalomyelitis mouse model. Fitoterapia. 2022 Jan;156:105099. doi: 10.1016/j.fitote.2021.105099.
30. Li S, Li X, Chen F, Liu M, Ning L, Yan Y, Zhang S, Huang S, Tu C. Nobiletin mitigates hepatocytes death, liver inflammation, and fibrosis in a murine model of NASH through modulating hepatic oxidative stress and mitochondrial dysfunction. J Nutr Biochem. 2022 Feb;100:108888. doi: 10.1016/j.jnutbio.2021.108888.
31. Ikegawa T, Ushigome F, Koyabu N, Morimoto S, Shoyama Y, Naito M, Tsuruo T, Ohtani H, Sawada Y. Inhibition of P-glycoprotein by orange juice components, polymethoxyflavones in adriamycin-resistant human myelogenous leukemia (K562/ADM) cells. Cancer Lett. 2000 Nov 10;160(1):21-8. doi: 10.1016/s0304-3835(00)00549-8.
32. Murakami A, Nakamura Y, Torikai K, Tanaka T, Koshiba T, Koshimizu K, Kuwahara S, Takahashi Y, Ogawa K, Yano M, Tokuda H, Nishino H, Mimaki Y, Sashida Y, Kitanaka S, Ohigashi H. Inhibitory effect of citrus nobiletin on phorbol ester-induced skin inflammation, oxidative stress, and tumor promotion in mice. Cancer Res. 2000 Sep 15;60(18):5059-66.
33. Minagawa A, Otani Y, Kubota T, Wada N, Furukawa T, Kumai K, Kameyama K, Okada Y, Fujii M, Yano M, Sato T, Ito A, Kitajima M. The citrus flavonoid, nobiletin, inhibits peritoneal dissemination of human gastric carcinoma in SCID mice. Jpn J Cancer Res. 2001 Dec;92(12):1322-8. doi: 10.1111/j.1349-7006.2001.tb02156.x.
34. Huang J, Chang Z, Lu Q, Chen X, Najafi M. Nobiletin as an inducer of programmed cell death in cancer: a review. Apoptosis. 2022 Jun;27(5-6):297-310. doi: 10.1007/s10495-022-01721-4.
35. Kesharwani SS, Mallya P, Kumar VA, Jain V, Sharma S, Dey S. Nobiletin as a Molecule for Formulation Development: An Overview of Advanced Formulation and Nanotechnology-Based Strategies of Nobiletin. AAPS PharmSciTech. 2020 Aug 5;21(6):226.
36. Goh JXH, Tan LT, Goh JK, Chan KG, Pusparajah P, Lee LH, Goh BH. Nobiletin and Derivatives: Functional Compounds from Citrus Fruit Peel for Colon Cancer Chemoprevention. Cancers (Basel). 2019 Jun 21;11(6):867. doi: 10.3390/cancers11060867.
37. Park MH, Hong JT. Roles of NF-κB in Cancer and Inflammatory Diseases and Their Therapeutic Approaches. Cells. 2016;5(2):15. doi: 10.3390/cells5020015.
38. Bharti AC, Aggarwal BB. Nuclear factor-kappa B and cancer: its role in prevention and therapy. Biochem Pharmacol 2002; 64: 883–8. doi: 10.1016/S0006-2952(02)01154-1.
39. Surh YJ, Na HK. NF-kappaB and Nrf2 as prime molecular targets for chemoprevention and cytoprotection with anti-inflammatory and antioxidant phytochemicals. Genes Nutr. 2008 Feb;2(4):313-7. doi: 10.1007/s12263-007-0063-0.
40. Clark IM, Swingler TE, Sampieri CL, Edwards DR. The regulation of matrix metalloproteinases and their inhibitors. Int J Biochem Cell Biol. 2008;40:1362–1378..
41. Quintero-Fabián S, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez V, Lara-Riegos J, Ramírez-Camacho MA, Alvarez-Sánchez ME. Role of Matrix Metalloproteinases in Angiogenesis and Cancer. Front Oncol. 2019 Dec 6;9:1370. doi: 10.3389/fonc.2019.01370.
42. Chien SY, Hsieh MJ, Chen CJ, Yang SF, Chen MK. Nobiletin inhibits invasion and migration of human nasopharyngeal carcinoma cell lines by involving ERK1/2 and transcriptional inhibition of MMP-2. Expert Opin Ther Targets. 2015 Mar;19(3):307-20. doi: 10.1517/14728222.2014.992875.
43. Baek SH, Kim SM, Nam D, Lee JH, Ahn KS, Choi SH, Kim SH, Shim BS, Chang IM, Ahn KS. Antimetastatic effect of nobiletin through the down-regulation of CXC chemokine receptor type 4 and matrix metallopeptidase-9. Pharm Biol. 2012 Oct;50(10):1210-8. doi: 10.3109/13880209.2012.664151.
44. Petzold T, Orr AW, Hahn C, Jhaveri KA, Parsons JT, Schwartz MA. Focal adhesion kinase modulates activation of NF-kappaB by flow in endothelial cells. Am J Physiol Cell Physiol. 2009 Oct;297(4):C814-22. doi: 10.1152/ajpcell.00226.2009.
45. Lee YC, Cheng TH, Lee JS, Chen JH, Liao YC, Fong Y, Wu CH, Shih YW. Nobiletin, a citrus flavonoid, suppresses invasion and migration involving FAK/PI3K/Akt and small GTPase signals in human gastric adenocarcinoma AGS cells. Mol Cell Biochem. 2011 Jan;347(1-2):103-15. doi: 10.1007/s11010-010-0618-z.
46. Cheng HL, Hsieh MJ, Yang JS, Lin CW, Lue KH, Lu KH, Yang SF. Nobiletin inhibits human osteosarcoma cells metastasis by blocking ERK and JNK-mediated MMPs expression. Oncotarget. 2016 Jun 7;7(23):35208-23. doi: 10.18632/oncotarget.9106.
47. Kim MO, Moon DO, Heo MS, Lee JD, Jung JH, Kim SK, Choi YH, Kim GY: Pectenotoxin-2 abolishes constitutively activated NF-κB, leading to suppression of NF-κB related gene products and potentiation of apoptosis. Cancer Letter. 2008, 271: 25-33. 10.1016/j.canlet.2008.05.034.
48. Ozes ON, Mayo LD, Gustin JA, Pfeffer SR, Pfeffer LM, Donner DB: NF-κB activation by tumor necrosis factor requires the Akt serine-threonine kinase. Nature. 1999, 401: 82-85.
49. Uden PV, Kenneth NS, Rocha S: Regulation of hypoxia-inducible factor-1α by NF-κB. Biochemical Journal. 2008, 412: 477-484. 10.1042/BJ20080476.
50. Chen J, Creed A, Chen AY, Huang H, Li Z, Rankin GO, Ye X, Xu G, Chen YC. Nobiletin suppresses cell viability through AKT pathways in PC-3 and DU-145 prostate cancer cells. BMC Pharmacol Toxicol. 2014 Oct 24;15:59. doi: 10.1186/2050-6511-15-59.
51. Chen J, Chen AY, Huang H, Ye X, Rollyson WD, Perry HE, Brown KC, Rojanasakul Y, Rankin GO, Dasgupta P, Chen YC. The flavonoid nobiletin inhibits tumor growth and angiogenesis of ovarian cancers via the Akt pathway. Int J Oncol. 2015;46(6):2629-38. doi: 10.3892/ijo.2015.2946.
52. Jiang H, Chen H, Jin C, Mo J, Wang H. 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 signaling pathway. J BUON. 2020 Mar-Apr;25(2):1070-1075. PMID: 32521908.
53. Wang JG, Jian WJ, Li Y, Zhang J. Nobiletin promotes the pyroptosis of breast cancer via regulation of miR-200b/JAZF1 axis. Kaohsiung J Med Sci. 2021 Jul;37(7):572-582. doi: 10.1002/kjm2.12371.
54. Sulli G, Lam MTY, Panda S. Interplay between circadian clock and cancer: new frontiers for cancer treatment. Trends Cancer. 2019;5:475–94.
55. Kim E, Kim YJ, Ji Z, Kang JM, Wirianto M, Paudel KR, Smith JA, Ono K, Kim J, Eckel-Mahan K, Zhou, Lee HK, Yoo JY and Yoo SH. ROR activation by Nobiletin enhances antitumor efficacy via suppression of IκB/NF-κB signaling in triple-

negative breast cancer. Cell Death Dis. 2022;13:374. https://doi.org/10.1038/s41419-022-04826-5

56. Grandis JR, Drenning SD, Zeng Q, Watkins SC, Melhem MF, Endo S, Johnson DE, Huang L, He Y, Kim JD. Constitutive activation of Stat3 signaling abrogates apoptosis in squamous cell carcinogenesis in vivo. Proc Natl Acad Sci U S A. 2000 Apr 11;97(8):4227-32. doi: 10.1073/pnas.97.8.4227.
57. Xu Z, Wu D, Fu D, Tang C, Ge J, Zhang Z, Zhou W. Nobiletin inhibits viability of human renal carcinoma cells via the JAK2/STAT3 and PI3K/Akt pathway. Cell Mol Biol (Noisy-le-grand). 2020 Jul 31;66(5):199-203.
58. Sp N, Kang DY, Kim DH, Park JH, Lee HG, Kim HJ, Darvin P, Park YM, Yang YM. Nobiletin Inhibits CD36-Dependent Tumor Angiogenesis, Migration, Invasion, and Sphere Formation Through the Cd36/Stat3/Nf-Kb Signaling Axis. Nutrients. 2018 Jun 15;10(6):772. doi: 10.3390/nu10060772.
59. Ma Y, Ren X, Patel N, Xu X, Wu P, Liu W, Zhang K, Goodin S, Li D, Zheng X. Nobiletin, a citrus polymethoxyflavone, enhances the effects of bicalutamide on prostate cancer cells via down regulation of NF-κB, STAT3, and ERK activation. RSC Adv. 2020 Mar 10;10(17):10254-10262. doi: 10.1039/c9ra10020b.
60. Ma W, Feng S, Yao X, Yuan Z, Liu L, Xie Y. Nobiletin enhances the efficacy of chemotherapeutic agents in ABCB1 overexpression cancer cells. Sci Rep. 2015 Dec 22;5:18789. doi: 10.1038/srep18789.
61. Yang J, Nie J, Ma X, Wei Y, Peng Y, Wei X. Targeting PI3K in cancer: mechanisms and advances in clinical trials. Mol Cancer. 2019 Feb 19;18(1):26. doi: 10.1186/s12943-019-0954-x.
62. Irby RB, Yeatman TJ. Role of Src expression and activation in human cancer. Oncogene. 2000 Nov 20;19(49):5636-42. doi: 10.1038/sj.onc.1203912.
63. 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. Nobiletin Inhibits Cell Viability via the SRC/AKT/STAT3/YY1AP1 Pathway in Human Renal Carcinoma Cells. Front Pharmacol. 2019 Jul 9;10:690. doi: 10.3389/fphar.2019.00690.
64. Li N, Zhang Z, Jiang G, Sun H, Yu D. Nobiletin sensitizes colorectal cancer cells to oxaliplatin by PI3K/Akt/MTOR pathway. Front Biosci (Landmark Ed). 2019 Jan 1;24(2):303-312. doi: 10.2741/4719.
65. Shi MD, Liao YC, Shih YW, Tsai LY. Nobiletin attenuates metastasis via both ERK and PI3K/Akt pathways in HGF-treated liver cancer HepG2 cells. Phytomedicine. 2013 Jun 15;20(8-9):743-52. doi: 10.1016/j.phymed.2013.02.004.
66. Tian T, Li X, Zhang J. mTOR Signaling in Cancer and mTOR Inhibitors in Solid Tumor Targeting Therapy. Int J Mol Sci. 2019 Feb 11;20(3):755. doi: 10.3390/ijms20030755.
67. Goan YG, Wu WT, Liu CI, Neoh CA, Wu YJ. Involvement of Mitochondrial Dysfunction, Endoplasmic Reticulum Stress, and the PI3K/AKT/mTOR Pathway in Nobiletin-Induced Apoptosis of Human Bladder Cancer Cells. Molecules. 2019 Aug 8;24(16):2881. doi: 10.3390/molecules24162881.
68. Zheng GD, Hu PJ, Chao YX, Zhou Y, Yang XJ, Chen BZ, Yu XY, Cai Y. Nobiletin induces growth inhibition and apoptosis in human nasopharyngeal carcinoma C666-1 cells through regulating PARP-2/SIRT1/AMPK signaling pathway. Food Sci Nutr. 2019 Feb 10;7(3):1104-1112. doi: 10.1002/fsn3.953.
69. Megumi Ikeda, Ken-ichi Masumura, Keiko Matsui, Hiroyuki Kohno, Keiko Sakuma, Takuji Tanaka and Takehiko Nohm. Chemopreventive EŠects of Nobiletin against Genotoxicity Induced by 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in the Lung of gpt delta Transgenic Mice. Genes and Environment, Vol. 28, No. 3 pp. 84–91 (2006)
70. Matsumoto T, Nishikawa T, Furukawa A, Itano S, Tamura Y, Hasei T, Watanabe T. Antimutagenic Effects of Polymethoxy Flavonoids of Citrus unshiu. Nat Prod Commun. 2017 Jan;12(1):23-26. PMID: 30549817.
71. Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, Prueitt RL, Yanaihara N, Lanza G, Scarpa A, Vecchione A, Negrini M, Harris CC, Croce CM. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.
72. Lytle JR, Yario TA, Steitz JA. Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR. Proc Natl Acad Sci U S A. 2007 Jun 5;104(23):9667-72.
73. Khraiwesh B, Arif MA, Seumel GI, Ossowski S, Weigel D, Reski R, Frank W. Transcriptional control of gene expression by microRNAs. Cell. 2010 Jan 8;140(1):111-22.
74. Farooqi AA, Qureshi MZ, Coskunpinar E, Naqvi SK, Yaylim I, Ismail M. MiR-421, miR-155 and miR-650: emerging trends of regulation of cancer and apoptosis. Asian Pac J Cancer Prev. 2014;15(5):1909-12. doi: 10.7314/apjcp.2014.15.5.1909.
75. Mytsyk Y, Dosenko V, Borys Y, Kucher A, Gazdikova K, Busselberg D, Caprnda M, Kruzliak P, Farooqi AA, Lubov M. MicroRNA-15a expression measured in urine samples as a potential biomarker of renal cell carcinoma. Int Urol Nephrol. 2018 May;50(5):851-859. doi: 10.1007/s11255-018-1841-x.
76. Farhan M, Malik A, Ullah MF, Afaq S, Faisal M, Farooqi AA, Biersack B, Schobert R, Ahmad A. Garcinol Sensitizes NSCLC Cells to Standard Therapies by Regulating EMT-Modulating miRNAs. Int J Mol Sci. 2019 Feb 13;20(4):800. doi: 10.3390/ijms20040800.
77. Farooqi AA, Fuentes-Mattei E, Fayyaz S, Raj P, Goblirsch M, Poltronieri P, Calin GA. Interplay between epigenetic abnormalities and deregulated expression of microRNAs in cancer. Semin Cancer Biol. 2019 Oct;58:47-55. doi: 10.1016/j.semcancer.2019.02.003.
78. Wen R, Umeano AC, Essegian DJ, Sabitaliyevich UY, Wang K, Farooqi AA. Role of microRNA-410 in molecular oncology: A double edged sword. J Cell Biochem. 2018 Nov;119(11):8737-8742. doi: 10.1002/jcb.27251.
79. Liu PF, Farooqi AA, Peng SY, Yu TJ, Dahms HU, Lee CH, Tang JY, Wang SC, Shu CW, Chang HW. Regulatory effects of noncoding RNAs on the interplay of oxidative stress and autophagy in cancer malignancy and therapy. Semin Cancer Biol. 2022 Aug;83:269-282. doi: 10.1016/j.semcancer.2020.10.009.
80. Yaylim İ, Farooqi AA, Telkoparan-Akillilar P, Saso L. Interplay between Non-coding RNAs and NRF2 in Different Cancers: Spotlight on miRNAs and Long non-coding RNAs. J Pharmacol Exp Ther. 2022 Jun 6:JPET-MR-2021-000921. doi: 10.1124/jpet.121.000921.
81. Farooqi AA, Zahid R, Naureen H, Attar R, Gazouli M, Berardi R, Szelachowska J, Matkowski R, Pawlak E. Regulation of ROCK1/2 by long non-coding RNAs and circular RNAs in different cancer types. Oncol Lett. 2022 May;23(5):159. doi: 10.3892/ol.2022.13279.
82. Tang JY, Chuang YT, Shiau JP, Yang KH, Chang FR, Hou MF, Farooqi AA, Chang HW. Long Noncoding RNAs and Circular RNAs Regulate AKT and Its Effectors to Control Cell Functions of Cancer Cells. Cells. 2022; 11(19):2940. https://doi.org/10.3390/cells11192940
83. Farooqi AA, Nayyab S, Martinelli C, Berardi R, Katifelis H, Gazouli M, Cho WC. Regulation of Hippo, TGFβ/SMAD, Wnt/β-Catenin, JAK/STAT, and NOTCH by Long Non-Coding RNAs in Pancreatic Cancer. Front Oncol. 2021 Jun 9;11:657965. doi: 10.3389/fonc.2021.657965.
84. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A,

Maier L, Mackowiak SD, Gregersen LH, Munschauer M, Loewer A, Ziebold U, Landthaler M, Kocks C, le Noble F, Rajewsky N. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature. 2013 Mar 21;495(7441):333-8. doi: 10.1038/nature11928.

85. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J. Natural RNA circles function as efficient microRNA sponges. Nature. 2013 Mar 21;495(7441):384-8. doi: 10.1038/nature11993.
86. Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS One. 2012;7(2):e30733. doi: 10.1371/journal.pone.0030733.
87. Han SH, Han JH, Chun WJ, Lee SS, Kim HS, Lee JW. Nobiletin Inhibits Non-Small-Cell Lung Cancer by Inactivating WNT/β-Catenin Signaling through Downregulating miR-15-5p. Evid Based Complement Alternat Med. 2021 Dec 30;2021:7782963. doi: 10.1155/2021/7782963.
88. Gao XJ, Liu JW, Zhang QG, Zhang JJ, Xu HT, Liu HJ. Nobiletin inhibited hypoxia-induced epithelial-mesenchymal transition of lung cancer cells by inactivating of Notch-1 signaling and switching on miR-200b. Pharmazie. 2015 Apr;70(4):256-62.
89. Bayoumi M, Arafa MG, Nasr M, Sammour OA. Nobiletin-loaded composite penetration enhancer vesicles restore the normal miRNA expression and the chief defence antioxidant levels in skin cancer. Sci Rep. 2021 Oct 12;11(1):20197. doi: 10.1038/s41598-021-99756-1.
90. Zhang X, Zheng K, Li C, Zhao Y, Li H, Liu X, Long Y, Yao J. Nobiletin inhibits invasion via inhibiting AKT/GSK3β/β-catenin signaling pathway in Slug-expressing glioma cells. Oncol Rep. 2017 May;37(5):2847-2856. doi: 10.3892/or.2017.5522.
91. Da C, Liu Y, Zhan Y, Liu K, Wang R. Nobiletin inhibits epithelial-mesenchymal transition of human non-small cell lung cancer cells by antagonizing the TGF-β1/Smad3 signaling pathway. Oncol Rep. 2016 May;35(5):2767-74. doi: 10.3892/or.2016.4661.
92. Feng SL, Tian Y, Huo S, Qu B, Liu RM, Xu P, Li YZ, Xie Y. Nobiletin potentiates paclitaxel anticancer efficacy in A549/T xenograft model: Pharmacokinetic and pharmacological study. Phytomedicine. 2020 Feb;67:153141. doi: 10.1016/j.phymed.2019.153141.
93. Wu J, Lee SW, Zhang X, Han F, Kwan SY, Yuan X, Yang WL, Jeong YS, Rezaeian AH, Gao Y, Zeng YX, Lin HK. Foxo3a transcription factor is a negative regulator of Skp2 and Skp2 SCF complex. Oncogene. 2013 Jan 3;32(1):78-85. doi: 10.1038/onc.2012.26.
94. Chen T, Liu L, Zou Y, Hu X, Zhang W, Zhou T, Luo X, Fu W, Xu J. Nobiletin downregulates the SKP2-p21/p27-CDK2 axis to inhibit tumor progression and shows synergistic effects with palbociclib on renal cell carcinoma. Cancer Biol Med. 2021 Feb 15;18(1):227-244. doi: 10.20892/j.issn.2095-3941.2020.0186.