

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 pursuit 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- κ B pathway

Importantly, nuclear transcription factor- κ B (NF- κ B) 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- κ B in the development and progression of cancer. Moreover, inhibition of NF- κ B 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- κ B by natural products in cancer chemoprevention (39).

Further, NF- κ B has shown the ability to bind with the promoter regions of Matrix metalloproteinases and activated NF- κ B has been linked with uncontrolled MMPs. Both MMP-2 and MMP-9 are the downstream targets of Nuclear Factor kappa B (NF- κ B) (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 adhe-

sion) that further leads to migration and invasion. Importantly, MMP-2 and MMP-9 are frequently associated with the poor prognosis of cancer treatment (41).

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- κ B 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- κ B binding sites. Nobiletin mediated inhibition of constitutive NF- κ B 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- κ B and the previous literature emanates the role of focal adhesion kinase (FAK) in the regulation NF- κ B 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- κ B and its binding to NF- κ B response elements (45). This suggests that nobiletin can inhibit/prevent carcinogenesis via FAK/Akt- NF- κ B- MMP-2/9 pathway.

In osteocarcinoma cell lines (U2OS and HOS cells), nobiletin at the concentrations of 100 μ M can downregulate MMP-2/9 by inhibiting extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and NF- κ B. Further, nobiletin inhibited the migration, invasion and the mobility of osteocarcinoma cells. This suggests the possible role of NF- κ B 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- κ B and NF- κ B can directly regulate hypoxia-inducible factor-1 α (HIF-1 α) (49). Another study in prostate cancer cells (PC-3 and DU-145) has identified that the nobiletin inhibited nuclear translocation of NF- κ B. Nobiletin inhibited phosphorylation of AKT and downregulated the expression of HIF-1 α and VEGFA (50). A similar study validated the inhibition of VEGFA via AKT-NF- κ B-HIF-1 α 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 μ M by inducing G0/G1 arrest, depleting cyclin D1 and CDK4 expression. Further, nobiletin exhibited a dose-dependent inhibition of NF- κ B, postulating its possible role in the anti-metastatic potential of nobiletin (52).

Nobiletin induced an increase in the nuclear levels of NF- κ B 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

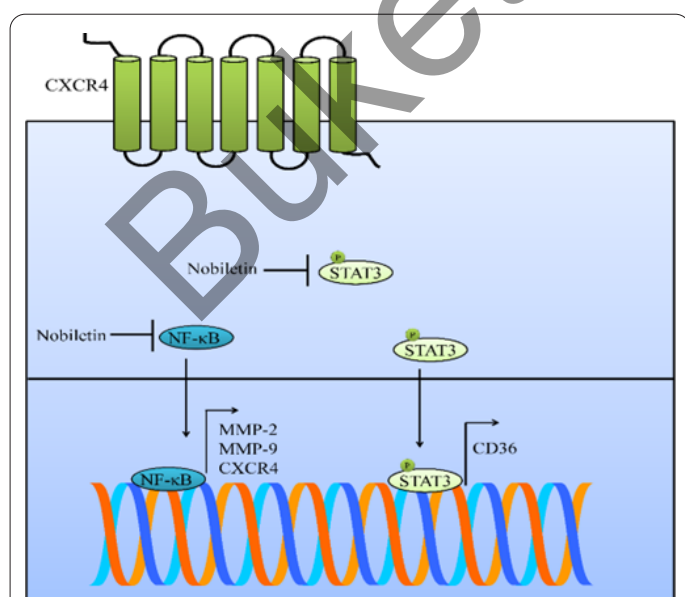


Figure 1. Nobiletin mediated inhibition of nuclear accumulation of NF- κ B and STAT3. NF- κ B stimulated the expression of MMP-2/9 and CXCR4. Whereas, STAT3 transcriptionally upregulated CD36. Nobiletin downregulated transcriptional networks of NF- κ B and STAT3.

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- κ B 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- κ B activation and NF- κ B-mediated regulation of RORs. Interestingly, nobiletin has been shown to upregulate the binding of ROR to response elements at I κ B α 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- κ B 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, TNF α 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- κ B 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- κ B 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 NNK 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

TGF β 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).

TGF β increased the expression of Snail, Slug, Twist and ZEB1. However, TGF β -mediated upregulation of target gene network was reversed by nobiletin. Moreover, nobiletin potently inhibited transcriptional activities of SMADs induced by TGF β in A549 cells. SMAD3 overexpression severely impaired nobiletin-mediated inhibitory effects on TGF β -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

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